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Advancements and Challenges in Diagnostic Approaches for Alzheimer's Disease: A Comprehensive Review

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Abstract

This article explores the advancements and challenges in diagnostic approaches for Alzheimer's disease (AD). The article investigates the role of artificial intelligence in improving diagnostic accuracy, the potential of neuroimaging techniques for early detection and disease progression tracking, early-stage detection, and monitoring of AD. In addition, it also discusses the challenges associated with these approaches. This review provides valuable insights into the current diagnostic techniques for AD. It highlights future opportunities for advancements in computer science to enhance early diagnosis and management of this disease. Moreover, it presents detailed information about the recent datasets of AD.

Keywords: Alzheimer's Disease; AD Detection Methods; Single and Multi-modality Approaches; Model Complexity Reduction; Risk Score; AD Datasets.

1 | Introduction

Alzheimer's disease (AD) is a degenerative neurological disorder leading to a decline in cognitive abilities, such as memory, language, and reasoning. It is the most common cause of dementia, a disease characterized by decreased mental capacity and memory. AD is widespread in those aged 65 and above, though it can affect people of any age. Unfortunately, there is no known final cure for AD. However, treatments are available to manage the symptoms, as the neurons in the brain responsible for memory, language, and thinking are the first to be affected by AD. As a result, memory, language, and reasoning issues are frequently the first signs. Even though these symptoms are novel to the affected person, the brain alterations that produce them are believed to have started 20 years or more before the symptoms. However, AD is a progressive condition that worsens with time. The rate of progression and the talents that are impacted differ from person to person. More neurons sustain damage with time, affecting more regions of the brain. More assistance from family, friends, and professional carers is required to do everyday tasks, including dressing and bathing, and to keep the person safe. Alzheimer's patients may experience mood, demeanor, or conduct changes. One behavior that warrants special attention is wandering, defined as someone leaving a particular area without being able to follow their footsteps back. Wandering people run the danger of severe harm or perhaps death if they become lost. Finally, Alzheimer's disease causes brain alterations that include the accumulation of the protein

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beta-amyloid outside neurons and twisted strands of the protein tau inside neurons. They are accompanied by brain tissue deterioration and neuronal death. Other alterations include atrophy and inflammation of brain tissue [5].

1.1 |AD Stages

The progression of AD is divided into three stages (See Figure 1) [26, 35, 77]:

Early Stage: Memory loss and confusion are the first symptoms of Alzheimer's disease. Other signs may include difficulty completing familiar tasks, difficulty finding the right words, and changes in mood or behavior.

Middle Stage: Memory loss and confusion worsen during this stage. Patients may experience disorientation in time and place, decreased communication ability, and increased risk of wandering.

Late Stage: Patients may lose the ability to recognize family and friends, experience significant weight loss, and become incontinent. They may also become bedridden and require full-time care.

For these reasons, AI can be used to track the progression of AD by using pattern –recognition algorithms to detect subtle changes in the patient's behavior over time. AI can also be used to analyze brain scans and other medical data to see early signs of the disease. AI can also be used to identify biomarkers associated with the disease and to track the disease's progression by monitoring the biomarkers' levels. AI can also be used to develop personalized treatments and interventions for AD, which can potentially slow down the progression of the disease and improve the quality of life for patients [25].

Consequently, it is essential to identify patients who are at a high risk of progressing from moderate cognitive impairment to AD through earlier intensive monitoring, focused examinations, and effective management. Several machine learning (ML) methods have recently been applied to detect AD progression [6].

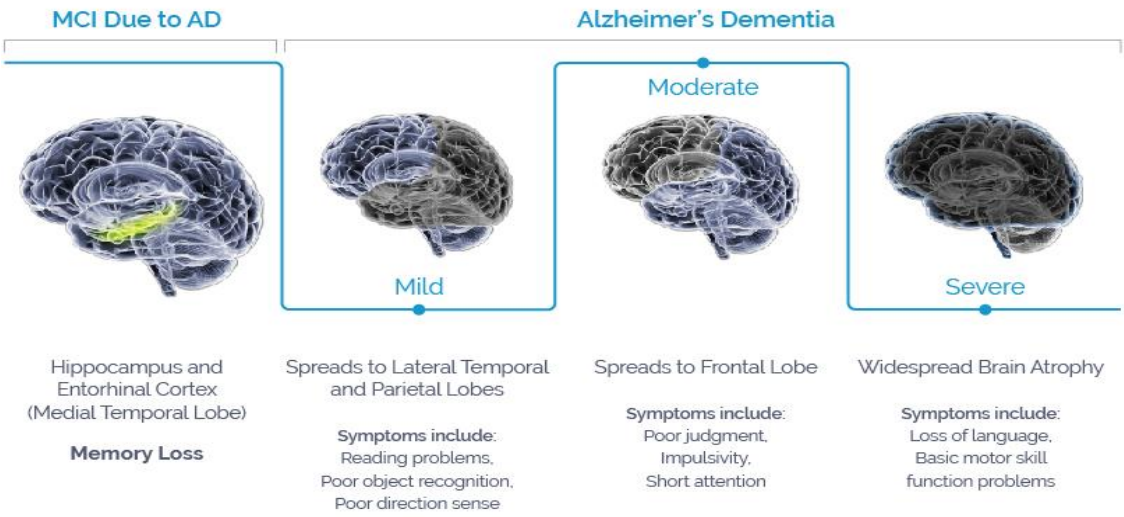

Figure 1. Summary showing the AD progress in different stages along with their symptoms [26].

1.2 |AD Biomarkers

As AD is a complicated neurological condition, various biomarkers may be used to diagnose and track the disease's course. Based on the kind of knowledge they offer about the brain; these biomarkers may be divided into many groups. The types of AD biomarkers are as follows:

Structural biomarkers: Structural biomarkers offer details on the composition of the brain, such as the dimensions and contours of various brain areas. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans are examples of structural biomarkers. Structural MRI is the most popular method

for identifying structural biomarkers in AD research. It can identify brain volume, thickness, and form alterations over time. In [12, 28] they highlighted the benefits of discovering biomarkers in AD for proper diagnosis, understanding the disease's underlying mechanism, and producing medicines in the future.

Functional Biomarkers: Functional biomarkers give data on the activation of various brain areas. Functional biomarkers include Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI). PET scans can detect activity in specific brain areas, such as those associated with memory and cognition. fMRI detects variations in brain blood flow and oxygenation. In [22] prior methods for AD diagnosis criteria were changed to focus on biomarkers rather than initial symptom evaluation. Furthermore, Robin et al. [56] presented digital biomarkers along with speech-based biomarkers, which showed an interest in measuring cognition and function during daily activities. Table 1 highlights some of the significant differences in structural MRI, PET, and CT modalities' abilities to act as biomarkers for AD.

Biofluid biomarkers: measure biological substances in the blood or cerebrospinal fluid (CSF) [22]. These biomarkers, like brain amyloid and tau proteins, can indicate the existence of AD pathology. CSF biomarkers are more sensitive than blood biomarkers; obtaining a sample requires a lumbar puncture. Amyloid beta (Aβ) and tau proteins are two examples of biofluid indicators [32]. The limits, understanding, and present status of frontotemporal dementia biofluid-based biomarkers for routine diagnosis and disease trajectories were also highlighted [13].

Genetic Biomarkers: Genetic biomarkers are alterations in DNA that can raise the likelihood of acquiring Alzheimer's disease. The apolipoprotein E (APOE) gene is linked with an increased risk of developing AD, and mutations in particular genes, such as APP, PSEN1, and PSEN2, are related to early-onset familial. As Sherif. F et al. [58] used whole genome sequencing (WGS) data to uncover causative AD SNPs and gene-SNP interactions using multiple Bayesian network structure learning techniques. They concentrated on polymorphisms in the top 10 genes linked to AD as discovered by genome-wide association (GWA) studies. In addition, Sherif. F et al. [59] wanted to increase AD prediction accuracy by uncovering higher-order epistasis interactions between genetic variations. The proposed framework predicted AD risk with excellent accuracy, and the revealed genetic variations and their interactions have the potential to be exploited as biomarkers for AD diagnosis and therapy.

Finally, using biomarkers for AD diagnosis and progression monitoring is a growing field of study and clinical practice, and the optimal combination of biomarkers may vary depending on individual patient features and disease stage [21, 61].

Table 1. The differences between structural biomarkers MRI, PET, and CT in Alzheimer's disease (AD).

Modality	Biomarker Type	Biomarker Features	Sensitivity to AD	Advantages	Limitations
MRI	Structural	Gray matter volume, cortical thickness, white matter integrity	High	Non-invasive, can detect early changes in brain structure	Expensive, not widely available
PET	Biofluid	Amyloid-beta and tau protein accumulatio, glucose-metabolism, cerebral blood flow	High	It can detect early AD pathology changes and differentiate AD from other dementias.	Expensive, requires radioactive tracers, and results can be affected by medications and comorbidities.
CT	Structural	Brain atrophy , ventricular enlargement	Low	Widely available, relatively inexpensive	Poor sensitivity to early AD changes exposes a patient to ionizing radiation

1.3 |Current State of AI in Diseases Research

As a result of the recent developments in AI for disease detection, techniques such as using Machine Learning algorithms to spot anomalies in imaging data (like CT or MRI scans), using Natural Language Processing (NLP) to diagnose illnesses based on patient symptoms, using computer vision to spot skin conditions, and using AI-powered chatbots to give health advice are all within reach. Additionally, AI can detect disease outbreaks, predict disease spread, and personalize treatment plans.

AI has shown significant potential in assisting in the early identification and diagnosis of AD. Recent research has concentrated on the development and interpretation of many types of biomarkers for AD, such as genetic [58], biofluid [22], and functional biomarkers [56]. Machine learning algorithms have been used to find the most informative genetic variations and their interactions, as well as to reveal inherent patterns and mechanisms underlying huge amounts of extremely varied biological data. Bayesian networks have been used to identify genetic biomarkers for Alzheimer's disease as well as to anticipate higher-order epistasis interactions between genetic variations [59].

This review article will present an overview of the most recent research using deep-learning algorithms (summarized in Table 2) to evaluate the process of AD, as well as explore the existing capabilities and future directions of AI for early detection and diagnosis of AD.

Table 2. The recent achievements of AD detection, diagnosis, and prediction concerning AI approaches [19,47].

Year	Achievement	AI Approach	Methodology/ Techniques	Dataset Used	Key Findings/ Outcomes
2017	Improved Early Detection	Deep Learning	Convolutional Neural Networks (CNN)	ADNI, OASIS	Enhanced accuracy in identifying early signs of AD using structural MRI scans.
2018	Multi-Modality Fusion	Hybrid Models	MRI-PET Fusion, Ensemble Learning	ADNI, etc.	Combining MRI and PET data improved diagnostic accuracy.
2019	Predictive Biomarker Identification	Machine Learning	Feature Selection, SVM, Random Forest	ADNI, UK Biobank, etc.	Identification of novel biomarkers associated with AD progression, aiding in predicting disease development.
2020	Differential Diagnosis	Ensemble Methods	Stacking, Gradient Boosting	ADNI, Dementia Bank, etc.	More accurate differentiation between AD and other dementia subtypes.
2021	Longitudinal Tracking of Progression	Longitudinal Analysis	Deep Learning, Recurrent Neural Nets	ADNI, Alzheimer's Research UK	AI models for tracking AD progression over time, facilitating better understanding of disease dynamics.
2022	Personalized Treatment Recommendations	Precision Medicine	Biomarker Profiling, Clinical Data	ADNI	AI-driven personalized treatment strategies based on patient's biomarker profile and medical history.
2023	Early Identification of High-Risk AD	Predictive Modeling	Machine Learning, Risk Stratification	ADNI, Framingham Heart Study	Accurate identification of individuals at high risk of developing AD in the future

The goal of this study is to provide a complete and comprehensive evaluation of AI-based automated diagnostic systems, particularly those designed for AD detection and diagnosis. In addition, the research seeks to identify and clarify any limits and downsides associated with these AI-driven diagnostic tools. The researchers used a variety of relevant terms, such as dementia, deep learning, machine learning, feature

selection, data modalities, and automated diagnostic systems, to assemble publications that correspond with the study`s primary areas. To reach its goals, the study collected an extensive collection of research publications published between 2015 and 2023. This time span guarantees that the review is up to date on the latest advancements and trends in the area.

The major goal of this investigation was to extract significant insights, patterns, and trends related to the use of AI-based diagnostic systems for AD, particularly the integration of several data modalities such as images, clinical features, and speech data. This review also aims to identify and express the limits and downsides of these AI-based automated diagnostic tools. This study aims to add to the current body of knowledge about AI-based diagnostic tools for AD by synthesizing findings and comments from the chosen papers. Ultimately, the goal is to provide significant insights that can direct future research efforts, stimulate the creation of more effective diagnostic tools, and allow the refining of AI-driven technologies.

The review is organized into Section 2. Traditional method for AD detection showing their limitations and drawbacks, Section 3. Current capabilities and future directions of AI for early detection and diagnosis of AD, Section 4. AI-model complexity reduction, Section 5. AD risk score, Section 6. Disease progression, and Section 7. Current AD datasets.

2 | Traditional Methods for AD Detection

Researchers and medical professionals employ a variety of AD diagnostic methods. These techniques can be classified as clinical, imaging, or biomarker-based. Each approach has a particular function in diagnosing or predicting Alzheimer's disease. Here's a brief description of some of the most prevalent AD detection methods [2, 27]:

A. Clinical Evaluation:

- Medical History: Gather data on the patient's medical history, cognitive problems, and family history of Alzheimer's disease.
- Cognitive Testing: Various cognitive tests are administered to examine memory, language, attention, and other cognitive skills.
- Functional Assessment: An individual's capacity to carry out everyday activities and duties.

B. Neuroimaging Techniques:

- Magnetic Resonance Imaging (MRI): This type of imaging is used to identify structural abnormalities in the brain, such as atrophy or shrinkage.
- Positron Emission Tomography (PET): Can assess brain metabolism and the buildup of amyloid plaques or tau tangles, which are hallmarks of Alzheimer's disease.
- SPECT (Single-Photon Emission Computed Tomography) is another imaging technology used to measure cerebral blood flow and function.

C. Biomarker Evaluation:

- Cerebrospinal Fluid (CSF) Biomarkers: Detecting degenerative alterations in the brain by measuring specific proteins (e.g., amyloid beta, tau) in the cerebrospinal fluid.
- Biomarkers derived from blood: Blood indicators that may indicate the existence of Alzheimer's disease or its risk factors are being studied by researchers.

D. *Genetic Testing:* Genetic testing can detect specific gene variants (e.g., APOE4) that are more likely to develop Alzheimer's disease.

E. *Neuropsychological Testing:* To uncover patterns of impairment, in-depth examinations of cognitive ability, memory, language, and other functions are done.

F. *Digital Biomarkers:* Using digital gadgets, wearables, or smartphone apps to monitor behavioral and cognitive changes that may suggest AD.

However, depending on the approach utilized, various AD detection methods have significant limitations and disadvantages (as shown in Table 3).

Nevertheless, it is crucial to remember that these drawbacks are incomplete and may only apply to some AD detection methods. Furthermore, some of these drawbacks may be offset by the possible benefits of utilizing a specific AD detection approach, such as the capacity to diagnose AD at an early stage when treatment may be more successful.

Table 3. Limitations and disadvantages of the currently used AD detection methods.

Detection Method	Limitations and disadvantages
Clinical Evaluation	Early-stage Alzheimer's disease symptoms are mild and readily misinterpreted. Inadequate sensitivity and specificity for early detection. A failure to differentiate AD from other types of dementia.
Neuroimaging Techniques	Some imaging modalities, such as PET and MRI, are expensive. Imaging abnormalities may not be specific to AD, resulting in false positives. Imaging may not detect early-stage AD alterations.
Biomarker Evaluation	CSF sample is invasive for biomarker analysis. Blood-based biomarkers may need to be more sensitive and selective for detecting AD. Access to biomarker tests is limited, and there needs to be more uniformity between laboratories. Some biomarkers' predictive usefulness is still being investigated.
Genetic Testing	Genetic mutations (for example, APOE4) associated with AD risk do not ensure disease development.
Neuropsychological Testing	Early or insignificant cognitive impairments in the preclinical phases of AD may go undetected. Age, education, and culture may all impact the results. It takes time and requires many resources. Limited sensitivity in diagnosing brain diseases linked with AD.
Digital Biomarkers	Digital biomarker assays are currently being validated and standardized. Concerns about data privacy and security arise when using digital health data. Some digital biomarkers' dependability and accuracy require more investigations.

3 |Traditional Methods for AD Detection

The key issues surrounding the implementation of AI into the existing clinical workflows include sharing data and its privacy, transparency of algorithms, data standardization, integration, and interoperability between multiple working platforms, concern for patient safety, and reliability and precision of the results. Where AI methods and approaches (machine learning or deep learning) were based on: Image datasets, Clinical datasets, Genetic datasets, and Voice datasets, these approaches and methods are summarized below [25, 62]:

Machine Learning: Machine learning is an AI that uses algorithms to learn and adapt based on data. It can be used to detect patterns in brain scans, medical images, and other data to identify indicators of AD.

Natural Language Processing (NLP) is an AI technique that enables machines to understand and process natural language. It can be used to analyze conversations and interactions with patients to detect changes in language and behavior indicative of AD.

Deep Learning: Deep learning is an AI that uses layered neural networks to learn from data. It can be used to analyze brain scans and other data to detect patterns associated with AD.

Image Analysis: Image analysis is an AI technique that uses algorithms to analyze images. It can be used to detect changes in the brain scans of AD patients.

Gene Mapping: Gene mapping is an AI technique that uses algorithms to compare the genetic makeup of AD patients to healthy individuals. It can be used to identify genetic markers associated with AD.

AI-based approaches were proposed to diagnose, detect, and predict AD, including using machine learning algorithms such as Support Vector Machine (SVM), Random Forest, and Decision Tree to analyze medical imaging data, biomarkers, genetic data, or other medical records. AI can also detect cognitive changes in patients by analyzing speech and language patterns or tracking eye movements. AI can also predict AD progression by analyzing patient data and applying predictive models. It provides a deep-learning approach to classify and diagnose different diseases for image-based medical diagnoses. Deep learning is a new AI machine-learning technique, and its medical applications have generated much interest over the past few years. It is designed to mimic the layers of neurons in the human brain to process and extract information, allowing computers to learn without being explicitly programmed [70]. Moreover, AI is rapidly being employed in both single-modality and multi-modality AD detection approaches [53].

3.1 | Single-modality Approaches

AI-based MRI data analysis: AI algorithms may be used to analyze MRI data to detect changes in brain structure associated with AD, such as hippocampal decrease. Deep learning algorithms, for example, may be trained to automatically segment the hippocampus and other brain areas from MRI scans, which can assist in the early diagnosis of AD. As Frizzell et al. [17] examined AI research that used MRI imaging to evaluate normal aging, moderate cognitive impairment, and Alzheimer's disease dementia. Moreover, Shimron &Perlman [60] emphasized the potential of AI in simplifying and improving the MRI imaging workflow, resulting in quicker and more accurate diagnoses. MRI data analysis might be automated by employing AI approaches, allowing physicians to focus more on interpretation and decision-making.

PET data analysis using AI algorithms: AI algorithms may be used to analyze PET data to detect changes in brain metabolism or the deposition of amyloid plaques. AI algorithms may be trained to recognize and quantify amyloid plaques in PET scans, which can help in the early identification of Alzheimer's disease. Sitek et al. [65] emphasized the potential of AI to improve and optimize all areas of the PET imaging chain, from patient scheduling to image interpretation. The article investigated the development, standardization, and clinical application of artificial intelligence in PET imaging. Then Saboury et al. [57] covered the use of artificial intelligence (AI) in clinical practice in nuclear medicine, especially PET imaging, as well as the benefits and problems that come with it.

3.2 | Multi-modality Approaches

AI-based fusion of MRI and PET data: AI algorithms can be utilized to combine data from MRI and PET scans to provide additional information regarding changes in brain structure and function related to AD. Deep learning algorithms may be used to integrate MRI and PET data to predict AD's progress. Among the deep learning algorithms utilized for multimodal medical data mining in AI-based fusion of MRI and PET data that are briefly reviewed are:

Early Fusion: Early fusion strategies are used in several investigations to connect multimodal data. In this article, they used a joint fusion strategy to perform image-image fusion of PET and MRI images, in which clinical and imaging characteristics were concatenated into a single feature vector before input into the neural network [29].

Multimodal Deep Learning: Multimodal deep learning approaches have been investigated for biological data fusion. Deep neural networks are used to simulate the complicated interactions between multiple modalities in these approaches. For example, Stahlschmidt et al. [67] outperform shallow data fusion approaches and have been used in various industries, including medical imaging.

Multimodal Image Fusion: Deep learning algorithms utilizing multimodal imaging, such as MRI and PET, have showed potential for computer-aided diagnosis in the context of Alzheimer's disease diagnosis. These strategies rely on the merging of multimodal pictures to increase the accuracy of Alzheimer's disease diagnosis [66].

Fusion Strategies: Deep learning-based fusion algorithms are used to combine and interpret multimodal medical data. These methodologies seek to collect the complementing information offered by many modalities, hence improving overall analysis and prediction accuracy [8].

Therefore, this review will focus on AD detection using image modality as the early diagnosis and detection of AD in its early stages will prevent its progression and reaches a stable state for the patient. Many different technologies were used to solve the problem of the diagnosis and detection of this disease. Several studies have been reviewed in Table 4, where MRI is the most frequently used modality for diagnosing AD.

Table 4. Summarize several studies for detecting and diagnosing AD using image modality**.**

Ref.	Study objective	Applied Techniques	Validation method	Sample size	Feature	Optimal results	Optimal approach	Data set	limitation
BariAntor et al [6]	Identify and classify brain dementia diseases	Applied shallow learning algorithms to attain the optimum detection algorithm for dementia.	stratified sampling: 80% train-validate, 20% test	OSIS data with 375 Row* 15 Col.	MRI images	SVM reached 92% and 91.9% accuracy for F1-Score, AUC, and recall.	SVM.	OASIS	NA
Battineni et al. [7]	Using MRI to attain more features aiding in early-stage AD diagnosis and predicting neurodegener ative disorder.	Developed a hybrid model to increase the detection and prediction accuracy of AD symptoms and evidence in MRI.	N-fold cross-validation	373 MRI tests for 150 subjects >60	MRI images	Reached an accuracy of 99.1 % using the proposed hybrid approach.	Naive Bayes (NB). ANN. K-nearest neighbor (KNN). SVM.	Alzheimer' s Disease Research Center (ADRC)	The number of samples was very small. Consequent ly, the results could have been more accurate and guaranteed the proper AD diagnosis and prediction.
Chitradevi & Prabha [11]	Use the brain subregion approach to detect, classify, and diagnose AD, finding symptoms and regions.	They Developed a model using GWO for segmentation and AlexNet to classify the infected subregions with AD.	Clinical Mini-Mental State Examinatio n (MMSE)sco re validation	100 AD subjects. 100 Normal Control subjects.	MRI images	Accuracy reached 98% using GWO for segmentati on and 95% using AlexNet classifier for classificatio n.	Grey Wolf Optimization (GWO). Genetic Algorithm (GA). Cuckoo Search (CS).	Real-time MRI scans were collected from Chettinad Health City, Chennai.	NA
Farooq et al. [15]	diagnosis of Alzheimer's and outline its stages	4-way classifier: Mild Cognitive Impairment (MCI), Late Mild Cognitive Impairment (LMCI), and healthy person	25% test 75%train while 10% was chosen validation.	149 patients with 355 MRI	MRI images	accuracy was 98.3% on average for the three proposed models	GoogLeNet, ResNet-18 and ResNet-152	ADNI	NA

The limitations of previously proposed models are as follows:

Fisher et al. [16]	Forecast AD and MCI progression	Applying unsupervised ML model; Conditional Restricted Boltzmann Machine (CRBM)	5-fold cross-validation. On each of 5 folds, a CRBM 80% train (75% training, 5% valid), 20% test	18-month longitudinal trajectories of 1909 patients with MCI or AD	ADAS-Cog and MMSE scores, laboratory tests, and background information	Obtained a new model that can overcome the lack of clinical data. Moreover, the model was flexible enough to handle more diseases.	statistical model	(CAMD) Online Data Repository for AD (CODR-AD)	NA
Islam and Zhang [30,31]	perform a multi-classifier of the disease into four major classes	deep learning module using CNN	Train/Test	416 patients ranging from 18-96	MRI images	an accuracy of 95% and 75% in two types, but the accuracy in the remaining classes was 62% and 33%	three deep convolutional neural networks with slightly different configurations.	OASIS	NA
Ji et al. [33]	Classify and distinguish between AD, mild cognitive impairment, and normal control based on extracted Grey Matter and White Matter from brain Image scans. Then feedforward these features to Three base ConvNets.	ensemble learning approach for AD early diagnosis using deep learning	training, validation, and testing in a proportion of 3:1:1.	615 MRI images were split into 179 AD, 254 MCI, and 182 NC	MRI images	The accuracy was 97.65% for AD/MCI and 98.59% for AD/NC.	The base classifiers were ResNet50, NASNet, and MobileNet.	ADNI	The proposed model could only perform direct classifications if the results were obtained by dividing the whole system to classify two diseases once at a time. Results were obtained by assembling the complete results.
Khan et al. [34]	predicted AD and distinguish between AD, Normal Control (NC), Mild Cognitive Impairment (MCI)	Transfer learning by applying VGG	5-fold cross-validation with an 80%-20% training-testing split	50 patients in three classes: AD, MCI, and NC	MRI images	the accuracy was increased to 95.19%. To distinguish between diseases.	VGG-19	ADNI	Small dataset
Liu et al. [43]	Diagnosis of AD using the spectrogram features acquired from speech.	Proposed a new speech-based dataset (VBSD) and model.	k fold cross-validation; leave one cross-validation	504 speech data: 254 AD speech data and 250 HC speech.	Spectrogram features extracted from speech.	The accuracy was 0.833 on VBSD and 0.844 on Dem@Care.	Logisticgression CV. LinearSVC. MLP.	VBSD. Dem@Care.	Small accuracy and F1-score made the proposed model unsuitable enough to

						F1-Score was 86.9% VBSD and 89.4% on Dem@Care			ensure the detection and diagnosis results.
Lu et al. [45]	Diagnosis AD employs a large and diverse dataset.	Applied deep learning and transferred learning to detect AD using MRI scans over significant datasets	leave-sites-out 5-fold cross-validation	50,876 subjects collected from 217 sources	MRI images	Accuracy was 94.2% over an unseen dataset using a sex classifier as a base model, which reached an accuracy of 95%.	Resnet-V2 CNN	ADNI AIBL OASIS	NA
Park et al. [50]	predict and clarify AD incidents in older patients within a continuous period series.	Build ML model using Logistic Regression (LR), Support Vector Machine (SVM), and Random Forest (RF)	nested stratified 5-fold cross-validation with five iterations	40,736 individuals with age above 65: 614 definite AD patients	Clinical data: laboratory values, health profiles, history of family illness	, definite AD with an accuracy of 82.3%, and probable AD with an accuracy of 78.8% overbalanced and unbalanced datasets.	LR. SVM. RF.	Korean National Health Insurance Service database NHIS-NSC	NA
Subramoniam et al. [68]	Propose AD predictor using MRI technology	Developed a neural model using TL and MRI to identify and predict AD from brain scans.	Train/Test	6400 MRI scans	MRI images	Accuracy was above 99%, applying resnet-101 for classification and prediction.	VGG Resnet	Scans collected from Kaggle	The collected dataset was not real clinical data. Training epochs were very small.
Tuan et al. [71]	Detect and diagnose AD using 3d brain MRI.	Proposed a computational model using enhanced deep learning approaches.	3-Fold validation	98 Normal subjects and 99 probable 's AD subjects. Ages in the range [60,96]	3d brain MRI images	Accuracies were 88% and 80% when applied (U-Net+GMM) for segmentation and (CNN + XGBoost + SVM) for Classification.	XGBoost. SVM. CNN.	OASIS	The proposed model only stated the existence of AD and did not classify its stage and degree.

Lack of a definitive biomarker: Alzheimer's disease is a complex disorder without a single biomarker or test that can definitively diagnose the disease. This makes it difficult to accurately diagnose and differentiate it from other conditions with similar symptoms.

Limited availability of imaging techniques: Imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans can help to diagnose Alzheimer's disease. However, they can be costly, time-consuming, and unavailable in all healthcare settings.

Difficulty detecting early-stage disease: Detecting Alzheimer's disease in its early stages is difficult as the symptoms are often subtle and non-specific. This makes it difficult to accurately diagnose the disease in its early stages when treatment can be most effective.

Challenges in monitoring progression: As the disease progresses, it is difficult to monitor the changes in symptoms and accurately measure the disease's progression. This makes it difficult to determine the effectiveness of treatments and track the patient's progress.

Lack of effective treatments: Currently, no treatments can ultimately stop or reverse the progression of Alzheimer's disease. This makes it challenging to provide effective therapies to patients with the disease.

Lack of validation: Many proposed models need to be adequately validated, making it difficult to assess their accuracy.

As a result of these problems, the researchers will propose a detection model for AD by applying a single-modality approach using MRI datasets. This approach will utilize hyperparameter tuning by proposing a mathematical model. Moreover, the proposed methodology will propose an improved approach to early detection and diagnosis of Alzheimer's in its early stages; First, segment the brain images to extract the significant features and symptoms of disease indicators. Secondly, perform classification and clustering into four major classes associated with the degree and stage of the disease in each stage. Attempt to overcome hardware requirements for the proposed system by reducing and slimming system structure and complexity, considering the precision and accuracy of the overall system, enabling it to perform perfectly over ordinary hardware. Consequently, taking precautions prevents and stops brain tissue degeneration from reaching a stable state.

4 | AI-model Complexity Reduction

Reducing the complexity of AI models for AD detection, diagnosis, and progression is an active area of research**.** The difficulties connected with reducing the complexity of AI models [20]:

Various modeling approaches: One of the issues in effective modeling is the diversity of modeling methodologies across fields. Distinct professions may use distinct modeling tools and processes, making integration and consistency complex.

Integration of third-party data: AD research frequently necessitates incorporating data from several sources, each of which may be in a different format and necessitate complex transformations.

Complex conversions: It might be challenging to ensure the smooth integration of numerous data sources.

Modeling-effort: The process of building, training, and optimizing complex models can be resource-intensive and time-consuming.

Interpretability and explainability: While reducing complexity, it is crucial to maintain the interpretability and explainability of the AI models.

These issues must be addressed to guarantee the successful use of AI-based complexity reduction strategies in AD research. Researchers have recently used machine learning and deep learning methodologies to investigate alternative ways to reduce AD detection models' complexity. Feature selection or feature engineering is one way to reduce complexity reduction in which researchers find and pick essential elements from input data that contribute to AD detection. These strategies decrease the model's complexity and improve its interpretability by lowering the dimensionality of the input space. Furthermore**,** ensemble approaches have minimized complexity in AD detection models.

Recent studies conducted on reducing AD detection model complexity are provided below:
Wang et al. [75] supposed a network pruning approach that identifies the structural redundancy of a CNN and prunes filters in the selected layer(s) with the most redundancy. As it took wide and large networks as input models, but during training, insignificant channels were automatically identified and pruned afterward,

yielding thin and compact models with comparable accuracy. In addition, they proposed a novel learning scheme for CNNs to simultaneously reduce the model size, decrease the run-time memory footprint, and lower the number of computing operations without compromising accuracy.

While Gil et al. [20] suggested a modeling framework that employs AI approaches to decrease modeling labor while still assuring decision-making utility, the framework offered an intuitive user interface that assisted analysts in structuring their modeling challenge and automating key processes. The study's goal was to simplify expert models and enhance decision-making procedures.

AI model complexity reduction is a promising strategy for reducing modeling complexity and improving decision-making processes. However, obstacles are involved with establishing accurate and effective AI models for complex systems, which must be addressed to ensure the models' dependability and accuracy.

5 | Risk Score

As AD was the most widespread dementia, it was a severe global public health concern. A complicated interplay between genes, environmental factors, and lifestyle choices was believed to underlie the disease's genesis. Since the degenerative process started decades before dementia diagnosis, it was essential to identify younger, non-demented persons at a heightened risk for AD as early as possible. Consequently, many attempts and research were performed to formulate the AD score factor formula.

Therefore, the AD risk score was used to assess the risk of developing Alzheimer's disease. It was based on a combination of risk factors such as age, family history, genetic factors, lifestyle, diet, and medical history. Higher scores indicate a greater likelihood of developing Alzheimer's disease. The score was intended to be used as a guide to help individuals and their healthcare providers understand their risk and make informed decisions about lifestyle and medical management [33,40,55].

Here is a simple graph showing some AD risk factors (summarized in Figure 2):
Age: The risk of AD increases with age.
Genetics: APOE-ε4 is the most prevalent genetic risk factor for AD.
Lifestyle: Unhealthy lifestyle factors such as smoking, lack of exercise, and poor diet may increase the risk of AD.
Medical conditions: Certain medical conditions, such as high blood pressure, diabetes, and obesity, may increase the risk of AD.
Traumatic brain injury: A history of traumatic brain injury may increase the risk of AD [10, 48, 75].

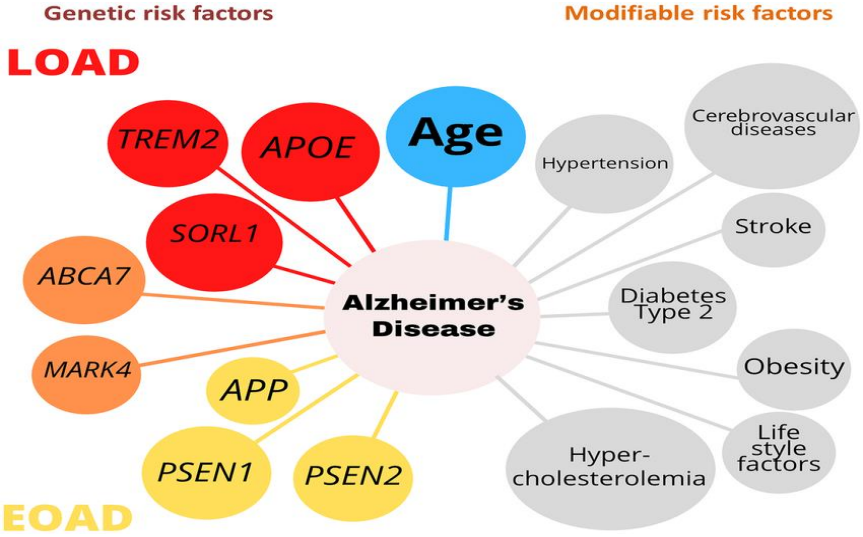

Figure 2 AD risk factors and disease causes [10,48,75].

A summary of research papers on AD risk scores from 2019, along with their results and drawbacks, is listed below:

Gao et al. [19] used polygenic risk scores and electronic health information to predict AD. Using information from the Alzheimer Disease Genetics Consortium, the study created polygenic risk scores for AD and age-at-onset of AD. The machine learning algorithm enhanced AD risk prediction accuracy by examining various variables and discovering fresh feature patterns. In addition, Revathi et al. [55] constructed a model to aid in the early detection and diagnosis of AD. The cognitive function of the person who may have dementia was assessed using the neuropsychological test known as the Cognitive Ability Test (CAT) in the second stage after the impact of chronic diseases was first analyzed using SVM and RF. Finally, utilizing clinical data, the proposed model's accuracy was 89 percent, enabling early detection and the identification of risk factors. Then Li et al. [40] proposed deep-learning genomics (DLG), which identified the genes associated with AD, using the advancements in genomic research. The suggested system comprised quality assurance, single-nucleotide polymorphism coding, and ResNet framework classification. Compared to conventional genome-wide association studies, the accuracy reached 98.78 %; the suggested model revealed novel genetic biomarkers for AD progression (including rs6311 and rs6313 in HTR2A, rs1354269 in NAV2, and rs690705 in RFC3). The Polygenic Risk Scores (PRS) for AD proposed by Leonenko et al. [39] offer special opportunities for accurately identifying those at high and low risk for AD. A model with two predictors (APOE and PRS excluding APOE region) for SNP selection yields the highest prediction accuracy. The suggested model identified the best methods for polygenic analysis when determining an individual's risk for AD. Conversely, Wang et al. [77] created an AD progression risk score using unsupervised machine learning. The researchers used an unsupervised machine learning technique to create an AD progression risk score. However, the study needed a validation cohort, limiting the findings' generalizability. However, Yu et al.[78]undertook a systematic review and meta-analysis encompassing prospective observational studies and randomized controlled trials. The primary objective was to construct a substantiated outline of modifiable risk factors associated with Alzheimer's disease (AD). The central focus of the review was to enhance comprehension of the assessments of credibility and to offer insights into the trajectory of future research endeavors. The study highlighted the essential requirement for a numerical representation of AD's prevention attributes, utilizing the amalgamation of these two mutually complementary research methodologies. While Silva et al. [64] outlined the pathophysiological mechanism and the primary risk factors for AD, it listed the disease genes (β -amyloid peptide (Aβ) and neurofibrillary tangles (NFT) of P-tau in neuronal cytoplasm) as well as some prevention factors like diet, exercise, and cognitive reserve which relate to a decreased risk of disease incidence. Overall, these studies shed light on the creation and application of AD risk scores. The absence of validation cohorts, ongoing discussions over the polygenic perspective of AD, and the need for more research to build evidence-based profiles of AD modifiable risk factors are only a few of the studies' drawbacks.

6 | Disease Progression

AI techniques have been studied recently in computer science research to model AD development and forecast disease implications. AD is an untreatable, degenerative brain disease that eventually impairs one's ability to do even the most basic activities by gradually destroying memory and cognitive skills. For elderly adults, it is the most typical cause of dementia. In most of this research, only baseline neuroimaging data are used. However, a specialist typically reviews the patient's medical history before establishing a diagnosis because AD is a complicated chronic disease. Additionally, due to their high cost, neuroimaging data are always limited or unavailable, especially in developing countries. Consequently, much research, especially using AI methods, was performed to track the disease progression and try to find a mechanism to predict AD in its early stages to slow it down.

El-Sappagh et al. [14] compared various ML optimization methods with time-series methodologies to predict the progression of AD over a predetermined period. The patient's diseases, cognitive scores, and medication history were among the cost-effective time-series characteristics used to optimize the proposed models. The results showed that the random forest (RF) model performs with the highest level of accuracy when compared to other models, with an accuracy of 90.51 %. While Normative models based on deep autoencoders were

proposed by Pinaya et al. [52] using structural neuroimaging data from individuals with mild cognitive impairment and Alzheimer's disease. Then, it was determined which brain regions were associated with this variation and evaluated how each patient differed from the norm. The model identified the ventricular system and medial temporal regions, including the hippocampus, as crucial areas for determining the deviation score. Moreover, the results indicated it could identify the brain regions with the greatest deviation from the predicted normative value using an autoencoder-based approach. In addition, an analysis of machine learning techniques for simulating the evolution of AD dementia using clinical data was conducted in a 2021 comprehensive literature review. According to the analysis, most studies concentrated on utilizing publicly accessible data to forecast how AD dementia will develop. However, the generalizability of the results is constrained by the absence of standardized clinical data and the small sample sizes of several investigations [36]. Wang Z. et al. [77] used an unsupervised machine learning technique to create a risk score for AD development. The research discovered that the risk score was a reliable indicator of how AD will proceed in its early stages. However, the study's generalizability needs to have a validation cohort. Using a deep learning approach (a multi-modal RNN), Lee et al. [37] developed an integrative approach for predicting MCI to AD conversion as it integrates the data of longitudinal cerebrospinal fluid (CSF) and cognitive performance biomarkers with cross-sectional neuroimaging biomarkers. The proposed methodology, therefore, shows that the prediction model for MCI conversion to AD generated up to 75% accuracy when using only a single modality of data individually. The prediction model achieved the best performance with 81 % accuracy when including longitudinal multi-domain data. Finally, AD currently has no disease-modifying treatments, which was made worse by the absence of standard diagnostic techniques for locating people early enough in the disease process to get therapy. Recent studies have investigated the use of disease progression models to model AD progression and forecast disease outcomes. However, further investigation is required to provide standardized clinical data for AI techniques to enhance disease prediction and to create evidence-based profiles of AD-modifiable risk variables.

7 | Current AD Datasets

AD datasets are used in Alzheimer's disease (AD) research. These datasets contain information from people with Alzheimer's disease (AD), people with moderate cognitive impairment (MCI), and cognitively normal people. They may include cognitive tests, medical history, physical and neurological exams, brain imaging (MRI, PET), and genetic testing. The most common datasets are listed below:

7.1 | Alzheimer's Disease Research Center (ADRC) of Washington University Dataset

It is a popular dataset for Alzheimer's disease (AD) research. It includes information from over 4,000 people, including healthy older persons, those with moderate cognitive impairment (MCI), and people with Alzheimer's disease (AD). The dataset has been gathered since 1979, making it one of the longest-running Alzheimer's research. It comprises cognitive tests, medical history, physical and neurological exams, brain imaging (MRI, PET), and genetic testing, among other things. The dataset also contains longitudinal data, with follow-up evaluations performed on average every 3-4 years. The dataset is freely accessible to academics, allowing for cooperation and the exchange of findings between study organizations [73].

7.2 | Alzheimer's Disease Neuroimaging Initiative (ADNI)

The ADNI dataset is a commonly used and freely available dataset for AD research. It is a joint initiative to improve early detection, diagnosis, and AD monitoring by neuroimaging and other biomarkers. The ADNI dataset includes information from both AD patients and healthy people. The ADNI AD dataset was summarized and explained in Table 5. ADNI is separated into stages, each with its own data-gathering techniques and participant cohorts. This dataset enables researchers to monitor disease development, uncover biomarkers linked to AD, and create prediction models for early detection [3, 51].

Table 5. ADNI dataset of AD; shows the components along with its description.

Dataset Component	Description
Subjects	ADNI includes participants with various cognitive statuses, including healthy controls, mild cognitive impairment (MCI), and AD patients.
Demographics	Information about participants' age, gender, education level, and other relevant demographic characteristics.
Clinical Assessments	Data from various clinical assessments, such as Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Alzheimer's Disease Assessment Scale (ADAS).
Neuroimaging Data	Includes Magnetic Resonance Imaging (MRI) scans and Positron Emission Tomography (PET) scans for brain imaging to analyze structural and functional changes in the brain.
Genetic Data	Genetic information, such as Apolipoprotein E (APOE) genotype, is available for some participants.
Biomarkers	Data on various biomarkers, including cerebrospinal fluid (CSF) biomarkers like amyloid beta and tau protein levels, which are associated with AD pathology.
Cognitive Scores	Cognitive test scores assessing memory, attention, language, and other cognitive domains are available.
Follow-up Data	Longitudinal data to track changes in cognitive and functional abilities over time in participants.

7.3 | Korean National Health Insurance Service Database (NHIS-NSC Cohort)

A large-scale health database in South Korea. The NHIS-NSC cohort contains health and medical information on South Korean nationals participating in the National Health Insurance (NHI) program. It is one of the world's largest and most comprehensive population-based healthcare databases. The collection covers numerous years and contains information on millions of people. The dataset includes various types of information: Demographic Data, Healthcare Claims Data, Diagnosis Information, Drug Prescription Data, Health Examination Data, and Vaccination Data [37, 69].

7.4 | The UK Biobank

It is a comprehensive, large-scale health dataset that includes information from more than 500,000 participants recruited across the UK. It provides various health-related information that may be utilized to explore numerous areas of health and diseases, including AD and other complex diseases. Some data types typically available in the UK Biobank dataset are shown in Table 6 [9, 42, 72].

Table 6. The data types of the UKbiobank dataset [UKBiobank].

Data Type	Description
Demographics	Age, gender, ethnicity, education level, and other demographic information of the participants.
Health and Lifestyle	Data on medical history, lifestyle factors, diet, physical activity, smoking status, and alcohol consumption.
Cognitive Assessment	Results from cognitive tests, including memory, attention, and other cognitive domains for a subset of participants.
Genetic Data	Whole-genome genotyping data, including genetic variants and single-nucleotide polymorphisms (SNPs).
Neuroimaging Data	Brain imaging data (MRI) is available for a subset of participants, enabling the study of brain structure.
Biomarker Data	Measurements of various biomarkers related to health conditions may include AD-relevant markers.
Follow-up Data	Longitudinal data to study changes in health outcomes and conditions over time.

7.5 |Open Access Series of Imaging Studies (OASIS) Brains Datasets

They collect clinical information and MRI images from participants in research on healthy aging and AD. The datasets comprise T1-, T2-, proton density-, fluid-attenuated inversion recovery (FLAIR), diffusion tensor imaging (DTI), resting-state functional MRI (fMRI), and arterial spin labeling (ASL) images. The OASIS Brains Datasets are mainly concerned with magnetic resonance imaging (MRI) scans of the brain, which provide significant information for researching brain structure and function in diverse populations. These datasets have many versions summarized in Table 7 [49].

Table 7. Different versions of the OASIS brain datasets; OASIS-1, OASIS-2, and OASIS-3.

Dataset Name	OASIS-1	OASIS-2	OASIS-3
Year of Data Collection	1999-2000	2005-2007	2014-2018
Participants	416	150	1,674
Age Range	18-96	18-96	18-96
MRI Scans	T1-weighted, T2-weighted, proton density-weighted, fluid-attenuated inversion recovery (FLAIR)	T1-weighted, T2-weighted, FLAIR	T1-weighted, T2-weighted, FLAIR, diffusion tensor imaging (DTI), resting-state functional MRI (fMRI), arterial spin labeling (ASL)
Clinical Diagnoses	Normal aging and Alzheimer's disease	Normal aging and Alzheimer's disease	Normal aging, mild cognitive impairment, and Alzheimer's disease

7.6 | Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL)

It covered people aged 60 and up, including healthy people, those with moderate cognitive impairment (MCI), and people with AD. Many data were gathered, including clinical, genetic, neuroimaging, cognitive, and lifestyle information. This dataset's kay aspect was summarized in Table 8 [1, 23, 24].

Table 8. The critical aspects of AIBL dataset [AIBL].

Study Name	Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL)
Objective	Investigate early detection and tracking of AD, identify biomarkers and risk factors, and understand disease progression.
Participants	Individuals aged 60 years and older
Cohort	Healthy individuals, mild cognitive impairment (MCI), AD
Data Collection	Clinical, genetic, neuroimaging, neuropsychological, and lifestyle information
Biomarkers	Genetic factors, blood markers, cerebrospinal fluid (CSF) biomarkers, neuroimaging (PET, MRI)
Study Design	Longitudinal, with multiple assessments over several years
Collaborating Institutions	CSIRO, Edith Cowan University, Austin Health, Florey Institute of Neuroscience and Mental Health

7.7 |Alzheimer's Disease Repository Without Borders (ARWiBo)

It is a cross-sectional dataset comprised of over 2,600 patients enrolled in Brescia and surrounding areas. The database contained information on healthy elderly controls (CTR), people with mild cognitive impairment (MCI), and those with Alzheimer's disease (AD). Images include structural images and PET scans [4, 41].

7.8 |The minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD)

This project sought to uncover structural brain abnormalities linked to AD. T1-weighted MRI images, which give precise anatomical information about the brain, were utilized in the MIRIAD imaging procedure. The

study was designed longitudinally, with participants getting MRI scans at regular intervals. Researchers may use this longitudinal technique to study changes in brain structure over time and assess AD progression. The following Table 9 summarizes this dataset [46,63].

Table 9. The key aspects of MIRIAD.

Study Name	Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD)
Objective	Investigate structural brain changes in AD
Participants	Individuals with Alzheimer's disease and healthy controls
Data Collection	Structural magnetic resonance imaging (MRI) scans
Study Design	Longitudinal, with repeated MRI scans at regular intervals
Imaging Protocol	T1-weighted MRI
Interval Between Scans	Approximately 6 to 12 months
Analysis	Quantitative measurement of brain volume and atrophy rates
Findings	Characterize brain changes and atrophy patterns in AD
Availability	Data available for research purposes upon request

The AD datasets mentioned in this review were an excellent resource for studying and developing computational techniques for understanding and diagnosing AD. The datasets included clinical, genetic, neuroimaging, and other relevant data from a large cohort of people with AD and healthy controls. Researchers used these datasets to investigate various machine learning and data mining approaches for identifying biomarkers, predicting disease progression, and developing novel algorithms for the early diagnosis and detection of AD. The availability of these datasets has supported the growth of computer science research in AD. It has the potential to significantly improve diagnostic accuracy and patient treatment in the future.

8 | Conclusion

In summary, AD has become the focus of research in the field of informatics, due to its increasing prevalence and urgent need for accurate and effective diagnostic methods. The convergence of advanced technologies, such as artificial intelligence, machine learning, and data analytics, has significantly contributed to the development of innovative tools and methods for diagnosis, prognosis, and treatment of AD. Through the integration of different data modalities, including medical images, clinical records, and molecular data, informatics has enabled the creation of multifaceted diagnostic systems. As the field develops, it becomes clear that interdisciplinary collaboration between computer science, neuroscience, and medical research is paramount. Basically, the field of computer science is extremely promising in contributing to AD research. It is at the forefront of innovation, providing tools that have the potential to transform the way we diagnose, manage, and ultimately find a cure for this devastating disease.

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Author Contribution

Author A.S. Elmotelb, Fayroz F. Sherif participated in all concerning manuscript starting from the idea till preparing and writing the final manuscript while Author Mahmoud Fakhr and Amr M. Abdelatif prepared required figures and tables and revised the manuscript.

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Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy-preserving nature of the data but are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest in the research.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors

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