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Exploring Machine Learning Techniques for Early Detection of Alzheimer's Disease Using Multimodal Data

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Abstract:
Background: *Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which pathological changes can occur years before clinical symptoms become apparent. Early detection is therefore important for timely intervention. Current diagnostic methods include cognitive assessments, neuroimaging, and biomarker analysis, but these approaches may not reliably identify the disease during its earliest stages and can be expensive or difficult to implement for large-scale screening. Machine learning (ML) has increasingly been applied to this problem because it can identify patterns within complex biomedical datasets.*
Materials and Methods: *This paper presents a structured review and comparative analysis of machine learning techniques applied to early AD detection using multimodal data. Studies were systematically analysed based on input modalities, including MRI, PET, EEG, CSF biomarkers, genetic data, and clinical scores. Model architectures evaluated included classical machine learning, deep learning, ensemble, and hybrid models. Datasets and reported evaluation metrics were also comparatively assessed to identify performance trends across approaches.*
Results: *The findings indicate consistent performance differences between single-modality and multimodal approaches. Multimodal fusion and longitudinal modelling demonstrated superior sensitivity for detecting early disease stages. Deep learning models, particularly convolutional and hybrid architectures, generally outperformed classical methods on high-dimensional imaging datasets. However, classical machine learning models showed greater interpretability and stability when applied to structured clinical data.*
Conclusion: *Despite promising diagnostic performance, significant challenges remain, including small and homogeneous cohorts, incomplete multimodal datasets, limited model interpretability, and inconsistent definitions of disease stages across studies. This review highlights the importance of standardized evaluation protocols, larger longitudinal datasets, and explainable multimodal models to support reliable clinical translation. Overall, the findings suggest that multimodal deep learning frameworks represent the most promising direction for next-generation AD diagnostic systems, provided current methodological and clinical limitations are effectively addressed.*

Key Words: *Alzheimer's disease; Machine learning; Deep learning; Multimodal data; Early diagnosis; Neurodegenerative disorders.*

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I. Introduction

Accounting for 60–70% of dementia cases and affecting over 55 million people worldwide, Alzheimer's disease (AD) is the most common neurodegenerative disorder. The number of cases is expected to increase to approximately 139 million by 2050, making AD a major public health concern with substantial social and economic consequences. The global cost of dementia care already exceeds $1.3 trillion annually and is projected to rise significantly in the coming decades (Alzheimer's Disease International, 2024).

Despite decades of research, AD remains incurable. Current pharmacological treatments, including cholinesterase inhibitors and memantine, provide limited symptomatic relief and may modestly slow cognitive decline. Because these interventions cannot reverse neurodegeneration, identifying the disease at an early stage has become an important focus of Alzheimer's research.

The pathological processes associated with AD begin many years before clinical symptoms appear. The disease is characterized by two primary biomarkers: extracellular amyloid-β (Aβ) plaque deposition and intracellular neurofibrillary tangles formed from hyperphosphorylated tau. These abnormalities impair synaptic function, disrupt neural communication, and contribute to progressive neuronal loss, particularly in memory-related regions such as the hippocampus and cerebral cortex. As these changes accumulate gradually over time, diagnosing AD during its earliest stages remains difficult (Jack et al., 2018).

Current diagnostic approaches rely on a combination of clinical assessment, neuropsychological testing, and biomarker evaluation through neuroimaging techniques such as MRI and PET or cerebrospinal fluid (CSF) analysis. Cognitive assessments including the Mini-Mental State Examination (MMSE) and the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) are commonly used. However, these methods often detect impairment only after substantial neuronal damage has occurred, which may emerge 10–20 years after the underlying pathology begins. Neuroimaging techniques can identify amyloid accumulation and neurodegeneration but are often costly and not widely accessible. Similarly, invasive procedures such as lumbar puncture for CSF analysis, together with the expense of repeated testing, can limit timely diagnosis. Studies estimate that up to 30% of individuals with Alzheimer’s disease remain undiagnosed or receive an incorrect diagnosis because early clinical symptoms are often subtle (Alzheimer’s Disease International, 2024).

Machine learning (ML) has increasingly been applied to the early detection of AD and may help address several limitations of conventional diagnostic approaches. ML algorithms can analyse large and complex datasets, including brain imaging data (sMRI, fMRI, PET), molecular biomarkers (CSF Aβ, tau levels, and plasma proteins), and genetic information, at a scale that is difficult to achieve through manual analysis. This supports automated screening and the integration of information from multiple data sources. In addition, ML methods can identify subtle patterns within high-dimensional medical datasets that may not be readily apparent through conventional analysis, allowing potential risk factors and preclinical disease indicators to be detected before the onset of noticeable symptoms.

II. Objective and Scope of the Study

This research aims to undertake a systematic exploration of ML methodologies applied to multimodal AD datasets. The objectives are:

1. To compare the performance of different ML models for early (prodromal) Alzheimer’s detection.
2. To evaluate the contribution of different modalities (MRI, PET, CSF biomarkers, cognitive scores).
3. To survey the landscape of ML model types (CNNs, SVMs, random forests, deep learning methods) and their performance in AD detection.
4. To identify key challenges and issues with real-world clinical translation, offering recommendations for future research and application.

III. Methodology

This study followed a structured and systematic approach to review, categorize, and synthesize recent research on machine learning–based early diagnosis of Alzheimer’s disease. The methodology comprised five major stages: selection of relevant literature, classification of studies based on data modality and model architecture, extraction of evaluation metrics, comparative assessment, and identification of research gaps and future directions.

1. **Literature search and paper selection.**
   An initial literature search was conducted across major databases including PubMed, IEEE Xplore, Frontiers, and Google Scholar using combinations of keywords such as *“Alzheimer’s disease,” “machine learning,”* and *“early diagnosis.”* This search returned approximately 480 articles. After removing 74 duplicate records, 206 papers were screened based on title and abstract relevance. Following this screening, 25 studies were reviewed in full text, of which 16 papers met the inclusion criteria and were selected for detailed comparative analysis.
2. **Inclusion and exclusion criteria.**
   Full texts were assessed against predefined criteria. Included studies:
   a. Used ML/DL for AD diagnosis or prognosis
   b. Provided sufficient methodological detail for comparison
   c. Used public datasets or well-described clinical cohorts
   d. Were free for access
3. **Classification of input modalities and model architectures**
   For each selected paper, I classified the study based on two key criteria: the type of data input (distinguishing between single-modality inputs, such as MRI or PET , and multimodal inputs that combine multiple complementary sources), and the model architecture used(such as RFs, ensemble methods, CNNs, or SVMs). This straightforward classification approach allowed for the creation of a clear, structured table summarizing each paper.
4. **Extraction of evaluation measures**
   Reported quantitative outcomes and experimental settings were tabulated for each paper (e.g., reported metrics, cross-validation strategy, external validation if any). These extracted items form the evidence base for later comparative synthesis.

5. **Comparative analysis**
   Using the curated tables, I performed side-by-side comparisons to uncover performance patterns, methodological trade-offs, and reproducibility trends across modalities and model classes. This step prioritized equitable comparisons (similar datasets, same validation schemes) to avoid misleading conclusions.
6. **Identification of gaps and directions.**
   Finally, I synthesized recurring methodological limitations and unmet needs observed across studies to propose targeted future research directions. These observations guide the discussion sections that follow.

IV. Data Modalities Used in Alzheimer's Detection

1. **MRI (Magnetic Resonance Imaging):** MRI is widely used in the assessment of neurodegenerative diseases because it can reveal structural brain changes before clinical symptoms become fully apparent. In Alzheimer's disease, MRI allows visualization of cortical thinning, ventricular enlargement, and hippocampal atrophy, all of which are associated with early disease pathology (Jack et al., 2011). Deep learning studies suggest that MRI data contain information related to disease progression, enabling automated models to track transitions from mild cognitive impairment to advanced AD (Alzubaidi et al., 2025). However, MRI alone often has difficulty distinguishing AD from other forms of dementia that present with similar patterns of brain atrophy (Jack et al., 2010).
2. **PET (Positron Emission Tomography):** PET provides molecular and metabolic information that cannot be obtained through structural MRI alone (Poul Flemming Høilund–Carlsen et al., 2023; Alzubaidi et al., 2025). FDG-PET identifies patterns of glucose hypometabolism, while amyloid and tau PET imaging detect pathological protein accumulation associated with AD (Poul Flemming Høilund–Carlsen et al., 2023; Alzubaidi et al., 2025). These functional abnormalities may appear several years before detectable structural degeneration, making PET useful for early detection and disease staging.
3. **EEG (Electroencephalography):** EEG is a non-invasive technique that records electrical brain activity using scalp electrodes and can identify alterations in neural rhythms associated with AD (McBride et al., 2025). Common findings include increased delta and theta activity, reduced alpha and beta power, decreased functional connectivity, and lower signal complexity. These changes are associated with impaired communication across neural networks (McBride et al., 2025).
4. **CSF Biomarkers:** Cerebrospinal fluid (CSF) biomarkers, particularly Aβ42, total tau, and phosphorylated tau, are widely regarded as key biological indicators of AD because they directly reflect underlying disease pathology rather than clinical symptoms alone (Blennow & Zetterberg, 2018; Olsson et al., 2016). However, obtaining CSF samples requires lumbar puncture, which limits routine clinical application. The limited availability of large-scale CSF datasets also restricts the generalizability of machine learning models trained on these data (Cacciaglia et al., 2024).
5. **Genetic Data:** Genetic factors contribute to AD risk, with the APOE ε4 allele being the most extensively studied genetic risk factor (Corder et al., 1993; Yamazaki et al., 2023). Machine learning methods can combine information from thousands of genetic markers to estimate disease risk or progression likelihood (Alzubaidi et al., 2025). However, genetic information alone does not fully account for differences in disease presentation, as environmental and lifestyle factors also influence AD risk (Yamazaki et al., 2023).
6. **Multimodal Approaches:** Multimodal approaches integrate diverse biomarkers to better capture the complexity of AD pathology (Alzubaidi et al., 2025). MRI–PET fusion reveals both structural degeneration and its underlying causes, while CSF, genetic, and clinical data add mechanistic and behavioural context (Cacciaglia et al., 2024). Hybrid and ensemble deep learning models benefit most from this integration, improving disease staging, prognosis, and interpretability, making multimodal AI central to next-generation diagnostic systems (Alzubaidi et al., 2025).

V. Commonly Used Datasets

The success of machine learning in AD detection heavily depends on the availability of large, well-labelled datasets. The most commonly used ones are as below:

1. **ADNI** (Alzheimer's Disease Neuroimaging Initiative) - the most widely used open-access dataset, providing multimodal MRI, PET, genetic, and clinical data for over 1,500 participants.
2. **OASIS** (Open Access Series of Imaging Studies) - commonly used for MRI-based studies focusing on early-stage and structural analysis due to its high-quality, T1-weighted brain scans.

A recurring challenge in all datasets is data heterogeneity, stemming from scanner differences, inconsistent labelling, and variable clinical protocols. Furthermore, sample sizes for early-stage AD and MCI remain limited, impeding model generalization.

VI. Generalised Flow

VII. Comparative analysis of selected papers

	Title	Model Used	Dataset	Data Description	Result	Accuracy	Limitations
1	Early-Stage Alzheimer's Disease Prediction Using Machine Learning Models	Decision Tree, Random Forest, Support Vector Machine. XGBoost, Voting Classifier	MRI (OASIS)	MRI data from 150 patients (ages 60–96) was analysed. 72 patients were classified as non-demented throughout the study. 64 patients were classified as demented and remained so throughout the study.	1.Random Forest/XGBoost and Voting achieved the best results 2. Men were more likely to be classified having Alzheimer's Disease than women. 3. Demented patients had fewer years of education than non-demented patients. 4. Non-demented groups exhibited greater brain volume than demented groups. 5. The demented group showed a higher concentration of patients in the 70–80-year-old range compared to the non-demented group.	80.46% - DT 86.92% - RF 81.67% - SVM 85.92% - XGBoost 85.12% - Voting Classifier	1. Too small sample size - reduces generalisability

2	Automatic classification of MR scans in Alzheimer’s disease	SVM	T1 Weighted MRI	The study used MRI data from four groups: 1.Group I & III (Rochester, MN, USA): Community and referral samples of probable/definite AD patients and matched controls. Scans acquired over ~10 years on GE Signa 1.5T scanners. 2. Group II (Dementia Research Centre, UCL): Patients with pathologically confirmed AD and matched controls. Scans acquired with balanced parameters across different scanners. Group IV: Subjects with pathologically confirmed FTLD and AD.	1. SVMs successfully separate patients with AD from healthy aging subjects. 2. They perform well in the differential diagnosis of two different forms of dementia. 3. The method is robust and can be generalized across different centres.	95.6% - combined data 81% - mild AD	1. Balancing between whole-brain and region-specific analysis affects accuracy depending on disease stage and type. 2. Scanner variability and image quality require careful control to ensure model generalization across centres.
3	Detection of Alzheimer's Disease Using Logistic Regression and Clock Drawing Errors	Logistic Regression	Clock drawing, Verbal fluency, Genetic History BMI, BP data	The study used participant data from the ADNI, including older adults aged 55–90, limited to cognitively normal (CN) individuals and Alzheimer’s disease (AD) patients. The dataset combined Clock Drawing Test (command and copy) error features with basic demographic and clinical variables such as age, education, gender, and verbal fluency scores.	Verbal fluency improves AUC	AUC Without Verbal Fluency - 0.825 AUC With Verbal Fluency - 0.91	1.Low Diversity: Dataset not broad enough for wider generalization. 2. Focus: Only on Amnestic AD variant. This limits applicability to all AD types. 3. Groups: Restricted to CN and AD. Exclusion of intermediate states (like MCI) oversimplifies screening.
4	Classification of Alzheimer's Disease using Machine Learning Techniques	k-NN, Decision Tree, Rule Induction, Naive Bayes, Generalised Linear Model, Neural Networks	1.Demographic attributes 2.Cognitive assessment test scores 3. Clinical features like APOE4 gene and brain volume measures	The study used a subset of the TADPOLE challenge dataset, which contains longitudinal clinical, demographic, cognitive, and biomarker data	k-NN and Neural Network performed best among tested approaches	K-NN - 43.26% DT - 74.22% Rule Induction - 69.69% Naive Bayes - 74.65% Generalized Linear Model - 88.24% DL - 78.32%	1.Only 530 participants (106 per stage) selected. Limits model generalizability. 2. Missing Data: Only high-coverage features kept, possibly discarding

				from participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI), including individuals at five AD stages (cognitively normal through Alzheimer's).			important variables. 3. Classes: Stages were unevenly distributed and hard to distinguish, which impacts classification performance.
5	Deep Learning Model to Predict Diagnosis of Alzheimer Disease by Using 18F-FDG PET	CNN	18 FDG PET	This study used brain 18F-FDG PET neuroimaging scans retrospectively collected from the ADNI for AD, MCI-AD, and CN subjects, and from the European DLB Consortium for dementia with Lewy bodies (DLB), totalling 757 cases with PET scans labelled by clinical diagnosis.	Outperformed human radiologists, early diagnosis	DLB - 96.2% AD - 96.4% MCI - 71.4% CN - 94.7%	1. Moderate sample size per class (especially MCI, DLB), limiting model robustness. 2. PET Data: High-dimensional, heterogeneous across sites. Extensive preprocessing required, which may introduce variability. 3. Generalizability: Not confirmed outside the ADNI dataset
6	Early detection and classification of Alzheimer's disease using YOLOv11 CAD system	YOLOv11 Neural Network	T2 MRI & DTI	The study uses a subset of the ADNI dataset with 3,069 elderly participants across cognitive stages (CN, EMCI, LMCI, MCI, and AD), with a near-balanced gender split. The data include MRI (1,173–3,012 samples) and DTI (35–90 samples per class) acquired in axial, coronal, and sagittal views	Precision 93.6%, Recall 91.6%, mAP 96.7%	CN - 0.947 MCI - 0.901 EMCI - 0.936 LMCI - 0.962(Precision)	1. Limited Generalizability: Model trained mainly on ADNI data. 2. YOLOv11 fusion requires well-aligned, high-quality MRI and DTI images. performance degrades with missing or noisy data.
7	An efficient method for early Alzheimer's disease detection based on MRI images using deep convolutional neural networks	CNN	MRI	Non-demented (67,200 images), very mild demented (13,700 images), mild demented (5,200 images), and moderate demented(488) taken from OASIS database	Highest rates among peer models	Accuracy - 99.68% F1-score 99.25%	1. Model trained only on MRI data may miss non-structural information (e.g. clinical scores) relevant to AD. 2. Unbalanced dataset with relatively less moderately demented patients

8	Studying the Manifold Structure of Alzheimer's Disease: A Deep Learning Approach Using Convolutional Autoencoders	Deep Convolutional Autoencoder	T1 Weighted MRI	2182 MRI images from 479 subjects from the ADNI database. Other data from the dataset were also used including age, tau protein concentration in CSF, presence of the ApoE4 variant, the MMSE or the ADAS	Revealed structural manifold of AD and helped discriminate stages	80%	
9	Multimodal deep learning models for early detection of Alzheimer's disease	Stacked Denoising Auto-Encoders, 3D CNN	MRI, clinical data, genetic (SNPs)	ADNI1, ADNI2, and ADNI-GO data from 2,004 participants, combining clinical/EHR data (2,004 subjects), baseline MRI scans (503 subjects, 9,108 voxels per scan), and whole-genome sequencing data (808 subjects). Multimodal availability varies, with 220 subjects having all three modalities, while others include clinical-genetic or clinical-imaging combinations.	1.MRI: 3D CNN is superior to shallow models. 2.EHR: Deep Autoencoder model is comparable to shallow models. 3.SNP Data: Deep Autoencoder model is superior to shallow models. Multimodal Fusion Results 4. Imaging + SNP: Shallow model outperforms deep models. 5. Imaging + HER, SNP + EHR: Deep model outperforms shallow models. 6. Imaging + EHR + SNP: Deep model outperforms shallow models.	HC vs AD(MRI) - 86% AD(EHR) - 85% HC vs AD(SNP) - 89%	1.Dataset Imbalance: Many subjects lack all three modalities (MRI, clinical, SNP), causing uneven data and potential bias. 2. Generalizability: Model trained only on ADNI. Performance may not transfer well to other clinical settings. 3. Model Complexity: Deep multimodal models are difficult to interpret clinically, obscuring the specific contribution of each modality to decisions.
10	Brain MRI analysis for Alzheimer's disease diagnosis using an ensemble system of deep convolutional neural networks	Ensemble of deep CNNs	MRI	Acquired from the OASIS dataset. 416 subjects aged 18–96, and for each of them, 3 or 4 T1-weighted sMRI scans were available.	Presented comparative experiments for AD classifiers	Accuracy - 93.18% Precision - 94% Recall - 93% F1-score - 92%	1. Ensemble CNN uses only selected 2D MRI slices, potentially losing critical 3D spatial/anatomical context for AD pathology. 2. Performance relies on predefined slice extraction, making the pipeline sensitive to slice choice and reducing automation.

11	Predicting Alzheimer's Disease Using LSTM	Long Short-Term Memory (LSTM)	MRI, PET, DTI	The study utilized longitudinal time sequence data from the ADNI database, which contained records for 1105 unique subjects. The experiments were conducted on a subset of the data, which was pre-processed to include 900 CN, 900 MCI, and 900 AD records for training the prediction model.	The Cortical Thickness Average (TA) feature is a significant feature to predict the progression of AD.	AD vs NC - 0.935 MCI vs NC - 0.697 AD vs MCI - 0.798	1.2D Slice Inputs: Model uses selected 2D MRI slices instead of full 3D volumes, potentially missing critical spatial relationships for AD pathology. 2. Transfer Learning: CNN backbones pre-trained on non-medical datasets (e.g., ImageNet) may not optimally capture neuroanatomical features specific to brain MRI.
12	Classification of Alzheimer's Disease by Combination of Convolutional and Recurrent Neural Networks Using FDG-PET Images	Combination of 2D CNN and BGRU	FDG-PET	This research evaluated its method using baseline FDG-PET images acquired from the ADNI database. The total cohort comprised 339 subjects, including 93 AD patients, 146 subjects with MCI, and 100 CN.	Adding BGRU significantly improves classification accuracy. The sagittal direction with BGRU achieves the best accuracy.	AD vs. NC - 95.3% MCI vs. NC - 83.9%(Weighted fusion)	1. 3D FDG-PET scans are broken down into 2D slice sequences, potentially losing volumetric context that full 3D models could capture. 2. The model uses only FDG-PET imaging, excluding other biomarkers or clinical data that could enhance diagnostic robustness.
13	An Efficient Ensemble Approach for Alzheimer's Disease Detection Using an Adaptive Synthetic Technique and Deep Learning	Ensemble of CNN and EfficientNet,	Data descriptions from ADNI and other PET-beta-amyloid studies	The experiments were conducted using two publicly available datasets of MRI brain images. The primary multiclass dataset used for classification contained a total of 13,760 images before oversampling, divided across four categories: Normal Controls, Very Mild Demented, Mild Demented, and Moderate Demented.	The DenseNet-121+Xception ensemble model achieved an 18% higher accuracy than the individual DenseNet-121 and Xception models. Another ensemble model achieved 1.46% better results when we compared it with individual EfficientNet-B2.	97.35%	1. Hand-engineered feature dependence: The approach relies on predefined feature extraction and selection steps, making performance sensitive to feature design choices rather than fully data-driven learning. 2. Single-modality focus: Only one primary data modality is analysed, limiting the model's ability to capture complementary structural, functional, or clinical information.

14	An Efficient Classifier for Alzheimer's Disease Genes Identification	SVM	Gene-Coding Protein Sequences	The study constructed its dataset of protein sequences from the UniProt database. After selection and redundancy removal, the final benchmark dataset contained 1,742 protein sequences in total, which were used to represent positive (279 AD-related) and negative (1,463 non-AD) samples for training and testing.	Demonstrated that sequence information of gene-coding proteins can be used to predict AD without MRI.	85.70%	1. Class Imbalance: Severe data imbalance (279 AD vs. 1,463 Non-AD proteins, 1:5 ratio) can bias predictions and inflate accuracy. 2. Limited Feature: Model uses only the frequency of two consecutive amino acids (400D vector), potentially missing complex patterns, or crucial structural information.
15	Automated Multiclass Classification of Spontaneous EEG Activity in Alzheimer's Disease and Mild Cognitive Impairment	MLP neural network	EEG(Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, and O2)	The research employed EEG data to discriminate between disease stages. The dataset was collected from a cohort of 51 subjects, who were equally divided into three groups: 17 AD patients, 17 MCI subjects, and 17 NC subjects.	AD elicits changes in the EEG background activity: a slowing of EEG rhythms, alterations in the frequency distribution of the power spectrum, a complexity loss, a regularity increase and a variability decrease.	LDA - 58.82% QDA - 60.78% MLP - 62.75%	1. Small Sample Size: 5122 trials but from only 111 subjects (37/group) 2. Low accuracy
16	k-Skip-n-Gram-RF: A Random Forest Based Method for Alzheimer's Disease Protein Identification	Random Forest with adaptive k-skip-n-gram features	Sequence information of proteins	The dataset consisted of protein sequences related to AD that were extracted and processed from the UniProt database. The final benchmark dataset used for the method evaluation included a total of 2,022 protein sequences, composed of 279 AD positive samples and 1,743 non-AD negative samples after undergoing redundancy reduction.	Achieved competitive results with efficient protein-sequence based method.	85.50%	1. Severe Class Imbalance: The dataset has 279 AD vs. 1,743 Non-AD proteins (~ 1:6 ratio). This bias can skew the classifier toward the majority class and inflate performance metrics. 2. Limited Feature: Model uses only k-skip-2-gram features, which may miss complex structural patterns, and crucial biological features

VIII. Discussion

This study examines patterns in the performance, reliability, and clinical applicability of machine learning methods for AD detection. Differences are evident across data modalities, model architectures, and dataset characteristics.

One consistent observation is the performance difference between single-modality and multimodal approaches. Models based on MRI, PET, cognitive scores, or CSF biomarkers can achieve reasonable classification accuracy but may not capture the full range of pathological changes associated with AD. Multimodal fusion combines structural, functional, and clinical information, which can improve sensitivity to early disease stages. In Paper 9, unimodal accuracies of 86% (MRI), 85% (EHR), and 89% (SNP) were exceeded by the multimodal model. Similarly, Paper 11 reported that longitudinal MRI, PET, and DTI features improved disease progression prediction (AD vs NC AUC = 0.935), whereas MCI vs NC performance using static imaging reached 0.697. These findings suggest that multimodal and longitudinal approaches provide a broader representation of disease progression than single-modality systems.

Differences were also observed across model types. Deep learning approaches generally achieved higher performance than classical machine learning methods on high-dimensional imaging datasets. Classical models such as decision trees, random forests, and support vector machines depend on handcrafted features, which may limit performance when disease-related patterns are complex and non-linear. In Paper 1, MRI-based classical models achieved accuracies of 80.46% (DT), 86.92% (RF), and 81.67% (SVM). By comparison, CNN-based models reported higher performance, with Paper 7 achieving 99.68% accuracy using MRI data and Paper 5 reporting over 96% accuracy on FDG-PET data, exceeding both traditional machine learning approaches and human radiologist performance. However, classical models remain useful because of their interpretability and relatively stable performance on structured clinical data.

Feature-processing methods also affected model performance and stability. Techniques such as PCA and LASSO reduced feature dimensionality and improved interpretability while helping to limit overfitting in classical models. In Paper 3, the inclusion of verbal fluency scores improved AUC, while Paper 8 demonstrated that autoencoder-derived MRI features captured structural changes more effectively than handcrafted features.

Hybrid architectures that combined spatial and temporal learning produced further improvements in several studies. The CNN–BGRU model in Paper 12 achieved an MCI vs NC accuracy of 83.9%, compared with 71.4% reported by the CNN-based PET model in Paper 5. Ensemble and stage-aware approaches also showed consistent performance across different disease stages. For example, the YOLOv11-based system in Paper 6 achieved precision scores of 0.947 for CN, 0.936 for EMCI, 0.962 for LMCI, and 0.901 for MCI. In contrast, the CNN model presented in Paper 7, despite its high overall accuracy, relied on an imbalanced dataset and structural MRI data alone, which may limit its generalizability to early and intermediate disease stages.

Several limitations were identified across the reviewed studies. Many investigations relied on small or homogeneous cohorts, reducing the generalizability of reported findings. Multimodal datasets frequently contained missing modalities, limiting the effectiveness of fusion-based methods. Deep learning models also continue to face challenges related to interpretability and clinical acceptance. In addition, differences in evaluation protocols and disease-stage definitions, particularly for early and late MCI, make direct comparisons between studies more difficult.

From a clinical perspective, machine learning methods have demonstrated encouraging results but require further validation before routine deployment. Classical models offer greater transparency, whereas deep learning approaches generally achieve higher accuracy and improved sensitivity to early-stage disease. Current evidence suggests that multimodal deep learning systems may be useful components of future diagnostic workflows, although issues related to dataset diversity, interpretability, standardized staging, and clinical implementation remain unresolved.

IX. Future Prospects

As machine learning applications in healthcare and biomedical research continue to develop, several areas warrant further investigation to improve model performance, reliability, and clinical applicability.

The use of larger and more diverse datasets is important for improving model generalizability and reducing bias. In healthcare applications, models trained on data collected from multiple institutions often perform more consistently than those developed using smaller local datasets. Survey studies have identified dataset size and population diversity as important factors influencing the reliability of AI systems in medicine (Aghdam et al., 2025).

The integration of multiple data modalities, including clinical records, medical imaging, genomic information, and speech data, may provide a broader view of patient health. Multimodal machine learning combines information from different sources to capture relationships that may not be evident when using a single modality. This approach has been applied to tasks such as diagnosis, prognosis, and treatment planning (Zhang et al., 2011; Kavitha et al., 2022).

Federated learning (FL) is a decentralized machine learning framework that allows multiple institutions to train a shared model without exchanging raw patient data. Instead, each institution trains the model locally and shares model parameters with a central server for aggregation. This approach addresses privacy concerns while enabling the use of distributed datasets that may otherwise be unavailable because of legal and ethical restrictions on data sharing (Teo et al., 2024). One example is its application during the COVID-19 pandemic, where a federated model trained on chest imaging and clinical data from several hospitals demonstrated better generalizability than models trained using data from a single site, while maintaining local control of patient information throughout the training process (Dayan et al., 2021).

Model interpretability remains an important consideration, particularly in clinical settings where predictions may influence patient management and treatment decisions. Explainable artificial intelligence (XAI) methods seek to make model outputs and decision processes more understandable to clinicians and other stakeholders, which may support trust, transparency, and regulatory acceptance (Taiyeb Khosroshahi et al., 2025).

The translation of machine learning research into routine clinical practice also remains a significant challenge. In addition to technical performance, successful implementation requires extensive validation, integration into existing clinical workflows, and compliance with healthcare regulations. Studies indicate that only a limited number of advanced AI systems have reached routine clinical use, suggesting that further development and evaluation are still needed (Cecot et al., 2024).

Longitudinal data analysis represents another area of continued interest. By incorporating patient information collected over time, machine learning models can identify temporal patterns associated with disease progression, treatment response, and long-term outcomes. Several studies have shown that longitudinal approaches can improve predictive performance compared with models based solely on cross-sectional data (Cascarano et al., 2023).

Taken together, these developments indicate several directions for future research. Larger and more representative datasets, multimodal learning strategies, privacy-preserving frameworks such as federated learning, improved interpretability, and rigorous clinical validation may contribute to the development of machine learning systems that are more reliable and suitable for healthcare applications.

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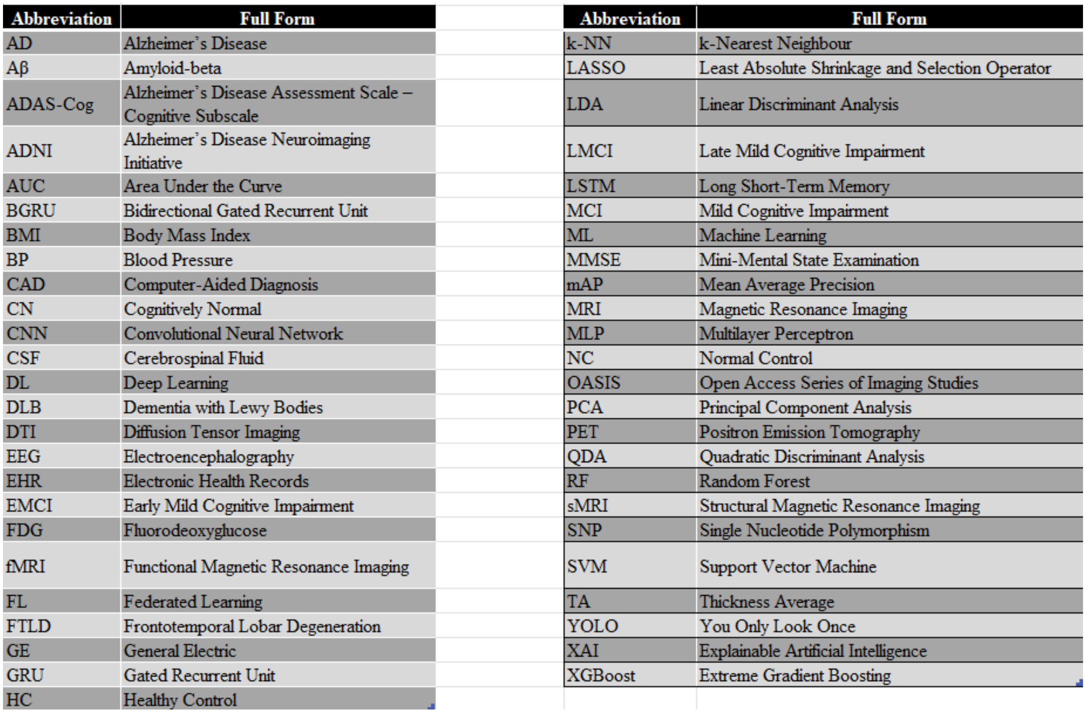
Appendix A



Abbreviation	Full Form	Abbreviation	Full Form
AD	Alzheimer's Disease	k-NN	k-Nearest Neighbour
Aβ	Amyloid-beta	LASSO	Least Absolute Shrinkage and Selection Operator
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale	LDA	Linear Discriminant Analysis
ADNI	Alzheimer's Disease Neuroimaging Initiative	LMCI	Late Mild Cognitive Impairment
AUC	Area Under the Curve	LSTM	Long Short-Term Memory
BGRU	Bidirectional Gated Recurrent Unit	MCI	Mild Cognitive Impairment
BMI	Body Mass Index	ML	Machine Learning
BP	Blood Pressure	MMSE	Mini-Mental State Examination
CAD	Computer-Aided Diagnosis	mAP	Mean Average Precision
CN	Cognitively Normal	MRI	Magnetic Resonance Imaging
CNN	Convolutional Neural Network	MLP	Multilayer Perceptron
CSF	Cerebrospinal Fluid	NC	Normal Control
DL	Deep Learning	OASIS	Open Access Series of Imaging Studies
DLB	Dementia with Lewy Bodies	PCA	Principal Component Analysis
DTI	Diffusion Tensor Imaging	PET	Positron Emission Tomography
EEG	Electroencephalography	QDA	Quadratic Discriminant Analysis
EHR	Electronic Health Records	RF	Random Forest
EMCI	Early Mild Cognitive Impairment	sMRI	Structural Magnetic Resonance Imaging
FDG	Fluorodeoxyglucose	SNP	Single Nucleotide Polymorphism
fMRI	Functional Magnetic Resonance Imaging	SVM	Support Vector Machine
FL	Federated Learning	TA	Thickness Average
FTLD	Frontotemporal Lobar Degeneration	YOLO	You Only Look Once
GE	General Electric	XAI	Explainable Artificial Intelligence
GRU	Gated Recurrent Unit	XGBoost	Extreme Gradient Boosting
HC	Healthy Control		

Appendix B

1. **Logistic Regression**
   Logistic regression is a standard baseline model in clinical research because it produces one coefficient per feature, allowing clinicians to interpret how each variable influences disease risk. It is widely used for predicting Alzheimer's likelihood from demographic factors, cognitive tests, and basic clinical measurements. In *"Detection of Alzheimer's Disease Using Logistic Regression and Clock Drawing Errors"* (Paper 3), logistic regression was applied to non-imaging data from the ADNI dataset. The inclusion of verbal fluency scores significantly improved performance, increasing AUC from 0.825 to 0.91. This demonstrates its effectiveness for low-dimensional, interpretable clinical features, though performance declines when disease patterns become highly non-linear.

2. **Decision Tree**
   Decision trees use simple rule-based splits, producing an interpretable structure that can integrate imaging metrics, cognitive scores, and biomarkers. In *"Early-Stage Alzheimer's Disease Prediction Using Machine Learning Models"* (Paper 1), decision trees applied to MRI-derived features from the OASIS dataset achieved 80.46% accuracy, substantially lower than ensemble-based methods. This highlights a key limitation: single trees tend to overfit small datasets and struggle with complex disease patterns.

3. **Random Forest**
   Random Forests improve upon decision trees by combining multiple trees trained on different subsets of data and features, enhancing robustness. In Paper 1, Random Forest achieved 86.92% accuracy, outperforming the standalone decision tree. Similarly, protein-based studies such as *"k-Skip-n-Gram-RF"* (Paper 16) classified Alzheimer's-related proteins with 85.5% accuracy, demonstrating effectiveness across both imaging-derived and biological sequence features.

4. **Support Vector Machine (SVM)**
   SVMs are well suited for high-dimensional medical imaging data with limited samples. In *"Automatic Classification of MR Scans in Alzheimer's Disease"* (Paper 2), SVMs applied to multicentre T1-weighted MRI achieved 95.6% accuracy on combined datasets and 81% accuracy for mild AD, indicating strong cross-site generalization.

5. **XGBoost (Extreme Gradient Boosting)**
   XGBoost is widely used for structured Alzheimer's data due to its ability to model complex feature interactions while controlling overfitting. In Paper 1, XGBoost achieved 85.92% accuracy, closely matching Random Forest and outperforming simpler classifiers, particularly when modelling interactions between demographic, volumetric, and clinical variables.

6. **Ensemble Voting**
   Voting ensembles combine predictions from multiple models to stabilize performance. In Paper 1, a voting classifier combining Decision Tree, Random Forest, SVM, and XGBoost achieved 85.12% accuracy, demonstrating how model diversity can reduce bias and improve robustness.

7. **Convolutional Neural Network (CNN)**
   CNNs automatically learn spatial features from imaging data and achieve high accuracy when sufficient training data are available, though interpretability is limited. In *"Deep Learning Model to Predict Diagnosis of Alzheimer Disease Using 18F-FDG PET"* (Paper 5), CNNs achieved over 96% accuracy, outperforming human radiologists. Similarly, Paper 7 reported 99.68% accuracy on MRI data.

8. **Deep Convolutional Autoencoder**
   Autoencoders learn compact representations of brain images, capturing meaningful structural patterns while reducing dimensionality. In *"Studying the Manifold Structure of Alzheimer's Disease"* (Paper 8), autoencoder-based features supported disease-stage discrimination and visualization, achieving approximately 80% accuracy.

9. **Long Short-Term Memory (LSTM)**
   LSTMs are used to model temporal dependencies in longitudinal Alzheimer's data, such as repeated MRI scans and cognitive assessments, making them suitable for disease progression analysis.

10. Bidirectional GRU (BGRU)

BGRUs are often paired with CNNs to model temporal evolution of spatial features. In *"Classification of Alzheimer's Disease by Combination of Convolutional and Recurrent Neural Networks Using FDG-PET Images"* (Paper 12), CNNs extracted spatial features while BGRUs modeled their sequential variation, achieving 95.3% accuracy for AD vs. normal controls.

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