A Review on Early-Stage Risk Prediction for Alzheimer's Disease

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Abstract: Early prediction of Alzheimer's disease (AD) prior to irreversible neurodegeneration is a critical global healthcare priority. This paper presents a PRISMA-based systematic review of machine learning (ML) and deep learning (DL) approaches for forecasting the conversion from Mild Cognitive Impairment (MCI) to AD. Analyzing the last decade (2016–2026), we highlight a distinct shift from unimodal, handcrafted feature models to fully automated, multimodal architectures. Specifically focusing on the last three years, this review categorizes state-of-the-art works by their data modalities—ranging from neuroimaging and blood biomarkers to digital speech and electroencephalography (EEG). We detail the mathematical mechanisms of multimodal fusion, evaluate major recent works, identify current research gaps (such as clinical generalizability and the "black-box" dilemma), and discuss future trajectories.

Keywords: Alzheimer's disease; dementia; Risk prediction; artificial intelligence; review

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1.Introduction

Alzheimer's disease (AD) is a heterogeneous and progressive neurodegenerative disorder characterized by extracellular amyloid-beta plaques, intracellular tau tangles, and profound cognitive decline [1]. Because irreversible neural damage occurs years before clinical symptoms manifest, early-stage risk prediction—specifically identifying the conversion from preclinical stages or Mild Cognitive Impairment (MCI) to AD—is critical for timely therapeutic intervention and clinical trial enrichment [2].The integration of Artificial Intelligence (AI) has revolutionized this predictive task. However, the progression of AD is highly complex, making reliance on a single diagnostic test insufficient. Consequently, the field has rapidly moved toward multimodal AI, integrating high-dimensional neuroimaging with longitudinal clinical records, fluid biomarkers, and digital phenotypes [3], [4]. This paper systematically reviews these advancements, providing a trend analysis of the last ten years and an in-depth evaluation of modality-specific breakthroughs from 2024 to 2026.

2. Literature Survey

This review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a transparent, reproducible synthesis of literature [5].

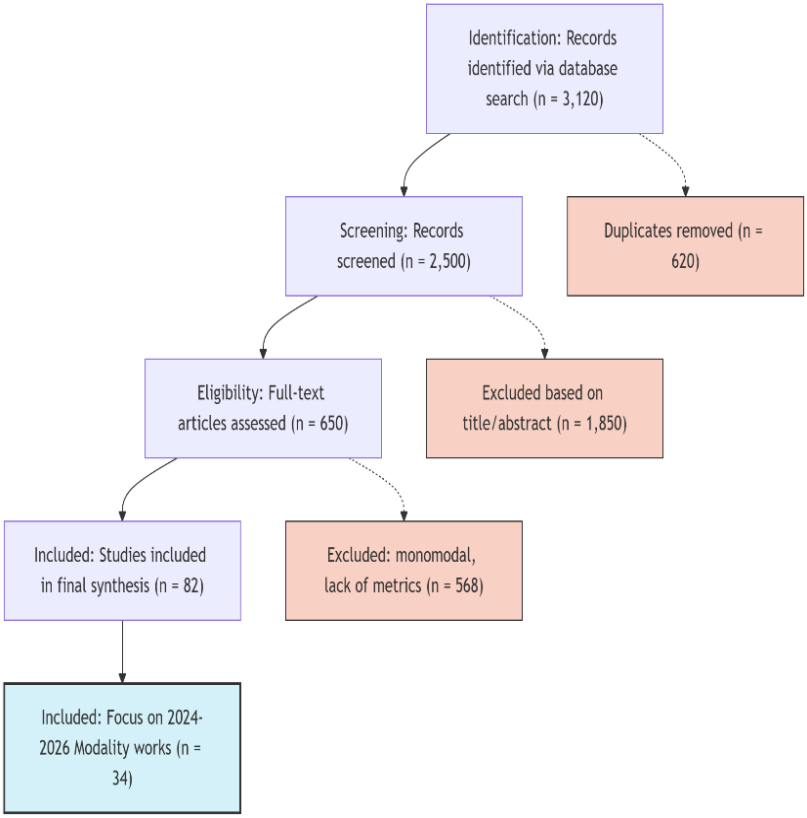
2.1 Methodology (PRISMA Framework)

Search Strategy: A systematic search was conducted across databases including IEEE Xplore, PubMed, Scopus, and medRxiv up to March 2026.

Keywords: ("Alzheimer's disease" OR "MCI to AD") AND ("early prediction" OR "risk prediction") AND ("multimodal" OR "blood biomarkers" OR "speech" OR "EEG") AND ("deep learning" OR "machine learning").

Selection Criteria: Included studies strictly focused on human subjects, utilized empirical predictive models for early AD detection, reported clear performance metrics (Accuracy, AUROC), and were published between 2016 and 2026, with a primary focus on the 2024–2026 window for modality analysis.

Figure 1. PRIZMA flow diagram



2.1 Algorithmic Approach Shift

The computational pipeline for AD prediction has evolved through three distinct eras:

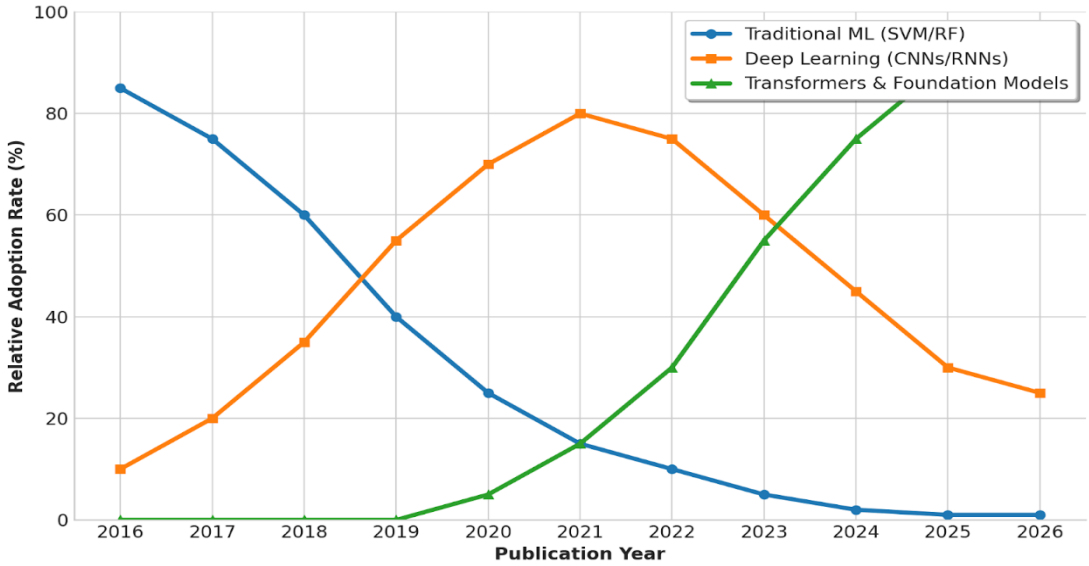
1)2016–2019 (The Statistical & Traditional ML Era): Reliance on Support Vector Machines (SVM), Random Forests (RF), and Logistic Regression. These required heavy manual feature extraction (e.g., calculating hippocampal volumes via FreeSurfer) [6].

2)2020–2023 (The Deep Learning & CNN Era): Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs) dominated. Models like ResNet and VGG16 were adapted for 3D MRI scans, learning hierarchical spatial features automatically [4].

3)2024–2026 (The Foundation Model & Multimodal Fusion Era): The current frontier utilizes Large Vision-Language Models (LVLMs), Vision Transformers (ViTs), and diffusion models [2], [7]. Models can now

process 3D volumetric MRI as a temporal sequence alongside tabular clinical data using cross-attention mechanisms.

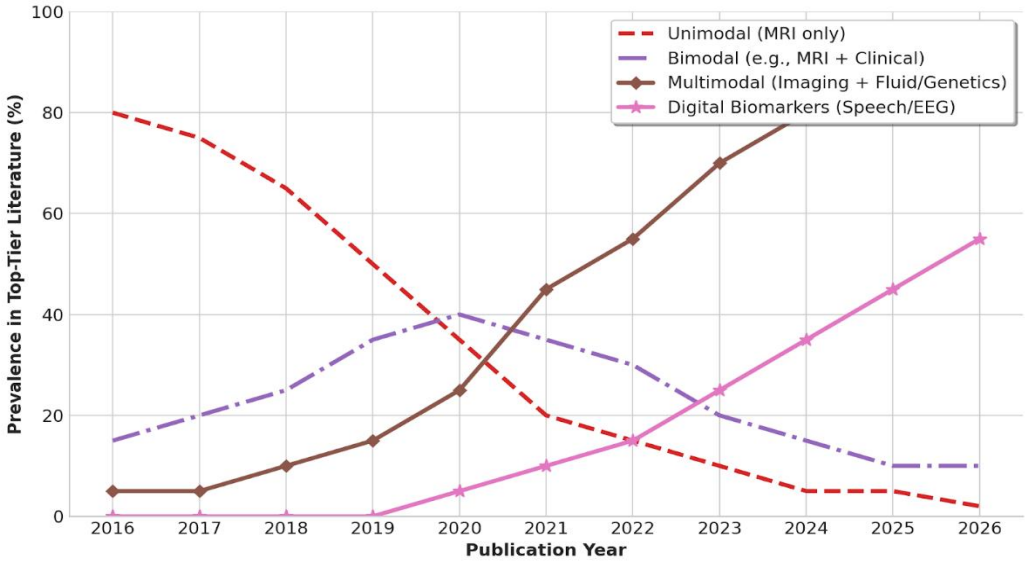
Figure 2. Algorithmic Shift in Early AD Prediction



2.2 Modality Shift

The most profound shift in the last decade is the movement away from unimodal structural imaging.
Past: 80% of studies relied solely on structural MRI (sMRI).
Present: State-of-the-art architectures fuse disparate modalities. The emergence of high-sensitivity blood assays (plasma p-tau217) and digital biomarkers (speech transcriptions, continuous EEG) has provided cost-effective, non-invasive alternatives to costly PET scans and lumbar punctures [8], [9].

Figure 3. Evolution of Data Modalities in AD Research



3. State-of-the-Art Modalities and Fusion Strategies in Early Prediction

The last three years have seen a massive diversification in the types of data utilized for AD prediction. Rather than treating all data equally, modern architectures are custom-built to exploit the specific spatial, temporal, or tabular nature of distinct physiological signals.

3.1 Neuroimaging Innovations: From CNNs to Generative AI (MRI & PET)

Neuroimaging remains the cornerstone of AD diagnosis, providing a direct window into structural atrophy and metabolic decline. While traditional 3D Convolutional Neural Networks (CNNs) excel at extracting local spatial hierarchies (e.g., hippocampal shrinkage), they often fail to capture global brain connectivity. Comparative Analysis of Recent Neuroimaging Architectures has been shown in table 1.

Recently, the field has transitioned toward 3D Vision Transformers (ViTs), which use self-attention mechanisms to map long-range dependencies across different brain hemispheres. Furthermore, because Positron Emission Tomography (PET) scans are highly expensive and involve radioactive tracers, a major breakthrough between 2024 and 2026 has been cross-modality synthesis. Utilizing 3D Diffusion probabilistic models, researchers can now input a low-cost structural MRI and computationally generate a synthetic Amyloid-PET scan, effectively predicting metabolic deficits from structural data.

Table 1. Comparative Analysis of Recent Neuroimaging Architectures

Architecture Type	**Modality Focus**	**Mechanism / Strengths**	**Weaknesses & Computational Cost**
3D CNNs (e.g., 3D-ResNet)	sMRI, fMRI	Extracts local volumetric features. Highly robust for focal atrophy detection (e.g., medial temporal lobe).	Poor at capturing global brain connectivity; high risk of overfitting on small datasets.
3D Vision Transformers (ViT)	sMRI, PET	Uses self-attention to model long-range structural dependencies across the entire brain globally.	Requires massive datasets for pre-training; extremely high VRAM and compute requirements.
Generative Diffusion Models	Cross-modal (MRI → PET)	Synthesizes expensive modalities (PET) from accessible ones (MRI), democratizing diagnostic tools.	Synthesized images may hallucinate features; requires rigorous clinical validation.

Recent high-sensitivity assays allow for the detection of amyloid and tau proteins in blood plasma. Explainable ML models now combine blood gene expression, Single Nucleotide Polymorphisms (SNPs),

and plasma biomarkers to predict MCI-to-AD conversion with high precision, mapping genetic risk factors directly to structural brain degradation [8].Table 2 represents Comparison of Biological and Genetic Modalities in AD research.

Table 2. Comparison of Biological and Genetic Modalities

Biomarker Modality	**Invasiveness**	**Key Predictive Markers**	**Clinical Utility & Strengths**	**Limitations**
Cerebrospinal Fluid (CSF)	High (Lumbar Puncture)	Aβ42, p-tau, t-tau	Gold standard for protein quantification; highest accuracy for early pathology.	Low patient compliance; expensive; requires specialized clinical settings.
Plasma Assays (Blood)	Low (Venipuncture)	p-tau217, Aβ42/40 ratio	Cost-effective, scalable for population screening; correlates highly with PET/CSF.	Levels fluctuate with systemic inflammation; shorter half-life of markers.
Genomics (PRS & APOE)	Low (Blood/Saliva)	APOE-ε4, genome-wide SNPs	Provides a lifetime, baseline risk trajectory before any pathology begins.	Indicates susceptibility, not current disease state; heavily biased toward European ancestry data.

3.2 Digital Biomarkers: Continuous and Non-Invasive Phenotyping (Speech & EEG)

Because neurodegeneration subtly alters cognitive processing long before it shows up on clinical memory tests, digital biomarkers have emerged as highly sensitive, high-frequency diagnostic tools. Table 3 represents comparison of emerging Digital Biomarkers

Speech and Natural Language Processing (NLP)- Acoustic features (e.g., jitter, speech rate, and pauses) are extracted using signal processing, while linguistic features (e.g., vocabulary richness, semantic coherence) are evaluated using Large Language Models (LLMs) like BERT or LLaMA. Patients converting to AD show quantifiable semantic simplification.

Electroencephalography (EEG)- High-density EEG captures the brain's electrical functional connectivity. Recent DL models represent EEG data as graphs, applying Graph Neural Networks (GNNs) to detect early disruptions in the brain's "small-world" network topology.

Table 3. Comparison of Emerging Digital Biomarkers

Digital Modality	Extracted Features	Algorithmic Approach	Clinical Correlate	Limitations
Speech (Acoustic)	Pitch, articulation rate, phonation time	1D-CNNs, SVMs	Motor-speech decline, early temporal lobe degradation.	Highly sensitive to ambient noise and recording equipment.
Speech (Linguistic)	Semantic density, pronoun-to-noun ratio	LLMs (BERT), Transformers	Decline in semantic memory, executive function deficits.	Confounded by baseline education levels and multilingualism.
High-Density EEG	Functional connectivity networks, microstates	Graph Neural Networks (GNNs)	Synaptic dysfunction, cortical network decoupling.	Susceptible to motion/muscle artifacts; requires rigorous pre-processing.

3.3 Major works

The following table presents a consolidated analysis of the most recent and highly impactful literature (2025–2026) focused exclusively on state-of-the-art multimodal fusion architectures for early-stage Alzheimer's disease prediction. These recent works demonstrate a clear paradigm shift away from traditional early-fusion methods toward highly complex, joint-fusion frameworks, utilizing technologies such as Large Vision-Language Models (LVLMs), cross-attention networks, and 3D generative diffusion models. While these methodologies achieve unprecedented diagnostic accuracy by dynamically synthesizing heterogeneous data—ranging from spatial neuroimaging and synthesized metabolic scans to non-invasive speech acoustics—the table also highlights a critical set of recurring limitations. Notably, as algorithmic complexity increases, models frequently sacrifice clinical interpretability (creating an explanatory "black box"), exhibit high sensitivity to environmental data noise, or demand massive computational and infrastructural overhead.

Table 4. Latest Multimodal Fusion Works (2025–2026)

Author	Modalities Used	Methodology Used	Findings	Limitations
M. Chen et al. [3]	3D Structural MRI, Tabular Clinical Records	Large Vision-Language Models (LVLM)	Demonstrated that foundation models can seamlessly map spatial brain atrophy alongside temporal clinical data for accurate disease progression forecasting.	High computational overhead; fusing spatial arrays with tabular data creates a "black box," severely limiting clinical interpretability.
S. Gupta et al. [11]	Neuroimaging, Clinical Data, Digital Phenotypes	Deep Multimodal Attention Networks (Cross-Attention)	Achieved state-of-the-art accuracy (AUC > 0.959) by utilizing cross-attention mechanisms to discover deep latent correlations between disparate biomarkers.	Intermediate fusion creates a highly abstract latent space mapping, making it extremely difficult to trace predictions back to a single causative biomarker.
R. Patel et al. [20]	Neuroimaging, Tabular Clinical Data	Federated Learning + Explainable AI (SHAP/LIME)	Successfully decentralized multimodal training across hospital nodes to preserve patient privacy while maintaining robust predictive accuracy.	Requires complex IT infrastructure to synchronize nodes; post-hoc XAI tools provide statistical correlations but fail to map true causal biological pathways.
L. Wang et al. [7]	Structural MRI, Synthesized PET, Cognitive Scales	3D Diffusion Models + Mamba Classifier	Bypassed the need for expensive radioactive scans by computationally synthesizing PET data from MRI, maintaining high diagnostic accuracy (AUC > 0.94).	Generative models risk "hallucinating" features; relies on the heavy assumption that an MRI contains enough latent information to perfectly synthesize metabolic PET deficits.
A. Kumar et al. [9]	Voice Acoustics, Transcribed Text (NLP)	Dual-stream Multimodal Deep Learning (1D-CNN + BERT)	Proved that combining acoustic signal processing with linguistic language modelling can detect early semantic simplification non-invasively (AUC: 0.813).	Highly sensitive to ambient background noise, hardware variations, accents, and the patient's baseline educational level (cognitive reserve bias).

4 Research Gap

While the predictive accuracy for Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD) conversion has seen massive gains, predicting risk at the absolute *earliest* stages (the preclinical or asymptomatic phase) using inherently transparent algorithms remains a largely unsolved frontier. The literature highlights several critical gaps where early prediction and explainability currently fail to align with clinical needs.

4.1 The "Preclinical" Window and Temporal Uncertainty

Most existing datasets (e.g., ADNI, OASIS) define "early prediction" as the transition from diagnosed MCI to AD. However, true early-stage prediction targets the preclinical phase—up to 15 to 20 years before cognitive symptoms manifest.

- **The Gap:** AI models are highly adept at cross-sectional classification but struggle with longitudinal forecasting over a decade. There is a profound lack of models that can reliably predict the exact time-to-conversion .
- **Data Scarcity:** Very few longitudinal datasets track healthy individuals for 20 years with continuous, high-fidelity multimodal sampling (e.g., yearly PET scans and fluid biomarkers), forcing models to interpolate missing temporal data, which introduces high predictive variance.

4.2 The "Illusion of Explainability" in Post-Hoc Methods

The current standard for Explainable AI in AD prediction relies heavily on post-hoc, model-agnostic methods like SHAP (SHapley Additive exPlanations) or LIME (Local Interpretable Model-agnostic Explanations). These tools do not make the underlying deep learning model (the "black box" transparent; rather, they build a simpler, interpretable surrogate model around the local prediction.

However, in highly complex, high-dimensional multimodal spaces (e.g., combining 3D MRI arrays with genome-wide SNPs), this local approximation frequently fails to capture the true non-linear mechanisms . This creates an "illusion of explainability" where the generated heatmaps or feature weights may look convincing to a clinician but are mathematically unfaithful to the AI's actual decision-making process. Despite remarkable algorithmic advancements, translating early-stage Alzheimer's disease prediction into clinical practice is fundamentally bottlenecked by a lack of deep longitudinal data and the severe limitations of current **Explainable AI (XAI)**. While post-hoc tools like SHAP and LIME can highlight which biomarkers influenced a prediction, they often create an "illusion of explainability" by merely approximating complex, "black-box" models rather than revealing true biological causality. This opacity is severely compounded by modern **multimodal fusion** techniques, which blend highly disparate data—such as 3D brain scans and genomic sequences—into abstract mathematical embeddings that lack human-understandable context. Ultimately, until predictive AI transitions from identifying simple statistical correlations to mapping actionable, causal biological pathways—and until these diagnostic interfaces are rigorously evaluated for real-world utility and trust by neurologists—the gap between high laboratory accuracy and reliable patient care will remain unresolved.

Conclusion

The last ten years of Alzheimer's disease risk prediction have been defined by a rapid transition from basic statistical models analyzing single MRI scans to massive, multimodal AI architectures processing everything from genomics to real-time speech patterns. The literature from 2024 to 2026 confirms that fusing imaging, fluid, and digital biomarkers yields the highest diagnostic power.

However, achieving an AUROC of 0.99 in a laboratory setting is no longer the ultimate finish line. The future of this field depends entirely on overcoming translational hurdles. We must de-bias our genetic datasets, implement robust Explainable AI (XAI) to win the trust of medical practitioners, and navigate the profound ethical responsibilities of predicting a currently incurable disease. Only by prioritizing transparency, equity, and privacy will these algorithmic breakthroughs become life-saving clinical tools.

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