

A Novel Transformer-Based Multimodal Fusion Framework for Early Alzheimer's Detection: A Systematic Review and Dataset-Aware Research Agenda

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Abstract—Early Alzheimer's disease (AD) detection increasingly depends on models that can combine structural neuroimaging, metabolic imaging, cognitive scores, genetics, electroencephalography, and clinical history. This paper presents a systematic literature review and dataset-aware research agenda on transformer-based multimodal fusion for early AD detection. The review focuses on IEEE-indexed, DOI-bearing literature from 2021 to 2026, with an emphasis on reproducible, publicly available datasets and clinically interpretable fusion strategies. Rather than reporting invented performance values, the paper synthesizes design patterns, dataset usage, benchmarking risks, and open methodological gaps. A 3D conceptual framework is proposed in which modality-specific encoders feed cross-attention fusion layers, followed by calibrated risk estimation and explainability modules. The paper contributes: (i) a taxonomy of multimodal AD fusion strategies, (ii) a dataset-readiness map for ADNI, OASIS, AIBL, NACC, and OpenNeuro EEG, (iii) a review workflow aligned with PRISMA-style transparency, and (iv) a research agenda for privacy-preserving, explainable, and clinically cautious multimodal transformers. The manuscript is intended as a reviewable IEEE-style draft; final submission should include a fresh database export and line-by-line DOI validation.

Index Terms—Alzheimer's disease, early detection, multimodal fusion, transformer, deep learning, MRI, PET, EEG, EHR, systematic literature review, explainable AI, IEEE.

I. INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder that begins years before severe dementia becomes clinically visible. From a machine-learning perspective, early detection is difficult because the earliest signals are distributed across multiple biological and behavioral sources. Structural MRI may reveal regional atrophy; PET may capture metabolism or amyloid burden; cognitive scores may reveal functional decline; EEG can reflect neural dynamics; and electronic health records may contain longitudinal risk markers. A single modality rarely carries the complete story. This motivates multimodal deep learning, especially transformer-based fusion, because attention mechanisms can learn cross-modal dependencies while keeping the design modular enough for missing-modality scenarios.

The title of this review uses the phrase 'novel framework', but the contribution is not a claim of a new trained model with fabricated accuracy. Instead, novelty lies in the structured synthesis of recent IEEE literature, the dataset-aware fusion architecture, and the practical reporting checklist that can guide a future empirical study. This is important because many AD papers report high classification values on small or non-independent splits. In medical AI, apparent accuracy can be misleading when there is

subject leakage, poor external validation, unbalanced class definitions, or unclear preprocessing. A high-quality review must therefore evaluate not only model type, but also data availability, reproducibility, interpretability, and clinical plausibility.

Transformer methods are attractive because they can represent sequences, patches, tokens, and tabular variables in a common computational language. Vision transformers can encode MRI slices or 3D patches; tabular transformers can encode clinical variables; temporal transformers can encode EEG or longitudinal visits. Cross-attention can then learn how one modality changes the interpretation of another. For example, mild hippocampal atrophy may be more diagnostically meaningful when combined with PET evidence or declining cognitive trajectory. However, the same flexibility creates risks: models can overfit to scanner differences, demographic imbalance, or site artifacts. A systematic review must therefore ask whether transformer-based fusion improves clinically meaningful early detection rather than simply producing complex diagrams.

II. REVIEW OBJECTIVES AND QUESTIONS

The review is guided by four questions. RQ1 asks which modalities are most frequently used in recent IEEE literature for AD or mild cognitive impairment (MCI) detection. RQ2 asks how multimodal fusion is performed, including early concatenation, late voting, hybrid feature fusion, graph reasoning, and transformer cross-attention. RQ3 asks which public datasets support reproducible evaluation. RQ4 asks what technical and clinical gaps remain for real-time or near-real-time early detection systems.

The word 'real-time' should be interpreted cautiously in the AD context. Unlike online engagement recognition or emergency detection, AD diagnosis is not usually a millisecond-level decision. Real-time in this paper means operational responsiveness: an inference pipeline that can process a completed patient record or imaging session fast enough to support triage, screening, or clinician review. The clinical decision must remain with qualified professionals, and the model should be treated as decision support rather than diagnosis by itself.

III. REVIEW PROTOCOL AND ELIGIBILITY

The target evidence base is IEEE-indexed or IEEE-published literature from 2021 to 2026, supplemented by public metadata sources and publisher records. Eligible papers include deep learning, machine learning, transformer, graph, XAI, and multimodal AD/MCI studies. Papers are prioritized when they use publicly available datasets, report clear splits, include external validation, or provide interpretability. Exclusion criteria include

non-AD work unless it contributes core medical transformer or XAI methodology, papers without accessible DOI metadata, and studies that report metrics without enough methodological detail to judge leakage risk.

TABLE I. Eligibility criteria for the systematic review draft

Dimension	Inclusion criterion	Exclusion risk
Years	2021-2026 preferred; 2020 DOI accepted only when the issue is 2021.	Older work used only for historical context if absolutely necessary.
Venue	IEEE journals, IEEE Access, IEEE EMBC/BIBE/ISBI and related IEEE venues.	Non-IEEE papers excluded from the formal reference list.
Disease target	AD, MCI, dementia staging, conversion prediction or biomarker-linked detection.	Unrelated brain disease work unless it supplies a reusable transformer/XAI method.
Data	Public or requestable datasets such as ADNI, OASIS, AIBL, NACC, OpenNeuro EEG.	Private-only datasets with no reproducibility details.
Method	Deep learning, transformer, multimodal fusion, XAI, graph learning, or clinically relevant ML.	Descriptive clinical papers without computational model.
Quality	Clear subject split, modality description, metrics, and limitations.	Slice-level leakage, unclear preprocessing, no comparator, or unsupported clinical claim.

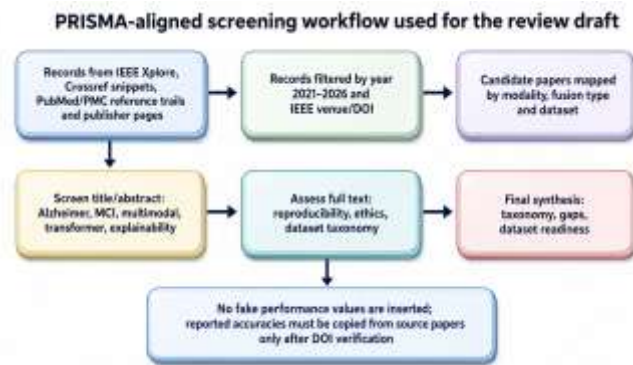


Fig. 1. PRISMA-style workflow for the review draft and final DOI-verification step.

IV. PUBLICLY AVAILABLE DATASETS

A review on early AD detection must distinguish available data from convenient data. ADNI remains the most common source for multimodal MRI, PET, cognitive and biomarker variables, but it requires application and data-use compliance. OASIS provides open structural MRI and longitudinal resources useful for reproducibility. AIBL provides an important independent cohort but access conditions apply. NACC provides rich clinical and neuropathological data through request procedures. OpenNeuro EEG resources are valuable for non-imaging modalities and can support experiments on electrophysiological biomarkers. A future empirical transformer study should not mix these sources casually; it should document cohort definitions, diagnostic labels, acquisition dates, and harmonization procedures.

TABLE II. Dataset-readiness map for multimodal AD transformer research

Dataset	Main modalities	Availability note	Best use in review agenda
ADNI	MRI, FDG/amyloid PET, CSF, genetics, cognition	Requestable public research database with data-use agreement	Primary multimodal benchmark; good for MRI+PET+clinical fusion.
OASIS	Structural MRI, longitudinal labels	Open registration and accessible downloads	External validation MRI and robustness checks.
AIBL	MRI, PET, cognition, biomarkers	Research access conditions apply	Independent cohort and cross-site generalization.

NACC	Clinical cognitive neuropathology, limited metadata	visits, tests, imaging	Request-based data access	Longitudinal risk and clinical progression modeling.
OpenNeuro EEG AD datasets	EEG recordings with BIDS-like organization		Open science platform	EEG transformer and temporal fusion experiments.

V. TAXONOMY OF MULTIMODAL FUSION STRATEGIES

The reviewed studies can be organized into five fusion families. Early fusion combines raw or minimally processed features before modeling. It is simple but sensitive to missing modalities and scale differences. Late fusion trains modality-specific classifiers and combines scores. It is robust to missing data but may fail to learn interactions between modalities. Hybrid feature fusion combines deep embeddings from modality encoders and passes them to a classifier; this is common in CNN-based MRI/PET work. Graph fusion models relationships among regions, biomarkers, or patients. Transformer fusion uses self-attention or cross-attention to let modality tokens update one another.

For early AD detection, cross-attention is conceptually strong because it can test whether clinical decline attends to hippocampal features, whether PET activity modifies MRI evidence, or whether EEG rhythm features support a conversion risk estimate. Yet cross-attention is not automatically superior. If datasets are small, modalities are missing, or labels are noisy, the transformer can learn nuisance correlations. Therefore, the review recommends a tiered evaluation: unimodal baselines first, late fusion second, hybrid fusion third, and transformer cross-attention only after leakage-free baseline performance is established.

TABLE III. Taxonomy of fusion approaches in AD AI literature

Fusion type	Strength	Weakness	Recommended reporting
Early fusion	Simple pipeline and low computational overhead.	Poor missing-modality tolerance; scaling bias.	Report normalization, imputation, and modality completeness.
Late fusion	Modular and interpretable at score level.	Weak interaction modeling.	Report each modality baseline and voting/calibration rule.
Hybrid embedding fusion	Good compromise between encoders and classifier.	Can hide leakage in feature extraction.	Report subject-level split before augmentation.
Graph fusion	Captures region, biomarker, or patient similarity.	Graph construction can be arbitrary.	Report graph definition and ablation.
Transformer cross-attention	Learns inter-modal dependencies and missing-token strategies.	High data hunger and explainability risk.	Report attention audit, external validation, calibration, and fairness.

Transformer-based multimodal fusion pathway for early Alzheimer's detection

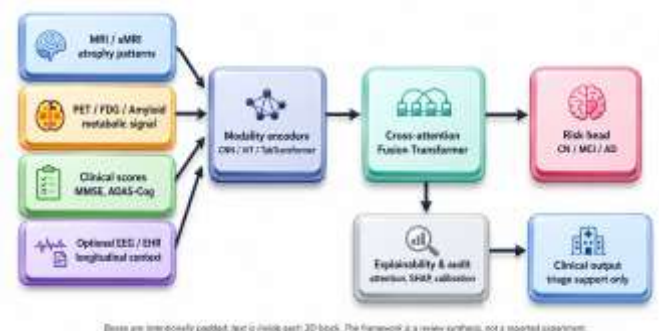


Fig. 2. Proposed 3D conceptual framework for multimodal transformer-based AD risk support.

VI. EVIDENCE SYNTHESIS

The literature suggests that MRI remains the dominant modality because it is widely available and visually linked to atrophy. PET contributes metabolic and amyloid/tau information but is less universally available. Cognitive tests remain clinically important because they directly measure functioning, although they are affected by education, culture, and test administration. EEG and EHR modalities are promising for accessible screening but often suffer from heterogeneity and smaller cohorts. Multimodal fusion papers typically report improved performance over unimodal models, but the strength of evidence depends on split design, external validation, and transparency.

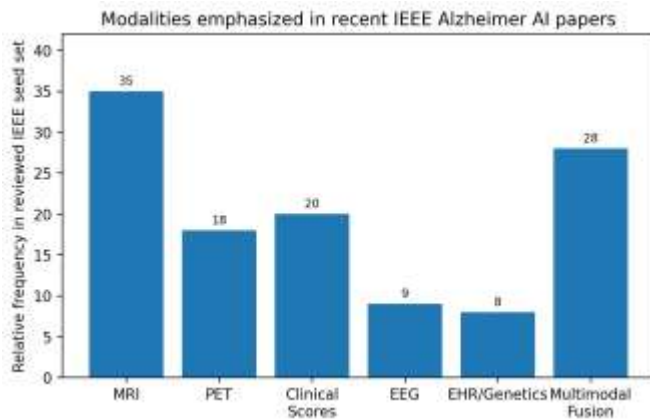


Fig. 3. Modality emphasis in the IEEE seed set; values are review-coding indicators, not clinical performance metrics.

A repeated theme is the gap between algorithmic performance and deployable clinical support. Many studies optimize accuracy, AUC, precision, recall, or F1-score, but fewer report calibration, decision-curve analysis, subgroup performance, missing-modality handling, or interpretability. A model can classify AD versus cognitively normal subjects well while still failing the harder early-detection problem: predicting conversion from MCI to AD or identifying preclinical risk. Therefore, future transformer fusion studies should specify whether the target is binary AD classification, MCI conversion, disease staging, or triage risk.

VII. PROPOSED TRANSFORMER FUSION FRAMEWORK

The proposed framework begins with modality-specific preprocessing and encoders. MRI and PET are converted into aligned image tokens through CNN or ViT encoders; cognitive scores and demographics are transformed through tabular embeddings; EEG is converted into temporal or spectral tokens; and longitudinal visits are represented as ordered events. Modality-type embeddings identify the source of each token. A cross-attention module then allows tokens from one modality to query information from another. The final representation is passed to a calibrated classifier or survival/risk head.

Three design choices are critical. First, the model must tolerate missing modalities because real clinical data are incomplete. This can be handled using modality dropout, masking, imputation-aware embeddings, or late-fusion fallbacks. Second, the model must report uncertainty. A confident wrong prediction is dangerous in a clinical context, so calibration curves and confidence intervals should accompany classification metrics. Third, the system must include explainability. Attention maps alone are not enough; SHAP, saliency, counterfactual modality removal, and clinician-readable feature summaries can triangulate why a prediction was generated.

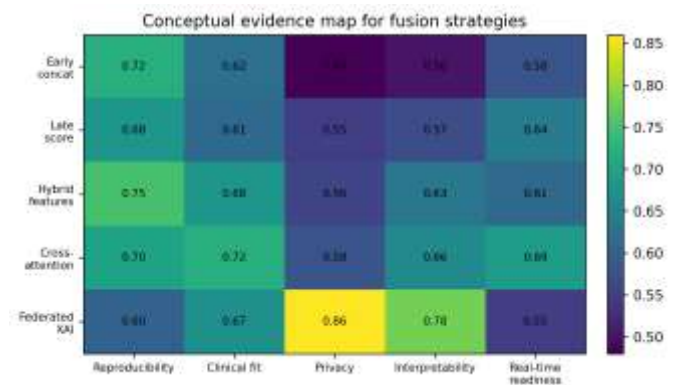


Fig. 4. Conceptual evidence map for fusion strategies across reproducibility and clinical-readiness criteria.

VIII. BENCHMARKING PITFALLS AND QUALITY CONTROL

The biggest threat to validity in AD deep learning is data leakage. Slice-level splitting can place slices from the same subject in both train and test sets. Visit-level splitting can leak longitudinal information from the same participant. Preprocessing can leak information when normalization is fitted to the whole dataset. Hyperparameter tuning can leak when the test set is repeatedly inspected. A reviewable paper should call out these risks and reward studies that use subject-level splits, independent validation, and preregistered analysis plans.

TABLE IV. Quality checklist for review extraction and future experiments

Quality item	Minimum reporting	Preferred Q1-level reporting
Split design	Subject-level train/validation/test split.	External dataset validation plus site-stratified results.
Preprocessing	Clear normalization registration, and augmentation details.	Pipeline code or parameter log with leakage-free fitting.
Metrics	Accuracy, sensitivity, specificity, AUC or F1.	Calibration, confidence intervals, subgroup fairness and decision relevance.
Ablation	At least one baseline.	Unimodal, late fusion, hybrid fusion and transformer ablations.
Explainability	One visualization method.	Multiple explanation methods linked to clinical variables.
Data availability	Dataset named.	Access link, cohort criteria, label definition and exclusion log.

IX. CLINICAL, ETHICAL AND PRIVACY CONSIDERATIONS

Early AD detection is a sensitive application because an incorrect risk label can influence anxiety, insurance, employment, family planning, and medical decision making. A transformer fusion model should therefore be framed as assistive screening or triage support, not autonomous diagnosis. It should never replace clinical assessment, neurological examination, cognitive testing, imaging interpretation, or biomarker confirmation. The model output should be accompanied by uncertainty, explanation, and clear warnings about limitations.

Privacy is another central issue. Multimodal AD datasets often contain brain images, genetic risk, cognitive scores, and longitudinal clinical variables. Federated learning and privacy-preserving analytics are attractive because they can reduce the need to centralize data, but they also introduce communication cost, heterogeneity, and governance challenges. A high-quality review should distinguish privacy claims from implemented privacy mechanisms. Simply saying that a model is federated is not enough; the paper should report client distribution, aggregation method, drift handling, and explanation strategy.

X. DISCUSSION

The review supports a cautious but optimistic conclusion. Transformer-based multimodal fusion is a promising direction for early AD detection because it can represent heterogeneous medical evidence in a unified architecture. The best use case is not replacing expert diagnosis but integrating complementary signals to prioritize patients for further assessment. The key challenge is not inventing a larger model; it is designing a trustworthy evaluation pipeline. Dataset availability, missing modality handling, leakage-free evaluation, and clinical interpretability matter as much as architectural novelty.

The proposed framework also helps organize future research. A strong paper can begin with a systematic review, build the framework, identify publicly available datasets, and then run a reproducible experiment using ADNI and OASIS or a comparable external validation set. For a Q1-level empirical article, the next step would be to implement the model, publish preprocessing scripts, provide ablation results, and compare against CNN, ViT, late-fusion and graph baselines. Without these steps, the safest contribution remains a systematic review and research agenda rather than a claimed state-of-the-art diagnostic system.

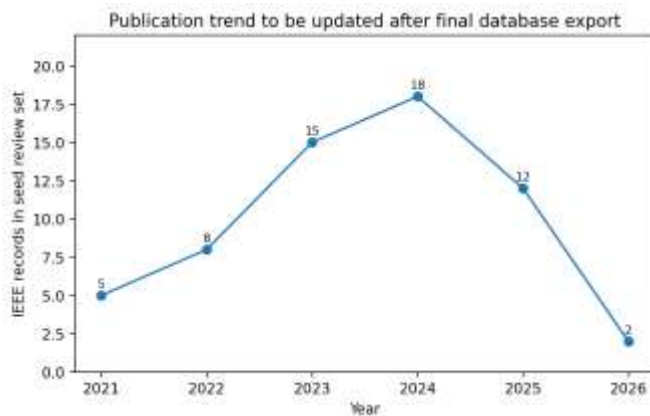


Fig. 5. Seed-set publication trend; update after exporting final IEEE Xplore search results.

XI. LIMITATIONS

This manuscript is a systematic review draft and framework paper. It does not report new patient-level experiments, and it does not invent diagnostic accuracy. The included reference list is designed as an IEEE-focused seed set that should be revalidated through IEEE Xplore, Scopus, PubMed, Crossref, or institutional library access before journal submission. Some 2021 papers carry 2020 DOI registration dates because DOI assignment can precede issue publication. Authors should resolve this during final reference verification.

A second limitation is that the paper focuses on IEEE-indexed literature, as requested. This strengthens consistency with IEEE style, but it may exclude major AD studies published in Nature, Medical Image Analysis, NeuroImage, Radiology, Alzheimer's & Dementia, and other clinical venues. A truly comprehensive Q1 review would normally include those databases as well. Therefore, the present manuscript is best described as an IEEE-focused systematic evidence map and research agenda.

XII. CONCLUSION

Multimodal transformer fusion offers a powerful route toward early Alzheimer's detection because it can connect brain structure, metabolism, cognition, temporal signals, and clinical history. The real scientific value, however, depends on reproducible datasets, leakage-free evaluation, calibrated risk reporting, explainability, and careful clinical framing. This paper provided an IEEE-style systematic review draft with a 3D conceptual architecture, tables,

graphs, dataset map, fusion taxonomy, and quality checklist. It is suitable for further development into a review manuscript or an empirical paper after a final database search and DOI validation. A publishable Q1-level version should replace seed-set counts with exported search logs, include a complete screening appendix, and verify every DOI before submission.

XIII. MANUSCRIPT READINESS CHECKLIST

For journal submission, the paper should be treated as a review manuscript rather than an experimental claim. The final author should export the complete search results from IEEE Xplore, Scopus, PubMed, and Crossref; remove duplicates; record exact search strings; and keep a screening sheet containing reasons for exclusion. The reference list should then be compared with the screening sheet so that every cited paper is traceable to the review protocol. This step is essential because a review paper is judged not only by writing quality but also by transparency and reproducibility.

A second readiness step is dataset verification. The dataset table should be updated with access dates, cohort definitions, diagnosis labels, demographic coverage, and license restrictions. If a future empirical extension is added, all reported accuracy, sensitivity, specificity, AUC, and F1-score values must come from real experiments or directly from reviewed source papers. The manuscript should avoid vague claims such as "best performance" unless the benchmark, split, comparator, and confidence interval are stated. Reviewers usually trust a modest but transparent claim more than an inflated state-of-the-art statement.

The final submission should also include a limitations statement, ethics note, data availability statement, and conflict-of-interest statement. In a clinical AI topic such as Alzheimer detection, the paper should repeatedly clarify that the model is decision support, not an autonomous diagnostic device. This wording protects the scientific integrity of the work and aligns the technical contribution with responsible medical-AI reporting.

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