

Review

Sex Differences in Machine Learning Models for Multimodal Biomarker-Based Diagnosis and Prognosis of Alzheimer's Disease

Adeel Ahmed Abbasi, Nasrollah Moradikor *

International Center for Neuroscience Research, Institute for Intelligent Research, Tbilisi, Georgia;
E-Mails: abbasiad2022@gmail.com; moradikor@neuroscience.edu.ge; ORCID: 0000-0001-9905-6845

* **Correspondence:** Nasrollah Moradikor; E-Mail: moradikor@neuroscience.edu.ge; ORCID: 0000-0001-9905-6845

Academic Editor: Fabrizio Stasolla

OBM Neurobiology
2026, volume 10, issue 4
doi:10.21926/obm.neurobiol.2604354

Received: July 13, 2026
Accepted: September 21, 2026
Published: October 09, 2026

Abstract

Alzheimer's disease (AD) impacts the brain in multiple ways and has varied clinical features and progression. Sex differences exist in the epidemiology and fundamental biology of AD. Machine learning (ML) tools can integrate and analyze multiple biomarkers, improving AD diagnosis and prognosis. However, machine learning tools underuse and under-explore predictive modeling of sex differences. This translational narrative review synthesises the existing literature on studies that explore sex differences in Machine Learning models that utilise data collection techniques that incorporate biomarkers from Positron Emission Tomography (PET) scans, Magnetic Resonance Imaging (MRI) scans, Cerebrospinal Fluid (CSF), serum assays, genetic variants, including single-nucleotide polymorphisms (SNPs), and Electroencephalography (EEG). We emphasize the role of sex in biomarker manifestations which include but are not limited to: the dissimilarity of amyloid and tau in PET imaging, the effects of sex in structural and functional brain alterations in MRI, sex-specific alterations in cerebrospinal fluid (CSF) composition (e.g., A β 42 concentration, total tau, and phospho-tau) and the alterations in peripheral and systemic inflammatory and metabolic blood markers, the modulation of genetic risk particularly in relation to APOE and some of the single nucleotide polymorphisms (SNPs), and the variability in sex differences in EEG network



© 2026 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

disruption and/or modularity. When sex is incorporated as a biological variable or when sex-stratified models are created, new ML methods, such as deep learning, ensemble techniques, and multimodal fusion frameworks, demonstrate promising diagnostic and prognostic capabilities. Many studies, however, remain constrained by modest datasets, a lack of external validation, and limited interpretability, thereby limiting clinical applicability. This review highlights the importance of sex-aware modeling techniques to advance precision medicine in AD. We offer several methodological suggestions, including analysing disaggregated sex data, aligning data across multiple approaches, using explainable AI, and including longitudinal data. Filling these gaps may help develop ML tools that offer accurate, fair, and clinically useful early detection and prognosis of AD across a wide range of populations.

Keywords

Alzheimer's disease; machine learning; multimodal biomarkers; diagnosis; artificial intelligence

1. Introduction: Reframing Alzheimer's Through a Sex-Aware AI Lens

Alzheimer's Disease (AD) is the leading cause of global dementia and is becoming a significant and multifaceted public health concern. The increasing prevalence and severe clinical and biological variability of Alzheimer's disease exemplify the growing burden of the disease [1, 2]. Cognitive decline, neuropathology, and intervention response can drastically differ in patients with AD [3]. Genetic susceptibility, environmental exposure, ageing, and a variety of biological differences, particularly sex, contribute to this variability [4]. Sexual dimorphism in Alzheimer's Disease also extends beyond epidemiological data, such as the majority proportion of affected women, which constitutes a more profound distinction in the pathobiology of the disease [5]. Sex has been shown to affect tau and amyloid pathology, neuroinflammation, synaptic susceptibility, and the brain's network organization [6]. Menopause, related to the decline in estrogen, is believed to be linked with the acceleration of neurodegeneration in females.

In contrast, males may have different, yet vascular- and metabolic-risk-related patterns [7]. These differences suggest that sex may be one of the most important factors influencing disease initiation, progression, and biomarker expression, rather than an extraneous variable [8]. Though the techniques for ML in AD diagnosis and prognosis have been improving, most of the suggested models are sex-agnostic [9]. When sex is incorporated, studies routinely treat it as a simple covariate and rarely model it directly as a biological interacting component [10]. Imbalanced sex representation in training and test data also biases and distorts outcomes. Many available machine learning models also show little sex-dependent relevance, further diminishing their translational relevance and generalisation to disparate populations. These machine learning models fail to quantify the underlying patterns and convey them in an interpretable manner adequately [10]. There is an urgent need to move from a conventional emphasis on separate biomarker identification to a more holistic, sex-aware, multimodal intelligence [11]. Analyses of biomarkers from neuroimaging, fluid assays, genetics, and electrophysiology often simplify these inputs by treating

them as independent. This approach corrects that by considering interactions among these inputs and, importantly, the many ways these interactions can change by sex. While we identify new ways sex-aware incident modeling strategies can be useful, we can leverage them within multimodal ML frameworks to identify hidden disease pathways, improve predictive scores, and optimize precision medicine for AD [12]. Therefore, the purpose of this narrative review is to gather available data to understand better the sex-based distinctions in ML models, including several interconnected biomarkers, such as MRI, PET, CSF, serum, and genetic changes, including SNPs, as well as EEG, used in the diagnosis and prognosis of AD. We also intend to find critical gaps in current methods, spotlight new sex-focused analytical approaches, and offer a translational pathway toward building biologically informed and more equitable AI tools in neurodegenerative research.

2. Method

This translational narrative review examines sex differences in machine learning (ML) models incorporating multimodal biomarkers for Alzheimer's disease (AD). We searched PubMed, Scopus, and Web of Science for studies published from January 2010 through December 2025. The search strategy was designed to identify studies addressing AD biomarkers, ML methodologies, multimodal data integration, and sex-related differences. Search terms were organized into four concept groups: AD-related terms ("Alzheimer's disease" OR "Alzheimer disease" OR "AD"), biomarker and modality terms ("PET" OR "positron emission tomography" OR "MRI" OR "magnetic resonance imaging" OR "CSF" OR "cerebrospinal fluid" OR "serum" OR "blood biomarkers" OR "genetic" OR "SNP" OR "EEG" OR "electroencephalography"), ML-related terms ("machine learning" OR "deep learning" OR "artificial intelligence" OR "multimodal" OR "multimodal fusion"), and sex-related terms ("sex differences" OR "sex-specific" OR "sex-stratified" OR "gender"). Within each concept group, related terms were combined using OR, whereas the four concept groups were combined using AND. Studies were included if they: (1) were published between January 2010 and December 2025; (2) investigated human AD or clinically relevant AD populations; (3) evaluated AD-related biomarkers or biomarker modalities, including PET, MRI, CSF, blood/serum biomarkers, genetics/SNPs, or EEG; (4) applied ML, deep learning, artificial intelligence, or multimodal data-integration approaches; and (5) reported, analyzed, or discussed findings related to biological sex, sex-specific performance, sex-stratified analyses, or sex-related differences in biomarkers or ML model performance. Studies were excluded if they were unrelated to AD, did not involve ML-based analysis, lacked relevant biomarker or multimodal data, focused exclusively on non-human models without translational relevance, or did not provide information relevant to sex differences. We did not automatically exclude studies using a single modality, but considered them primarily when they provided evidence directly relevant to understanding sex differences or informing multimodal ML approaches. We identified additional relevant studies by screening the reference lists of included articles and relevant reviews. We narratively synthesized the selected literature to identify patterns in sex-related biomarker differences, sex-specific ML performance, and approaches for integrating multimodal biomarkers. These findings informed the development of a translational framework for sex-informed multimodal artificial intelligence in AD. Given the narrative nature of this review and the heterogeneity of the included studies, we did not perform a formal meta-analysis or quantitative statistical synthesis.

3. Conceptual Framework: Sex as a Biological Variable in Multimodal AI

A detailed understanding of how sex differences impact the study of Alzheimer's disease and the development of multimodal machine learning (ML) algorithms proceeds with an understanding of sex as distinct from gender. Sex comprises genetics (XX, XY, and combinations thereof), endocrine, and reproductive characteristics; gender includes social position, practices, and behaviour [13]. In biomedical AI, this distinction is often blurred, leading to models that fail to capture biological variability effectively [14]. In the context of modelling using biomarkers, sex is essential because it contextually determines molecular pathways, neural structures, and susceptibility to diseases such as Alzheimer's. At the same time, it can be argued that gender has a secondary impact that can alter disease susceptibility, mainly through behavioural and environmental factors like the available resources and the social structures a person or population is exposed to. Thus, from this perspective, sex is the primary factor of the two and is crucial in modelling the mechanisms and outcomes of Alzheimer's disease [8].

3.1 Mechanistic Basis of Sex Differences

From the perspective of modelling biomarkers, sex contributes the most specificity to the variables of molecular pathways, neural structures, and predisposition to various illnesses, including Alzheimer's disease. Gender makes a mainly secondary contribution, primarily through behaviour and environment, such as available resources and the social structures. With that in mind, sex is the more significant of the two and is vital in modelling the mechanisms and impacts of Alzheimer's disease [15]. The decreased levels of estrogen during menopause can lead to amyloid and tau pathology, in addition to metabolic dysregulation in the brain, creating a temporal and increased vulnerability for females [16]. Sex differences in immune responses in the central nervous system exist. These differences, including microglial activation, cytokine release, and inflammatory signaling, likely modify the timing and pattern of the disease [17]. Sex differences in the effects of endothelial function, blood-brain barrier integrity, perivascular spaces, and other cardiometabolic risk factors on the blood-brain barrier and neurodegeneration may be partly captured by diverse fluid-based (CSF, blood, and other body fluids) biomarkers and a variety of neuroimaging findings [18]. These differences may alter brain structure and function, as observed with imaging tools such as MRI, and may modulate amyloid and tau pathologies. Furthermore, these mechanisms interact, shaping integrated biomarker networks across modalities [19].

3.2 Toward a Sex-Aware Multimodal Fusion Framework

Standard ML models generally treat multimodal biomarkers such as PET, MRI, CSF, serum, genetic variants, and EEG as separate components, using basic fusion techniques (such as early or late fusion) to combine them [19]. This method misses that the relationships between modalities may also be sex-dependent [20]. We propose a sex-aware multimodal fusion pipeline that encodes sex as a feature rather than a descriptor and adjusts feature extraction and weighting accordingly. Model architectures (e.g., attention layers, graph-based models) enable models to construct and learn relationships among multimodal biomarkers [21]. This allows modality contributions to differ by sex and disease stage. Merging sex-dependent submodels with common representations encapsulates both general and unique behaviour [22]. This framework posits that sex differences

are not in biomarker mutations, but in how sex shapes relationships across biomarker modalities. Sex differences may underlie the relationships between amyloid burden (PET) and cognitive decline, and between genetic risk variants and EEG networks, in males and females, respectively [23]. Consequently, models that omit interaction effects will miss key disease signatures. By framing sex as a biological form of multimodal integration rather than a peripheral covariate, this framework will enhance our understanding and enable the development of more precise machine learning (ML) models for Alzheimer’s disease (AD) diagnosis and prognosis [24] (Figure 1).

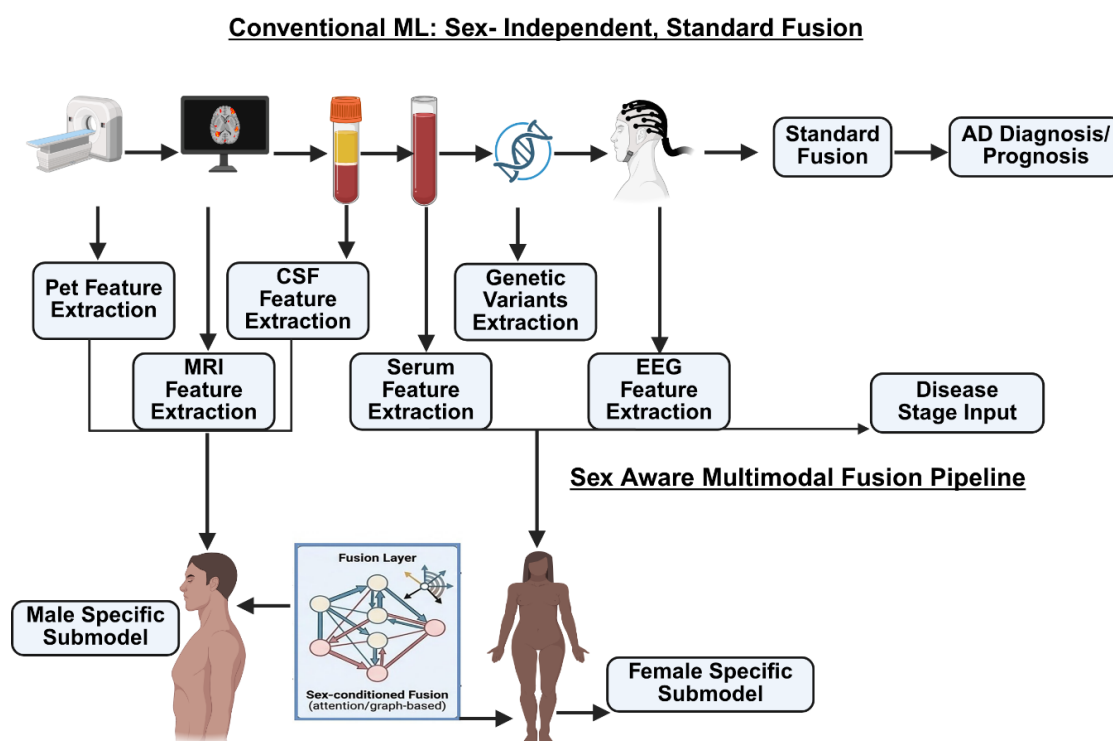


Figure 1 Sex-Aware Multimodal Fusion Framework for Diagnosis and Prognosis of Alzheimer’s disease (Figure created with BioRender). This figure differentiates typical machine learning (ML) techniques from the described sex-informed multimodal fusion pipeline. Traditional ML combines biomarkers from modalities such as PET, MRI, cerebrospinal fluid (CSF), serum, genetic biomarkers, and EEG. A standard ML fusion technique is used that does not account for sex, resulting in generalised diagnostic/prognostic outputs. In contrast, the lower panel shows a sex-informed approach that incorporates sex differences during feature extraction, weighting, and multimodal input fusion. Sex-conditioned fusion layers, such as attention or graph-based models, capture cross-modal interactions affected by sex. The model integrates both male and female submodules while retaining common shared representations. This enhances the ability to learn both overlaps and sex-divergent disease patterns. This design enables the model architecture to account for sex-related biomarker-disease pathway relationships in AD, thereby improving prediction accuracy, interpretability, and biological relevance.

4. Multimodal Biomarkers in AD: Beyond Isolated Signals

In Alzheimer's Disease (AD), traditional biomarkers have included neuroimaging, fluid biomarkers, genetics, and electrophysiology. Studies have implemented them in isolation. This reductionist analytical framework overlooks that AD is a systems-level disorder in which molecular, structural, and functional changes unfold within a densely organized, interconnected network [2, 25]. Examining their method from a multimodal perspective offers the possibility to both increase the accuracy of prognosis and diagnosis and to elucidate how their interrelationships are modulated by sex. Sex differences may reflect shifts in the coupling/decoupling of the various modalities rather than changes in the concentration of a single biomarker [26].

4.1 Neuroimaging Biomarkers

Various neuroimaging modalities, including Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), provide macro-level perspectives into the pathogenesis of Alzheimer's Disease (AD) [27]. PET imaging allows for the indirect in vivo measurement of amyloid- β and tau deposition. Meanwhile, MRI captures structural brain atrophy, cortical thinning, and alterations in the connectivity of the brain's large-scale networks [28]. Imaging studies have noted different trajectories of disease based on sex. At similar clinical stages, females show accelerated hippocampal atrophy and greater tau deposition. In males, there may be a greater association with vascular pathology and decline [29]. Outside these independent observations, another important emerging insight concerns the differences in the relationships between PET/MRI markers in men and women. For example, equal numbers of participants in neuroimaging show the same amount of PET Amyloid signal, but women may show greater degradation compared to men. These findings might indicate greater susceptibility and/or a lower threshold for resiliency [30]. These results illustrate a propagated pathology across brain systems that differs between males and females. This helps explain how pathology burden is distributed across brain systems and how it contributes to overall disease burden [31].

4.2 Fluid Biomarkers

Fluid biomarkers reveal molecular pathological changes and systemic responses to disease by analysing CSF and peripheral blood (serum or plasma). Some of the main fluid CSF biomarkers include A β 42, A β 40 (and the A β 42/A β 40 ratio), total tau (t-tau), and phosphorylated tau (p-tau), alongside emerging synaptic and neuroinflammatory markers. These biomarkers reflect amyloid plaque deposition and neurofibrillary degeneration, synaptic dysfunction, and glial-mediated inflammatory responses. The serum biomarkers increasingly capture neurodegeneration, inflammation, and metabolic dysfunction [32]. These markers show sex-based differences in both baseline levels and their longitudinal changes. For instance, females may show higher tau-related pathology at the same amyloid levels [33]. Inflammatory and metabolic profiles in serum often vary significantly between the sexes [33]. These observations suggest that, to avoid misuse, biomarker thresholds and diagnostic cutoffs should be sex-specific [34]. An original and relatively overlooked viewpoint is that peripheral biomarkers may better align with sex-specific systemic factors, such as immune responses, hormone signaling, and cardiometabolic health. Therefore, serum-based

markers might complement, and even surpass, CSF measures in identifying sex-dimorphic disease mechanisms that affect regions outside the central nervous system [35].

4.3 Genetic and Genomic Markers

Single-nucleotide polymorphisms (SNPs) and polygenic risk scores allow researchers to measure genetic susceptibility and predict the risk associated with Alzheimer's Disease [36]. Nevertheless, the effects of genetic polymorphisms differ by sex. For instance, the apolipoprotein E (APOE) $\epsilon 4$ allele shows sex-modified genetic susceptibility, with females demonstrating a disproportionate increase in both risk and progression rate compared to males [37]. Sex adds complexity not only to single-gene effects but also to multiple-gene and gene-environment interactions. It shapes how lifestyle, hormonal, and comorbidity factors interact with genetic risk. This informs the idea of sex-dependent penetrance, that the same mutation can result in different phenotypes based on sex [38]. For ML models, this means that features of a genetic background traditionally treated as invariant predictors should, in genetics, be treated as predictors whose values change in accordance with sex and their relationships with other domains of biomarkers [39].

4.4 Electrophysiological Biomarkers (EEG)

Dynamic EEG can continuously quantify brain activity, including oscillations, synchrony, and network efficiency. In Alzheimer's disease, EEG shows weakened and slowed dominant oscillations, as well as reduced interconnectedness and complexity of neural signals [40]. EEG patterns differ between the sexes, and discrepancies in oscillatory and network architecture may reflect distinct mental functions. For example, females may show earlier and/or accelerated disruption in some frequency bands, whereas males may exhibit different network compensation or decline [41]. A particularly new perspective is that EEG might be the most sensitive method for early detection of sex-specific functional changes that precede measurable structural or molecular changes. EEG may also be the best method for linking molecular pathology to cognitive function and is highly important in multimodal ML frameworks [42].

4.5 Integrative Perspective

Overall, these results suggest that the multimodal biomarkers should not be conceived of as parallel channels of information, but as elements of an interacting, sex-modulated network [43]. Biomarker research on AD will trend toward integrating frameworks to model how genetic susceptibility alters the molecular pathology of disease; how the pathology accelerates structural neurodegeneration; how neurodegeneration modifies the brain's functional dynamics; and how sex influences these processes [44].

5. Quantitative Evidence Comparing Sex-Agnostic and Sex-Aware Models

Although direct head-to-head comparisons of sex-agnostic and sex-aware models on ADNI data remain limited, some evidence provides quantifiable measures to assess the performance of sex-stratified models [45]. In a supervised machine learning study on ADNI data, sex-stratified models distinguished different clusters of AD subtypes in men (accuracy = 0.85, AUC = 0.83) and in women (accuracy = 0.81, AUC = 0.81). Sex-specific subtype clusters were homogeneous, and genetic

features were discriminative [46]. These results show that separate analysis of male and female biological samples can differentiate sex-specific biological subtypes. Another study on sex-specific DNA methylation changes related to Alzheimer's Disease shows that sex-specific logistic regression models with DNA methylation risk scores gave males an AUC of 0.70 and females 0.74, while using age alone (AUCs of 0.64 and 0.68 for males and females, respectively) led to worse results [47]. This shows that sex-specific biomarker panels can detect diseases and medical conditions better than general models. In multi-modal modeling, ClinPatch-AD is a clinically informed, transformer-based model that incorporates sex as a clinical feature [48]. It achieved comparable performance between men (AUC = 0.942) and women (AUC = 0.957), suggesting that this framework uses sex as a supporting factor rather than a decisive component. The authors evaluated this model on the OASIS dataset rather than ADNI. Thus, more systematic studies are needed on ADNI to compare both datasets more precisely [49]. Overall, the presented results suggest that the diagnostic accuracy of sex-stratified and sex-aware models improves, and it is also possible to uncover sex-specific biological pathways related to the subtypes [50]. The lack of studies that directly compare sex-agnostic and sex-aware models on the same ADNI cohort using the same methods is a significant limitation of the current research. Future research should examine whether the added complexity of sex-aware models yields clinically meaningful improvements in prognostic accuracy [51].

5.1 Trade-Offs in Sex-Stratified and Multi-Task Models

Sex-specific models are built separately for males and females. Each model learns different sex-specific phenomena. Sex-specific models may find sex-specific biological pathways that would be hidden when combined [52]. This approach has disadvantages, namely reduced data when the dataset is split. When a dataset is split by a variable, in this case sex, each model has less data. Additionally, this reduces confidence and increases the risk of overfitting, especially with high-dimensional and rare data [53].

Furthermore, sex-stratified models are very expensive to train. They require twice the training resources, and researchers tune hyperparameters independently for each sex. These model complexities mean that they may learn sex-associated confounders (e.g., hormonal status, BMI) rather than real biological differences during training [54]. This, in turn, makes the models' findings harder to interpret. Finally, they cannot model interactions between sex and age and/or the APOE genotype. This limits them even further. Multi-task learning (MTL) models can be trained on all these outcomes, and more, to predict all outcomes of interest for both sexes [55].

MTL aids generalization by using the intersection of multiple tasks. If one task is poorly defined, MTL uses other tasks to identify mislabeled or missing data. MTL uses one shared set of parameters to learn multiple tasks. However, using MTL encourages a trade-off. MTL balances loss functions across tasks, risking negative transfer if the tasks are poorly correlated [56]. Task non-correlation is a potential risk in AD, due to varying biomarker trajectories and clinical outcomes by sex. Designing, training, and interpreting multi-task learning (MTL) models requires careful consideration, including selecting the right architecture and choosing an appropriate loss-weighting strategy [57]. If a model's shared representations are dominated by the majority sex or the more predominant task, MTL models may even obscure sex-specific patterns. A relatively new approach, sex-aware multi-task modeling, adds sex as an interacting variable within the architecture and enables the modeling of simultaneous shared and sex-specific representations [58]. These solutions require larger

datasets and more complex architectures, and they require more effort to understand sex-specific parameters. The choice of method depends on the research question, dataset size, and the clinician's goal [59]. Future research should focus on creating more resources and making more datasets available, then using them as benchmarks to determine the most efficient method in sex-specific AD biomarker research [59].

6. Machine Learning Approaches: Are Models Truly Learning Biology or Bias

High-dimensional data from neuroimaging, fluid biomarkers, and electrophysiology are combined using advanced ML algorithms for biomarker-based diagnosis and prognosis of Alzheimer's disease AD [60]. The question remains: what are models of the fundamental disease biology actually learning? Are they capturing biologic disease processes, or are they learning bias in institutionalised datasets, particularly those defined by sex [44].

6.1 Traditional ML vs Deep Learning

In AD research, support vector machines, random forests, and logistic regression have been used because they are traditional machine learning methods that are easy to interpret, robust, and effective for small datasets [61]. Typically, PET, MRI, CSF, serum, or EEG results are associated with custom features. Although models are often validated in experimental settings, the models described here are limited because they cannot capture important nonlinear relationships and cross-modal dependencies that characterize disease complexity [62]. Deep learning (DL) models, such as convolutional neural networks (CNNs), recurrent neural networks (RNNs), and transformer-based architectures, can learn intricate, hierarchical, and nonlinear patterns from unrefined or minimally processed input data [63]. Because they can manage complex interactions across modalities, these methods can be used effectively for multimodal integration. Nevertheless, in AD cohorts, particularly for sex representation, large, well-distributed datasets are typically lacking, which impedes cross-modality integration [64].

6.2 Multimodal Fusion Strategies

Multimodal biomarkers have been among ML's most notable contributions to AD. For instance, models integrating structural MRI and FDG-PET have achieved classification accuracies of 90%, substantially outperforming single-modality approaches. Similarly, AI-driven frameworks combining patient history, MRI, neuropsychological tests, and APOE genotype have successfully predicted PET-estimated A β and tau status, with tau prediction AUROC improving from 0.53 to 0.84 when all multimodal features were included [65]. Sex-stratified multimodal models have further revealed distinct AD subtypes, with genetic-based models identifying subtype clusters comprising 34% of men and 47% of women with AD [66]. Fusion approaches include early fusion, where multiple modalities are fused at the model input during training [67]. While this approach is simple and efficient, it assumes equal feature relevance and often overlooks modality-specific characteristics and sex-related differences. With late fusion, independent models are built and trained for each modality, and their outputs are aggregated (e.g., averaged or voted upon) [68]. While this retains modality-specific information, it may overlook cross-modality interactions. Hybrid and attention-based models are sophisticated frameworks that combine modalities at intermediate levels, using

either attention mechanisms or gating functions [69]. These models can holistically evaluate cross-modal contributions and improve cross-linking between modalities. Building on the current advancements, an important limitation, especially considering that the majority of models either completely exclude the inclusion of sex or, if included, consider sex as a static covariate, is that the majority of models do not integrate sex as a relational and intersecting element within the network [70].

6.3 Sex-Aware ML Paradigms: Moving Beyond Covariate Adjustment

Sex-stratified models involve separate models for males and females to avoid confounding in pooled data when identifying sex-specific patterns. In response, some innovative models now include sex in their design [71]. This approach is simple but may reduce statistical power and underestimate shared characteristics. Multi-task learning, where sex branches a shared backbone model, learns common representations, while sex-specific branches capture divergent patterns [72]. This framework is especially encouraging for multimodal data where shared biology and sex-specific variation are balanced. Causal AI approaches aim to build models that identify causal relationships between variables, rather than relying on correlations [73]. By modelling sex causally, such approaches identify sex's effects on relationships among genetics, biomarkers, and clinical outcomes, suggesting a more biologically informed framework for understanding AD [74].

6.4 Bias Amplification in AI Systems

In the context of ML applications, bias amplification, the tendency of models to reinforce existing biases found within the training data, is a high-priority concern. In AD research, this can occur because of unequal sex representation, data quality discrepancies, or sex-related confounding variables (e.g., age, education, and comorbidities) [75]. Consequently, models may perform well across demographics but have lower accuracy or systematic biases toward one sex. Additionally, when sex-specific biological differences are not modelled, ML systems may misinterpret meaningful sex differences as noise or as irrelevant/secondary characteristics. This not only reduces predictive performance but also lowers interpretability and clinical trust [59].

6.5 Toward Biologically Informed AI

To overcome these challenges, implement ML strategies that are species- and sex-informed, incorporate biological knowledge, and integrate domain and computational expertise. These models need to demonstrate the following capabilities: capturing non-linear, cross-modal relationships; modelling the interrelationships among species and sex as modifiers of these relationships; and reducing bias through balanced datasets, stratified validation, and rigorous evaluation metrics [76]. The goal moves beyond improving prediction accuracy to improving ML models' ability to represent the true biological complexity of AD. In turn, this results in more accurate, equitable, and clinically useful insights [77].

7. Cross-Modal Interactions: The Missing Link in Sex Differences

A major drawback of the current research on biomarkers in Alzheimer's disease (AD) is the juxtaposition of the modalities, neuroimaging, fluid markers, genetics, and electrophysiology, each

treated as an independent entity from the others. Much disease-relevant information is ascribed to an individual biomarker [78]. However, AD is a network disorder, characterised by pathology that originates from interactions across different biological scales, many of which are sex-dependent. An important yet largely unexplored aspect of precision neurology is understanding how different modalities interface with one another rather than acting in isolation [79].

7.1 Sex-Dependent Cross-Modal Relationships

Both positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers capture fundamental pathologies of Alzheimer's disease (AD) via PET imaging of regional distributions of amyloid and tau pathology and via neuroinflammatory responses in the CSF. Importantly, their agreement is not always consistent [32]. Research shows that PET-CSF discordance can vary by sex, with some cases in which females may present with augmented tau PET imaging and CSF pathology that is similar or less prominent [80]. This could indicate sex-specific differences in protein clumping, clearance, and blood-brain barrier function. These disparities challenge the notion of substitutable biomarkers and underscore the need for models that account for and incorporate sex-related variation across methods [35].

7.2 MRI-EEG Coupling

Studies of structural versus functional alterations in the brain have often been conducted in isolation. However, studying their interrelationships would be critical to developing our understanding of disease progression. In MRI, degeneration is visualised in the brain's anatomical regions, whereas in EEG, it is observed on a time scale [81]. To some extent, we can assume that structural atrophy varies by sex. Some studies suggest a stronger association between structural atrophy and functional decline in males. In females, functional preservation is more pronounced and may include enhanced compensatory mechanisms [82]. These differences imply that resilience and compensatory processes in the brain may differ by sex, and that MRI and EEG collaboration can clarify declines previously obscured [83].

7.3 Genetics-Biomarker Modulation

Genetic risk factors, including single-nucleotide polymorphisms (SNPs) and polygenic risk scores, interact with downstream biomarker expression and vary by sex [84]. Sex-differentiated hormonal and/or immune conditions may enhance or diminish the influence of genetic variation on amyloid and tau pathology and neuroinflammation [85]. This produces a multifaceted situation in which the roles of genetics in biomarkers vary across sex, leading to distinct biological pathways. Whether such relationships appear in ML models suggests they may represent important predictive signals or erroneously depict causal mechanisms [39].

7.4 Network-Based Interpretation of Disease Progression

This summarizes the changes in AD pathology. The edges represent fluid interactions, while nodes represent biomarkers [86]. Sex does more than change node values, such as biomarker levels; it reflects more than simple numerical shifts. It changes the whole structure. It reconfigures the overall structure, changing the strength, direction, timing, and function of interactions between

modalities [87]. Perspectives aligned with systems biology and graph-based modeling view disease progression as a series of interconnected transitions through a network. Most importantly, such networks may differ fundamentally between males and females, even when single biomarker levels are comparable [88].

7.5 Proposed Model: Sex-Specific Biomarker Interaction Networks

To address these challenges, we propose sex-specific biomarker interaction networks, where the following holds: Each modality (PET, MRI, CSF, serum, genetics, EEG, etc.) is represented as a node or a set of nodes; edges encode statistical, functional, or causal relationships amongst the modalities; network topology is separately or conditionally learned for each sex, and Temporal dynamics that differentiate disease progression are included [89]. This method can be executed utilising graph neural networks, multimodal transformers, and other interaction-aware machine learning architectures. Importantly, it facilitates the discovery of sex-specific pathways rather than relying solely on feature importance in a pooled model [90].

7.6 Implications: Distinct Disease Pathways, Not Just Different Levels

This model has major ramifications. If sex differences exist in cross-modal interactions, then AD cannot be regarded as a single condition that manifests with variable severity. Instead, it must be viewed as a condition with partially distinct biological pathways in males and females [91]. This departs from existing diagnostic thresholds, biomarker evaluations, and treatment approaches. From a translational perspective, integrating sex-based interactions into ML applications would enhance diagnostic accuracy and reduce biomarker discordance, enable sensitive cross-modal signatures for early detection, and improve personalized, sex-focused treatment strategies [89]. Overall, cross-modal interactions could bridge gaps in understanding sex differences in AD, and integrating them into ML would be an essential step toward precision-aimed, biology-inspired neuroscience [92].

8. Prognostic Modelling and Disease Trajectories

One aspect of Alzheimer's Disease that has become a major focus for machine learning (ML) practitioners is prognostic modeling, with an emphasis not only on identifying the presence of the disease but also on estimating its future progression [93]. This includes projecting the progression from mild cognitive impairment (MCI) to AD, predicting decline, and identifying those in the cohort at risk of rapid advancement [94]. Nevertheless, new data indicate that these patterns are not consistent and are deeply influenced by sex, prompting a need for sex-conscious predictive models [95].

8.1 Prediction of MCI → AD Conversion

Arguably, the most clinically applicable example of MCI and ML is predicting early AD in MCI patients. In the context of MCI-to-AD conversion, integrated multimodal models combining imaging data (e.g., PET and MRI) and structural data (e.g., CSF, genomic, and EEG) yield impressive accuracy [96]. Conversion risk is not evenly distributed by sex. For instance, female subjects tend to show greater progression across varying comorbid burdens. This may reflect an increased vulnerability to

tau pathology or a decreased cognitive reserve [97]. Most existing models draw on pooled datasets, assuming that all data exhibit uniform patterns of advancement across the studied populations. As a result, sex-specific risk profiles decrease, and individual patient prediction is, at best, suboptimal [98].

8.2 Prediction of Cognitive Decline Rates

Rather than outputting only binary conversions, ML models increasingly emulate the progressive, multidimensional decline of cognitive functions, including memory, executive functions, and global functioning [99]. These models often use longitudinal data and time-series approaches to depict disease progression, while accounting for sex differences [100]. For example, despite similar cognitive performance at baseline, females may experience a more rapid cognitive decline after symptom onset. In contrast, males may demonstrate a more noticeable, yet consistent, cognitive decline [101]. These differences suggest that the rate of decline cannot be solely attributed to the pathology burden, but also to sex-related resilient states and compensatory mechanisms [79].

8.3 Sex-Specific Progression Patterns

The assumption that there is a single typical pathway for the progression of Alzheimer's Disease is being increasingly questioned. Disease progression appears to occur via multiple pathways and may differ systemically between men and women. For instance, females may show earlier increases in tau biomarkers, as well as differences in the order of pathological changes and in the relationship between biomarker presence and the onset of clinical symptoms [102]. Recognizing these trends is necessary for accurate prognosis and customized interventions for individual patients. To capture these trends, researchers increasingly use longitudinal machine learning (ML) models incorporating recurrent neural networks (RNNs), temporal convolutional networks, and survival analysis models [103]. These models capture the evolution of multimodal biomarkers over time and describe disease progression across stages. However, most longitudinal models do not incorporate sex as a variable and, as a result, do not consider whether relationships between biomarkers may differ across populations [100]. Integrating sex stratification, sex-based interaction terms, or sex-based modules can improve these models to capture the diverse temporal trends [20] (Figure 2).

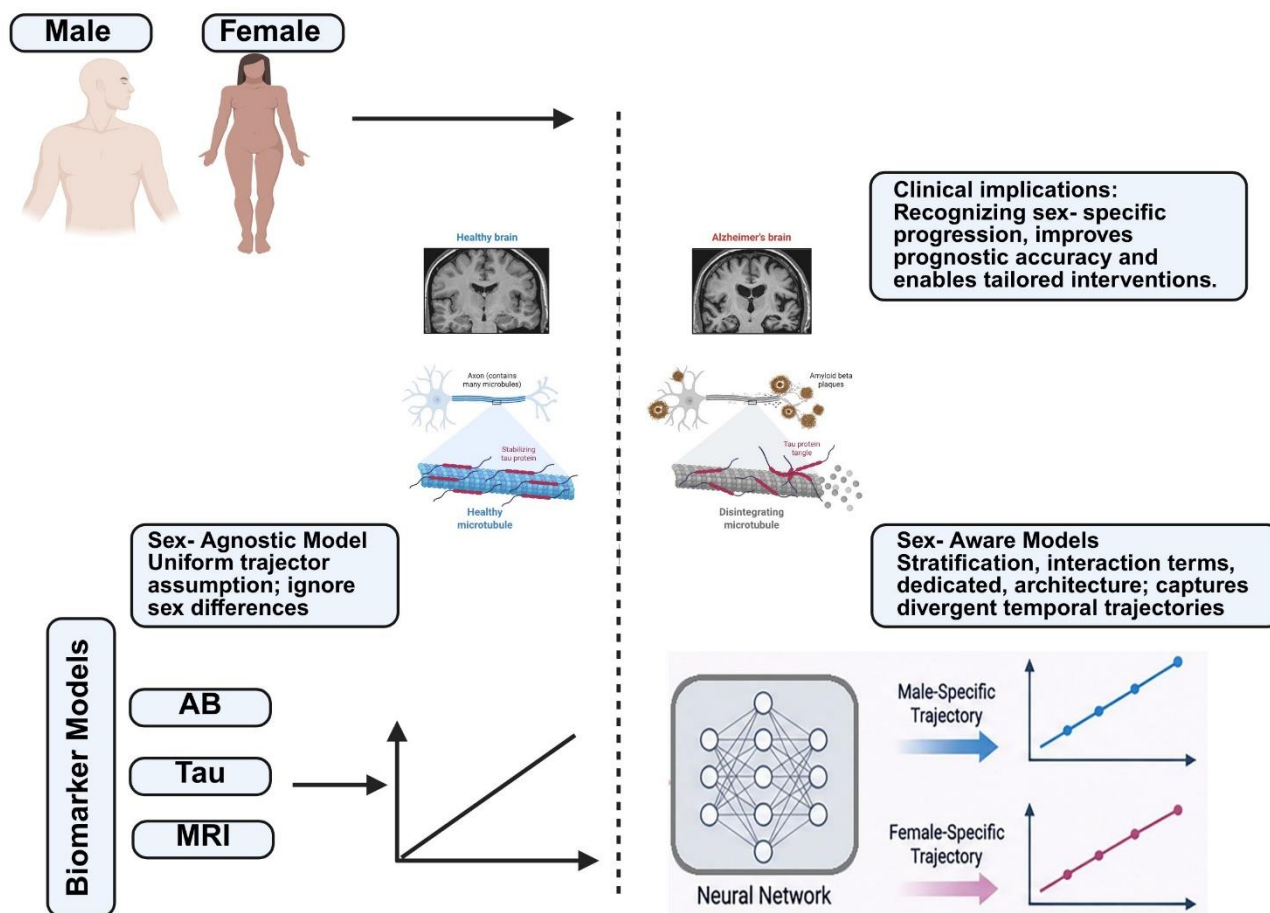


Figure 2 Sex-Specific Progression Patterns in Alzheimer's disease (Figure created with BioRender).

The diagram demonstrates the divergence in the progression of disease between males and females across key biomarkers. In the male population, disease progression occurs through the $A\beta$ step, then the tau step, followed by structural brain changes observed on MRI, and finally the neurodegeneration step, which leads to the subsequent clinical step. In females, while the amyloid accumulation pattern remains consistent, evidence suggests that tau pathology may progress at a differential rate, potentially contributing to sex-specific differences in clinical presentation. However, the extent to which these biomarker-level differences translate into significant sex-specific clinical progression remains an area of active investigation. The lower panel contrasts various modelling techniques, highlighting both sex-dependent changes and distinct sex-specific correlations among biomarkers and clinical endpoints. Sex-independent modelling assumes that the disease and integrated biomarkers ($A\beta$, tau, MRI, signs, and symptoms) change consistently across all sexes. For the sake of simplicity, this approach ignores sex-related differences at the expense of a thorough understanding of the complexities involved in the disease progression. Sex-aware models, by contrast, use stratification, interaction terms, and bespoke architectures such as neural networks to capture male- and female-specific trajectories. Accounting for differences in biomarker and temporal dynamics between sexes improves prognostic accuracy and enables personalised interventions.

8.4 Novel Perspective: Trajectory-Based Clustering Differs by Sex

Trajectory-based clustering is a novel biomarker- and cognitive-decline-based grouping methodology that combines promising new research with existing cognitive frameworks. Rather than using traditional diagnostic classifications, this methodology emphasises subcategories based on disease progression [104]. Additionally, evidence suggests these clusters may be biased toward one sex or may be sex-specific. For example, among the clusters that consider clinical progression, the Vascular and Metabolic clusters are typically more prevalent in males. The same clinical case may have different implications by sex [105]. This leads to an important conclusion: sex affects how quickly disease progresses and how disease pathways are structured. Including sex-sensitive strategies in prognostic modeling offers several major advantages: more accurate prediction of individual disease trajectories, improved identification of the most at-risk populations, and better classification for clinical studies and treatment strategies [106]. Emphasizing dynamic, sex-informed prognostics rather than static prognostics in AD trajectory modeling reflects progress toward more targeted prognostics in AD, extending beyond biomarker profiles and linking them to the underlying pathophysiology [107].

9. Explainable AI and Interpretability in Sex-Specific Models

When machine learning (ML) is used for Alzheimer's disease (AD) research, model generalizability is not the only criterion for establishing clinical viability. Achieving interpretability in a decision-making model that handles intricate logical nuances is paramount. Clinicians and researchers must be able to enter the model and understand the reasons behind each prediction/decision the system makes [108]. This concern deepens in sex-specific modelling. Here, reliable and just conclusions require identifying and unraveling algorithmic biases that conflict with true biological differences. Interpretation is integral for closing the gap between computational models and practical clinical use. Understanding models is critical in advanced scenarios such as the early diagnosis or prognosis of AD [109]. Explicit processes in explainable models can frame predictions in terms of the mechanisms described for a given disease. This improves prediction reliability, i.e., predictions are based on biological phenomena rather than spurious correlations [110]. In this context, explainability is not a technical option but a clinical requirement, as interpretability in model fairness and generalizability can uncover hidden biases, such as sex [111].

9.1 Explainability Tools in Multimodal ML

Researchers have developed a variety of methods to interpret sophisticated ML models, including SHAP (Shapley Additive exPlanations). This approach measures each element's impact on the overall prediction through cooperative game theory [112]. In multimodal AD models, SHAP determines the overall contribution of individual biomarkers, including amyloid burden, MRI-based atrophy, and CSF tau, in risk estimation. Unlike SHAP, LIME (Local Interpretable Model-agnostic Explanations) approximates complex models and provides case-specific explanations by using simpler, interpretable models near a prediction [113]. This is especially helpful for interpreting personalised predictions by gender in male and female patients. Attention maps in deep learning models show which inputs (brain regions, signal characteristics, or signal types) the model values [114]. These maps show advanced spatial and functional patterns of sex differences, including

variation in hippocampal atrophy and cortical connectivity. Collectively, these methods facilitate the perceptive integration of population-scale and patient-specific data, which is critical for precision medicine [115].

9.2 Identifying Sex-Specific Feature Importance

Explainable AI clarifies how sex-based characteristics differ in relevance across domains. Analyzing model performance for males and females independently reveals which biomarkers are differentially predictive by sex, why some biomarkers may be more relevant for one sex than the other, and how the predictive importance of different modalities is sex-interactive [39]. For instance, tau-related biomarkers could be predominant in females, whereas in males, features captured through imaging of structures and/or vasculature may carry more weight. This type of work takes a step toward elucidating sex-specific pathophysiological frameworks of the disease and may inform the design of more targeted diagnostic approaches [30]. An important emerging point is that, for a given ML model and prediction, the model may rely on differentiation regardless of the number of valid biomarkers used, and it may show similar accuracy across both groups. This suggests the model learns and uses different decision pathways by sex [116]. This raises important considerations. It contests the idea of a singular, cohesive disease model. It highlights the risks of neglecting sex-specific biology in combined analyses and argues for addressing model interpretability alongside performance metrics [117]. The next generation of ML frameworks in AD should prioritize interpretability, include sex-segregated analyses, and provide biologically relevant rationales. This combination will transform explainable AI from a validation-oriented approach into a framework for discovering sex-dissimilar disease pathways, enabling more accurate and fair clinical decision-making [118].

10. Translational Challenges: From Model to Clinic

Although ML approaches for predicting biomarker transformations have advanced, an unacceptable gap remains in translating these innovations from the research lab into clinical practice for Alzheimer's disease (AD) [119]. Technical, methodological, and ethical barriers contribute to the delay of model development and real-world application, many of which are worsened with respect to sex-specific differences. AD datasets typically include a higher proportion of females, reflecting the disease's higher prevalence in females [120]. Nonetheless, this representation does not support robust analysis. Numerous studies collect and analyse data without considering sex differences and, subsequently, sex-stratified development, resulting in studies masking sex-specific trends. In effect, models may focus on prominent trends while ignoring subtle, yet statistically significant differences [121]. This paradox, in which ML systems generate inequitable predictions and remain analytically irresolvable, results from data overrepresentation. We employ a variety of computer-aided diagnostic tools, including PET and MRI scans, CSF and blood markers, and genetic and EEG data, to make multimodal ML diagnostic predictions [75].

Nevertheless, institutions tend to acquire these data using different protocols, platforms, and preprocessing pipelines. This heterogeneous approach to data harmonization creates opportunities for confounding factors to obscure true biological signals, with an even greater impact on sex-differentiated analyses [122]. Interactions among sex-related biological variability, differences in imaging resolution, and/or assay sensitivity may yield contradictory results. Therefore,

standardizing acquisition, preprocessing, and feature extraction is important for reliable cross-modality integration. Limited reproducibility of ML models is a major hindrance to clinical translation [123]. Many previous works reported positive results using internal datasets, but external studies have not replicated them. This raises concern for sex-conscious modelling, as generalizability to diverse populations and demographics is essential. Poorly externally validated models risk overfitting to a specific dataset, severely limiting their clinical value [124].

To address this problem, we require transparent reporting, open datasets, and standardised evaluation frameworks. Machine learning (ML) in healthcare is under increasing regulatory scrutiny, emphasizing safety, transparency, and equity [125]. Sex-specific models also complicate equity, transparency, and accountability: ensuring they do not systemically disadvantage either sex; providing interpretable outputs that clinicians can easily understand; and clearly identifying who is responsible for model decisions when used in clinical workflows [126]. Data privacy, informed consent, and the ethical use of sensitive biological data remain concerns, especially with genetic or multimodal datasets [127]. Sex bias may be the most neglected impediment to the development of precision medicine. When a medical machine learning model omits sexed biology, it cannot predict outcomes while keeping dynamics at the level of particular populations [128]. This undermines the primary goal of precision medicine: to tailor diagnosis and treatment to the patient's individual biology. Concerning sex bias, a change of attitude is necessary. Instead of focusing on the inclusion of the variable, the analysis of sex differences should be prioritised over treating sex as a confounder. This should be replaced with the appreciation of sex as a core biological variable. Lastly, the focus should shift from the general model's outcome variability to the final results for the given subpopulation [129]. Bridging both ends of the model-clinic continuum requires collaboration from multiple fields. Key components include designing sex-aware datasets and benchmarking standards, cohesive multimodal data acquisition and preprocessing, extensive external validation across populations, and integrating ethical and regulatory frameworks into model design [109]. Overcoming these challenges will enable the field to deploy ML tools that not only boost accuracy but also promote equity and interpretability, and that can be used in clinics. This will initiate the development of precision medicine for Alzheimer's Disease (AD) [130].

11. Clinical Implications: From Sex-Aware Biomarker Modeling to Personalised Diagnosis and Treatment

The impact of sex-based differences on early signs and symptoms of Alzheimer's disease (AD) has been addressed earlier in the chapter along with the role of machine learning tools in modeling the differences. However, the most pertinent question is whether this matters for the individual patient [131]. Early studies in clinical trials, diagnostics, and multi-omics analyses highlight the importance of designing sex-specific approaches to clinical situations. These approaches determine which patients a biomarker-based diagnosis applies to, predict different response patterns to already approved drugs, and identify sex-based drugs (i.e., therapeutic targets) to act upon [132]. Because they have been approved, lecanemab and donanemab require evidence-based patient selection using biomarkers. ALFA+ data show that CSF biomarkers predict amyloid PET differently across sexes: the AUC of the A β 42/40 ratio was 91.0% in women and 83.8% in men, and for p-tau181/A β 42 it was 93.0% in women and 88.4% in men [133]. Setting a cutoff for men and women alike results in either a high false-negative rate for women or a high false-positive rate for men. Sex awareness in ML

models allows them to adapt classification decisions based on patient sex. This decreases misclassification and tailors treatment eligibility for each patient [133]. Additionally, post-hoc analyses of the Phase 3 trials of lecanemab (CLARITY-AD) and donanemab (TRAILBLAZER-ALZ2) suggest that treatment benefit differs by sex. In general, men have shown greater cognitive improvement with lecanemab, while women have shown a greater response to donanemab. Sex is considered a substantial covariate of drug clearance in population pharmacokinetic models, and lecanemab is thought to have greater exposure in women as a result of differences in sex and body weight as well as in the distribution of body volumes [134]. A sex-aware multi-task model could learn and explain sex as an interacting variable by predicting trajectories for males and females separately, allowing measurement of patient-based expected benefit. Beyond prediction of treatment response, sex-aware analysis of genomic data can uncover sex-specific drug targets, which have the potential to create new and revolutionary ways of treating diseases [135]. A sex-stratified large-scale GWAS (genome-wide association study) focused on approx. 1 million individuals and included proteogenomic and multi-omics data, prioritized 125 female-biased and 21 male-biased risk genes, with female-biased pathways including amyloid processing and immune and microglia processing [74]. Using computational techniques, sex hormone-related drugs targeting the Epidermal Growth Factor Receptor (EGFR) were prioritized in women. In addition, sex-specific drugs like Haptoglobin (HP) were identified. HP is a sex-specific gene linked to oxidative stress and APOE. AI-based subphenotyping of a large cohort of AD patients (>8000) revealed different comorbidity patterns [136]. In particular, circulatory diseases were more predominant in men, while women presented with a higher prevalence of urinary stones. The results show that ML models can provide sex-specific comorbidities for AD patients [137]. They thus can help in the development of holistic treatment plans to combat AD and sex-specific comorbidities. Sex-specific ML models are not a luxury in clinical practice; they support more precise diagnosis, individualized treatment, accelerated drug discovery, and patient-centered integrated care [138].

12. Future Directions: Toward Precision Neurology

Developing thorough, individualized, real-time systems that go beyond standard clinic-based assessments will guide future Alzheimer's disease (AD) research. Electronic wearables and EEG, enhanced with digital biomarkers, can continuously collect real-world behaviour, physiology, and cognitive state data [139]. These strategies can reveal subtle, emerging, and potentially sexually differentiated changes in cognition, sleep, daily activities, and brain function. Conventional techniques often miss these changes. Therefore, federated learning enhances model reliability and generalizability while protecting data privacy and leveraging extensive, diverse datasets distributed across sites [140]. These developments enable customized risk-prediction modeling to incorporate multiple biomarker modalities while capturing individual variability, such as sex-related differences in disease onset or progression. An implementation roadmap is needed to translate these advanced models into clinical practice [141]. This includes improving data collection through systematic scrutiny of sex differences across the life course. Importantly, creating standardized, multimodal frameworks that integrate neuroimaging, fluid biomarkers, genetics, and electrophysiology will facilitate reproducibility and comparability across cohorts [142]. Incorporating clinically interpretable AI will be crucial to closing the gap between computational predictions and medical decision-making, enabling clinicians to understand and trust model outputs [143]. Integrating

technological advancement with biological and clinical insight will enable the shift toward precision neurology. Precision neurology will provide contextual diagnoses, prognoses, and interventions, as neurology recognises the role that sex and other factors play in disease outcomes [62].

13. Conclusion

We have compiled extensive literature showing that Alzheimer’s Disease (AD) is not a uniform entity/subtype but a biologically complex disorder that is at least partly shaped by sex differences. Across biomarkers such as PET, MRI, CSF, and serum, as well as genetic and EEG imaging, we consistently find differences in pathology progression, interactions, and clinical presentation between males and females. As mentioned, traditional machine learning (ML) methods are inadequate for handling this complexity, as they often treat sex as a simple per-sample covariate and fail to account for it as an active biological modifier. Crucially, incorporating cross-modal interactions showed how sex differentiates biomarker amplitudes and correlations, creating uneven disease pathways and prediction patterns. Building on these results, we advocate for sex-aware multimodal AI and promote models that represent multivariate biology and frame interactions within integrated data, as this approach can have a remarkable impact on both research and clinical practice. For researchers, it inspires the modeling of the intricate mechanisms of disease biology. In the clinic, it can improve diagnostic precision, refine prognostic risk assessment, and tailor therapy to disease mechanisms and pathways. Implementing sex-aware intelligence in multimodal machine learning (ML) systems is essential for genuine precision medicine in Alzheimer’s Disease (AD). Moreover, it safeguards the fair and efficient application of Artificial Intelligence (AI) for all patients (Table 1).

Table 1 Sex Differences in Multimodal Biomarkers and Machine Learning Implications in Alzheimer’s disease.

Domain	Sex-Specific Insights & Cross-Modal Interactions	Implications for ML Models	References
Neuroimaging (PET & MRI)	Females exhibit higher tau burden and faster hippocampal atrophy at similar disease stages; sex-dependent PET-MRI discordance suggests differential neurodegeneration despite similar amyloid load.	Incorporate sex-aware feature weighting and interaction modelling between PET and MRI; avoid uniform thresholds.	[30, 144]
CSF Biomarkers	Sex differences in Aβ42, t-tau, and p-tau levels; females often show higher tau relative to amyloid; PET-CSF mismatch varies by sex.	Apply sex-specific cutoffs and integrate CSF with imaging in multimodal frameworks.	[35, 145]
Serum/Plasma Biomarkers	Peripheral inflammation, metabolic dysfunction, and neurodegeneration markers differ by sex; systemic factors influence brain pathology differently.	Include serum biomarkers as sex-sensitive predictors reflecting systemic-brain interactions.	[146, 147]

Genetic Markers (SNPs)	APOE ε4 confers greater risk in females; sex modifies gene expression and penetrance; gene-environment interactions differ.	Model gene-sex interactions explicitly; integrate polygenic risk with multimodal biomarkers.	[148, 149]
EEG Biomarkers	Sex differences in neural oscillations, connectivity, and network efficiency; early functional disruptions may be more detectable in females.	Integrate EEG as an early functional modality; use sex-aware weighting in multimodal fusion.	[150, 151]
Multimodal Integration	Cross-modal interactions (PET-CSF, MRI-EEG, genetics-biomarkers) differ by sex, indicating distinct disease pathways.	Develop sex-aware multimodal fusion models capturing interaction networks rather than independent features.	[21, 152]
Machine Learning Models	Most models treat sex as a covariate, ignoring its role as a biological modifier.	Implement sex-stratified models, multi-task learning, and causal frameworks.	[153, 154]
Explainable AI	Most models treat sex as a covariate, ignoring its role as a biological modifier.	Apply SHAP, LIME, and attention-based interpretation stratified by sex.	[153, 155]

Author Contributions

AAA conceptualized the review, designed the framework, and drafted the manuscript. NM provided overall supervision and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Competing Interests

The authors declare no competing interests.

Data Availability

No datasets were generated or analyzed during the current study.

AI-Assisted Technologies Statement

Artificial intelligence (AI) tools were used solely for basic grammar correction and language refinement in the preparation of this manuscript. Specifically, OpenAI's ChatGPT was employed to improve the readability and linguistic clarity of the English text. All scientific content, data interpretation, and conclusions were developed independently by the author. The authors have

thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

References

1. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021; 17: 327-406.
2. Ajayi EI, Babatunde IO, Oladele JO. Carotenoids and their formulation supplements in Alzheimer's disease. *NeuroLife*. 2024; 2: 1-24.
3. Kamatham PT, Shukla R, Khatri DK, Vora LK. Pathogenesis, diagnostics, and therapeutics for Alzheimer's disease: Breaking the memory barrier. *Ageing Res Rev*. 2024; 101: 102481.
4. Sarigiannis D, Karakitsios S, Anesti O, Stem A, Valvi D, Sumner SC, et al. Advancing translational exposomics: Bridging genome, exposome and personalized medicine. *Hum Genom*. 2025; 19: 48.
5. Aggarwal NT, Mielke MM. Sex differences in Alzheimer's disease. *Neurol Clin*. 2023; 41: 343-358.
6. Capilla-López MD, Deprada A, Andrade-Talavera Y, Martínez-Gallego I, Coatl-Cuaya H, Sotillo P, et al. Synaptic vulnerability to amyloid- β and tau pathologies differentially disrupts emotional and memory neural circuits. *Mol Psychiatry*. 2025; 30: 2966-2979.
7. Wang Y, Mishra A, Brinton RD. Transitions in metabolic and immune systems from pre-menopause to post-menopause: Implications for age-associated neurodegenerative diseases. *F1000Res*. 2020; 9: F1000-Faculty Rev-68. doi: 10.12688/f1000research.21599.1.
8. Price BR, Walker KA, Eissman JM, Suryadevara V, Sime LN, Hohman TJ, et al. Sex differences and the role of estrogens in the immunological underpinnings of Alzheimer's disease. *Alzheimers Dement*. 2025; 11: e70139.
9. Wang YT. Sex disparities in Alzheimer's disease biomarker-informed tau pathology and the underlying mechanisms. Montreal, Canada: McGill University; 2024.
10. Shansky RM, Murphy AZ. Considering sex as a biological variable will require a global shift in science culture. *Nat Neurosci*. 2021; 24: 457-464.
11. Sharma D. Artificial intelligence, machine learning and omic data integration in osteoarthritis. *Osteoarthr Cartil*. 2025; 34: 311-320.
12. Neale N, Lona-Durazo F, Ryten M, Gagliano Taliun SA. Leveraging sex-genetic interactions to understand brain disorders: Recent advances and current gaps. *Brain Commun*. 2024; 6: fcae192.
13. Kolahchi Z, Henkel N, Eladawi MA, Villarreal EC, Kandimalla P, Lundh A, et al. Sex and gender differences in Alzheimer's disease: Genetic, hormonal, and inflammation impacts. *Int J Mol Sci*. 2024; 25: 8485.
14. Hasanzadeh F, Josephson CB, Waters G, Adedinsewo D, Azizi Z, White JA. Bias recognition and mitigation strategies in artificial intelligence healthcare applications. *NPJ Digit Med*. 2025; 8: 154.
15. Alrouji M, Alshammari MS, Alhajlah S, Tasqeeruddin S, Ashraf GM, Dinislam K, et al. Neuroinflammaging and sex-specific mechanisms: Biomarker discovery and emerging technological approaches in aging brain disorders. *Engineering*. 2026. doi: 10.1016/j.eng.2025.12.030.

16. Mervosh N, Devi G. Estrogen, menopause, and Alzheimer's disease: Understanding the link to cognitive decline in women. *Front Mol Biosci.* 2025; 12: 1634302.
17. Beauchamp LC, Palumbo LA, Lanser TB, Baig M, Cox LM. Sex-dependent immune activation shapes disease progression in a model of Parkinson's disease. *Biol Sex Differ.* 2025; 17: 13.
18. Skillbäck T, Blennow K, Zetterberg H, Shams S, Machado A, Pereira J, et al. Sex differences in CSF biomarkers for neurodegeneration and blood-brain barrier integrity. *Alzheimers Dement.* 2021; 13: e12141.
19. Yu M, Sporns O, Saykin AJ. The human connectome in Alzheimer disease-relationship to biomarkers and genetics. *Nat Rev Neurol.* 2021; 17: 545-563.
20. Khramtsova EA, Wilson MA, Martin J, Winham SJ, He KY, Davis LK, et al. Quality control and analytic best practices for testing genetic models of sex differences in large populations. *Cell.* 2023; 186: 2044-2061.
21. Camastra C, Pelagi A, Quattrone A, Sarica A. Benchmarking multimodal deep fusion strategies for heterogeneous neuroimaging and cognitive data using a controlled sex classification task. *Brain Sci.* 2026; 16: 405.
22. Tserendondog T, Gotov BE, Luvsansambuu U, Pae DS, Park H. Neural synchrony and attention dynamics during naturalistic video viewing: A gender comparison using EEG and deep learning approaches. *Biomed Signal Process Control.* 2026; 119: 109763.
23. Zeighami Y, Tremblay C, Dadar M. Sex differences in vulnerability to tau pathology: Impact on cognitive decline. *Alzheimers Dement.* 2025; 21: e70634.
24. Davila A, Xu Z, Li S, Rozewicki J, Wilamowski J, Kotelnikov S, et al. AbAdapt: An adaptive approach to predicting antibody-antigen complex structures from sequence. *Bioinform Adv.* 2022; 2: vbac015.
25. Varghese T, Sheelakumari R, James JS, Mathuranath PS. A review of neuroimaging biomarkers of Alzheimer's disease. *Neurol Asia.* 2013; 18: 239-248.
26. Bluma M, Chiotis K, Nordberg A. Integration over reduction: Multimodal PET and fluid biomarkers in Alzheimer's disease and beyond. *Curr Opin Neurol.* 2026; 39: 176-184.
27. Zhang XY, Yang ZL, Lu GM, Yang GF, Zhang LJ. PET/MR imaging: New frontier in Alzheimer's disease and other dementias. *Front Mol Neurosci.* 2017; 10: 343.
28. Pemberton HG, Collij LE, Heeman F, Bollack A, Shekari M, Salvadó G, et al. Quantification of amyloid PET for future clinical use: A state-of-the-art review. *Eur J Nucl Med Mol Imaging.* 2022; 49: 3508-3528.
29. Inguanzo A, Poulakis K, Oltra J, Maioli S, Marseglia A, Ferreira D, et al. Atrophy trajectories in Alzheimer's disease: How sex matters. *Alzheimers Res Ther.* 2025; 17: 79.
30. Boccalini C, Peretti DE, Scheffler M, Mu L, Griffa A, Testart N, et al. Sex differences in the association of Alzheimer's disease biomarkers and cognition in a multicenter memory clinic study. *Alzheimers Res Ther.* 2025; 17: 46.
31. Lamontagne-Kam D, Ulfat AK, Hervé V, Vu TM, Brouillette J. Implication of tau propagation on neurodegeneration in Alzheimer's disease. *Front Neurosci.* 2023; 17: 1219299.
32. Kang JH, Korecka M, Lee EB, Cousins KA, Tropea TF, Chen-Plotkin AA, et al. Alzheimer disease biomarkers: Moving from CSF to plasma for reliable detection of amyloid and tau pathology. *Clin Chem.* 2023; 69: 1247-1259.
33. Lopez-Lee C, Torres ER, Carling G, Gan L. Mechanisms of sex differences in Alzheimer's disease. *Neuron.* 2024; 112: 1208-1221.

34. Lobo R, Jaffe AS. Sex-specific thresholds for cardiac biomarkers-we need to move forward. *Rev Cardiovasc Med*. 2023; 24: 86.
35. Milà-Alomà M, Van Hulle C, Brugulat-Serrat A, Casals Brodú M, González-Escalante A, Sánchez-Benavides G, et al. Sex differences in Alzheimer's disease CSF biomarkers and their association with A β pathology on PET in cognitively unimpaired individuals. *Alzheimers Res Ther*. 2025; 17: 235.
36. Romic E, Karlsson I, Karalija N, Adolfsson AN, Adolfsson R, Kauppi K. Pathway-based polygenic risk of Alzheimer's disease highlights immune genes in cognitive decline. *Alzheimers Dement*. 2026; 12: e70209.
37. Ungar L, Altmann A, Greicius MD. Apolipoprotein E, gender, and Alzheimer's disease: An overlooked, but potent and promising interaction. *Brain Imaging Behav*. 2014; 8: 262-273.
38. Lamri A, De Paoli M, De Souza R, Werstuck G, Anand S, Pigeyre M. Insight into genetic, biological, and environmental determinants of sexual-dimorphism in type 2 diabetes and glucose-related traits. *Front Cardiovasc Med*. 2022; 9: 964743.
39. Meyer L, Mulder D, Wallace J. A supervised machine learning approach with feature selection for sex-specific biomarker prediction. *NPJ Syst Biol Appl*. 2025; 11: 69.
40. Alidadi M, Hamavar R, Abbasi E, Nabavifard S, Mohebbi M, Asl BM. EEG-based Alzheimer's disease detection: Past, present, and future. *Measurement*. 2025; 262: 120096.
41. Wang S. Sex differences in functional connectivity patterns during mental rotation task: An event-related EEG study. *Behav Sci*. 2026; 16: 144.
42. Tanaka M, Yamada E, Mori F. Neurophysiological markers of early cognitive decline in older adults: A mini-review of electroencephalography studies for precursors of dementia. *Front Aging Neurosci*. 2024; 16: 1486481.
43. Pithakumar A, Basha S, Pai AR, Mahato KK. From pathogenesis to precision medicine: Targeting immune imbalance in multiple sclerosis. *Ageing Res Rev*. 2025; 113: 102921.
44. Cacabelos R. Special Issue: "New trends in Alzheimer's disease research: From molecular mechanisms to therapeutics: 2nd edition". *Int J Mol Sci*. 2025; 26: 7175.
45. Edwards TA, Zhai T, Nho K, Saykin AJ, Long Q, Shen L. Sex-based differences in the association of epigenetic age acceleration with Alzheimer's disease biomarkers and cognitive measures. *AMIA Jt Summits Transl Sci Proc*. 2025; 2025: 141-148.
46. He C, Zhou Y, Chen Y, Jing Y. Research on interpretable machine learning models for diagnosis and staging of mild cognitive impairment. *Front Neurol*. 2025; 16: 1708525.
47. Silva TC, Zhang W, Young JI, Gomez L, Schmidt MA, Varma A, et al. Distinct sex-specific DNA methylation differences in Alzheimer's disease. *Alzheimers Res Ther*. 2022; 14: 133.
48. Milà-Alomà M, Hausle I, Myoraku A, Sorensen C, Thropp P, Shaw LM, et al. Sex differences in Alzheimer's disease plasma biomarker levels and clinical utility. *Alzheimers Dement*. 2026; 22: e71244.
49. Klingenberg M, Stark D, Eitel F, Budding C, Habes M, Ritter K, et al. Higher performance for women than men in MRI-based Alzheimer's disease detection. *Alzheimers Res Ther*. 2023; 15: 84.
50. Thomas JT, Thorp JG, Huider F, Grimes PZ, Wang R, Youssef P, et al. Sex-stratified genome-wide association meta-analysis of major depressive disorder. *Nat Commun*. 2025; 16: 7960.
51. Ma X, Ibrahim AA, Ma L, Ma X, Ma Z, Liu Y, et al. Sex-specific prediction models of Alzheimer's disease: A gene expression analysis. *Int J Med Sci*. 2026; 23: 852-863.

52. Bourquard T, Lee K, Al-Ramahi I, Pham M, Shapiro D, Lagisetty Y, et al. Functional variants identify sex-specific genes and pathways in Alzheimer's disease. *Nat Commun.* 2023; 14: 2765.
53. Joeres R, Blumenthal DB, Kalinina OV. Data splitting to avoid information leakage with DataSAIL. *Nat Commun.* 2025; 16: 3337.
54. Rong K, Yi Ke Ran GL, Zhou C, Yi X. Intelligent predictive risk assessment and management of sarcopenia in chronic disease patients using machine learning and a web-based tool. *Eur J Med Res.* 2025; 30: 345.
55. Mi X, Zhang YC, Zhang XJ, He HB, Chen XC, Dai XM. The impact of APOE genotype, age, and sex on gut microbiota in a mouse model of Alzheimer's disease: An exploration of their interactions. *Biol Sex Differ.* 2026; 17: 113.
56. Tardy M, Mateus D. Leveraging multi-task learning to cope with poor and missing labels of mammograms. *Front Radiol.* 2022; 1: 796078.
57. Mou FS, Ahmed T, Huda MN, Nandi AK. Artificial neural networks fighting real neural decline: A systematic review of AI in Alzheimer's research. *Artif Intell Rev.* 2026; 59: 124.
58. Chen ZS, Galatzer-Levy IR, Bigio B, Nasca C, Zhang Y. Modern views of machine learning for precision psychiatry. *Patterns.* 2022; 3: 100602.
59. Straw I, Rees G, Nachev P. Sex-based performance disparities in machine learning algorithms for cardiac disease prediction: Exploratory study. *J Med Internet Res.* 2024; 26: e46936.
60. Ren F, Wei J, Chen Q, Hu M, Yu L, Mi J, et al. Artificial intelligence-driven multi-omics approaches in Alzheimer's disease: Progress, challenges, and future directions. *Acta Pharm Sin B.* 2025; 15: 4327-4385.
61. Pallikkavaliyaveetil N, Chandrasekaran S. Small data, big challenges: Machine-and deep-learning strategies for data-limited drug discovery. *Adv Drug Deliv Rev.* 2025; 229: 115762.
62. Ben-Jaafar A, Sinha A, Nkrumah-Boateng PA, Roy S, Sanker V, Mohamed S, et al. Artificial intelligence-based biomarkers for the diagnosis and treatment of neurological conditions: A narrative review. *Mol Brain.* 2026; 19: 26.
63. Alzubaidi L, Zhang J, Humaidi AJ, Al-Dujaili A, Duan Y, Al-Shamma O, et al. Review of deep learning: Concepts, CNN architectures, challenges, applications, future directions. *J Big Data.* 2021; 8: 53.
64. Viswan V, Shaffi N, Malathy E, Chemmalar Selvi G, Kavitha BR, Abdesselam A, et al. Multimodal fusion and explainability of artificial intelligence models in Alzheimer's disease detection. *Brain Inform.* 2026; 13: 5.
65. Zhou W, Wang Y, Wu Y, Li X, Liu H, Wang H, et al. AI-driven multimodal precision diagnosis and progression prediction of Alzheimer's disease: Data fusion mechanisms, clinical applications, and research trends (2017-2024). *Digit Health.* 2026; 12. doi: 10.1177/20552076251412649.
66. Wei X, Zhang T, Xiong R, Zhang Q, Zhang J, Jin Z, et al. Mapping heterogeneous brain structural subtypes in Alzheimer's disease and mild cognitive impairment using normative models. *Transl Psychiatry.* 2026; 16: 168.
67. Krones F, Marikkar U, Parsons G, Szmul A, Mahdi A. Review of multimodal machine learning approaches in healthcare. *Inf Fusion.* 2025; 114: 102690.
68. Stahlschmidt SR, Ulfenborg B, Synnergren J. Multimodal deep learning for biomedical data fusion: A review. *Brief Bioinform.* 2022; 23: bbab569.
69. Yu B, Zhang G, Wang Q, Wang L. DDAF-Net: Decoupled and differentiated attention fusion network for object detection. *Sensors.* 2026; 26: 1812.

70. Bappi MI, Richter DJ, Kolekar SS, Kim K. HCLmNet: A unified hybrid continual learning strategy multimodal network for lung cancer survival prediction. *PLoS One*. 2026; 21: e0316509.
71. Hoth KF, Voorhies K, Wu AC, Lange C, Potash JB, Lutz SM. The role of sex in genetic association studies of depression. *J Psychiatry Brain Sci*. 2022; 7: e220013.
72. Li J, Huang L, Wei Z, Zhang W, Qin Q. Multi-task learning with deformable convolution. *J Vis Commun Image Represent*. 2021; 77: 103109.
73. Liu Y, Zhu K, Peng W, Liu Z, Mao X. Multi-omics and artificial intelligence for precision drug discovery and potential clinical applications. *Signal Transduct Target Ther*. 2026; 11: 210.
74. Shwab EK, Pathak GA, Harvey J, Belloy ME, Fischer CE, Lutz MW, et al. Leveraging multiomic approaches to elucidate mechanisms of heterogeneity in Alzheimer's disease: Neuropsychiatric symptoms, co-pathologies, and sex differences. *Alzheimers Dement*. 2025; 21: e70549.
75. Vrudhula A, Kwan AC, Ouyang D, Cheng S. Machine learning and bias in medical imaging: Opportunities and challenges. *Circ Cardiovasc Imaging*. 2024; 17: e015495.
76. Amaya-Santos S, Vargas C, Bermúdez-Tamayo C. Frameworks encompassing intersectional perspective of artificial intelligence in healthcare. Scoping review. *Public Health Pract*. 2025; 11: 100713.
77. Soladoye AA, Aderinto N, Osho D, Olawade DB. Explainable machine learning models for early Alzheimer's disease detection using multimodal clinical data. *Int J Med Inform*. 2025; 204: 106093.
78. Grasso SM, Santos-Santos MÁ, Clark AL. On the complexity of biomarker-driven diagnoses of Alzheimer's disease. *J Neuropsychol*. 2025; 19: 176-185.
79. Zhu D, Montagne A, Zhao Z. Alzheimer's pathogenic mechanisms and underlying sex difference. *Cell Mol Life Sci*. 2021; 78: 4907-4920.
80. Li A, Klinger HM, Seto M, Birkenbihl C, Properzi MJ, Farrell M, et al. Elevated temporal tau PET predicts faster cognitive decline in women than men: A meta-analysis. *Alzheimers Dement*. 2026; 22: e71031.
81. Proudfoot M, Bede P, Turner MR. Imaging cerebral activity in amyotrophic lateral sclerosis. *Front Neurol*. 2019; 9: 1148.
82. Keller K, Menon V. Gender differences in the functional and structural neuroanatomy of mathematical cognition. *Neuroimage*. 2009; 47: 342-352.
83. Arenaza-Urquijo EM, Boyle R, Casaletto K, Anstey KJ, Vila-Castelar C, Colverson A, et al. Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimers Dement*. 2024; 20: 5695-5719.
84. Huang Y, Shan Y, Zhang W, Lee AM, Li F, Stranger BE, et al. Deciphering genetic causes for sex differences in human health through drug metabolism and transporter genes. *Nat Commun*. 2023; 14: 175.
85. Groot C, Holstege H, Ossenkoppele R. Do genetic factors contribute to sex-specific differences in resilience to amyloid pathology? *Brain*. 2022; 145: 2239-2241.
86. Li W, Yang D, Yan C, Chen M, Li Q, Zhu W, et al. Characterizing network selectiveness to the dynamic spreading of neuropathological events in Alzheimer's disease. *J Alzheimers Dis*. 2022; 86: 1805-1816.
87. Kotoski A, Wiafe SL, Stephen JM, Wang YP, Wilson TW, Calhoun VD. Dynamic inter-modality source coupling reveals sex differences in children based on brain structural-functional network

- connectivity: A multimodal MRI study of the ABCD dataset. 2025. doi: 10.1101/2025.07.23.666366.
88. Galindez G, Sadegh S, Baumbach J, Kacprowski T, List M. Network-based approaches for modeling disease regulation and progression. *Comput Struct Biotechnol J*. 2023; 21: 780-795.
89. Yang Y, Hu L, Chen Y, Gu W, Xie Y, Nie S. Sex-specific imaging biomarkers for Parkinson's disease diagnosis: A machine learning analysis. *J Imaging Inform Med*. 2025; 38: 1062-1075.
90. Patel B, Orlichenko A, Patel A, Qu G, Wilson TW, Stephen JM, et al. Explainable multimodal graph isomorphism network for interpreting sex differences in adolescent neurodevelopment. *Appl Sci*. 2024; 14: 4144.
91. Dumitrescu L, Mayeda ER, Sharman K, Moore AM, Hohman TJ. Sex differences in the genetic architecture of Alzheimer's disease. *Curr Genet Med Rep*. 2019; 7: 13-21.
92. Sundermann EE, Banks SJ, Bondi MW, Martinez MA, Biegon A, Rotblatt LJ, et al. Sex differences in the relationship of biomarker change to memory decline in early Alzheimer's disease: An observational cohort study. *Biol Sex Differ*. 2026; 17: 38.
93. Christodoulou RC, Woodward A, Pitsillos R, Ibrahim R, Georgiou MF. Artificial intelligence in Alzheimer's disease diagnosis and prognosis using PET-MRI: A narrative review of high-impact literature post-Tauvid approval. *J Clin Med*. 2025; 14: 5913.
94. Baytaş İM. Predicting progression from mild cognitive impairment to Alzheimer's dementia with adversarial attacks. *IEEE J Biomed Health Inform*. 2024; 28: 3750-3761.
95. Saminathan P, Corey M, Gibbons A, Rayadurgam M, Reddy N, Ramesh P, et al. Sex differences in metabolite-immune circuits of neuroinflammation. *Immunol Rev*. 2026; 338: e70114.
96. Ai M, Liu Y, Liu D, Yan C, Wang X, Chen X. Research progress in predicting the conversion from mild cognitive impairment to Alzheimer's disease via multimodal MRI and artificial intelligence. *Front Neurol*. 2025; 16: 1596632.
97. Giacomucci G, Moschini V, Ceccarelli A, Padiglioni S, Morinelli C, Mazzeo S, et al. Gender differences in cognitive reserve: An impact on progression in subjective cognitive decline? *Alzheimers Dement*. 2025; 17: e70174.
98. Xie R, Herder C, Sha S, Brenner H, Carlsson S, Schöttker B. Improved sex-specific cardiovascular risk prediction with multi-omics data in people with type 2 diabetes. *Cardiovasc Diabetol*. 2025; 25: 25.
99. Giorgio J, Landau SM, Jagust WJ, Tino P, Kourtzi Z. Modelling prognostic trajectories of cognitive decline due to Alzheimer's disease. *Neuroimage Clin*. 2020; 26: 102199.
100. Zhuang L, Park SH, Skates SJ, Prosper AE, Aberle DR, Hsu W. Advancing precision oncology through modeling of longitudinal and multimodal data. *IEEE Rev Biomed Eng*. 2025; 19: 182-200.
101. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging*. 2016; 31: 166-175.
102. Huang Y, Xu J, Fan Z, Hu Y, He X, Chen A, et al. Identifying Alzheimer's disease progression subphenotypes via a graph-based framework using electronic health records. *J Healthc Inform Res*. 2026; 10: 317-339.
103. Parvin N, Joo SW, Jung JH, Mandal TK. Multimodal AI in biomedicine: Pioneering the future of biomaterials, diagnostics, and personalized healthcare. *Nanomaterials*. 2025; 15: 895.

- 104.Sönmez TF, Harvey DJ, Beckett LA. An unsupervised learning approach for clustering joint trajectories of Alzheimer's disease biomarkers: An application to ADNI data. *Alzheimers Dement.* 2025; 21: e14524.
- 105.Caldi Gomes L, Hänzelmann S, Hausmann F, Khatri R, Oller S, Parvaz M, et al. Multiomic ALS signatures highlight subclusters and sex differences suggesting the MAPK pathway as therapeutic target. *Nat Commun.* 2024; 15: 4893.
- 106.McClements L, Kautzky-Willer A, Kararigas G, Ahmed SB, Stallone JN. The role of sex differences in cardiovascular, metabolic, and immune functions in health and disease: A review for "sex differences in health awareness day". *Biol Sex Differ.* 2025; 16: 33.
- 107.D'Argenio V, Tomaiuolo R, Barger S, Sancesario G. Alzheimer's 2030: From precision genomics to artificial intelligence. *Genes.* 2026; 17: 233.
- 108.Govindarajan R, Thirunadanasikamani K, Napa KK, Sathya S, Murugan JS, Priya KC. Development of an explainable machine learning model for Alzheimer's disease prediction using clinical and behavioural features. *MethodsX.* 2025; 15: 103491.
- 109.Weinberger N, Hery D, Mahr D, Adler SO, Stadlbauer J, Ahrens TD. Beyond the gender data gap: Co-creating equitable digital patient twins. *Front Digit Health.* 2025; 7: 1584415.
- 110.Carriero A, de Hond A, Cappers B, Paulovich F, Abeln S, Moons KG, et al. Explainable AI in healthcare: To explain, to predict, or to describe? *Diagn Progn Res.* 2025; 9: 29.
- 111.Amann J, Blasimme A, Vayena E, Frey D, Madai VI. Explainability for artificial intelligence in healthcare: A multidisciplinary perspective. *BMC Med Inform Decis Mak.* 2020; 20: 310.
- 112.Ponce-Bobadilla AV, Schmitt V, Maier CS, Mensing S, Stodtmann S. Practical guide to SHAP analysis: Explaining supervised machine learning model predictions in drug development. *Clin Transl Sci.* 2024; 17: e70056.
- 113.Vimbi V, Shaffi N, Mahmud M. Interpreting artificial intelligence models: A systematic review on the application of LIME and SHAP in Alzheimer's disease detection. *Brain Inform.* 2024; 11: 10.
- 114.Wan Z, Fu W, Hossain J, Gollo LL, Wu K. Attention-guided multimodal neuroimaging fusion network for modeling brain aging pattern. 2026. doi: 10.64898/2026.03.28.713645.
- 115.Williamson J, James SA, Mukli P, Yabluchanskiy A, Wu DH, Sonntag W, et al. Sex difference in brain functional connectivity of hippocampus in Alzheimer's disease. *GeroScience.* 2024; 46: 563-572.
- 116.Angelini G, Malvaso A, Schirripa A, Campione F, D'Addario SL, Toschi N, et al. Unraveling sex differences in Parkinson's disease through explainable machine learning. *J Neurol Sci.* 2024; 462: 123091.
- 117.Cabot JH, Ross EG. Evaluating prediction model performance. *Surgery.* 2023; 174: 723-726.
- 118.Agrawal R, Gupta T, Gupta S, Chauhan S, Patel P, Hamdare S. Fostering trust and interpretability: Integrating explainable AI (XAI) with machine learning for enhanced disease prediction and decision transparency. *Diagn Pathol.* 2025; 20: 105.
- 119.Zhao Q, Zhang C, Zhang W, Zhang S, Liu Q, Guo Y. Applications and challenges of biomarker-based predictive models in proactive health management. *Front Public Health.* 2025; 13: 1633487.
- 120.Mahr D, Hebich M, Weinberger N. Toward demographic robustness in digital patient twins: Addressing the gender data gap. *Digit Health.* 2025; 11. doi: 10.1177/20552076251386660.

121. Straw I, Wu H. Investigating for bias in healthcare algorithms: A sex-stratified analysis of supervised machine learning models in liver disease prediction. *BMJ Health Care Inform.* 2022; 29: e100457.
122. Fachrul M, Méric G, Inouye M, Pamp SJ, Salim A. Assessing and removing the effect of unwanted technical variations in microbiome data. *Sci Rep.* 2022; 12: 22236.
123. Foti R, Storti G, Palmesano M, Calicchia A, Foti R, Ciprandi G, et al. AI-driven innovations for quality control and standardization: Future strategies in adipose-derived stem cell manufacturing. *Int J Mol Sci.* 2026; 27: 2388.
124. Cherezov D, Fu P, Madabhushi A. Quantitative assessment of impact of technical and population-based factors on fairness of AI models for chest X-ray scans. *Comput Biol Med.* 2025; 198: 111147.
125. Abulibdeh R, Celi LA, Sejdić E. The illusion of safety: A report to the FDA on AI healthcare product approvals. *PLOS Digit Health.* 2025; 4: e0000866.
126. Habli I, Lawton T, Porter Z. Artificial intelligence in health care: Accountability and safety. *Bull World Health Organ.* 2020; 98: 251-256.
127. Pham T. Ethical and legal considerations in healthcare AI: Innovation and policy for safe and fair use. *R Soc Open Sci.* 2025; 12: 241873.
128. Ho JQ, Hartanto A, Koh A, Majeed NM. Gender biases within artificial intelligence and ChatGPT: Evidence, sources of biases and solutions. *Comput Hum Behav Artif Hum.* 2025; 4: 100145.
129. Lee SK. Sex as an important biological variable in biomedical research. *BMB Rep.* 2018; 51: 167-173.
130. Maleki Varnosfaderani S, Forouzanfar M. The role of AI in hospitals and clinics: Transforming healthcare in the 21st century. *Bioengineering.* 2024; 11: 337.
131. Massoumzadeh P, Tiemann Powles S, Naghashzadeh M, Rizzo J, Hu J, Yaeger L, et al. Sex differences in Alzheimer's disease: A systematic review of two decades of neuroimaging research. *Br J Radiol.* 2026; 99: 702-713.
132. Yen NT, Tien NT, Thu NQ, Ducatez F, Mauhin W, Lidove O, et al. A multi-omics-empowered framework for precision diagnosis and treatment of lysosomal diseases. *J Pharm Anal.* 2025; 15: 101274.
133. Cerman J, Škorvagová A, Vyhnálek M, Veverová K, Dvořák K, Kozák Š, et al. Concordance between amyloid PET and CSF biomarkers in clinical setting: A cross-platform comparison and in-depth analysis of discordant cases. *Sci Rep.* 2025; 15: 39963.
134. Teipel SJ, Tang Y, Khachaturian A. Sex differences in treatment effects of lecanemab and donanemab: A Bayesian reanalysis of CLARITY-AD and TRAILBLAZER-ALZ2. *Alzheimers Dement.* 2025; 11: e70155.
135. Bohn L, Vandenberg P, Fah H, Rajah MN, Einstein G, Dixon RA. Evaluating sex and gender as separate and interactive predictors of memory aging trajectory classes: An integrative data-driven approach. *Biol Sex Differ.* 2026; 17: 80.
136. Luo M, Zhao FK, Ouyang CH, Wang YM, Luo Y, Bian J. Recent advances in nanomaterial-based precision medicine for orthotopic tumor therapy. *J Nanobiotechnol.* 2026; 24: 168.
137. Ferraro PM, Taylor EN, Curhan GC. Factors associated with sex differences in the risk of kidney stones. *Nephrol Dial Transplant.* 2023; 38: 177-183.

138. Karnwal A, Rehman AU, Jassim AY, Kumar G, Al-Tawaha AR, Nesterova N. Artificial intelligence in cancer diagnosis and therapy using sex and gender as precision biomarkers. *Discov Oncol.* 2026; 17: 1049.
139. Ullah R, Akbar S, Nawaz R, Ali Z, Singh VK, Bukhari SA. Digital biomarkers for early detection of Alzheimer's disease: A comprehensive review and bibliometric analysis. *J Dement Alzheimers Dis.* 2026; 3: 18.
140. Pan J, Fan Z, Smith GE, Guo Y, Bian J, Xu J. Federated learning with multi-cohort real-world data for predicting the progression from mild cognitive impairment to Alzheimer's disease. *Alzheimers Dement.* 2025; 21: e70128.
141. Ryali S, Zhang Y, de Los Angeles C, Supekar K, Menon V. Deep learning models reveal replicable, generalizable, and behaviourally relevant sex differences in human functional brain organization. *Proc Natl Acad Sci U S A.* 2024; 121: e2310012121.
142. Witt A, Politis M, Norton R, Womersley K. Integrating sex and gender into biomedical research requires policy and culture change. *NPJ Womens Health.* 2024; 2: 23.
143. Xian T, Mehandjiev N, Constantinides P, Chen YW, Quboa Q, Kitchen G. Clinician preferences for explainable AI in critical care: A comparative study of interpretable models and visualizations for intubation decision support. *Int J Med Inform.* 2026; 210: 106287.
144. Honnangi S, Kajagar A, Shetgeri S, Korgaonkar T, Shahapur S, Khanai R. Gender-aware ADHD detection framework combining XGBoost and FLAML models: Exploring predictive features in women advancing personalized ADHD diagnosis. *Comput Sci Math Forum.* 2025; 12: 6.
145. Afxenti S, Zachariou M, Athieniti E, Lambrianides A, Pantzaris M, Spyrou GM. Integrating imaging and omics for enhanced subtyping of mild cognitive impairment associated with Alzheimer's disease. *J Transl Med.* 2025; 23: 1240.
146. Müller L, Di Benedetto S, Müller V. Influence of biological sex on neuroinflammatory dynamics in the aging brain. *Front Aging Neurosci.* 2025; 17: 1670175.
147. Jiang W, Zhang Z, Fan Y, Zhou L, Wang R, Hu T, et al. Sex differences in inflammation and gut-brain barrier dysfunction in adolescent depression: Implications for predicting non-suicidal self-injury. *J Affect Disord.* 2026; 405: 121561.
148. Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: Triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol.* 2016; 160: 134-147.
149. Li H, Zeng J, Snyder MP, Zhang S. Modeling gene interactions in polygenic prediction via geometric deep learning. *Genome Res.* 2025; 35: 178-187.
150. Shirzadi S, Dadgostar M, Einalou Z, Erdoğan SB, Akin A. Sex based differences in functional connectivity during a working memory task: An fNIRS study. *Front Psychol.* 2024; 15: 1207202.
151. Douglas N, Oosterhuis M, Valderrama CE. Evaluating the impact of demographic factors on subject-independent EEG-based emotion recognition approaches. *Diagnostics.* 2026; 16: 144.
152. Mak E, Kantarci K, Arvanitakis Z. Sex differences in in vivo biomarkers of neurodegenerative dementia. *Front Dement.* 2025; 4: 1706177.
153. Garcia-Sifuentes Y, Maney DL. Reporting and misreporting of sex differences in the biological sciences. *Elife.* 2021; 10: e70817.
154. Oliveira ML, Yang S, Sampaio-Oliveira M, Freitas DQ, Haiter-Neto F, Lim SH, et al. Multi-task deep learning for sex and age estimation from panoramic radiographs in a Brazilian young population. *Int Dent J.* 2026; 76: 109381.

155. Liu H, Wu M, Wei P, Fan H, Hou M. Using SHAP and LIME to explain machine learning models predicting comorbid depression and stroke from daily dietary nutrient intake in a US population-based study. *Food Sci Nutr.* 2026; 14: e71401.