Research article

Early Diagnosis of Alzheimer's Disease Before Tau Clumps Appear in Scans

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Abstract

Millions of people worldwide suffer from Alzheimer's disease (AD), the most prevalent cause of dementia and a progressive neurological illness. Its defining features are cognitive decline, neuronal death, and the buildup of tau tangles and amyloid-beta plaques in the brain. The diagnosis of AD has historically relied on identifying these protein clumps using neuroimaging methods, including positron emission tomography scans and cerebrospinal fluid studies. However, there are few options for early intervention because these pathological markers frequently appear in the mid-to-late stages of AD. Alternative diagnostic methods that can detect Alzheimer's risk before severe neurodegeneration happens are therefore desperately needed. According to new research, metabolic dysfunction, specifically insulin resistance linked to Type 2 diabetes, might be a precursor to AD. Neuronal function depends on insulin, and changes in glucose metabolism have been linked to neuroinflammation and cognitive decline. Furthermore, by examining large datasets to find early-stage illness markers, artificial intelligence-based approaches have shown promise in enhancing diagnostic accuracy. Researchers aim to shift the diagnostic paradigm towards early detection by combining metabolic and AI-driven biomarkers, which could lead to improved patient outcomes through prompt intervention.

Keywords: Alzheimer's disease, metabolic biomarkers, biomarker discovery, dementia detection, insulin resistance, diagnosis, tau clumps, artificial intelligence

Date of Submission: 24.02.2025 **Date of Acceptance:** 10.07.2025

DOI: https://doi.org/10.5526/esj.415

Background

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 55 million people globally, with nearly 10 million new cases reported each year (World Health Organisation, 2023). It is a progressive neurodegenerative condition marked by memory loss, language difficulties, disorientation, and functional decline. The average age of diagnosis is around 65 years, although changes in the brain often begin years or even decades earlier. Currently, diagnosis often occurs at a relatively late stage, once cognitive impairment becomes apparent and irreversible neuronal damage has already occurred (Jack et *al.,* 2018). This delay significantly limits the effectiveness of potential therapeutic interventions.

Traditionally, the amyloid cascade hypothesis has been the leading explanation for AD pathogenesis. This theory posits that the accumulation of amyloid-beta (Aβ) peptides in the brain triggers a cascade of events culminating in tau hyperphosphorylation, neuronal dysfunction, and ultimately, cognitive decline (Busche and Hyman, 2020). Detection of amyloid-beta plaques through cerebrospinal fluid analysis or Positron Emission Tomography (PET) imaging can precede symptom onset by up to 20 years, making it a valuable early diagnostic biomarker (Palmqvist *et al.,* 2017). However, the relationship between amyloid burden and symptom severity remains inconsistent, leading researchers to consider other pathological features.

Tau pathology, specifically the abnormal phosphorylation and aggregation of tau protein into neurofibrillary tangles, is now considered a more direct correlate of cognitive impairment (Franzmeier *et al.,* 2020). Tau buildup disrupts intracellular transport and neuronal stability, directly impairing brain function. Importantly, tau-related changes are typically visible on neuroimaging only after significant neuronal damage has occurred, thereby limiting their use-fulness in the very early stages of diagnosis.

Given the limitations of current biomarkers, researchers are increasingly examining systemic biomarkers, particularly those associated with metabolic abnormalities, as alternative diagnostic tools. Insulin resistance, a hallmark of Type 2 diabetes, has been linked to neuroinflammation, mitochondrial dysfunction, and synaptic damage processes that unify several theories of AD pathogenesis (Arnold *et al.,* 2018; Alves *et al.,* 2021). Moreover, disrupted energy metabolism in the brain has been linked to impaired neural circuit function, further supporting the metabolic connection to AD (Kapogiannis and Mattson, 2018). These findings suggest that individuals with

DOI: https://doi.org/10.5526/esj.415

metabolic disorders may exhibit AD-related neuropathology years before traditional biomarkers become detectable.

Another promising avenue for early diagnosis of AD is the use of artificial intelligence (AI). AI-powered tools, including deep neural networks and machine learning algorithms, can analyse large-scale clinical, genetic, and imaging datasets to detect subtle patterns indicative of early AD (Kumar *et al.,* 2024). Predictive modelling using AI enhances early diagnostic accuracy and holds promise for personalised treatment planning in at-risk individuals.

The Price of Alzheimer's Individually

People with AD and their families bear a heavy financial burden, primarily from lost wages, medical costs, and long-term care. Among the significant cost projections are:

In the US:

- As stated by the Alzheimer's Association (2023), the average lifetime cost of care for a person with Alzheimer's is $392,874.
- Without successful therapies, the $345 billion in payments for AD and other dementias in 2023 is expected to rise to almost $1 trillion by 2050 (Alzheimer's Association, 2023).
- Depending on the stage of the disease, families may incur annual out-of-pocket expenses ranging from $10,000 to $50,000.

In Europe:

- According to Prince *et al.* (2015), the annual cost of dementia care in Europe is predicted to be €250 billion.
- Costs for individual patients vary by country, but they may exceed €30,000 per year, with long-term care being the most expensive aspect.

Worldwide:

- Dementia is predicted to cost the world $2.8 trillion by 2050, up from an anticipated $1.3 trillion in 2019 (World Alzheimer Report, 2019).

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The Association Between Alzheimer's Disease and Insulin Resistance

It is becoming more widely acknowledged that insulin resistance, a defining feature of Type 2 diabetes, may be a contributing factor to neurodegeneration. Important brain processes like cell survival, neurotransmitter release, and synaptic plasticity are all regulated by insulin. A series of pathological alterations may arise when insulin signalling is compromised, as is the case with diabetes.

One example is glucose hypometabolism. The brain requires glucose for energy, and AD patients have been shown to have decreased glucose absorption even before cognitive symptoms appear. This metabolic deficit may exacerbate neuronal mortality and synaptic dysfunction (Alves *et al.,* 2021; Arnold *et al.,* 2018).

Chronic low-grade inflammation in the brain, characterised by the increased production of pro-inflammatory cytokines, also plays a significant role in the progression of AD. This neuroinflammatory response is often observed in individuals with insulin resistance, where elevated levels of cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) are present (De Felice and Ferreira, 2014). These inflammatory mediators contribute to neuronal damage by promoting oxidative stress, disrupting synaptic signalling, and accelerating tau hyperphosphorylation (Heneka *et al.,* 2015). Furthermore, microglial activation in response to metabolic dysfunction enhances the release of these cytokines, establishing a self-perpetuating cycle of inflammation and neurodegeneration. As a result, neuroinflammation serves as both a marker and a mediator of cognitive decline in AD, further reinforcing the pathological link between metabolic disease and neurodegeneration.

Insulin resistance impairs mitochondrial activity, which results in oxidative stress and damage to neurons (Kapogiannis and Mattson, 2018). According to research, insulin resistance may increase tau phosphorylation, which in turn accelerates the development of neurofibrillary tangles, a defining feature of AD pathology (Busche and Hyman, 2020).

Based on these results, tracking metabolic biomarkers, including insulin sensitivity, blood glucose variations, and inflammatory markers, may enable the identification of AD before conventional tau-based diagnostics become practical.

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Using AI to Diagnose Alzheimer's Disease Early

With its substantial benefits in processing massive datasets and recognising intricate illness patterns, AI technologies are transforming medical diagnostics. AI is being used in AD in a variety of ways:

- Machine learning for biomarker analysis: AI systems can examine genetic information, metabolic profiles, and electronic medical records to identify early indicators of AD. According to Kumar *et al.* (2024), machine learning models have proven to recognise high-risk patients based on minute alterations in glucose metabolism, inflammatory markers, and cognitive performance.
- Analysis of neuroimaging: AI-powered image processing can identify subtle structural and functional brain alterations that occur before symptoms appear. Deep learning models trained on MRI and PET images can accurately classify early-stage AD (Franzmeier *et al.,* 2020).
- The role of retinal imaging in brain health: AI-assisted retinal imaging has been investigated as a non-invasive technique for identifying early neurodegenerative alterations, as the retina and the brain share anatomical similarities (Kumar *et al.,* 2024). AI models that analyse retinal scans have shown promise in identifying early vascular and neuronal abnormalities associated with AD. Retinal imaging offers a non-invasive window into cerebral pathology, as the retina shares embryological and anatomical features with the brain (Cheung *et al.,* 2021). AI-driven analysis has detected changes, including retinal nerve fibre layer thinning, microvascular alterations, and amyloid-related deposits, all of which correlate with AD-related neurodegeneration (Sánchez *et al.,* 2020; Jo *et al.,* 2022). These findings highlight the potential of AI-enhanced retinal screening as a cost-effective, accessible method for early detection of AD, particularly in at-risk populations.

Future Directions and Possible Clinical Implications

There are numerous encouraging clinical ramifications when metabolic indicators and AI are used in early Alzheimer's diagnosis. Early therapeutic interventions, including lifestyle modifications, pharmacological treatment, and cognitive training, can be implemented when individuals at risk of AD are identified through the presence of metabolic biomarkers, prior to the accumulation of tau pathology. Detecting markers such as insulin resistance, dysregulated glucose metabolism, or mitochondrial dysfunction allows for proactive strategies aimed at slowing disease progression and

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preserving cognitive function (Arnold *et al.,* 2018; Kapogiannis and Mattson, 2018). AI in personalised medicine can assist in customising treatment plans according to a patient's genetic risk factors and metabolic profile.

Additionally, non-invasive screening tools, such as AI-assisted metabolic biomarker analysis and retinal imaging, may offer affordable and easily accessible alternatives to costly, invasive procedures such as CSF analysis and PET scans.

Future research should aim to validate these approaches on a large scale in various populations to guarantee their efficacy in clinical settings. Developing and incorporating predictive models into standard medical care requires interdisciplinary partnerships involving neurologists, data scientists, and endocrinologists.

Early Diagnosis Offers Financial Benefits

By enabling earlier interventions that slow the progression of the disease, early diagnosis through metabolic screening and AI-based techniques could significantly reduce healthcare expenses. One possible cost-saving advantages are:

- Delaying the advancement of the disease by only five years: Studies have shown that delaying the onset of AD by five years may result in a roughly 50% decrease in cases and a significant reduction in healthcare expenses (Brookmeyer *et al.,* 2018). As a result, medical and long-term care costs could be reduced by hundreds of billions of dollars a year.
- Cutting down on emergency room visits and hospitalisations: Hospitalisation rates are higher for AD patients due to infections, falls, and the consequences of the disease's progression. According to the Alzheimer's Association (2023), early intervention might save $7,000 to $15,000 annually per patient by preventing needless hospitalisations.
- Reducing the cost of long-term care: Most AD patients eventually require full-time care support or nursing home care, which costs between $80,000 and $100,000 annually in the United States. By extending independent living, slowing progress might result in a 20–30% reduction in these costs (Gaugler *et al.,* 2022).

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The Price of Technologies for Early Diagnosis

Although the implementation of AI-based metabolic screenings and early diagnostic tools comes with some upfront expenses, research suggests that they could result in significant long-term savings:

- Costs associated with screening for AI: Compared to PET scans, which cost between $5,000 and $7,000 per scan, AI-driven blood tests and retinal imaging are expected to cost between $500 and $1,000 per individual (Kumar *et al.,* 2024). Implementing AI widely could lower overall diagnostic costs by 40–50%, increasing accessibility to screening.
- Economic Rationale for Investing: According to a 2009 study by Weimer and Sager, investing in early detection techniques could result in a 10:1 return on investment by lowering hospitalisation and long-term care expenses.

By funding AI-based early detection initiatives, governments could save billions of dollars in public healthcare costs over time.

Conclusion

Amyloid-beta and tau detection are the mainstays of traditional Alzheimer's diagnostics, which frequently diagnose the illness too late for effective treatment. Nonetheless, mounting data points to insulin resistance and metabolic dysfunction as potential early markers of AD, offering a significant chance for an earlier diagnosis. AI-driven approaches significantly improve diagnostic accuracy by examining large datasets and identifying minor illness signals before tau clumps appear in scans. Moreover, mounting evidence highlights insulin resistance and metabolic dysfunction as potential early markers of AD, offering a critical window for earlier diagnosis. AI-driven approaches significantly enhance diagnostic accuracy by analysing large-scale datasets and detecting subtle disease signals well before tau clumps appear on neuroimaging. This suggests that integrating AI into diagnostic systems has the potential to transform early detection of AD, enabling timely interventions. In addition to improving patient outcomes, early diagnosis also presents a compelling financial advantage by reducing the long-term costs associated with advanced-stage care. In addition to improving patient outcomes, early diagnosis presents a compelling financial argument by significantly reducing medical expenses. Future research will be necessary to confirm these

DOI: https://doi.org/10.5526/esj.415

techniques and apply them in clinical settings, which could revolutionise the diagnosis and treatment of AD.

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DOI: https://doi.org/10.5526/esj.415