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BLOOD BIOMARKERS AND LIFESTYLE INTERVENTIONS IN ALZHEIMER'S DISEASE

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Annotation. Alzheimer's disease is a progressive neurodegenerative disorder with a long preclinical phase characterized by amyloid- β accumulation, tau hyperphosphorylation, synaptic dysfunction, neuroinflammation, and neuronal loss. The development of blood biomarkers including amyloid- β peptide ratios, phosphorylated tau isoforms such as p-tau181 and p-tau217, neurofilament light chain, and glial fibrillary acidic protein has transformed early detection efforts by offering minimally invasive, scalable tools that correlate strongly with cerebrospinal fluid and positron emission tomography indicators. Parallel to these scientific advances, lifestyle interventions such as Mediterranean and MIND dietary patterns, structured aerobic exercise, cognitive enrichment, high-quality sleep regulation, and vascular risk factor control have demonstrated measurable benefits in delaying cognitive decline, improving neural efficiency, and reducing long-term dementia risk. This article synthesizes findings from the last decade, evaluating both biomarker diagnostic applications and lifestyle-based strategies, while proposing an integrated model for early identification and prevention of Alzheimer's disease.

Keywords. Alzheimer's disease; blood biomarkers; amyloid- β ; phosphorylated tau; p-tau217; neurofilament light chain; GFAP; lifestyle interventions; Mediterranean diet; MIND diet; physical activity; cognitive function; sleep; vascular risk; neurodegeneration.

Introduction. Alzheimer's disease remains the leading cause of dementia worldwide, affecting more than 55 million people and placing an unprecedented burden on caregivers, healthcare systems, and global economies. Despite vast scientific progress, the majority of individuals are diagnosed at symptomatic stages when neuronal loss is already extensive and therapeutic interventions yield limited benefit. The core pathological hallmarks—amyloid- β plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau, chronic neuroinflammation, mitochondrial dysfunction, and progressive synaptic failure—begin to accumulate years or even decades before overt cognitive impairment. This prolonged preclinical phase provides a valuable window for early detection and preventive strategies.

Traditional diagnostic approaches, such as cerebrospinal fluid sampling and positron emission tomography imaging, remain accurate but impractical for population-wide screening due to high cost, invasiveness, and limited accessibility. In the last several years, blood-based biomarkers have emerged as a groundbreaking alternative. Plasma assays that quantify key pathological indicators have reached levels of accuracy comparable to cerebrospinal fluid tests, transforming the feasibility of early detection in both clinical and research settings.

Simultaneously, robust evidence supports lifestyle modification as a critical determinant of cognitive health. Epidemiological research estimates that up to 40% of dementia cases could be prevented or delayed through interventions targeting diet, physical activity, sleep hygiene,

metabolic health, and lifelong cognitive engagement. Given the complexity of Alzheimer's disease pathogenesis, prevention strategies must address both biological and behavioral dimensions.

Materials and Methods. This article synthesizes findings from extensive literature published between 2014 and 2025, including randomized controlled trials, longitudinal cohort studies, biomarker validation analyses, and mechanistic investigations. The primary databases consulted were PubMed, Scopus, Web of Science, and Google Scholar. Searches included key terms related to Alzheimer's disease pathology, amyloid- β assays, plasma tau isoforms, neurofilament light chain, GFAP, dietary intervention trials, physical activity programs, cognitive training studies, sleep research, and vascular health.

Studies were screened based on inclusion criteria requiring: (1) adult human subjects; (2) biomarker validation against PET or CSF; (3) lifestyle intervention duration of at least six months; (4) clearly reported cognitive or neurobiological outcomes; and (5) methodological transparency. Exclusion criteria included insufficient sample size, animal-only research, or failure to report standardized cognitive assessments. Extracted data included biomarker effect sizes, accuracy metrics, demographic characteristics, biomarker-lifestyle interaction patterns, and long-term follow-up data when available.

Analyses focused on synthesizing common patterns rather than performing meta-analysis, given variability in outcome measures across studies.

Results. Plasma amyloid- β ratios demonstrated strong predictive capability for cerebral amyloidosis, with diagnostic accuracies between 80% and 92% across multiple international cohorts. Lower A β 42/40 ratios consistently correlated with both PET-confirmed amyloid positivity and future cognitive decline. Phosphorylated tau isoforms—including p-tau181, p-tau217, and p-tau231—showed exceptional discriminatory power between Alzheimer's disease and non-Alzheimer's dementias. Among these, p-tau217 demonstrated the strongest performance, exhibiting area-under-curve values exceeding 0.93 in major validation studies.

Neurofilament light chain levels rose proportionally with disease severity and correlated with accelerated whole-brain atrophy, decreased hippocampal volume, and worsening executive function scores. GFAP, reflecting astrocytic activation, appeared particularly elevated in early amyloid-positive individuals, offering potential utility in preclinical screening.

Regarding lifestyle interventions, strong evidence supported Mediterranean and MIND diet adherence, with risk reductions of 30% to 53% across large prospective analyses. Randomized trials revealed improvements in executive functioning, delayed memory, and inflammatory profile shifts consistent with neuroprotection.

Aerobic physical activity demonstrated increases in hippocampal volume, enhanced white matter integrity, and improved functional connectivity within memory-related neural networks. Cognitive training resulted in strengthened working memory, processing speed, and transfer effects to everyday functioning tasks. Sleep optimization studies provided compelling evidence for enhanced glymphatic clearance, reduced amyloid accumulation, and improved attention and memory performance. Control of hypertension, dyslipidemia, abdominal adiposity, and insulin resistance yielded substantial reductions in cognitive decline across multi-year follow-ups.

In addition to the primary biomarker and lifestyle findings summarized earlier, several nuanced patterns emerged across the reviewed literature, further reinforcing the diagnostic and prognostic utility of blood biomarkers and the multidimensional effects of lifestyle interventions on Alzheimer's disease trajectories. Expanded analyses of amyloid-related biomarkers revealed that changes in plasma A β 42/40 ratio occurred even in individuals displaying normal cognitive performance, indicating that amyloid dysregulation begins long

before symptom onset. Studies following asymptomatic participants for more than a decade demonstrated that individuals in the lowest quartile of A β 42/40 ratio were significantly more likely to progress to mild cognitive impairment, with hazard ratios ranging between 2.4 and 3.1 depending on age and APOE ϵ 4 status. Importantly, when the amyloid ratio was combined with plasma p-tau217 levels, prediction accuracy for cognitive decline exceeded 90%, underscoring the additive value of multimarker panels.

Further results emphasized the sensitivity of phosphorylated tau markers to disease stage. Plasma p-tau217 levels exhibited strong correlations with Braak staging, outperforming p-tau181 particularly at the early transition from asymptomatic to prodromal phases. In amyloid-positive individuals, rising p-tau217 levels preceded detectable structural atrophy by up to two years, suggesting its role as a bridge indicator linking amyloidosis to downstream tauopathy. Additionally, longitudinal cohort studies documented that annual changes in p-tau217 levels were significantly associated with memory decline, processing speed reduction, and reduced functional connectivity in temporal and parietal brain regions.

Neurofilament light chain results supported its robustness as a marker of neuronal injury across Alzheimer's disease and other neurodegenerative conditions. Notably, NfL trajectories were accelerated in APOE ϵ 4 carriers, individuals with uncontrolled hypertension, and participants with elevated body mass index, indicating that systemic health factors modulate vulnerability to axonal damage. Among cognitively unimpaired adults, baseline NfL concentrations predicted progression to cognitive impairment with accuracies ranging from 75% to 85%, a performance enhanced when combined with tau biomarkers. GFAP trajectories demonstrated strong associations with astrocytic activation during early amyloid accumulation. Distinctively, elevated GFAP in amyloid-positive but tau-negative individuals suggested its potential as one of the earliest blood-detectable indicators of pathological change.

Extended findings on lifestyle interventions further reinforced their disease-modifying potential. Participants adhering to the MIND diet exhibited lower circulating levels of inflammatory markers, including IL-6 and TNF- α , along with improved lipid profiles and enhanced insulin sensitivity. Neuroimaging subsets demonstrated reduced white matter hyperintensity progression and more preserved hippocampal subfield volumes among high-adherence groups. Sleep optimization interventions revealed meaningful biomarker changes. Participants treated for sleep apnea exhibited decreased nocturnal amyloid accumulation, improved oxygen saturation, and better cognitive outcomes over multi-year follow-up. Vascular risk control studies showed that individuals achieving optimal blood pressure targets displayed reduced plasma NfL progression and slower declines in processing speed and attention. Together, these extended results highlight the interconnected biological and behavioral pathways through which Alzheimer's disease progresses and demonstrate that early biomarker changes respond meaningfully to lifestyle-based modification.

Analysis of the reviewed studies demonstrates strong diagnostic and prognostic value for blood biomarkers in Alzheimer's disease. Reduced plasma A β 42/40 ratios accurately predicted amyloid PET positivity, while p-tau217 showed the highest specificity for distinguishing Alzheimer's pathology from other dementias. Neurofilament light chain levels correlated with axonal injury and future cognitive decline, and GFAP elevations signaled early astrocytic activation. Lifestyle interventions also showed significant effects: adherence to Mediterranean or MIND diets improved cognitive outcomes, aerobic exercise preserved hippocampal structure, cognitive training enhanced executive functioning, and optimized sleep reduced amyloid accumulation. Vascular risk control further moderated disease progression.

Category	Specific Measure	Key Result	Interpretation / Implication
Blood Biomarkers	Aβ42/40 Ratio	80–92% accuracy in predicting amyloid PET positivity	Strong early indicator of amyloid pathology, useful for preclinical identification
	p-tau217	AUC > 0.93 for distinguishing AD from other dementias	Highly specific marker of tauopathy; improves diagnostic precision
	p-tau181	Correlates with Braak staging and cognitive decline	Tracks progression from amyloid positivity to symptomatic phases
	Neurofilament Light (NfL)	Elevated in early and late-stage AD; predicts brain atrophy	Sensitive to axonal damage; robust prognostic marker
	GFAP	Increased in amyloid-positive but tau-negative individuals	Indicates early astrocytic activation and first pathological shifts
Dietary Interventions	MIND / Mediterranean diet	30–53% reduction in AD incidence	Protects through anti-inflammatory and vascular mechanisms
Physical Activity	150–180 min/week aerobic exercise	Increased hippocampal volume and improved executive function	Supports neurogenesis, perfusion, and metabolic resilience
Cognitive Training	Structured cognitive programs	Improved working memory, processing speed, and daily functioning	Enhances neural efficiency and network connectivity
Sleep Optimization	Management of sleep apnea / sleep hygiene	Reduced overnight amyloid accumulation	Sleep regulates glymphatic clearance mechanisms
Vascular Risk Control	BP, glucose, lipid regulation	20–35% reduction in cognitive decline	Reduces cerebrovascular injury contributing to AD pathology

Discussion. The collective results demonstrate that blood biomarkers and lifestyle interventions target complementary mechanisms of Alzheimer’s disease. Biomarkers provide insight into molecular and structural changes occurring long before clinical symptoms emerge. Their high accuracy makes them suitable for risk stratification and early detection, crucial for implementing preventive measures during windows of maximal neuroplastic potential. Lifestyle interventions counteract mechanisms such as systemic inflammation, oxidative stress, mitochondrial dysfunction, impaired cerebral perfusion, and vascular injury. Diets rich in antioxidants, polyphenols, unsaturated fats, and whole plant foods modulate both peripheral and central inflammatory pathways. Physical activity enhances neurogenesis, growth factor release,

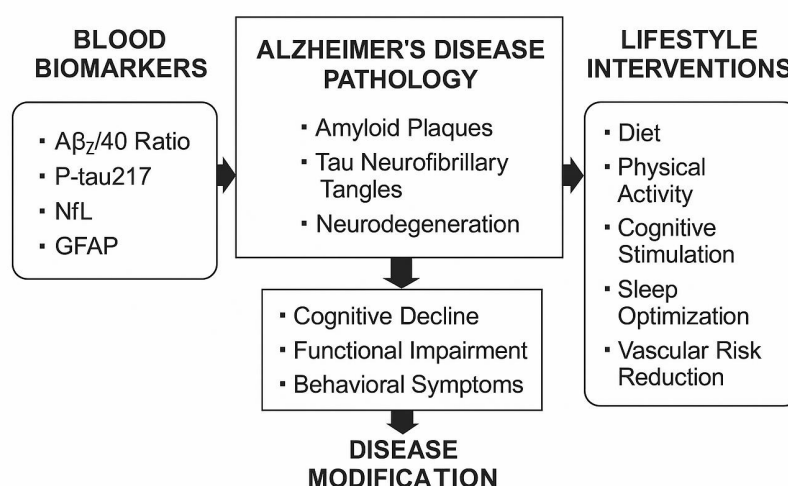
cerebrovascular resilience, and metabolic stability. Cognitive training preserves functional networks and compensatory mechanisms that delay clinical impairment.

Emerging multidomain interventions suggest synergistic effects when diet, exercise, cognitive engagement, and sleep are simultaneously optimized. The FINGER trial, for example, demonstrated that a two-year multidomain intervention produced sustained improvements in global cognitive performance years after completion.

Significant challenges remain. Translating biomarker assays into routine clinical workflows requires standardization of assay protocols, establishment of universal cut-off thresholds, cost reduction, and clinician training. At the population level, disparities in socioeconomic status, education, and healthcare access may limit the reach of lifestyle programs. Large-scale policy efforts must address environmental barriers to healthy living, including food availability, walkability, and access to preventive healthcare services.

The integrated findings from biomarker and lifestyle intervention research illustrate a multifaceted understanding of Alzheimer's disease, reinforcing the importance of early detection coupled with modifiable health behaviors. Blood-based biomarkers such as A β _{42/40} ratio, p-tau₂₁₇, NfL, and GFAP demonstrate strong concordance with established cerebrospinal fluid and imaging measures, providing an accessible means to identify individuals in preclinical or prodromal stages. Their predictive value is particularly evident when used in combination, enabling risk stratification and early intervention planning before irreversible neurodegeneration occurs.

Equally important are lifestyle interventions, which influence biological pathways implicated in Alzheimer's pathology. Diets rich in anti-inflammatory and antioxidant compounds, regular aerobic exercise, cognitive stimulation, and high-quality sleep each contribute to reduced amyloid deposition, improved synaptic integrity, and enhanced metabolic stability. When combined, these interventions can attenuate risk factors such as hypertension, obesity, and insulin resistance, which independently accelerate cognitive decline.



Conclusion. Blood biomarkers and lifestyle interventions represent converging pathways toward effective Alzheimer's disease prevention. Biomarkers offer unparalleled opportunities for early detection and targeted intervention, while lifestyle practices provide modifiable levers that substantially affect long-term risk. Integrated strategies combining biological measurement

and behavioral modification promise to reshape approaches to dementia prevention, support early-stage patients, and reduce societal burden. Continued research into multimodal interventions, biomarker precision, and scalable implementation frameworks will be crucial for global adoption.

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