Metabolic syndrome and Alzheimer's disease: Mechanistic links and precision prevention (Review)

HANLU CHEN[1,2*], TAO DING[1-3*], YIFAN ZHU[1,2], MEI YANG[3], FANGSHENG WANG[1-3], PUWEN CHEN[1,3], HAIHONG LIN[1,2], HUAPEI KANG[1,3], MAOHONG HU[2], JUN ZHOU[4] and XIAOLING WANG[1-3]

[1]Department of Laboratory Medicine, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi 341000, P.R. China; [2]College of Medical Technology, Gannan Medical University, Ganzhou, Jiangxi 341000, P.R. China; [3]The First School of Clinical Medicine, Gannan Medical University, Ganzhou, Jiangxi 341000, P.R. China; [4]Department of Laboratory Medicine, Beijing Jishuitan Hospital Guizhou Hospital, Guiyang, Guizhou 550000, P.R. China

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Abstract. Metabolic syndrome (MetS) is associated with increased risk of Alzheimer's disease (AD), however, the majority of previous studies regard MetS as an isolated risk factor and focus on single pathways, lacking systematic understanding of combined effects among multiple metabolic components. The present review systematically summarizes the multifaceted mechanisms by which MetS promotes AD pathology, including insulin resistance and cerebral energy dysregulation, oxidative stress and mitochondrial dysfunction, neuroinflammation and glial cell activation, vascular dysfunction and dysregulation of the renin-angiotensin system, as well as the central convergent signaling pathway involving glycogen synthase kinase-3β. The present review further highlights emerging regulatory mechanisms involving the gut-brain axis, epigenetic reprogramming, sex differences and hormonal effects and senescent microenvironment. By emphasizing the peripheral-central crosstalk and interactive amplification of MetS components, the present review aimed to position AD as a central manifestation of systemic metabolic disorders in the brain and propose a multi-domain precision strategy integrating lifestyle intervention, metabolic drug repurposing, gut microbiota regulation, anti-aging therapy and biomarker-guided subtype classification for intervention against MetS-associated AD.

Correspondence to: Dr Jun Zhou, Department of Laboratory Medicine, Beijing Jishuitan Hospital Guizhou Hospital, 25 Shachong South Road, Guiyang, Guizhou 550000, P.R. China
E-mail: 814354216@qq.com

Dr Xiaoling Wang, Department of Laboratory Medicine, The First Affiliated Hospital of Gannan Medical University, 128 Jinling West Road, Ganzhou, Jiangxi 341000, P.R. China
E-mail: wangxiaoling1@gmu.cn

*Contributed equally

Abbreviations: Ang II, angiotensin II; APP, amyloid precursor protein; AT1R, Ang II type 1 receptor; Aβ, amyloid-β; ACE, Ang-converting enzyme; BACE1, b-site APP cleaving enzyme 1; BBB, blood-brain barrier; CMA, chaperone-mediated autophagy; DASH, Dietary Approaches to Stop Hypertension; GLP-1, glucagon-like peptide-1; GM, gut microbiota; GSK-3β, glycogen synthase kinase-3β; IGF, insulin-like growth factor; IR, insulin resistance; MAPT, microtubule-associated protein τ; MetS, metabolic syndrome; NFT, neurofibrillary tangle; ox-LDL, oxidized low-density lipoprotein; RAS, renin-Ang system; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIRT3, silent information regulator 2-like protein 3; TNF-α, tumor necrosis factor-α

Key words: metabolic syndrome, Alzheimer's disease, insulin resistance, inflammatory factor, gut-brain axis, aging microenvironment

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1. Introduction

Metabolic syndrome (MetS) and Alzheimer's disease (AD), major global public health challenges, are widely acknowledged by the academic community to have a complex, bidirectional promoting association (1,2). MetS comprises a cluster of interconnected risk factors associated with cardiovascular disease and diabetes, including abnormal glucose metabolism, elevated blood pressure and triglycerides, reduced high-density lipoprotein cholesterol and obesity (particularly central obesity) (3). Its pathogenesis may involve defects in adipocyte differentiation and increased visceral fat, triggering reactive oxygen species (ROS) production via nicotinamide adenine dinucleotide phosphate oxidase activation, leading to oxidative stress. This decreases levels of anti-inflammatory

adiponectin, and increases the release of tumor necrosis factor (TNF)-α, IL-6, plasminogen activator inhibitor-1 and oxidized low-density lipoprotein (ox-LDL), culminating in inflammation and thrombosis (4). AD is a neurodegenerative disorder characterized by progressive memory loss and dementia, with pathological hallmarks including amyloid Aβ deposition, neurofibrillary tangles (NFTs), neuronal loss, synaptic dysfunction and brain atrophy; AD is influenced by various factors such as genetics, aging, hypertension and diabetes (5,6).

MetS and its components are risk factors for the development of AD. A prospective cohort study showed that individuals with MetS have a 25% higher risk of dementia, with the risk increasing alongside the number of MetS components (7). Other research has linked MetS and its components with an increased risk of young-onset dementia (8). In addition, a predominantly USA-based cohort of patients with subclinical MetS showed a higher probability of developing neurocognitive decline, AD and associated dementias, with an even higher risk when cerebral small-vessel disease was present (9). How MetS influences AD requires further investigation. Current research is often limited to single pathways or late-stage interventions, failing to elucidate the cascade from systemic metabolic disturbances to brain injury and lacking an integrated preventive and therapeutic perspective encompassing risk prediction, early intervention and precision treatment.

To overcome the aforementioned limitations, the present review aimed to outline the pathophysiological mechanisms of MetS-driven AD and propose precise strategies ranging from basic lifestyle interventions to metabolic drugs that improve AD pathology, including targeted therapies to provide new insights for breaking the cycle between MetS and AD and achieving early prevention and treatment of AD.

2. Core mechanisms linking MetS with AD

Insulin resistance (IR) and brain energy metabolism disorder. Insulin is a key hormone regulating glucose, lipid and protein metabolism, modulating blood glucose by promoting glucose uptake, enhancing glycogen and lipid synthesis and inhibiting hepatic gluconeogenesis and lipolysis (10). When insulin sensitivity or signal responsiveness declines, IR develops (11). IR is classified into primary and secondary types based on its pathogenesis: Primary insulin resistance results from genetic defect with compensatory hyperinsulinemia and cannot be fully reversed by weight loss. Secondary IR is caused by acquired factors such as obesity (particularly visceral obesity), adipose tissue hypoplasia or dysfunction, excessive secretion of glucagon, hyperglycemia and certain medications, with obesity being the most common cause (12). Adipose tissue dysfunction (excessive lipolysis, inflammation, hypoxia and macrophage infiltration) serves a key role in the onset and progression of obesity-associated IR (13), which is a crucial pathological basis for the impact of MetS on the central nervous system.

In the central nervous system, insulin and insulin-like growth factor (IGF)-1/2 signaling are key for brain energy metabolism, synaptic plasticity and cognitive function (14). Expression of insulin, IGF-1/2 and their receptors is notably reduced in the brain tissue of patients with AD, particularly in the hippocampus and hypothalamus (15). Disrupted insulin signaling promotes the activation of the Aβ precursor protein/Aβ pathway, increasing Aβ production. Excess insulin competitively inhibits insulin-degrading enzyme, impairing Aβ clearance and accelerating amyloid plaque formation (16). In the absence of overt peripheral metabolic abnormality, local brain IR can directly impair synaptic transmission and nural plasticity by decreasing the expression and phosphorylation levels of glutamate receptor subunits (17). Furthermore, IR induced by a high-fat diet (HFD) leads to abnormal palmitoylation of the α-amino-3-hydroxy-5-methyl-4-isoxazolep ropionic acid receptor subunit Glutamate receptor subunit GluA1 via activation of the forkhead box O3a signaling axis, hindering its membrane surface transport, thereby inhibiting long-term potentiation and impairing learning and memory function (18) (Fig. 1).

Oxidative stress and mitochondrial dysfunction. Previous studies have confirmed that oxidative stress precedes Aβ deposition and NFT formation (19) and impaired energy metabolism occurs before cognitive deficit in early AD (20), suggesting that oxidative stress and mitochondrial dysfunction may be early drivers of the AD pathological cascade. Mitochondrial dysfunction leads to an imbalance in the electron transport chain and ROS production (21). MetS contributes to decreased mitochondrial respiratory chain activity and membrane potential and excessive ROS production through multiple pathways, including impaired glucose use, inhibited insulin signaling, disordered fatty acid metabolism, a positive feedback loop between inflammation and ROS and compromised mitophagy (22,23). ROS and mitochondrial damage reinforce each other, leading to an energy crisis, accelerated Aβ and τ pathology, activation of neuroinflammation and ultimately contributing to AD development.

ROS promotes oxidative modification of the amyloid precursor protein (APP) protein. Mitochondrial energy deficit upregulates the β-secretase activity of β-site APP cleaving enzyme 1 (BACE1) activity, making oxidized APP protein more susceptible to cleavage by β-secretase, leading to increased Aβ production (24). ROS inhibits serine/threonine-protein phosphatase 2A and activates glycogen synthase kinase-3β (GSK-3β), promoting τ hyperphosphorylation and NFT formation (25). Mitochondria are trafficked to synaptic compartments within neurons to sustain neuronal growth and development. Mitochondrial damage leads to neuronal energy crisis, subsequently decreasing synaptic plasticity (26). This effect on synaptic memory is associated with interactive regulation involving the cAMP response element-binding protein/regulator of calcineurin 1 pathway (27,28). Damaged mitochondria release mitochondrial DNA and ROS as damage-associated molecular patterns, thus activating the NLR family pyrin domain-containing 3 inflammasome, and producing IL-1β and TNF-α, which exacerbate Aβ and τ pathology (29,30). These interconnected steps form a cycle from MetS to oxidative stress and mitochondrial dysfunction, leading to Aβ/τ pathology, neuronal death, cognitive decline and ultimately manifesting as AD.

Silent information regulator 2-like protein 3 (SIRT3) is a NAD^+-dependent deacetylase primarily localized in mitochondria that serves important roles in cellular metabolism,

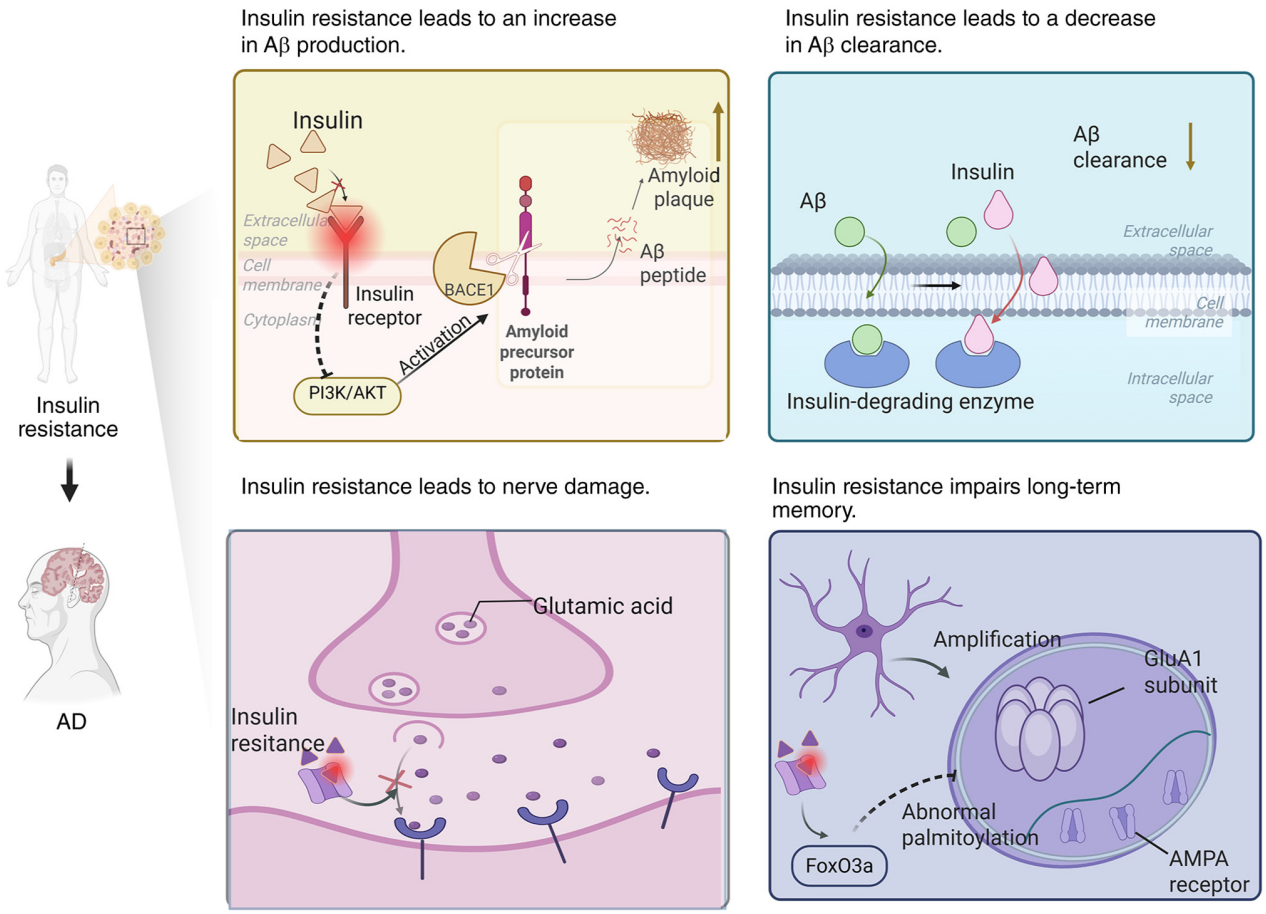


Figure 1. Association between insulin resistance and AD. Insulin resistance drives AD progression through four major pathways. Insulin resistance impairs insulin receptor signaling, which alters amyloid precursor protein processing and increases the production of Aβ peptides, facilitating amyloid plaque formation. Insulin resistance decreases the activity of insulin-degrading enzyme, a cytosolic and endosomal metalloprotease responsible for Aβ degradation, thereby decreasing Aβ clearance. Insulin resistance disrupts glutamate homeostasis at synapses, triggering excitotoxicity and neuronal damage. Insulin resistance promotes abnormal palmitoylation of the GLUA1 subunit of AMPA receptors via FOXO3a, which impairs AMPA receptor function and leads to deficit in long-term memory. AD, Alzheimer's disease; Aβ, amyloid β; GluA1, glutamate receptor subunit A1; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropi onic acid receptor; BACE1, β-site amyloid precursor protein cleaving enzyme 1.

energy homeostasis, oxidative stress, autophagy and cell survival (31). As the most abundant mitochondrial deacetylase expressed in the nervous system, SIRT3 regulates electron transport chain activity, stabilizes mitochondrial membrane potential and enhances antioxidant capacity (32). In MetS models, blood glucose, fatty acids and inflammatory signals inhibit SIRT3 expression or activity, leading to mitochondrial protein hyperacetylation, increased ROS and accelerated mitochondrial metabolic dysregulation (33,34), rendering neurons more vulnerable to Aβ and τ pathology, and accelerating AD progression.

Neuroinflammation and glial cell activation. MetS is not a static condition but a dynamic state of bodily disturbance accompanied by inflammation. This inflammation disrupts peripheral and central immune homeostasis, particularly microglial function, and converts metabolic crisis into pathological catastrophe in the brain, driving the onset and progression of AD (35).

Obesity, the primary pathological phenotype of MetS, represents a chronic stress state in adipose tissue (36,37). Adipocyte hypertrophy or local hypoxia induces macrophage infiltration, prompting the coordinated release of pro-inflammatory adipokines and forming a local 'inflammatory storm' (38). Damaged adipose tissue secretes TNF-α and IL-6, inducing persistent low-grade chronic inflammation (39,40). Monocytes are recruited to adipose tissue and polarize into pro-inflammatory M1-type macrophages, releasing IL-1β, IL-18 and ROS, thus continuously amplifying inflammatory signals (41). Metabolic abnormality and inflammatory responses exhibit a positive feedback association: Inflammatory factors such as TNF-α interfere with insulin receptor substrate tyrosine phosphorylation, inhibiting insulin signal transduction and exacerbating IR (42,43). Hyperglycemia and free fatty acids activate classical inflammatory pathways such as NF-κB (44), forming a vicious cycle where metabolic abnormalities induce inflammation, and inflammation exacerbates metabolic disorder.

Against a backdrop of sustained systemic inflammation, peripheral inflammatory signals affect the central nervous system through multiple routes. Inflammatory factors can directly enter the brain when the blood-brain barrier (BBB) is compromised. With an intact BBB, peripheral inflammation activates brain endothelial cells, 'transducing' the inflammatory signal to the central nervous system (45,46). Microglia chronically exposed to inflammatory stimuli become hyperactivated,

polarizing into a neurotoxic disease-associated phenotype (47). In AD, hyperactivated microglia exhibit three aspects of dysfunction: i) Impaired phagocytic clearance, which decreases Aβ clearance efficiency; ii) sustained release of ROS and pro-inflammatory factors damaging neurons and synapses; and iii) aberrantly enhanced synaptic pruning, which non-selectively engulfs functional synapses (48,49). Microglia can transform into an anti-inflammatory phenotype under specific microenvironments; therefore, regulating microglial phenotypic balance, rather than simply inhibiting their activation, is a potential therapeutic strategy for MetS-associated AD (50).

Inflammatory factors released by microglia (such as IL-1β and TNF-α) activate astrocytes, shifting them from a supportive phenotype to a pro-inflammatory state, impairing metabolic and nutritional support for neurons and secreting inflammatory mediators (51). Activated astrocytes typically form a 'glial barrier' around Aβ plaques, potentially hindering pathological protein clearance and enhancing plaque neurotoxicity. Sustained inflammatory signaling activates inflammasomes through dysregulated autophagy and mitochondrial dysfunction, driving neurodegeneration (52).

Renin-angiotensin (Ang) system (RAS) dysfunction and vascular disturbance. Systemic metabolic disturbance and chronic inflammation associated with MetS persistently activate RAS, disrupting cerebrovascular homeostasis and promoting neurodegeneration. RAS comprises renin, Ang, Ang-converting enzyme (ACE) and Ang II (53), functionally divided into the classical axis [ACE-Ang II-Ang II type 1 receptor (AT_1R)], mediating vasoconstriction, inflammation and oxidative stress, and the protective axis [ACE2-Ang-(1-7)-Mas], promoting vasodilation and anti-inflammation. These two axes maintain dynamic balance under physiological conditions, however, in the context of MetS, visceral fat expresses and releases nearly all RAS components via autocrine and paracrine mechanisms (54,55). Adipocyte hypertrophy and hypoxia in obesity enhance the production of renin, ACE and Ang II (56). Simultaneously, high levels of free fatty acids and ox-LDL induce the overexpression of AT1R and increase Ang II generation by activating the chymase pathway in peripheral blood mononuclear cells, amplifying classical RAS axis activity in endothelial cells and macrophages (57,58).

Persistent overactivation of RAS is associated with cognitive decline (59). In brain tissue of patients with AD, the expression of ACE, Ang II and AT1R is enhanced, and elevated cerebrospinal fluid ACE levels are associated with the degree of Aβ deposition (60). Mechanistically, Ang II upregulates BACE1 (61) and γ-secretase activity (62), thus promoting Aβ generation, and promotes abnormal τ phosphorylation via GSK-3β activation (63). At the vascular level, sustained vasoconstriction and decreased nitric oxide bioavailability mediated by Ang II cause chronic cerebral hypoperfusion, impair lymphatic system function and compromise Aβ clearance (64). Additionally, Ang II-induced oxidative stress and inflammation disrupt tight junctions in cerebrovascular endothelial cells (65), leading to structural and functional damage to the BBB, facilitating the entry of peripheral inflammatory factors and neurotoxic substances into the brain parenchyma, hindering Aβ efflux to the periphery and further exacerbating neuroinflammation and plaque deposition (66). As excessive RAS activation contributes to cognitive decline, RAS inhibition may improve cognitive function in selected populations. For instance, brain-penetrating ACE inhibitors can slow AD progression (67), and RAS modulation delays the conversion from mild cognitive impairment (MCI) to AD (68). Nevertheless, these beneficial effects are strongly modulated by host factors such as genetic background. Cognitive protection conferred by ACE inhibitors is only observed in individuals without the APOE ε4 allele (ApoE4) (68). Notably, MetS-associated RAS imbalance does not act on the vascular system in isolation, but mutually amplifies the chronic inflammatory state, activates glial cells and induces brain IR, thus promoting AD development along the 'metabolic-vascular-immune axis' (69). Therefore, RAS should be considered as a key pathological node in AD rather than a single therapeutic target (Fig. 2).

GSK-3β: A key hub molecule. GSK-3 is a multifunctional serine/threonine kinase, which was initially named for its role in glycogen metabolism (70). GSK-3 has two primary isozymes, with GSK-3β associated with body metabolism and brain development (71). GSK-3β is primarily involved in the Wingless (Wnt)/β-catenin, NF-κB and phosphoinositide 3-kinase/protein kinase B pathways (72,73) and acts as a downstream effector of the insulin signaling Akt pathway. IR inactivates Akt, leading to GSK-3β hyperactivation (74). The Wnt/β-catenin pathway is a key regulatory network for maintaining the function of neurons, oligodendrocytes and microglia (75). Under inflammatory conditions, hyperactivated GSK-3β promotes microglial polarization towards a pro-inflammatory phenotype, releasing inflammatory factors (76) and induces vascular inflammation, disrupts the BBB and Aβ clearance and promotes mitochondrial dysfunction triggering neuronal apoptosis (77-79).

GSK-3β is a key enzyme mediating AD pathology (80). As one of the most important τ protein kinases in the body, activated GSK-3β can directly phosphorylate τ protein at multiple sites (81), causing τ to detach from microtubules and aggregate into NFTs. Furthermore, GSK-3β modulates γ-secretase activity, promoting the production of the more aggregation-prone Aβ42 (82). Notably, Aβ oligomers activate GSK-3β (83), creating a cycle. ApoE4 exacerbates AD-like pathology in mice with type 2 diabetes mellitus (T2DM) by upregulating GSK-3β activity (84). Lithium can inhibit GSK-3β activity, and lithium treatment prevents pathological changes and memory loss in AD and aging wild-type mice (85). Furthermore, traditional Chinese medicine formulas, such as Danggui Shaoyao San, serve as GSK-3β inhibitors, participating in reducing AD risk both *in vitro* and *in vivo* (86,87). In summary, GSK-3β is one of the most direct molecular bridges connecting peripheral metabolic disturbance and central nervous system pathology (Fig. 3).

3. Emerging mechanisms

Gut microbiota (GM)-brain axis. The gut-brain axis refers to the bidirectional signaling pathway between the gastrointestinal tract and the central nervous system. Bidirectional signals exist between the gut and the brain, interacting through neural, hormonal and immune regulation. Within this axis, the brain regulates intestinal motility and secretory

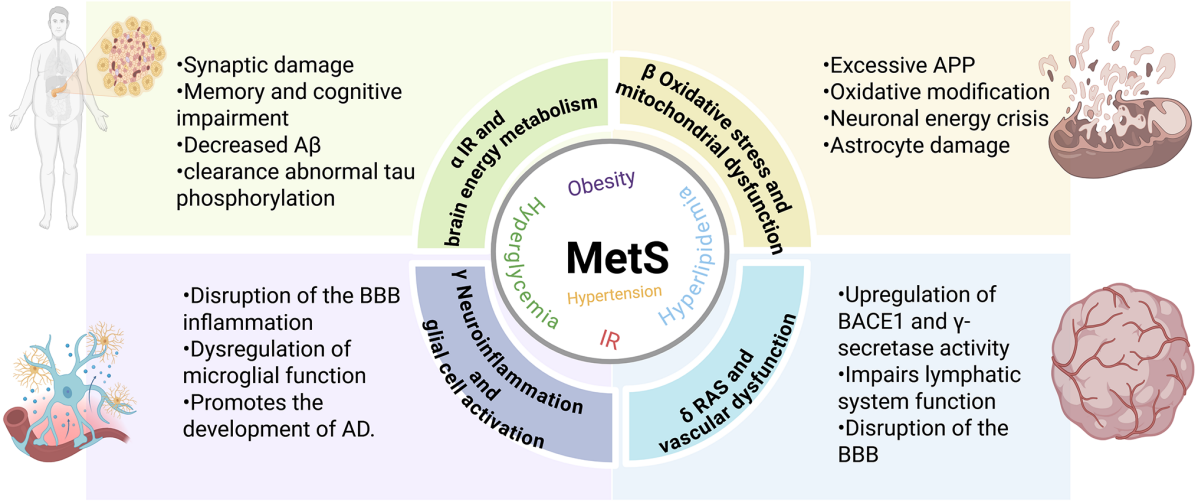


Figure 2. Mechanisms by which MetS drives AD. The core pathological components of Mets (obesity, hypertension, IR, dyslipidemia) drive the key pathologies of AD (Aβ plaque deposition, neurofibrillary tangles, neuronal damage and cognitive decline) via four key pathways: Brain energy metabolism disorder due to IR, oxidative stress and mitochondrial dysfunction, neuroinflammation and vascular dysfunction. MetS, metabolic syndrome; AD, Alzheimer's disease; Aβ, amyloid β; APP, amyloid precursor protein; BBB, blood-brain barrier; RAS, renin-angiotensin system; IR, insulin resistance.

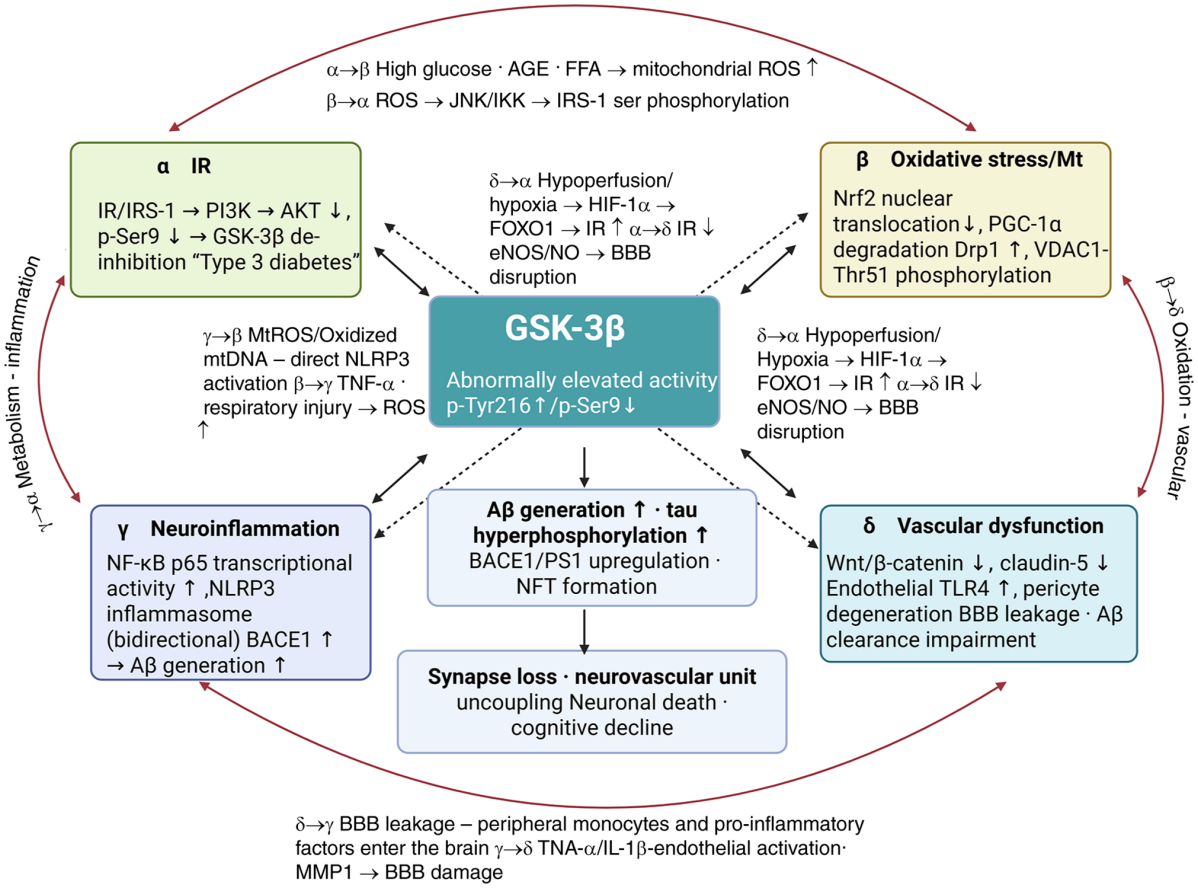


Figure 3. Key regulatory network of GSK-3β in metabolic disorder-driven Alzheimer's disease. The schematic depicts the pathological loop of metabolic syndrome-associated Alzheimer's disease. The crosstalk between IR, mitochondrial oxidative stress, neuroinflammation and vascular dysfunction drives GSK-3β hyperactivation and promotes Aβ production and τ hyperphosphorylation, leading to synapse loss, neuronal injury and cognitive decline. Red solid lines show associations between two adjacent mechanisms; dashed lines indicate opposing mechanisms; black solid lines indicate the association of each mechanism with GSK-3β. GSK, glycogen synthase kinase; AGE, advanced glycation end product; FFA, free fatty acid; ROS, reactive oxygen species; p-, phosphorylated; IKK, IκB kinase; IRS, insulin receptor substrate; HIF, hypoxia-inducible factor; eNOS, endothelial nitric oxide synthase; PGC, peroxisome proliferator-activated receptor γ coactivator; Drp, dynamin-related protein; VDAC, voltage-dependent anion channel; TLR, toll-like receptor; PS1, presenilin 1; NFT, neurofibrillary tangle; mt, mitochondrial..

functions via the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, thereby altering the gut microbial environment (88,89). Conversely, the gut GM serves a dominant role through the enteric nervous system, the vagus nerve

and its metabolites (short-chain fatty acids) (90). Therefore, the GM is associated with maintaining normal energy metabolism in the brain, and GM dysregulation may increase the risk of neurodegenerative disease. HFD induces GM imbalance in mice and exacerbates cognitive dysfunction in AD mouse models (91). Chen *et al* (92), by studying germ-free 3xTg mice, found that GM imbalance exacerbates AD pathology, potentially through induced chronic inflammatory mechanisms. GM imbalance, by enriching pro-inflammatory bacteria such as *Bacteroidetes*, activates the CCAAT/enhancer-binding protein β/asparagine endopeptidase pathway and polyunsaturated fatty acid-associated neuroinflammation, thus promoting Aβ deposition, τ phosphorylation and microglial activation, worsening AD pathology. Furthermore, GM dysregulation may promote AD development by altering intestinal function, microbial metabolite synthesis and secretion, as well as compromising the integrity of BBB (90).

Epigenetic regulation. Epigenetics refers to reversible modifications that regulate gene expression without altering the DNA sequence; epigenetic modification is a key factor in AD pathogenesis, involving dysregulations in histone modifications, DNA methylation and non-coding RNAs (93). Maternal HFD can confer susceptibility to MetS across generations via epigenetic mechanisms, affecting offspring neurodevelopment (94). Fusco *et al* (95) reported maternal metabolic abnormality decreases offspring histone H3K9ac and H3K4me3 modifications through gametic mechanisms, thereby inhibiting hippocampal brain-derived neurotrophic factor expression, leading to impaired synaptic plasticity and memory in the offspring. Furthermore, previous studies (96-98) have found altered methylation levels of multiple genes in the AD brain, particularly genes associated with Aβ metabolism and τ phosphorylation such as APP, BACE1 and microtubule-associated protein τ (MAPT). The APP gene promoter region is demethylated under AD pathology, leading to APP upregulation and increased Aβ deposition (96). Simultaneously, BACE1, the key enzyme cleaving APP to produce Aβ, is upregulated by modifications such as hypomethylation, further accelerating Aβ deposition (97). MAPT gene is also induced, leading to additional τ protein phosphorylation (98). The aforementioned studies indicate that epigenetics directly regulate AD-related gene expression and impair synaptic function, thus triggering neurodegenerative lesions.

Epigenetic modifications require metabolic substrates. Metabolic disturbance directly alters the pool sizes of key metabolites in cells, thereby affecting epigenetic modification levels (99). In summary, MetS serves as a potent epigenetic reprogrammer, actively and persistently altering gene expression programs in the brain, thus driving AD pathology. This provides a strong explanation for why midlife MetS has long-term effects on AD risk in old age (100). Epigenetic changes are typically dynamic and reversible, and are present in body fluids such as blood. Therefore, DNA methylation patterns in blood hold promise as biomarkers for early AD diagnosis and prognosis. Notably, recent research has found epigenome erosion and loss of cell identity in late-stage AD (101), offering insight for AD treatment. This suggests the possibility of restoring chromatin state stability using epigenetic modulators such as histone deacetylase inhibitors or methyltransferase regulators, and adopting stage-specific therapeutic interventions, although epigenetic intervention is in the preclinical stage (102).

Sex differences and hormonal effects. Epidemiological evidence indicates that female patients have a higher risk of developing AD than male patients, with this disparity becoming more pronounced following menopause (103,104). This may be related to differences in estrogen levels. Hypometabolism during the perimenopausal period leads to greater fluctuations in estrogen levels (105). Estrogen activates estrogen receptor β to regulate inflammasomes and neuronal mitochondrial function (106). Low estrogen levels silence receptor-mediated innate immunity, triggering systemic and central inflammation, while inducing neuronal energy crisis, collectively increasing AD pathological burden (106). Additionally, estrogen-activated receptor modulation of cascade signaling pathways involves amyloid clearance (107,108), τ phosphorylation and autophagic clearance. τ burden in postmenopausal patients is significantly higher than in age-matched male patients, whereas this difference is not apparent in premenopausal patients (109). This phenomenon of τ vulnerability during the 'menopause window' may be associated with declining estrogen levels (110,111). Furthermore, previous studies have demonstrated associations between testosterone deficiency and cognitive decline and metabolic abnormality in male patients, with testosterone supplementation decreasing τ pathological burden (112,113).

In summary, sex hormones indirectly regulate metabolism and brain health. The specific mechanisms may involve receptor activation affecting the hypothalamic-pituitary-adrenal axis (114) and inflammatory response, however, more substantial causal evidence and mechanistic integration are needed to strengthen this association. Hormone therapy can decrease AD risk (115,116), while other research proposes a therapeutic window, suggesting estrogen supplementation initiated years after menopause onset may be ineffective or harmful (117), and is closely related to age, timing of administration and formulation type (118).

Senescent microenvironment and disordered cell communication. The aging microenvironment is a detrimental tissue state dominated by senescent cells and their secretions. Excess fatty acids not only damage glial cells and neurons but also induce brain cell senescence (119). In a study by Hou *et al* (120), HFD mice showed elevated levels of the senescence marker p16 protein in the cortex and hippocampus, telomere shortening and impaired autophagy, leading to aging brain characteristics. Brain cell senescence promotes τ pathology, neuroinflammation and neurodegenerative disease progression (121). Senescent endothelial cells disrupt the BBB, mediating central inflammation and leading to neuronal loss (122); senescent glial cells secrete senescence-associated secretory phenotype (SASP) factors, transmitting inflammatory signals and disrupting neuron-glia communication, thus exacerbating neurodegenerative processes (123). Microglia can be activated via specific signaling pathways and crosstalk with astrocytes in a Wnt-dependent manner, a cell communication mechanism regulating synaptic remodeling (124). Senescent or dysfunctional microglia disrupt this Wnt-dependent intercellular

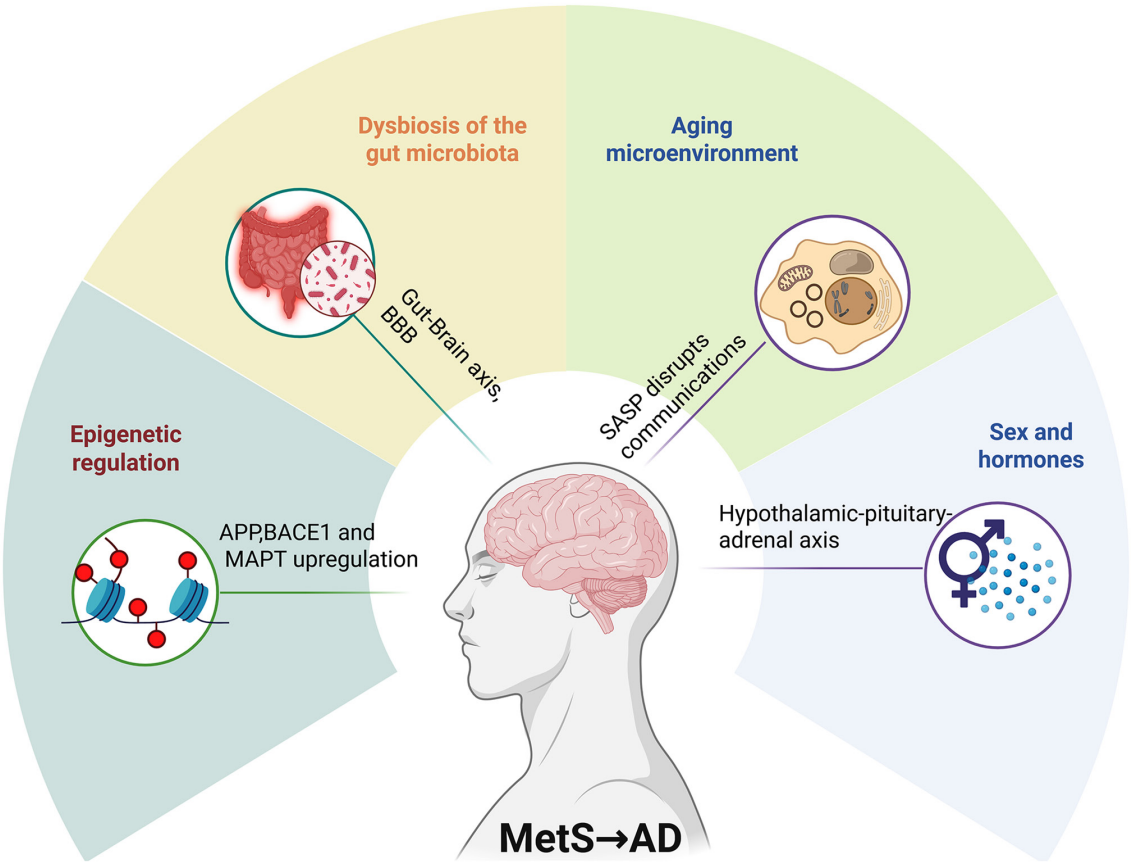


Figure 4. Factors regulating the association between MetS and AD. Dysbiosis, senescent microenvironment, epigenetic regulation and sex and hormonal influences regulate the progression of AD. Gut microbiota imbalance may induce neuroinflammation via the gut-brain axis; the aging microenvironment may interfere with neuronal communication via the SASP. Epigenetic regulation may participate in AD pathology by affecting the upregulation of APP, BACE1 and MAPT proteins. Sex and hormones regulate AD-associated processes via the hypothalamic-pituitary-adrenal axis. SASP, senescence-associated secretory phenotype; MetS, metabolic syndrome; AD, Alzheimer's disease; APP, amyloid precursor protein; BACE1, β-site amyloid precursor protein cleaving enzyme 1; MAPT, microtubule-associated protein tau; BBB, blood-brain barrier.

crosstalk, releasing excessive pro-inflammatory mediators and glutamate, directly impairing neurons and damaging synapses (125); SASP-associated factors from senescent astrocytes may drive microglia towards a pro-inflammatory, harmful activation state, impairing Aβ clearance ability (126). Additionally, factors such as IL-6 (a SASP component) may be involved in τ phosphorylation (127). Overall, an aging brain microenvironment may accelerate the onset of neurodegenerative disease. This suggests that researching drugs targeting senescence could represent a novel therapeutic direction.

4. Metabolic mechanism-based intervention strategies

Although no curative treatment for AD is available, insights derived from the aforementioned multi-level crosstalk network linking MetS with AD (Fig. 4) suggest that future preventive and therapeutic strategies may shift from conventional symptomatic approaches toward a novel paradigm of precision prevention and treatment. This paradigm is characterized by metabolic regulation-based intervention combined with multi-target combinatorial strategies (Fig. 5).

Lifestyle intervention. The pathogenesis of AD is partially associated with metabolic dysregulation, which is associated with daily lifestyle patterns. Accumulating epidemiological evidence has identified unhealthy lifestyle factors, including tobacco smoking, alcohol consumption (128), sedentary behavior (129) and sleep disturbances (130), as risk factors for AD. Furthermore, prolonged exposure to high-stress environments or negative emotional states impairs memory and cognitive function (131). These two categories of risk factors have strong evidence, as indicated by meta-analysis (132). Therefore, cessation of unhealthy habits, engagement in regular physical activity and maintenance of adequate sleep duration are key preventive measures for individuals at high risk of AD. In addition, promoting active social participation and routine health examinations may delay the pathological progression of AD (133).

In addition to lifestyle modification, nutritional improvement is a critical component in the prevention and management of AD. The pathogenesis of AD is associated with chronic metabolic disease such as hypertension, DM and obesity, as well as unhealthy dietary behavior. A previous study demonstrated that modification of risk factors and lifestyle may prevent or delay 40% of AD and associated dementia cases (134). The World Health Organization recommends that daily fat intake should not exceed 30% of total energy intake in patients with AD, with saturated fatty acids accounting for <10% of total energy supply, while high intake of high-carbohydrate foods is discouraged (135). A previous study (136)

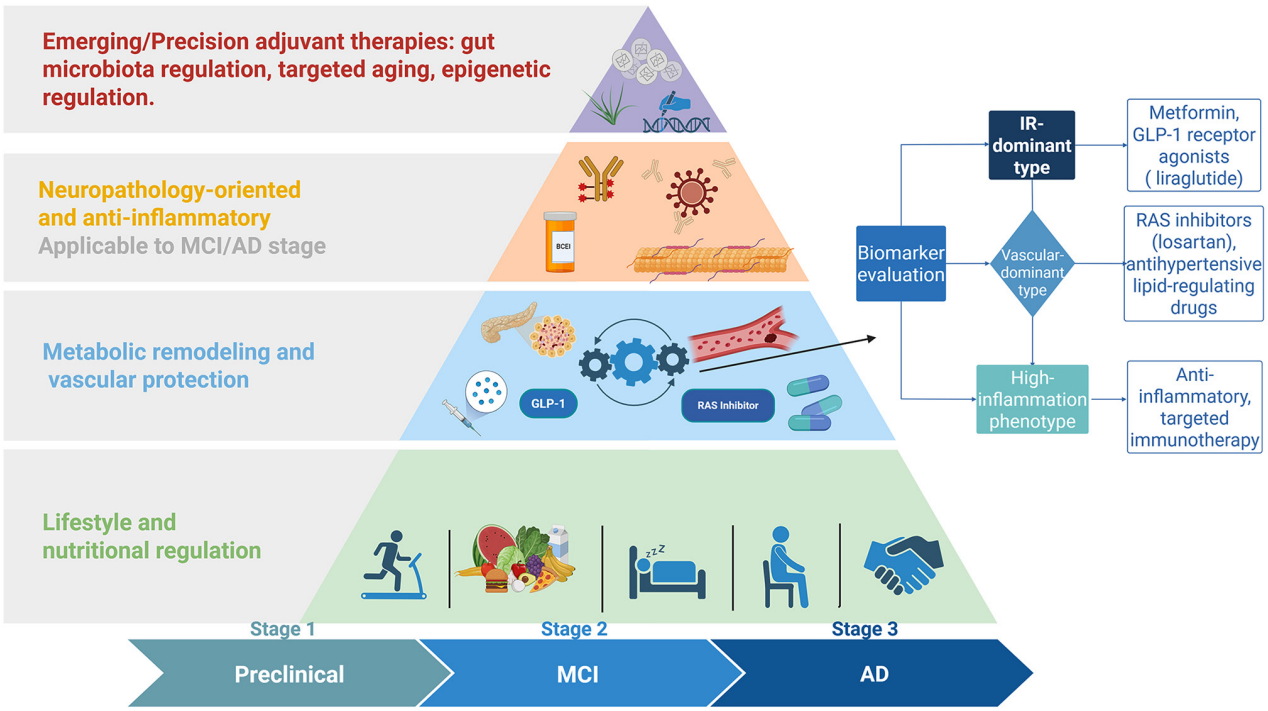


Figure 5. Hierarchical roadmap for precise prevention and treatment of AD based on multiple mechanisms. The model illustrates prevention and stratified intervention strategies for AD from the preclinical stage, MCI, to diagnosed AD. The foundation is based on lifestyle and nutritional regulation, followed by metabolic remodeling and vascular protection, neuropathology-guided anti-inflammatory treatment and emerging precision adjunctive therapy (gut microbiota regulation, targeted anti-aging, epigenetic regulation). The decision tree on the right provides personalized intervention plans based on biomarker assessment, targeting IR- and vascular-dominant and high-inflammation phenotypes. AD, Alzheimer's disease; MCI, mild cognitive impairment; IR, insulin resistance; GLP, glucagon-like peptide; RAS, renin-angiotensin system.

proposed the Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay diet, a dietary pattern specifically designed for AD that combines features of the Mediterranean and DASH diets. This encourages consumption of green leafy vegetables and limits red meat, contributing to improved cognitive function. Furthermore, patients with advanced AD often develop malnutrition due to behavioral and psychological symptoms, including cognitive impairment and sensory dysfunction. In such cases, appropriate supplementation of brain-healthy nutrients, such as vitamins E and B12 and flavonoids, is recommended (137,138).

Drug repurposing targeting core pathways. The repurposing of existing metabolic drugs for the prevention and treatment of AD is an emerging research direction (139). The pharmacological strategies for managing MetS-associated AD have shifted from conventional symptom management toward a 'metabolic-neuroprotective' intervention based on shared pathological mechanisms (Table I) (135-172).

Drugs that target IR, which is the core of metabolic disorder, show potential for AD intervention. A large body of long-term epidemiological evidence (140-142) indicates that patients with T2DM treated with metformin exhibit a decreased risk of AD. Metformin not only improves peripheral glucose metabolism but also alleviates cerebral IR by activating the AMP/activated protein kinase pathway, thereby conferring neuroprotection (143). Furthermore, metformin serves as an activator of chaperone-mediated autophagy (CMA), promoting APP degradation, decreasing Aβ generation and reversing both molecular and behavioral AD phenotypes (144). These findings provide a perspective for metformin in AD treatment, repurposing CMA regulation and providing experimental evidence for clinical practice.

Antidiabetic drugs, namely glucagon-like peptide-1 (GLP-1) receptor agonists, has demonstrated more direct neuroprotective potential (146-155). Unlike metformin, which improves peripheral metabolism, these drugs activate GLP-1 receptors in the hypothalamus, exerting potent anti-inflammatory and weight-decreasing effects (145,146), while also inhibiting apoptosis and decreasing Aβ and α-synuclein aggregation in AD models (147,148). Liraglutide is a disease-modifying drug under development for AD, and has demonstrated improvement in cognitive function and brain atrophy in phase II clinical trial (149). Semaglutide, a drug in the same class, has been shown in preclinical study to decrease Aβ plaques and NFTs in the brains of AD model mice, and to regulate glucose transporter type 4 to improve glucose metabolism (150). However, semaglutide yielded negative results in the phase III EVOKE/EVOKE+ clinical trial (151). The reasons for this failure require further research. Currently, however, the limited penetration of these fatty acid-modified GLP-1 receptor agonists across the BBB results in insufficient metabolic regulation (152-154). Du *et al* (155) developed a new GLP-1 receptor agonist called Oral Hypoglycemic Peptide 2, which can cross the BBB via the brain endothelial cell transport channels and evade the lysosomes responsible for degrading exogenous substances, thereby achieving accumulation in the hippocampus of AD model mice. This supplements the preclinical evidence (156,157) supporting

Table I. Potential intervention strategies and mechanisms of metabolic syndrome-driven AD.

Intervention strategy	Category	Direct target/mechanism	Effects on AD	(Refs.)
Lifestyle modification	Basic intervention	Metabolic regulation, anti-inflammation	Prevention/delay of cognitive decline	(134-138)
Metformin	Antidiabetic drug	Activates AMPK, induces CMA	Promotes APP degradation and decreases Aβ in preclinical models limited human cognitive evidence	(143,144)
GLP-1 agonists	Antidiabetic drug	Partially crosses BBB, anti-inflammatory, anti-apoptotic	Attenuates Aβ/τ pathology and improves cerebral metabolism	(145-155)
Losartan	Antihypertensive drug	Inhibits Ang II-AT_1R axis	Decreases Aβ burden and preserves BBB integrity preclinically; scarce human cognitive data	(158)
GV-971	Gut-brain axis regulator	Remodels gut microbiota, inhibits peripheral immune infiltration	Alleviates neuroinflammation preclinically and clinically	(160-162)
Pro-/prebiotics	Gut-brain axis regulator	Modulates microbial metabolism	May improve cognition; inconsistent human results	(163)
Rapamycin	Aging regulator	Decreases SASP, attenuates inflammation	Improves brain aging microenvironment and indirectly modulates AD pathogenesis preclinically	(168)
Senolytics	Senolytic agent	Eliminates senescent glial cells	Improves cognition in animals	(170)
Stem cells/exosomes	Regenerative medicine	Delivers neurotrophic factors, modulates immunity, promotes angiogenesis	Remodels brain microenvironment	(173,174)
Resveratrol + curcumin	Combined natural small molecules	Interferes with Aβ production, regulates inflammatory signaling	Overcomes poor monotherapy efficacy	(175,176)

Aβ, amyloid-β; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; Ang II, angiotensin II; AT_1R, Ang II type 1 receptor; APP, amyloid precursor protein; BBB, blood-brain barrier; CMA, chaperone-mediated autophagy; GLP-1, glucagon-like peptide-1; SASP, senescence-associated secretory phenotype.

the use of GLP-1 receptor agonists for the prevention of AD. Similarly, functional food-derived compounds such as ginsenosides (119) protect the brain from damage induced by HFD by inhibiting oxidative stress, cell senescence and inflammatory responses, improving autophagic function and regulating lipid metabolism, while decreasing τ phosphorylation and glial activation.

The progression of AD is typically accompanied by vascular dysfunction; therefore, drugs targeting the RAS should not be overlooked. Losartan, while controlling vascular risk, has been shown to independently decrease cerebral Aβ burden, achieving dual cardiovascular and neurological benefits (158). Other examples include telmisartan and azilsartan (159). However, studies (157,158) in this area are limited and are mostly conducted in animal models or are at early clinical stages, thus necessitating further research for development of potential therapeutic target for the prevention and treatment of AD.

Emerging intervention directions. Targeting the gut-brain axis has emerged as a novel strategy. Sodium oligomannate has been approved in China for the treatment of mild-to-moderate AD (160). It reshapes the GM, decreases the production of pro-inflammatory metabolites, thereby inhibiting the infiltration of peripheral immune cells into the brain, and alleviates neuroinflammation (161,162), which clinically validates the feasibility of treating AD through gut-based interventions. Prebiotics (such as inulin) serve as 'nourishment' for beneficial bacteria, promoting the production of short-chain fatty acids with systemic anti-inflammatory effects (163). Direct

Table II. Multidimensional biomarker subtyping system for metabolic syndrome-associated Alzheimer's disease.

Subtype	Biomarkers	Detection methods	(Refs.)
Metabolic disorder	HOMA-IR, fasting insulin, lipid profile, ceramide, free fatty acids, BMI, waist circumference, visceral fat area	Blood test, anthropometry, abdominal ultrasound/CT	(182,183)
Inflammatory/ immunological	hs-CRP, IL-6, TNF-α, sTREM2, GFAP, monocyte subpopulation, NK cell activity	Blood/CSF test, flow cytometry	(184-187)
Vascular dysfunction	VCAM-1, VEC, endothelial progenitor cells; ASL-MRI perfusion; DCE-MRI, CSF/serum albumin ratio	Blood test, multimodal brain MRI	(188,189)
Genetic/core pathology	ApoE ε4, TREM2 R47H, plasma/ CSF Aβ42/40, p-τ181, p-τ217, hippocampal volume	Genetic testing, blood/ CSF biomarkers, brain MRI	(190,191)

Aβ, amyloid-β; ApoE, apolipoprotein E; ASL, arterial spin labeling; BMI, body mass index; CSF, cerebrospinal fluid; CT, computer tomography; DCE, dynamic contrast-enhanced; GFAP, glial fibrillary acidic protein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; NK, natural killer; p-, phosphorylated; TREM2, triggering receptor expressed on myeloid cells 2; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VEC, vascular endothelial cell.

supplementation with probiotics (specific strain combinations) has shown potential for cognitive improvement in small-scale study (164).

During healthy aging, protective genes is upregulated as an adaptive response; in Alzheimer's disease, this adaptive mechanism becomes dysregulated (165). Ferulic acid heptyl ester aims to restore this healthy aging mechanism and reverse memory deficits in late-stage AD (166). Furthermore, rapamycin, the most extensively studied agent in aging regulation (167), decreases secretion of SASP-associated factors and alleviates inflammation (168), potentially exerting indirect effects on neurodegenerative disease, although it has limited direct impact on the nervous system (169). Another class of agents, senolytics, may delay, prevent or reverse the aging process by eliminating senescent glial cells, thereby improving cognitive function (170). Stem cell and exosome therapies have attracted increasing attention (171,172). Mesenchymal stem cells or their secreted exosomes reshape the damaged brain microenvironment through multi-target mechanisms, including delivering neurotrophic factors, modulating immune responses and promoting angiogenesis (173,174).

Precision and combination therapy. Given the multi-mechanistic nature of MetS in driving AD, single-target interventions may not completely halt disease progression. Therefore, in addition to lifestyle and pharmacological interventions, multi-target combination therapy strategies (175,176), similar to those used in cancer chemotherapy, have been applied to the study of complex degenerative disease such as AD. A preclinical study proposed a combined intervention using resveratrol and curcumin; this combination interferes with Aβ aggregation and modulates inflammatory pathways, demonstrating the potential for more sustained therapeutic effects in experimental models (177).

In light of the poor clinical outcomes of anti-amyloid monoclonal antibody monotherapy (178), integration of natural small molecules with monoclonal antibody therapy may provide a new research direction for the personalized, precision targeted treatment of AD.

However, not all patients should receive the same combination regimen. Clinically, the predominant metabolic abnormality in patients with MetS vary (179-181): Certain patients present with severe IR as the key feature, while others exhibit vascular damage and cerebral hypoperfusion as prominent manifestations and others show significant systemic inflammation. Biomarker testing provides an objective basis for identifying individual differences and guiding the selection of appropriate combination strategies (182-191) (Table II). By incorporating a biomarker-based classification system to match patients with interventions tailored to predominant pathological characteristics, strategies for the treatment of AD may emerge.

5. Discussion

MetS is a key driver of AD (4). It increases AD pathological deposition and disrupts the coordination between brain cells through multiple mechanisms such as IR, mitochondrial damage, intestinal-brain axis disorder, induction of inflammation, aging, autophagy and epigenetic regulation (1,35), leading to central nervous system degeneration. These mechanisms affect each other and cross-act on AD through common bidirectional pathways (100). The present review aimed to examine the association between metabolism and AD, as well as potential interventions for early-stage AD from a metabolic perspective (132).

Although the ‘type 3 diabetes hypothesis, which proposes that Alzheimer's disease represents a form of brain-specific IR independent of peripheral diabetes, has been proposed for the association between IR and AD, the causal details are unclear and several limitations remain, including poor translatability of animal models and inconsistent findings from human clinical trials (192,193). In addition, although emerging mechanisms such as the GM-brain axis have become research topics, the

sample size and depth of human studies are limited, and some associations are still speculative (194). Thus, it is necessary to increase the sample size to study the specific mechanisms. In addition to metabolism, it is not possible to exclude the interference factors caused by age, genes and complications induced by other disease (195-197).

AD is not only about plaque accumulation or neuronal death, but also about the collapse of the entire brain ecosystem. From peripheral metabolic disorder to central nervous system lesions, the association between AD and MetS reflects the concentrated manifestation of systemic metabolic disease in the brain. The prevention and treatment of MetS-related AD requires using multi-omics technology to identify high-risk subtypes, and initiating multi-target, individualized joint intervention in the reversible stage. This combines systemic health management with the aging process of the brain.

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Availability of data and materials

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Authors' contributions

WXL and ZJ conceived the study. CHL and DT drafted the manuscript and created the figures. ZYF, YM, WFS, CPW, LHH, HMH and KHP performed the literature search. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Patel V and Edison P: Cardiometabolic risk factors and neurodegeneration: A review of the mechanisms underlying diabetes, obesity and hypertension in Alzheimer's disease. J Neurol Neurosurg Psychiatry 95: 581-589, 2024.
2. Rojas M, Chávez-Castillo M, Pirela D, Parra H, Nava M, Chacín M, Angarita L, Añez R, Salazar J, Ortiz R, *et al*: Metabolic syndrome: Is it time to add the central nervous system? Nutrients 13: 2254, 2021.
3. Pasinetti GM and Eberstein JA: Metabolic syndrome and the role of dietary lifestyles in Alzheimer's disease. J Neurochem 106: 1503-1514, 2008.
4. Al-Kuraishy HM, Jabir MS, Albuhadily AK, Al-Gareeb AI and Rafeeq MF: The link between metabolic syndrome and Alzheimer disease: A mutual relationship and long rigorous investigation. Ageing Res Rev 91: 102084, 2023.
5. Ozben T and Ozben S: Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. Clin Biochem 72: 87-89, 2019.
6. Sarhan M, Wohlfeld C, Perry-Mills A, Meyers J, Fadel J, Murphy EA, Bonilha L and Fan D: The pathophysiology of mixed Alzheimer's disease and vascular dementia. Theranostics 15: 9793-9818, 2025.
7. Chen TS, Mi NN, Lao HY, Wang CY, Lo WLA, Mao YR, Tang Y, Pei Z, Yuan JQ and Huang DF: Investigating the nexus of metabolic syndrome, serum uric acid, and dementia risk: A prospective cohort study. BMC Med 22: 115, 2024.
8. Lee JY, Han K, Kim J, Lim JS, Cheon DY and Lee M: Association between metabolic syndrome and young-onset dementia: A nationwide population-based study. Neurology 104: e213599, 2025.
9. Gosalia J, Spicuzza JMD, Bowlus CK, Pawelczyk JA and Proctor DN: Linking metabolic syndrome, cerebral small vessel disease, and cognitive health: Insights from a subclinical population study using TriNetX. Geroscience 47: 3791-3806, 2025.
10. Kleinridders A, Ferris HA, Cai W and Kahn CR: Insulin action in brain regulates systemic metabolism and brain function. Diabetes 63: 2232-2243, 2014.
11. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR and de la Monte SM: Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease-is this type 3 diabetes? J Alzheimers Dis 7: 63-80, 2005.
12. Mokáň M and Galajda P: Primary and secondary insulin resistance. Vnitr Lek 65: 264-272, 2019 (In Czech).
13. Ahmed B, Sultana R and Greene MW: Adipose tissue and insulin resistance in obese. Biomed Pharmacother 137: 111315, 2021.
14. Li L, He H and Wang Y: Insulin and IGF signaling in the brain: Multilevel regulation of synaptic and network homeostasis. Front Endocrinol (Lausanne) 17: 1793536, 2026.
15. Chen R, Lu X, Xiao A and Ma J: Role of insulin-like growth factor-2 in Alzheimer's disease induced memory impairment and underlying mechanisms. Front Cell Neurosci 18: 1520253, 2025.
16. de la Monte SM: Contributions of brain insulin resistance and deficiency in amyloid-related neurodegeneration in Alzheimer's disease. Drugs 72: 49-66, 2012.
17. Grillo CA, Woodruff JL, Macht VA and Reagan LP: Insulin resistance and hippocampal dysfunction: Disentangling peripheral and brain causes from consequences. Exp Neurol 318: 71-77, 2019.
18. Spinelli M, Fusco S, Mainardi M, Scala F, Natale F, Lapenta R, Mattera A, Rinaudo M, Li Puma DD, Ripoli C, *et al*: Brain insulin resistance impairs hippocampal synaptic plasticity and memory by increasing GluA1 palmitoylation through FoxO3a. Nat Commun 8: 2009, 2017.
19. Roy RG, Mandal PK and Maroon JC: Oxidative stress occurs prior to amyloid Aβ plaque formation and tau phosphorylation in Alzheimer's disease: Role of glutathione and metal ions. ACS Chem Neurosci 14: 2944-2954, 2023.
20. Swerdlow RH: Mitochondria and mitochondrial cascades in Alzheimer's disease. J Alzheimers Dis 62: 1403-1416, 2018.
21. Dhapola R, Beura SK, Sharma P, Singh SK and HariKrishnaReddy D: Oxidative stress in Alzheimer's disease: Current knowledge of signaling pathways and therapeutics. Mol Biol Rep 51: 48, 2024.

22. González P, Lozano P, Ros G and Solano F: Hyperglycemia and oxidative stress: An integral, updated and critical overview of their metabolic interconnections. Int J Mol Sci 24: 9352, 2023.
23. Zhao Y and Zhao B: Oxidative stress and the pathogenesis of Alzheimer's disease. Oxid Med Cell Longev 2013: 316523, 2013.
24. Leuner K, Schütt T, Kurz C, Eckert SH, Schiller C, Occhipinti A, Mai S, Jendrach M, Eckert GP, Kruse SE, *et al*: Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation. Antioxid Redox Signal 16: 1421-1433, 2012.
25. D'Alessandro MCB, Kanaan S, Geller M, Praticò D and Daher JPL: Mitochondrial dysfunction in Alzheimer's disease. Ageing Res Rev 107: 102713, 2025.
26. Du H, Guo L, Yan S, Sosunov AA, McKhann GM and Yan SS: Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. Proc Natl Acad Sci USA 107: 18670-18675, 2010.
27. Saura CA and Valero J: The role of CREB signaling in Alzheimer's disease and other cognitive disorders. Rev Neurosci 22: 153-169, 2011.
28. Delikkaya B, Moriel N, Tong M, Gallucci G and de la Monte SM: Altered expression of insulin-degrading enzyme and regulator of calcineurin in the rat intracerebral streptozotocin model and human apolipoprotein E-ε4-associated Alzheimer's disease. Alzheimers Dement (Amst) 11: 392-404, 2019.
29. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, *et al*: Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 36: 401-414, 2012.
30. Jabaut J, Ather JL, Taracanova A, Poynter ME and Ckless K: Mitochondria-targeted drugs enhance Nlrp3 inflammasome-dependent IL-1β secretion in association with alterations in cellular redox and energy status. Free Radic Biol Med 60: 233-245, 2013.
31. Hong C, Wei Y, Wang Y, Lv G, Dong X and Huang X: The mechanism and therapeutic potential of SIRT3 in central nervous system diseases: A review. Front Pharmacol 16: 1652296, 2025.
32. Yin J, Li S, Nielsen M, Carcione T, Liang WS and Shi J: Sirtuin 3 attenuates amyloid-β induced neuronal hypometabolism. Aging (Albany NY) 10: 2874-2883, 2018.
33. Hirschey MD, Shimazu T, Huang JY, Schwer B and Verdin E: SIRT3 regulates mitochondrial protein acetylation and intermediary metabolism. Cold Spring Harb Symp Quant Biol 76: 267-277, 2011.
34. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stančáková A, Goetzman E, Lam MM, Schwer B, *et al*: SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell 44: 177-190, 2011.
35. Ali NH, Al-Kuraishy HM, Al-Gareeb AI, Alexiou A, Papadakis M, Bahaa MM, Alibrahim F and Batiha GE: New insight on the potential detrimental effect of metabolic syndrome on the Alzheimer disease neuropathology: Mechanistic role. J Cell Mol Med 28: e70118, 2024.
36. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, Beguinot F and Miele C: Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci 20: 2358, 2019.
37. Elzinga SE, Guo K, Turfah A, Henn RE, Webber-Davis IF, Hayes JM, Pacut CM, Teener SJ, Carter AD, Rigan DM, *et al*: Metabolic stress and age drive inflammation and cognitive decline in mice and humans. Alzheimers Dement 21: e70060, 2025.
38. Kunz HE, Hart CR, Gries KJ, Parvizi M, Laurenti M, Dalla Man C, Moore N, Zhang X, Ryan Z, Polley EC, *et al*: Adipose tissue macrophage populations and inflammation are associated with systemic inflammation and insulin resistance in obesity. Am J Physiol Endocrinol Metab 321: E105-E121, 2021.
39. Hotamisligil GS: Inflammation and metabolic disorders. Nature 444: 860-867, 2006.
40. Kawai T, Autieri MV and Scalia R: Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol 320: C375-C391, 2021.
41. Peng C, Jiang H, Jing L, Yang W, Guan X, Wang H, Yu S, Cao Y, Wang M, Ma H, *et al*: Macrophage SUCLA2 coupled glutaminolysis manipulates obesity through AMPK. Nat Commun 16: 1738, 2025.
42. Hotamisligil GS, Shargill NS and Spiegelman BM: Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. Science 259: 87-91, 1993.
43. Hotamisligil GS, Budavari A, Murray D and Spiegelman BM: Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-alpha. J Clin Invest 94: 1543-1549, 1994.
44. Boden G, She P, Mozzoli M, Cheung P, Gumireddy K, Reddy P, Xiang X, Luo Z and Ruderman N: Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-kappaB pathway in rat liver. Diabetes 54: 3458-3465, 2005.
45. Hoogland ICM, Houbolt C, van Westerloo DJ, van Gool WA and van de Beek D: Systemic inflammation and microglial activation: Systematic review of animal experiments. J Neuroinflammation 12: 114, 2015.
46. Buttini M, Limonta S and Boddeke HW: Peripheral administration of lipopolysaccharide induces activation of microglial cells in rat brain. Neurochem Int 29: 25-35, 1996.
47. Simpson DSA and Oliver PL: ROS generation in microglia: Understanding oxidative stress and inflammation in neurodegenerative disease. Antioxidants (Basel) 9: 743, 2020.
48. Ennerfelt HE and Lukens JR: The role of innate immunity in Alzheimer's disease. Immunol Rev 297: 225-246, 2020.
49. Triviño JJ and von Bernhardi R: The effect of aged microglia on synaptic impairment and its relevance in neurodegenerative diseases. Neurochem Int 144: 104982, 2021.
50. Wicks EE, Ran KR, Kim JE, Xu R, Lee RP and Jackson CM: The translational potential of microglia and monocyte-derived macrophages in ischemic stroke. Front Immunol 13: 897022, 2022.
51. Saijo K and Glass CK: Microglial cell origin and phenotypes in health and disease. Nat Rev Immunol 11: 775-787, 2011.
52. Paik S, Kim JK, Shin HJ, Park EJ, Kim IS and Jo EK: Updated insights into the molecular networks for NLRP3 inflammasome activation. Cell Mol Immunol 22: 563-596, 2025.
53. Kanugula AK, Kaur J, Batra J, Ankireddypalli AR and Velagapudi R: Renin-angiotensin system: Updated understanding and role in physiological and pathophysiological states. Cureus 15: e40725, 2023.
54. Ailhaud G, Fukamizu A, Massiera F, Negrel R, Saint-Marc P and Teboul M: Angiotensinogen, angiotensin II and adipose tissue development. Int J Obes Relat Metab Disord 24 (Suppl 4): S33-S35, 2000.
55. Ailhaud G, Teboul M and Massiera F: Angiotensinogen, adipocyte differentiation and fat mass enlargement. Curr Opin Clin Nutr Metab Care 5: 385-389, 2002.
56. Li Z, Liu H, He J, Wang Z, Yin Z, You G, Wang Z, Davis RE, Lin P, Bergsagel PL, *et al*: Acetyl-CoA synthetase 2: A critical linkage in obesity-induced tumorigenesis in myeloma. Cell Metab 33: 78-93.e7, 2021.
57. Yamamoto K, Kakino A, Takeshita H, Hayashi N, Li L, Nakano A, Hanasaki-Yamamoto H, Fujita Y, Imaizumi Y, Toyama-Yokoyama S, *et al*: Oxidized LDL (oxLDL) activates the angiotensin II type 1 receptor by binding to the lectin-like oxLDL receptor. FASEB J 29: 3342-3356, 2015.
58. Murakami K, Uehara Y, Abe S, Inoue Y, Ideishi M, Saku K and Urata H: Positive correlation between chymase-like angiotensin II-forming activity in mononuclear cells and serum cholesterol level. J Cardiol 50: 291-298, 2007.
59. Loera-Valencia R, Eroli F, Garcia-Ptacek S and Maioli S: Brain renin-angiotensin system as novel and potential therapeutic target for Alzheimer's disease. Int J Mol Sci 22: 10139, 2021.
60. Kauwe JSK, Bailey MH, Ridge PG, Perry R, Wadsworth ME, Hoyt KL, Staley LA, Karch CM, Harari O, Cruchaga C, *et al*: Genome-wide association study of CSF levels of 59 Alzheimer's disease candidate proteins: Significant associations with proteins involved in amyloid processing and inflammation. PLoS Genet 10: e1004758, 2014.
61. Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, *et al*: Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 286: 735-741, 1999.
62. Liu J, Liu S, Matsumoto Y, Murakami S, Sugakawa Y, Kami A, Tanabe C, Maeda T, Michikawa M, Komano H and Zou K: Angiotensin type 1a receptor deficiency decreases amyloid β-protein generation and ameliorates brain amyloid pathology. Sci Rep 5: 12059, 2015.
63. Tian M, Zhu D, Xie W and Shi J: Central angiotensin II-induced Alzheimer-like tau phosphorylation in normal rat brains. FEBS Lett 586: 3737-3745, 2012.
64. Kisler K, Nelson AR, Montagne A and Zlokovic BV: Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat Rev Neurosci 18: 419-434, 2017.

65. Cau SB, Bruder-Nascimento A, Silva MB, Ramalho FNZ, Mestriner F, Alves-Lopes R, Ferreira N, Tostes RC and Bruder-Nascimento T: Angiotensin-II activates vascular inflammasome and induces vascular damage. Vascul Pharmacol 139: 106881, 2021.
66. Mokgokong R, Wang S, Taylor CJ, Barrand MA and Hladky SB: Ion transporters in brain endothelial cells that contribute to formation of brain interstitial fluid. Pflugers Arch 466: 887-901, 2014.
67. Ohrui T, Tomita N, Sato-Nakagawa T, Matsui T, Maruyama M, Niwa K, Arai H and Sasaki H: Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. Neurology 63: 1324-1325, 2004.
68. Wharton W, Goldstein FC, Zhao L, Steenland K, Levey AI and Hajjar I: Modulation of renin-angiotensin system may slow conversion from mild cognitive impairment to Alzheimer's disease. J Am Geriatr Soc 63: 1749-1756, 2015.
69. Zhang P, Song C, Shi J, Wei Z, Wang J, Huang W, Zhang R, Wang J, Yang X, Wang G, *et al*: Endothelium-specific endoglin triggers astrocyte reactivity via extracellular vesicles in a mouse model of Alzheimer's disease. Mol Neurodegener 20: 84, 2025.
70. Hemmings BA and Cohen P: Glycogen synthase kinase-3 from rabbit skeletal muscle. Methods Enzymol 99: 337-345, 1983.
71. Kurgan N, Whitley KC, Maddalena LA, Moradi F, Stoikos J, Hamstra SI, Rubie EA, Kumar M, Roy BD, Woodgett JR, *et al*: A low-therapeutic dose of lithium inhibits GSK3 and enhances myoblast fusion in C2C12 cells. Cells 8: 1340, 2019.
72. Doble BW and Woodgett JR: Role of glycogen synthase kinase-3 in cell fate and epithelial-mesenchymal transitions. Cells Tissues Organs 185: 73-84, 2007.
73. Forde JE and Dale TC: Glycogen synthase kinase 3: A key regulator of cellular fate. Cell Mol Life Sci 64: 1930-1944, 2007.
74. Dewachter I, Ris L, Jaworski T, Seymour CM, Kremer A, Borghgraef P, De Vijver H, Godaux E and Van Leuven F: GSK3beta, a centre-staged kinase in neuropsychiatric disorders, modulates long term memory by inhibitory phosphorylation at serine-9. Neurobiol Dis 35: 193-200, 2009.
75. Magdesian MH, Carvalho MMVF, Mendes FA, Saraiva LM, Juliano MA, Juliano L, Garcia-Abreu J and Ferreira ST: Amyloid-beta binds to the extracellular cysteine-rich domain of Frizzled and inhibits Wnt/beta-catenin signaling. J Biol Chem 283: 9359-9368, 2008.
76. Martin M, Rehani K, Jope RS and Michalek SM: Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. Nat Immunol 6: 777-784, 2005.
77. Ramirez SH, Fan S, Zhang M, Papugani A, Reichenbach N, Dykstra H, Mercer AJ, Tuma RF and Persidsky Y: Inhibition of glycogen synthase kinase 3beta (GSK3beta) decreases inflammatory responses in brain endothelial cells. Am J Pathol 176: 881-892, 2010.
78. Wang W, Li M, Wang Y, Wang Z, Zhang W, Guan F, Chen Q and Wang J: GSK-3β as a target for protection against transient cerebral ischemia. Int J Med Sci 14: 333-339, 2017.
79. Wang T, Zhang J, Wei H, Wang X, Xie M, Jiang Y and Zhou J: Matrine-induced nephrotoxicity via GSK-3β/nrf2-mediated mitochondria-dependent apoptosis. Chem Biol Interact 378: 110492, 2023.
80. Llorens-Martín M, Jurado J, Hernández F and Avila J: GSK-3β, a pivotal kinase in Alzheimer disease. Front Mol Neurosci 7: 46, 2014.
81. Spittaels K, Van den Haute C, Van Dorpe J, Geerts H, Mercken M, Bruynseels K, Lasrado R, Vandezande K, Laenen I, Boon T, *et al*: Glycogen synthase kinase-3beta phosphorylates protein tau and rescues the axonopathy in the central nervous system of human four-repeat tau transgenic mice. J Biol Chem 275: 41340-41349, 2000.
82. Ly PTT, Wu Y, Zou H, Wang R, Zhou W, Kinoshita A, Zhang M, Yang Y, Cai F, Woodgett J and Song W: Inhibition of GSK3β-mediated BACE1 expression reduces Alzheimer-associated phenotypes. J Clin Invest 123: 224-235, 2013.
83. Cedazo-Mínguez A, Popescu BO, Blanco-Millán JM, Akterin S, Pei JJ, Winblad B and Cowburn RF: Apolipoprotein E and beta-amyloid (1-42) regulation of glycogen synthase kinase-3beta. J Neurochem 87: 1152-1164, 2003.
84. Wang Y, Gao Y, Wang Y, Zhang F, Sun F, Wang X, Xie J, Xu Z, Zhang J, Xu H, *et al*: ApoE4 upregulates GSK-3β to aggravate alzheimer-like pathologies and cognitive impairment in type 2 diabetic mice. CNS Neurosci Ther 31: e70575, 2025.
85. Aron L, Ngian ZK, Qiu C, Choi J, Liang M, Drake DM, Hamplova SE, Lacey EK, Roche P, Yuan M, *et al*: Lithium deficiency and the onset of Alzheimer's disease. Nature 645: 712-721, 2025.
86. Zhang KX, Sheng N, Ding PL, Zhang JW, Xu XQ and Wang YH: Danggui shaoyao san alleviates early cognitive impairment in Alzheimer's disease mice through IRS1/GSK3β/Wnt3a-β-catenin pathway. Brain Behav 14: e70056, 2024.
87. Tang CF, Li F, Ma LH, Wang QN, Xie PF, Xiang L, Zhu YJ, Wang YY, Zhang YZ, Shi JJ, *et al*: Danggui Shaoyao San attenuates depressive-like behaviors in mice via TLR4/NF-kappaB p65/JAK-STAT3/AKT-GSK3beta signaling pathways: Modulation of hippocampal neurogenesis and neuroinflammation. Front Nutr 12: 1652968, 2025.
88. Rhee SH, Pothoulakis C and Mayer EA: Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol 6: 306-314, 2009.
89. Mayer EA: Gut feelings: The emerging biology of gut-brain communication. Nat Rev Neurosci 12: 453-466, 2011.
90. Zhu X, Han Y, Du J, Liu R, Jin K and Yi W: Microbiota-gut-brain axis and the central nervous system. Oncotarget 8: 53829-53838, 2017.
91. Sanguinetti E, Collado MC, Marrachelli VG, Monleon D, Selma-Royo M, Pardo-Tendero MM, Burchielli S and Iozzo P: Microbiome-metabolome signatures in mice genetically prone to develop dementia, fed a normal or fatty diet. Sci Rep 8: 4907, 2018.
92. Chen C, Liao J, Xia Y, Liu X, Jones R, Haran J, McCormick B, Sampson TR, Alam A and Ye K: Gut microbiota regulate Alzheimer's disease pathologies and cognitive disorders via PUFA-associated neuroinflammation. Gut 71: 2233-2252, 2022.
93. Lardenoije R, Iatrou A, Kenis G, Kompotis K, Steinbusch HW, Mastroeni D, Coleman P, Lemere CA, Hof PR, van den Hove DL and Rutten BP: The epigenetics of aging and neurodegeneration. Prog Neurobiol 131: 21-64, 2015.
94. Dunn GA and Bale TL: Maternal high-fat diet effects on third-generation female body size via the paternal lineage. Endocrinology 152: 2228-2236, 2011.
95. Fusco S, Spinelli M, Cocco S, Ripoli C, Mastrodonato A, Natale F, Rinaudo M, Livrizzi G and Grassi C: Maternal insulin resistance multigenerationally impairs synaptic plasticity and memory via gametic mechanisms. Nat Commun 10: 4799, 2019.
96. Yokoyama AS, Rutledge JC and Medici V: DNA methylation alterations in Alzheimer's disease. Environ Epigenetics 3: dvx008, 2017.
97. Gasparoni G, Bultmann S, Lutsik P, Kraus TFJ, Sordon S, Vlcek J, Dietinger V, Steinmaurer M, Haider M, Mulholland CB, *et al*: DNA methylation analysis on purified neurons and glia dissects age and Alzheimer's disease-specific changes in the human cortex. Epigenetics Chromatin 11: 41, 2018.
98. Li P, Marshall L, Oh G, Jakubowski JL, Groot D, He Y, Wang T, Petronis A and Labrie V: Epigenetic dysregulation of enhancers in neurons is associated with Alzheimer's disease pathology and cognitive symptoms. Nat Commun 10: 2246, 2019.
99. Wang X, Pan Y, Zhu H, Hao G, Huang Y, Barnes V, Shi H, Snieder H, Pankow J, North K, *et al*: An epigenome-wide study of obesity in African American youth and young adults: Novel findings, replication in neutrophils, and relationship with gene expression. Clin Epigenetics 10: 3, 2018.
100. Dong H, Sun Y, Nie L, Cui A, Zhao P, Leung WK and Wang Q: Metabolic memory: Mechanisms and diseases. Signal Transduct Target Ther 9: 38, 2024.
101. Xiong X, James BT, Boix CA, Park YP, Galani K, Victor MB, Sun N, Hou L, Ho LL, Mantero J, *et al*: Epigenomic dissection of Alzheimer's disease pinpoints causal variants and reveals epigenome erosion. Cell 186: 4422-4437.e21, 2023.
102. Coppedè F: The potential of epigenetic therapies in neurodegenerative diseases. Front Genet 5: 220, 2014.
103. Beam CR, Kaneshiro C, Jang JY, Reynolds CA, Pedersen NL and Gatz M: Differences between women and men in incidence rates of dementia and Alzheimer's disease. J Alzheimers Dis 64: 1077-1083, 2018.
104. No authors listed: 2021 Alzheimer's disease facts and figures. Alzheimers Dement 17: 327-406, 2021.
105. Brinton RD, Yao J, Yin F, Mack WJ and Cadenas E: Perimenopause as a neurological transition state. Nat Rev Endocrinol 11: 393-405, 2015.
106. Waters EM, Yildirim M, Janssen WGM, Lou WYW, McEwen BS, Morrison JH and Milner TA: Estrogen and aging affect the synaptic distribution of estrogen receptor β-immunoreactivity in the CA1 region of female rat hippocampus. Brain Res 1379: 86-97, 2011.
107. Carro E, Trejo JL, Gomez-Isla T, LeRoith D and Torres-Aleman I: Serum insulin-like growth factor I regulates brain amyloid-beta levels. Nat Med 8: 1390-1397, 2002.

108. Brinton RD: Estrogen regulation of glucose metabolism and mitochondrial function: Therapeutic implications for prevention of Alzheimer's disease. Adv Drug Deliv Rev 60: 1504-1511, 2008.
109. Tsiknia AA, Edland SD, Sundermann EE, Reas ET, Brewer JB, Galasko D and Banks SJ; Alzheimer's Disease Neuroimaging Initiative: Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression. Mol Psychiatry 27: 4314-4322, 2022.
110. Carroll JC, Rosario ER, Chang L, Stanczyk FZ, Oddo S, LaFerla FM and Pike CJ: Progesterone and estrogen regulate Alzheimer-like neuropathology in female 3xTg-AD mice. J Neurosci 27: 13357-13365, 2007.
111. Muñoz-Mayorga D, Guerra-Araiza C, Torner L and Morales T: Tau phosphorylation in female neurodegeneration: Role of estrogens, progesterone, and prolactin. Front Endocrinol (Lausanne) 9: 133, 2018.
112. Yang Y, Liang F, Gao J, Dong Y, Zhang Y, Yang G, Soriano SG, Feng HJ and Xie Z: Testosterone attenuates sevoflurane-induced tau phosphorylation and cognitive impairment in neonatal male mice. Br J Anaesth 127: 929-941, 2021.
113. Islam RM, Bell RJ, Green S, Page MJ and Davis SR: Safety and efficacy of testosterone for women: A systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol 7: 754-766, 2019.
114. Young EA, Altemus M, Parkison V and Shastry S: Effects of estrogen antagonists and agonists on the ACTH response to restraint stress in female rats. Neuropsychopharmacology 25: 881-891, 2001.
115. Xiong J, Kang SS, Wang Z, Liu X, Kuo TC, Korkmaz F, Padilla A, Miyashita S, Chan P, Zhang Z, *et al*: FSH blockade improves cognition in mice with Alzheimer's disease. Nature 603: 470-476, 2022.
116. Nerattini M, Jett S, Andy C, Carlton C, Zarate C, Boneu C, Battista M, Pahlajani S, Loeb-Zeitlin S, Havryulik Y, *et al*: Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia. Front Aging Neurosci 15: 1260427, 2023.
117. Whitmer RA, Quesenberry CP, Zhou J and Yaffe K: Timing of hormone therapy and dementia: The critical window theory revisited. Ann Neurol 69: 163-169, 2011.
118. Mosconi L, Nerattini M, Williams S and Fink M: New horizons in menopause, menopausal hormone therapy, and Alzheimer's disease: Current insights and future directions. J Clin Endocrinol Metab 110: 911-921, 2025.
119. Dalvi PS, Chalmers JA, Luo V, Han DY, Wellhauser L, Liu Y, Tran DQ, Castel J, Luquet S, Wheeler MB and Belsham DD: High fat induces acute and chronic inflammation in the hypothalamus: Effect of high-fat diet, palmitate and TNF-α on appetite-regulating NPY neurons. Int J Obes (Lond) 41: 149-158, 2017.
120. Hou J, Jeon B, Baek J, Yun Y, Kim D, Chang B, Kim S and Kim S: High fat diet-induced brain damaging effects through autophagy-mediated senescence, inflammation and apoptosis mitigated by ginsenoside F1-enhanced mixture. J Ginseng Res 46: 79-90, 2022.
121. Palomares D, Vanparys AAT, Jorgji J, Paître E, Kienlen-Campard P and Suelves N: Telomere-driven senescence accelerates tau pathology, neuroinflammation and neurodegeneration in a tauopathy mouse model. Acta Neuropathol Commun 13: 206, 2025.
122. Graves SI and Baker DJ: Implicating endothelial cell senescence to dysfunction in the ageing and diseased brain. Basic Clin Pharmacol Toxicol 127: 102-110, 2020.
123. DiBattista AM, Sierra F and Masliah E: NIA workshop on senescence in brain aging and Alzheimer's disease and its related dementias. Geroscience 42: 389-396, 2020.
124. Faust TE, Lee YH, O'Connor CD, Boyle MA, Gunner G, Durán-Laforet V, Ferrari LL, Murphy RE, Badimon A, Sakers K, *et al*: Microglia-astrocyte crosstalk regulates synapse remodeling via Wnt signaling. Cell 188: 5212-5230. e21, 2025.
125. Di Benedetto S, Müller L, Wenger E, Düzel S and Pawelec G: Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. Neurosci Biobehav Rev 75: 114-128, 2017.
126. Li X, Li C, Zhang W, Wang Y, Qian P and Huang H: Inflammation and aging: Signaling pathways and intervention therapies. Signal Transduct Target Ther 8: 239, 2023.
127. Capogna E, Watne LO, Sørensen Ø, Guichelaar CJ, Idland AV, Halaas NB, Blennow K, Zetterberg H, Walhovd KB, Fjell AM and Vidal-Piñeiro D: Associations of neuroinflammatory IL-6 and IL-8 with brain atrophy, memory decline, and core AD biomarkers-in cognitively unimpaired older adults. Brain Behav Immun 113: 56-65, 2023.
128. Tang H, Shaaban CE, DeKosky ST, Smith GE, Hu X, Jaffee M, Salloum RG, Bian J and Guo J: Association of education attainment, smoking status, and alcohol use disorder with dementia risk in older adults: A longitudinal observational study. Alzheimers Res Ther 16: 206, 2024.
129. Gogniat MA, Khan OA, Li J, Park C, Hudson Robb W, Zhang P, Sun Y, Moore EE, Houston ML, Pechman KR, *et al*: Increased sedentary behavior is associated with neurodegeneration and worse cognition in older adults over a 7-year period despite high levels of physical activity. Alzheimers Dement 21: e70157, 2025.
130. Shi L, Chen SJ, Ma MY, Bao YP, Han Y, Wang YM, Shi J, Vitiello MV and Lu L: Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Med Rev 40: 4-16, 2018.
131. McEwen BS and Morrison JH: Brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79: 16-29, 2013.
132. Yu JT, Xu W, Tan CC, Andrieu S, Suckling J, Evangelou E, Pan A, Zhang C, Jia J, Feng L, *et al*: Evidence-based prevention of Alzheimer's disease: Systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. J Neurol Neurosurg Psychiatry 91: 1201-1209, 2020.
133. Ornish D, Madison C, Kivipelto M, Kemp C, McCulloch CE, Galasko D, Artz J, Rentz D, Lin J, Norman K, *et al*: Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: A randomized, controlled clinical trial. Alzheimers Res Ther 16: 122, 2024.
134. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, *et al*: Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396: 413-446, 2020.
135. Stefaniak O, Dobrzyńska M, Drzymała-Czyż S and Przysławski J: Diet in the prevention of Alzheimer's disease: Current knowledge and future research requirements. Nutrients 14: 4564, 2022.
136. Chen H, Dhana K, Huang Y, Huang L, Tao Y, Liu X, Melo van Lent D, Zheng Y, Ascherio A, Willett W and Yuan C: Association of the mediterranean dietary approaches to stop hypertension intervention for neurodegenerative delay (MIND) diet with the risk of dementia. JAMA Psychiatry 80: 630-638, 2023.
137. Wen B, Han X, Gong J, Wang P, Sun W, Xu C, Shan A, Wang X, Luan H, Li S, *et al*: Nutrition: A non-negligible factor in the pathogenesis and treatment of Alzheimer's disease. Alzheimers Dement 21: e14547, 2025.
138. Uhl G, Kannan B, Choi J and Henderson I: Alzheimer's disease prevention by flavonols and their analogs. J Prev Alzheimers Dis 13: 100361, 2026.
139. Chen Q, Cao T, Li N, Zeng C, Zhang S, Wu X, Zhang B and Cai H: Repurposing of anti-diabetic agents as a new opportunity to alleviate cognitive impairment in neurodegenerative and neuropsychiatric disorders. Front Pharmacol 12: 667874, 2021.
140. Sun M, Chen WM, Wu SY and Zhang J: Metformin in elderly type 2 diabetes mellitus: Dose-dependent dementia risk reduction. Brain 147: 1474-1482, 2024.
141. Wu CY, Ouk M, Wong YY, Anita NZ, Edwards JD, Yang P, Shah BR, Herrmann N, Lanctôt KL, Kapral MK, *et al*: Relationships between memory decline and the use of metformin or DPP4 inhibitors in people with type 2 diabetes with normal cognition or Alzheimer's disease, and the role APOE carrier status. Alzheimers Dement 16: 1663-1673, 2020.
142. Campbell JM, Stephenson MD, de Courten B, Chapman I, Bellman SM and Aromataris E: Metformin use associated with reduced risk of dementia in patients with diabetes: A systematic review and meta-analysis. J Alzheimers Dis 65: 1225-1236, 2018.
143. Dutta S, Shah RB, Singhal S, Dutta SB, Bansal S, Sinha S and Haque M: Metformin: A review of potential mechanism and therapeutic utility beyond diabetes. Drug Des Devel Ther 17: 1907-1932, 2023.
144. Xu X, Sun Y, Cen X, Shan B, Zhao Q, Xie T, Wang Z, Hou T, Xue Y, Zhang M, *et al*: Metformin activates chaperone-mediated autophagy and improves disease pathologies in an Alzheimer disease mouse model. Protein Cell 12: 769-787, 2021.

145. Secher A, Jelsing J, Baquero AF, Hecksher-Sørensen J, Cowley MA, Dalbøge LS, Hansen G, Grove KL, Pyke C, Raun K, *et al*: The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest 124: 4473-4488, 2014.
146. Gao Y, Ottaway N, Schriever SC, Legutko B, García-Cáceres C, de la Fuente E, Mergen C, Bour S, Thaler JP, Seeley RJ, *et al*: Hormones and diet, but not body weight, control hypothalamic microglial activity. Glia 62: 17-25, 2014.
147. Holubová M, Hrubá L, Popelová A, Bencze M, Pražienková V, Gengler S, Kratochvílová H, Haluzík M, Železná B, Kuneš J, *et al*: Liraglutide and a lipidized analog of prolactin-releasing peptide show neuroprotective effects in a mouse model of β-amyloid pathology. Neuropharmacology 144: 377-387, 2019.
148. Zhang L, Zhang L, Li L and Hölscher C: Semaglutide is neuroprotective and reduces α-synuclein levels in the chronic MPTP mouse model of Parkinson's disease. J Parkinsons Dis 9: 157-171, 2019.
149. Edison P, Femminella GD, Ritchie C, Nowell J, Holmes C, Walker Z, Ridha B, Raza S, Livingston NR, Frangou E, *et al*: Liraglutide in mild to moderate Alzheimer's disease: A phase 2b clinical trial. Nat Med 32: 353-361, 2026.
150. Wang ZJ, Li XR, Chai SF, Li WR, Li S, Hou M, Li JL, Ye YC, Cai HY, Hölscher C and Wu MN: Semaglutide ameliorates cognition and glucose metabolism dysfunction in the 3xTg mouse model of Alzheimer's disease via the GLP-1R/SIRT1/GLUT4 pathway. Neuropharmacology 240: 109716, 2023.
151. Cummings JL, Atri A, Sano M, Zetterberg H, Scheltens P, Knop FK, Johannsen P, Wichmann CA, Abschneider RM, Leon T and Feldman HH: Efficacy and safety of oral semaglutide 14 mg (flexible dose) in early-stage symptomatic Alzheimer's disease (evoke and evoke+): Two phase 3, randomised, placebo-controlled trials. Lancet 407: 2167-2179, 2026.
152. Alhowail AH, Al Mouslem AK, Almatrafi MA and Aldubayan MA: Semaglutide in cognitive dysfunction: Neuroprotective potential, clinical trial limitations, and a prevention-focused framework. Front Aging Neurosci 18: 1851072, 2026.
153. Hölscher C: GLP-1 and GIP class drugs have neuroprotective properties in Alzheimer's and Parkinson's disease. Front Neurosci 20: 1906426, 2026.
154. Feng J and Jin T: Current understanding and controversy on brain access of GLP-1 and GLP-1 receptor agonists. J Transl Intern Med 13: 201-210, 2025.
155. Du Y, Sun C, Wu L, Wu Z, Tong Y, Tian H, Mao Y, Shi X, Ding H, Xie W, *et al*: Oral GLP-1 receptor agonist promotes astrocyte-neuron lactate and lipid transfer with neuroprotective effects. Cell Metab 38: 1633-1649.e7, 2026.
156. Kong F, Wu T, Dai J, Zhai Z, Cai J, Zhu Z, Xu Y and Sun T: Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: A systematic review and meta-analysis of preclinical stu. Front Pharmacol 14: 1205207, 2023.
157. Zhang Y, Chen H, Feng Y, Liu M, Lu Z, Hu B, Chen L, Zhang Y, Liu J, Cai F, *et al*: Activation of AMPK by GLP-1R agonists mitigates Alzheimer-related phenotypes in transgenic mice. Nat Aging 5: 1097-1113, 2025.
158. Drews HJ, Yenkoyan K, Lourhmati A, Buadze M, Kabisch D, Verleysdonk S, Petschak S, Beer-Hammer S, Davtyan T, Frey WH II, *et al*: Intranasal losartan decreases perivascular beta amyloid, inflammation, and the decline of neurogenesis in hypertensive rats. Neurotherapeutics 16: 725-740, 2019.
159. Alzahrani YM, Alim A Sattar MA, Kamel FO, Ramadan WS and Alzahrani YA: Possible combined effect of perindopril and Azilsartan in an experimental model of dementia in rats. Saudi Pharm J 28: 574-581, 2020.
160. Xiao S, Chan P, Wang T, Hong Z, Wang S, Kuang W, He J, Pan X, Zhou Y, Ji Y, *et al*: A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. Alzheimers Res Ther 13: 62, 2021.
161. Liu S, Gao J, Zhu M, Liu K and Zhang HL: Gut microbiota and dysbiosis in Alzheimer's disease: Implications for pathogenesis and treatment. Mol Neurobiol 57: 5026-5043, 2020.
162. Yu Z, Yang Y, Chan RB, Shi M, Stewart T, Huang Y, Liu Z, Lan G, Sheng L, Tian C, *et al*: GV-971 attenuates α-Synuclein aggregation and related pathology. CNS Neurosci Ther 30: e14393, 2024.
163. Alonso-Allende J, Milagro FI and Aranaz P: Health effects and mechanisms of inulin action in human metabolism. Nutrients 16: 2935, 2024.
164. Seo DO and Holtzman DM: Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. Exp Mol Med 56: 86-94, 2024.
165. Salihoglu R, Can Ş, Dandekar T and Bencurova E: Integrated multi-tissue transcriptomics reveals antagonistic pleiotropy in aging and Alzheimer's disease. Comput Struct Biotechnol J 35: 0134, 2026.
166. Liu F, Tang YL, Zhang ZB, Tan YH, Lin SH, Wang NY, Li JN, Pan ZJ, Li JF, Huang JF, *et al*: Modifying glucose metabolism reverses memory defects of Alzheimer's disease model at late stages. Adv Sci (Weinh) 13: e06695, 2026.
167. Mannick JB and Lamming DW: Targeting the biology of aging with mTOR inhibitors. Nat Aging 3: 642-660, 2023.
168. Selvarani R, Mohammed S and Richardson A: Effect of rapamycin on aging and age-related diseases-past and future. Geroscience 43: 1135-1158, 2021.
169. Lee DJW, Hodzic Kuerec A and Maier AB: Targeting ageing with rapamycin and its derivatives in humans: A systematic review. Lancet Healthy Longev 5: e152-e162, 2024.
170. Lagoumtzi SM and Chondrogianni N: Senolytics and senomorphics: Natural and synthetic therapeutics in the treatment of aging and chronic diseases. Free Radic Biol Med 171: 169-190, 2021.
171. Kim AL, Lee WK, Kwon S, Han I and Choi BH: Therapeutic efficacy of mesenchymal stem cells (MSCs) on Alzheimer's DIsease: Review of clinical results. Tissue Eng Regen Med 23: 343-365, 2026.
172. Zhang Y, Li Z, Guan H, Qiu Z and Zou C: Engineering exosomes for Alzheimer's disease: Multi-target therapeutic strategies from pathogenesis to clinical translation. Clin Transl Med 15: e70548, 2025.
173. Yarahmadi A, Dorri Giv M, Hosseininejad R, Rezaie A, Mohammadi N, Afkhami H and Farokhi A: Mesenchymal stem cells and their extracellular vesicle therapy for neurological disorders: Traumatic brain injury and beyond. Front Neurol 16: 1472679, 2025.
174. Wang X, Yang F, Chen P, Yang M, Deng Y and Zhan Z: Mesenchymal stem cell-derived extracellular vesicles in Alzheimer's disease: A novel cell-free therapeutic strategy and diagnostic biomarker. Int J Nanomedicine 20: 14375-14391, 2025.
175. Das V and Hajdúch M: Oncology drug repurposing as a blueprint for Alzheimer's therapy. Alzheimers Dement (N Y) 12: e70231, 2026.
176. Gong CX, Dai CL, Liu F and Iqbal K: Multi-targets: An unconventional drug development strategy for Alzheimer's disease. Front Aging Neurosci 14: 837649, 2022.
177. Le Boeuf W, Hefny AA, Karuturi RC and Rao PPN: Combination of resveratrol and curcumin with anti-amyloid monoclonal antibodies aducanumab and lecanemab leads to greater inhibition of amyloid-beta aggregation. ACS Chem Neurosci 17: 987-997, 2026.
178. Cummings J, Osse AML, Cammann D, Powell J and Chen J: Anti-amyloid monoclonal antibodies for the treatment of Alzheimer's disease. BioDrugs 38: 5-22, 2024.
179. Bhat NR: Linking cardiometabolic disorders to sporadic Alzheimer's disease: A perspective on potential mechanisms and mediators. J Neurochem 115: 551-562, 2010.
180. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, *et al*: NIA-AA research framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14: 535-562, 2018.
181. Li Q, Su S, Feng Y, Jia M, Zhan J, Liao Z, Li J and Li X; Alzheimer's Disease Neuroimaging Initiative: Potential role of blood pressure variability and plasma neurofilament light in the mechanism of comorbidity between Alzheimer's disease and cerebral small vessel disease. Alzheimers Dement 20: 4891-4902, 2024.
182. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, *et al*: Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest 122: 1316-1338, 2012.
183. Jazvinšćak Jembrek M, Hof PR and Šimić G: Ceramides in Alzheimer's disease: Key mediators of neuronal apoptosis induced by oxidative stress and Aβ accumulation. Oxid Med Cell Longev 2015: 346783, 2015.
184. Wang X, Shi Z, Qiu Y, Sun D and Zhou H: Peripheral GFAP and NfL as early biomarkers for dementia: Longitudinal insights from the UK Biobank. BMC Med 22: 192, 2024.

185. Deczkowska A, Weiner A and Amit I: The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway. Cell 181: 1207-1217, 2020.
186. Munawara U, Catanzaro M, Xu W, Tan C, Hirokawa K, Bosco N, Dumoulin D, Khalil A, Larbi A, Lévesque S, *et al*: Hyperactivation of monocytes and macrophages in MCI patients contributes to the progression of Alzheimer's disease. Immun Ageing 18: 29, 2021.
187. Le Page A, Bourgade K, Lamoureux J, Frost E, Pawelec G, Larbi A, Witkowski JM, Dupuis G and Fülöp T: NK cells are activated in amnestic mild cognitive impairment but not in mild Alzheimer's disease patients. J Alzheimers Dis 46: 93-107, 2015.
188. Lau SF, Wu W, Wong HY, Ouyang L, Qiao Y, Xu J, Lau JH, Wong C, Jiang Y, Holtzman DM, *et al*: The VCAM1-ApoE pathway directs microglial chemotaxis and alleviates Alzheimer's disease pathology. Nat Aging 3: 1219-1236, 2023.
189. Tarawneh R, Kasper RS, Sanford J, Phuah CL, Hassenstab J and Cruchaga C: Vascular endothelial-cadherin as a marker of endothelial injury in preclinical Alzheimer disease. Ann Clin Transl Neurol 9: 1926-1940, 2022.
190. Cooper JG, Ghodsi M, Stukas S, Leach S, Brooks-Wilson A and Wellington CL: APOE ε4 carrier status modifies plasma p-tau181 concentrations in cognitively healthy super-seniors. Alzheimers Dement 20: 4373-4380, 2024.
191. Li RX, Ma YH, Tan L and Yu JT: Prospective biomarkers of Alzheimer's disease: A systematic review and meta-analysis. Ageing Res Rev 81: 101699, 2022.
192. de la Monte SM: Type 3 diabetes is sporadic Alzheimer's disease: Mini-review. Eur Neuropsychopharmacol 24: 1954-1960, 2014.
193. Kandimalla R, Thirumala V and Reddy PH: Is Alzheimer's disease a type 3 diabetes? A critical appraisal. Biochim Biophys Acta Mol Basis Dis 1863: 1078-1089, 2017.
194. Kapoor B, Biswas P, Gulati M, Rani P and Gupta R: Gut microbiome and Alzheimer's disease: What we know and what remains to be explored. Ageing Res Rev 102: 102570, 2024.
195. No authors listed: 2024 Alzheimer's disease facts and figures. Alzheimers Dement 20: 3708-3821, 2024.
196. Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, *et al*: New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet 54: 412-436, 2022.
197. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C, *et al*: Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet 404: 572-628, 2024.

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