Exercise and fluoxetine in Alzheimer's disease: Molecular mechanisms of synergistic and antagonistic effects (Review)

MEI WU[1] and YAN LI[1-3]

[1]Department of Exercise Physiology, School of Sport Science, Beijing Sport University, Beijing 100084, P.R. China;
[2]Beijing Key Laboratory of Sports Performance and Skill Assessment, Beijing Sport University, Beijing 100084, P.R. China;
[3]Key Laboratory of Physical Fitness and Exercise, Ministry of Education, Beijing Sport University, Beijing 100084, P.R. China

Received March 19, 2026; Accepted May 19, 2026

DOI: 10.3892/ijmm.2026.5908

Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β deposition, tau pathology, synaptic dysfunction, neuronal loss and neuroinflammation. Regular physical activity is a key non-pharmacological strategy that can ameliorate cognitive impairment and multiple AD-related pathological features across experimental models by improving mitochondrial function and quality control, strengthening antioxidant defenses, suppressing neuroinflammation and supporting synaptic plasticity. These effects are closely linked to enhanced neurotrophic signaling and cerebrovascular regulation, both of which contribute to resilience against AD-associated cognitive decline. Fluoxetine, a selective serotonin reuptake inhibitor widely prescribed for depression, has also shown potential benefits in AD models, including modulation of mitochondrial and redox homeostasis, inflammatory signaling and neuroplasticity. The present review integrates evidence on the convergent and divergent molecular targets of exercise and fluoxetine within core AD pathways, highlighting scenarios in which combined interventions may produce synergistic effects, as well as conditions that could lead to antagonistic effects. By mapping shared nodes and potential points of interference, the present review aims to clarify mechanistic hypotheses and inform the design of optimized, clinically translatable strategies that integrate lifestyle and pharmacological approaches for AD.

Correspondence to: Dr Yan Li, Department of Exercise Physiology, School of Sport Science, Beijing Sport University, 48 Xinxi Road, Haidian, Beijing 100084, P.R. China
E-mail: bsuliyan@bsu.edu.cn

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; ALP, autophagy-lysosome pathway; AMPK, adenosine monophosphate-activated protein kinase; APP, amyloid precursor protein; ASC, apoptosis-associated speck-like protein containing a CARD; BACE1, β-site APP-cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; Drp1, dynamin-related protein 1; GSH, glutathione; HPA, hypothalamic-pituitary-adrenal; MCI, mild cognitive impairment; Mn-SOD, manganese superoxide dismutase; MQC, mitochondrial quality control; NLRP3, NOD-like receptor family pyrin domain containing 3; PDH, pyruvate dehydrogenase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PP2A, protein phosphatase 2A; PSD-95, postsynaptic density protein 95; ROS, reactive oxygen species; SSRI, selective serotonin reuptake inhibitor; TFAM, mitochondrial transcription factor A; TFEB, transcription factor EB; TLR4, toll-like receptor 4; TrkB, tropomyosin receptor kinase B; APOE, apolipoprotein E

Key words: AD, exercise, fluoxetine, mitochondria, inflammation, oxidative stress

Contents

1. Introduction

Against the backdrop of a globally aging population, aging is still widely regarded as the primary risk factor for Alzheimer's disease (AD) (1). Demographic trends show that the number of older adults is increasing worldwide. Currently, ~5% of individuals over the age of 60 years have been diagnosed with dementia, a figure that rises to ~30% among those >85 years old (2,3). AD accounts for 60-80% of all dementia cases (4), and its prevalence continues to increase as the population ages. According to the World Health Organization, 57 million individuals worldwide were living with dementia in 2021, and

nearly 10 million new cases occur every year (5). Without breakthrough interventions, this number of individuals living with dementia is projected to rise to 78 million by 2030 and 139 million by 2050 (6).

The AD continuum spans from early, often clinically silent brain changes to progressive impairment in memory and cognition, ultimately leading to long-term functional dependence. AD is commonly divided into preclinical AD, mild cognitive impairment (MCI) due to AD and dementia due to AD. The dementia stage is further subdivided into mild, moderate and severe stages (7). In the early phase, the main symptom is occasional memory lapses, with particular difficulty in remembering newly acquired information. As the disease progresses to the middle stage, memory and language problems worsen, multi-step activities of daily living are impaired, personality and behavior change, and other systems such as language, vision and the respiratory system may gradually be affected (8). In the late stage, there is more severe memory loss, disorientation and a need for round-the-clock care. Patients often experience poor outcomes or death due to complications such as aspiration, aspiration pneumonia and infections caused by swallowing difficulties (9). Pathologically, amyloid-β (Aβ) deposition, tau-related neurofibrillary tangles, synaptic dysfunction and neuroinflammation constitute the key pathological network of AD (10,11). However, drug development targeting a single pathological process still faces challenges in real-world settings, including limited efficacy, narrow therapeutic windows and substantial individual variability (12). These limitations have prompted researchers to shift their focus toward multi-target, comprehensive intervention strategies that are feasible for long-term implementation and more accessible to patients (13).

Exercise is considered to be an important non-pharmacological approach for the prevention and treatment of AD because of its low cost, scalability, and wide-ranging systemic and central benefits. Existing studies have suggested that regular exercise can improve AD-related symptoms through multiple pathways, including enhancing mitochondrial function and metabolism, boosting antioxidant capacity, inhibiting neuroinflammation and promoting synaptic plasticity (14-16). Fluoxetine, a commonly used selective serotonin (5-HT) reuptake inhibitor (SSRI) in clinical practice, serves a key role in mood regulation and also exhibits potential neuroprotective effects, including promoting autophagy, exerting anti-inflammatory and antioxidant effects, and enhancing neuroplasticity (17-19). Preclinical evidence indicates that fluoxetine may modulate Aβ metabolism and tau-related pathways in the brain, although its disease-modifying effects in patients with AD remain insufficiently established (20,21). Given that exercise and fluoxetine may converge on the 5-HT system, hypothalamic-pituitary-adrenal (HPA) axis, brain-derived neurotrophic factor (BDNF)-related neuroplasticity and immune-metabolic pathways, combined intervention integrating exercise and pharmacotherapy may represent a biologically plausible personalized treatment strategy (22,23). However, the long-term benefits of exercise are largely mediated by adaptive remodeling induced by repeated moderate physiological stress, whereas prolonged pharmacological inhibition of serotonin reuptake by fluoxetine and medication-related adverse effects may affect exercise tolerance, adherence and neuroendocrine or metabolic responses (23-25). Therefore, the net effect of combined intervention remains uncertain and requires further validation.

Therefore, the present review focuses on the coexistence of synergy and antagonism, summarizing the evidence and mechanisms by which exercise and fluoxetine influence key pathological pathways in AD. Based on shared targets, the current review outlines potential windows of benefit, as well as scenarios in which combined intervention may fail. The aim of the present review is to provide testable hypotheses for subsequent mechanistic research and clinical translation.

2. Beneficial effects of exercise on AD

Exercise and mitochondria. Mitochondria occupy a central position in AD because they integrate energy metabolism, calcium homeostasis, redox regulation and cell survival, making mitochondrial dysfunction a plausible hub at which multiple pathological processes converge (26,27). Recent reviews have synthesized evidence indicating that mitochondrial dysfunction is closely linked to the core pathological features of AD and may participate early in disease evolution (27-29). This interpretation is strengthened by longitudinal evidence from AD mice showing that mitochondrial dysfunction develops in parallel with cognitive decline and pathological progression (30). Once mitochondrial integrity is compromised, bioenergetic defects, oxidative stress, inflammatory activation and defective autophagy no longer remain isolated abnormalities, but instead begin to reinforce one another, thereby creating a self-amplifying process that promotes neuronal stress, synaptic vulnerability, and further accumulation of Aβ- and tau-related pathology (29). Within this conceptual framework, exercise becomes important not because it targets a single molecular event, but because it may reshape the adaptive capacity of the mitochondrial network itself (31). The concept is consistent with mitohormesis, in which transient, low-level mitochondrial stress induced by exercise activates adaptive signaling responses involving reactive oxygen species (ROS), the mitochondrial unfolded protein response and mitochondria-derived peptides (31-33). In AD mice, treadmill exercise has been shown to reduce the Aβ burden, activate sirtuin 1 (SIRT1)-related protective signaling, attenuate mitochondrial dysfunction and enhance mitophagy, suggesting that exercise may influence several interconnected AD-related pathological processes rather than targeting one isolated downstream pathological feature (34,35).

Within the framework of mitochondrial quality control (MQC), AD-related mitochondrial dysfunction can be interpreted not merely as mitochondrial damage, but as a progressive impairment of quality control processes involving mitochondrial renewal, repair, transport and clearance (36). In SH-SY5Y cells, Aβ and glia maturation factor disrupt the balance between fission and fusion proteins, indicating a direct shift toward excessive mitochondrial fragmentation (37). Specifically, in neurons from patients diagnosed with AD, an abnormal interaction between Aβ and dynamin-related protein 1 (Drp1) has been reported, while fibroblasts from patients with sporadic AD display abnormal mitochondrial morphology and distribution (38,39). Together with mechanistic studies and reviews, these findings support a broader pattern in which mitochondrial

fission 1 protein- and Drp1-driven fission is enhanced, while mitofusin (Mfn)1-, Mfn2- and Opa1-mediated fusion and repair are weakened (40-43). Once fragmented mitochondria can no longer be effectively repaired, redistributed or replaced, abnormalities in dynamics are translated into transport defects, insufficient synaptic localization and local energy failure. This may explain why a calcium-dependent mechanism involving Miro can stall mitochondrial trafficking at the cellular level (44), while AD-related axonopathy and transport deficits aggravate synaptic instability and neurodegeneration at the tissue level (45,46). This MQC-based framework also extends to metabolic dysfunction, since impaired mitochondrial maintenance may contribute to defects in neuronal energy production and glucose utilization. Human evidence shows that AD is associated with brain glucose dysregulation, reduced regional glucose uptake, impaired oxidative phosphorylation and reduced mitochondrial enzyme activity (47-50). Mechanistic studies have further suggested that these metabolic defects are linked to altered amyloid precursor protein (APP) processing, β-site APP-cleaving enzyme 1 (BACE1) upregulation, tau-related injury, and reduced activity of cytochrome *c* oxidase (COX), pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (50,51). Animal studies have further demonstrated impaired mitochondrial biogenesis, defective axonal transport, synaptic degeneration, reduced ATP production, increased oxidative stress and disruption of the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)-nuclear respiratory factors (NRFs)-mitochondrial transcription factor A (TFAM) axis in AD animal models compared with age-matched wild-type or non-transgenic controls (49,52-54). Taken together, these findings suggest that a central mitochondrial defect in AD may involve the progressive failure of mitochondrial renewal, redistribution and removal, meaning that mitochondrial dysfunction is sustained not by a single isolated mitochondrial abnormality, but by disruption of the broader MQC network (55).

From this perspective, the value of exercise lies not simply in improving one biochemical index, but in helping restore coordination across MQC (36,56). Most direct evidence for the view that exercise may help restore coordination across MQC in AD still comes from animal models (32,35,57-62), whereas the broader mechanistic rationale is supported by general exercise and mitochondrial research showing that exercise can regulate mitochondrial biogenesis, metabolism, dynamics, calcium handling and mitophagy (34,36,63,64). In AD model mice and rats, regular exercise improves mitochondrial ultrastructure, increases ATP levels, enhances respiratory chain function, upregulates brain glucose transporter expression, promotes glycolysis and oxidative phosphorylation, and increases the expression or activity of key metabolic regulators such as PDH and COX (57,58,60). Exercise also shifts mitochondrial dynamics toward a more favorable state by increasing Mfn1 levels and suppressing excessive Drp1-related fission (58). These findings imply that exercise does not simply increase ATP availability in AD-related neural tissue, but may improve the capacity of neuronal mitochondrial systems to match energy production with demand, maintain bioenergetic stability under energy-deficient stress and coordinate organelle turnover. This interpretation is consistent with evidence showing that long-term running enhances lysosomal biogenesis (65) and vesicle trafficking via adenosine monophosphate-activated protein kinase (AMPK), transcription factor EB (TFEB) and Rab7/Rab9, thereby promoting clearance of Aβ and damaged mitochondria, and improving cognition in APP/presenilin 1 (APP/PS1) mice (59). More broadly, exercise-induced activation of AMPK and the PGC-1α-NRFs-TFAM pathway supports mitochondrial DNA maintenance, transcription and mitochondrial renewal (35,60,63,64). Exercise may also improve inter-organelle signaling through regulation of voltage-dependent anion channel 1, suppression of mitochondrial permeability transition pore opening and stabilization of calcium handling at the endoplasmic reticulum-mitochondria interface relative to the dysregulated calcium transfer observed in AD-related conditions (36,66,67). The role of exercise in mitophagy is particularly important. The PTEN-induced kinase 1/Parkin pathway provides the classical framework for selective elimination of damaged mitochondria (68), whereas in AD, defective autophagy-lysosome pathway activity, p62 accumulation, impaired LC3 conversion and lysosomal dysfunction limit the clearance of both damaged mitochondria and Aβ (69,70). In animal models, exercise restores mitophagy and autophagic flux, improves TFEB-related lysosomal regulation, reduces Aβ deposition, and rescues mitochondrial and synaptic function (35,59,61,62).

Exercise and oxidative stress. Evidence from human neuropathological studies and mitochondria-related reviews suggests that oxidative damage emerges before overt clinical signs of AD and before substantial Aβ deposition, indicating that oxidative stress is not merely a downstream byproduct of pathology, but an early force that contributes to disease vulnerability and progression (71-74). Oxidative stress refers to an imbalance between pro-oxidants, such as ROS and reactive nitrogen species, and antioxidant defenses, including enzymatic and non-enzymatic antioxidant systems such as superoxide dismutase, catalase, glutathione peroxidase and glutathione, together with disruption of redox signaling and regulation (75). When ROS production exceeds the capacity of antioxidant systems, this imbalance can promote mitochondrial dysfunction, neuroinflammation and progressive impairment of neural structure and function, thereby driving neurodegeneration forward (76). This framework also helps explain the apparent paradox of exercise. Although physical exercise acutely increases ROS generation at the whole-body and skeletal muscle levels (77), regular exercise is consistently associated with reduced disease risks of cardiometabolic and neurodegenerative diseases, including cardiovascular disease, type 2 diabetes and dementia, and broader health benefits (78). The key issue, therefore, is not whether ROS are generated, but whether the magnitude and duration of ROS signals remain low-to-moderate and transient enough to trigger adaptive responses rather than oxidative injury. At low-to-moderate levels, mitochondrial ROS act as signaling molecules that induce mitohormetic adaptation and activate exercise-responsive transcriptional programs, thereby supporting mitochondrial biogenesis and antioxidant defense (32).

This redox-adaptation logic becomes clearer when the antioxidant system is viewed as a dynamic buffering network rather than a static defensive barrier. The antioxidant system is composed of antioxidant enzymes, including superoxide

dismutase (SOD), glutathione peroxidase (GPx) and catalase, and non-enzymatic antioxidants, including glutathione (GSH), that work together to neutralize oxidants, interrupt chain reactions and preserve the redox balance (79-82). In mitochondria, superoxide generated by the electron transport chain is converted by manganese SOD (Mn-SOD) into hydrogen peroxide, which is then reduced through the GSH system by GPx or decomposed by catalase into water and oxygen (80-82). During this process, GSH is oxidized to GSH disulfide (GSSG); therefore, the GSH/GSSG ratio is an informative index of the intracellular redox status, and its decline suggests that ROS generation has exceeded the reducing capacity of endogenous antioxidant defenses (83). Experimental evidence further indicates that the GSH/GSSG ratio declines early in AD and continues to worsen as pathology progresses (84). This pattern suggests that antioxidant failure develops progressively rather than abruptly in AD. In the early stages, the brain may still partially compensate for increased ROS production by increasing the activity of enzymes such as SOD and GPx; however, the persistent oxidative burden gradually exhausts this reserve. As a result, the redox imbalance shifts from a limited adaptive response to a more self-sustaining pathological state (84). When considering this progressive loss of redox balance, the beneficial effect of exercise is more convincingly understood as redox recalibration rather than simple ROS suppression (24,85). In AD models, exercise alleviates the pathological burden and cognitive impairment, while also improving mitochondrial adaptation. In rodent brain tissue, endurance training can upregulate Mn-SOD and GSH levels in the hippocampus, lower the levels of the lipid peroxidation product malondialdehyde (MDA), alleviate oxidative stress and enhance the mitochondrial ROS scavenging capacity (86-88). Broader exercise research in mixed clinical populations and healthy adults, including individuals with cardiometabolic, oncological and neurological conditions, has similarly demonstrated improved oxidative stress biomarker profiles and enhanced antioxidant capacity compared with baseline values or non-exercise control conditions (89,90).

However, this benefit has physiological limitations. Long-term high-intensity exercise can increase ROS production beyond the clearance capacity of cellular and mitochondrial antioxidant systems, leading to lipid peroxidation, protein oxidation and DNA damage (91). Once this threshold is exceeded, oxidative stress no longer supports adaptation, but instead damages mitochondrial structure and function, impairs energy metabolism, and further amplifies oxidative and inflammatory signaling (91,92). Therefore, the value of exercise in AD lies not in eliminating ROS altogether, but in maintaining redox stress within a range that favors adaptation over degeneration.

Exercise and neuroinflammation. Persistent accumulation of protein aggregates, mitochondrial stress and oxidative imbalance not only injures neurons directly but also continuously reshapes the inflammatory environment of the brain. Within this setting, activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is better understood as a point where these pathological signals converge (93). After microglia internalize Aβ, lysosomal damage accompanied by ionic imbalance and oxidative stress can activate the NLRP3 inflammasome (94,95). Aβ aggregates and hyperphosphorylated tau may further strengthen this activation through lysosomal rupture, K^+ efflux and mitochondria-related danger signals (94-96). This activation not only facilitates tau pathology, but may also enhance apoptosis-associated speck-like protein containing a CARD (ASC)-mediated Aβ aggregation and weaken microglial Aβ clearance (96-98). In addition, IL-1β continuously released by the activated NLRP3 inflammasome can promote tau phosphorylation and aggregation through regulation of tau-related kinases and phosphatases (96). Inflammatory activity may arise early in the disease course (99), and once established, NLRP3-related neuroinflammation can participate in sustained pathological progression in AD (98). These mechanisms together create a vicious cycle of pathological deposition and inflammatory activation, driving the progression of AD pathology (96-98).

When this process is considered together with autophagy and MQC, its pathological importance becomes clear. Impaired autophagy favors NLRP3 activation, whereas enhancement of autophagy and mitophagy can suppress inflammasome-related neuroinflammation (62,100,101). This helps explain why the anti-inflammatory value of exercise is unlikely to lie only in lowering inflammatory markers. Exercise may act on upstream conditions that sustain inflammatory activation, including defective autophagy and mitochondrial abnormalities (62,101). Exercise-related modulation of the autophagy-inflammation crosstalk has also been documented in healthy older adults aged 65-78 years (102), and broader evidence has linked exercise to improved inflammatory regulation in aging and neurodegeneration (103,104). In APP/PS1 mice, exercise also reduces the amyloid-related burden (105). Systematic evidence across adult populations further demonstrates that moderate-intensity aerobic exercise, moderate resistance exercise, and combined aerobic and resistance training may downregulate key molecules related to the NLRP3 inflammasome, lower the levels of IL-1β and caspase-1, and decrease the expression levels of ASC and NLRP3 genes (106). The underlying mechanisms may be associated with the upregulation of autophagy-related proteins, including Beclin1, LC3 and autophagy related 12, promotion of MQC and enhancement of autophagic flux (102,104,105). However, high-intensity aerobic exercise may exert the opposite effect (106). This is important because inflammatory responsiveness changes with age (107), meaning that the biological effect of exercise depends on whether the training dose promotes adaptive inflammatory regulation or, conversely, excessive inflammatory stress.

The same line of reasoning also helps explain why toll-like receptor 4 (TLR4) and microglia remain central to exercise-related neuroprotection. NLRP3 inflammasome activation follows the classic two-signal model. In the priming stage, pathogen-associated molecular patterns bind to TLR4, the toll/IL-1 receptor/resistance protein domain of which transduces signals through MyD88, activating TNF receptor associated factor 6 and initiating the NF-κB signaling pathway. This process induces the expression of NLRP3 and precursors of pro-inflammatory cytokines, including IL-1β and IL-18 (108), placing the cell in a primed inflammatory state. In this context, TLR4 exhibits a dual role. Acute low-dose TLR4 ligands can activate microglia, enhancing their phagocytic capacity for Aβ and reduce Aβ plaque burden in AD mice.

Conversely, sustained high-dose TLR4 activation can lead to excessive microglial activation, resulting in the massive release of pro-inflammatory cytokines and ROS, which suppresses Aβ phagocytosis (109-112). Chronic physical exercise can effectively reduce TLR4 levels in the brains of APP mice and modulate TLR4 activity to reduce neuroinflammation and mitigate AD-related pathology (62).

Microglial accumulation around Aβ plaques reflects an active response to amyloid deposition (111,113). These cells can assist in clearing Aβ aggregates via phagocytosis (114), but they can also release neurotoxic proteases and inflammatory factors that promote Aβ accumulation (113,115). Against this background, the significance of exercise lies not in indiscriminate suppression of inflammation, but in shifting microglial responses toward a state that supports Aβ clearance while limiting excessive cytokine and ROS release. In AD animal models, treadmill exercise can reduce neuroinflammation and glial activation, and is associated with microglial modification, whereas voluntary wheel running alters the immune profile, is associated with cognitive improvement and reduces amyloid burden (86,116,117). Duration also appears to matter, as experimental evidence has indicated duration-dependent neuroinflammatory responses, and meta-analyses in AD have suggested that the overall benefit of exercise interventions is heterogeneous rather than uniform (118-120). Taken together, these findings suggest that the anti-inflammatory effect of exercise is best understood as a regulatory process that helps restore the balance among immune surveillance, protein clearance and tissue protection.

Exercise and synaptic plasticity. Compared with extensive neuronal loss, which represents a relatively late pathological outcome, synaptic injury provides a more direct and earlier functional basis for cognitive impairment in AD (121). Soluble Aβ oligomers impair synaptic plasticity and memory-related behavior in experimental models, and Aβ-induced synaptic and memory deficits do not appear to depend entirely on tau as an obligatory mediator (122,123). As pathology progresses, fibrillar amyloid deposition can also induce local synaptic abnormalities and neuritic branch breakage (124). Therefore, the transition from abnormal protein aggregation to circuit dysfunction begins at the synapse level, the most vulnerable structural and functional unit (122-124). Structural alterations, such as changes in dendritic complexity, have already been observed in triple-transgenic AD (3xTg-AD) mice (125), indicating that synaptic instability develops in parallel with broader remodeling of the neuronal architecture. Long-term treadmill exercise preserves spatial working memory and ameliorates Aβ-induced memory impairment (58,126), and these effects are associated with enhanced structural synaptic plasticity and BDNF-related signaling (127,128). These exercise-related cognitive and synaptic effects may be linked to AMPK, PGC-1α, fibronectin type III domain containing 5 and BDNF-related pathways, as well as reductions in hippocampal BACE and APP expression (129,130). Reviews have further indicated that regular physical exercise can attenuate pathological and functional deterioration in AD- and dementia-related contexts, although the magnitude and nature of the response vary with training protocol, disease model and neuroimmunoendocrine context, including sex-related differences (131-133).

In 3xTg-AD mice, synaptic ultrastructural abnormalities in the hippocampus and prefrontal cortex include shortened synaptic active zones, widened synaptic clefts, reduced curvature and thinned postsynaptic density, all of which are ameliorated by treadmill exercise (128). At the molecular level, exercise-related rescue of plasticity is better understood as the coordinated restoration of presynaptic and postsynaptic organization rather than as a change in any single marker (134-136). This interpretation is consistent with evidence showing that exercise-based paradigms, either alone or combined with additional stimulation strategies, can support adult neurogenesis and circuit remodeling in AD- or aging-related conditions (137,138). In addition, findings indicating that exercise reverses behavioral and electrophysiological impairments caused by reduced adult neurogenesis, while also acting more generally as an epigenetic modulator of brain plasticity and cognition, point in the same direction (139,140).

Dendrites and dendritic spines form immediate structural substrates of excitatory synaptic transmission. Under physiological conditions, spine morphology, stability and turnover remain highly dynamic, and this dynamic range is itself a prerequisite for learning-related plasticity (141). AD-related pathology progressively erodes this flexibility. In 3xTg-AD mice, changes in dendritic complexity are accompanied by impaired structural synaptic plasticity across the hippocampus and prefrontal cortex (128). Treadmill exercise can prevent or reverse the overall loss of dendritic spines and preserve the distribution of functionally distinct spine populations, thereby maintaining connectivity at the microscopic level (128). This effect is mechanistically important because aerobic exercise can regulate the Rho/cofilin pathway to reverse synaptic loss, indicating that exercise does not merely preserve existing synapses, but also restores the cytoskeletal conditions required for synaptic remodeling (142). This exercise-related protection of structural plasticity is not limited to synapses and dendritic spines, but also extends to white matter integrity, because myelin and oligodendrocyte function provide structural support for efficient axonal signal propagation. In 3xTg-AD mice, abnormal myelination and disturbed oligodendrocyte differentiation weaken the structural support required for efficient axonal signal propagation, thereby compromising network function (143). Long-term treadmill exercise intervention attenuates these abnormalities, promotes oligodendrocyte maturation, increases myelin density and restores myelin-related homeostasis, indicating that exercise protects plasticity not only at the synaptic interface but also along the axonal pathway that sustains circuit-level communication (143).

Electrophysiological findings further strengthen this interpretation. In APP/PS1 mice, treadmill exercise facilitates synaptic plasticity through the regulation of hippocampal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor activity (144). These findings show that exercise acts across multiple linked levels of synaptic organization, including ultrastructure, synaptic proteins, dendritic remodeling, myelin integrity, adult neurogenesis and receptor-dependent electrophysiological transmission. Exercise should therefore be viewed not as a nonspecific behavioral intervention, but as a biologically grounded strategy that acts across multiple levels of synaptic organization to preserve and restore the structural and functional basis of plasticity in AD.

Exercise in the context of genotype-specific vulnerability and epigenetic regulation. The beneficial effects of exercise on mitochondrial homeostasis, redox balance, neuroinflammation and synaptic plasticity do not operate independently of genotype. Their magnitude and durability may be shaped by individual genetic vulnerabilities and epigenetic states (139,145-147). Current evidence suggests that AD-related mitochondrial, redox, inflammatory and synaptic pathways are conditioned by apolipoprotein E (APOE)-dependent vulnerability and by epigenetic programs that determine whether metabolic and inflammatory stress is converted into persistent pathology (148-152). Accordingly, APOE genotype-specific regulation lies further upstream than the aforementioned mechanisms. APOE4 does not merely quantitatively increase risk, but also redirects the cellular trajectory of AD toward stronger pro-inflammatory microglial activation, and weaker synaptic and myelination-related programs, whereas APOE2 is associated with a comparatively protective profile (148,149). APOE genotype-specific methylation patterns linked to AD pathology and estrogen response further indicate that genetic susceptibility is embedded within a pre-existing regulatory background before downstream defects in MQC, oxidative amplification, persistent inflammation and synaptic decline become self-reinforcing (149). Within this framework, exercise is unlikely to eliminate APOE4-associated molecular abnormalities, such as pro-inflammatory microglial activation and weakened synaptic and myelination-related programs, but may attenuate the vascular, metabolic, amyloid-related or cognitive manifestations of these abnormalities. Available studies have demonstrated that higher midlife physical activity weakened the association between APOE4-related amyloid retention and AD-like cerebral hypometabolism (153), whereas aerobic training preferentially improved hippocampal blood flow in hypertensive APOE4 carriers (154). In addition, a post hoc analysis in mild AD suggested that APOE4 carriers may derive greater preservation of cognition and physical performance from exercise intervention (153-155). However, a recent systematic review has indicated that genotype-stratified exercise evidence remains limited and inconsistent (145). A cautious conclusion is therefore that exercise may preferentially influence modifiable vascular, metabolic and functional features associated with APOE states, whereas convincing evidence that it directly reverses APOE4-driven molecular pathology is still lacking (145,153-155). The aforementioned exercise-related mechanisms are summarized in Figs. 1 and 2, and the key exercise-induced protective mechanisms relevant to AD are summarized in Table SI (34,35,57-59,61,62,86,87,102,105,116,117,127,142-144).

3. Role of fluoxetine in AD

Depression is closely related to AD, not only as an important risk factor (156), but also through a bidirectional association and causal relationship between the two (157-160). An autopsy study has shown that patients with AD and a lifetime history of major depression had nearly twice the amount of Aβ deposition and neurofibrillary tangles in the hippocampal region compared with patients with AD without depression (161). There are a number of shared pathways between the two, including neurotransmitter dysregulation, neuroinflammation, abnormalities in the HPA axis and deficits in neuroplasticity (162,163). Fluoxetine, an SSRI antidepressant, is classically understood to increase synaptic 5-HT levels by inhibiting serotonin reuptake (23) and has exhibited potential benefits in AD models (21,164-166). Fluoxetine can enhance the levels of monoamines, including 5-HT, dopamine (DA) and norepinephrine (NE), in the brains of animals, promote neurogenesis and, by reducing oxidative stress and neuroinflammation, improve depressive behaviors as well as learning, memory and cognitive function in AD rats (167,168). Furthermore, fluoxetine effectively reduces Aβ deposition and tau protein abnormalities in the brain (21,167,168).

Enhancement of mitochondrial function. Fluoxetine has been found to potentially improve mitochondrial function by regulating MQC and mitochondria-associated cell death pathways in various models (169,170). In terms of MQC, fluoxetine can promote mitophagy and enhance the colocalization of autophagosomes and mitochondria, while simultaneously inducing the translocation of Parkin from the cytoplasm to the mitochondria (169). Mitochondria-localized Parkin further facilitates the degradation of the mitochondrial outer membrane protein translocase of outer mitochondrial membrane 20, promoting the recognition and selective clearance of damaged mitochondria, and reducing the accumulation of mitochondria-derived ROS. In addition to enhancing mitophagy, fluoxetine can inhibit mTOR signaling by promoting the translocation of p53 from the cytoplasm to the nucleus and upregulating the expression of key autophagy molecules, including autophagy related 7 and Beclin-1, thereby enhancing the overall autophagy process (169). When a p53 inhibitor is applied or the p53 gene is knocked out, the aforementioned pro-autophagic effects are completely reversed, indicating that this process is dependent on p53 signaling (169). Both *in vivo* and *in vitro* evidence also indicates that fluoxetine can increase the LC3-II/LC3-I ratio, promote autophagosome formation and facilitate autophagosome-lysosome fusion, accompanied by reduced p62 accumulation, suggesting that autophagic flux is improved and that chronic mild stress or corticosterone-induced autophagy blockade can be relieved by fluoxetine. In terms of mitochondria-related damage pathways, in 3xTg-AD primary neurons, fluoxetine reduces the number of TUNEL-positive cells and improves mitochondrial intrinsic apoptosis-related readouts, including increasing the Bcl-2/Bax and Bcl-xL/Bax ratios and decreasing cleaved caspase-3 levels, suggesting that while it enhances MQC, it can also suppress mitochondrial pathway-mediated apoptotic cascades (170). Overall, these effects help alleviate neuronal damage and provide a mechanistic basis for the improvement of mitochondrial function (169,170).

Anti-inflammatory and antioxidant effects. Neuroinflammatory responses are common pathological and physiological features shared by depression and AD, and the chronic inflammatory changes associated with depression can further promote AD progression (171). Fluoxetine has demonstrated clear neuroprotective potential in chronically stressed animals, with its core mechanisms centered on inhibiting neuroinflammation, alleviating oxidative stress and regulating apoptosis-related pathways (172). Fluoxetine exerts anti-inflammatory effects

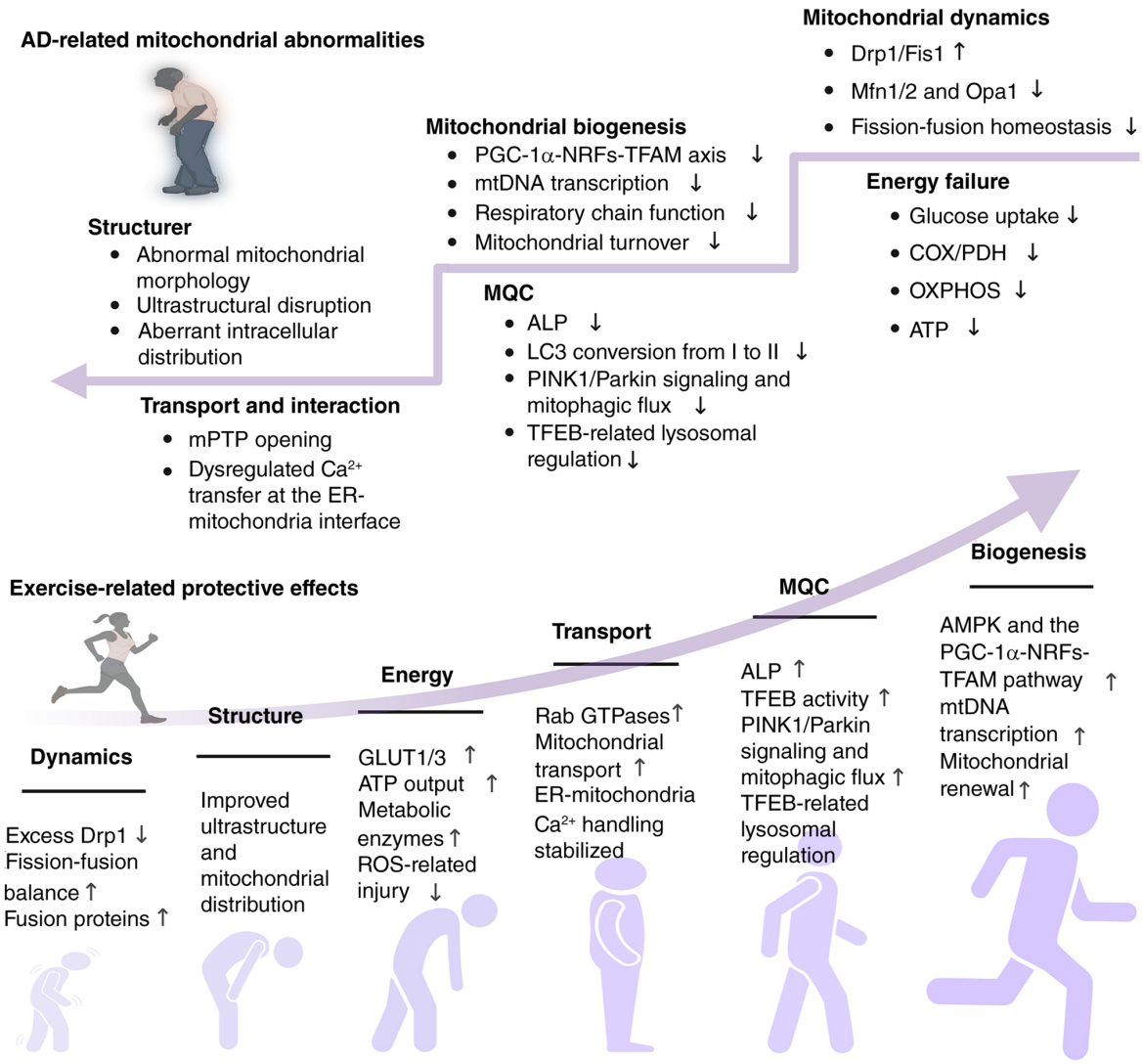

Figure 1. Exercise-related pathways involved in MQC and bioenergetic homeostasis in AD. This schematic summarizes major mitochondrial abnormalities associated with AD, including alterations in mitochondrial structure, biogenesis, dynamics, energy metabolism, intracellular transport and interaction, and MQC/ALP-related processes. The transport- and interaction-related abnormalities include mPTP opening and dysregulated Ca^{2+} transfer at the ER-mitochondria interface. The figure also illustrates key exercise-related pathways that may counteract these abnormalities, including regulation of GLUT1/3-dependent energy supply, Rab GTPase-related mitochondrial transport, stabilization of ER-mitochondria Ca^{2+} handling, ALP activation, TFEB activity, PINK1/Parkin signaling and mitophagic flux, TFEB-related lysosomal regulation, fusion/fission balance, and activation of AMPK and the PGC-1α-NRFs-TFAM pathway in mitochondrial biogenesis. These pathways are linked to improved mitochondrial distribution and ultrastructure, restoration of energy metabolism, reduced ROS-related injury, restoration of mitochondrial dynamics, enhanced MQC, and increased mitochondrial renewal. Upward and downward arrows indicate upregulation/enhancement and downregulation/reduction, respectively. AD, Alzheimer's disease; ALP, autophagy-lysosome pathway; AMPK, adenosine monophosphate-activated protein kinase; Ca^{2+}, calcium ion; COX, cytochrome *c* oxidase; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; Fis1, mitochondrial fission 1 protein; GLUT, glucose transporter; Mfn1/2, mitofusin 1/2; mPTP, mitochondrial permeability transition pore; MQC, mitochondrial quality control; mtDNA, mitochondrial DNA; NRF, nuclear respiratory factor; Opa1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PINK1, PTEN-induced kinase 1; Rab, Ras-related protein in brain; ROS, reactive oxygen species; TFAM, mitochondrial transcription factor A; TFEB, transcription factor EB.

through multiple pathways. In microglia, fluoxetine inhibits TLR4/MyD88/NF-κB signaling, reduces lipopolysaccharide (LPS)-induced expression of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, and decreases nitric oxide production, thereby limiting amplification of inflammatory cascades (173-179). Furthermore, fluoxetine can inhibit NF-κB nuclear translocation and downregulate TLR4/NLRP3 inflammasome signaling, thereby reducing the expression of pro-inflammatory mediators (167). In a sleep-deprivation model, fluoxetine could suppress p-AKT/p-STAT3-related signaling, reduce NLRP3 inflammasome activation and pro-IL-1β/pro-IL-18 production, interfere with NLRP3 inflammasome assembly, and decrease p-ERK and p-GSK3β levels, thereby reducing caspase-1-dependent maturation and release of IL-1β and IL-18, and potentially limiting GSDMD cleavage and pyroptosis-related inflammatory cell death (180,181). Because activated caspase-1 can also cleave gasdermin D (GSDMD) to generate the N-terminal GSDMD fragment and initiate pyroptosis, this pathway links NLRP3 inflammasome activation to cytokine maturation, inflammatory cell death and neuroinflammatory amplification (181). Related animal experiments have also demonstrated that, when DA and 5-HT were simultaneously depleted in the hippocampus of C57BL/6N mice, inducing microglial reactivity

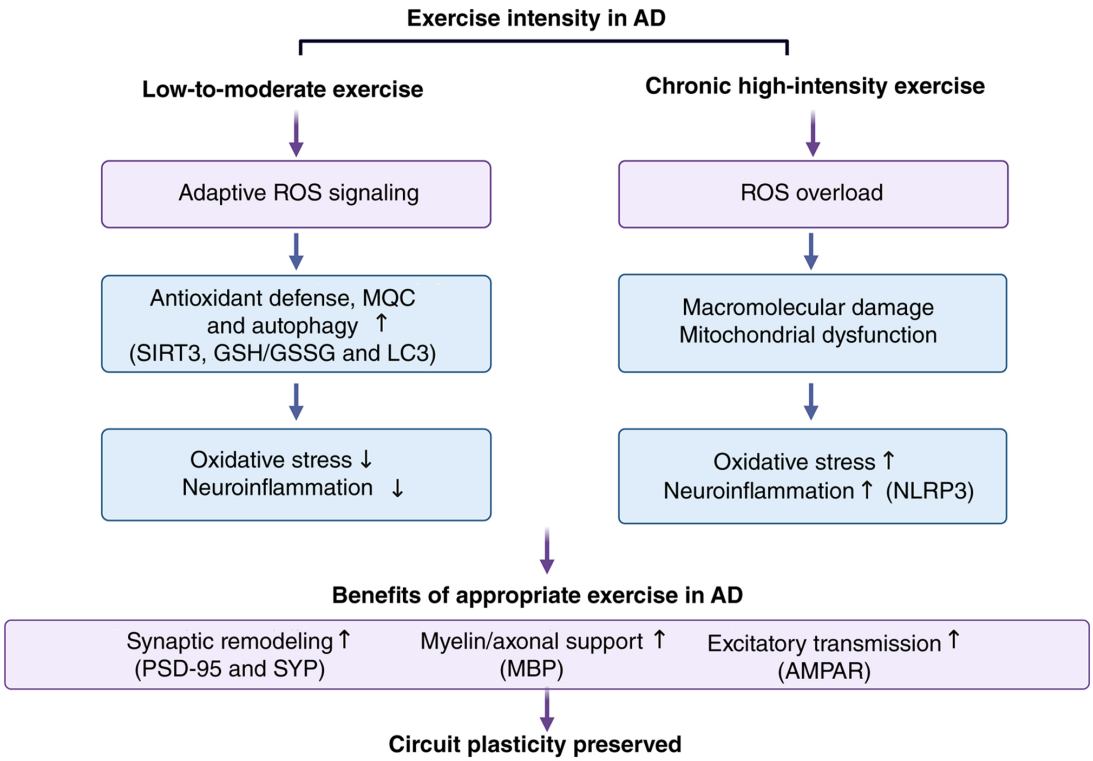

Figure 2. Intensity-dependent exercise effects on oxidative stress, neuroinflammation, myelination and synaptic plasticity in AD. Low-to-moderate exercise promotes adaptive ROS signaling, and enhances antioxidant defense, MQC and autophagy, thereby reducing oxidative stress and neuroinflammation. By contrast, chronic high-intensity exercise may induce ROS overload, leading to macromolecular damage, mitochondrial dysfunction and neuroinflammation associated with NLRP3 inflammasome activation. Appropriate exercise ultimately supports synaptic remodeling, myelin/axonal support and excitatory transmission, contributing to the preservation of circuit plasticity in AD. Upward and downward arrows indicate enhancement and reduction, respectively. AD, Alzheimer's disease; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GSH, glutathione; GSSG, glutathione disulfide; MBP, myelin basic protein; MQC, mitochondrial quality control; NLRP3, NOD-like receptor family pyrin domain containing 3; PSD-95, postsynaptic density protein 95; ROS, reactive oxygen species; SIRT3, sirtuin 3; SYP, synaptophysin.

characterized by NLRP3 inflammasome activation and IL-1β release, fluoxetine could completely prevent the elevation of NLRP3 and IL-1β levels in the mouse hippocampus (182,183). In addition, fluoxetine can regulate astrocytes to exert antioxidant and anti-apoptotic effects. In non-transgenic AD models, fluoxetine not only reduces the expression of pro-oxidative enzymes, including inducible nitric oxide synthase and NADPH oxidase 2, induced by pro-oxidative agents, but also alleviates oxidative stress damage by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) endogenous antioxidant pathway (167,175), thereby reducing neuronal apoptosis. Together, these antioxidant and anti-inflammatory effects may contribute to neuroprotection by reducing inflammatory amplification and oxidative injury while supporting endogenous antioxidant responses.

Enhancement of synaptic plasticity. Chronic fluoxetine treatment effectively enhances synaptic plasticity in brain regions such as the hippocampus and cortex. Fluoxetine can increase the dendritic density in the cornu ammonis area (CA)1/2 and CA3 regions of the hippocampus (184,185), and enhance GSK3β phosphorylation (186). In APP/PS1 mice, fluoxetine has also been reported to improve impaired hippocampal neurogenesis and memory by enhancing integrin-linked kinase (ILK)-AKT-GSK3β pathway activity (187). At the same time, caspase-3-dependent cleavage of AKT modulates tau phosphorylation via GSK3β kinase in transgenic AD mouse models (188), reducing AD-related damage at the pathological level. In addition, in 3xTg-AD mice and their primary neurons, fluoxetine increases protein phosphatase 2A (PP2A) activity and activates the Wnt/β-catenin signaling pathway. Activation of the PP2A-Wnt/β-catenin axis shifts APP processing from the amyloidogenic to the non-amyloidogenic pathway, as evidenced by decreased BACE1 and PS1 levels, and increased a disintegrin and metalloproteinase domain-containing protein 10, soluble APPα (sAPPα) and C-terminal fragment 83 levels, thereby lowering Aβ levels. At the same time, fluoxetine upregulates the levels of synapse-related proteins, such as postsynaptic density protein 95 (PSD-95) and synaptophysin, as well as BDNF levels, indicating that fluoxetine treatment may restore the levels of molecular markers associated with synaptic structure and function, while reducing Aβ burden (170). Insufficient BDNF release is a key pathophysiological link between depression and AD. When functional single nucleotide polymorphisms, such as Val66Met, are present, BDNF signaling is severely impaired, promoting abnormal Aβ accumulation and synaptic dysfunction, which eventually leads to cognitive decline (189,190). Fluoxetine can increase hippocampal BDNF levels and activate the cAMP response element-binding protein (CREB)/phosphorylated-CREB/BDNF signaling pathway, thereby supporting synaptic protein expression, synaptic plasticity and cognitive function in 3xTg-AD mice (191). In addition, BDNF/tropomyosin receptor kinase B (TrkB) signaling may contribute to fluoxetine-related neuroplasticity (192). In

3xTg-AD mice, fluoxetine-mediated increases in dendritic complexity are accompanied by increased expression of synaptic proteins, including glutamate ionotropic receptor NMDA type subunit 2A, glutamate ionotropic receptor NMDA type subunit 2B, glutamate ionotropic receptor AMPA type subunit 1, glutamate ionotropic receptor AMPA type subunit 2, postsynaptic density protein 93, PSD-95, synapsin I and synaptotagmin. These changes are also accompanied by enhanced long-term potentiation, suggesting an improvement in AD-related synaptic dysfunction (21,191). Several animal studies have demonstrated that low-dose fluoxetine could stabilize 5-HT_4 receptor-mediated mossy fiber synaptic modulation, whereas high doses could enhance 5-HT and D1 dopaminergic regulation (193-196). Chronic fluoxetine treatment can also induce dematuration of granule cells, restoring their synaptic characteristics to a youthful state, and this effect persists even after drug withdrawal (194,196,197). However, these plasticity changes have not been consistently induced at clinically equivalent doses; therefore, whether the plasticity effects of fluoxetine are related to excessive dosing still requires further investigation (196).

The significance of fluoxetine in AD research lies more in its repositioning based on comorbid pathways rather than in its role as a traditional AD-specific therapeutic agent (21). Existing evidence suggests that fluoxetine can reduce the pathological burden on neurons at multiple levels (21,167,170,175,191). On the one hand, fluoxetine promotes mitochondrial autophagy and autophagic flux and inhibits mitochondrial-related apoptotic cascades, thereby alleviating energy and redox imbalances (169,170). On the other hand, fluoxetine suppresses TLR4/MyD88/NF-κB and NLRP3 inflammasome-related signals while activating endogenous antioxidant defenses, such as Nrf2/HO-1 (167,173-180). As a result, fluoxetine exerts inhibitory and buffering effects within the amplifying feedback loop that couples inflammation and oxidative stress (167,175,180). Additionally, fluoxetine-mediated regulation of plasticity-related pathways, such as the CREB/BDNF, ILK-AKT-GSK3β and PP2A-Wnt/β-catenin pathways, provides a mechanistic explanation for the restoration of synaptic function and the shift in tau/APP processing (170,187,191,196).

However, the aforementioned evidence is mainly derived from animal and cellular models, and often depends on relatively long treatment durations or specific dose windows (21). The effects of fluoxetine on plasticity also exhibit dose sensitivity and directional differences (196), suggesting that its neuroprotective effects cannot be extrapolated to clinically equivalent doses or heterogeneous human populations (21,198). Therefore, although current evidence does not establish fluoxetine as a direct disease-modifying treatment for AD (21,198), in cases of AD combined with depression, anxiety or sleep disorders (159,199), fluoxetine may indirectly support cognitive and functional outcomes by improving the monoaminergic imbalance and inflammation/stress axis dysregulation (159,165,196). Nevertheless, evidence supporting fluoxetine as a direct disease-modifying intervention against core AD pathology remains insufficient. Future studies should establish testable clinical translational pathways under clarified staging and comorbidity stratification, focusing on dosage, treatment course, timing of intervention and key biomarker identification. The mechanisms through which fluoxetine may modulate AD-related processes are summarized in Figs. 3 and 4. Preclinical evidence on fluoxetine in AD models is summarized in Table I (167,170,175,184,187,191).

4. Synergistic mechanisms of exercise and fluoxetine in AD

Although both exercise and fluoxetine have been demonstrated to have beneficial effects on AD, the mechanisms and efficacy of their combined use require further investigation. Exercise and fluoxetine share a number of common targets in their mechanisms of action in AD treatment. Researchers have constructed cross-regional brain gene expression profiles for AD based on 22 large-scale AD gene expression datasets to explore the therapeutic effects of exercise and fluoxetine. The results showed that exercise ranked third among the predicted therapeutic candidates and was predicted to reverse the expression patterns of hundreds of AD-dysregulated genes across functional categories, including cytoskeleton-related and vascular development-related genes. In the uniform manifold approximation and projection analysis, exercise also showed the best match with AD profiles. Fluoxetine ranked fourth, and its composite dataset ranked 12th in male AD profiles and 11th female AD profiles. The fluoxetine composite dataset was predicted to reverse AD-related expression changes in 249 dysregulated genes, including genes involved in nervous system development. In addition, expression changes in 44 overlapping AD-dysregulated genes, including BDNF, were predicted to be reversed by both exercise and fluoxetine. The combination of exercise and fluoxetine was predicted to reverse AD-related expression changes in 549 genes (200), suggesting the complementary potential of fluoxetine combined with exercise in AD treatment. However, preclinical and related evidence suggests that the effects of combining exercise and fluoxetine are not necessarily additive or superior (201,202). One hypothesis is that fluoxetine may not reproduce the broader neurogenic and adaptive effects induced by exercise, and that its pharmacological actions may interfere with exercise-induced adaptive signaling under certain dose, timing or intensity conditions (201,202). Therefore, in-depth research on their shared targets may reveal the molecular mechanisms by which their combined use improves AD, offering novel strategies for the prevention and treatment of neurodegenerative disorders.

Combined intervention with exercise and fluoxetine may have complementary potential in AD, but this potential should be interpreted as a hypothesis grounded in convergent mechanisms rather than as established evidence of robust synergy. Transcriptomic evidence suggests that exercise and fluoxetine can reverse partially overlapping AD-related gene-expression changes (200). This finding is important not because it proves therapeutic synergy, but because it suggests that exercise and fluoxetine may act on partially shared but non-identical regulatory networks. Mechanistically, the potential complementarity between exercise and fluoxetine may arise from their actions on several interacting pathological nodes in AD, including MQC, redox homeostasis, neuroinflammation and synaptic plasticity (200,203,204). Exercise can improve mitochondrial maintenance in AD models by promoting PTEN-induced kinase 1/Parkin-mediated mitophagy, SIRT1-FOXO1/3 signaling and lysosomal clearance (59,61). Fluoxetine may

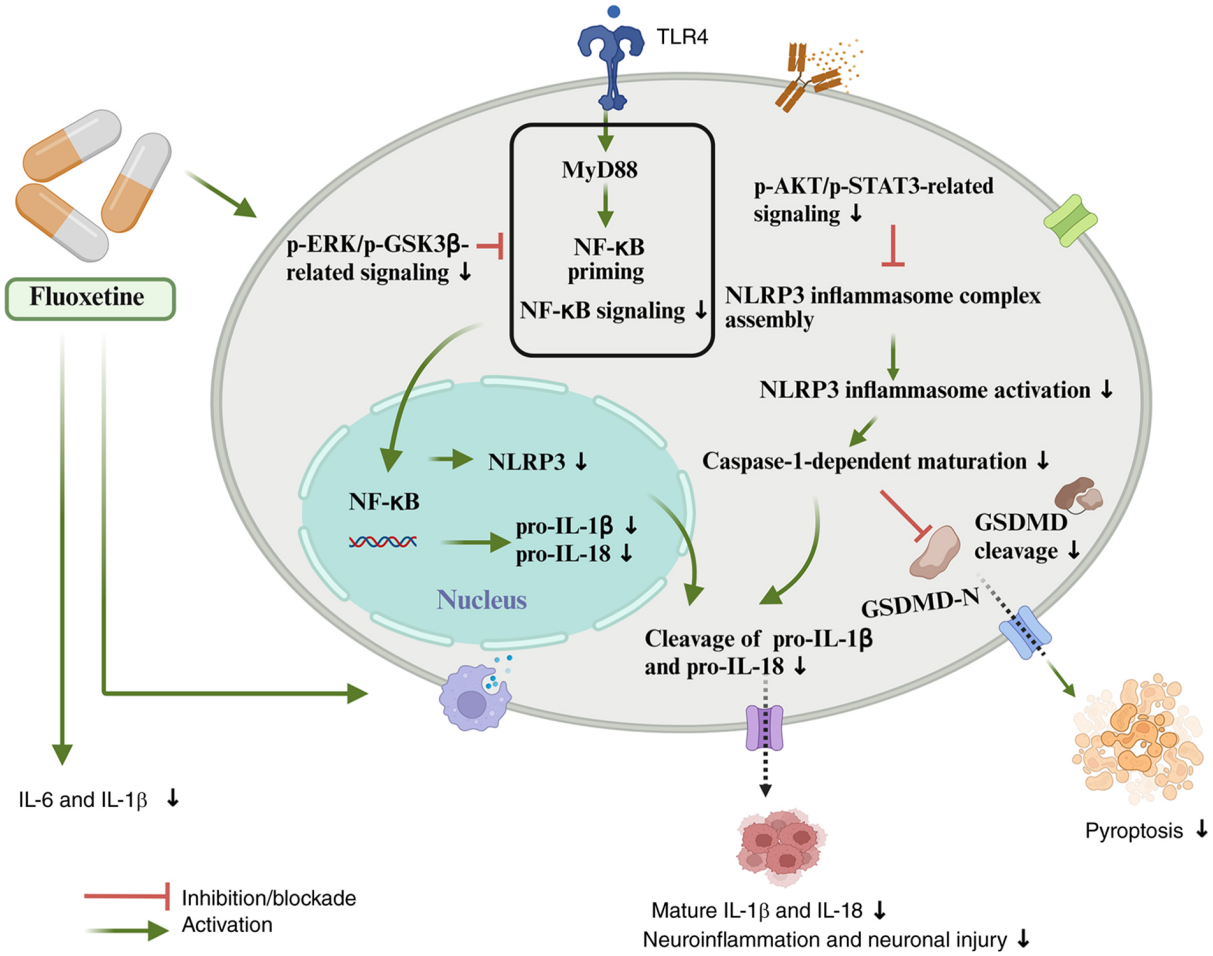

Figure 3. Fluoxetine-associated modulation of the microglial NLRP3 inflammasome axis and neuroinflammation in Alzheimer's disease. This schematic diagram summarizes microglial priming and activation processes involving TLR4/MyD88/NF-κB signaling, p-AKT/p-STAT3-related signaling, p-ERK/p-GSK3β-related signaling, NLRP3 inflammasome complex assembly and activation, caspase-1-dependent maturation of IL-1β and IL-18, GSDMD cleavage, and downstream inflammatory injury and pyroptosis-related events. Fluoxetine-associated changes shown in the figure include decreased IL-6 and IL-1β levels, decreased p-AKT/p-STAT3-related and p-ERK/p-GSK3β-related signaling, reduced NF-κB signaling, decreased NLRP3 and pro-IL-1β/pro-IL-18 levels, suppressed NLRP3 inflammasome complex assembly, reduced NLRP3 inflammasome activation, reduced caspase-1-dependent maturation of IL-1β and IL-18, decreased GSDMD cleavage and reduced pyroptosis. Green arrows indicate promotion, enhancement or pathway progression. Red blunt-ended lines indicate inhibition or suppression where shown. Black downward arrows indicate decreased expression, activity or levels. GSDMD, gasdermin D; GSDMD-N, gasdermin D N-terminal fragment; MyD88, myeloid differentiation primary response 88; NLRP3, NOD-like receptor family pyrin domain containing 3; p-, phosphorylated; TLR4, toll-like receptor 4.

support related mitochondrial quality-control processes by promoting autophagic flux, Parkin translocation and damaged mitochondria clearance in stress-related models (169). Therefore, exercise and fluoxetine may converge on mitochondrial maintenance, although direct evidence of synergistic mitochondrial restoration in AD remains limited. In terms of oxidative stress and neuroinflammation, exercise enhances mitochondrial antioxidant defenses and reduces ROS-related injury in APP/PS1 mice (205), whereas fluoxetine reduces Aβ-related oxidative damage, inhibits pro-oxidant enzyme expression and activates Nrf2/HO-1 signaling in AD-related models (167,175). Exercise also attenuates AD-related neuroinflammation and modulates microglial or gut-brain inflammatory signaling (206,207), whereas fluoxetine inhibits TLR4/NLRP3-related inflammatory signaling, and enhances microglial phagocytosis and autophagy (167,179). Therefore, exercise and fluoxetine may weaken the positive feedback loop between oxidative stress and inflammation, but evidence that combined treatment produces stable additive or synergistic anti-inflammatory effects in AD is still insufficient. Regarding synaptic plasticity, exercise and fluoxetine have each been linked to improved synaptic remodeling and plasticity-related signaling in AD models (21,208). The value of considering exercise and fluoxetine together may therefore lie not in assuming simple additivity, but in determining whether exercise-induced adaptive remodeling can be aligned with fluoxetine-mediated neurochemical regulation within an appropriate biological window. The potential complementarity between exercise and fluoxetine may also involve 5-HT, HPA axis and BDNF-related signaling, but combined effects in AD should still be interpreted cautiously (18,200,209).

Collaborative modulation of 5-HT pathways in the intervention of AD progression. As a neurotransmitter widely distributed in both the central and peripheral nervous systems, 5-HT can influence the progression of AD by regulating Aβ deposition, tau hyperphosphorylation, neuroinflammation, and interactions with cholinergic and BDNF systems (210). The 5-HT pathway

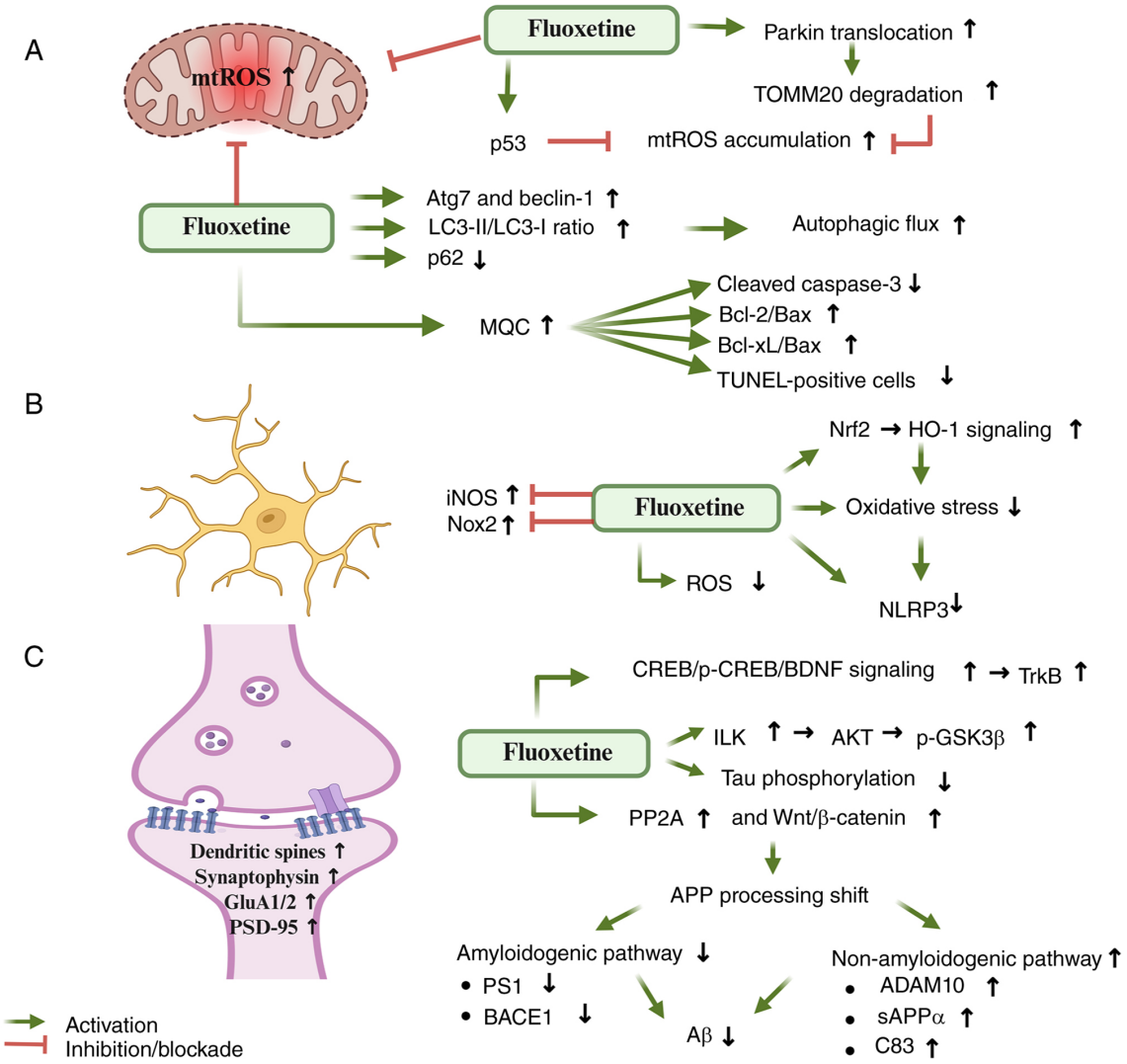

Figure 4. Molecular mechanisms of fluoxetine related to MQC, oxidative stress and synaptic plasticity in AD. (A) Schematic diagram showing fluoxetine-associated regulation of mtROS control, Parkin translocation, TOMM20-related mitochondrial protein turnover, and autophagy/mitophagy-related markers, including Atg7/Beclin-1, the LC3-II/LC3-I ratio and p62. This panel also shows changes in overall autophagic flux and mitochondrial apoptosis-related markers, including cleaved caspase-3, Bcl-2/Bax, Bcl-xL/Bax and TUNEL-positive cells. (B) Schematic diagram summarizing fluoxetine-related modulation of oxidative stress-associated enzymes and antioxidant signaling pathways, including Nrf2/HO-1-related signaling, together with links to inflammasome-associated activity. (C) Schematic diagram summarizing fluoxetine-associated pathways related to synaptic plasticity and AD pathology, including CREB/BDNF-related signaling, ILK-AKT-GSK3β signaling, PP2A and Wnt/β-catenin signaling. In the APP processing branch, fluoxetine-associated PP2A-Wnt/β-catenin activation is linked to an APP processing shift. This shift is shown by decreased amyloidogenic pathway activity, with reduced BACE1 and PS1 levels, and increased non-amyloidogenic pathway activity, with increased ADAM10, sAPPα and C83 levels. These changes are associated with reduced Aβ levels. Green arrows indicate promotion or enhancement. Red blunt-ended lines indicate inhibition or suppression. Black horizontal arrows indicate downstream signaling relationships or pathway progression. Black upward arrows indicate increased expression, activity or levels. Black downward arrows indicate decreased expression, activity or levels. Aβ, amyloid-β; AD, Alzheimer's disease; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; APP, amyloid precursor protein; Atg7, autophagy related 7; BACE1, β-site APP-cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; C83, C-terminal fragment 83; CREB, cAMP response element-binding protein; GluA1/2, glutamate ionotropic receptor AMPA type subunit 1/2; HO-1, heme oxygenase 1; ILK, integrin-linked kinase; iNOS, inducible nitric oxide synthase; MQC, mitochondrial quality control; mtROS, mitochondrial ROS; NLRP3, NOD-like receptor family pyrin domain containing 3; Nox2, NADPH oxidase 2; Nrf2, nuclear factor erythroid 2-related factor 2; p-, phosphorylated; PP2A, protein phosphatase 2A; PS1, presenilin 1; PSD-95, postsynaptic density protein 95; ROS, reactive oxygen species; sAPPα, soluble APPα; TOMM20, translocase of outer mitochondrial membrane 20; TrkB, tropomyosin receptor kinase B.

can be activated by exercise or fluoxetine, making it an important target for the regulation of AD by both interventions, as well as a main mechanism underlying their synergistic effects. Both exercise and fluoxetine can effectively enhance the functional activity of 5-HT in the central and peripheral nervous systems (210). Fluoxetine mainly increases the synaptic 5-HT concentration by inhibiting the 5-HT transporter (210) and modulates receptors such as 5-HT_2 receptor (211) and 5-HT_4 receptor (212) to enhance downstream signaling, while exercise elevates 5-HT levels and receptor expression in multiple brain regions by promoting the proliferation of serotonergic neurons in the raphe nuclei (213) and increasing the influx of free tryptophan into the brain (210,214,215), thus laying a common neurochemical foundation for subsequent multipathway interventions in AD. On this basis, exercise and fluoxetine can jointly activate the PI3K/AKT pathway, allowing downstream AKT to phosphorylate and inhibit GSK3β activity (186,210), while simultaneously activating the MEK/ERK pathway to increase

Table I. Preclinical evidence on the effects of fluoxetine in AD models.

A, Effects on mitochondria

Authors, year	Model	Fluoxetine treatment	Key mechanisms	(Refs.)
Huang *et al*, 2018	3xTg-AD mice	10 mg/kg/day, i.g., 4 months	CTFs ↓, BACE1 ↓, PS1 ↓, sAPPβ ↓, C99 ↓, $TUNEL^+$ ↓	(170)

B, Effects on ROS

Authors, year	Model	Fluoxetine treatment	Key mechanisms	(Refs.)
Abu-Elfotuh *et al*, 2022	$AlCl_3$-induced AD rats	10 mg/kg/day, p.o., 4 weeks	SOD ↑, TAC ↑, Nrf2/HO-1 ↑, MDA ↓	(167)
Caruso *et al*, 2021	Non-Tg mice with i.c.v. AβO injection	10 mg/kg/day, i.p., 3 weeks	ROS ↓, iNOS ↓, Nox2 mRNA ↓, TGF-β1 ↑	(175)

C, Effects on inflammation

Authors, year	Model	Fluoxetine treatment	Key mechanisms	(Refs.)
Huang *et al*, 2018	3xTg-AD mice	10 mg/kg/day, i.g., 4 months	p-GSK3β (Tyr216)/GSK3β ↓, Wnt/β-catenin ↑, p-PP2A (Tyr307)/ PP2Ac ↓	(170)
Abu-Elfotuh *et al*, 2022	$AlCl_3$ (70 mg/kg/day; i.p.)-induced AD rats	10 mg/kg/day, p.o., 4 weeks	IL-1β ↓, IL-6 ↓, TNF-α ↓, NF-κB ↓, TLR4 ↓, NLRP3 ↓, caspase-1 ↓	(167)

D, Effects on synaptic plasticity

Authors, year	Model	Fluoxetine treatment	Key mechanisms	(Refs.)
Huang *et al*, 2018	3xTg-AD mice	10 mg/kg/day, i.g., 4 months	PSD-93 ↑, PSD-95 ↑, PP2A-Wnt/β-catenin activity ↑	(170)
Zhou *et al*, 2019	APP/PS1 mice	10 mg/kg/day, i.p., 10 weeks	Dendritic spines in Hpc CA1/2 and CA3 ↑, DG PSD-95 ↑, SYP ↑	(184)
Xu *et al*, 2018	APP/PS1 mice	10 mg/kg/day, i.p., 4 weeks	ILK/p-ILK ↑, p-AKT ↑, p-GSK3β (Ser9) ↑	(187)
Huang *et al*, 2018	3xTg-AD mice	10 mg/kg/day, i.g., 4 months	Bcl-2/Bax ↑, Bcl-xL/Bax ↑, cleaved caspase-3 ↓	(170)
Abu-Elfotuh *et al*, 2022	$AlCl_3$-induced AD rats	10 mg/kg/day, p.o., 4 weeks	BDNF ↑, 5-HT ↑, DA ↑, NE ↑	(167)
Sun *et al*, 2017	3xTg-AD mice	10 mg/kg/day, i.p., 15 days	CA1 neurons ↑, DG neurons ↑, dendritic spines ↑, CREB/p- CREB/BDNF ↑	(191)

↑, increased/upregulated; ↓, decreased/downregulated; 3xTg-AD, triple-transgenic AD; 5-HT, serotonin; AβO, amyloid-β oligomers; AD, Alzheimer's disease; APP/PS1, amyloid precursor protein/presenilin 1; BACE1, β-site amyloid precursor protein-cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; CA1/2/3, cornu ammonis area 1/2/3; $AlCl_3$, aluminum chloride; CREB, cAMP response element-binding protein; CTF, C-terminal fragment; DA, dopamine; DG, dentate gyrus; HO-1, heme oxygenase 1; Hpc, hippocampus; i.c.v., intracerebroventricular; i.g., intragastric; ILK, integrin-linked kinase; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal; MDA, malondialdehyde; NE, norepinephrine; NLRP3, NOD-like receptor family pyrin domain containing 3; non-Tg, non-transgenic; Nox2, NADPH oxidase 2; Nrf2, nuclear factor erythroid 2-related factor 2; p-, phosphorylated; p.o., *per os*; PP2A, protein phosphatase 2A; PP2Ac, protein phosphatase 2A catalytic subunit; PSD-93, postsynaptic density protein 93; PSD-95, postsynaptic density protein 95; PS1, presenilin 1; ROS, reactive oxygen species; sAPPβ, soluble amyloid precursor protein β; SOD, superoxide dismutase; SYP, synaptophysin; TAC, total antioxidant capacity; TLR4, toll-like receptor 4.

α-secretase activity, and inhibit BACE1 and γ-secretase functions (170), thereby promoting non-amyloidogenic cleavage of APP and enhancing the production of neuroprotective sAPPα, while reducing the production and deposition of Aβ (216,217).

Exercise can also directly act on Aβ protofibrils via 5-HT, disrupting their β-sheet and salt bridge stability and further impeding Aβ deposition (218). Exercise and fluoxetine can jointly regulate PP2A and the Wnt/β-catenin pathway (170), synergistically inhibiting the abnormal phosphorylation of tau protein through multiple mechanisms. At the neuroimmune level, exercise and fluoxetine may converge on the inhibition of NF-κB-related inflammatory signaling and pro-inflammatory factor release (219,220), thereby contributing to a central-peripheral synergistic anti-inflammatory network. Exercise and fluoxetine can both activate the CREB/BDNF axis, with the 5-HT system as a key mediator (221), enhancing BDNF expression through multiple pathways, such as the PI3K/AKT and calcium/calmodulin-dependent protein kinase IV/MAPK pathways (222,223), thereby improving synaptic plasticity and neurogenesis (191,224,225). Fluoxetine can enhance central cholinergic function by increasing 5-HT levels, thereby promoting the interaction between 5-HT and σ-1 receptors in the brain (226) to facilitate acetylcholine release. Exercise has similar effects (214,227,228), and together both interventions can alleviate cholinergic system dysfunction associated with AD. These mechanisms suggest that although exercise and fluoxetine act through different means, they share multiple molecular pathways centered on the 5-HT system, exerting additive or complementary effects on key processes such as Aβ metabolism, tau pathology, neuroinflammation, neurotrophic support and cholinergic function, thus providing a systematic theoretical foundation for combined interventions in AD.

Synergistic interactions within the BDNF signaling pathway. BDNF is a protein encoded by multiple BDNF transcripts that requires binding to specific receptors on the surface of neurons to exert its effects. Aβ interferes with the binding of BDNF to TrkB, thereby inhibiting neuroprotective signaling pathways, such as the Raf-MAPK/ERK and PI3K/AKT pathways (229), which diminishes the role of BDNF in neuronal survival, functional maintenance and brain plasticity. Both exercise and fluoxetine can directly reduce Aβ deposition, and each independently increases BDNF levels in different brain regions (230), suggesting that their combined use is more effective than either alone (231). One study examined voluntary exercise and fluoxetine treatment separately and reported that each intervention increased BDNF mRNA and protein levels in the hippocampal neuronal somata and enhanced BDNF localization in the CA3 dendritic regions, particularly the stratum lucidum and radiatum. This increase was mainly associated with the BDNF exon 6-containing transcript variant (232). As aforementioned, exercise and fluoxetine are both related to activation of the central 5-HT pathway. *In vitro* experiments have demonstrated that 10-50-μM 5-HT induced dendritic targeting of BDNF mRNA in cultured hippocampal neurons, and that this dendritic targeting was largely dependent on the BDNF exon 6-containing transcript variant, further suggesting that exercise and fluoxetine may regulate the dendritic BDNF mRNA localization through 5-HT-related downstream pathways (232).

Synergistic enhancement of HPA axis regulation. HPA axis dysfunction serves an important role in depression and has a marked impact on the early stages of AD (233). Patients with depression or AD may exhibit HPA axis-related abnormalities, including elevated cortisol levels, hippocampal atrophy and glucocorticoid receptor signaling imbalance, although the temporal pattern of HPA axis changes may differ across disease stages and study populations (159). Animal experiments have demonstrated that chronic stress and increased circulating cortisol levels could directly promote the accumulation of Aβ and tau, induce maladaptive immune responses, accelerate brain atrophy and synaptic dysfunction, and thereby accelerate the progression of AD (233). To the best of our knowledge, no studies have directly shown the effects of combining exercise with fluoxetine on the HPA axis and corticosterone levels in patients with AD; however, Mahdirejei *et al* (18) found that under conditions of HPA axis dysfunction in LPS-induced depressive mice, fluoxetine improved HPA axis dysfunction and reduced corticosterone levels. In the same study, swimming exercise improved HPA axis function and reduced corticosterone levels more effectively than fluoxetine alone, whereas the combined fluoxetine and swimming exercise intervention produced greater normalization of HPA axis function and corticosterone levels than either intervention alone (18). In a rat model of post-traumatic stress disorder, compared with untreated single prolonged stress (SPS) model rats, fluoxetine and the combination of moderate treadmill exercise and fluoxetine improved SPS-induced HPA axis inhibition, and this effect was accompanied by restoration of hippocampal BDNF levels and normalization of apoptosis-related markers, including Bax, caspase-3, Bcl-2 and the Bax/Bcl-2 ratio (234). This provides a reference for the joint modulation of AD-related pathology by the two interventions.

5. Mechanisms of antagonistic interactions between exercise and fluoxetine in the context of AD

There are differences in how various forms and intensities of exercise affect different diseases. For example, a single session of high-intensity exercise can produce excessive ROS, increase oxidative stress and elevate the levels of inflammatory factors in the body (235). Prolonged high-intensity exercise can disrupt the oxidative system balance in the body, thereby accelerating disease progression (91). The dosage and biological effects of fluoxetine are closely related to factors such as species, strain, age and sex (236-238). Therefore, although the combination of exercise and fluoxetine has certain therapeutic potential, if key variables, including exercise intensity and type, fluoxetine dosage, and timing of use, are not properly coordinated, the efficacy might be diminished and disease progression could theoretically even be accelerated under conditions of excessive exercise-related stress (91,235-238).

The risk of antagonistic interactions between fluoxetine and exercise may stem from fundamental differences in the way they regulate intracellular signaling. Exercise relies mainly on moderate physiological stress to trigger adaptive responses in the body, whereas fluoxetine has been reported to inhibit certain ROS- and inflammation-related pathways that overlap with exercise-induced adaptive signaling (173,239-242). For example, in the regulation of ROS signaling, the low levels of ROS produced by moderate-intensity exercise are an important signal for activating adaptive responses, such as

the body's antioxidant defenses and mitochondrial biogenesis (32,239,240). This is one of the core mechanisms underlying the neuroprotective effects of exercise. However, fluoxetine has been reported to exert antioxidant effects and reduce ROS production in some experimental settings (173,241). If the drug intervenes too early or too strongly after exercise, it may theoretically blunt ROS-dependent signaling, thus weakening the long-term benefits of exercise, such as enhanced mitochondrial function (85,239,240). Regarding inflammatory pathways, the anti-inflammatory benefits of exercise are the result of long-term adaptation, a process partly related to early cytokine- and redox-sensitive signaling events triggered by acute bouts of exercise as an initiating signal, such as transient activation of the NF-κB pathway (240,243). However, fluoxetine has been reported to inhibit inflammatory pathways, including the NF-κB and NLRP3 pathways, in experimental models of microglial or macrophage activation (173,242). This inhibition, if excessive or poorly timed, may interfere with the beneficial preparatory inflammatory signals generated at the onset of exercise, thereby potentially interfering with the body's long-term establishment of its own anti-inflammatory and immune regulation capacity (85,173,240,242,243).

This potential antagonism at the level of signal regulation introduces uncertainty regarding the effects of combination therapy with fluoxetine and exercise. The side effects potentially induced by fluoxetine, such as fatigue/asthenia, somnolence, dizziness or weakness, may further intensify this antagonistic risk by compromising exercise tolerance or exercise performance (25,244). Research has shown that exercise could effectively improve physical abilities in the elderly (245), while fluoxetine-related adverse effects may interfere with exercise capacity (25,244). In a study involving 11 months of long-term intervention in 3xTg-AD mouse models, both the exercise group and the combined exercise plus fluoxetine group showed increases in the survival of newly generated cells labeled with 5-bromo-2'-deoxyuridine; however, the increase in the combined group was less pronounced than that in the exercise-only group, with the positive effects of exercise being diminished by fluoxetine. Furthermore, mice in the combined group fell more times in the rotarod test, with fluoxetine causing obvious motor coordination disorders in 20-month-old mice, a problem not observed in the exercise-only group (201). These findings suggest that the side effects of this combination therapy may partly offset its potential benefits.

As a common biomarker for depression and AD (159, 189,246), BDNF has been examined in early intervention studies of adolescent depression (247,248) and pre-pubertal depression-related models (202,249). Schoeman *et al* (202) found that, in preadolescent stress-sensitive rats, interventions required strict matching of medication dosage and exercise intensity; combining the two blindly not only failed to produce long-term synergistic effects but could even result in antagonism. In terms of immediate effects, both low-dose fluoxetine and low-intensity exercise alone had potential antidepressant benefits, and their combination showed a synergistic effect. However, moderate-intensity exercise (due to stress overload) and high-dose fluoxetine (due to the inhibition of motor function) did not yield effective antidepressant effects. Regarding long-term effects, low-dose fluoxetine and low-intensity exercise, when used individually, could continue to improve depressive behavior in adulthood. However, combined interventions before adolescence offered no long-term benefits and may even be antagonistic. On the one hand, during combined treatment, noradrenergic activation signals from exercise and serotonergic modulation from fluoxetine simultaneously acted on the immature brain, causing disordered synaptic selection and reducing the number of functional synapses in the noradrenergic system, thereby eliminating the antidepressant effect. On the other hand, during combined treatment with exercise and fluoxetine, exercise itself may mildly increase 5-HT levels, and together with the SSRI effect of fluoxetine, may lead to an excessive 5-HT concentration in the synaptic cleft. Sustained high 5-HT levels strongly activated α2 heteroreceptors, which strongly inhibited NE release, ultimately disabling activation of the noradrenergic system and negating the antidepressant effect (202). Finally, Schoeman *et al* (202) pointed out that fluoxetine may suppress the CREB pathway, inhibiting exercise-induced BDNF synthesis, resulting in insufficient BDNF levels to maintain antidepressant effects, and thus, counteracting the synergistic benefit of the two interventions. This contradicts the aforementioned synergistic effect in AD treatment, suggesting that the combined effects of exercise and fluoxetine on the BDNF pathway, as well as their biological mechanisms for improving neurodegeneration, require further investigation. However, exercise intensity, fluoxetine dosage, timing of interventions and targeting of different age groups all have impacts on therapeutic outcomes (202,247,248).

Exercise and fluoxetine intersect at several key points in AD-related networks. Both can influence MQC and autophagic flux (169,250), inhibit inflammasomes and NF-κB-mediated amplification loops (173,242,251,252), and regulate synaptic plasticity and stress load via the CREB/BDNF and HPA axis (189,253-256). In terms of pathway coverage, the combined interventions are theoretically complementary, possibly even reducing pathology across multiple pathways simultaneously at certain stages (169,173,189,242,250-256). However, the current findings are inconsistent, suggesting that synergy is not guaranteed (201,202). The core conflict lies in the different ways in which the two interventions regulate signaling. The long-term benefits of exercise partly depend on short-term increases in ROS levels and mild inflammation as adaptive remodeling signals (85,239,240,243), whereas fluoxetine may suppress these stress- or inflammation-related adaptive signals and reduce the oxidative load (173,241,242). When the medication dosage is high, the intervention is introduced too early or the exercise intensity is already near the threshold, signaling may be excessively suppressed, thereby weakening the training-induced windows for mitochondrial biogenesis, autophagic adaptation and neurogenesis, or even compounding issues with motor coordination and tolerance (85,169,201,202,239-241,243,250,257). Therefore, future research should conduct stratified validation using unified outcome measures, focusing on disease staging, depression comorbidity and physical/cognitive risk (such as fall risk) as core stratification variables (189,201,202,253). This approach should systematically compare different exercise prescriptions in combination with fluoxetine dosage, duration and timing to define the boundaries between synergistic and antagonistic effects (85,201,202,239-241,243,257).

6. Boundaries of current evidence and challenges in clinical translation

The aforementioned pathway-level interpretations involve mitochondrial homeostasis, oxidative stress, neuroinflammation, autophagic flux and CREB/BDNF- and HPA axis-related signaling. Because the core evidence for these mechanistic interpretations is still predominantly derived from cell systems and animal models of AD (258,259), these findings should not be taken as evidence that the same pathway-level effects can be fully reproduced in clinical patients with AD. Although these models can reproduce Aβ deposition and selected inflammatory phenotypes with considerable fidelity, they do not adequately capture the slow neuronal attrition, cerebrovascular injury, metabolic comorbidity and neuropsychiatric burden that characterize late-onset AD in humans (258-260). Consequently, such models are well suited to determining whether a given pathological pathway can be engaged by exercise or pharmacological intervention but are less suited to establishing whether modulation of that pathway is sufficient to alter the course of disease in patients. The aforementioned evidence on mitochondrial homeostasis, oxidative stress, neuroinflammation and synaptic plasticity should therefore be primarily considered as evidence of mechanistic tractability, rather than as proof of disease modification already validated at the clinical level (133,258-262).

The central difficulty in interpreting the exercise literature is not the absence of positive findings, but the fact that exercise should not be treated as a single uniform intervention. Variations in intensity, duration and timing do not merely influence the magnitude of the effect, they often alter the nature of the biological response itself (263-265). Treadmill training, voluntary wheel running, swimming and resistance exercise are not interchangeable in terms of stress load, metabolic demand or central adaptive signaling (263,264). Once translated into clinical populations, these differences are further amplified by heterogeneity in physical reserve, adherence, supervision and comorbidities. Observational studies (266,267), randomized trials (268-270) and systematic syntheses (271,272) collectively suggest that exercise may benefit cognition and function in MCI and AD; however, the effects are not uniformly robust, and those that prove reproducible are often directional rather than prescriptive. The importance of studies such as EXERT lies precisely in returning the question to the clinical setting, namely, in clarifying that whether exercise is beneficial depends not only on mechanistic plausibility, but also on identifying the populations, disease stages and prescriptions for which preclinical promise can be converted into durable benefit (133,270-272).

The translational constraints surrounding fluoxetine are even more concentrated. Current support for its effects on AD-related cognition and pathology remains overwhelmingly preclinical, while clinical studies are few, generally small and insufficiently consistent for systematic reviews to yield clear conclusions (21). The problem is not simply one of cross-species dose conversion, but of nonequivalent exposure across species. Fluoxetine displays marked interindividual pharmacokinetic variability, such that the same nominal dose in humans may give rise to substantially different plasma concentrations and metabolic profiles (273,274). In light of this, the aforementioned pro-autophagic, anti-inflammatory and plasticity-related effects are best regarded as indications of which pathways merit clinical interrogation, rather than as evidence that a clinically actionable therapeutic window has already been defined (273-275).

In the context of the present review, synergy and antagonism between exercise and fluoxetine should therefore be treated as conditional propositions rather than fixed conclusions. Shared pathways do not automatically translate into clinical gain, and signals that point in opposite directions do not necessarily imply true mechanistic incompatibility. Rather than accumulating additional isolated positive findings, it is important to construct stratified clinical studies in MCI and early AD that explicitly account for depressive comorbidity, standardize exercise prescriptions with respect to intensity, duration and initiation stage, redefine fluoxetine dosing in terms of clinically relevant exposure, and integrate mechanistic biomarkers with cognitive and functional outcomes within the same design. Only after these boundary conditions have been defined can the mechanistic links discussed in the present review, including mitochondrial regulation, neuroinflammation, autophagy, HPA axis regulation and synaptic plasticity, be tested as clinically meaningful targets rather than only as preclinical pathway-level observations (21,270,272,275). Given that the interaction between exercise and fluoxetine is likely to be conditional rather than fixed, the principal biological and clinical factors that may favor synergy or increase the likelihood of antagonism are summarized in Table SII (7,8,13-18,21,23-25,32,85,89,119,120,158,245,258-262,270-272).

7. Conclusion

The present review summarizes the molecular effects of exercise and fluoxetine in AD, with a focus on mitochondrial regulation, redox homeostasis, neuroinflammation, autophagy, HPA axis function and synaptic plasticity. Current evidence suggests that exercise can act on multiple AD-related pathways through adaptive physiological remodeling (59,61,85,205-208), whereas fluoxetine may influence overlapping targets through serotonergic regulation, anti-inflammatory effects, antioxidant responses and neuroplasticity-related signaling (167,169,170,173-180,187,191,232-235). These shared mechanisms provide a biological basis for potential complementarity between the two interventions. Nevertheless, synergy should not be assumed. The interaction between exercise and fluoxetine is likely to depend on the disease stage, exercise prescription, fluoxetine exposure, intervention timing, comorbidity profile and physical reserve. Excessive exercise load, poorly tolerated fluoxetine exposure or inappropriate timing may reduce the expected benefit or increase the risk of non-additive effects. Therefore, the combined use of exercise and fluoxetine should be regarded as a conditional and testable strategy rather than an established clinical rule. Future studies should use stratified clinical designs to identify the AD subgroups, intervention windows and biomarker profiles associated with safe and beneficial combined exercise and fluoxetine treatment.

Acknowledgements

Not applicable.

Funding

The present study was funded by the National Natural Science Foundation of China (grant no. 32000838) and the Chinese Universities Scientific Fund (grant no. 2024JNPD002).

Availability of data and materials

Not applicable.

Authors' contributions

MW was involved in conceptualization, the literature search and data curation, wrote the original draft, and reviewed and edited the manuscript. YL supervised the study, was involved in conceptualization, and reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the 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 (ChatGPT) 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. Liu Y, Tan Y, Zhang Z, Yi M, Zhu L and Peng W: The interaction between ageing and Alzheimer's disease: Insights from the hallmarks of ageing. Transl Neurodegener 13: 7, 2024.
2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W and Ferri CP: The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement 9: 63-75.e62, 2013.
3. Gardner RC, Valcour V and Yaffe K: Dementia in the oldest old: A multi-factorial and growing public health issue. Alzheimers Res Ther 5: 27, 2013.
4. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J and van der Flier WM: Alzheimer's disease. Lancet 397: 1577-1590, 2021.
5. World Health Organization (WHO): Dementia. Fact sheet. WHO, Geneva, 2025. https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed on May 29, 2026.
6. World Health Organization (WHO): World failing to address dementia challenge. News release. WHO, Geneva, 2021. https://www.who.int/news/item/02-09-2021-world-failing-to-address-dementia-challenge. Accessed on May 29, 2026.
7. Aisen PS, Cummings J, Jack CR Jr, Morris JC, Sperling R, Frölich L, Jones RW, Dowsett SA, Matthews BR, Raskin J, *et al*: On the path to 2025: Understanding the Alzheimer's disease continuum. Alzheimers Res Ther 9: 60, 2017.
8. Tarawneh R and Holtzman DM: The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harb Perspect Med 2: a006148, 2012.
9. Kalia M: Dysphagia and aspiration pneumonia in patients with Alzheimer's disease. Metabolism 52 (10 Suppl 2): S36-S38, 2003.
10. Guo T, Zhang D, Zeng Y, Huang TY, Xu H and Zhao Y: Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol Neurodegener 15: 40, 2020.
11. Goedert M: Neurodegeneration Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. Science 349: 1255555, 2015.
12. 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.
13. 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.
14. Tang J, Liang X, Dou X, Qi Y, Yang C, Luo Y, Chao F, Zhang L, Xiao Q, Jiang L, *et al*: Exercise rather than fluoxetine promotes oligodendrocyte differentiation and myelination in the hippocampus in a male mouse model of depression. Transl Psychiatry 11: 622, 2021.
15. Qin L, Liang X, Qi Y, Luo Y, Xiao Q, Huang D, Zhou C, Jiang L, Zhou M, Zhou Y, *et al*: MPFC PV(+) interneurons are involved in the antidepressant effects of running exercise but not fluoxetine therapy. Neuropharmacology 238: 109669, 2023.
16. Tutakhail A, Nazari QA, Khabil S, Gardier A and Coudore F: Muscular and mitochondrial effects of long-term fluoxetine treatment in mice, combined with physical endurance exercise on treadmill. Life Sci 232: 116508, 2019.
17. Sun Y, Evans J, Russell B, Kydd R and Connor B: A benzodiazepine impairs the neurogenic and behavioural effects of fluoxetine in a rodent model of chronic stress. Neuropharmacology 72: 20-28, 2013.
18. Mahdirejei HA, Peeri M, Azarbayjani MA and Fattahi Masrour F: Fluoxetine combined with swimming exercise synergistically reduces lipopolysaccharide-induced depressive-like behavior by normalizing the HPA axis and brain inflammation in mice. Pharmacol Biochem Behav 232: 173640, 2023.
19. Dam M, Tonin P, De Boni A, Pizzolato G, Casson S, Ermani M, Freo U, Piron L and Battistin L: Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke 27: 1211-1214, 1996.
20. Caraci F, Tascedda F, Merlo S, Benatti C, Spampinato SF, Munafò A, Leggio GM, Nicoletti F, Brunello N, Drago F, *et al*: Fluoxetine prevents Aβ(1-42)-induced toxicity via a paracrine signaling mediated by transforming-growth-factor-β1. Front Pharmacol 7: 389, 2016.
21. Bougea A, Angelopoulou E, Vasilopoulos E, Gourzis P and Papageorgiou S: Emerging therapeutic potential of fluoxetine on cognitive decline in Alzheimer's disease: Systematic Review. Int J Mol Sci 25: 6542, 2024.
22. Chen L, Li A, Zhou J, Chen W and Kou Y: Effectiveness of different therapeutic measures combined with aerobic exercise as an intervention in patients with depression: A systematic review and network meta-analysis. Front Psychiatry 16: 1573557, 2025.
23. Andersen J, Stuhr-Hansen N, Zachariassen LG, Koldsø H, Schiøtt B, Strømgaard K and Kristensen AS: Molecular basis for selective serotonin reuptake inhibition by the antidepressant agent fluoxetine (Prozac). Mol Pharmacol 85: 703-714, 2014.
24. Radak Z, Chung HY, Koltai E, Taylor AW and Goto S: Exercise, oxidative stress and hormesis. Ageing Res Rev 7: 34-42, 2008.
25. Hirschbeck A, Leao DS, Wagner E, Hasan A and Roeh A: Psychiatric medication and physical performance parameters - Are there implications for treatment? Front Psychiatry 13: 985983, 2022.
26. Karran E, Mercken M and De Strooper B: The amyloid cascade hypothesis for Alzheimer's disease: An appraisal for the development of therapeutics. Nat Rev Drug Discov 10: 698-712, 2011.
27. Ashleigh T, Swerdlow RH and Beal MF: The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis. Alzheimers Dement 19: 333-342, 2023.
28. Kazemeini S, Nadeem-Tariq A, Shih R, Rafanan J, Ghani N and Vida TA: From plaques to pathways in Alzheimer's disease: The mitochondrial-neurovascular-metabolic hypothesis. Int J Mol Sci 25: 11720, 2024.
29. Nasb M, Tao W and Chen N: Alzheimer's disease puzzle: Delving into pathogenesis hypotheses. Aging Dis 15: 43-73, 2024.

30. Reutzel M, Grewal R, Joppe A and Eckert GP: Age-dependent alterations of cognition, mitochondrial function, and beta-amyloid deposition in a murine model of Alzheimer's disease-A longitudinal study. Front Aging Neurosci 14: 875989, 2022.
31. Bernardo TC, Marques-Aleixo I, Beleza J, Oliveira PJ, Ascensão A and Magalhães J: Physical exercise and brain mitochondrial fitness: The possible role against Alzheimer's disease. Brain Pathol 26: 648-663, 2016.
32. Merry TL and Ristow M: Mitohormesis in exercise training. Free Radic Biol Med 98: 123-130, 2016.
33. Yoon TK, Lee CH, Kwon O and Kim MS: Exercise, mitohormesis, and mitochondrial ORF of the 12S rRNA Type-C (MOTS-c). Diabetes Metab J 46: 402-413, 2022.
34. Koo JH, Kang EB, Oh YS, Yang DS and Cho JY: Treadmill exercise decreases amyloid-β burden possibly via activation of SIRT-1 signaling in a mouse model of Alzheimer's disease. Exp Neurol 288: 142-152, 2017.
35. Zhao N, Yan QW, Xia J, Zhang XL, Li BX, Yin LY and Xu B: Treadmill exercise attenuates Aβ-induced mitochondrial dysfunction and enhances mitophagy activity in APP/PS1 transgenic mice. Neurochem Res 45: 1202-1214, 2020.
36. Feng L, Li B, Yong SS, Wen X and Tian Z: The emerging role of exercise in Alzheimer's disease: Focus on mitochondrial function. Ageing Res Rev 101: 102486, 2024.
37. Ahmed ME, Selvakumar GP, Kempuraj D, Thangavel R, Mentor S, Dubova I, Raikwar SP, Zaheer S, Iyer S and Zaheer A: Synergy in disruption of mitochondrial dynamics by Aβ (1-42) and glia maturation factor (GMF) in SH-SY5Y cells is mediated through alterations in fission and fusion proteins. Mol Neurobiol 56: 6964-6975, 2019.
38. Wang X, Su B, Fujioka H and Zhu X: Dynamin-like protein 1 reduction underlies mitochondrial morphology and distribution abnormalities in fibroblasts from sporadic Alzheimer's disease patients. Am J Pathol 173: 470-482, 2008.
39. Manczak M, Calkins MJ and Reddy PH: Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: Implications for neuronal damage. Hum Mol Genet 20: 2495-2509, 2011.
40. Chen H and Chan DC: Mitochondrial dynamics-fusion, fission, movement, and mitophagy-in neurodegenerative diseases. Hum Mol Genet 18(R2): R169-R176, 2009.
41. Scheibye-Knudsen M, Fang EF, Croteau DL, Wilson DM III and Bohr VA: Protecting the mitochondrial powerhouse. Trends Cell Biol 25: 158-170, 2015.
42. Wang X, Su B, Lee HG, Li X, Perry G, Smith MA and Zhu X: Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci 29: 9090-9103, 2009.
43. Kandimalla R and Reddy PH: Multiple faces of dynamin-related protein 1 and its role in Alzheimer's disease pathogenesis. Biochim Biophys Acta 1862: 814-828, 2016.
44. Saotome M, Safiulina D, Szabadkai G, Das S, Fransson A, Aspenstrom P, Rizzuto R and Hajnóczky G: Bidirectional Ca^{2+}-dependent control of mitochondrial dynamics by the Miro GTPase. Proc Natl Acad Sci USA 105: 20728-20733, 2008.
45. Stokin GB, Lillo C, Falzone TL, Brusch RG, Rockenstein E, Mount SL, Raman R, Davies P, Masliah E, Williams DS and Goldstein LS: Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. Science 307: 1282-1288, 2005.
46. Sheng ZH and Cai Q: Mitochondrial transport in neurons: Impact on synaptic homeostasis and neurodegeneration. Nat Rev Neurosci 13: 77-93, 2012.
47. An Y, Varma VR, Varma S, Casanova R, Dammer E, Pletnikova O, Chia CW, Egan JM, Ferrucci L, Troncoso J, *et al*: Evidence for brain glucose dysregulation in Alzheimer's disease. Alzheimers Dement 14: 318-329, 2018.
48. de Leon MJ, Convit A, Wolf OT, Tarshish CY, DeSanti S, Rusinek H, Tsui W, Kandil E, Scherer AJ, Roche A, *et al*: Prediction of cognitive decline in normal elderly subjects with 2-[(18)F]fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET). Proc Natl Acad Sci USA 98: 10966-10971, 2001.
49. Armand-Ugon M, Ansoleaga B, Berjaoui S and Ferrer I: Reduced mitochondrial activity is early and steady in the entorhinal cortex but it is mainly unmodified in the frontal cortex in Alzheimer's disease. Curr Alzheimer Res 14: 1327-1334, 2017.
50. Bubber P, Haroutunian V, Fisch G, Blass JP and Gibson GE: Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. Ann Neurol 57: 695-703, 2005.
51. Wasim R: Bioenergetic failure and oxidative stress: Mitochondrial contributions to Alzheimer's disease. Inflammopharmacology 33: 5273-5289, 2025.
52. Sheng B, Wang X, Su B, Lee HG, Casadesus G, Perry G and Zhu X: Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. J Neurochem 120: 419-429, 2012.
53. Calkins MJ, Manczak M, Mao P, Shirendeb U and Reddy PH: Impaired mitochondrial biogenesis, defective axonal transport of mitochondria, abnormal mitochondrial dynamics and synaptic degeneration in a mouse model of Alzheimer's disease. Hum Mol Genet 20: 4515-4529, 2011.
54. Singulani MP, Pereira CPM, Ferreira AFF, Garcia PC, Ferrari GD, Alberici LC and Britto LR: Impairment of PGC-1α-mediated mitochondrial biogenesis precedes mitochondrial dysfunction and Alzheimer's pathology in the 3xTg mouse model of Alzheimer's disease. Exp Gerontol 133: 110882, 2020.
55. Cai Q and Tammineni P: Alterations in mitochondrial quality control in Alzheimer's disease. Front Cell Neurosci 10: 24, 2016.
56. Pradeepkiran JA, Islam MA, Sehar U, Reddy AP, Vijayan M and Reddy PH: Impact of diet and exercise on mitochondrial quality and mitophagy in Alzheimer's disease. Ageing Res Rev 108: 102734, 2025.
57. Pang R, Wang X, Pei F, Zhang W, Shen J, Gao X and Chang C: Regular exercise enhances cognitive function and intracephalic GLUT expression in Alzheimer's disease model mice. J Alzheimers Dis 72: 83-96, 2019.
58. Klein CP, Hoppe JB, Saccomori AB, Dos Santos BG, Sagini JP, Crestani MS, August PM, Hözer RM, Grings M, Parmeggiani B, *et al*: Physical exercise during pregnancy prevents cognitive impairment induced by amyloid-β in adult offspring rats. Mol Neurobiol 56: 2022-2038, 2019.
59. Wang X, Zhu YT, Zhu Y, Sun YL, Huang J, Li Z, Wang Y, Wu JC, Qin ZH and Lin F: Long-term running exercise alleviates cognitive dysfunction in APP/PSEN1 transgenic mice via enhancing brain lysosomal function. Acta Pharmacol Sin 43: 850-861, 2022.
60. Belviranlı M, Okudan N and Sezer T: Exercise upregulates Mitsugumin 53 and ameliorates behavioral deficits and mitochondrial biogenesis in a sporadic Alzheimer's disease model in rats. Arch Gerontol Geriatr 141: 106078, 2026.
61. Zhao N, Zhang X, Li B, Wang J, Zhang C and Xu B: Treadmill exercise improves PINK1/Parkin-mediated mitophagy activity against Alzheimer's disease pathologies by upregulated SIRT1-FOXO1/3 axis in APP/PS1 mice. Mol Neurobiol 60: 277-291, 2023.
62. Morais GP, de Sousa Neto IV, Veras ASC, Teixeira GR, Paroschi LO, Pinto AP, Dos Santos JR, Alberici LC, Cintra DEC, Pauli JR, *et al*: Chronic exercise protects against cognitive deficits in an Alzheimer's disease model by enhancing autophagy and reducing mitochondrial abnormalities. Mol Neurobiol 62: 12791-12810, 2025.
63. Hood DA, Memme JM, Oliveira AN and Triolo M: Maintenance of skeletal muscle mitochondria in health, exercise, and aging. Annu Rev Physiol 81: 19-41, 2019.
64. Jia D, Tian Z and Wang R: Exercise mitigates age-related metabolic diseases by improving mitochondrial dysfunction. Ageing Res Rev 91: 102087, 2023.
65. Settembre C, Di Malta C, Polito VA, Garcia Arencibia M, Vetrini F, Erdin S, Erdin SU, Huynh T, Medina D, Colella P, *et al*: TFEB links autophagy to lysosomal biogenesis. Science 332: 1429-1433, 2011.
66. Endlicher R, Drahota Z, Štefková K, Červinková Z and Kučera O: The mitochondrial permeability transition pore-current knowledge of its structure, function, and regulation, and optimized methods for evaluating its functional state. Cells 12: 1273, 2023.
67. de Ridder I, Kerkhofs M, Lemos FO, Loncke J, Bultynck G and Parys JB: The ER-mitochondria interface, where Ca(2+) and cell death meet. Cell Calcium 112: 102743, 2023.
68. Onishi M, Yamano K, Sato M, Matsuda N and Okamoto K: Molecular mechanisms and physiological functions of mitophagy. EMBO J 40: e104705, 2021.
69. Nixon RA: The role of autophagy in neurodegenerative disease. Nat Med 19: 983-997, 2013.
70. Nilsson P and Saido TC: Dual roles for autophagy: Degradation and secretion of Alzheimer's disease Aβ peptide. Bioessays 36: 570-578, 2014.
71. Moreira PI, Cardoso SM, Santos MS and Oliveira CR: The key role of mitochondria in Alzheimer's disease. J Alzheimers Dis 9: 101-110, 2006.

72. Moreira PI, Santos MS and Oliveira CR: Alzheimer's disease: A lesson from mitochondrial dysfunction. Antioxid Redox Signal 9: 1621-1630, 2007.
73. Moreira PI, Carvalho C, Zhu X, Smith MA and Perry G: Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochim Biophys Acta 1802: 2-10, 2010.
74. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, *et al*: Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol 60: 759-767, 2001.
75. Jones DP: Redefining oxidative stress. Antioxid Redox Signal 8: 1865-1879, 2006.
76. Uttara B, Singh AV, Zamboni P and Mahajan RT: Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol 7: 65-74, 2009.
77. Powers SK, Duarte J, Kavazis AN and Talbert EE: Reactive oxygen species are signalling molecules for skeletal muscle adaptation. Exp Physiol 95: 1-9, 2010.
78. Warburton DE, Nicol CW and Bredin SS: Health benefits of physical activity: The evidence. CMAJ 174: 801-809, 2006.
79. Sies H: Oxidative stress: A concept in redox biology and medicine. Redox Biol 4: 180-183, 2015.
80. Marí M, Morales A, Colell A, García-Ruiz C and Fernández-Checa JC: Mitochondrial glutathione, a key survival antioxidant. Antioxid Redox Signal 11: 2685-2700, 2009.
81. Fukai T and Ushio-Fukai M: Superoxide dismutases: Role in redox signaling, vascular function, and diseases. Antioxid Redox Signal 15: 1583-1606, 2011.
82. Ribas V, García-Ruiz C and Fernández-Checa JC: Glutathione and mitochondria. Front Pharmacol 5: 151, 2014.
83. Di Meo S, Reed TT, Venditti P and Victor VM: Role of ROS and RNS sources in physiological and pathological conditions. Oxid Med Cell Longev 2016: 1245049, 2016.
84. Saharan S and Mandal PK: The emerging role of glutathione in Alzheimer's disease. J Alzheimers Dis 40: 519-529, 2014.
85. Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, Stumvoll M, Kahn CR and Blüher M: Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci USA 106: 8665-8670, 2009.
86. Zhang X, He Q, Huang T, Zhao N, Liang F, Xu B, Chen X, Li T and Bi J: Treadmill exercise decreases Aβ deposition and counteracts cognitive decline in APP/PS1 mice, possibly via hippocampal microglia modifications. Front Aging Neurosci 11: 78, 2019.
87. Li B, Liang F, Ding X, Yan Q, Zhao Y, Zhang X, Bai Y, Huang T and Xu B: Interval and continuous exercise overcome memory deficits related to β-amyloid accumulation through modulating mitochondrial dynamics. Behav Brain Res 376: 112171, 2019.
88. Marques-Aleixo I, Santos-Alves E, Balca MM, Rizo-Roca D, Moreira PI, Oliveira PJ, Magalhaes J and Ascensao A: Physical exercise improves brain cortex and cerebellum mitochondrial bioenergetics and alters apoptotic, dynamic and auto(mito)phagy markers. Neuroscience 301: 480-495, 2015.
89. Mallett GS and McGrath K: Effect of endurance exercise on markers of oxidative stress: A systematic review. J Sci Sport Exerc 7: 175-196, 2025.
90. Feng W, Wang Y, Gu X, Yu D and Liu Z: Exercise as a modulator of systemic inflammation and oxidative stress biomarkers across clinical and healthy populations: An umbrella meta-analysis. BMC Sports Sci Med Rehabil 17: 360, 2025.
91. Banerjee AK, Mandal A, Chanda D and Chakraborti S: Oxidant, antioxidant and physical exercise. Mol Cell Biochem 253: 307-312, 2003.
92. Forrester SJ, Kikuchi DS, Hernandes MS, Xu Q and Griendling KK: Reactive oxygen species in metabolic and inflammatory signaling. Circ Res 122: 877-902, 2018.
93. Van Zeller M, Dias D, Sebastião AM and Valente CA: NLRP3 inflammasome: A starring role in Amyloid-β- and tau-driven pathological events in Alzheimer's disease. J Alzheimers Dis 83: 939-961, 2021.
94. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ and Golenbock DT: The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol 9: 857-865, 2008.
95. Parajuli B, Sonobe Y, Horiuchi H, Takeuchi H, Mizuno T and Suzumura A: Oligomeric amyloid β induces IL-1β processing via production of ROS: Implication in Alzheimer's disease. Cell Death Dis 4: e975, 2013.
96. Ising C, Venegas C, Zhang S, Scheiblich H, Schmidt SV, Vieira-Saecker A, Schwartz S, Albasset S, McManus RM, Tejera D, *et al*: NLRP3 inflammasome activation drives tau pathology. Nature 575: 669-673, 2019.
97. Venegas C, Kumar S, Franklin BS, Dierkes T, Brinkschulte R, Tejera D, Vieira-Saecker A, Schwartz S, Santarelli F, Kummer MP, *et al*: Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer's disease. Nature 552: 355-361, 2017.
98. Hanslik KL and Ulland TK: The role of microglia and the NLRP3 inflammasome in Alzheimer's disease. Front Neurol 11: 570711, 2020.
99. Tarkowski E, Andreasen N, Tarkowski A and Blennow K: Intrathecal inflammation precedes development of Alzheimer's disease. J Neurol Neurosurg Psychiatry 74: 1200-1205, 2003.
100. Qiu WQ, Ai W, Zhu FD, Zhang Y, Guo MS, Law BY, Wu JM, Wong VK, Tang Y, Yu L, *et al*: Polygala saponins inhibit NLRP3 inflammasome-mediated neuroinflammation via SHP-2-mediated mitophagy. Free Radic Biol Med 179: 76-94, 2022.
101. Ramos ELP, Sousa Neto IV, Pinto AP, Cintra DE, Ropelle ER, Pauli JR, de Freitas EC, Mineo TWP and da Silva ASR: Mechanisms underlying the interplay between autophagy and the inflammasome in age-related diseases: Implications for exercise immunology. Ageing Res Rev 110: 102821, 2025.
102. Mejías-Peña Y, Estébanez B, Rodriguez-Miguelez P, Fernandez-Gonzalo R, Almar M, de Paz JA, González-Gallego J and Cuevas MJ: Impact of resistance training on the autophagy-inflammation-apoptosis crosstalk in elderly subjects. Aging (Albany NY) 9: 408-418, 2017.
103. de Lemos Muller CH, de Matos JR, Grigolo GB, Schroeder HT, Rodrigues-Krause J and Krause M: Exercise training for the elderly: Inflammaging and the central role for HSP70. J Sci Sport Exerc 1: 97-115, 2019.
104. Sujkowski A, Hong L, Wessells RJ and Todi SV: The protective role of exercise against age-related neurodegeneration. Ageing Res Rev 74: 101543, 2022.
105. Zhang XL, Zhao N, Xu B, Chen XH and Li TJ: Treadmill exercise inhibits amyloid-β generation in the hippocampus of APP/PS1 transgenic mice by reducing cholesterol-mediated lipid raft formation. Neuroreport 30: 498-503, 2019.
106. Cristerna-Huerta SV, Vega-Burgueño M, Vergara-Jiménez MJ, Martínez-López E and Barrón-Cabrera E: Assembly and activation of the NLRP3 inflammasome and cytokine quantification in response to exercise in adults with different metabolic conditions: A systematic review. Front Sports Act Living 7: 1602208, 2025.
107. Harry GJ, Lefebvre d'Hellencourt C, Bruccoleri A and Schmechel D: Age-dependent cytokine responses: trimethyltin hippocampal injury in wild-type, APOE knockout, and APOE4 mice. Brain Behav Immun 14: 288-304, 2000.
108. Takeuchi O and Akira S: Pattern recognition receptors and inflammation. Cell 140: 805-820, 2010.
109. DiCarlo G, Wilcock D, Henderson D, Gordon M and Morgan D: Intrahippocampal LPS injections reduce Abeta load in APP+PS1 transgenic mice. Neurobiol Aging 22: 1007-1012, 2001.
110. Herber DL, Roth LM, Wilson D, Wilson N, Mason JE, Morgan D and Gordon MN: Time-dependent reduction in Abeta levels after intracranial LPS administration in APP transgenic mice. Exp Neurol 190: 245-253, 2004.
111. Malm TM, Koistinaho M, Pärepalo M, Vatanen T, Ooka A, Karlsson S and Koistinaho J: Bone-marrow-derived cells contribute to the recruitment of microglial cells in response to beta-amyloid deposition in APP/PS1 double transgenic Alzheimer mice. Neurobiol Dis 18: 134-142, 2005.
112. Paudel YN, Angelopoulou E, Piperi C, Othman I, Aamir K and Shaikh MF: Impact of HMGB1, RAGE, and TLR4 in Alzheimer's disease (AD): From risk factors to therapeutic targeting. Cells 9: 383, 2020.
113. Cai Z, Hussain MD and Yan LJ: Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease. Int J Neurosci 124: 307-321, 2014.
114. Grathwohl SA, Kälin RE, Bolmont T, Prokop S, Winkelmann G, Kaeser SA, Odenthal J, Radde R, Eldh T, Gandy S, *et al*: Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. Nat Neurosci 12: 1361-1363, 2009.
115. Hansen DV, Hanson JE and Sheng M: Microglia in Alzheimer's disease. J Cell Biol 217: 459-472, 2018.
116. Mu L, Xia D, Cai J, Gu B, Liu X, Friedman V, Liu QS and Zhao L: Treadmill exercise reduces neuroinflammation, glial cell activation and improves synaptic transmission in the prefrontal cortex in 3xTg-AD mice. Int J Mol Sci 23: 12655, 2022.

117. Nichol KE, Poon WW, Parachikova AI, Cribbs DH, Glabe CG and Cotman CW: Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. J Neuroinflammation 5: 13, 2008.
118. Connolly MG, Bruce SR and Kohman RA: Exercise duration differentially effects age-related neuroinflammation and hippocampal neurogenesis. Neuroscience 490: 275-286, 2022.
119. Roy SK, Wang JJ and Xu YM: Effects of exercise interventions in Alzheimer's disease: A meta-analysis. Brain Behav 13: e3051, 2023.
120. Cui MY, Lin Y, Sheng JY, Zhang X and Cui RJ: Exercise intervention associated with cognitive improvement in Alzheimer's disease. Neural Plast 2018: 9234105, 2018.
121. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA and Katzman R: Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. Ann Neurol 30: 572-580, 1991.
122. Puzzo D, Argyrousi EK, Staniszewski A, Zhang H, Calcagno E, Zuccarello E, Acquarone E, Fa M, Li Puma DD, Grassi C, *et al*: Tau is not necessary for amyloid-β-induced synaptic and memory impairments. J Clin Invest 130: 4831-4844, 2020.
123. Selkoe DJ: Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res 192: 106-113, 2008.
124. Tsai J, Grutzendler J, Duff K and Gan WB: Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nat Neurosci 7: 1181-1183, 2004.
125. Zhang Y, Xiao Z, He Z, Chen J, Wang X and Jiang L: Dendritic complexity change in the triple transgenic mouse model of Alzheimer's disease. PeerJ 8: e8178, 2020.
126. Wang Q, Xu Z, Tang J, Sun J, Gao J, Wu T and Xiao M: Voluntary exercise counteracts Aβ25-35-induced memory impairment in mice. Behav Brain Res 256: 618-625, 2013.
127. García-Mesa Y, Pareja-Galeano H, Bonet-Costa V, Revilla S, Gómez-Cabrera MC, Gambini J, Giménez-Llort L, Cristòfol R, Viña J and Sanfeliu C: Physical exercise neuroprotects ovariectomized 3xTg-AD mice through BDNF mechanisms. Psychoneuroendocrinology 45: 154-166, 2014.
128. Mu L, Cai J, Gu B, Yu L, Li C, Liu QS and Zhao L: Treadmill exercise prevents decline in spatial learning and memory in 3×Tg-AD mice through enhancement of structural synaptic plasticity of the hippocampus and prefrontal cortex. Cells 11: 244, 2022.
129. Azimi M, Gharakhanlou R, Naghdi N, Khodadadi D and Heysieattalab S: Moderate treadmill exercise ameliorates amyloid-β-induced learning and memory impairment, possibly via increasing AMPK activity and up-regulation of the PGC-1α/FNDC5/BDNF pathway. Peptides 102: 78-88, 2018.
130. Alkadhi KA and Dao AT: Exercise decreases BACE and APP levels in the hippocampus of a rat model of Alzheimer's disease. Mol Cell Neurosci 86: 25-29, 2018.
131. Giménez-Llort L, García Y, Buccieri K, Revilla S, Suñol C, Cristofol R and Sanfeliu C: Gender-specific neuroimmunoendocrine response to treadmill exercise in 3xTg-AD mice. Int J Alzheimers Dis 2010: 128354, 2010.
132. George EK and Reddy PH: Can healthy diets, regular exercise, and better lifestyle delay the progression of dementia in elderly individuals? J Alzheimers Dis 72(S1): S37-S58, 2019.
133. De Sousa RAL, Rodrigues CM, Mendes BF, Improta-Caria AC, Peixoto MFD and Cassilhas RC: Physical exercise protocols in animal models of Alzheimer's disease: A systematic review. Metab Brain Dis 36: 85-95, 2021.
134. Jeanneret V, Ospina JP, Diaz A, Manrique LG, Merino P, Gutierrez L, Torre E, Wu F, Cheng L and Yepes M: Tissue-type plasminogen activator protects the postsynaptic density in the ischemic brain. J Cereb Blood Flow Metab 38: 1896-1910, 2018.
135. Fan X, Wang H, Ping J, Li M, Gu J and Qian W: Synaptic scaffold protein PSD-95: A therapeutic target for Alzheimer's disease. Biochem Pharmacol 242: 117401, 2025.
136. Reddy PH, Mani G, Park BS, Jacques J, Murdoch G, Whetsell W Jr, Kaye J and Manczak M: Differential loss of synaptic proteins in Alzheimer's disease: Implications for synaptic dysfunction. J Alzheimers Dis 7: 103-117; discussion 173-80, 2005.
137. Li WY, Gao JY, Lin SY, Pan ST, Xiao B, Ma YT, Xie K, Shen W, Liu ZT, Li GY, *et al*: Effects of involuntary and voluntary exercise in combination with acousto-optic stimulation on adult neurogenesis in an Alzheimer's mouse model. Mol Neurobiol 59: 3254-3279, 2022.
138. El-Domiaty HF, El-Roghy ES and Salem HR: Combination of magnesium supplementation with treadmill exercise improves memory deficit in aged rats by enhancing hippocampal neurogenesis and plasticity: A functional and histological study. Appl Physiol Nutr Metab 47: 296-308, 2022.
139. Fernandes J, Arida RM and Gomez-Pinilla F: Physical exercise as an epigenetic modulator of brain plasticity and cognition. Neurosci Biobehav Rev 80: 443-456, 2017.
140. Sakalem ME, Seidenbecher T, Zhang M, Saffari R, Kravchenko M, Wördemann S, Diederich K, Schwamborn JC, Zhang W and Ambrée O: Environmental enrichment and physical exercise revert behavioral and electrophysiological impairments caused by reduced adult neurogenesis. Hippocampus 27: 36-51, 2017.
141. Berry KP and Nedivi E: Spine dynamics: Are they all the same? Neuron 96: 43-55, 2017.
142. Li Y, Zhao L, Gu B, Cai J, Lv Y and Yu L: Aerobic exercise regulates Rho/cofilin pathways to rescue synaptic loss in aged rats. PLoS One 12: e0171491, 2017.
143. Qiu D, Zhou S, Donnelly J, Xia D and Zhao L: Aerobic exercise attenuates abnormal myelination and oligodendrocyte differentiation in 3xTg-AD mice. Exp Gerontol 182: 112293, 2023.
144. Yu L, Li Y, Lv Y, Gu B, Cai J, Liu QS and Zhao L: Treadmill exercise facilitates synaptic plasticity in APP/PS1 mice by regulating hippocampal AMPAR activity. Cells 13: 1608, 2024.
145. Spencer FSE, Elsworthy RJ, Breen L, Bishop JRB, Dunleavy C and Aldred S: The effect of the APOE4 genotype on physiological and cognitive health in randomised controlled trials with an exercise intervention: A systematic review and meta-analysis. Trials 26: 20, 2025.
146. Head D, Bugg JM, Goate AM, Fagan AM, Mintun MA, Benzinger T, Holtzman DM and Morris JC: Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. Arch Neurol 69: 636-643, 2012.
147. Cadwallader CJ, VandeBunte AM, Fischer DL, Chen C, Diaz VE, Lee SY, Chan B, Lario-Lago A, Rojas JC, Ramos EM, *et al*: BDNF Val66Met polymorphism moderates associations between physical activity and neurocognitive outcomes in older adults. Alzheimers Dement (N Y) 11: e70106, 2025.
148. Li Z, Martens YA, Ren Y, Jin Y, Sekiya H, Doss SV, Kouri N, Castanedes-Casey M, Christensen TA, Miller Nevalainen LB, *et al*: APOE genotype determines cell-type-specific pathological landscape of Alzheimer's disease. Neuron 113: 1380-1397. e7, 2025.
149. Panitch R, Sahelijo N, Hu J, Nho K, Bennett DA, Lunetta KL, Au R, Stein TD, Farrer LA and Jun GR: APOE genotype-specific methylation patterns are linked to Alzheimer disease pathology and estrogen response. Transl Psychiatry 14: 129, 2024.
150. Marzi SJ, Leung SK, Ribarska T, Hannon E, Smith AR, Pishva E, Poschmann J, Moore K, Troakes C, Al-Sarraj S, *et al*: A histone acetylome-wide association study of Alzheimer's disease identifies disease-associated H3K27ac differences in the entorhinal cortex. Nat Neurosci 21: 1618-1627, 2018.
151. Nativio R, Lan Y, Donahue G, Sidoli S, Berson A, Srinivasan AR, Shcherbakova O, Amlie-Wolf A, Nie J, Cui X, *et al*: An integrated multi-omics approach identifies epigenetic alterations associated with Alzheimer's disease. Nat Genet 52: 1024-1035, 2020.
152. Corces MR, Shcherbina A, Kundu S, Gloudemans MJ, Frésard L, Granja JM, Louie BH, Eulalio T, Shams S, Bagdatli ST, *et al*: Single-cell epigenomic analyses implicate candidate causal variants at inherited risk loci for Alzheimer's and Parkinson's diseases. Nat Genet 52: 1158-1168, 2020.
153. Jeon SY, Byun MS, Yi D, Lee JH, Ko K, Sohn BK, Lee JY, Ryu SH, Lee DW, Shin SA, *et al*: Midlife lifestyle activities moderate APOE ε4 effect on in vivo Alzheimer's disease pathologies. Front Aging Neurosci 12: 42, 2020.
154. Kaufman CS, Honea RA, Pleen J, Lepping RJ, Watts A, Morris JK, Billinger SA, Burns JM and Vidoni ED: Aerobic exercise improves hippocampal blood flow for hypertensive Apolipoprotein E4 carriers. J Cereb Blood Flow Metab 41: 2026-2037, 2021.
155. Jensen CS, Simonsen AH, Siersma V, Beyer N, Frederiksen KS, Gottrup H, Hoffman K, Høgh P, Frikke-Schmidt R, Sobol NA, *et al*: Patients with Alzheimer's disease who carry the APOE ε4 allele benefit more from physical exercise. Alzheimers Dement (N Y) 5: 99-106, 2019.
156. Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, Puente-Martínez A, Casado-Yusta S, Olaya B and Santabárbara J: Depression as a risk factor for Alzheimer's disease: A systematic review of longitudinal meta-analyses. J Clin Med 10: 1809, 2021.

157. Harerimana NV, Liu Y, Gerasimov ES, Duong D, Beach TG, Reiman EM, Schneider JA, Boyle P, Lori A, Bennett DA, *et al*: Genetic evidence supporting a causal role of depression in Alzheimer's disease. Biol Psychiatry 92: 25-33, 2022.
158. Lyketsos CG and Olin J: Depression in Alzheimer's disease: Overview and treatment. Biol Psychiatry 52: 243-252, 2002.
159. Untu I, Davidson M, Stanciu GD, Rabinowitz J, Dobrin RP, Vieru DS and Tamba BI: Neurobiological and therapeutic landmarks of depression associated with Alzheimer's disease dementia. Front Aging Neurosci 17: 1584607, 2025.
160. Monereo-Sánchez J, Schram MT, Frei O, O'Connell K, Shadrin AA, Smeland OB, Westlye LT, Andreassen OA, Kaufmann T, Linden DEJ and van der Meer D: Genetic overlap between Alzheimer's disease and depression mapped onto the brain. Front Neurosci 15: 653130, 2021.
161. Rapp MA, Schnaider-Beeri M, Grossman HT, Sano M, Perl DP, Purohit DP, Gorman JM and Haroutunian V: Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry 63: 161-167, 2006.
162. Bajaj S and Mahesh R: Converged avenues: Depression and Alzheimer's disease-shared pathophysiology and novel therapeutics. Mol Biol Rep 51: 225, 2024.
163. Zhan Q, Kong F, Shao S, Zhang B and Huang S: Pathogenesis of depression in Alzheimer's disease. Neurochem Res 49: 548-556, 2024.
164. Liu PP, Xie Y, Meng XY and Kang JS: History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal Transduct Target Ther 4: 29, 2019.
165. Aboukhatwa M, Dosanjh L and Luo Y: Antidepressants are a rational complementary therapy for the treatment of Alzheimer's disease. Mol Neurodegener 5: 10, 2010.
166. Mowla A, Mosavinasab M, Haghshenas H and Borhani Haghighi A: Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol 27: 484-487, 2007.
167. Abu-Elfotuh K, Al-Najjar AH, Mohammed AA, Aboutaleb AS and Badawi GA: Fluoxetine ameliorates Alzheimer's disease progression and prevents the exacerbation of cardiovascular dysfunction of socially isolated depressed rats through activation of Nrf2/HO-1 and hindering TLR4/NLRP3 inflammasome signaling pathway. Int Immunopharmacol 104: 108488, 2022.
168. Abu-Elfotuh K, Ragab GM, Salahuddin A, Jamil L and Abd Al Haleem EN: Attenuative effects of fluoxetine and triticum aestivum against aluminum-induced Alzheimer's disease in rats: The possible consequences on hepatotoxicity and nephrotoxicity. Molecules 26: 6752, 2021.
169. Shu X, Sun Y, Sun X, Zhou Y, Bian Y, Shu Z, Ding J, Lu M and Hu G: The effect of fluoxetine on astrocyte autophagy flux and injured mitochondria clearance in a mouse model of depression. Cell Death Dis 10: 577, 2019.
170. Huang M, Liang Y, Chen H, Xu B, Chai C and Xing P: The role of fluoxetine in activating Wnt/β-catenin signaling and repressing β-amyloid production in an Alzheimer mouse model. Front Aging Neurosci 10: 164, 2018.
171. Caraci F, Copani A, Nicoletti F and Drago F: Depression and Alzheimer's disease: Neurobiological links and common pharmacological targets. Eur J Pharmacol 626: 64-71, 2010.
172. Zhao Y, Shang P, Wang M, Xie M and Liu J: Neuroprotective effects of fluoxetine against chronic stress-induced neural inflammation and apoptosis: Involvement of the p38 activity. Front Physiol 11: 351, 2020.
173. Du RH, Tan J, Sun XY, Lu M, Ding JH and Hu G: Fluoxetine inhibits NLRP3 inflammasome activation: implication in depression. Int J Neuropsychopharmacol 19: pyw037, 2016.
174. Mendez-David I, Tritschler L, Ali ZE, Damiens MH, Pallardy M, David DJ, Kerdine-Römer S and Gardier AM: Nrf2-signaling and BDNF: A new target for the antidepressant-like activity of chronic fluoxetine treatment in a mouse model of anxiety/depression. Neurosci Lett 597: 121-126, 2015.
175. Caruso G, Grasso M, Fidilio A, Torrisi SA, Musso N, Geraci F, Tropea MR, Privitera A, Tascedda F, Puzzo D, *et al*: Antioxidant activity of fluoxetine and vortioxetine in a non-transgenic animal model of Alzheimer's disease. Front Pharmacol 12: 809541, 2021.
176. Liu FY, Cai J, Wang C, Ruan W, Guan GP, Pan HZ, Li JR, Qian C, Chen JS, Wang L and Chen G: Fluoxetine attenuates neuroinflammation in early brain injury after subarachnoid hemorrhage: A possible role for the regulation of TLR4/MyD88/NF-κB signaling pathway. J Neuroinflammation 15: 347, 2018.
177. Yao Y, Lin D, Chen Y, Liu L, Wu Y and Zheng X: Fluoxetine alleviates postoperative cognitive dysfunction by attenuating TLR4/MyD88/NF-κB signaling pathway activation in aged mice. Inflamm Res 72: 1161-1173, 2023.
178. Diniz LP, Tortelli V, Matias I, Morgado J, Bérgamo Araujo AP, Melo HM, Seixas da Silva GS, Alves-Leon SV, de Souza JM, Ferreira ST, *et al*: Astrocyte transforming growth factor beta 1 protects synapses against Abeta oligomers in Alzheimer's disease model. J Neurosci 37: 6797-6809, 2017.
179. Park SH, Lee YS, Yang HJ and Song GJ: Fluoxetine potentiates phagocytosis and autophagy in microglia. Front Pharmacol 12: 770610, 2021.
180. Xia M, Li X, Yang L, Ren J, Sun G, Qi S, Verkhratsky A and Li B: The ameliorative effect of fluoxetine on neuroinflammation induced by sleep deprivation. J Neurochem: December 9, 2017 (Epub ahead of print).
181. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F and Shao F: Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature 526: 660-665, 2015.
182. La Barbera L, Krashia P, Loffredo G, Cauzzi E, De Paolis ML, Montanari M, Saba L, Spoleti E, Ficchì S, Zaccone C, *et al*: Midbrain degeneration triggers astrocyte reactivity and tau pathology in experimental Alzheimer's disease. Mol Neurodegener 20: 105, 2025.
183. Cirrito JR, Disabato BM, Restivo JL, Verges DK, Goebel WD, Sathyan A, Hayreh D, D'Angelo G, Benzinger T, Yoon H, *et al*: Serotonin signaling is associated with lower amyloid-β levels and plaques in transgenic mice and humans. Proc Natl Acad Sci USA 108: 14968-14973, 2011.
184. Zhou CN, Chao FL, Zhang Y, Jiang L, Zhang L, Fan JH, Wu YX, Dou XY and Tang Y: Fluoxetine delays the cognitive function decline and synaptic changes in a transgenic mouse model of early Alzheimer's disease. J Comp Neurol 527: 1378-1387, 2019.
185. Ma J, Gao Y, Tang W, Huang W and Tang Y: Fluoxetine protects against dendritic spine loss in middle-aged APPswe/PSEN1dE9 double transgenic Alzheimer's disease mice. Curr Alzheimer Res 17: 93-103, 2020.
186. Li X, Zhu W, Roh MS, Friedman AB, Rosborough K and Jope RS: In vivo regulation of glycogen synthase kinase-3beta (GSK3beta) by serotonergic activity in mouse brain. Neuropsychopharmacology 29: 1426-1431, 2004.
187. Xu XF, Wang YC, Zong L, Chen ZY and Li Y: Elevating Integrin-linked Kinase expression has rescued hippocampal neurogenesis and memory deficits in an AD animal model. Brain Res 1695: 65-77, 2018.
188. Chu J, Lauretti E and Praticò D: Caspase-3-dependent cleavage of AKT modulates tau phosphorylation via GSK3β kinase: Implications for Alzheimer's disease. Mol Psychiatry 22: 1002-1008, 2017.
189. Gao L, Zhang Y, Sterling K and Song W: Brain-derived neurotrophic factor in Alzheimer's disease and its pharmaceutical potential. Transl Neurodegener 11: 4, 2022.
190. Lim YY, Villemagne VL, Laws SM, Pietrzak RH, Snyder PJ, Ames D, Ellis KA, Harrington K, Rembach A, Martins RN, *et al*: APOE and BDNF polymorphisms moderate amyloid β-related cognitive decline in preclinical Alzheimer's disease. Mol Psychiatry 20: 1322-1328, 2015.
191. Sun DS, Gao LF, Jin L, Wu H, Wang Q, Zhou Y, Fan S, Jiang X, Ke D, Lei H, *et al*: Fluoxetine administration during adolescence attenuates cognitive and synaptic deficits in adult 3xTgAD mice. Neuropharmacology 126: 200-212, 2017.
192. Attiq A, Afzal S, Raman H and Ahmad W: Neuroinflammation to neurodegeneration: Boulevard of broken nerves. Int Immunopharmacol 161: 115015, 2025.
193. Kobayashi K, Ikeda Y, Haneda E and Suzuki H: Chronic fluoxetine bidirectionally modulates potentiating effects of serotonin on the hippocampal mossy fiber synaptic transmission. J Neurosci 28: 6272-6280, 2008.
194. Kobayashi K, Ikeda Y, Sakai A, Yamasaki N, Haneda E, Miyakawa T and Suzuki H: Reversal of hippocampal neuronal maturation by serotonergic antidepressants. Proc Natl Acad Sci USA 107: 8434-8439, 2010.
195. Kobayashi K, Haneda E, Higuchi M, Suhara T and Suzuki H: Chronic fluoxetine selectively upregulates dopamine D_1-like receptors in the hippocampus. Neuropsychopharmacology 37: 1500-1508, 2012.
196. Kobayashi K, Ikeda Y, Asada M, Inagaki H, Kawada T and Suzuki H: Corticosterone facilitates fluoxetine-induced neuronal plasticity in the hippocampus. PLoS One 8: e63662, 2013.

197. Imoto Y, Kira T, Sukeno M, Nishitani N, Nagayasu K, Nakagawa T, Kaneko S, Kobayashi K and Segi-Nishida E: Role of the 5-HT4 receptor in chronic fluoxetine treatment-induced neurogenic activity and granule cell dematuration in the dentate gyrus. Mol Brain 8: 29, 2015.
198. Qin M, Wu J, Zhou Q, Liang Z and Su Y: Global cognitive effects of second-generation antidepressants in patients with Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. J Psychiatr Res 155: 371-379, 2022.
199. Chai Y, Shokri-Kojori E, Saykin AJ and Yu M: Anxious-depressive symptoms and sleep disturbances across the Alzheimer disease spectrum. Nat Ment Health 3: 594-612, 2025.
200. Hill MA and Gammie SC: Alzheimer's disease large-scale gene expression portrait identifies exercise as the top theoretical treatment. Sci Rep 12: 17189, 2022.
201. Marlatt MW, Potter MC, Bayer TA, van Praag H and Lucassen PJ: Prolonged running, not fluoxetine treatment, increases neurogenesis, but does not alter neuropathology, in the 3xTg mouse model of Alzheimer's disease. Curr Top Behav Neurosci 15: 313-340, 2013.
202. Schoeman JC, Steyn SF, Harvey BH and Brink CB: Long-lasting effects of fluoxetine and/or exercise augmentation on bio-behavioural markers of depression in pre-pubertal stress sensitive rats. Behav Brain Res 323: 86-99, 2017.
203. Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, Green M, Harper D, Ren B, Forester BP, *et al*: Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res Rev 72: 101503, 2021.
204. Tönnies E and Trushina E: Oxidative stress, synaptic dysfunction, and Alzheimer's disease. J Alzheimers Dis 57: 1105-1121, 2017.
205. Bo H, Kang W, Jiang N, Wang X, Zhang Y and Ji LL: Exercise-induced neuroprotection of hippocampus in APP/PS1 transgenic mice via upregulation of mitochondrial 8-oxoguanine DNA glycosylase. Oxid Med Cell Longev 2014: 834502, 2014.
206. Yuan S, Yang J, Jian Y, Lei Y, Yao S, Hu Z, Liu X, Tang C and Liu W: Treadmill exercise modulates intestinal microbes and suppresses LPS displacement to alleviate neuroinflammation in the brains of APP/PS1 mice. Nutrients 14: 4134, 2022.
207. Liang F, Sun F, Guo C and Zhong H: Treadmill exercise alleviates Alzheimer's disease pathologies in APP/PS1 mice through modulation of microglial glucose metabolic reprogramming. Front Aging Neurosci 17: 1734837, 2025.
208. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, Gonçalves RA, Clarke JR, Beckman D, Staniszewski A, *et al*: Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 25: 165-175, 2019.
209. Shafia S, Nikkhah F and Akhoundzadeh K: Effect of combination fluoxetine and exercise on prefrontal BDNF, anxiety-like behavior and fear extinction in a female rat model of post-traumatic stress disorder (PTSD): A comparison with male animals. Behav Brain Funct 19: 1, 2023.
210. Wu Q, He Q, Zhang X, Chen S and Xue X: Systemic modulators: potential mechanism for the 5-HT system to mediate exercise amelioration in Alzheimer's disease. Aging Dis 16: 2770-2802, 2024.
211. Qiao J, Wang J, Wang H, Zhang Y, Zhu S, Adilijiang A, Guo H, Zhang R, Guo W, Luo G, *et al*: Regulation of astrocyte pathology by fluoxetine prevents the deterioration of Alzheimer phenotypes in an APP/PS1 mouse model. Glia 64: 240-254, 2016.
212. Müller FE, Schade SK, Cherkas V, Stopper L, Breithausen B, Minge D, Varbanov H, Wahl-Schott C, Antoniuk S, Domingos C, *et al*: Serotonin receptor 4 regulates hippocampal astrocyte morphology and function. Glia 69: 872-889, 2021.
213. Wu C, Yang L, Li Y, Dong Y, Yang B, Tucker LD, Zong X and Zhang Q: Effects of exercise training on anxious-depressive-like behavior in Alzheimer rat. Med Sci Sports Exerc 52: 1456-1469, 2020.
214. Pietrelli A, Matković L, Vacotto M, Lopez-Costa JJ, Basso N and Brusco A: Aerobic exercise upregulates the BDNF-Serotonin systems and improves the cognitive function in rats. Neurobiol Learn Mem 155: 528-542, 2018.
215. Chaouloff F, Elghozi JL, Guezennec Y and Laude D: Effects of conditioned running on plasma, liver and brain tryptophan and on brain 5-hydroxytryptamine metabolism of the rat. Br J Pharmacol 86: 33-41, 1985.
216. Ke HC, Huang HJ, Liang KC and Hsieh-Li HM: Selective improvement of cognitive function in adult and aged APP/PS1 transgenic mice by continuous non-shock treadmill exercise. Brain Res 1403: 1-11, 2011.
217. Hassan A, Robinson M and Willerth SM: Modeling the effects of yoga on the progression of Alzheimer's disease in a dish. Cells Tissues Organs 206: 263-271, 2018.
218. Gong Y, Zhan C, Zou Y, Qian Z, Wei G and Zhang Q: Serotonin and melatonin show different modes of action on $A\beta_{42}$ protofibril destabilization. ACS Chem Neurosci 12: 799-809, 2021.
219. Torrisi SA, Geraci F, Tropea MR, Grasso M, Caruso G, Fidilio A, Musso N, Sanfilippo G, Tascedda F, Palmeri A, *et al*: Fluoxetine and vortioxetine reverse depressive-like phenotype and memory deficits induced by Aβ(1-42) oligomers in mice: A key role of transforming growth factor-β1. Front Pharmacol 10: 693, 2019.
220. Liu W, Sheng H, Xu Y, Liu Y, Lu J and Ni X: Swimming exercise ameliorates depression-like behavior in chronically stressed rats: Relevant to proinflammatory cytokines and IDO activation. Behav Brain Res 242: 110-116, 2013.
221. Kim TW, Lim BV, Kim K, Seo JH and Kim CJ: Treadmill exercise alleviates stress-induced impairment of social interaction through 5-hydroxytryptamine 1A receptor activation in rats. J Exerc Rehabil 11: 192-197, 2015.
222. Tiraboschi E, Tardito D, Kasahara J, Moraschi S, Pruneri P, Gennarelli M, Racagni G and Popoli M: Selective phosphorylation of nuclear CREB by fluoxetine is linked to activation of CaM kinase IV and MAP kinase cascades. Neuropsychopharmacology 29: 1831-1840, 2004.
223. Tharmaratnam T, Tabobondung T, Tabobondung T and Doherty S: Synergistic effects of brain-derived neurotrophic factor (BDNF) and exercise intensity on memory in the adolescent brain: A commentary. Environ Health Prev Med 23: 12, 2018.
224. Jin L, Gao LF, Sun DS, Wu H, Wang Q, Ke D, Lei H, Wang JZ and Liu GP: Long-term ameliorative effects of the antidepressant fluoxetine exposure on cognitive deficits in 3×TgAD mice. Mol Neurobiol 54: 4160-4171, 2017.
225. Bhattarai P, Cosacak MI, Mashkaryan V, Demir S, Popova SD, Govindarajan N, Brandt K, Zhang Y, Chang W, Ampatzis K and Kizil C: Neuron-glia interaction through serotonin-BDNF-NGFR axis enables regenerative neurogenesis in Alzheimer's model of adult zebrafish brain. PLoS Biol 18: e3000585, 2020.
226. Ishima T, Fujita Y and Hashimoto K: Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. Eur J Pharmacol 727: 167-173, 2014.
227. Kurosawa M, Okada K, Sato A and Uchida S: Extracellular release of acetylcholine, noradrenaline and serotonin increases in the cerebral cortex during walking in conscious rats. Neurosci Lett 161: 73-76, 1993.
228. Shamsipour S, Sharifi G and Taghian F: An 8-week administration of Bifidobacterium bifidum and Lactobacillus plantarum combined with exercise training alleviates neurotoxicity of Aβ and spatial learning via acetylcholine in Alzheimer rat model. J Mol Neurosci 71: 1495-1505, 2021.
229. Tong L, Balazs R, Thornton PL and Cotman CW: Beta-amyloid peptide at sublethal concentrations downregulates brain-derived neurotrophic factor functions in cultured cortical neurons. J Neurosci 24: 6799-6809, 2004.
230. Neeper SA, Gómez-Pinilla F, Choi J and Cotman C: Exercise and brain neurotrophins. Nature 373: 109, 1995.
231. Russo-Neustadt AA, Beard RC, Huang YM and Cotman CW: Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. Neuroscience 101: 305-312, 2000.
232. Baj G, D'Alessandro V, Musazzi L, Mallei A, Sartori CR, Sciancalepore M, Tardito D, Langone F, Popoli M and Tongiorgi E: Physical exercise and antidepressants enhance BDNF targeting in hippocampal CA3 dendrites: Further evidence of a spatial code for BDNF splice variants. Neuropsychopharmacology 37: 1600-1611, 2012.
233. Milligan Armstrong A, Porter T, Quek H, White A, Haynes J, Jackaman C, Villemagne V, Munyard K, Laws SM, Verdile G and Groth D: Chronic stress and Alzheimer's disease: the interplay between the hypothalamic-pituitary-adrenal axis, genetics and microglia. Biol Rev Camb Philos Soc 96: 2209-2228, 2021.
234. Shafia S, Vafaei AA, Samaei SA, Bandegi AR, Rafiei A, Valadan R, Hosseini-Khah Z, Mohammadkhani R and Rashidy-Pour A: Effects of moderate treadmill exercise and fluoxetine on behavioural and cognitive deficits, hypothalamic-pituitary-adrenal axis dysfunction and alternations in hippocampal BDNF and mRNA expression of apoptosis-related proteins in a rat model of post-traumatic stress disorder. Neurobiol Learn Mem 139: 165-178, 2017.

235. Gassner M, Balaskovits P, Melchior P, Wagner M, Wagner KH and König D: Reactive oxygen species and IL-6 responses to resistance-based HIIT: A time-dependent analysis. Free Radic Biol Med 242: 250-257, 2026.
236. Hodes GE, Hill-Smith TE, Suckow RF, Cooper TB and Lucki I: Sex-specific effects of chronic fluoxetine treatment on neuroplasticity and pharmacokinetics in mice. J Pharmacol Exp Ther 332: 266-273, 2010.
237. Homberg JR, Olivier JD, Blom T, Arentsen T, van Brunschot C, Schipper P, Korte-Bouws G, van Luijtelaar G and Reneman L: Fluoxetine exerts age-dependent effects on behavior and amygdala neuroplasticity in the rat. PLoS One 6: e16646, 2011.
238. Holick KA, Lee DC, Hen R and Dulawa SC: Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. Neuropsychopharmacology 33: 406-417, 2008.
239. Radak Z, Zhao Z, Koltai E, Ohno H and Atalay M: Oxygen consumption and usage during physical exercise: the balance between oxidative stress and ROS-dependent adaptive signaling. Antioxid Redox Signal 18: 1208-1246, 2013.
240. Ji LL, Gomez-Cabrera MC and Vina J: Exercise and hormesis: Activation of cellular antioxidant signaling pathway. Ann N Y Acad Sci 1067: 425-435, 2006.
241. Caiaffo V, Oliveira BD, de Sá FB and Evêncio Neto J: Anti-inflammatory, antiapoptotic, and antioxidant activity of fluoxetine. Pharmacol Res Perspect 4: e00231, 2016.
242. Liu D, Wang Z, Liu S, Wang F, Zhao S and Hao A: Anti-inflammatory effects of fluoxetine in lipopolysaccharide(LPS)-stimulated microglial cells. Neuropharmacology 61: 592-599, 2011.
243. Petersen AM and Pedersen BK: The role of IL-6 in mediating the anti-inflammatory effects of exercise. J Physiol Pharmacol 57 (Suppl 10): S43-S51, 2006.
244. Serralde-Zúñiga AE, Gonzalez Garay AG, Rodríguez-Carmona Y and Melendez G: Fluoxetine for adults who are overweight or obese. Cochrane Database Syst Rev 10: CD011688, 2019.
245. Forte R and De Vito G: Comparison of neuromotor and progressive resistance exercise training to improve mobility and fitness in community-dwelling older women. J Sci Sport Exerc 1: 124-131, 2019.
246. Kishi T, Yoshimura R, Ikuta T and Iwata N: Brain-derived neurotrophic factor and major depressive disorder: Evidence from meta-analyses. Front Psychiatry 8: 308, 2018.
247. Lee J, Lee KH, Kim SH, Han JY, Hong SB, Cho SC, Kim JW and Brent D: Early changes of serum BDNF and SSRI response in adolescents with major depressive disorder. J Affect Disord 265: 325-332, 2020.
248. Lee B, Shin E, Song I and Chang B: Depression in adolescence and brain-derived neurotrophic factor. Front Mol Neurosci 15: 947192, 2022.
249. Badenhorst NJ, Brand L, Harvey BH, Ellis SM and Brink CB: Long-term effects of pre-pubertal fluoxetine on behaviour and monoaminergic stress response in stress-sensitive rats. Acta Neuropsychiatr 29: 222-235, 2017.
250. Liang J, Wang C, Zhang H, Huang J, Xie J and Chen N: Exercise-induced benefits for Alzheimer's disease by stimulating mitophagy and improving mitochondrial function. Front Aging Neurosci 13: 755665, 2021.
251. Rosa JM, Camargo A, Wolin IAV, Kaster MP and Rodrigues ALS: Physical exercise prevents amyloid β_{1-40}-induced disturbances in NLRP3 inflammasome pathway in the hippocampus of mice. Metab Brain Dis 36: 351-359, 2021.
252. Choi DH, Kwon IS, Koo JH, Jang YC, Kang EB, Byun JE, Um HS, Park HS, Yeom DC, Cho IH and Cho JY: The effect of treadmill exercise on inflammatory responses in rat model of streptozotocin-induced experimental dementia of Alzheimer's type. J Exerc Nutrition Biochem 18: 225-233, 2014.
253. Björkholm C and Monteggia LM: BDNF-a key transducer of antidepressant effects. Neuropharmacology 102: 72-79, 2016.
254. Rafa-Zabłocka K, Kreiner G, Bagińska M and Nalepa I: Selective depletion of CREB in serotonergic neurons affects the upregulation of brain-derived neurotrophic factor evoked by chronic fluoxetine treatment. Front Neurosci 12: 637, 2018.
255. Stranahan AM, Lee K and Mattson MP: Central mechanisms of HPA axis regulation by voluntary exercise. Neuromolecular Med 10: 118-127, 2008.
256. Surget A, Tanti A, Leonardo ED, Laugeray A, Rainer Q, Touma C, Palme R, Griebel G, Ibarguen-Vargas Y, Hen R and Belzung C: Antidepressants recruit new neurons to improve stress response regulation. Mol Psychiatry 16: 1177-1188, 2011.
257. Kryst J, Majcher-Maślanka I and Chocyk A: Effects of chronic fluoxetine treatment on anxiety- and depressive-like behaviors in adolescent rodents-systematic review and meta-analysis. Pharmacol Rep 74: 920-946, 2022.
258. Drummond E and Wisniewski T: Alzheimer's disease: Experimental models and reality. Acta Neuropathol 133: 155-175, 2017.
259. Sasaguri H, Nilsson P, Hashimoto S, Nagata K, Saito T, De Strooper B, Hardy J, Vassar R, Winblad B and Saido TC: APP mouse models for Alzheimer's disease preclinical studies. EMBO J 36: 2473-2487, 2017.
260. Haaksma ML, Vilela LR, Marengoni A, Calderón-Larrañaga A, Leoutsakos JS, Olde Rikkert MGM and Melis RJF: Comorbidity and progression of late onset Alzheimer's disease: A systematic review. PLoS One 12: e0177044, 2017.
261. Qian Z, Li Y and Ye K: Advancements and challenges in mouse models of Alzheimer's disease. Trends Mol Med 30: 1152-1164, 2024.
262. Granzotto A, Vissel B and Sensi SL: Lost in translation: Inconvenient truths on the utility of mouse models in Alzheimer's disease research. Elife 13: e90633, 2024.
263. Egan B and Zierath JR: Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab 17: 162-184, 2013.
264. Hawley JA, Hargreaves M, Joyner MJ and Zierath JR: Integrative biology of exercise. Cell 159: 738-749, 2014.
265. Sato S, Basse AL, Schönke M, Chen S, Samad M, Altıntaş A, Laker RC, Dalbram E, Barrès R, Baldi P, *et al*: Time of exercise specifies the impact on muscle metabolic pathways and systemic energy homeostasis. Cell Metab 30: 92-110.e4, 2019.
266. Rovio S, Kåreholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A and Kivipelto M: Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 4: 705-711, 2005.
267. Kim YJ, Han KD, Baek MS, Cho H, Lee EJ and Lyoo CH: Association between physical activity and conversion from mild cognitive impairment to dementia. Alzheimers Res Ther 12: 136, 2020.
268. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR and Almeida OP: Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. JAMA 300: 1027-1037, 2008.
269. Hoffmann K, Sobol NA, Frederiksen KS, Beyer N, Vogel A, Vestergaard K, Brændgaard H, Gottrup H, Lolk A, Wermuth L, *et al*: Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: A Randomized controlled trial. J Alzheimers Dis 50: 443-453, 2016.
270. Baker LD, Pa JA, Katula JA, Aslanyan V, Salmon DP, Jacobs DM, Chmelo EA, Hodge H, Morrison R, Matthews G, *et al*: Effects of exercise on cognition and Alzheimer's biomarkers in a randomized controlled trial of adults with mild cognitive impairment: The EXERT study. Alzheimers Dement 21: e14586, 2025.
271. Demurtas J, Schoene D, Torbahn G, Marengoni A, Grande G, Zou L, Petrovic M, Maggi S, Cesari M, Lamb S, *et al*: Physical activity and exercise in mild cognitive impairment and dementia: an umbrella review of intervention and observational studies. J Am Med Dir Assoc 21: 1415-1422.e6, 2020.
272. López-Ortiz S, Lista S, Valenzuela PL, Pinto-Fraga J, Carmona R, Caraci F, Caruso G, Toschi N, Emanuele E, Gabelle A, *et al*: Effects of physical activity and exercise interventions on Alzheimer's disease: An umbrella review of existing meta-analyses. J Neurol 270: 711-725, 2023.
273. Sagahón-Azúa J, Medellín-Garibay SE, Chávez-Castillo CE, González-Salinas CG, Milán-Segovia RDC and Romano-Moreno S: Factors associated with fluoxetine and norfluoxetine plasma concentrations and clinical response in Mexican patients with mental disorders. Pharmacol Res Perspect 9: e00864, 2021.
274. Jannuzzi G, Gatti G, Magni P, Spina E, Pacifici R, Zuccaro P, Torta R, Guarneri L and Perucca E: Plasma concentrations of the enantiomers of fluoxetine and norfluoxetine: Sources of variability and preliminary observations on relations with clinical response. Ther Drug Monit 24: 616-627, 2002.
275. Díaz-Tufinio CA, Palma-Aguirre JA and Gonzalez-Covarrubias V: Pharmacogenetic variants associated with fluoxetine pharmacokinetics from a bioequivalence study in healthy subjects. J Pers Med 13: 1352, 2023.