Table SI. Exercise-induced effects that may reduce the risk of AD.

A, Effects on mitochondria

First author/s, year	Model/participants	Exercise	Key mechanisms	(Refs.)
Pang *et al*, 2019	APP/PS1 mice	Forced swimming (1 h/day; 6 days/week; 4 weeks); water temperature, 21-23˚C; water depth, 40 cm; no external loading reported	Improved mitochondrial morphology (clearer boundaries and compact/intact cristae), Ctx/Hpc ATP ↑, GLUT1/GLUT3 ↑	(57)
Wang *et al*, 2022	APP/PS1 mice	Wheel running, 18 r/min, 40 min/day, 6 days/week, 5 months, voluntary	AMPK ↑, TFEB ↑, LC3 ↑, Rab7/Rab9 ↑	(59)
Zhao *et al*, 2020; Zhao *et al*, 2023	APP/PS1 mice	Treadmill exercise, 45 min/day, 5 days/week for 12 weeks, after a 6-day familiarization period; 5 m/min for 5 min, 8 m/min for 5 min, 12 m/min for 30 min and 5 m/min for 5 min	PINK1 ↑, Parkin ↑, LC3 ↑, PGC-1α/TFAM ↑, NRFs ↑, SIRT1 ↑, FOXO1/3 ↓	(35,61)
Klein *et al*, 2019	Aβ peptide oligomer-injected rats	Involuntary swimming, no additional load, 30 min/day, 5 days/week, 4 weeks; water temperature, 32±1˚C	α-KGDH ↑, complex IV ↑, Mfn1 ↑, Drp1 ↓	(58)
Koo *et al*, 2017	NSE/APP mice	Treadmill running, 5 days/week for 12 weeks after 5-day acclimation; 10 m/min, 30-50 min/day in weeks 1-4, then 12 m/min, 50-60 min/day in weeks 5-12	SIRT1/PGC-1α ↑	(34)
Morais *et al*, 2025	APP/PS1 mice	Treadmill exercise; acute: After 5 days of adaptation (6 m/min, 10 min/day), one bout at 60% MAP, 0% incline, for 45 min; chronic: 8 weeks, 4 sessions/week, at 60% MAP, 0% incline, 15-45 min/session with progressive increase	REV-ERBα ↑, NR1D1 gene expression ↑, ALP ↑	(62)

B, Effects on ROS

First author/s, year	Model/participants	Exercise	Key mechanisms	(Refs.)
Zhang *et al*, 2019	APP/PS1 mice	Treadmill running, 5 days/week for 12 weeks after 5-day acclimation; 10 m/min, 30-50 min/day in weeks 1-4, then 12 m/min, 50-60 min/day in weeks 5-12	Hpc Mn-SOD ↑, GSH ↑, MDA ↓	(86)
Li *et al*, 2019	APP/PS1 mice	Treadmill exercise; after 3 days of adaptation (10-15 m/min, 15 min/day), mice underwent 12 weeks of training, 5 days/week; HIIT: 9 bouts at 85% Smax for 1.5 min interspersed with 9 bouts at 45% Smax for 2 min; MICT: Continuous running at 60% Smax, distance-matched	ROS ↓, H_2O_2 ↓, MDA ↓, SOD ↑, CAT ↑, Drp1 ↓, FIS1 ↓, Mfn1 ↑, Mfn2 ↑, OPA1 ↑	(87)

C, Effects on inflammation

First author/s, year	Model/participants	Exercise	Key mechanisms	(Refs.)
Mu *et al*, 2022	3xTg-AD mice	Treadmill exercise, after 3-day adaptation, 12 weeks, 5 days/week: 12 m/min for 10 min plus 15 m/min for 50 min, 0° incline, 1 h/day, 50-65% VO_2max	IL-1β ↓, IL-6 ↓, TNFα ↓, GSK3β activity ↓	(116)
Zhang *et al*, 2019	APP/PS1 mice	Treadmill exercise for 12 weeks, 5 days per week, 45 min per	ADAM10 ↑	(105)

		session, at 5-12 m/min		
Morais *et al*, 2025	APP/PS1 mice	Treadmill exercise; acute: After 5 days of adaptation (6 m/min, 10 min/day), one bout at 60% MAP, 0% incline, for 45 min; chronic: 8 weeks, 4 sessions/week, at 60% MAP, 0% incline, 15-45 min/session with progressive increase	TLR4 ↓	(62)
Nichol *et al*, 2008	Tg2576 AD mice	Voluntary wheel running in cage for 3 weeks; self-paced; mean wheel rotations/day, 3,954±877	IL-1β ↓, TNF-α ↓, IFN-γ ↑, MIP-1α ↑, IL-10 ↑	(117)
Zhang *et al*, 2019	APP/PS1 mice	Treadmill running, 5 days/week for 12 weeks after 5-day acclimation; 10 m/min, 30-50 min/day in weeks 1-4, then 12 m/min, 50-60 min/day in weeks 5-12	Microglia (M2/M1 ratio) ↑, pro-inflammatory cytokines ↓	(86)
Mejías-Peña *et al*, 2017	Elderly subjects (69.6±1.5 years)	Resistance training, 2 sessions/week for 8 weeks after a 10-min cycle ergometer warm-up; leg press, biceps curl and pec deck; for each of the three exercises, week 1: 3x8 at 60% 1RM; week 2: 3x10 at 60% 1RM; week 3: 3x12 at 60% 1RM; week 4: 3x8 at 70% 1RM; week 5: 3x10 at 70% 1RM; week 6: 3x12 at 70% 1RM; week 7: 3x8 at 80% 1RM; week 8: 3x10 at 80% 1RM	Beclin-1 ↑, ATG12 ↑, ATG16 ↑, LAMP2 ↑, NLRP3 inflammasome ↓, caspase-1/pro-caspase-1 ↓, Bcl-2 ↓, Bcl-xL ↓, Bad ↓, Bad/Bcl-2 ratio ↓, caspase-3 ↓	(102)

D, Effects on synaptic plasticity

First author/s, year	Model/participants	Exercise	Key mechanisms	(Refs.)
Pang *et al*, 2019	APP/PS1 mice	Forced swimming (1 h/day, 6 days/week, 4 weeks); water temperature, 21-23˚C; water depth, 40 cm; no external loading reported	PSD-95 ↑, SYP ↑	(57)
Li *et al*, 2017	Aging rats	Treadmill aerobic exercise, 5-day adaptation (10 m/min, 10-20 min/day), then 12 weeks at 12 m/min, 0% incline, 60 min/day, 3 or 5 days/week	Ctx age-related Rac1/Cdc42 elevation ↓, Hpc age-related Rac1/Cdc42 reduction reversed, cofilin ↓, synaptophysin/synaptic density ↑	(142)
Qiu *et al*, 2023	3xTg-AD mice	Treadmill exercise, 1-week adaptation (10 m/min, 0° incline, 30 min/day for 2 days, then 60 min/day for 3 days), followed by 6 months of training at 10 m/min for the first 10 min and 12 m/min for the remaining 50 min, 0° incline, 60 min/day, 5 days/week	NG2 protein and mRNA ↑	(143)
Yu *et al*, 2024	APP/PS1 mice	Treadmill running, 5 days/week for 8 weeks after 3-day acclimation; 12 m/min for 10 min and 15 m/min for 50 min, 60 min/day, at 0% incline	GluA1/2 ↑, GluA1 (S831/S845) phosphorylation ↑, AMPAR ↑, LTP ↑	(144)
García-Mesa *et al*, 2014	3xTg-AD mice	Voluntary wheel running, 3 months, free access, with	p-CREB/CREB ↑, BDNF ↑	(127)

		continuous activity recording		
Pang *et al*, 2019	APP/PS1 mice	Forced swimming (1 h/day; 6 days/week; 4 weeks); water temperature, 21-23˚C; water depth, 40 cm; no external loading reported	BDNF ↑	(57)
Klein *et al*, 2019	Aβ peptide oligomer-injected rats	Involuntary swimming, no additional load, 30 min/day, 5 days/week, 4 weeks; water temperature, 32±1˚C	SYP ↑	(58)

↑, increased/upregulated; ↓, decreased/downregulated; 1RM, one-repetition maximum; 3xTg-AD, triple-transgenic AD; Aβ, amyloid-β; AD, Alzheimer's disease; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; ALP, autophagy-lysosome pathway; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMPK, AMP-activated protein kinase; APP/PS1, amyloid precursor protein/presenilin 1; ATG12, autophagy related 12; ATG16, autophagy related 16; BDNF, brain-derived neurotrophic factor; CAT, catalase; Cdc42, cell division cycle 42; CREB, cAMP response element-binding protein; H_2O_2, hydrogen peroxide; HIIT, high-intensity interval training; Ctx, cortex; Drp1, dynamin-related protein 1; GluA1/2, glutamate ionotropic receptor AMPA type subunit 1/2; GLUT1/GLUT3, glucose transporter 1/3; GSH, glutathione; Hpc, hippocampus; LAMP2, lysosome-associated membrane protein 2; LTP, long-term potentiation; MDA, malondialdehyde; MAP, maximal aerobic power; Mfn1, mitofusin 1; Mfn2, mitofusin 2; MICT, moderate-intensity continuous training; MIP-1α, macrophage inflammatory protein-1α; Mn-SOD, manganese superoxide dismutase; NG2, neural/glial antigen 2; NLRP3, NOD-like receptor family pyrin domain containing 3; NR1D1, nuclear receptor subfamily 1 group D member 1; NRF, nuclear respiratory factor; NSE/APP, neuron-specific enolase/amyloid precursor protein; p-, phosphorylated; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; PINK1, PTEN-induced kinase 1; PSD-95, postsynaptic density protein 95; r/min, revolutions per minute; REV-ERBα, nuclear receptor subfamily 1 group D member 1α; ROS, reactive oxygen species; SIRT1, sirtuin 1; Smax, maximal running speed; SOD, superoxide dismutase; SYP, synaptophysin; TFAM, mitochondrial transcription factor A; TFEB, transcription factor EB; TLR4, toll-like receptor 4; VO_2max, maximal oxygen uptake; α-KGDH, α-ketoglutarate dehydrogenase.

Table SII. Conditional framework defining circumstances under which exercise and fluoxetine may be more likely to interact synergistically or antagonistically in AD.

First author/s, year	Interaction domain	Conditions more likely to favor synergy	Conditions more likely to favor antagonism	Biological or clinical rationale	(Refs.)
Aisen *et al*, 2017; Tarawneh and Holtzman, 2012; Livingston *et al*, 2024; Lyketsos and Olin, 2002	Disease stage and clinical context	MCI or early AD, particularly when depressive symptoms, anxiety or sleep disturbance reduce adherence to rehabilitation or regular exercise	Moderate-to-severe AD, particularly when accompanied by marked frailty, limited exercise tolerance or reduced functional reserve	Combined treatment is more likely to be beneficial when the main objective is to improve adherence, relieve mood-related barriers and target potentially reversible dysfunction, rather than to reverse advanced multisystem decline	(7,8,13,158)
Radak *et al*, 2008; Merry and Ristow, 2016; Ristow *et al*, 2009; Mallett and McGrath, 2025	Exercise prescription	Regular, sustainable, low-to-moderate intensity aerobic exercise, with modality tailored to tolerance and functional capacity	Excessive exercise load, poorly matched modality, or training approaching or exceeding the adaptive threshold	Exercise-related benefit depends in part on adaptive remodeling triggered by manageable physiological stress; excessive loading may shift the response from adaptation toward oxidative, inflammatory or functional burden	(24,32,85,89)
Tutakhail *et al*, 2019; Bougea *et al*, 2024; Andersen *et al*, 2014; Hirschbeck *et al*, 2022	Fluoxetine exposure	Low-dose initiation, gradual titration and individualized treatment course	High-dose exposure, adverse effects that reduce exercise participation or adherence, or an exposure level that functionally suppresses exercise responsiveness	Although fluoxetine may support mood and engage overlapping neurobiological targets, excessive exposure may reduce exercise capacity or interfere with adaptive signaling relevant to mitochondrial remodeling, autophagic regulation and neuroplasticity	(16,21,23,25)
Tutakhail *et al*, 2019; Mahdirejei *et al*, 2023; Radak *et al*, 2008; Ristow *et al*, 2009	Timing of combined intervention	Pharmacological support introduced in a manner that facilitates participation in training without interrupting early adaptive responses	Fluoxetine introduced too early relative to training adaptation or under conditions in which adaptive signals are still being established	Part of the proposed benefit of exercise depends on transient ROS- and inflammation-related signaling; excessive or prematurely timed pharmacological suppression may blunt these initiating signals	(16,18,24,85)
Livingston *et al*, 2024; Haaksma *et al*, 2017; Demurtas *et al*, 2020	Comorbidity profile	Depression, anxiety, sleep disturbance or cardiometabolic comorbidity, in which improved adherence, vascular-metabolic regulation and sustained participation are realistic therapeutic goals	Chronic pain, osteoporosis, osteoarthritis, Parkinsonian features or coordination disorders that narrow the safe exercise window	The net effect of combined treatment depends on whether comorbidity broadens or constrains the compatibility window between pharmacological support and safe, sustainable training	(13,260,271)
Hirschbeck *et al*, 2022; Forte and De Vito, 2019; Demurtas *et al*, 2020	Physical reserve and safety considerations	Adequate mobility and tolerance, allowing exercise to be implemented consistently and progressively	Unsteady gait, impaired coordination, pronounced fatigue or elevated fall risk	In vulnerable patients, the key issue shifts from theoretical pathway complementarity to whether the combined intervention compromises safety, balance or exercise feasibility	(25,245,271)
Tang *et al*, 2021; Qin *et al*, 2023; Tutakhail *et al*, 2019; Sun *et al*, 2013;	Overall interpretation of interaction	Biologically plausible complementarity across shared targets, including stress regulation, inflammatory modulation and	Non-additive or potentially adverse interaction when exercise load, drug exposure	Synergy should not be assumed; the combined effect is more appropriately interpreted as conditional rather than deterministic	(14-18,21)

Mahdirejei *et al*, 2023; Bougea *et al*, 2024		neuroplasticity	and patient condition are poorly matched		
Roy *et al*, 2023; Cui *et al*, 2018; Drummond and Wisniewski, 2017; Sasaguri *et al*, 2017; Qian *et al*, 2024; Granzotto *et al*, 2024; Demurtas *et al*, 2020; Baker *et al*, 2025; López-Ortiz *et al*, 2023	Level of supporting evidence	Mechanistically supported and hypothesis-generating	Clinically unconfirmed; antagonistic risk cannot be excluded under mismatched conditions	The current evidence base remains predominantly preclinical; accordingly, both beneficial and detrimental interaction patterns should be interpreted as hypotheses for future subgroup analyses, rather than as established clinical rules	(119,120,258,259, 261,262,270-272)

AD, Alzheimer's disease; MCI, mild cognitive impairment; ROS, reactive oxygen species.