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Review

Exercise, Metabolic Regulation, and Ferroptotic Vulnerability in Alzheimer's Disease: A Causal Evidence Appraisal

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Abstract

Exercise may influence Alzheimer's disease (AD) through metabolic, redox, and inflammatory pathways that intersect with ferroptosis, but the causal meaning of individual marker changes depends on experimental design. This structured critical evidence reappraisal examined the causal depth supported by AD-specific exercise studies meeting operational ferroptosis-relevant endpoint criteria. PubMed, Web of Science Core Collection, and Scopus were searched through 31 July 2026, with mechanistic bridge searches, a targeted update on 5 October, and PubMed currency checks through 31 October 2026. Three AD exercise studies were re-extracted at the outcome level and evaluated with an author-developed, non-preregistered, retrospectively applied four-level framework intended for external evaluation. Belaya et al. and Li et al. support Level 1. Choi et al. provisionally supports marker-based Level 2 because reported exercise-related differences span iron and lipid/antioxidant domains; however, the published assay size of $n = 6$/group is difficult to reconcile with F(3,23), tempering confidence in that assignment. Marker-based Level 2 indicates a vulnerability-consistent metabolic profile rather than functional confirmation of altered susceptibility. Overall, current AD exercise evidence remains concentrated at Levels 1–2, while ferroptotic execution and exercise-specific mediation require direct cell-death attribution, dependency/rescue testing, temporal ordering, and factorial exercise-by-perturbation designs. The eligible corpus was animal-based, underscoring the need for human biomarker studies linked to central AD-relevant measures.

Keywords: Alzheimer's disease; exercise; ferroptosis; iron homeostasis; glutathione metabolism; lipid peroxidation; metabolic regulation; neuroinflammation

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Academic Editor: Hikaru Hori

Received: 20 October 2026
Revised: 3 November 2026
Accepted: 15 November 2026
Published: 18 November 2026

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia [1]. Its clinical course develops within interacting amyloid, tau, vascular, metabolic, inflammatory, and redox abnormalities rather than a single isolated lesion [2–5]. This heterogeneity has encouraged interest in regulated cell-death pathways that could integrate several forms of cellular stress [5–7]. Ferroptosis is an iron-dependent form of regulated cell death driven by membrane phospholipid peroxidation [8,9]. Human AD tissue and experimental models show abnormalities in cerebral iron distribution, lipid oxidation, and the cystine/glutamate antiporter system Xc− (SLC7A11/SLC3A2) [10], while NRF2 and GPX4 regulate stress-responsive transcription and phospholipid-hydroperoxide detoxification [11]. These obser-

vations establish biological relevance, while an exercise-dependent ferroptosis mechanism requires additional direct evidence. From a metabolism-oriented perspective, iron handling, cystine–glutathione availability, phospholipid composition, and peroxide-detoxification capacity form an integrated biochemical interface through which exercise could modify ferroptotic vulnerability. Accordingly, this review focuses on the strongest ferroptosis-related causal claim supported by individual AD exercise experiments.

The central evidentiary question concerns what ferroptosis-related measurements allow one to infer in AD. Increased iron, reduced GPX4, altered NRF2, or higher malondialdehyde can mark a tissue state compatible with ferroptotic stress, yet direct attribution to ferroptotic cell death may remain uncertain [8–11]. A stronger mechanistic claim therefore requires progression through distinct inferential steps: a ferroptosis-related response, a vulnerability-consistent metabolic or functional profile, ferroptotic execution in the relevant cell population, and finally causal mediation of a functional outcome. Keeping these steps distinct helps prevent a small marker panel from carrying more mechanistic weight than the experiment can support.

Exercise adds a second layer of complexity because it alters multiple systems at once. In AD models, training can modify cerebral perfusion, metabolism, inflammatory tone, mitochondrial adaptation, and neurotrophic signaling [12–14]. The most explicitly ferroptosis-framed AD-specific exercise study also reported coordinated changes in prefrontal iron-related proteins and the system Xc−/GPX4 network after aerobic training [15]. Outside AD, cellular and neurological studies implicate irisin, TrkB-related mechanisms, NRF2, BDNF, extracellular vesicles, and other exercise-responsive signals in ferroptosis-associated injury [16–21]. These findings are useful mechanistically, but disease context, exercise specificity, spatial resolution, and causal depth differ substantially across them.

Unlike our previous cross-disease review [22], which broadly mapped exercise–ferroptosis evidence across neurodegenerative disorders, the present review focuses on the three eligible AD exercise studies and reappraises their endpoint-level evidence. Its main contribution is to calibrate the strength of mechanistic inference by distinguishing exercise effects from genotype effects and marginal findings and applying common evidence-advancement criteria.

We apply these rules to Belaya et al. [23], Choi et al. [24], and Li et al. [15], link each assignment to study-level reporting and risk-of-bias limitations, and identify the experiments required to advance from marker response to ferroptotic execution and exercise-specific mediation. Table 1 summarizes the distinction from the prior review.

Table 1. Itemized comparison of the present causal reappraisal with the prior cross-disease review by Han et al.

Dimension	Han et al. [22], Int. J. Mol. Sci. 27, 6628	Present Manuscript	Distinctive Contribution
Primary question	How exercise may regulate ferroptosis across multiple neurodegenerative diseases; broad mapping of direct, supporting, and non-exercise mechanisms.	How far individual AD exercise experiments support escalating causal claims from marker response to mediation.	Changes the question from pathway mapping to claim calibration.

Table 1. *Cont.*

Dimension	Han et al. [22], Int. J. Mol. Sci. 27, 6628	Present Manuscript	Distinctive Contribution
Unit of analysis	Disease/pathway/study-level narrative synthesis.	AD study plus exercise-relevant endpoint, with statistical direction/uncertainty and assay-specific sample information where recoverable.	Prevents genotype effects, exercise effects, and marginal outcomes from being pooled narratively.
Evidence and causal architecture	Broad cross-disease evidence-source mapping with a general distinction between direct evidence and mechanistic plausibility.	Two independent axes: evidence source (AD exercise with ferroptosis-relevant endpoints vs. supportive/contextual) and causal depth (Levels 1–4), with explicit advancement criteria.	Separates disease relevance from causal strength and yields auditable study assignments.
Distinctive contribution and metabolic focus	Broad pathway synthesis across multiple neurodegenerative diseases.	Endpoint-level AD reanalysis organized around iron homeostasis, cystine–GSH–GPX4 defense, phospholipid peroxidation/remodeling, and metabolic–inflammatory/peripheral signaling.	Changes specific study interpretation rather than merely narrowing disease scope or extending the search date.

2. Methods

2.1. Literature Search

This study was conducted as a structured critical evidence reappraisal of exercise-related ferroptosis evidence in Alzheimer's disease (AD). The literature search covered PubMed, Web of Science Core Collection, and Scopus from database inception through 31 July 2026. Search concepts were organized around three domains: AD-related conditions, ferroptosis-associated biology, and exercise exposure. Terms within each domain were combined using "OR", and the three conceptual domains were combined using "AND", with database-specific adaptations where required. The complete executable search strategies for the three databases are provided in Supplementary Table S9.

The AD-related search block included Alzheimer disease, Alzheimer's disease, amyloid-beta, tau, cognitive impairment, and dementia. Ferroptosis-related concepts included ferroptosis, iron homeostasis, iron overload, lipid peroxidation, GPX4, SLC7A11, NRF2, ACSL4, ferritin, ferroportin, transferrin receptor, and ferritinophagy. Exercise-related concepts included exercise, physical activity, aerobic exercise, treadmill exercise, voluntary running, resistance exercise, interval training, high-intensity interval training, combined training, exercise preconditioning, and environmental enrichment. Environmental enrichment was retained as a high-sensitivity retrieval term because it can incorporate substantial physical activity, although it was evaluated separately from clearly defined exercise interventions during evidence classification.

Because the primary AD exercise literature was limited in mechanistic depth, structured supplementary searches were also conducted to identify evidence relevant to interpretation of specific ferroptosis-related pathways. These searches focused on iron-regulatory mechanisms, the system Xc−–GSH–GPX4 defense axis, lipid-peroxidation and ACSL4-related

processes, ferroptosis-responsive exercise mediators, and neurological or aging models in which perturbation, rescue, or cell-resolved approaches had been applied. Complete bridge-search strategies are provided in Supplementary Table S8.

Reference lists of eligible studies and relevant reviews were examined manually to identify additional primary reports. Backward citation checking from Li et al. [15] identified Belaya et al. [23] and Choi et al. [24] as directly relevant AD exercise studies satisfying the study-selection criteria. The earlier cross-disease review by Han et al. [22] was used for contextual comparison and citation tracing, whereas the present study-level appraisal was based on the corresponding original experimental reports. The available search records and operational eligibility criteria are summarized in Supplementary Table S10.

2.2. Study Selection

Study selection proceeded through database retrieval, duplicate handling, title and abstract screening, full-text assessment, evidence-source classification, and study-level appraisal. The available documentation supported verification of the final study corpus and its eligibility criteria, although record-level information was less complete for some earlier screening stages, including database-specific retrieval totals, duplicate counts, detailed deduplication procedures, reviewer participation at individual stages, and full-text exclusion records. For this reason, the evidence-provenance and study-classification process is emphasized, while numerical reconstruction of incompletely documented historical screening stages is avoided.

The primary AD exercise corpus included original experimental studies that met four criteria: (i) use of an AD model or human AD population; (ii) inclusion of a clearly defined exercise exposure; (iii) assessment of at least one endpoint relevant to ferroptosis biology; and (iv) availability of an exercise comparison that permitted interpretation of the direction of the exercise-related effect. Reports were considered outside the primary corpus when they represented secondary or substantially overlapping publications, addressed conditions outside AD, provided insufficient characterization of exercise exposure, examined outcomes outside the ferroptosis-related domains considered in this appraisal, or contained exercise-related contrasts that could not be interpreted with reasonable confidence. The detailed operational inclusion and exclusion criteria are provided in Supplementary Table S10.

Application of these criteria identified three primary AD exercise studies: Belaya et al. [23], Choi et al. [24], and Li et al. [15]. These studies formed the basis for AD-specific evidence appraisal. H.H. and M.H. independently reassessed the eligibility of these studies, independently extracted exercise-relevant outcomes from the original reports, and independently applied the study-level evidence criteria. Differences in extraction or classification were resolved through discussion. The available records were used to support study-level verification rather than formal estimation of inter-rater agreement.

Exercise studies conducted in other neurological, injury, aging, or disease models were considered separately as bridge evidence when they contributed mechanistic information that was limited in the AD exercise literature. Relevant features included pathway perturbation or rescue, mediator validation, cell-death attribution, and cell- or region-resolved analysis. Environmental-enrichment studies were treated as multimodal contextual evidence because their exposure combines physical, cognitive, sensory, and social components. Pharmacological, cellular, genetic, and observational studies using other experimental exposures were used primarily to inform biological plausibility, target tractability, or experimental design. These evidence sources were therefore distinguished from the primary AD exercise corpus during interpretation.

The evidence synthesis was qualitative because the included studies differed substantially in disease model, exercise exposure, anatomical compartment, outcome definition,

and analytical structure. For each primary AD exercise study, extraction focused on the exercise-relevant comparison, direction of effect, reported statistical uncertainty, endpoint-specific analytical sample information where available, and the presence of perturbation or rescue designs. Reporting status was recorded separately from experimental status so that limited reporting, analytical uncertainty, and endpoints outside the reported design were not treated as equivalent forms of evidence.

2.3. Evidence Appraisal Framework

The four-level framework is author-developed and non-preregistered. It was applied retrospectively for the present appraisal, and its reproducibility and external validity require independent evaluation. Level 1 represents a supported change in at least one ferroptosis-associated molecule or process. Level 2 represents a vulnerability-consistent profile supported by coherent changes across at least two mechanistically distinct ferroptosis domains within the same biological compartment. Direct susceptibility testing can strengthen a Level 2 interpretation, but the Level 2 label itself is used here to denote vulnerability-consistent evidence rather than functional confirmation of altered susceptibility. Level 3 reflects ferroptotic cell death together with ferroptosis-specific dependency or rescue in the same spatial and temporal context. Level 4 further incorporates temporal ordering and an exercise-by-perturbation interaction supporting exercise-specific mechanistic mediation. Detailed advancement rules are summarized in Table 2 and Supplementary Table S4; borderline trends or multiple markers derived from one broad pathway are treated as supportive context rather than independent grounds for advancement.

Table 2. Operational criteria for the four inferential evidence levels used in this review.

Level	Necessary Criteria	Supportive Findings	Conditions Requiring Additional Evidence for Advancement
Level 1—ferroptosis-related response	Supported change in ≥1 ferroptosis-associated molecule/process in a relevant compartment; statistical evidence is interpreted together with effect direction, precision when available, and analysis structure.	Concordant direction across related assays; appropriate compartment and timing.	A trend with limited statistical support, or generic oxidative stress, inflammation, cognition, or injury, provides limited basis for advancement unless linked to a ferroptosis domain.
Level 2—vulnerability-consistent profile	Supported changes in ≥2 mechanistically distinct ferroptosis domains within the same biological compartment, forming a vulnerability-consistent profile. Direct susceptibility testing may strengthen this interpretation but does not convert Level 2 into evidence of ferroptotic execution.	Labile-iron measures, GPX4 activity, GSH/GSSG, defined lipid-peroxide/lipidomic readouts, cell-resolved localization, and—where available—direct susceptibility testing.	Multiple markers from one broad pathway, terminal marker abundance alone, or nonspecific injury/cell death provide limited basis for advancement; functional confirmation and execution require more direct testing.

Table 2. *Cont.*

Level	Necessary Criteria	Supportive Findings	Conditions Requiring Additional Evidence for Advancement
Level 3—ferroptotic execution	Ferroptotic cell death in the matched spatial/temporal compartment PLUS a ferroptosis-specific dependency/rescue test.	Defined oxidized phospholipids, cell-resolved lipid injury, target reversal or ferroptosis-sensitive rescue.	TUNEL/apoptosis, generic cell death, or morphology alone provide limited specificity; a multidomain marker panel gains inferential strength when paired with ferroptosis-specific death attribution and dependency testing.
Level 4—exercise-specific ferroptosis mediation	All Level-3 criteria PLUS temporal ordering and an exercise × perturbation interaction showing that perturbation selectively changes the exercise effect on ferroptotic death and downstream function.	Appropriately positioned downstream rescue that restores the interrupted ferroptosis phenotype and expected functional benefit.	A perturbation main effect or pleiotropic-node dependence alone provides limited mediation specificity; stronger inference requires an exercise × perturbation interaction with an appropriate non-exercise perturbation control.

Evidence source was considered separately from causal depth. AD exercise studies, exercise bridge studies from other disease or injury contexts, AD mechanistic studies involving other experimental exposures, and broader contextual evidence therefore contribute differently to interpretation. Mechanistically informative studies from other models can refine experimental design and identify candidate pathways, while AD-specific grading remains anchored to the primary AD exercise corpus. Advancement beyond Levels 1–2 requires matched evidence for ferroptotic execution and pathway-specific dependency or rescue.

2.4. Study-Level Appraisal and Metabolic–Inflammatory Synthesis Framework

Because this article is framed as a critical appraisal, study-level design and reporting were examined alongside mechanistic interpretation. Applicable animal studies in Supplementary Table S5 were assessed descriptively with SYRCLE risk-of-bias domains [25], while sample size, sex, age, intervention prescription, timing, tissue/cell context, attrition, prospective power justification, and perturbation/rescue design were extracted separately. The SYRCLE table serves as a descriptive appraisal and remains separate from the causal-level assignment. Conservative "Unclear" judgments are used when source reports provide limited information for verifying a domain; Supplementary Table S6 states the source-based rationale for the judgments that can be made more specifically. The original risk-of-bias workflow was organized as a descriptive source-based assessment rather than as a prospectively duplicated reviewer exercise, so the manuscript reports the available appraisal transparently and refrains from retrospective agreement-statistic estimation. Supplementary Tables S5–S7 provide the evidence matrix, risk-of-bias appraisal, and reporting-completeness matrix.

To facilitate interpretation for metabolism-oriented readers, the mechanistic synthesis was organized around four interacting domains: (i) iron homeostasis and the labile iron pool; (ii) cystine uptake, glutathione metabolism, and GPX4-dependent phospholipid-peroxide detoxification; (iii) ACSL4-dependent phospholipid remodeling and

lipid-peroxidation susceptibility; and (iv) exercise-responsive peripheral and inflammatory signals that can modify these metabolic processes. This organization treats metabolic and inflammatory dysregulation as mechanistically relevant dimensions of a neurodegenerative disorder and asks how far exercise-responsive changes in these domains support claims of ferroptotic vulnerability, execution, or mediation. The literature search, study-selection, and evidence-provenance workflow is summarized in Figure 1.

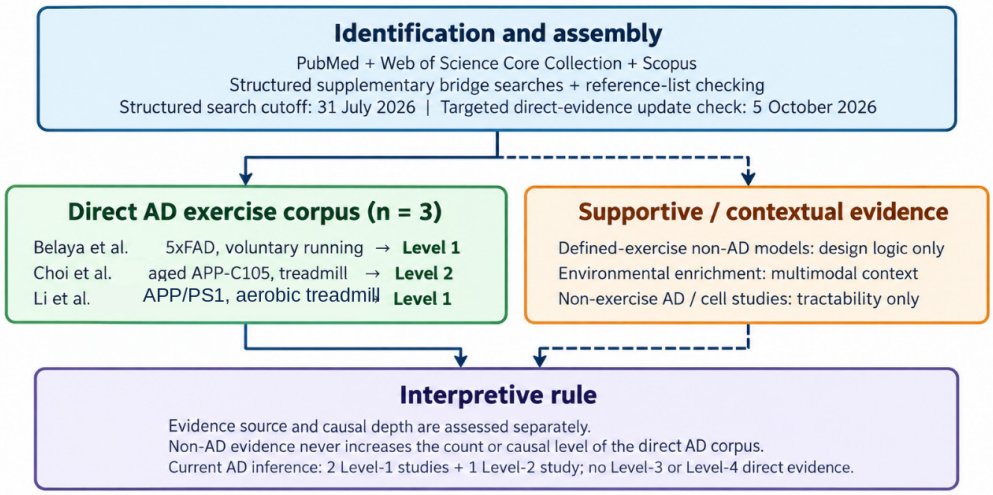


Figure 1. Evidence-provenance map for the present reappraisal. Evidence source and causal depth are evaluated separately; supportive or contextual studies inform mechanistic interpretation while AD-specific grading remains anchored to the primary corpus. Numerical retrieval, deduplication, and screening information is summarized in Supplementary Table S10 to the extent supported by verifiable records. The study labels in the figure correspond to Belaya et al. [23], Choi et al. [24], and Li et al. [15].

3. Metabolic Determinants and Evidentiary Boundaries of Ferroptotic Vulnerability in Alzheimer's Disease

3.1. Metabolic Marker Responses Versus Ferroptotic Vulnerability

A ferroptosis-related response is a change in a molecule or process that participates in ferroptosis biology yet, by itself, provides limited evidence about whether the tissue has become more or less susceptible to ferroptotic injury. Examples include altered TfR1 or FPN expression, changes in ferritin abundance, higher NRF2 or GPX4 protein, lower MDA or 4-hydroxynonenal, or altered ACSL4. The principal limitation is specificity. TfR1 and FPN report iron transport rather than the size of the redox-active iron pool; GPX4 abundance may differ from enzymatic activity [26]; NRF2 regulates a broad stress response; and MDA or 4-hydroxynonenal identifies lipid damage while providing limited specificity regarding the oxidized phospholipid, membrane compartment, or route of oxidation [9,11]. For this reason, isolated changes in these readouts are classified here as Level 1 ferroptosis-related responses.

A stronger inference requires several mechanistically connected domains to change coherently in the same biological compartment. Iron handling shapes the catalytic environment for oxidation; the system Xc−/GSH/GPX4 network determines phospholipid-hydroperoxide detoxification; and membrane lipid composition influences how readily peroxidation propagates [8,9,11]. Human AD tissue shows altered iron distribution together with lipid peroxidation and perturbed system Xc− expression [10], while loss of FPN links iron retention with memory impairment [27]. NOX1–ferritinophagy studies in Parkinsonian models further illustrate how catalytic iron can be mobilized [28]. The empirical appraisal in this review focuses on iron handling, system Xc−/GSH/GPX4, lipid peroxi-

dation, and ACSL4 because these are the domains measured most often in the available exercise literature. Established GPX4-independent defense systems, including FSP1–CoQ10, DHODH–CoQ, and GCH1–BH4, also form part of ferroptosis biology [9], while the current AD exercise primary-corpus evidence offers limited basis for evaluating those routes. Coordinated changes in iron availability, antioxidant reserve, and lipid-peroxide burden can therefore support a Level 2 vulnerability-consistent metabolic profile, with direct functional susceptibility and ferroptotic cell-death attribution requiring further testing.

3.2. From Ferroptotic Vulnerability to Ferroptotic Execution

Ferroptotic execution requires evidence beyond susceptibility. A tissue can accumulate redox-active iron, lose antioxidant reserve, or sustain lipid damage while another process remains the dominant cause of cell death. Defined oxidized phospholipid species or lipidomic readouts are more discriminating than bulk MDA, and GPX4 activity or GSH/GSSG provides more mechanistic information than protein abundance alone. Under the operational framework used here, Level 3 requires both cell death in the same spatial and temporal compartment and a ferroptosis-specific dependency or rescue test; a multidomain marker profile accompanied only by nonspecific injury therefore supports a lower inferential level. This requirement helps distinguish ferroptotic execution from apoptosis, necrosis, or generalized tissue damage when terminal molecular markers overlap.

Execution also benefits from distinction from parallel or downstream injury programs. Apoptosis, pyroptosis, senescence, inflammation, mitochondrial dysfunction, and vascular injury can coexist with ferroptosis-related changes in AD [5,6]. A late fall in GPX4 after substantial neuronal loss may reflect loss of viable tissue, while a late rise in NRF2 may represent compensatory stress signaling. When spatially and temporally aligned injury evidence and a directional dependency test remain limited, the more defensible terms are ferroptosis-related response or altered ferroptotic vulnerability.

3.3. Spatial, Cellular, and Organelle Context Determines Interpretation

Spatial resolution matters because neurons, astrocytes, microglia, oligodendrocytes, and vascular cells differ in iron handling, membrane lipid composition, metabolic demand, and antioxidant reserve. Regional homogenates can therefore conceal a vulnerable minority population. Single-cell work implicates astrocytic FTH1/SAT1-related vulnerability [29], and exercise in aged rats has been linked to oligodendrocyte/white-matter ferroptosis-related patterns [30]. These observations favor compartment-matched evidence when the claim concerns ferroptotic cell death rather than a general tissue redox response.

Subcellular context can likewise modify interpretation. Mitochondrial iron use, redox cofactors, reactive oxygen production, and mitophagy may alter ferroptotic susceptibility, while mitochondrial morphology or membrane potential alone has limited diagnostic specificity for ferroptosis [31,32]. Organelle-resolved measurements therefore carry greater evidentiary weight when the proposed mechanism is explicitly organelle-specific and is linked to cell-death and dependency evidence.

3.4. Operational Evidence Levels and Metabolic Interpretation

Applying the advancement rules to the primary corpus yields Belaya et al. [23] at Level 1, Choi et al. [24] provisionally at marker-based Level 2, and Li et al. [15] at Level 1. Choi et al. spans iron and lipid-peroxidation/antioxidant domains; this assignment is best interpreted as a vulnerability-consistent metabolic profile, while assay-specific n/df uncertainty tempers confidence in stronger functional interpretation. A conservative sensitivity interpretation assigning Choi et al. to Level 1 would leave the central inference unchanged: the current AD exercise corpus remains below the criteria for Level 3 ferroptotic execution and Level 4

exercise-specific mediation. Li et al. remains Level 1 because statistically supported exercise effects are concentrated in the system Xc−/GPX4 defense domain, whereas 4-HNE findings are marginal and total iron is genotype-driven.

Evidence source and causal depth remain separate axes. Additional markers generally contribute to advancement when supported findings extend across mechanistically distinct processes, while mechanistically stronger studies from other disease or injury contexts can inform design with lower directness for AD-specific inference. Supplementary Table S5 makes these study-level judgments traceable and preserves heterogeneous findings rather than averaging them into a single protective narrative.

4. Exercise-Responsive Metabolic Regulation in AD: What Is Currently Supported by the Evidence?

4.1. AD Exercise Studies with Ferroptosis-Relevant Endpoints

Three AD exercise studies met the primary-corpus definition, and this small denominator governs all AD-specific conclusions. In 5xFAD mice, prolonged voluntary running altered iron-regulatory signals, while total cortical iron showed little evidence of an exercise effect ($p = 0.9$) [23]. Cortical ferritin mRNA showed a genotype × exercise interaction ($p < 0.01$) with a 5xFAD-EXE versus 5xFAD-SED difference ($p < 0.01$), while cortical hepcidin and IL-6 showed exercise main effects ($p < 0.05$) [23]. These findings remain within iron/inflammatory regulation and therefore support Level 1. Choi et al. [24] studied 24-month APP-C105 and wild-type mice ($n = 9$/group overall); the source methods specify Western-blot $n = 6$/group and immunohistochemistry $n = 3$/group, and the figure captions specify $n = 6$/group for the iron and oxidative-stress assays. The paper reports group effects for Fe^{2+} ($F(3,23) = 39.205$, $p = 0.001$), Fe^{3+} ($F(3,23) = 14.695$, $p = 0.001$), total Fe ($F(3,23) = 24.441$, $p = 0.001$), 4-HNE ($F(3,23) = 46.82$, $p = 0.001$), MDA ($F(3,23) = 22.34$, $p = 0.001$), and catalase ($F(3,23) = 14.100$, $p = 0.001$). Figure-level Bonferroni annotations indicate Tg-C versus Tg-TE differences at $p < 0.05$ for each of these iron and lipid/antioxidant endpoints, while the source presents significance annotations rather than exact adjusted pairwise p values. Under a conventional four-group one-way ANOVA, an error df of 23 corresponds to 27 analytical observations ($N - k = 23$ with $k = 4$), whereas a balanced $n = 6$/group assay corresponds to 24 observations. The published information therefore leaves the analytical denominator unresolved. Because the reported exercise-related differences span at least two mechanistically distinct domains, Choi et al. [24] is retained provisionally at marker-based Level 2. This level indicates a vulnerability-consistent metabolic profile; direct functional susceptibility requires additional testing, and confidence in the assignment is tempered by the analytical-denominator uncertainty.

Li et al. [15] provides the most explicitly ferroptosis-framed AD exercise dataset, while outcome-level re-extraction supports a more circumscribed cross-domain pattern. In the prefrontal cortex of APPswe/PSEN1dE9 mice, Xc− showed a significant AD exercise simple effect (AD-E versus AD-S, $p < 0.001$, $\eta^2 = 0.631$), and GPX4 Western blot showed an exercise main effect ($p = 0.002$, $\eta^2 = 0.374$). By contrast, the exercise main effect for 4-HNE fluorescence intensity was marginal ($p = 0.060$, $\eta^2 = 0.374$), the AD-E versus AD-S comparison for 4-HNE-positive area was marginal ($p = 0.070$, $\eta^2 = 0.353$), and the significant total-iron result was a genotype main effect ($p = 0.040$, $\eta^2 = 0.427$), with an exercise-specific reduction remaining uncertain. NRF2 exercise-related upregulation likewise remained statistically uncertain. The statistically supported exercise findings therefore remain concentrated in one defense domain, supporting a Level 1 classification. Together, the three studies report selected exercise-responsive changes in ferroptosis-related biology, while cross-study consistency for altered ferroptotic vulnerability, execution, or mediation remains limited. The study-level findings and corresponding evidence assignments are summarized in Table 3.

Table 3. AD exercise studies meeting ferroptosis-relevant endpoint criteria operationally defined for the present reappraisal and the highest causal level supported by reported exercise-related outcomes.

Study	Model/Exercise	Metabolic/Ferroptosis Domains	Key Exercise-Related Findings	Perturbation/Rescue	Level	Main Limitation
Belaya et al. [23]	Male 5xFAD + WT; voluntary wheel running for 6 months	Iron homeostasis/hepcidin–IL-6	Total cortical iron: little evidence of an exercise effect ($p = 0.9$). Cortical ferritin mRNA: genotype × exercise $p < 0.01$; 5xFAD-EXE vs. 5xFAD-SED $p < 0.01$. Cortical hepcidin and IL-6: main exercise effects $p < 0.05$. Findings remain within iron/inflammatory regulation.	Outside reported design	Level 1	One ferroptosis-relevant domain; cell-death/dependency testing remained outside the reported design. AD-specific interpretation is based on exercise-responsive iron-regulatory contrasts, while total cortical iron remained broadly stable.
Choi et al. [24]	24-month APP-C105 + WT; $n = 9$/group overall; relevant biochemical assays $n = 6$/group; histology $n = 3$/group; treadmill, 8 weeks, 5 d/week, 30 min/session	Iron regulation + lipid peroxidation/antioxidant biology	Fe^{2+}, Fe^{3+}, total Fe, 4-HNE, MDA, and catalase: significant four-group ANOVAs. Source-figure Bonferroni annotations support Tg-C vs. Tg-TE $p < 0.05$ for each endpoint; the source presents significance annotations rather than exact adjusted pairwise p values.	Outside reported design	Level 2 *	Provisional marker-based profile; the reported assay $n = 6$/group and F(3,23) imply different analytical denominators under a conventional balanced four-group ANOVA. Direct susceptibility, ferroptotic-death attribution, and dependency/rescue testing remained outside the reported design.
Li et al. [15]	Male 6-month APP/PS1 + C57BL/6J; treadmill, 8 weeks, 5 d/week, 60 min/day	System Xc−/GPX4 defense; 4-HNE and total iron	Xc−: AD-E vs. AD-S $p < 0.001$ ($\eta^2 = 0.631$). GPX4 WB: exercise main effect $p = 0.002$ ($\eta^2 = 0.374$). 4-HNE fluorescence/positive area: marginal $p = 0.060$–0.070. Total iron: genotype main effect $p = 0.040$, with exercise-specific reduction remaining uncertain; NRF2 exercise-related upregulation likewise remained uncertain.	Outside reported design	Level 1	Supported exercise effects were concentrated in one defense domain; other domains were marginal or genotype-driven; assay-specific n reporting was limited.

Note: * Provisional marker-based Level 2 denotes a vulnerability-consistent metabolic profile rather than functional confirmation of altered ferroptotic susceptibility; confidence is tempered by the unresolved assay n/df relationship in Choi et al. [24].

4.2. Evidence Gaps Across Exercise Modalities

Available AD exercise evidence remains dominated by voluntary running, treadmill, or aerobic protocols [15,23,24], with contextual dose and perfusion evidence from Moore et al. [33] and Lu et al. [12]. Direct comparative evidence for resistance, interval, and combined training remains limited when using a shared ferroptosis panel and a common physiological dose metric. Reviews across neurological conditions likewise report limited evidence beyond aerobic exercise and few direct modality comparisons [19,21,22]. A senescence-centered exercise review broadens the mechanistic hypothesis space while contributing contextual rather than independent primary AD exercise ferroptosis evidence [34]. Because the direct studies differ in model, exercise mode, tissue, and endpoint panel—and because their iron-related findings vary—the literature currently offers limited basis for ranking exercise modalities by their effects on ferroptosis-related vulnerability. The more immediate need is reproducible within- and between-modality comparison using mechanistically distinct ferroptosis domains.

4.3. Dose, Timing, and Disease-Stage Dependence

Exercise dose can change the redox state being sampled. Moderate exercise commonly elicits adaptive antioxidant responses, whereas excessive or unaccustomed loading can increase oxidative and nitrosative stress [35]. In AD models, exercise intensity also influences disease-relevant outcomes: graded treadmill training altered soluble amyloid-beta in a dose-dependent manner [33]. Neither observation establishes the shape of a ferroptosis dose response curve. A given treadmill speed can also represent different relative workloads across age, genotype, fitness, and disease burden, so comparisons based only on session duration or absolute speed can be misleading.

Timing also changes what is being measured. Acute exercise produces rapid shifts in oxygen demand, metabolites, catecholamines, and circulating factors, whereas repeated training produces slower vascular, mitochondrial, and transcriptional adaptations [13,14,22,35]. Tissue collected immediately after the final bout may capture transient stress; delayed sampling may better reflect the trained state while providing less visibility into an initiating signal. Disease stage can further narrow or widen the adaptive range. Apparent disagreement between studies may therefore reflect different physiological states when dose verification is limited and sampling is concentrated at a single time point.

Across the three primary-corpus AD exercise studies, important effect modifiers are unevenly represented. Belaya et al. [23] used long-term voluntary running in 5xFAD mice and reported exercise-sensitive cortical iron-regulatory changes, while total cortical iron remained broadly stable; Choi et al. [24] studied very old APP-C105 mice using an 8-week treadmill protocol and sampled motor cortex; Li et al. [15] studied 6-month-old APP/PS1 mice after 8 weeks of aerobic training and assessed prefrontal endpoints. Differences in genotype, disease stage, brain region, exercise modality/intensity, terminal sampling window, and limited sex-specific reporting substantially constrain cross-study comparability. Apparent disagreement may therefore reflect true biology, protocol differences, measurement differences, or some combination of these factors; the present evidence offers limited basis for distinguishing among them. Supplementary Table S5 records these design variables explicitly and uses “reporting detail limited” when the primary article provides limited information for a reliable judgment.

4.4. Supporting Evidence from Other Neurological Models and Transfer Limits

Supporting studies from other disease or injury models are used to illustrate experimental logic that is less represented in the three AD exercise studies in the primary corpus; the AD-specific evidence count and level remain anchored to the AD corpus. In cerebral

ischemia, exercise preconditioning linked skeletal-muscle exosomal miR-484 to ACSL4 using target validation and mediator manipulation [18]. In traumatic brain injury, STING manipulation tested pathway dependence of the exercise-associated ferroptosis phenotype [17]. In physiological aging, aerobic exercise provided cell-specific information concerning iron/oligodendrocyte vulnerability [30]. Fan et al. [36] is retained as multimodal environmental-enrichment context because separation of physical activity from cognitive, sensory, and social components is difficult. These studies primarily inform experimental design and mechanistic plausibility, while direct confirmation of the same mediator or causal chain in AD requires AD-specific testing.

These findings are best transferred to AD cautiously. Ischemia and trauma produce abrupt membrane injury, iron release, and inflammatory activation, whereas AD develops over prolonged amyloid, tau, vascular, and metabolic stress. A mediator that is necessary during acute injury may be redundant, compensatory, or stage-dependent in chronic neurodegeneration. Parkinson's disease offers additional mechanistic clues because dopaminergic neurons are sensitive to iron and lipid-peroxide imbalance [37], but its regional biology and motor-training context differ from AD. Cross-model evidence has greatest relevance to the AD mechanism when the same mediator is present in AD-relevant cells and is shown to respond to exercise in an AD model.

5. Why Current Evidence Supports a Cautious Interpretation of Ferroptosis as a Mediator of Exercise-Induced Neuroprotection

5.1. Marker Responsiveness and the Evidence Required for Ferroptotic Execution

The AD exercise primary corpus illustrates why marker responsiveness is best distinguished from functional susceptibility and ferroptotic execution. Belaya et al. [23] demonstrates exercise-related iron-homeostasis modulation, while total cortical iron remains broadly stable. Choi et al. [24] reports exercise-related differences across iron and lipid-peroxidation/antioxidant domains and provisionally meets the marker-based Level 2 criterion; this level denotes a vulnerability-consistent metabolic profile. Reporting uncertainty regarding the original n/df relationship tempers confidence in stronger interpretation even though figure-level post hoc annotations support Tg-C versus Tg-TE differences for key endpoints. Li et al. [15] provides statistically supported Xc−/GPX4-related responses, whereas 4-HNE effects are marginal and total iron is genotype-driven; it therefore remains Level 1. Progression of these terminal marker patterns to Level 3 would require matched ferroptotic cell-death attribution and ferroptosis-specific dependency/rescue evidence.

Similar terminal readouts can arise from mechanistically distinct interventions. Representative AD studies show convergence on overlapping ferroptosis-associated endpoints through VDR/NRF2 activation, KEAP1/NRF2 modulation, direct GPX4 support, and ACSL4-centered lipid remodeling [38–41]. Studies from other cognitive and metabolic-stress models reach related iron/lipid endpoints through different upstream routes [42–44]. This convergence supports target tractability and metabolic plausibility, while the specific route recruited by exercise in AD remains to be determined.

5.2. Current Spatial and Cellular Resolution of the Evidence

Spatial resolution differs across the three AD exercise studies in the primary corpus and limits straightforward biological pooling. Belaya et al. [23] assessed cortical iron regulation, Choi et al. [24] focused on motor-cortex iron/oxidative outcomes, and Li et al. [15] assessed prefrontal ferroptosis-related endpoints. Matched multi-region, cell-resolved comparison within the same AD exercise experiment remains scarce. Accordingly, a favorable regional average has limited generalizability to hippocampal, white-matter, vascular, or cell-specific

ferroptotic injury, and differences across studies may partly reflect anatomical sampling rather than mechanism.

Cell-type evidence also remains indirect for AD exercise. Astrocytic FTH1/SAT1 findings in AD tissue and oligodendrocyte-centered exercise findings in aging models demonstrate why tissue-level iron or lipid signals may have different cellular meanings [29,30]. These observations identify candidate cell populations, while AD exercise-specific attribution of the vulnerable cell population remains to be established. The present direct corpus therefore supports a cautious interpretation of cell-specific ferroptotic execution.

5.3. Temporal Ordering: Current Evidence and Remaining Needs

For a pathway to mediate an exercise effect, the proposed mediator should change before the downstream protection it is claimed to explain. The AD exercise studies in the primary corpus are dominated by terminal molecular measurements, so a late GPX4, iron, or lipid-peroxidation readout provides limited ability to distinguish an initiating mediator from a correlate of healthier surviving tissue. This temporal ambiguity is independent of the number of markers measured.

The same limitation is visible in supporting models, where many ferroptosis-related endpoints are sampled at terminal or sparsely spaced time points [17,18,30]. Acute, early-training, and established training states are biologically distinct; with sparse ordered sampling, separation of mediation from parallel adaptation remains challenging.

5.4. Causal Dependence: Evidence Needed for Mechanistic Validation

In AD, the key experiment extends beyond perturbation of a ferroptosis-related regulator and should distinguish pathway participation from ferroptosis-mediated neuroprotection. For example, NRF2 loss could attenuate an exercise benefit because NRF2 regulates many stress-response programs unrelated to ferroptosis. A convincing test should therefore determine sequentially whether exercise changes the candidate node, whether that change modifies ferroptotic cell death in the relevant cell population, and whether the change in ferroptosis explains the functional benefit. The preferred design is factorial: exercise versus sedentary conditions crossed with pathway perturbation versus control, with a formal exercise-by-perturbation interaction. If the perturbation independently worsens baseline disease, a simple exercise-versus-exercise-plus-perturbation contrast provides limited specificity because an adverse perturbation main effect can resemble selective interruption of the exercise mechanism. Mechanism-specific rescue should be positioned downstream of the disrupted step and should restore the ferroptosis phenotype and, where expected, the functional benefit while preserving the interpretability of unrelated exercise adaptations.

The perturbation studies from other disease or injury contexts described in Section 4.4 illustrate the additional information gained when a mediator is manipulated rather than merely measured [17,18]. Their relevance here is methodological. To date, the primary AD exercise corpus provides limited examples combining ferroptosis-specific cell-death evidence, temporal ordering, and a factorial exercise-by-perturbation dependency test within the same experiment. Figure 2 therefore distinguishes engagement of the NRF2/SLC7A11/GPX4 axis from the stronger claim that ferroptosis mediates exercise-induced neuroprotection.

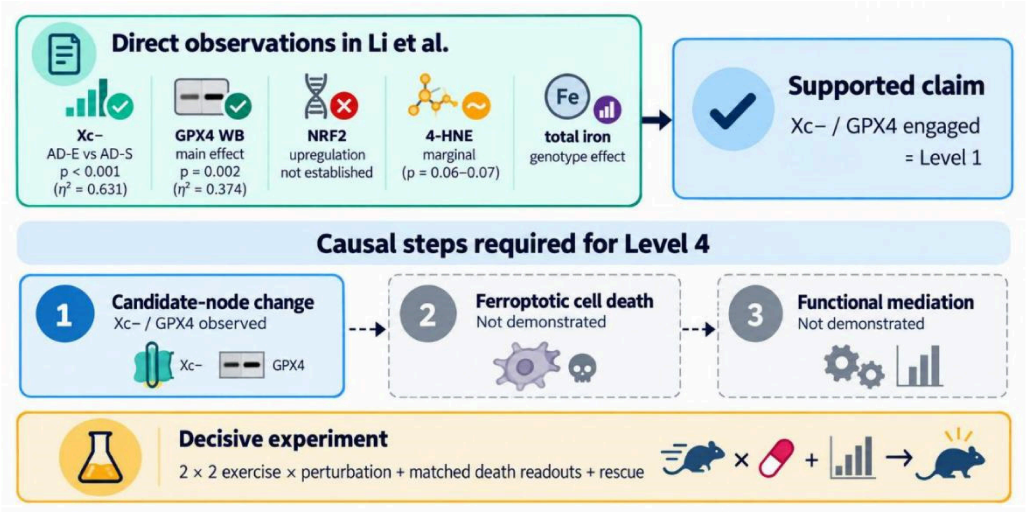


Figure 2. Evidence map for the proposed exercise–ferroptosis mechanism in AD. The Xc− result represents an AD-E versus AD-S comparison, whereas the GPX4 increase represents an exercise main effect with broader statistical scope than an AD-specific simple effect. Total iron reflects a genotype effect, 4-HNE findings are marginal, and NRF2 exercise-related upregulation remains statistically uncertain. Progression to stronger causal inference requires matched ferroptotic cell-death evidence, an exercise-by-perturbation interaction, and appropriately positioned rescue. The study shown in the figure is Li et al. [15]. Solid arrows indicate directional relations depicted within the figure, whereas dashed arrows denote proposed evidentiary progression that requires additional validation.

5.5. Metabolic–Inflammatory Crosstalk and Peripheral-to-Brain Signaling

Peripheral-to-brain signaling is relevant because exercise generates systemic signals outside the central nervous system. Exerkines, extracellular vesicles, metabolites, and non-coding RNAs can influence vascular function, inflammation, redox balance, and membrane lipid metabolism, while the extent to which an exercise-associated circulating factor reaches the relevant brain region and acts through ferroptosis may vary. BDNF is responsive to exercise in AD models [45], whereas some TrkB modulators also show receptor-independent radical-trapping activity [16], complicating pathway attribution. FNDC5/irisin has a similarly partial evidence profile: irisin reduced high-glucose-induced ferroptosis in HT22 cells while preserving GSH and GPX4 [20], and exercise-induced irisin has been linked to broader neurorepair contexts [46]. Together, these observations support biological plausibility, while an AD-specific exercise-to-brain ferroptosis pathway requires direct testing.

MicroRNAs provide another plausible relay, while the AD exercise evidence remains indirect. AD studies identify ferroptosis-related miRNA networks [47,48], and miR-30a-5p/SIRT1/NRF2 has been linked to hippocampal ferroptosis in chronic cerebral hypoperfusion independent of exercise [49]. The strongest exercise-related example is the miR-484/ACSL4 study in cerebral ischemia [18]. Evidence tracing a peripheral mediator from its source to brain target engagement and then testing the effect of mediator blockade in an AD exercise model remains scarce. Figure 3 summarizes the four biological domains while keeping these differences in evidence strength visible.

For readers less familiar with causal-inference terminology, Figure 3 provides a single integrated overview of the framework: it aligns the major metabolic domains with the current Level 1–2 AD evidence and visually identifies the additional links needed for Level 3 ferroptotic execution, Level 4 exercise-specific mediation, and peripheral-to-brain translation.

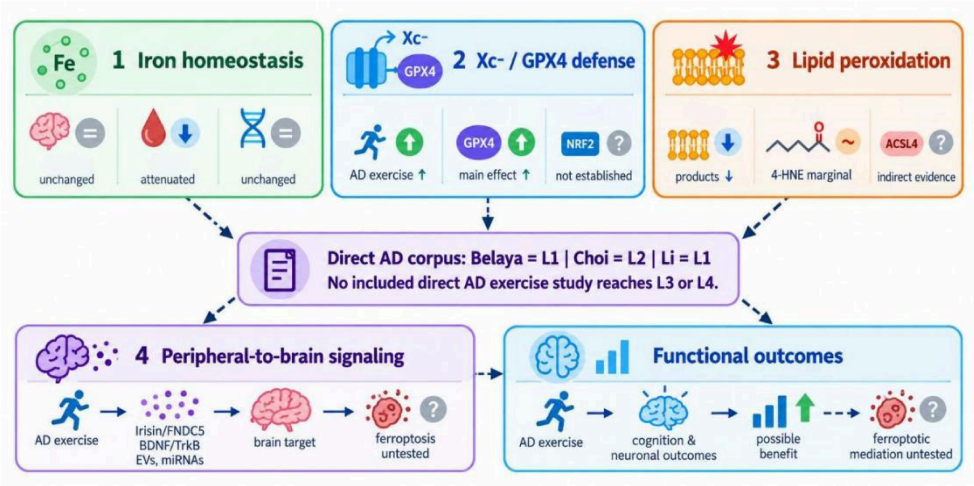


Figure 3. Integrated graphical summary of the evidence hierarchy and current knowledge gaps for exercise-responsive metabolic regulation of ferroptosis-related biology in AD. The GPX4 upward arrow denotes an exercise main effect with broader statistical scope than an AD-specific simple effect; the triangle denotes a vulnerability-consistent marker profile; question marks denote areas where evidence remains limited; and "evidence pending" indicates an evidentiary step that remains to be established rather than mechanistic refutation. Current AD exercise evidence remains concentrated at Levels 1–2. Evidence hierarchy: Level 1 response → Level 2 vulnerability-consistent profile → Level 3 ferroptotic execution → Level 4 exercise-specific mediation. Study labels correspond to Belaya et al. [23], Choi et al. [24], and Li et al. [15]. Arrows indicate directional organization of the proposed pathways; dashed arrows denote cross-domain or inferential links whose causal status remains to be established.

6. Research Priorities for Establishing Causal and Translational Validation

6.1. Experimental Standards for Causal Validation

Future causal studies should combine exercise, multi-domain ferroptosis phenotyping, temporal ordering, and a mechanism-specific dependency test in the same experimental program. Iron handling is better represented by labile or spatially resolved measures than by total iron alone; antioxidant defense should include SLC7A11, GSH/GSSG, and GPX4 activity; and lipid injury should be defined with phospholipid-peroxide or lipidomic readouts. These molecular endpoints should be linked to cell-resolved death in addition to nonspecific injury. Candidate-node manipulation (for example, NRF2, FPN, TfR1, ferritinophagy, GPX4, SLC7A11, or ACSL4) should be embedded in an exercise-by-perturbation factorial design. A significant perturbation main effect alone provides limited evidence that the node mediates exercise. Mediation is strengthened when the exercise effect on ferroptotic death is selectively attenuated under perturbation, when temporal ordering places the ferroptosis change before downstream protection, and when an appropriately positioned rescue restores the interrupted ferroptosis phenotype and functional outcome. Manipulation of pleiotropic nodes should therefore be paired with ferroptosis-specific death readouts so that mediation claims are supported by greater mechanistic specificity.

Competing injury programs should be measured in the same design where feasible. Apoptosis, pyroptosis, senescence, inflammation, mitochondrial dysfunction, and vascular injury can coexist with ferroptosis-related changes [5,6]. Transparent reporting is equally important: allocation procedures, blinded outcome assessment, attrition, adherence, adverse events, physiological exercise dose, and clearly defined ferroptosis endpoints should be reported explicitly. Sharing raw behavioral, molecular, and lipidomic values would also

improve cross-study comparison. Supplementary Table S2 summarizes the most informative next tests for the major candidate domains.

6.2. Model, Regional, and Cellular Heterogeneity

Model choice limits transferability. Acute ischemia and traumatic brain injury generate abrupt membrane disruption, iron release, and inflammatory activation, whereas AD develops through prolonged amyloid, tau, vascular, and metabolic stress [2,3,17,18]. Available animal models capture complementary components of human disease, while each differs from sporadic AD in pathology, time course, and systemic context [50]. Convergence across complementary models is therefore more informative than repeated confirmation in one strain, particularly when the proposed mediator is expected to vary with disease stage.

Anatomical and cellular heterogeneity requires the same caution. The prefrontal cortex provides the clearest direct exercise ferroptosis signal [15], yet hippocampal, white-matter, and vascular adaptations may contribute independently, especially during aging [30]. Multi-region studies can test whether a response is shared or compartment-specific rather than averaging biologically distinct tissues. Single-cell or spatial transcriptomics can nominate susceptible populations, but protein activity and lipid oxidation still require direct validation, ideally with cell-specific manipulation. Host factors such as sex, APOE genotype, metabolic status, medication exposure, and baseline fitness are plausible effect modifiers and should be defined prospectively when they are relevant to the model or clinical cohort.

6.3. Exercise Dose, Timing, and Sampling Standardization

Exercise protocols should report physiological dose rather than relying on a session label. AD-relevant outcomes vary with training load [33], and exercise intensity can alter redox adaptation [35]. Frequency, relative intensity, session duration, modality, progression, total workload, adherence, and the interval between the final bout and tissue collection should be specified. Absolute treadmill speed has limited equivalence as a relative-intensity measure across animals that differ in age, genotype, fitness, or disease burden; oxygen consumption, lactate, running capacity, heart rate where feasible, or workload normalized to baseline performance can help verify the intended exposure.

Sampling schedules should distinguish acute responses from training adaptation. Tissue collected immediately after exercise may capture transient oxidative stress and metabolite flux, whereas a washout period may better represent the trained state while providing less visibility into an initiating signal [13,14,22,35]. Acute, early-training, and chronic time points are therefore complementary. The term ‘longitudinal’ is best interpreted carefully because destructive brain sampling generally relies on prospectively defined terminal cohorts at different time points. Behavior, selected blood measures, and some imaging outcomes can be repeated within subjects, whereas brain lipidomics, cell-resolved injury/death measurements, labile-iron assays, and most biochemical analyses generally require staggered terminal cohorts. A rigorous design can therefore combine repeated non-destructive measures with staggered terminal cohorts so that the same core domains—iron localization, SLC7A11/GSH, GPX4 abundance and activity, defined lipid-peroxide products, ACSL4 or lipidomic measures, cell-resolved death, and cognition—are aligned across time. Antibody specificity, tissue handling, ex vivo oxidation, and normalization should also be standardized because technical variation can mimic biological disagreement.

6.4. Human Translation, Tissue Correspondence, and Biomarker Development

The translational challenge centers on uncertainty about what blood measurements represent in the brain. Current fluid-biomarker frameworks for neurodegenerative disease emphasize established signals such as amyloid-beta, phosphorylated tau, and markers of

neuronal injury [51]. By contrast, available ferroptosis-related signatures in hippocampal tissue and peripheral blood remain discovery-stage candidates [52,53], and direct validation of a peripheral marker against cell-resolved ferroptotic injury in the AD brain remains limited. Serum MDA, 4-hydroxynonenal, GPX4 activity, ferritin, and related gene signatures may also be influenced by systemic metabolism, inflammation, diet, muscle activity, and vascular disease. These measures are therefore best interpreted as exploratory correlates until central tissue correspondence is demonstrated. The searches yielded an animal-based eligible AD exercise corpus, highlighting a substantial opportunity for human studies using ferroptosis-relevant endpoints.

In human AD, the four-level framework can be used as a staged biomarker-development roadmap rather than as a diagnostic label. Candidate peripheral measures—including iron-related indices, GSH/GSSG, GPX4 activity, lipid-peroxidation products, targeted lipidomic or oxidized-phospholipid readouts, and exercise-responsive circulating signals—should initially be treated as exploratory Level 1-type responses. Because exercise simultaneously alters muscle, vascular, immune, and systemic metabolic compartments, peripheral signals are best interpreted as candidate indicators whose relevance to brain ferroptosis-related biology strengthens when they are linked prospectively to established AD fluid biomarkers, neuroimaging, cognition, or other validated indicators of neuronal injury [51–53]. Peripheral-to-central correspondence would strengthen biomarker validity and motivate direct central testing of a Level 2 vulnerability-consistent profile; it should not, by itself, be treated as a brain Level 2 assignment.

A practical translation sequence has three stages. Stage 1 should establish feasibility and response reproducibility using a standardized, physiologically verified exercise prescription, adherence monitoring, repeated sampling, and a multidomain panel spanning iron handling, GSH/GSSG, GPX4 activity, and lipid-peroxidation/lipidomic readouts. Stage 2 should test peripheral-to-central correspondence by relating reproducible peripheral changes to established AD biomarkers, neuroimaging, cognition, and other validated neuronal-injury measures. Stage 3 should test mechanistic necessity in complementary experimental systems using temporally ordered exercise-by-perturbation designs with ferroptosis-specific dependency/rescue. Human longitudinal mediation analyses may strengthen temporal inference, while Level 3 or Level 4 interpretation would require direct evidence for ferroptotic execution and exercise-specific mediation. This staged strategy supports biomarker development and reduces the risk that nonspecific oxidative-stress signals are overinterpreted as ferroptotic cell death.

6.5. Methodological Limitations of the Present Review

The present review has limitations that warrant a cautious interpretation of its claims. First, it is a structured critical reappraisal with a retrospectively documented search process rather than a prospectively preregistered systematic review. The original project preserved only part of the record-level audit trail for database-specific retrieval totals, duplicate counts, deduplication procedures, reviewer participation across historical screening stages, and full-text exclusions. These gaps remain a material reproducibility limitation and constrain reconstruction of a complete historical screening flow. Independent verification is therefore strongest for the executable three-database search strategies through 31 July 2026 (Supplementary Table S9), structured bridge-search strategies (Supplementary Table S8), study-level extraction/classification (Supplementary Table S5), and the update/currency-check information retained in Supplementary Table S10. The four candidate records listed for 31 October represent the verifiable subset retained from that check, while a full three-database rerun fell outside the scope of the revision-stage audit. Second, the AD exercise evidence base comprises three animal studies with important reporting and risk-of-bias uncertainty.

For Choi et al. [24], figure-level post hoc annotations support the relevant exercise-group contrasts, while the reported $n = 6$/group assay size and $F(3,23)$ denominator remain analytically inconsistent under a conventional balanced four-group one-way ANOVA. Across the animal corpus, many SYRCLE domains are rated Unclear because source reports provide limited procedural detail; these judgments indicate uncertainty rather than demonstrated high risk. Third, the four-level ladder is author-developed, non-preregistered, retrospectively applied, and requires independent evaluation of reproducibility and external validity. Fourth, the article intentionally shares biological domains and some supporting studies with our recent cross-disease review [22]; its separate contribution rests on endpoint-level AD reanalysis, explicit decision rules, changed study assignments, and study-level appraisal rather than disease narrowing alone. Fifth, bridge evidence from ischemia, TBI, aging, environmental enrichment, and cellular models serves a supportive role with lower directness than AD-specific exercise evidence. Collectively, these considerations support a hypothesis-generating interpretation and favor cautious generalization across exercise modalities, AD stages, brain regions, sexes, and humans pending direct validation.

7. Conclusions

The identified AD exercise corpus meeting ferroptosis-relevant endpoint criteria is small and therefore supports cautious mechanistic inference. Three animal studies met the primary-corpus definition: Belaya et al. and Li et al. are classified as Level 1, whereas Choi et al. is provisionally classified as marker-based Level 2. Current evidence remains concentrated at Levels 1–2, with ferroptotic execution and exercise-specific mechanistic mediation requiring further direct evaluation. For Choi et al., Level 2 denotes a vulnerability-consistent metabolic profile, and confidence is tempered by assay-specific n/df reporting uncertainty despite source-figure support for the relevant exercise-group contrasts. A conservative sensitivity interpretation placing Choi et al. at Level 1 would preserve the central conclusion that the current corpus does not yet satisfy Level 3 or Level 4 criteria. Individual studies report changes in selected iron-regulatory, antioxidant, or lipid-peroxidation endpoints, while consistency across models, brain regions, disease stages, and exercise prescriptions remains limited. Confidence is further tempered by the three-study animal evidence base and predominantly Unclear risk-of-bias domains. Accordingly, the proposed exercise–ferroptosis relationship is best viewed as a hypothesis-generating metabolic framework whose clinical relevance requires further validation. Exercise studies from other disease contexts and mechanistic studies using other exposures remain useful for experimental design and target tractability, while direct confirmation in AD requires AD-specific testing.

The most informative next studies will connect a verified physiological exercise dose with temporally ordered, region- and cell-resolved metabolic and ferroptosis phenotyping, including labile iron, GPX4 activity, GSH/GSSG, and defined phospholipid-peroxide or lipidomic endpoints. Mechanistic necessity should then be tested in factorial exercise-by-perturbation designs with ferroptosis-specific dependency/rescue and matched functional outcomes. In human studies, the framework should be used as a staged biomarker-development tool: peripheral multidomain responses should be linked to central or established AD measures before being interpreted mechanistically, and interpretation as ferroptotic execution or mediation becomes more defensible after direct validation. At present, ferroptosis is best treated as a candidate exercise-responsive metabolic mechanism for direct causal testing, with clinical exercise-prescription relevance requiring further evidence.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/metabo16110909/s1: Table S1. Core metabolic regulatory domains of ferroptotic vulnerability in AD and their evidentiary limits; Table S2. Evidence boundaries and decisive experiments for proposed exercise–ferroptosis pathways in AD; Table S3. Minimum design

and reporting framework for future AD exercise–ferroptosis studies; Table S4. Operational criteria for the four inferential evidence levels; Table S5. Study-level evidence matrix for AD exercise studies meeting ferroptosis-relevant endpoint criteria operationally defined for the present reappraisal and all primary studies formally classified as bridge or contextual evidence in the causal appraisal; Table S6. Descriptive SYRCLE risk-of-bias appraisal of animal studies formally classified in Supplementary Table S5; cell-only studies are not applicable; Table S7. Study-level reporting features relevant to mechanistic interpretation; Table S8. Complete bridge-search strategy used for the structured literature search (31 July 2026); Table S9. Complete primary database search strategies used for the structured literature search (31 July 2026); Table S10. Available search/screening audit records and explicit exclusion criteria. References cited in Tables S1–S10 are included in the main reference list and retain the same numbering.

Author Contributions: Conceptualization, H.H., M.H. and Y.S.; methodology, H.H., M.H. and S.L.; investigation and literature curation, H.H. and M.H.; resources, X.H. and Y.S.; writing—original draft preparation, H.H. and M.H.; writing—review and editing, S.L., X.H. and Y.S.; visualization, H.H. and M.H.; supervision, Y.S.; project administration, Y.S. All authors have read and agreed to the published version of the manuscript. H.H. and M.H. contributed equally to this work and share first authorship.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: This review generated study-level extraction and appraisal information from published sources; these materials are provided in the article and Supplementary Materials, while underlying primary data remain available in the cited source publications.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACSL4	acyl-CoA synthetase long-chain family member 4
AD	Alzheimer's disease
APOE	apolipoprotein E
APP/PS1	amyloid precursor protein/presenilin 1
Aβ	amyloid-beta
BDNF	brain-derived neurotrophic factor
DMT1	divalent metal transporter 1
Fe^{2+}	ferrous iron
FNDC5	fibronectin type III domain-containing protein 5
FPN	ferroportin
FTH1	ferritin heavy chain 1
GPX4	glutathione peroxidase 4
GSH	glutathione
GSSG	oxidized glutathione
MDA	malondialdehyde
miR-484	microRNA-484
NRF2	nuclear factor erythroid 2-related factor 2
SIRT1	sirtuin 1
SLC7A11	solute carrier family 7 member 11
SLC3A2	solute carrier family 3 member 2
STING	stimulator of interferon genes
system Xc−	cystine/glutamate antiporter system
TfR1	transferrin receptor 1
TrkB	tropomyosin receptor kinase B

References

1. Alzheimer's Association. 2026 Alzheimer's Disease Facts and Figures. *Alzheimer's Amp Dement.* **2026**, *22*, e71345. [CrossRef]
2. Fang, Y.; Han, Z.; Yang, S.; Chen, J.; Li, R.; Zhang, Z.; Song, J.; Wang, D.; Ban, Y. Ferroptosis and Alzheimer's Disease: Unraveling the Molecular Mechanisms and Therapeutic Opportunities. *Front. Cell Dev. Biol.* **2026**, *14*, 1758041. [CrossRef] [PubMed]
3. Quan, Y.; Liu, H.; Zhang, M.; Li, M.; He, B.; Wang, K.; Huang, X.; Zhou, S.; Han, Z.; Fan, H. Ferroptosis and Alzheimer's Disease: A New Insight into Neurodegeneration. *Front. Immunol.* **2026**, *17*, 1701767. [CrossRef] [PubMed]
4. Yang, Y.; Yang, F.; Yao, M.; Li, L.; Li, H. Decoding the Key Mechanisms of Ferroptosis and Inflammation: Emerging Therapeutic Targets for Alzheimer's Disease. *J. Alzheimer's Dis.* **2026**, *110*, 1584–1601. [CrossRef] [PubMed]
5. Zhang, Y.; Zhang, D.; Xiao, H. Regulated Neuronal Death in Alzheimer's Disease: Crosstalk and Convergence of Apoptosis, Pyroptosis, Senescence, and Ferroptosis. *J. Alzheimer's Dis.* **2026**, *111*, 32–55. [CrossRef] [PubMed]
6. Wang, Q.; Sun, J.; Chen, T.; Song, S.; Hou, Y.; Feng, L.; Fan, C.; Li, M. Ferroptosis, Pyroptosis, and Cuproptosis in Alzheimer's Disease. *ACS Chem. Neurosci.* **2023**, *14*, 3564–3587. [CrossRef] [PubMed]
7. Yeerlan, J.; He, B.; Hu, X.; Zhang, L. Global Research Trends and Hotspots for Ferroptosis, Necroptosis, and Pyroptosis in Alzheimer's Disease from the Past to 2023: A Combined Bibliometric Review. *J. Alzheimer's Dis. Rep.* **2024**, *8*, 129–142. [CrossRef] [PubMed]
8. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death. *Cell* **2012**, *149*, 1060–1072. [CrossRef] [PubMed]
9. Dixon, S.J.; Olzmann, J.A. The Cell Biology of Ferroptosis. *Nat. Rev. Mol. Cell Biol.* **2024**, *25*, 424–442. [CrossRef] [PubMed]
10. Ashraf, A.; Jeandriens, J.; Parkes, H.G.; So, P.-W. Iron Dyshomeostasis, Lipid Peroxidation and Perturbed Expression of Cystine/Glutamate Antiporter in Alzheimer's Disease: Evidence of Ferroptosis. *Redox Biol.* **2020**, *32*, 101494. [CrossRef] [PubMed]
11. Lane, D.J.R.; Metselaar, B.; Greenough, M.; Bush, A.I.; Ayton, S.J. Ferroptosis and NRF2: An Emerging Battlefield in the Neurodegeneration of Alzheimer's Disease. *Essays Biochem.* **2021**, *65*, 925–940. [CrossRef] [PubMed]
12. Lu, X.; Moeini, M.; Li, B.; De Montgolfier, O.; Lu, Y.; Bélanger, S.; Thorin, É.; Lesage, F. Voluntary Exercise Increases Brain Tissue Oxygenation and Spatially Homogenizes Oxygen Delivery in a Mouse Model of Alzheimer's Disease. *Neurobiol. Aging* **2020**, *88*, 11–23. [CrossRef] [PubMed]
13. Hao, Z.; Guo, X.; Wu, J. Revisiting the Benefits of Exercise for Alzheimer's Disease through the Lens of Ferroptosis: A New Perspective. *Aging Dis.* **2024**, *16*, 3268–3283. [CrossRef] [PubMed]
14. Li, X.; Guo, Z.; Li, Q.; Li, C.; Zhang, X. Potential Mechanisms of Exercise-Mediated Ferroptosis Regulation in Central Nervous System Diseases. *Mol. Neurobiol.* **2026**, *63*, 198. [CrossRef] [PubMed]
15. Li, C.; Cui, K.; Zhu, X.; Wang, S.; Yang, Q.; Fang, G. 8-Weeks Aerobic Exercise Ameliorates Cognitive Deficit and Mitigates Ferroptosis Triggered by Iron Overload in the Prefrontal Cortex of APPSwe/PSEN1dE9 Mice through Xc−/GPx4 Pathway. *Front. Neurosci.* **2024**, *18*, 1453582. [CrossRef] [PubMed]
16. Jakaria, M.; Belaidi, A.A.; Southon, A.; Dent, K.A.; Lane, D.J.R.; Bush, A.I.; Ayton, S. Receptor-Independent Anti-Ferroptotic Activity of TrkB Modulators. *Int. J. Mol. Sci.* **2022**, *23*, 16205. [CrossRef] [PubMed]
17. Chen, J.; Zhu, T.; Yu, D.; Yan, B.; Zhang, Y.; Jin, J.; Yang, Z.; Zhang, B.; Hao, X.; Chen, Z.; et al. Moderate Intensity of Treadmill Exercise Rescues TBI-Induced Ferroptosis, Neurodegeneration, and Cognitive Impairments via Suppressing STING Pathway. *Mol. Neurobiol.* **2023**, *60*, 4872–4896. [CrossRef] [PubMed]
18. Huang, M.; Cheng, S.; Li, Z.; Chen, J.; Wang, C.; Li, J.; Zheng, H. Preconditioning Exercise Inhibits Neuron Ferroptosis and Ameliorates Brain Ischemia Damage by Skeletal Muscle-Derived Exosomes via Regulating miR-484/ACSL4 Axis. *Antioxid. Redox Signal.* **2024**, *41*, 769–792. [CrossRef] [PubMed]
19. Thirupathi, A.; Marqueze, L.F.; Outeiro, T.F.; Radak, Z.; Pinho, R.A. Physical Exercise-Induced Activation of NRF2 and BDNF as a Promising Strategy for Ferroptosis Regulation in Parkinson's Disease. *Neurochem. Res.* **2024**, *49*, 1643–1654. [CrossRef] [PubMed]
20. Yang, L.; Zhou, X.; Heng, T.; Zhu, Y.; Gong, L.; Liu, N.; Yao, X.; Luo, Y. FNDC5/Irisin Mitigates High Glucose-Induced Neurotoxicity in HT22 Cell *via* Ferroptosis. *BST* **2024**, *18*, 465–475. [CrossRef] [PubMed]
21. Tang, S.; Zhang, J.; Chen, J.; Zhou, Z.; Lin, Q. Ferroptosis in Neurodegenerative Diseases: Potential Mechanisms of Exercise Intervention. *Front. Cell Dev. Biol.* **2025**, *13*, 1622544. [CrossRef] [PubMed]
22. Han, M.; Huang, H.; Yuan, X.; Fan, P.; Li, M. Exercise and Ferroptosis in Neurodegenerative Diseases: Direct Evidence, Mechanistic Links, and Translational Gaps. *Int. J. Mol. Sci.* **2026**, *27*, 6628. [CrossRef] [PubMed]
23. Belaya, I.; Kucháriková, N.; Górová, V.; Kysenius, K.; Hare, D.J.; Crouch, P.J.; Malm, T.; Atalay, M.; White, A.R.; Liddell, J.R.; et al. Regular Physical Exercise Modulates Iron Homeostasis in the 5xFAD Mouse Model of Alzheimer's Disease. *IJMS* **2021**, *22*, 8715. [CrossRef] [PubMed]
24. Choi, D.-H.; Kwon, K.-C.; Hwang, D.-J.; Koo, J.-H.; Um, H.-S.; Song, H.-S.; Kim, J.-S.; Jang, Y.; Cho, J.-Y. Treadmill Exercise Alleviates Brain Iron Dyshomeostasis Accelerating Neuronal Amyloid-β Production, Neuronal Cell Death, and Cognitive Impairment in Transgenic Mice Model of Alzheimer's Disease. *Mol. Neurobiol.* **2021**, *58*, 3208–3223. [CrossRef]

25. Hooijmans, C.R.; Rovers, M.M.; De Vries, R.B.; Leenaars, M.; Ritskes-Hoitinga, M.; Langendam, M.W. SYRCLE's Risk of Bias Tool for Animal Studies. *BMC Med. Res. Methodol.* **2014**, *14*, 43. [CrossRef] [PubMed]
26. Chen, X. Decoding GPX4 Regulation in Ferroptosis: Mechanisms and Therapeutic Implications. *Trends Mol. Med.* **2026**, *32*, 792–809. [CrossRef]
27. Bao, W.-D.; Pang, P.; Zhou, X.-T.; Hu, F.; Xiong, W.; Chen, K.; Wang, J.; Wang, F.; Xie, D.; Hu, Y.-Z.; et al. Loss of Ferroportin Induces Memory Impairment by Promoting Ferroptosis in Alzheimer's Disease. *Cell Death Differ.* **2021**, *28*, 1548–1562. [CrossRef] [PubMed]
28. Wang, H.; Mao, W.; Zhang, Y.; Feng, W.; Bai, B.; Ji, B.; Chen, J.; Cheng, B.; Yan, F. NOX1 Triggers Ferroptosis and Ferritinophagy, Contributes to Parkinson's Disease. *Free Radic. Biol. Med.* **2024**, *222*, 331–343. [CrossRef]
29. Dang, Y.; He, Q.; Yang, S.; Sun, H.; Liu, Y.; Li, W.; Tang, Y.; Zheng, Y.; Wu, T. FTH1- and SAT1-Induced Astrocytic Ferroptosis Is Involved in Alzheimer's Disease: Evidence from Single-Cell Transcriptomic Analysis. *Pharmaceuticals* **2022**, *15*, 1177. [CrossRef] [PubMed]
30. Gutierre, R.C.; Rocha, P.R.; Graciani, A.L.; Coppi, A.A.; Arida, R.M. Tau, Amyloid, Iron, Oligodendrocytes Ferroptosis, and Inflammaging in the Hippocampal Formation of Aged Rats Submitted to an Aerobic Exercise Program. *Brain Res.* **2025**, *1850*, 149419. [CrossRef] [PubMed]
31. Majerníková, N.; Marmolejo-Garza, A.; Salinas, C.S.; Luu, M.D.A.; Zhang, Y.; Trombetta-Lima, M.; Tomin, T.; Birner-Gruenberger, R.; Lehtonen, Š.; Koistinaho, J.; et al. The Link between Amyloid β and Ferroptosis Pathway in Alzheimer's Disease Progression. *Cell Death Dis.* **2024**, *15*, 782. [CrossRef]
32. Liu, A.; Xing, L.; Li, J.; Yao, M.; Song, J.; Guo, W.; Duan, P.; Li, H. The Interplay between Mitophagy and Ferroptosis in Alzheimer's Disease: Mechanisms and Therapeutic Implications. *J. Alzheimer's Dis.* **2026**, *110*, 1022–1037. [CrossRef] [PubMed]
33. Moore, K.M.; Girens, R.E.; Larson, S.K.; Jones, M.R.; Restivo, J.L.; Holtzman, D.M.; Cirrito, J.R.; Yuede, C.M.; Zimmerman, S.D.; Timson, B.F. A Spectrum of Exercise Training Reduces Soluble Aβ in a Dose-Dependent Manner in a Mouse Model of Alzheimer's Disease. *Neurobiol. Dis.* **2016**, *85*, 218–224. [CrossRef] [PubMed]
34. Yu, Y.; Chen, K. Exercise Mitigates Alzheimer's Disease by Targeting Ferroptosis Driven by Cellular Senescence. *Front. Cell Dev. Biol.* **2026**, *13*, 1742209. [CrossRef] [PubMed]
35. Meng, Q.; Su, C.-H. The Impact of Physical Exercise on Oxidative and Nitrosative Stress: Balancing the Benefits and Risks. *Antioxidants* **2024**, *13*, 573. [CrossRef] [PubMed]
36. Fan, B.; Zhang, Y.; Luo, Q.; Hao, C.; Liao, W. Physical and Social Environmental Enrichment Alleviate Ferroptosis and Inflammation with Inhibition of TLR4/MyD88/p38MAPK Pathway in Chronic Cerebral Hypoperfusion Rats. *Brain Res. Bull.* **2024**, *208*, 110897. [CrossRef] [PubMed]
37. Do Van, B.; Gouel, F.; Jonneaux, A.; Timmerman, K.; Gelé, P.; Pétrault, M.; Bastide, M.; Laloux, C.; Moreau, C.; Bordet, R.; et al. Ferroptosis, a Newly Characterized Form of Cell Death in Parkinson's Disease That Is Regulated by PKC. *Neurobiol. Dis.* **2016**, *94*, 169–178. [CrossRef] [PubMed]
38. Li, L.; Li, W.-J.; Zheng, X.-R.; Liu, Q.-L.; Du, Q.; Lai, Y.-J.; Liu, S.-Q. Eriodictyol Ameliorates Cognitive Dysfunction in APP/PS1 Mice by Inhibiting Ferroptosis via Vitamin D Receptor-Mediated Nrf2 Activation. *Mol. Med.* **2022**, *28*, 11. [CrossRef] [PubMed]
39. Deng, P.; Silva, M.; Yang, N.; Wang, Q.; Meng, X.; Ye, K.; Gao, H.; Zheng, W. Artemisinin Inhibits Neuronal Ferroptosis in Alzheimer's Disease Models by Targeting KEAP1. *Acta Pharmacol. Sin.* **2025**, *46*, 326–337. [CrossRef] [PubMed]
40. Yong, Y.; Yan, L.; Wei, J.; Feng, C.; Yu, L.; Wu, J.; Guo, M.; Fan, D.; Yu, C.; Qin, D.; et al. A Novel Ferroptosis Inhibitor, Thonningianin A, Improves Alzheimer's Disease by Activating GPX4. *Theranostics* **2024**, *14*, 6161–6184. [CrossRef] [PubMed]
41. Gong, K.; Zhou, S.; Xiao, L.; Xu, M.; Zhou, Y.; Lu, K.; Yu, X.; Zhu, J.; Liu, C.; Zhu, Q. Danggui Shaoyao San Ameliorates Alzheimer's Disease by Regulating Lipid Metabolism and Inhibiting Neuronal Ferroptosis through the AMPK/Sp1/ACSL4 Signaling Pathway. *Front. Pharmacol.* **2025**, *16*, 1588375. [CrossRef] [PubMed]
42. An, J.-R.; Su, J.-N.; Sun, G.-Y.; Wang, Q.-F.; Fan, Y.-D.; Jiang, N.; Yang, Y.-F.; Shi, Y. Liraglutide Alleviates Cognitive Deficit in Db/Db Mice: Involvement in Oxidative Stress, Iron Overload, and Ferroptosis. *Neurochem. Res.* **2022**, *47*, 279–294. [CrossRef] [PubMed]
43. Su, H.; Liu, Z.; Wei, J.; Liu, Y.; Zhong, Y.; Liu, X.; Tan, C.; Chen, L. PDK4 Suppresses High Glucose-Induced Microglial Ferroptosis by Restricting pro-Ferroptotic PUFA Biosynthesis. *NeuroReport* **2025**, *37*, 1–10. [CrossRef] [PubMed]
44. Yu, S.; Liu, W. Protective Effects of Salidroside against Ferroptosis through PPARG-Dependent Mechanism in Diabetes-Related Cognitive Impairment. *Exp. Neurol.* **2025**, *390*, 115261. [CrossRef] [PubMed]
45. Zhang, S.; Gu, B.; Zhen, K.; Du, L.; Lv, Y.; Yu, L. Effects of Exercise on Brain-Derived Neurotrophic Factor in Alzheimer's Disease Models: A Systematic Review and Meta-Analysis. *Arch. Gerontol. Geriatr.* **2024**, *126*, 105538. [CrossRef] [PubMed]
46. Song, H.; Jiang, Y.; Zhang, S.; Wu, C.; Deng, C.; Hu, W. Exercise-Induced Irisin: A Novel Strategy for Neuroinflammation Alleviation and Neurorepair in Diabetic Retinopathy. *IJMS* **2026**, *27*, 1849. [CrossRef] [PubMed]
47. Ramesh, M.; Govindaraju, T. MiR-7a–Klf4 Axis as a Regulator and Therapeutic Target of Neuroinflammation and Ferroptosis in Alzheimer's Disease. *NAR Mol. Med.* **2025**, *2*, ugaf022. [CrossRef] [PubMed]

48. Liu, W.; Rao, X.; Yu, L. Core Ferroptosis-Related Biomarkers and miRNA Regulatory Networks in Alzheimer's Disease. *Genes* **2026**, *17*, 224. [CrossRef] [PubMed]
49. Wang, L.; Li, M.; Liu, B.; Zheng, R.; Zhang, X.; Yu, S. miR-30a-5p Mediates Ferroptosis of Hippocampal Neurons in Chronic Cerebral Hypoperfusion-Induced Cognitive Dysfunction by Modulating the SIRT1/NRF2 Pathway. *Brain Res. Bull.* **2024**, *212*, 110953. [CrossRef] [PubMed]
50. Polis, B.; Samson, A.O. Addressing the Discrepancies Between Animal Models and Human Alzheimer's Disease Pathology: Implications for Translational Research. *JAD* **2024**, *98*, 1199–1218. [CrossRef] [PubMed]
51. Cao, Y.; Xu, Y.; Cao, M.; Chen, N.; Zeng, Q.; Lai, M.K.P.; Fan, D.; Sethi, G.; Cao, Y. Fluid-Based Biomarkers for Neurodegenerative Diseases. *Ageing Res. Rev.* **2025**, *108*, 102739. [CrossRef] [PubMed]
52. Wang, B.; Fu, C.; Wei, Y.; Xu, B.; Yang, R.; Li, C.; Qiu, M.; Yin, Y.; Qin, D. Ferroptosis-Related Biomarkers for Alzheimer's Disease: Identification by Bioinformatic Analysis in Hippocampus. *Front. Cell. Neurosci.* **2022**, *16*, 1023947. [CrossRef] [PubMed]
53. Wang, X.; Tian, Y.; Li, C.; Chen, M. Exploring the Key Ferroptosis-Related Gene in the Peripheral Blood of Patients with Alzheimer's Disease and Its Clinical Significance. *Front. Aging Neurosci.* **2022**, *14*, 970796. [CrossRef] [PubMed]

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