Exercise and dietary interventions in the regulation of hepatic mitophagy and liver recovery (Review)

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Abstract. The high metabolic demand of the liver renders it dependent on mitophagy for mitochondrial quality control. While exercise and nutritional interventions are known to influence hepatic mitophagy, the precise regulatory mechanisms remain incompletely understood. Mitophagy in the liver is influenced by a combination of exercise-related parameters, dietary factors and sex-specific biological factors. Drawing from 19 animal studies published between 2016 and 2026, the present narrative review examines how different exercise modalities and dietary interventions regulate hepatic mitophagy. Among models of obesity and metabolic dysfunction, structured endurance training and higher-intensity exercise protocols yield better capacity to re-establish coordinated mitochondrial quality control than voluntary or low-intensity physical activity protocols. Notably, a single bout of exercise can produce a transient elevation in mitophagic flux, whereas sustained training over time expands mitophagy capacity without necessarily maintaining heightened flux at rest. Moderate-intensity continuous training more effectively restores canonical PTEN-induced kinase 1/Parkin-dependent flux, whereas high-intensity interval training favors structural mitochondrial recovery and upstream energetic signaling, although the relative efficacy depends on the model, disease severity and readout assessed. In high-fat or Western dietary settings, mitophagy is often compromised, with exercise producing incomplete recovery unless paired with improved diet or weight loss. These responses are also influenced by sex differences: Females tend to maintain higher intrinsic mitochondrial quality with less inducible mitophagy, whereas males exhibit a greater reliance on exercise-induced activation of mitophagy. Paternal and maternal developmental programming has also emerged as an important modulator of mitophagy induction. In conclusion, mitophagy in the liver is modified by different exercise and dietary interventions in a manner that is further conditioned by sex and developmental history.

Contents

1. Introduction

As a major global health concern, non-alcoholic fatty liver disease (NAFLD), now termed metabolic dysfunction-associated steatotic liver disease (MASLD), is strongly associated with sedentary lifestyles and suboptimal dietary habits (1). High-fat, high-fructose, Western diets may promote lipid accumulation in the liver, while early-life nutritional insufficiency

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contributes to increased susceptibility to metabolic disease in later life (2,3). Despite the substantial differences in the nutritional profiles of high-fat/sucrose diets and nutritional insufficiency), both conditions result in hepatic mitochondrial dysfunction and defective mitochondrial quality control (4). The metabolic function of the liver depends on dynamic mitochondrial regulation that is affected by fluctuating nutrient availability (5). Lipid-induced oxidative stress in obesity or energy deprivation in malnutrition may contribute to hepatocellular injury and lead to non-alcoholic steatohepatitis (NASH) and fibrosis (6). Thus, preserving mitochondrial health through nutritional adjustments is key to maintaining normal liver function.

Mitochondrial health is maintained by mitophagy, which selectively degrades damaged or dysfunctional mitochondria in the liver (7). Efficient mitophagy in liver cells may prevent the accumulation of excess reactive oxygen species (ROS) and pro-apoptotic signaling (8). Two major mechanisms of mitophagy are the ubiquitin (Ub)-dependent pathways [PTEN-induced kinase 1 (PINK1) and Parkin] and receptor-dependent pathways [Bcl-2 interacting protein 3 (BNIP3), NIP3-like protein X (NIX; also known as BNIP3L) and FUN14 domain-containing protein 1 (FUNDC1)] (8,9). These pathways result in mitochondrial sequestration within autophagosomes, followed by lysosomal fusion that eventually leads to degradation and recycling of mitochondrial constituents (10). Mitophagic flux is commonly inferred from autophagic markers, including LC3 lipidation on autophagosome membranes and concomitant degradation of sequestome-1 (also known as p62) (11).

Mitochondrial renewal and quality control are strongly modulated by exercise (12). By promoting mitochondrial biogenesis through peroxisome proliferator-activated receptor (PPAR)γ coactivator 1-α (PGC-1α) and maintaining fusion-fission balance, exercise can modulate mitochondrial dynamics (13). A recent literature review reported that mitophagic flux is stimulated under certain conditions (14). In addition to exercise-induced effects, diet composition and overall energy balance influence mitophagy. Autophagy and mitophagy are activated by caloric restriction (CR) and fasting, and 24-h fasting strongly enhances BNIP3-associated mitophagy in the murine liver (15). Conversely, excessive high-calorie, high-fat intake impairs autophagy, which is evidenced by p62 accumulation and defective autophagic flux in the steatotic livers of obese animals and humans (16,17).

Biological sex and maternal or paternal programming are also recognized as modifiers of mitophagy in the liver. Sex-specific differences in mitochondrial function, hormone signaling and metabolic flexibility may influence basal mitophagy activity and its responsiveness to metabolic stress or exercise (18). Maternal and paternal nutritional status or physical activity before and during early development can also induce long-lasting metabolic programming effects that influence hepatic mitochondrial quality control later in life (19,20). The interplay of these variables likely accounts for much of the variability observed across experimental models, underscoring the need to account for sex and developmental background when drawing conclusions from mitophagy data.

Given the growing global burden of metabolic disease, understanding how exercise and nutritional factors jointly regulate mitophagy has become increasingly urgent. The present review examines the effect of different exercise modalities combined with nutritional interventions on hepatic mitophagy and liver recovery. Particular focus is placed on the PINK1/Parkin and BNIP3/NIX pathways, as well as tissue-specific, sex-related and intergenerational programming factors that help explain the variability observed across studies. Given that impaired mitochondrial quality control is a common pathogenic thread across steatotic, pharmacologically induced and other metabolic forms of liver injury, studies conducted outside the strict NAFLD/MASLD context are incorporated where they provide mechanistic insights relevant to the broader aims of the current review.

2. Literature review methodology

The literature search was conducted using PubMed (https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com), Cochrane (https://www.cochranelibrary.com) and Google Scholar (https://scholar.google.com) databases for articles published between March 2016 and May 2026. The search strategy combined key words related to mitochondrial quality control ('mitophagy', 'mitochondrial quality control'), liver disease ('non-alcoholic fatty liver disease', 'liver', 'metabolic-associated liver disease'), and interventions ('exercise', 'diet', 'fasting', 'caloric restriction'). The Boolean operators 'AND' and 'OR' were used to create the key word combinations. The study included only original articles that investigated mitophagy or mitochondrial quality control in the liver in relation to exercise with or without dietary or pharmacological interventions. Studies on non-liver tissues and non-English articles were excluded. Abstracts and titles were screened, followed by full-text assessment. Given the heterogeneity of models and outcomes, a narrative synthesis was adopted to integrate findings while highlighting mechanistic insights and knowledge gaps. A total of 19 articles were finally included in the present review (19,21-38).

3. Mechanistic pathways of mitophagy and their regulation by exercise and diet

Mitophagy begins with the sensing of dysfunctional mitochondria, progresses to autophagosome formation around the organelle and culminates in lysosomal degradation through a coordinated multistep process (8). Rather than functioning independently, Ub-dependent and receptor-mediated mitophagy pathways often cooperate to ensure efficient mitochondrial turnover (10). Different stress cues, such as hypoxia and mitochondrial depolarization, can activate BNIP3/NIX- and Parkin-mediated mitophagy, respectively, and converge on the same mitochondrial target (39). Both exercise and dietary interventions influence the balance and coordination of these mitophagy pathways (6,40).

The PINK1/Parkin pathway is activated by mitochondrial damage that stabilizes PINK1 on the outer membrane and drives Parkin-dependent ubiquitination of mitochondrial proteins, including voltage-dependent anion channel and mitofusin (MFN)2 (41). Adaptor proteins such as p62, neighbor of BRCA1 gene 1 protein (NBR1) and optineurin recognize Ub signals and link damaged mitochondria to LC3-positive

autophagosomes, which promote their degradation (11). p62 is degraded together with mitochondrial cargo, and its protein levels are commonly used as an indicator of mitophagic flux (11). Exercise is associated with increased LC3 lipidation and reduced p62 levels, which reflects active autophagic flux. However, high-fat feeding alone often results in hepatic p62 accumulation, which is consistent with disrupted mitochondrial turnover (16).

An alternative mitophagy pathway involves receptor-mediated processes that do not require Parkin activation (9). BNIP3 and NIX are stress-inducible proteins that respond to hypoxia, energetic stress and developmental cues by localizing to the mitochondrial outer membrane (39). These receptors link mitochondria directly to autophagosomes in a Ub-independent manner via LC3-interacting regions, while FUNDC1 adds further regulation through hypoxia-dependent phosphorylation (9). Exercise can swiftly engage receptor-mediated mitophagy, as BNIP3 levels rise in hepatic mitochondria immediately post-exercise (0 h), potentially preceding robust Parkin involvement (31). Consistent with this, several studies have reported that exercise preferentially activates BNIP3-dependent mitophagy rather than the Parkin pathway (42-44). In a weight-loss context, obese mice that exercised had marked upregulation of BNIP3 in the liver, which coincided with restoration of mitophagic flux, whereas diet-induced weight loss without exercise did not upregulate BNIP3 and yielded less mitophagy improvement (28). Thus, exercise performed under fasting conditions may engage receptor-mediated pathways more strongly than exercise during the fed state. These distinctions may partly explain inconsistencies among intervention studies.

These two pathway arms are linked by several bidirectional regulatory interactions rather than operating in parallel. BNIP3 interacts with PINK1 to inhibit its proteolytic cleavage, stabilizes PINK1 and reinforces Ub-dependent mitophagy. Conversely, Parkin can ubiquitinate NIX, and ubiquitinated NIX subsequently recruits NBR1 to further promote mitophagy (45). AMP-activated protein kinase (AMPK) adds further complexity: Beyond promoting unc-51-like autophagy activating kinase 1 (ULK1)-dependent autophagosome formation, AMPK can phosphorylate and stabilize BNIP3, directly linking energy sensing to receptor-mediated mitophagy independently of PINK1 (46,47). Nicotinamide adenine dinucleotide $(NAD)^+$-driven activation of sirtuin (SIRT)1, operating downstream of AMPK, links cellular energy status to mitophagy gene expression: SIRT1 deacetylates forkhead box O3 (FOXO3) to transcriptionally upregulate BNIP3 and LC3, while also targeting LC3 directly to facilitate autophagosome maturation (48,49). When engaged by exercise or fasting, these molecules [AMPK, SIRT1, FOXO3 and mammalian target of rapamycin (mTOR)] function as an integrated regulatory network governing both mitophagy arms in concert but not as independent switches. High-fat diet (HFD)-induced insulin resistance or lysosomal dysfunction can break down network coordination, explaining the paradoxical accumulation of upstream mitophagy markers alongside defective clearance commonly observed in NAFLD/MASLD (50).

Exercise intersects with the mitophagy machinery at more than one regulatory level. High-intensity exercise or prolonged endurance exercise can acutely stress mitochondria (such as through increased calcium cycling, ROS and fluctuations in membrane potential). In the liver, a single treadmill exercise bout does not immediately elevate Parkin on mitochondria, but evidence of Parkin-independent ubiquitination has emerged within ~2 h post-exercise (31). This Parkin-independent ubiquitination likely involves alternative E3 ligases, such as mitochondrial Ub ligase 1, which ubiquitinates mitochondrial substrates including MFN2 and ULK1 to facilitate mitophagic clearance independently of the canonical PINK1/Parkin axis (9,51). This suggests that mitochondrial disturbances during exercise may first activate receptor pathways (such as BNIP3) and engage PINK1/Parkin only later, if needed. ROS generated during exercise should not be viewed solely as harmful by-products; they serve as both triggers and effector molecules in the mitochondrial quality control pathways (45,52). Moderate increases in mitochondrial ROS serve as signaling molecules that stabilize PINK1 and activate BNIP3/NIX, whereas excessive ROS production due to accumulated defective mitochondria induces lipid peroxidation, inflammation and cell death (45,53).

Exercise training can induce the expression of autophagy and mitophagy-related genes (14,40). Endurance training elevates PGC-1α, which co-activates transcription factor EB and other transcription factors for lysosomal and autophagy genes (13). A previous study showed that chronic exercise increases hepatic BNIP3 protein concentration (24). Additionally, exercise can affect FOXO3 activity: FOXO3 is activated by endurance exercise and is known to transcriptionally induce BNIP3 and LC3 in skeletal muscle, linking exercise to increased autophagy gene expression (54). Diets also serve a role: Fasting increases BNIP3 expression in the liver and muscle via FOXO3 and hypoxia-inducible factor 1α (HIF-1α) signaling, whereas a HFD may downregulate BNIP3 (observed as ~30% lower BNIP3 protein in the livers of Western diet-fed mice) (22,55).

LC3-II levels, as a proxy for autophagosome formation, and downstream lysosomal clearance are responsive to exercise status and dietary composition (14). A recurring dissociation in metabolic liver disease is intact PINK1/Parkin signaling alongside blocked lysosomal clearance; doxorubicin-treated livers exemplify this, where exercise preconditioning restores mitochondrial function via SIRT3-mediated deacetylation rather than through enhanced mitophagic flux as such (26). These data collectively underscore that upstream pathway activation, while required, does not guarantee functional mitochondrial removal unless the full degradative cascade proceeds to completion. 'Stalled' mitophagy has been documented in the livers of HFD-fed mice, where abundant phosphorylated (p)-Ub serine 65 (Ub Ser65) and p62 coexist with minimal Parkin activation, indicating that mitophagy is initiated but cannot proceed to full execution. When paired with weight loss, exercise resolves this block, with concurrent reductions in p62 and phosphorylated (p)-Ub serving as evidence of restored flux (28).

The direction of exercise-induced changes in hepatic BNIP3, Parkin and LC3-II varies considerably across studies, ranging from marked upregulation to normalization or suppression following training (21,24,26,29). Baseline disease severity, exercise modality, duration, sex, nutritional status and tissue sampling timing all likely contribute to

this variability. Notably, acute exercise transiently amplifies mitophagy signaling, whereas repeated training appears to dampen pathological overactivation by improving mitochondrial efficiency (24,31). What appears contradictory may thus reflect distinct adaptive phases rather than genuine biological discordance.

Gonçalves *et al* (21) and Deng *et al* (37) reported that HFD suppressed hepatic PINK1 and Parkin while exercise restored them, indicating recovery clearance capacity (21,37) Hinkley *et al* (26) reported that exercise preconditioning improved mitochondrial function in doxorubicin-treated livers through SIRT3-mediated deacetylation, even as PINK1 and p62 remained persistently elevated. This introduces further interpretative complexity, as the concentrations of markers and functional recovery were dissociated. Zou *et al* (33) observed that HFD-fed zebrafish developed a suppressed mitophagy profile of reduced PINK1 and Parkin, and elevated p62. Notably, chronic swimming exercise did not restore PINK1 but increased Parkin beyond control levels; however, p62 declined, reflecting reactivation of flux rather than simple marker normalization (33) This pattern suggests that exercise can restore effective mitophagic flux even when upstream markers appear dysregulated at baseline, reinforcing the concept that marker concentrations alone are insufficient indicators of functional mitophagy without concurrent assessment of downstream clearance.

McCoin *et al* (31) and Dethlefsen *et al* (24) highlighted how the temporal scale of exercise shapes its mitophagic signature. Acute exercise activated flux within 2 h post-exercise, whereas chronic training produced LC3-II/LC3-I normalization that, without proper flux assessment, could be misattributed to reduced mitophagy (24,31). Finally, Li *et al* (34) demonstrated that moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) had different primary effectors. MICT preferentially restored PINK1-dependent signaling and reduced endoplasmic reticulum (ER) stress, whereas HIIT more strongly promoted optic atrophy protein 1 (OPA1)-mediated mitochondrial fusion. This highlights that exercise can yield divergent marker profiles that are not contradictory but rather reflect different mechanistic entry points into the mitophagy network (34).

In conclusion, exercise and diet can modulate mitophagy at the level of initiating signals (such as PINK1 stabilization and BNIP3 expression), upstream signaling (for example, AMPK, mTOR and SIRTs) and downstream execution (including autophagosome formation and lysosomal degradation). Fig. 1 summarizes how exercise- and nutrition-related signals regulate mitophagy through Ub-dependent and receptor-mediated pathways. Exercise, fasting and CR activate AMPK, which suppresses mTOR, phosphorylates ULK1 and engages SIRT1-FOXO3 signaling to transcriptionally induce BNIP3 and LC3. They also affect mitochondrial stress signals and promote PINK1/Parkin-mediated ubiquitination and LC3-positive autophagosome formation, while stress cues such as hypoxia and estrogen (via FOXO3 and HIF-1α) also engage receptor-mediated mitophagy via BNIP3, NIX and FUNDC1. While coordinated pathway activity supports mitochondrial quality and respiration, chronic consumption of high-fat or Western diets compromises lysosomal function, causing impaired mitophagy and buildup of dysfunctional mitochondria commonly observed in NAFLD.

4. Sex- and tissue-specific differences in exercise-induced mitophagy

Sex differences influence basal hepatic mitophagy and adaptive response to exercise. Higher intrinsic mitochondrial quality and lower mitophagic flux have been found in female individuals, whereas male individuals have higher baseline mitophagic flux that coincides with reduced coupling efficiency and elevated oxidative stress (23,25). Even under sedentary conditions, female mice have higher electron transport chain content, greater respiratory capacity and reduced ROS production, despite comparable or elevated BNIP3 and Parkin levels, this suggests a reduced reliance on active mitochondrial turnover (23,25). After a period of voluntary exercise, male mice have been shown to exhibit notable improvements: Mitochondrial coupling improves and their previously elevated mitophagy markers normalize to 'female-like' levels (25). In female mice, exercise does less in terms of mitophagy marker changes (since they are already considered optimal); however, the capacity to further increase mitochondrial respiration with training is blunted in female mice with BNIP3 knockout. This indicates that BNIP3-mediated mitophagy is important for females to gain maximal benefit from exercise, even if their baseline mitophagic flux is low. In addition, partial PGC-1α deficiency has been reported to not have as large an effect on blunting exercise-induced mitochondrial respiratory adaptations compared with BNIP3 knockout in female mice, indicating that quality control (mitophagy) rather than just biogenesis may be the limiting factor for female adaptation (25).

However, the characterization of female individuals as having uniformly 'lower' mitophagic flux requires qualification. Moore *et al* (27) reported that female Wistar rats had higher baseline LC3-II/I, autophagy-related (ATG)12-ATG5 conjugate and p-AMPK/AMPK ratios than male rats, thus suggesting greater basal autophagy and energy-sensing activity, a finding that appears to contradict the lower flux reported by McCoin *et al* (25). This apparent contradiction is best explained by the methodological gap between the studies. Von Schulze *et al* (23) and McCoin *et al* (31) isolated hepatic mitochondria and blocked lysosomal degradation to measure mitophagy-specific flux, whereas Moore *et al* (27) relied on whole-liver homogenates for general autophagy markers, a distinction that precludes direct comparison (23,27,31). In whole-tissue lysates, elevated LC3-II or ATG12-ATG5 more probably captures global autophagic turnover than mitochondria-targeted clearance, an interpretation reinforced by the observation that general autophagy markers were elevated as a sex effect rather than tracking mitophagy-specific clearance in the study (27). These observations collectively suggest that female individuals operate with higher general autophagic activity, but lower and more tightly regulated mitophagy-specific flux, a functional division that investigators should account for when comparing mitophagy between the sexes.

When female mice undergo ovariectomy (OVX), the liver mitophagy response to acute exercise is notably impaired,

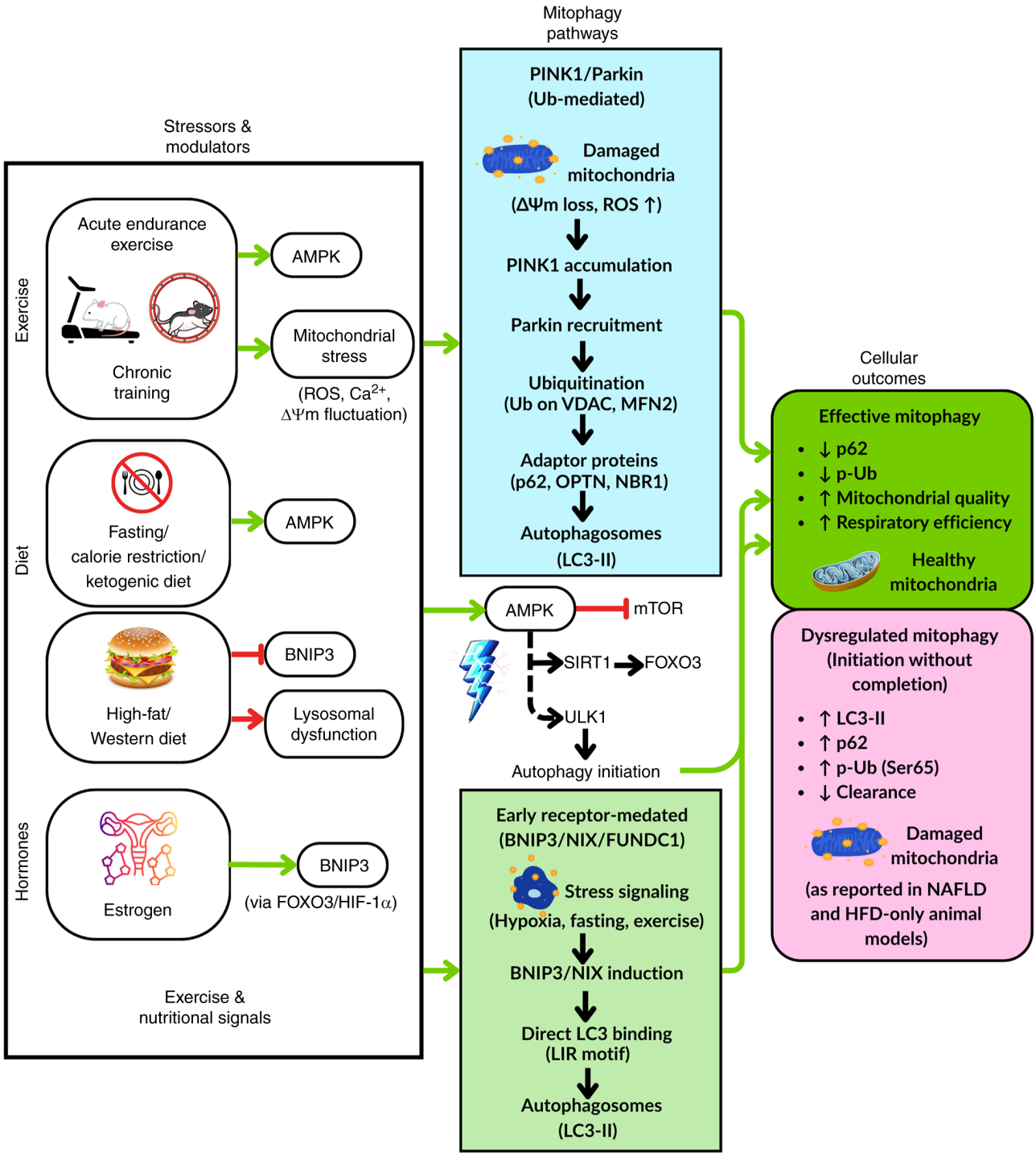

Figure 1. Integrated regulation of hepatic mitophagy by exercise and nutritional signals. AMPK, AMP-activated protein kinase; BNIP3, Bcl-2 interacting protein 3; FOXO3, forkhead box O3; FUNDC1, FUN14 domain-containing protein 1; HFD, high-fat diet; HIF-1α, hypoxia-inducible factor 1α; LIR, LC3-interacting region; MFN2, mitofusin 2; mTOR, mechanistic target of rapamycin; NAFLD, non-alcoholic fatty liver disease; NBR1, neighbor of BRCA1 gene 1 protein; NIX, NIP3-like protein X; OPTN, optineurin; p-Ub, phosphorylated-ubiquitin; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin 1; ULK1, unc-51 like autophagy activating kinase 1; VDAC, voltage-dependent anion channel; ΔΨm, mitochondrial membrane potential.

especially if they are also being fed a HFD. In sham-operated female mice (with intact ovaries), an acute treadmill run has been reported to induce robust mitophagic flux in the liver, evidenced by increased mitochondrial p62 accumulation under lysosomal blockade and, by proteomics, greater recruitment of LC3-II and adaptor proteins such as optineurin, NBR1 and nuclear dot protein 52 than in OVX mice. Female mice undergoing OVX and being fed a low-fat diet have been reported to still show a partial increase in mitophagy with exercise, whereas those fed a HFD exhibit almost no increase: Exercise fails to induce the normal signs of mitophagy in the absence of estrogen under lipid overload. Concomitantly, HFD-fed mice undergoing OVX had blunted exercise-induced improvements in mitochondrial respiration and redox signaling. This suggests estrogen is a permissive factor for effective mitophagy during exercise. In support of this, loss of ovarian function via OVX

blunted exercise-induced recruitment of DRP1 to hepatic mitochondria and reduced mitochondrial H_2O_2 signaling, thereby impairing the activation of exercise-induced mitophagic flux, particularly under HFD feeding (36). Franczak *et al* (36) revealed that impaired mitophagic flux in OVX animals fed a HFD extends beyond autophagosome formation to the fission machinery that precedes it. Diminished DRP1 and mitochondrial fission factor (MFF) recruitment to mitochondria suggests that estrogen loss may interfere with the segregation of damaged organelles before they can be targeted for autophagic clearance (36). Post-menopausal women and those with ovarian dysfunction may therefore derive less mitochondrial benefit from exercise, a gap that hormonal or dietary support could help to close.

Sex-specific hepatic mitophagy is further shaped by metabolic context. A single exercise bout has been reported to fail to alter whole-liver autophagy markers in chow-fed female mice; however, lysosomal inhibition in isolated mitochondrial fractions reveals a clear flux increase during the early post-exercise recovery period (~2 h post-exercise) (31). The discrepancy highlights that transient mitophagic events in the liver require assays performed in isolated mitochondrial fractions combined with lysosomal inhibition, rather than whole-liver homogenates, and some reported sex differences may reflect methodology rather than true biology. Male individuals appear to rely more heavily on exercise-induced mitophagy for quality control, whereas female individuals may benefit more from interventions that preserve baseline mitochondrial integrity.

Fig. 2 summarizes how sex, ovarian function and diet interact to influence exercise-induced hepatic mitophagy. In female mice with intact ovaries, high baseline mitochondrial quality shifts the exercise response toward biogenesis rather than mitophagy, although BNIP3-dependent clearance remains necessary for full adaptation. Male mice rely more on mitophagic turnover to achieve comparable mitochondrial quality, which normalizes their elevated markers to female-like levels with training. When OVX is combined with HFD, impaired DRP1 and MFF recruitment disrupts fission-dependent organelle segregation and abolishes exercise responsiveness, a deficit partially rescued by low-fat feeding. Sex, hormonal status and diet therefore act together to determine hepatic mitophagic capacity.

5. Effects of exercise modality, intensity and duration on mitophagy

Not all exercise engages mitophagy to the same degree. The mitophagic response depends heavily on the nature of the exercise stimulus. Mild daily activity preserves basal autophagic function but falls short of reversing the substantial mitophagy suppression observed in NASH (21). Voluntary wheel running has been shown to improve general autophagy in Western diet-fed mice but fails to restore BNIP3, pointing to a stimulus threshold that separates general autophagic flux from mitophagy-specific induction (22). LC3 lipidation and p62 clearance respond to modest AMPK-ULK1 activation, whereas BNIP3 upregulation requires the sustained HIF-1α and FOXO3 signaling that only higher-intensity or longer-duration exercise reliably generates. Dethlefsen *et al* (24) confirmed that this threshold can be crossed: Treadmill training elevated total hepatic BNIP3 concentration in high-fat high-fructose diet (HFF)-fed mice despite the adverse dietary background.

Acute and chronic exercise engage mitophagy through different temporal patterns. McCoin *et al* (31) reported that bulk autophagy markers were unchanged immediately after a 1-h treadmill run, whereas hepatic mitophagic flux was clearly detectable within 2 h in appropriately measured fractions. The absence of Parkin or DRP1 changes alongside simultaneous BNIP3 and optineurin recruitment indicated concurrent rather than sequential engagement of both mitophagy arms through Parkin-independent ubiquitination. Chronic repetition of the same stimulus, however, blunted this acute flux response (31). Dethlefsen *et al* (24) observed that an acute bout of exercise activated AMPK and increased PGC-1α mRNA in sedentary mice fed a HFF, but the same acute stimulus yielded a much smaller spike in those signals for mice that had undergone 5 weeks of training. Training also normalized the elevated LC3-II/LC3-I ratio observed in fatty liver and increased total BNIP3 levels without further increasing its active dimeric form, indicating an expansion of mitophagy capacity rather than sustained flux at rest (24). In this context, acute exercise serves as a transient stimulus for mitophagy, whereas chronic training resets the baseline capacity for mitochondrial turnover.

Mitophagy-induced adaptation to exercise is also influenced by its intensity. In male Wistar rats with dexamethasone-induced NAFLD, both moderate- and high-intensity treadmill training attenuated markers of excessive mitophagy signaling, significantly reducing the elevated hepatic Bcl-2 and LC3 gene expression seen in untreated animals with NAFLD, while concurrently increasing p62 protein levels (35). In a zebrafish model of NAFLD, Zou *et al* (33) reported that a HFD reduced PINK1 and Parkin while increasing p62, a pattern consistent with suppressed mitophagy. Swimming exercise pushed Parkin concentrations higher while reducing the levels of p62, an outcome that reflects reactivation of a dysfunctional Parkin pool rather than marker normalization (33). This dose-dependent benefit fits the mitohormesis framework, in which a controlled metabolic challenge promotes mitochondrial adaptation. The limits of this framework are demonstrated by Mokhtari-Andani *et al* (35), in which dexamethasone-treated rats exhibited paradoxically elevated p62 concentrations after exercise despite reduced Bcl-2 and LC3gene expression.

The time of day at which exercise is performed also adds a further layer of regulation to hepatic mitophagy outcomes. Zhang *et al* (30) demonstrated that identical exercise performed during the active phase (evening for mice) was more effective than rest-phase exercise in restoring mitochondrial dynamics and reducing aberrant mitophagy signaling in diabetic mice. Specifically, diabetic mice had elevated hepatic Parkin and LC3 concentrations (indicating excessive or maladaptive mitophagy and apoptosis); both morning and evening exercise significantly reduced Parkin and LC3 concentrations, with no significant difference between the two timings for these markers. Furthermore, both morning and evening exercise reduced Parkin and LC3 concentrations but through different primary mechanisms. Morning exercise primarily restored glucose handling and insulin sensitivity via glucose transporter type 4, whereas night exercise primarily realigned the

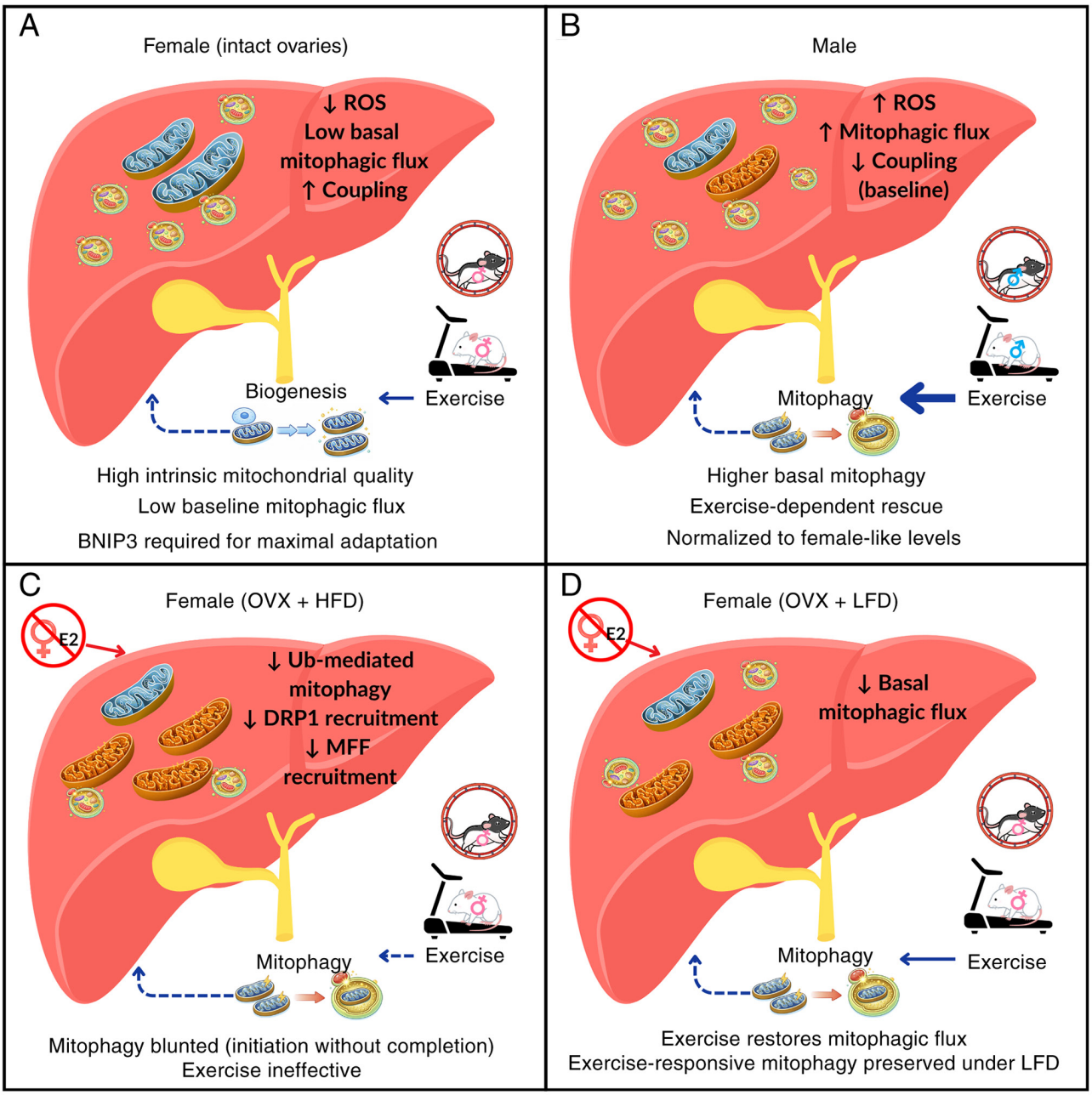

Figure 2. Sex-, hormone- and diet-dependent regulation of hepatic mitophagy and mitochondrial quality control. (A) Female mice with intact ovaries have high mitochondrial quality and low basal mitophagic flux, which favors exercise-induced biogenesis. (B) Male mice have higher basal mitochondrial stress and mitophagy, with exercise enhancing mitochondrial turnover. (C) OVX combined with HFD blunts Ub-mediated mitophagy and renders exercise ineffective, (D) whereas ovariectomized females on an LFD retain exercise-responsive mitophagy. BNIP3, Bcl-2 interacting protein 3; DRP1, dynamin-related protein 1; E2, estradiol; HFD, high-fat diet; LFD, low-fat diet; OVX, ovariectomy; Ub, ubiquitin; MFF, mitochondrial fission factor; ROS, reactive oxygen species.

circadian locomotor output cycles kaput (CLOCK)-mitophagy axis, which reduced CLOCK upregulation and improved mitochondrial ultrastructure (30). This represents a within-study contradiction where the same intervention at different times yields mechanistically distinct, partially non-overlapping effects, neither of which is comprehensively superior. For humans, this raises the question of whether morning or evening exercise may differently impact mitophagy in the liver or muscle (especially in metabolic disease or diabetes); however, to the best of our knowledge, human data are not yet available.

The comparison of HIIT and MICT has attracted growing attention, as each modality may engage distinct mitophagy-related effectors. Li *et al* (34) reported that MICT more effectively rescued PINK1 in HFD-fed male C57BL/6J mice, normalized LC3-II/LC3-I and BNIP3, and reduced ER stress, whereas HIIT was superior in restoring OPA1-mediated fusion and insulin signaling via PI3K/AKT/GSK3β; taken together, this positions MICT as the stronger driver of canonical PINK1/Parkin-dependent mitophagic flux. HIIT that restored Parkin without restoring PINK1 suggests Parkin can be recruited through PINK1-independent mechanisms, possibly via alternative E3 ligases or non-PINK1 p-Ub signals under HIIT-specific energetic conditions. Deng *et al* (37) further complicated this by reporting that HIIT was superior

to MICT for p-AMPK activation and mitochondrial improvement, implying a stronger HIIT-driven upstream stimulus for PINK1/Parkin signaling. The divergence between studies more plausibly reflects differences in animal model, HFD duration and outcome measures than genuine biological contradiction. Li *et al* (34) centered their analysis on mitochondria-associated membrane (MAM) integrity and ER stress, whereas Deng *et al* (37) prioritized AMPK-driven metabolic remodeling and the gut-liver axis. This suggests that MICT and HIIT access the mitophagy network through partially distinct entry points rather than producing opposing effects (34,37).

Wang *et al* (56) extended the mechanistic picture by demonstrating that HIIT can promote M1-to-M2 macrophage polarization in the liver of a HFD- and streptozotocin-induced type 2 diabetes mellitus (T2DM) mouse model through RAR-related orphan receptor α/Krüppel-like factor 4 signaling. As M1 macrophages impair mitophagic flux and lysosomal function through ROS and cytokine release, this shift in inflammatory tone may represent an indirect but functionally important route by which HIIT supports the restoration of mitophagy (56).

At the transcriptional level, Durak *et al* (38) reported that 24 weeks of exercise for HFD-fed female mice restored ATG3, PINK1, MFN1 and Parkin expression levels toward normal, supporting exercise-driven recovery of mitophagy and fusion gene programs. The upward direction of these changes superficially conflicts with Dethlefsen *et al* (24), where chronic training reduced LC3-II/LC3-I in HFF-fed males. In Durak *et al* (38), HFD feeding suppressed hepatic Parkin and MFN1 expression, and exercise restored these toward control levels, whereas PINK1 and ATG3 were further upregulated by exercise beyond both control and HFD levels. In Dethlefsen *et al* (24), mice had pathologically elevated LC3-II concentrations, and its reduction reflected normalization. Both outcomes represent the restoration of appropriate mitophagy regulation by exercise, and the comparison reinforces that marker direction alone is uninformative without knowledge of the starting point.

In conclusion, exercise must reach a certain threshold of intensity/duration to robustly engage mitophagy. Light physical activity appears to maintain overall health and support baseline autophagy, yet substantial mitochondrial impairment may only respond to more robust training stimuli. While vigorous exercise acutely activates mitophagy, ongoing training appears to adjust the baseline state of mitochondrial quality control. Integrating occasional high-intensity sessions with regular moderate activity may best balance short-term mitophagy activation and long-term mitochondrial remodeling. These findings indicate that exercise does not universally increase mitophagy; rather, exercise restores mitochondrial quality control according to the metabolic state and the degree of pre-existing mitochondrial dysfunction.

Table I compiles animal studies examining the interplay between exercise modalities and dietary or metabolic factors in shaping hepatic mitophagy. Structured endurance training, HIIT, MICT and voluntary exercise are contrasted across metabolic stress models, with the table mapping how the intensity and duration of each modality translate to distinct hepatic mitochondrial outcomes.

6. Dietary influences on mitophagy and interactions with exercise

Diet markedly affects mitochondrial turnover processes. The present review discusses how overnutrition (high-fat or Western diets), specific macronutrient compositions [for example, a ketogenic diet (KD)] and undernutrition (CR and fasting) modulate mitophagy and how the effects of exercise on mitophagy intersect with these states. The roles of weight-loss strategies and nutraceutical approaches are also considered.

High-fat and Western-style diets are known to rapidly induce hepatic steatosis and insulin resistance in rodent models. These are accompanied by early mitochondrial abnormalities, such as reduced respiratory capacity, disrupted mitochondrial dynamics and increased oxidative stress. Disruption of mitochondrial quality control occurs early, as even short-term exposure to a Western diet markedly reduces key mitochondrial proteins and BNIP3 concentrations, indicating suppressed mitophagy capacity before overt inflammation (22). The suppression of BNIP3 by a Western diet likely reflects hyperactivation of mTOR complex 1 by nutrient excess (57), which inhibits HIF-1α- and FOXO3-dependent BNIP3 transcription (58). Simultaneously, lipotoxicity-induced oxidative stress may enhance PINK1 stabilization on depolarized mitochondria (59), creating a paradoxical state in which the Ub-dependent arm is primed while the receptor-mediated arm is suppressed. While increased Parkin, BNIP3 activation and LC3-II accumulation have been documented in certain models, such patterns are more consistent with dysfunctional mitophagy signaling than with effective mitochondrial turnover (24). This apparent contradiction, Western diet suppressing BNIP3 (22) vs. HFF increasing the concentration of active BNIP3 homodimer (24), likely reflects the severity and composition of the dietary challenge. Short-term Western diet may suppress BNIP3 transcription through mTOR-mediated FOXO3 inhibition, whereas prolonged HFF feeding may drive compensatory BNIP3 dimerization as a failed attempt to clear overwhelmed mitochondria. Lysosomal dysfunction prevents effective flux despite elevated receptor signaling (22,24).

Exercise and dietary modification act synergistically to restore hepatic mitophagy in NAFLD. Both structured training and voluntary activity reduce steatosis and enhance general autophagic markers (higher LC3-II/I ratio, lower p62); however, BNIP3-mediated mitophagy is not consistently restored by physical activity alone under continued high-fat feeding (22), and robust mitophagy improvement in weight-loss models depends critically on combining exercise with dietary change (28). Rosa-Caldwell *et al* (28) indicated that dietary restriction alone increased the expression of PINK1 and Parkin, and normalized p62 and p-Ub Ser65, yet failed to restore the levels of BNIP3, outcomes achieved only when exercise was added; thus, the two pathway arms [the PINK1/Parkin-dependent (Ub-dependent) arm and the BNIP3-dependent receptor-mediated arm] may be under partially distinct control. PINK1 responds to any reduction in mitochondrial depolarization and can be partially rescued by CR, whereas BNIP3 requires FOXO3 and AMPK activation, which exercise alone reliably provides in the liver. Persistent p-Ub Ser65 upregulation in response to HFD, by contrast, indicates that PINK1 was active but Parkin-mediated

Table I. Animal studies examining the effects of exercise and dietary interventions on hepatic mitophagy and liver recovery.

First author, year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
Gonçalves *et al*, 2016	Treadmill running or VWR	HFD	HFD-induced NASH rats (9 weeks) underwent VPA or ET (8 weeks); hepatic mitochondrial permeability, biogenesis, dynamics, mitophagy and apoptosis markers were assessed.	HFD/NASH: ↑ mPTP susceptibility, ↑ Bax/ Bcl-2 ratio, ↓ TFAM/ MFN1/PINK1/Parkin VPA: ↑ PGC-1α/ Beclin-1, ↓ apoptotic signaling ET: ↓ mPTP susceptibility, ↑ PGC-1α/TFAM/MFN1/ MFN2/PI NK1/Parkin, ↓ Bax/Bcl-2 ratio/ caspase activity	ET more effectively restored mitochondrial quality control than VPA by enhancing biogenesis, fusion, mitophagy-related signaling and apoptosis regulation in NASH.	(21)
Rosa-Caldwell *et al*, 2017	VWR	WD	C57BL/6J mice were fed normal or WD (4 weeks) and assigned to SED or VWR groups (4 weeks); hepatic histology and mitochondrial biogenesis, dynamics and autophagy/mitophagy markers were assessed.	WD: ↓ Mitochondrial content (COX IV, Cyt c)/PGC-1α/fusion/ fission markers VWR (NC and WD): ↑ LC3-II/LC3-I, ↓ p62 WD: ↓ BNIP3 WD + VWR: partial protection from steatosis (trend, NS vs. WD-SED)	Moderate physical activity enhanced basal hepatic autophagy and attenuated early steatosis, while WD suppressed mitochondrial quality control and BNIP3-linked mitophagy capacity.	(22)
Von Schulze *et al*, 2018	VWR	LFD	Male and female WT, liver-specific PGC-1α$^{+/-}$, and BNIP3$^{-/-}$ mice; SED vs. VWR (4 weeks); hepatic mitochondrial respiration, coupling, ROS (H_2O_2) and mitophagy (LC3-II, p62) were detected.	Female mice: ↑ ETS content/respiratory capacity/coupling efficiency; ↓ H_2O_2 emission/mitophagic flux (LC3-II↓), independent of genotype Male mice: Baseline ↓ coupling and ↑ mitophagy; exercise resulted in ↑ coupling, ↓ LC3-II PGC-1α$^{+/-}$ or BNIP3$^{-/-}$: Minimal effect on sex-specific adaptations	Sex primarily determined hepatic mitochondrial adaptation: Female mice showed intrinsically efficient mitochondria, whereas male mice relied more on exercise-induced mitophagy for mitochondrial quality control.	(23)
Dethlefsen *et al*, 2018	Treadmill running	HFF	Male PGC-1α LKO and littermate control mice were fed a control diet/HFF (13 weeks), underwent treadmill training (5 weeks), with or without an additional acute exercise bout; hepatic autophagy and mitophagy markers, AMPK-mTOR, and	HFF diet: ↑ Parkin/ BNIP3 dimer/LC3-II/ LC3-I resulting in dysregulated autophagy/mitophagy Exercise training: ↓ LC3- II/LC3-I, ↑ PGC-1α mRNA/ total BNIP3 Acute exercise: ↑ p-AMPK/ PGC- 1α mRNA in	HFF disrupted hepatic autophagy regulation while increasing mitophagy signaling capacity. Exercise training partially normalized autophagy and enhanced mitophagic capacity largely independent of hepatic PGC-1α	(24)

Table I. Continued.

First author, year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
			PGC-1α mRNA were assessed.	untrained HFF-fed mice (minimal effect) PGC-1α LKO: Minimal impact on mitophagy	.	
Cunningham *et al*, 2018	VWR	WD	Female Wistar rats assigned to normal chow diet or WD with or without VWR during gestation. Offspring (male and female) assessed in young adulthood for hepatic steatosis, mitochondrial biogenesis markers and autophagy/mitophagy markers.	Maternal WD: ↑ Hepatic steatosis (male offspring) Maternal exercise: ↑ TFAM/PPARγ; ↑ NRF2 (all offspring); ↑ BNIP3/ATG12-ATG5 (WD male offspring); Sex effect (female vs. male): ↑ p62, BNIP3, ATG12:5, LC3-II/LC3-I and Keap1, ↓ Parkin Diet effect: ↑ LC3-II/LC3-I in male SED offspring (WD vs. ND)	Maternal physical activity enhanced hepatic mitochondrial biogenesis and mitophagy-related signaling in offspring, with pronounced sex-dependent effects, despite limited early protection against steatosis.	(19)
McCoin *et al*, 2019	VWR	HFD	Male and female WT, liver-specific PGC-1α heterozygous and BNIP3-knockout mice were fed a HFD (16 weeks), with or without VWR (final 8 weeks). Hepatic mitochondrial respiration, coupling efficiency, ROS emission and mitophagy markers were assessed.	Female mice: ↑ Coupling efficiency, ↓ H_2O_2 emission/ steatosis/mitophagy Exercise: ↑ Respiratory capacity mainly in WT and liver-specific PGC-1α heterozygous female mice, blunted in BNIP3-knockout female mice Male mice required exercise to normalize coupling and mitophagy to female-like levels	Hepatic mitochondrial responses to HFD and physical activity are primarily sex dependent. Female mice exhibited intrinsic mitochondrial efficiency, whereas male mice relied more on exercise-induced mitophagy for quality control.	(25)
Hinkley *et al*, 2019	Treadmill running	Pharmacological hepatotoxicity model (DOX)-, no dietary manipulation	Female SD rats underwent treadmill training (10 days) or were SED, followed by acute DOX administration. Hepatic mitochondrial respiration, coupling efficiency, oxidative capacity, mitophagy, mitochondrial biogenesis, protein acetylation and SIRT3 were assessed.	DOX (SED): ↑ State 4 respiration (proton leak)/PINK1/p62/ protein acetylation, ↓ RCR/citrate synthase/NRF1/ SIRT3 Exercise + DOX: ↓ State 4 respiration, ↑ RCR/citrate synthase/ mitochondrial efficiency, attenuation of protein hyperacetylation, preservation of SIRT3,	Exercise preconditioning prevented DOX-induced hepatic mitochondrial dysfunction primarily by preserving oxidative capacity and protein deacetylation status rather than by suppressing mitophagy signaling.	(26)

Table I. Continued.

First author year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
				PINK1 and p62 remained ↑, and Parkin remained ~		
Moore *et al*, 2020	VWR	KD, WD	Male and female Wistar rats with access to VWR were fed SC, WD or KD (7 weeks). Hepatic lipid content, oxidative stress, mitochondrial biogenesis and autophagy/mitophagy markers were assessed.	WD: ↓ LC3-II/LC3-I, ↑ p62 (impaired autophagy/mitophagy markers) KD + exercise: Suppressed hepatic *de novo* lipogenesis, ↑ PGC-1α, TFAM, citrate synthase Female rats: Higher baseline markers of mitochondrial biogenesis, autophagy/ mitophagy and energy sensing (↑ LC3- II/ LC3-I, ATG12:5, p-AMPK/AMPK) than males	KD and exercise enhanced hepatic mitochondrial remodeling and redox balance. Female rats showed greater intrinsic mitochondrial biogenesis and general autophagy markers, although mitophagy-specific flux was not assessed.	(27)
Rosa-Caldwell *et al*, 2022	VWR	HFD with weight-loss intervention	Male C57BL/6J mice were fed LFD, HFD, weight loss by diet alone or D/PA. Hepatic mitochondrial content, biogenesis, mitophagy and macroautophagy markers were assessed by immunoblotting.	HFD: ↓ COX IV and disrupted mitochondrial quality control (↑ p-UbSer65, ↑ p62) Diet alone: ↓ p62 and p-UbSer65 (minimal improvement) D/PA: ↑ PGC-1α/ mitochondrial content/BNIP3, normalized p62 and ↓ aberrant p-UbSer65 accumulation, indicating improved mitophagy	Weight loss combined with physical activity was superior to diet alone in restoring hepatic mitochondrial quality, enhancing BNIP3-mediated mitophagy and improving autophagy resolution in NAFLD.	(28)
Stevanović-Silva *et al*, 2022	Moderate-intensity treadmill + VWR	Maternal HFHS	Female rats were fed a control or HFHS diet, were SED or performed GE during pregnancy. Female offspring were fed a control diet and kept SED. Hepatic lipid accumulation, mitochondrial biogenesis, mitochondrial dynamics and mitophagy/autophagy markers were assessed.	Maternal HFHS (offspring): ↑ hepatic lipid stress markers/ Parkin/OPA1, ↓PGC-1α/TFAM (trend)/ mitochondrial dynamics mRNA GE (offspring): ↓ Hepatic triglycerides and NAFLD activity score, ↑ PGC-1α/TFAM/ MFN1/2/DRP1, ↓ Parkin/OPA1 Mitophagy/autophagy: LC3, PINK1 ~	GE counteracted maternal HFHS-induced mitochondrial dysregulation in female offspring primarily by enhancing mitochondrial biogenesis and dynamics, while preventing pathological accumulation of mitophagy signaling.	(29)

Table I. Continued.

First author, year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
Zhang *et al*, 2022	Treadmill running	No dietary manipulation	Male db/db mice (genetic T2DM model) underwent treadmill aerobic exercise (8 weeks), morning (rest phase) or night (active phase). Hepatic glucose/lipid metabolism, circadian clock proteins, mitochondrial morphology and dynamics, mitophagy and apoptosis were assessed.	T2DM: ↑ Blood glucose/serum cholesterol/CLOCK/ Parkin/LC3/apoptosis, ↓ OPA1/Fis1 Morning exercise: ↓ Glucose/Parkin/LC3/ apoptosis, ↑ insulin sensitivity/GLUT4 Night exercise: ↓ Glucose/cholesterol/ Parkin/LC3, ↓ CLOCK/apoptosis (greater than morning), ↑ mitochondrial networks and morphology	Morning exercise favored glucose handling and insulin sensitivity, whereas night exercise more effectively normalized CLOCK-linked mitophagy, mitochondrial structure and apoptosis.	(30)
McCoin *et al*, 2022	Treadmill running	No dietary manipulation	Adult female C57BL/6J mice performed a single acute bout of treadmill exercise; livers were collected immediately (0 h) or 2 h post-exercise. Mitophagic flux was assessed using leupeptin (lysosomal inhibitor), isolated hepatic mitochondria, mitophagy reporters (Cox8-GFP-mCherry), WB and mitochondrial proteomics.	All comparisons: Exercise vs. SED 0 h post-exercise: ~ LC3-II, ~ p62 (no flux); ↑ BNIP3/MFN2 (transient) 2 h post-exercise (+ leupeptin): ↑ LC3-II/p62/ mitochondrial Ub resulting in ↑ mitophagic flux Whole-liver homogenate (saline- and leupeptin-treated groups): ~LC3-II, ~ p62 Isolated mitochondria (WB, saline-treated groups only): ~ Parkin, ~ DRP1 Proteomics: ↑ BNIP3/OPTN/LC3-II (saline- and leupeptin-treated groups); ↑ Beclin-1 (leupeptin-treated groups)	A single exercise bout rapidly and transiently activated hepatic mitophagic flux, detectable during early recovery and mediated by Ub- and receptor-dependent pathways rather than global autophagy induction.	(31)
McCoin *et al*, 2022	Treadmill running	No dietary manipulation	Female mice performed 1 h treadmill exercise vs. SED and were sacrificed immediately (0 h) or 2 h post-exercise. Isolated hepatic mitochondria were analyzed by	Acute exercise: ↑ Mitochondrial processes for lipid localization/IL-5/ protein phosphorylation; proteome showed	A single exercise bout rapidly remodeled the hepatic mitochondrial proteome, and lysosomal inhibition revealed autophagolysosomal	(32)

Table I. Continued.

First author, year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
			untargeted proteomics (3,241 proteins) plus targeted validation (such as p62 and Ndufa4).	time-dependent clustering Exercise + leupeptin: Altered exercise-modulated protein profiles under lysosomal inhibition, suggesting autophagolysosomal turnover	turnover linked to mitochondrial quality-control processes.	
Zou *et al*, 2023	Swimming	HFD	Zebrafish were fed a HFD to induce NAFLD and subjected to chronic swimming exercise. Liver pathology, mitochondrial morphology and dynamics, mitochondrial biogenesis and mitophagy markers were assessed.	HFD: Impaired mitochondrial morphology, ↓ PGC-1α/PINK1/Parkin and ↑ p62 Swimming exercise: ↓ Liver injury/ fibrosis/p62, ↑ AMPK/SIRT1/PGC-1α/oxidative metabolism/Parkin/ mitochondrial dynamics	Exercise improved mitochondrial quality in NAFLD by simultaneously activating mitochondrial biogenesis and restoring mitophagy.	(33)
Li *et al*, 2024	Treadmill running	HFD	Male C57BL/6J mice divided into four groups: Normal diet + SED, HFD + SED, HFD + HIIT and HFD + MICT. Hepatic MAM formation assessed by immunofluorescence colocalization of IP3R and VDAC1. Mitophagy markers, mitochondrial dynamics, ER stress markers and hepatic insulin signaling were assessed.	HFD: ↓ IP3R-VDAC1 colocalization (MAMs)/PINK1/ Parkin/p-PI3K/p-AKT/ p-GSK3β, ↑ LC3-II/ LC3-I/BNIP3/Fis1/ p-PERK/p-eIF2α HFD + HIIT and HFD + MICT: ↑ IP3R-VDAC1 colocalization/ Parkin, ↓ Fis1/p-PERK HFD + MICT only: ↑ PINK1/Parkin, ↓ LC3-II/LC3-I/BNIP3/ p-eIF2α HFD + HIIT only: ↑ OPA1/Parkin	HFD-induced reduction in hepatic MAMs formation was associated with suppressed mitophagy and elevated ER stress, contributing to hepatic insulin resistance. HIIT and MICT restored MAMs formation and alleviated hepatic IR, with MICT demonstrating superior efficacy in restoring mitophagy and reducing ER stress.	(34)
Mokhtari-Andani *et al*, 2025	Treadmill running	DEX-induced NAFLD + silymarin	Male Wistar rats with DEX-induced NAFLD underwent moderate-intensity/high-intensity exercise (8 weeks), with or without silymarin supplementation. Hepatic mitophagy signaling was assessed.	DEX: ↑ PINK1/Bcl-2/Beclin-1/LC3, ↓ mTOR Moderate-intensity/high-intensity exercise: ↓ Bcl-2/LC3 mRNA, ↑ p62 protein levels compared with DEX Silymarin: ↓ Parkin/	Exercise attenuated pathological mitophagy signaling and restored mitochondrial quality control in pharmacologically induced NAFLD, with separate (non-	(35)

Table I. Continued.

First author, year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
				Bcl-2/LC3/PINK1 Moderate-intensity/ high-intensity exercise + silymarin: ↓ Bcl-2/LC3 mRNA	additive) benefits from nutraceutical support.	
Franczak *et al*, 2025	Treadmill running	HFD	Female C57BL/6J mice undergoing sham operation or OVX and fed a 4-week LFD or HFD performed acute exercise. Hepatic mitophagic flux, isolated-mitochondria proteomics (HFD groups), mitochondrial respiration and H_2O_2 emissions were measured.	Sham + exercise: ↑ mitochondrial p62 (WB, leupeptin); by proteomics ↑ E3-Ub ligases/UBB and adaptors (OPTN, NBR1, NDP52), ↑ LC3-II OVX + LFD: ↓ Basal mitophagic flux OVX + HFD: ↓↓ Exercise-induced mitophagy; ↓ mitochondrial H_2O_2 signaling and fatty acid-supported respiration; ↓ DRP1/ MFF recruitment	Ovarian function was required for full activation of exercise-induced hepatic mitophagic flux, particularly during HFD feeding. Loss of estrogen blunted redox signaling and mitochondrial quality control responses to exercise.	(36)
Deng *et al*, 2025	Treadmill running	HFD	Male SD rats divided into four groups: Normal-fat diet, HFD, MICT and HIIT. HFD induction (8 weeks) followed by treadmill training and HFD (8 weeks). Hepatic mitophagy markers, mitochondrial dynamics, mitochondrial biogenesis, lipid metabolism, inflammatory cytokines, gut microbiota and gut-liver axis parameters were assessed.	HFD: ↓ PINK1/ Parkin/PGC-1α/ CS/COX IV/MFN1/ MFN2, ↑ Fis1/ steatosis/TG/TC/ALT/ AST/leptin/LPS/IL-1β/IL-6/TNF-α HIIT + MICT: ↑ PINK1/Parkin/ PGC-1α/CS/COX IV/ MFN1/MFN2/p-AMPK, ↓Fis1/ steatosis/TG/TC/ALT/ AST/leptin/LPS/IL-1β/IL-6/TNF-α HIIT > MICT in improving mitochondrial function and regulation of AMPK/SREBP-1c/PPARα/CPT-1	HIIT demonstrated superior efficacy than MICT in improving hepatic mitochondrial function. Improvements in MASLD were mediated through the AMPK-PINK1/Parkin axis and gut-liver axis remodeling.	(37)
Durak *et al*, 2026	Treadmill running	HFD	Female C57BL/6J mice divided into control, HFD and exercise + HFD groups. Exercise started at week 6 until 24 weeks.	HFD: ↓ Parkin and MFN1 compared with the control group Exercise + HFD: ↑ ATG3/	Exercise altered the expression of mitophagy-related genes in the liver.	(38)

Table I. Continued.

First author, year	Type of exercise	Type of diet/ nutraceutical intervention	Method	Results	Key findings	(Refs.)
			Gene expression levels were evaluated in the liver.	PINK1/MFN1/ Parkin compared with in the HFD group		

ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AST, aspartate aminotransferase; ATG, autophagy-related; BNIP3, Bcl-2 interacting protein 3; CLOCK, circadian locomotor output cycles kaput; COX IV, cytochrome *c* oxidase subunit IV; CPT-1, carnitine palmitoyltransferase 1; CS, citrate synthase; Cyt c, cytochrome *c*; DEX, dexamethasone; DOX, doxorubicin; D/PA, diet plus physical activity; DRP1, dynamin-related protein 1; ER, endoplasmic reticulum; ET, endurance training; ETS, electron transport system; Fis1, mitochondrial fission protein 1; GE, gestational exercise; GLUT4, glucose transporter type 4; HFD, high-fat diet; HFF, high-fat high-fructose diet; HFHS, high-fat high-sucrose diet; HIIT, high-intensity interval training; IP3R, inositol 1,4,5-trisphosphate receptor; KD, ketogenic diet; LFD, low-fat diet; LKO, liver-specific knockout; LPS, lipopolysaccharide; MAM, mitochondria-associated membrane; MASLD, metabolic dysfunction-associated steatotic liver disease; MFF, mitochondrial fission factor; MFN1/2, mitofusin 1/2; MICT, moderate-intensity continuous training; mPTP, mitochondrial permeability transition pore; mTOR, mammalian target of rapamycin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NBR1, neighbor of BRCA1 gene 1 protein; NC, normal chow; ND, normal diet; NDP52, nuclear dot protein 52; NRF1, nuclear respiratory factor 1; NRF2, nuclear factor erythroid 2-related factor 2; OPA1, optic atrophy protein 1; OPTN, optineurin; OVX, ovariectomy; PGC-1α, PPARγ coactivator 1-α; PINK1, PTEN-induced kinase 1; p-, phosphorylated; PPAR, peroxisome proliferator-activated receptor; Ub, ubiquitin; UbSer65, Ub serine 65; RCR, respiratory control ratio; ROS, reactive oxygen species; SD, Sprague-Dawley; SED, sedentary; SIRT, sirtuin; SREBP-1c, sterol regulatory element-binding protein 1c; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TFAM, mitochondrial transcription factor A; TG, triglycerides; VDAC, voltage-dependent anion channel; VPA, voluntary physical activity; VWR, voluntary wheel running; WB, western blotting; WD, Western diet; WT, wild-type; ↑, increased/upregulated; ↓, decreased/downregulated; ~, unchanged.

clearance remained incomplete, a downstream bottleneck that exercise uniquely resolves.

Unlike Western-style feeding, a KD shifts hepatic metabolism toward fatty acid oxidation and ketogenesis, generating mitochondrial adaptations of a qualitatively different character. In rats with running wheel access, a previous study reported that a KD combined with exercise could suppress sterol regulatory element-binding protein 1/FAS-driven lipogenesis, improve glutathione redox balance, and elevate PGC-1α, TFAM and citrate synthase, indicating robust mitochondrial biogenesis (27). Higher hepatic LC3-II/I and ATG12-ATG5 were observed in female vs. male rats irrespective of diet, consistent with their greater baseline AMPK sensitivity; notably, KD did not raise LC3-II/I relative to standard chow, whereas Western diet lowered it (27). Some hepatic triglycerides accumulate under KD but without the inflammatory or dysfunctional features of Western diet-induced steatosis. Mechanistically, KD and exercise may converge on AMPK-ULK1 signaling: Ketosis suppresses mTOR through reduced glucose and amino acid availability while raising the AMP/ATP ratio, and exercise superimposes a further energetic demand, which drives AMPK-ULK1 signaling beyond what either intervention achieves alone (27). The result is a quasi-fasted metabolic state in which autophagic quality control is constitutively primed. As all animals in that study had running-wheel access (27), the contribution of exercise cannot be isolated; therefore, the possibility that, in the absence of exercise, a KD promotes steatosis rather than mitochondrial benefit remains to be confirmed in sedentary models.

Among longevity interventions, CR is one of the best characterized, with autophagy and mitophagy induction recognized as central mechanisms (60). Fasting activates these pathways rapidly in the liver: BNIP3 concentrations increase within 6 h and continue to increase through 24 h of nutrient deprivation in mice, reflecting early receptor-mediated mitophagy (61). Human skeletal muscle requires a longer fasting period to mount a comparable autophagic response (62). When combined with exercise, fasting or CR produces additive mitophagy activation through convergent AMPK and SIRT1 signaling, including in human muscle (48,63,64), although prolonged restriction risks impairing exercise capacity and should be applied judiciously.

The context dependence of exercise-induced mitophagy is illustrated by a chlorpyrifos exposure model, in which fat mobilization during exercise released hepatically accumulated toxicants that inhibited AMPK signaling and caused p62 accumulation, ultimately abrogating mitophagy despite continued physical activity (65). Toxicant-mediated AMPK inhibition appears to sever the upstream energetic signal that normally coordinates PINK1/Parkin and BNIP3 activation, leaving mitochondria without an adequate clearance signal even as oxidative stress continues. This scenario is functionally analogous to the lysosomal dysfunction seen in HFD models where upstream signaling is intact but downstream execution fails.

Specific dietary compounds can also modulate mitophagy. Mokhtari-Andani *et al* (35) revealed that exercise paradoxically elevated the concentrations of hepatic p62 while suppressing those of LC3 and Bcl-2 mRNA in dexamethasone-treated rats, a two-level dysfunction not observed in dietary NAFLD models. In addition, silymarin supplementation combined with exercise attenuated the serum lipid profile in the same model (35). Across the interventions reviewed, Western-style diets have been shown to consistently compromise mitophagy, while fasting, ketogenic feeding, CR and exercise promote mitochondrial turnover and interacted synergistically.

Effective mitochondrial quality control, therefore, depends on how nutritional context and exercise are aligned.

7. Maternal and paternal programming of mitophagy across generations

While maternal exercise is associated with beneficial metabolic outcomes in offspring, the majority of studies have prioritized traditional endpoints such as adiposity and insulin sensitivity rather than mitochondrial quality regulation. Cunningham *et al* (19) provided novel insight into offspring liver mitochondrial markers. In this previous study, female rats were fed either a Western diet or normal diet during pregnancy; half of each group had access to running wheels. The offspring were studied in young adulthood under normal diet conditions. Maternal exercise robustly upregulated markers of mitochondrial biogenesis (TFAM, PPARγ) and nuclear factor erythroid 2-related factor 2 in the offspring livers of both sexes, whereas mitophagy/autophagy markers BNIP3 and ATG12-ATG5 concentrations were increased specifically in Western diet-exposed male offspring. Female offspring had inherently higher levels of these markers than male offspring regardless of the maternal group, which corresponds with protection from steatosis even under maternal Western diet exposure (19).

Stevanović-Silva *et al* (29) explored whether maternal exercise could counteract the negative effects of a high-fat high-sucrose (HFHS) diet during pregnancy. In offspring of HFHS-fed mothers, reduced PGC-1α and TFAM disturbed fusion-fission dynamics and elevated Parkin expression pointed to subclinical mitochondrial stress preceding overt steatosis. Gestational exercise corrected these biogenic and dynamic markers and reduced Parkin expression, with LC3 and PINK1 unaltered in any group (29). That mitophagic flux markers were unchanged despite functional recovery supports the view that active mitophagy induction is unnecessary when mitochondrial architecture is adequately preserved. Two observations complicate the mechanistic picture. Parkin expression increased without a corresponding increase in that of PINK1, suggesting recruitment through non-canonical routes such as p-Ub signals from alternative kinases or calcium-mediated translocation. The concurrent increase in the expression of OPA1, a fusion-promoting protein, under HFHS stress most plausibly reflects compensatory mitochondrial elongation, a protective response that resists fission-dependent segregation of damaged organelles and paradoxically impairs quality control. Gestational exercise reversing this OPA1 elevation would indicate restored fission-fusion balance rather than diminished fusion capacity.

Stevanović-Silva *et al* (29) and Cunningham *et al* (19) reported divergent marker-level outcomes of maternal exercise in offspring liver. Cunningham *et al* (19) documented upregulation of BNIP3 and ATG12-ATG5 expression, suggesting enhanced mitophagy capacity, whereas Stevanović-Silva *et al* (29) detected reductions in Parkin and OPA1 expression without changes in those of LC3 and PINK1, a pattern interpreted as mitophagy restraint rather than induction. Differences in maternal diet type, offspring sex and assessment timing are the most plausible sources of this divergence. Notably, they may not be true contradictions: The findings of Cunningham *et al* (19) suggested that exercise programs induce greater mitophagy capacity in offspring (more machinery available), whereas those of Stevanović-Silva *et al* (29) suggested that exercise may prevent maladaptive mitophagy signaling in offspring (less pathological activation). These represent two different but compatible aspects of mitochondrial quality control programming across generations.

A previous study supported the idea that paternal lifestyle can induce epigenetic regulation that modulates offspring metabolism (20). Batista *et al* (20) exhibited improved metabolic outcomes, including HFD-induced obesity and hepatic steatosis, in offspring from fathers that underwent swim training before conception. The increased expression levels of genes associated with energy sensing regulation (protein kinase AMP-activated catalytic subunit α2/AMPKα2) and fatty acid oxidation (PPAR-1α and carnitine palmitoyltransferase 1) were also detected in offspring. This was accompanied by increased AMPK activity, which was consistent with improved mitochondrial stress management. Detection of parallel metabolic adaptations in paternal reproductive tissues suggested epigenetic mechanisms mediating intergenerational effects (20).

Fig. 3 compiles all 19 studies in Table I into a schematic overview illustrating how different dietary interventions (high-fat, western diet, weight loss and KD), acute or chronic exercise, exercise modality (HIIT vs. MICT), parental programming, sex and hormonal modulation, as well as pathological conditions and exercise preconditioning interact to regulate hepatic mitophagy. Moore *et al* (27) measured general autophagy markers (LC3-II/I, ATG12-ATG5) without mitophagy-specific readouts; the findings reflected autophagic rather than strictly mitophagic activity.

The present review has several limitations. No paired human liver study has measured hepatic PINK1, Parkin, BNIP3, LC3-II, p62 or mitophagic flux before and after a lifestyle intervention. All the evidence summarized herein derives from animal models, which differ from humans in metabolism, lifespan and susceptibility to MASLD. What exists is a looser chain of proximal evidence. Clinical trials have demonstrated that exercise and dietary interventions improve hepatic steatosis and, in some cases, biopsy-based metabolic dysfunction-associated steatohepatitis outcomes (66-70). A 2025 randomized trial reported that 16:8 time-restricted eating increased serum ATG5 but not Beclin-1 concentration without liver-tissue confirmation (71). Human observational studies have demonstrated that NAFLD/NASH is associated with altered hepatic mitochondrial respiration, oxidative stress and disease-state changes in mitophagy-related pathways (5,72). Finally, an exercise study measured the concentrations of peripheral myokines such as irisin as surrogate signals of mitochondrial stress (73). These findings support biological plausibility but cannot establish that exercise or diet improves hepatic mitophagy in humans, because circulating markers reflect systemic rather than hepatocyte-specific mitophagic clearance.

Sex and phenotype heterogeneity remain unresolved, as human trials rarely report sex-stratified mitophagy outcomes despite known sex differences in MASLD biology and exercise response. A fundamental limitation is that static LC3 or BNIP3 concentrations are uninformative about flux direction:

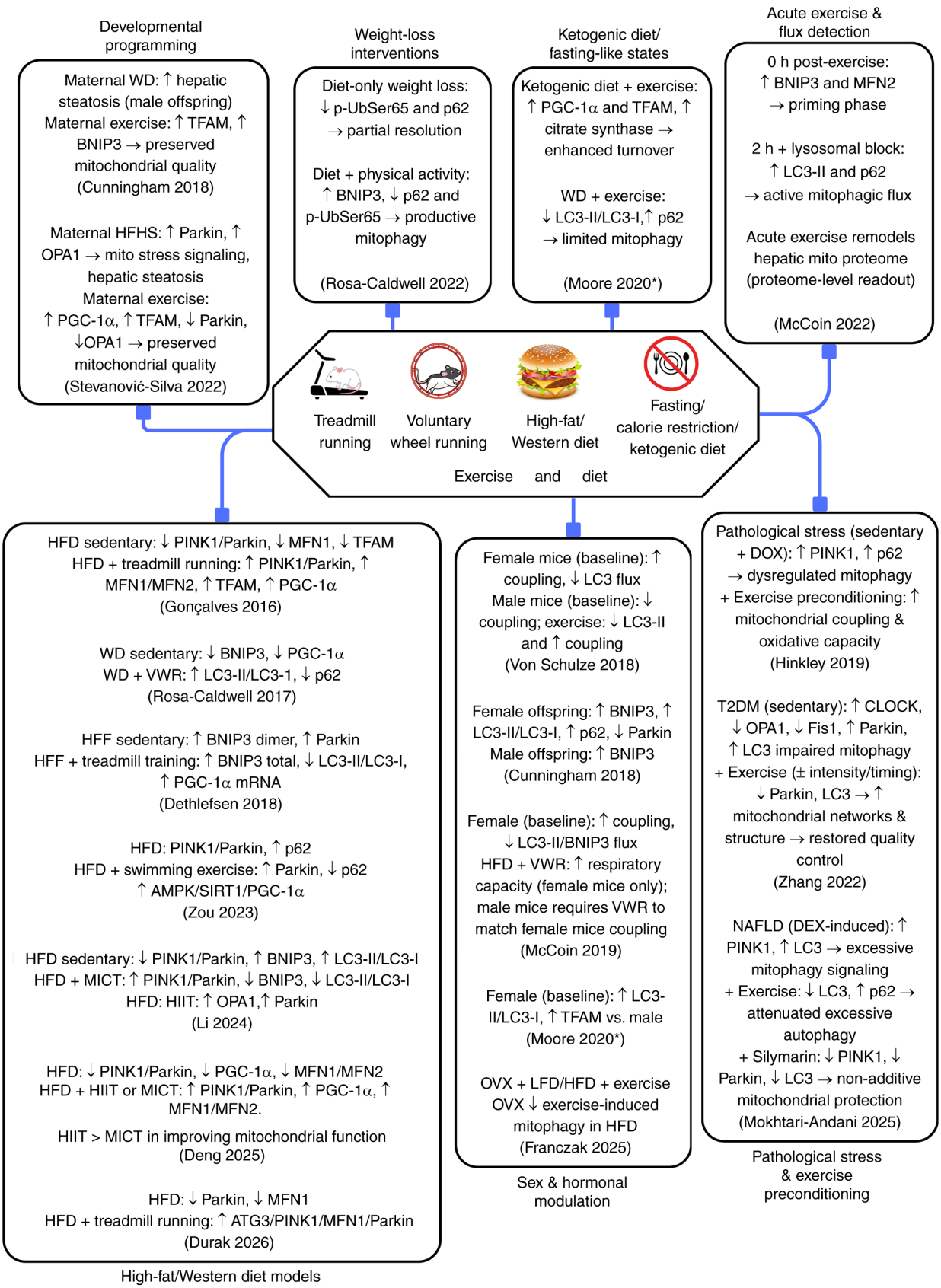

Figure 3. Integrated effects of exercise modality, dietary context, sex, hormonal status, developmental programming and pathological stress on hepatic mitophagy and mitochondrial quality control. All findings are from animal models and no human liver mitophagy data are included. *Evidence from Moore *et al* reflects general autophagy markers rather than mitophagy-specific readouts. AMPK, AMP-activated protein kinase; ATG3, autophagy-related 3; BNIP3, Bcl-2 interacting protein 3; CLOCK, circadian locomotor output cycles kaput; DEX, dexamethasone; DOX, doxorubicin; Fis1, mitochondrial fission protein 1; HFD, high-fat diet; HFF, high-fat high-fructose diet; HFHS, high-fat high-sucrose diet; HIIT, high-intensity interval training; LFD, low-fat diet; MFN, mitofusin; MICT, moderate-intensity continuous training; NAFLD, non-alcoholic fatty liver disease; OPA1, optic atrophy protein 1; OVX, ovariectomy; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; PINK1, PTEN-induced kinase 1; p-Ub, phosphorylated-ubiquitin; SIRT1, sirtuin 1; T2DM, type 2 diabetes mellitus; TFAM, mitochondrial transcription factor A; VWR, voluntary wheel running; WD, Western diet.

Marker accumulation may reflect more initiation or less degradation, and the reviewed literature contains multiple examples where the same profile corresponded to diametrically opposite biological states. Study heterogeneity arising from differences in diet, exercise type, duration, sex, age and genetic background compounds this interpretive challenge. Mitophagy itself adds further complexity, as both inadequate and excessive clearance can be detrimental. Progress will require delineating the adaptive-maladaptive threshold and validating non-invasive biomarkers such as plasma acylcarnitines, breath-test indices or cell-free mitochondrial DNA. Crosstalk between mitophagy and related quality-control processes, including biogenesis, fission-fusion dynamics and mitochondrial unfolded protein response, also remains insufficiently explored.

8. Pharmacological implications

Pharmacological and nutraceutical mitophagy inducers represent a promising but clinically underdeveloped therapeutic option for metabolic liver disease. These agents can be grouped by the mitophagy pathway they engage. Metformin stands out as the candidate with the strongest clinical evidence for mitophagy induction. In a randomized placebo-controlled trial, patients with T2DM who received metformin exhibited upregulation of PINK1, Parkin, MFN2, NIX, LC3-II and lysosome-associated membrane protein 2, together with AMPK activation, suggesting mitophagy induction as a glucose-lowering-independent effect (74). Mechanistically, metformin-driven AMPK activation concurrently phosphorylates ULK1, stabilizes BNIP3 and suppresses mTOR, engaging the mitophagy network at multiple levels simultaneously.

Urolithin A acts on mitophagy through PINK1 stabilization and p-Ub accumulation and has shown acceptable safety, bioavailability, and mitochondrial health benefits in Phase I human trials, although these findings derive from skeletal muscle studies and liver-specific data are lacking (75,76). NAD^+ precursors such as nicotinamide mononucleotide and nicotinamide riboside represent another mechanistically based approach: By replenishing NAD^+, they activate SIRT1, which promotes BNIP3/NIX-dependent mitophagy via FOXO3 deacetylation and facilitates autophagosome maturation through LC3 deacetylation (77,78). These effects lead to restored mitophagy in disease models including ATM deficiency and neurodegeneration; however, liver-specific mitophagy endpoints have not been assessed in human trials. More selective mitophagy-targeting agents are also emerging; for example, TJ0113 is a first-in-class small-molecule mitophagy inducer with favorable GLP-compliant preclinical safety data, but its current development is still outside liver disease (79). Ub-specific protease 30 (USP30) inhibitors represent a promising emerging class. USP30 is a deubiquitinase localized on the outer mitochondrial membrane that antagonizes Parkin-mediated ubiquitination, and its inhibition promotes mitophagy without requiring mitochondrial depolarization. MTX325, an orally bioavailable USP30 inhibitor, has entered Phase I clinical trials, although it has not yet been tested for metabolic liver disease (45,80,81). In the liver-specific context, recent NASH data have identified the tumor necrosis factor α-Myc-interacting zinc-finger protein 1/peroxiredoxin/Parkin axis as a potential therapeutic target, because disruption of this inflammatory feedback loop may restore Parkin-mediated hepatocyte mitophagy and reduce NASH progression (82). Harmol, a β-carboline alkaloid, also warrants mention here, as it mimics exercise-induced mitophagy through transient mitochondrial depolarization and AMPK engagement, with demonstrated efficacy in improving metabolic health in model organisms (83).

In addition to direct mitophagy inducers, mitochondrial dynamics regulators such as DRP1 may represent future therapeutic targets in NAFLD. While DRP1-mediated fission is necessary to segregate damaged organelles for mitophagic clearance, its overactivation promotes fragmentation, inflammation and fibrosis (8). Human NAFLD data identifying DRP1 as a marker of hepatic inflammation and fibrosis suggests that the therapeutic goal should be dynamic balance rather than fission enhancement as such (84). Future management of MASLD/metabolic dysfunction-associated steatohepatitis may require integrating lifestyle interventions with pharmacological mitophagy modulation, whether through AMPK activators, urolithin A or Parkin-targeted agents, although all such strategies await rigorous validation in liver-specific human trials.

9. Conclusion

The regulation of hepatic mitophagy is multidetermined and influenced by exercise type, nutritional context, biological sex and parental programming. Within the NAFLD setting, voluntary or low-intensity activity falls short of restoring mitophagic function, and higher-intensity protocols combined with dietary modification or weight loss appear necessary to drive meaningful mitochondrial improvement. Two major pathways of mitophagy (Ub- and receptor-mediated) are modulated by exercise, with energetic stress and hormonal milieu determining their relative contribution. Increased mitophagy signaling is not always associated with beneficial outcomes; therefore, efficient completion of lysosomal clearance serves an important role in mitochondria recovery. Adaptations to exercise and dietary interventions are further modified by sex hormones and maternal or paternal programming, which highlights the chronic and intergenerational dimensions of mitochondrial regulation. In summary, effective optimization of hepatic mitochondrial health should integrate exercise with nutritional state, biological sex and parental programming, recognizing mitophagy as a conditional therapeutic target. Thus, mitophagy should be considered a context-dependent therapeutic target rather than a pathway that should always be stimulated.

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Authors' contributions

All authors (JWG, DKJ, FK, SS and RL) conceptualized the study. JWG supervised the work and drafted the manuscript. DKJ and RL contributed to critical evaluation and interpretation of the literature. FK and SS assisted in literature organization and synthesis. Data authentication is not applicable. All authors revised the manuscript, and read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Artificial intelligence statement

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

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