

Exercise redox routing and mitochondrial quality-control ceilings in older skeletal muscle

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Abstract

Background: Aging skeletal muscle often shows reduced mitochondrial reserve, altered redox handling, impaired quality-control signaling, and greater vulnerability to unloading. Exercise is a consistent mitochondrial stimulus, but recent primary studies indicate that the relevant signal is not a single beneficial pathway. The same intervention class can induce proteostatic, bioenergetic, autophagic, and redox effects whose translational meaning depends on endpoint, timing, and baseline vulnerability.

Objective: This working paper defines a claim-bounded evidence map for exercise-linked mitochondrial redox routing and quality-control responses in older skeletal muscle.

Methods: PubMed and PubMed Central records were searched on 2026-10-02 for primary studies linking aging, skeletal muscle, exercise, mitochondrial function, redox biology, mitophagy, autophagy, PGC-1alpha, or mitochondrial DNA. Eight primary sources were coded by population, modality, timing, endpoint class, observed evidence, and claim boundary. No pooled effect estimate was calculated because designs ranged from acute biopsy studies and bed-rest countermeasures to randomized supplement-training studies and observational transcriptomics.

Results: Recent human and mechanistic evidence supported three bounded lanes. Exercise exposure was repeatedly linked to mitochondrial signaling or proteostasis, including PGC-1alpha transcriptional activation and mitochondrial translation biology [1,8]. In older adults, exercise countermeasures or resistance-based programs supported respiration, muscle-volume protection, H₂O₂-emission moderation, or redox balance under specific protocols [3,6]. Constraint evidence showed that antioxidant augmentation did not necessarily improve exercise redox signaling and that aged mitochondrial DNA may mark altered acute redox responses [5,7].

Conclusions: The supported claim is endpoint-specific mitochondrial adaptation, not treatment efficacy, supplement additivity, or single-marker prescription. Future tests should stratify older muscle by baseline mitochondrial quality, unloading exposure, and redox response before stronger translational claims are made.

Keywords: skeletal muscle aging; exercise; mitochondrial redox; mitophagy; PGC-1alpha; mitochondrial quality control

1 Introduction

Exercise remains one of the strongest physiological inputs for skeletal-muscle mitochondrial remodeling, yet older muscle does not present as a single deficit. Aging can involve lower mitochondrial respiratory reserve, altered reactive oxygen species handling, impaired proteostasis, altered autophagy or mitophagy, denervation pressure, and reduced tolerance to disuse. A useful translational synthesis therefore needs to separate exercise modality, timing, population, and endpoint class rather than treating all mitochondrial outcomes as interchangeable.

The current theory-corpus signal emphasized fuel inputs, oxidative phosphorylation, mitochondrial DNA maintenance, mitophagy, and biogenesis. Public reporting converted that signal into a testable literature question: in older skeletal muscle, which mitochondrial endpoints are directly supported by recent primary evidence after exercise or related stressors, and which claims exceed the evidence?

The claim ceiling is stated before the results. This synthesis can support statements that exercise or unloading countermeasures are associated with endpoint-specific mitochondrial adaptations in defined human or mammalian skeletal-muscle contexts. It cannot support disease-treatment efficacy, individualized prescription from a single biomarker, supplement additivity, or durable clinical benefit unless those outcomes were directly measured in the cited source.

2 Methods

The search date was 2026-10-02. PubMed searches used combinations of aging, skeletal muscle, exercise, mitochondrial, redox, older adults, mitophagy, resistance exercise, and SOMMA. Records were eligible when they were primary studies in human or mammalian skeletal muscle and measured exercise, unloading, antioxidant, redox, mitochondrial bioenergetic, mitophagy, autophagy, PGC-1alpha, mitochondrial translation, or mitochondrial DNA endpoints relevant to older muscle. Reviews, commentaries, unrelated tissue systems, and records without skeletal-muscle mitochondrial endpoints were excluded from coding. PMID, DOI where available, publication type, population, intervention or exposure, endpoint class, and abstract-level finding were checked against PubMed or PubMed Central metadata before inclusion.

Each source was coded into the accompanying machine-readable table by citation key, study design, population, modality, timing, endpoint class, observed evidence, and interpretive limitation. Endpoint classes were not pooled because the studies were heterogeneous by design and scale. A source was coded as supportive when it directly supported an exercise-linked mitochondrial adaptation, constraint when it limited a stronger interpretation, or mixed when it supported exercise adaptation while limiting a co-intervention claim. The evidence table mirrors the claim ceiling by pairing every finding with an explicit boundary.

Counts were computed from the coded evidence table. Figure source data, evidence coding, public explainer copy, manuscript source, and generated figures are included in the bundle. The analysis process figure documents the source-preserving workflow. The concept figure is labeled conceptual and distinguishes evidence-supported links from hypotheses. No identifiable patient data were used.

3 Results

3.1 Evidence synthesis

Eight primary sources were coded. Six were direct human or older-adult sources and two supplied mechanistic context for exercise-responsive PGC-1alpha or mitochondrial proteostasis. The evidence separated into support, constraint, and mixed lanes. Supportive studies connected exercise or exercise countermeasures

with PGC-1alpha transcription, mitochondrial translation/proteostasis, mitophagy-associated responses, respiration, muscle-volume protection, and redox efficiency [1,3,4,6,8]. Constraint studies limited stronger antioxidant or biomarker claims because MitoQ did not alter exercise-induced kinase phosphorylation or gene upregulation in older muscle, and aged mitochondrial DNA was associated with altered acute redox response rather than a ready prescribing rule [5,7]. The SOMMA transcriptomic evidence supported relevance of autophagy and mitophagy pathways to older adult function, but its cross-sectional structure did not establish intervention causality [2].

The native evidence table lists modality, timing, population, endpoint class, finding, and claim boundary for every coded source. The table is intended as a translational guardrail: each positive mitochondrial endpoint is paired with the narrowest supported interpretation. This structure prevents a respiration or signaling result from being converted into a clinical efficacy statement without direct clinical measurement.

3.2 Evidence-coded sensitivity analysis

The synthesis was robust to excluding older mechanistic precedent [8] because recent exercise and aging studies still supported endpoint-specific adaptation [1,3,4,6]. It was not robust to removing constraint evidence [5,7]. Without those sources, the paper would overstate antioxidant or biomarker-guided intervention readiness. The most conservative reading is therefore not that exercise uniformly improves all mitochondrial biology in older muscle, but that repeated exercise stress can route adaptation through several mitochondrial endpoints while baseline vulnerability and antioxidant exposure define boundaries.

4 Discussion

The coded evidence supports a routing model rather than a single-pathway model. Exercise can act upstream of PGC-1alpha signaling, mitochondrial translation, mitophagy-associated responses, and redox efficiency, but each endpoint has a different evidentiary status. Acute resistance exercise can activate mitophagy-associated biology in human skeletal muscle [4], whereas longer training or unloading-countermeasure protocols in older adults can improve respiration, redox balance, muscle volume, or H2O2-emission profiles under defined conditions [3,6]. Observational SOMMA data place autophagy and mitophagy gene expression near mobility and mitochondrial function, but do not convert those associations into causal treatment claims [2].

The constraint lane is scientifically important. MitoQ supplementation reduced maximal mitochondrial H2O2 emission capacity but did not improve the acute exercise redox-signaling response measured through phosphorylation or gene-expression endpoints [5]. Similarly, aged mitochondrial DNA was associated with altered acute redox responses after exercise, indicating a vulnerability axis rather than a validated prescription marker [7]. These findings argue against a simple antioxidant-addition model and favor endpoint-specific response testing.

The concept figure summarizes the interpretation: exercise stress is an input, adaptive signaling and quality-control endpoints are intermediate lanes, measured function is protocol-dependent, and the claim ceiling remains below treatment efficacy. Dashed links identify hypotheses that require direct testing before clinical transfer.

5 Limitations

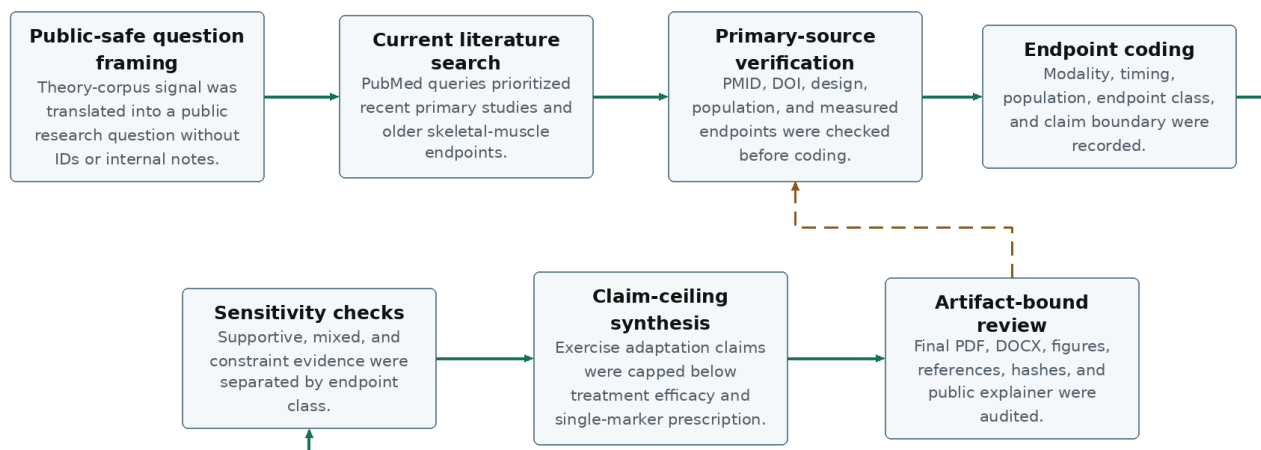
The synthesis used abstract- and metadata-verified primary sources rather than a registered systematic-review protocol. Designs were heterogeneous, so no pooled effect estimate was calculated. Several endpoints were measured in acute biopsy windows or controlled unloading contexts, which limits transfer to community exercise prescriptions. Some sources involved mechanistic or observational

Table 1. Primary-study evidence matrix with modality, timing, endpoint class, and claim boundary.

Study	Model and perturbation	Key finding	Interpretive limitation
de Smalen 2023	Mechanistic mouse and human-context analysis of sarcopenic muscle, PGC-1alpha perturbation, and exercise-associated mitochondrial translation.	Age-associated mitochondrial translation impairment was linked to PGC-1alpha/ERRalpha regulation and mitigated in exercise-associated contexts.	Supports mitochondrial proteostasis routing; does not alone establish clinical improvement in older adults.
Coen 2024	Observational SOMMA skeletal-muscle transcriptomic analysis in older adults.	Autophagy and selective-autophagy gene-expression patterns were associated with mobility, muscle volume, and mitochondrial function.	Associational evidence supports pathway relevance but not intervention causality.
Dulac 2025	Head-down tilt bed-rest intervention with and without multimodal exercise countermeasure.	Exercise prevented bed-rest-associated muscle-volume loss, mitochondrial ROS increase, and autophagy/denervation marker increases, and increased mitochondrial content and respiration.	Evidence applies to protected unloading physiology, not broad disease treatment.
Diaz-Castro 2024	Acute human resistance-exercise muscle-biopsy study.	A single bout of resistance exercise triggered mitophagy-associated responses in human skeletal muscle.	Shows acute quality-control activation; durable adaptation and older-adult functional transfer require separate evidence.
Broome 2025	Randomized double-blind placebo-controlled MitoQ supplementation followed by acute exercise.	MitoQ reduced maximal H2O2 emission capacity but did not alter respiration, exercise-induced kinase phosphorylation, or mitochondrial/antioxidant gene upregulation.	Constrains antioxidant-augmentation claims around exercise signaling in older muscle.
Flensted-Jensen 2026	Randomized polyphenol/placebo loading with 12-week resistance training plus small-dose HIIT.	Training improved fitness, lean mass, strength, and redox balance; polyphenols did not augment the adaptation and may have altered vitamin responses.	Supports exercise adaptation; supplement co-administration is not supported as additive.
Ruple 2026	Human young-versus-older adult acute exercise biopsy study.	Aged mitochondrial DNA was associated with altered acute redox responses after exercise in human skeletal muscle.	Indicates a vulnerability axis; does not prove that a single redox marker can prescribe an intervention.
Pilegaard 2003	Human acute exercise transcriptional study.	Exercise transiently activated PGC-1alpha transcription in human skeletal muscle.	Provides mechanistic precedent for acute signaling, not an aging-specific outcome.

Analysis workflow

Public-safe framing, current source verification, endpoint coding, bounded synthesis, and artifact review

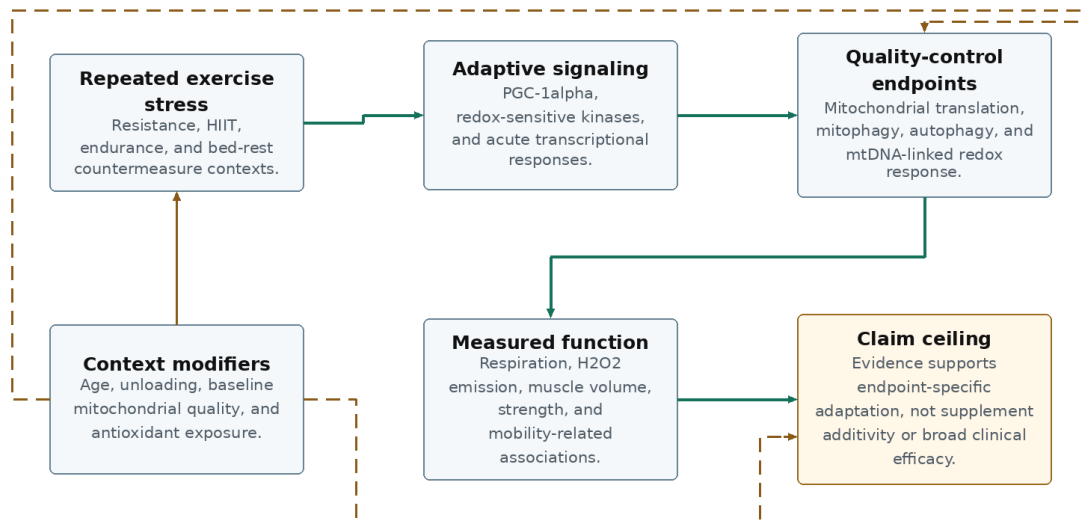


Solid arrows: source-preserving workflow. Dashed arrow: independent review may trigger revision and re-rendering.

Figure 1. Analysis process for the exercise redox-routing synthesis. Solid connectors show the path from public-safe question framing through current literature search, primary-source verification, endpoint coding, sensitivity checks, claim-ceiling synthesis, and artifact review; the dashed connector marks independent review that may trigger revision.

Conceptual adaptation boundary

Solid links summarize observed evidence classes; dashed links mark testable hypotheses, not treatment advice



Interpretation: adaptation strength depends on exercise context and baseline vulnerability; antioxidant co-intervention is a constraint lane.

Figure 2. Conceptual summary of exercise redox routing in older skeletal muscle. Solid links summarize observed evidence classes connecting exercise stress, adaptive signaling, quality-control endpoints, and measured function; dashed links identify hypotheses about vulnerability stratification and antioxidant constraints that require direct testing.

designs rather than randomized clinical outcomes. Sex-specific and age-stratified conclusions remain limited because the coded table could not harmonize participant-level data across studies.

6 Conclusions

Recent primary evidence supports endpoint-specific mitochondrial adaptation after exercise or exercise countermeasures in older skeletal-muscle contexts. The strongest public claim is that exercise can route mitochondrial remodeling through proteostasis, respiration, redox efficiency, mitophagy, autophagy, and mtDNA-linked vulnerability lanes depending on protocol and baseline state. The evidence does not support broad clinical efficacy, supplement additivity, or single-marker prescription.

Declarations

Data and code availability. The evidence table, machine-readable data, analysis code, figures, and QA record accompany this repository deposit.

Ethics statement. This literature synthesis used no identifiable patient data and required no new human-participant or animal research.

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AI assistance. AI tools assisted literature synthesis, drafting, data visualization, and formatting. Gemini provided an independent critique. Andrew Friedl remains solely responsible for the content and is the sole author.

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