The mitochondrial side of frailty

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Purpose of review
Frailty, a prevalent geriatric condition marked by reduced physiological reserve and greater vulnerability to stressors, is increasingly linked to mitochondrial dysfunction. This review summarizes current evidence on mitochondrial quality control, bioenergetics, and signaling in frailty, with emphasis on biomarker discovery and translational potential.

Recent findings
Preclinical and human studies have shown that impaired mitochondrial biogenesis, altered dynamics, and defective mitophagy contribute to frailty, sarcopenia, and immune dysregulation. Frail older adults exhibit reduced mitochondrial DNA content, diminished mitochondrial respiratory capacity, elevated reactive oxygen species generation, and distinctive metabolomic changes. Potential biomarkers include mitochondria-derived vesicles, circulating metabolites, and measures of peripheral blood mononuclear cell respiration, which may enable early detection of functional decline. Multivariate profiling approaches have identified sex-specific and shared molecular signatures converging on mitochondrial pathways. Interventions promoting mitochondrial health, including resistance training and targeted immunomodulation, hold promise in slowing frailty progression.

Summary
Mitochondrial dysfunction lies at the intersection of musculoskeletal, metabolic, and immune changes underpinning frailty. While integrative biomarker panels have defined metabolic signatures, early diagnosis and personalized therapies remain unmet needs. Longitudinal studies are required to establish causality, refine biomarker utility, and guide precision medicine strategies to preserve mitochondrial function, extend healthspan, and improve quality of life in aging populations.

Keywords
inflammaging, metabolic dysregulation, mitochondrial quality control, oxidative capacity, physical frailty

INTRODUCTION

Frailty is a prevalent geriatric condition characterized by diminished homeostatic reserve and progressive physiological decline, resulting in reduced tolerance to stressors and increased risk of negative health events. Frailty is a central focus of aging research, particularly within the framework of the geroscience hypothesis, which posits that the biological processes driving aging also underpin frailty as well as most age-related conditions, through an imbalance between accumulated molecular and cellular damage and declining resilience.

Progress in frailty research has been hindered by ongoing debates over its operational definition. While widely used constructs, most notably the phenotypic model by Linda Fried and the deficit accumulation model by Kenneth Rockwood, offer valuable frameworks, they diverge in classification and risk misidentification of at-risk individuals [1]. To address these limitations, there is growing interest in biologically anchored definitions of frailty that focus on measurable pathways and mechanisms, offering potential for earlier detection, more precise phenotyping, and targeted interventions [1].

Emerging evidence highlights both sex-specific biological contributors and shared age-associated determinants of frailty. Among these, mitochondrial dysfunction has gained particular attention. Early hypotheses pointed to declining mitochondrial bioenergetic capacity as a driver of reduced physiological resilience [1]. Subsequent metabolomics studies

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Curr Opin Clin Nutr Metab Care 2025, 28:000–000
DOI:10.1097/MCO.0000000000001175

KEY POINTS

- Mitochondrial dysfunction is a key contributor to frailty and sarcopenia.
- Multisystem dysregulation, including immune senescence and inflammaging, intersects with and contributes to mitochondrial decline in frailty.
- Multivariate biomarker analyses combining metabolic, inflammatory, and mitochondrial markers enhance the identification of frailty and enable sex-specific profiling.
- Mitochondria-derived vesicles are emerging as minimally invasive biomarkers reflective of systemic mitochondrial health.
- Validation of mitochondrial-related biomarkers in large studies with frail individuals is highly sought after for diagnostic and intervention purposes.

have reinforced this view identifying disrupted metabolic pathways, especially those involving carnitine and vitamin E, and suggesting impaired fatty acid transport, compromised oxidative phosphorylation, and inadequate antioxidant defense as crucial mechanisms [1]. Reduced carnitine availability limits mitochondrial energy production, while insufficient vitamin E exacerbates oxidative stress, perpetuating organelle damage [1].

More recently, the focus has expanded beyond bioenergetics to include mitochondrial quality control (MQC) mechanisms, such as mitophagy, biogenesis, and inter-organelle signaling, which are critical in maintaining cellular homeostasis. Their decline with age has been linked to inflammaging, a chronic state of low-grade inflammation characteristic of older adults, which is increasingly recognized as a biological bridge among aging, frailty, and multiple age-related diseases. However, disentangling the causal role of reduced mitochondrial quality in frailty remains challenging, in part due to methodological constraints in human studies [2].

Nevertheless, available evidence supports the idea that targeting mitochondrial health could aid in preventing or delaying frailty. While robust evidence from large longitudinal studies is still emerging, the field is now well positioned to advance from descriptive epidemiology toward mechanistic research to uncover biological foundations of frailty.

MITOCHONDRIA: FUNCTIONS, QUALITY CONTROL, AND SIGNALING ROLES

Mitochondria are central hubs of multiple cellular activities, orchestrating not only energy metabolism but also calcium and iron homeostasis, apoptotic signaling, and several biosynthetic processes. These functions rely on the coordinated interplay between structural integrity, bioenergetic competence, and dynamic quality control systems, including membrane potential maintenance, mitophagy, mitochondrial DNA (mtDNA) and protein synthesis, inter-organelle communication, and metabolic signaling.

The mitochondrial ultrastructure is optimized for efficient oxidative phosphorylation and protein import. The highly folded inner mitochondrial membrane (IMM) increases the surface area available for the electron transport chain, where electrons from NADH and $FADH_2$ flow to molecular oxygen, generating a proton motive force that drives ATP synthesis via ATP synthase.

Mitochondrial function is safeguarded by MQC mechanisms encompassing proteostasis, dynamics (fission/fusion), biogenesis, and mitophagy (Fig. 1) [3▪]. Biogenesis is a transcriptionally coordinated, cross-compartmental process driven by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which activates nuclear respiratory factors (NRF1/NRF2) and mitochondrial transcription factor A (TFAM), essential for mtDNA transcription and replication [4]. This process is fine-tuned by posttranslational modifications (e.g., phosphorylation) in response to metabolic signals such as AMP-activated protein kinase (AMPK), which shifts metabolism toward catabolic ATP-generating pathways under energy stress.

Approximately 99% of mitochondrial proteins are nuclear encoded, synthesized in the cytoplasm, and imported through the translocases of the outer and inner membranes (TOM/TIM complexes), which include several protein components like TOM20, TOM22, TOM40, and TIM23 [5]. Protein import is dependent on membrane potential and is regulated by multiple modifications, including phosphorylation, oxidative modifications, glycosylation, acetylation, and binding of ions or metabolites.

Mitochondrial shape, distribution, and turnover are governed by fission and fusion events that remodel the network in response to physiological needs, under the control of evolutionarily conserved proteins [6]. Dynamin-related protein 1 (DRP1) is a key regulator of mitochondrial fission. In response to cellular cues, DRP1 is recruited from the cytosol to the outer mitochondrial membrane (OMM), where it interacts with adaptor proteins such as mitochondrial dynamics proteins of 49 and 51 kDa (MID49, MID51) and mitochondrial fission factor (MFF). Upon binding, DRP1 oligomerizes into GTPase-driven spiral structures that constrict and ultimately sever the membrane. The absence or functional loss

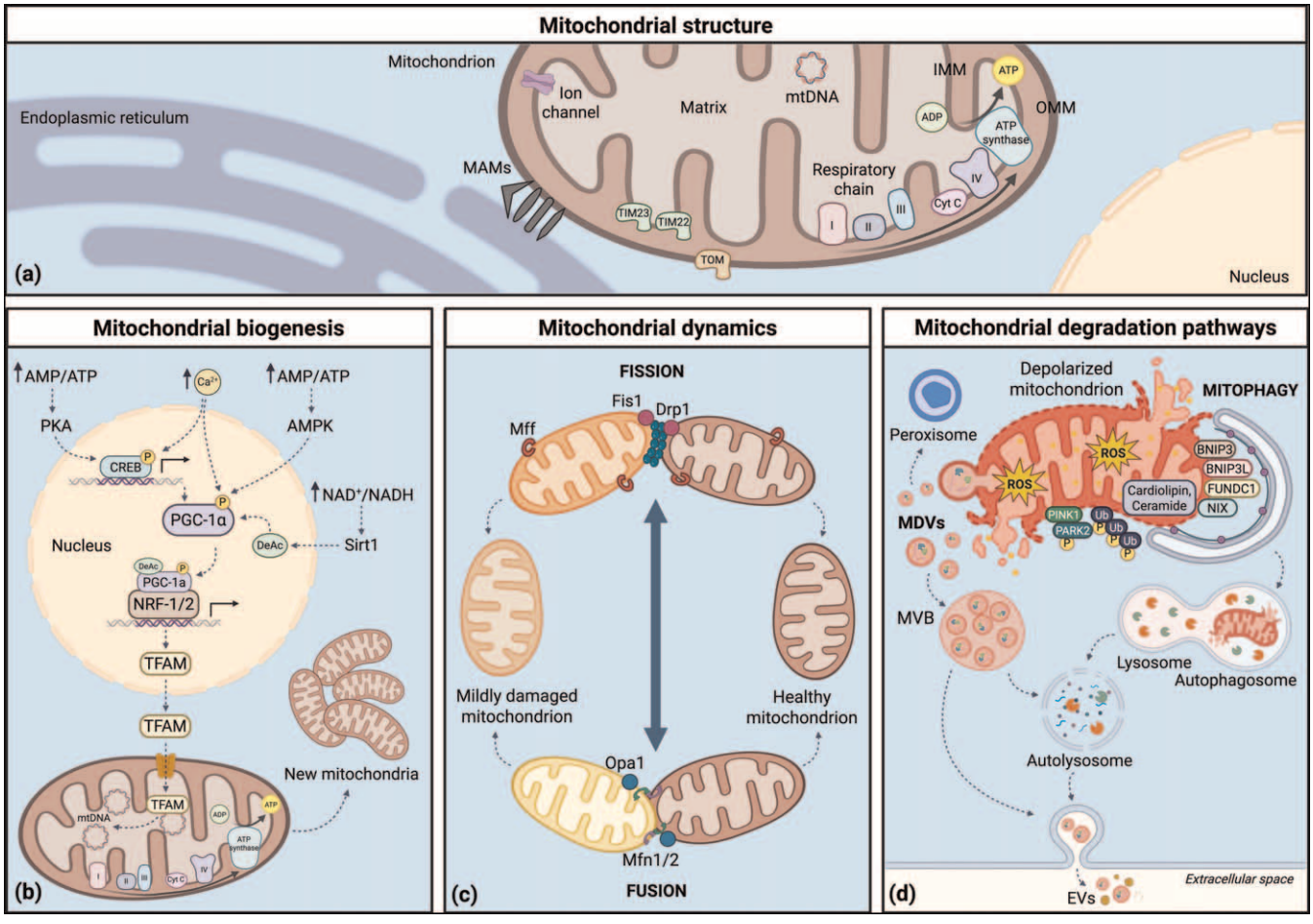

FIGURE 1. Overview of the mitochondrial structure and quality control mechanisms potentially contributing to frailty pathophysiology. (a) Mitochondria have a double-membrane system: the inner membrane forms cristae hosting the respiratory chain complexes, while the matrix contains mtDNA. TIM and TOM complexes regulate protein import, and mitochondria-associated membranes connect mitochondria with the endoplasmic reticulum. (b) Biogenesis is regulated by PGC-1α-dependent activation of NRF-1/2 and TFAM, promoting new organelle synthesis. (c) Dynamics result from the balance between fusion (Opa1, Mfn1/2) and fission (Fis1, Mff, Drp1), limiting damage. (d) Mitophagy eliminates dysfunctional mitochondria via autophagosome–lysosome fusion, while mildly damaged organelles can release mitochondria-derived vesicles (MDVs) that are degraded in peroxisomes/lysosomes or secreted as extracellular vesicles. ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BNIP3, BCL2-interacting protein 3; BNIP3L, BCL2 interacting protein 3 like; Ca^{2+}, calcium ion; CREB, cAMP response element-binding protein; Cyt C, cytochrome C; DeAc, deacetylated group; Drp1, dynamin-1-like protein; EV, extracellular vesicles; Fis1, mitochondrial fission 1 protein; FUNDC1, FUN14 domain-containing protein 1; IMM, inner mitochondrial membrane; MAMs, mitochondria associated membranes; MDVs, mitochondria-derived vesicles; Mff, mitochondrial fission factor; Mfn1/2, mitofusin 1/2; MQC, mitochondrial quality control; mtDNA, mitochondrial DNA; MVBs, multivesicular bodies; NAD^+/NADH, nicotinamide adenine dinucleotide oxidized/reduced; nDNA, nuclear DNA; NIX, NIP-3-like protein X; NRF-1/2, nuclear respiratory factor 1/2; OMM, outer mitochondrial membrane; Opa1, mitochondrial protein optic atrophy 1; P, phosphate group; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator-1; PINK1, PTEN-induced kinase 1; PKA, protein kinase A; ROS, reactive oxygen species; Sirt1, Sirtuin 1; TFAM, mitochondrial transcription factor A; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane; Ub, ubiquitin. Created in BioRender (accessed on August 7, 2025).

of DRP1 or its adaptors results in elongated, interconnected mitochondrial networks due to impaired division. Notably, fission events are frequently initiated at mitochondria–endoplasmic reticulum contact sites, which act as spatial landmarks for constriction and facilitate coordination with mtDNA nucleoid replication. This spatial coupling ensures even distribution of genetic material. Conversely, mitochondrial fusion facilitates the mixing of mitochondrial contents, allowing redistribution of proteins, lipids, and mtDNA to

complement functional deficits and dilute localized damage. This process supports bioenergetic efficiency, stress adaptation, and maintenance of a healthy mitochondrial network. Disruption of fusion, whether through genetic defects, posttranslational dysregulation, or chronic metabolic stress, has been implicated in aging, neurodegenerative conditions, and metabolic disorders, where impaired complementation accelerates the accumulation of dysfunctional organelles.

Mitophagy, a specialized and evolutionary conserved form of autophagy, enables the selective removal of damaged or dysfunctional mitochondria [2]. The PTEN-induced putative kinase 1 (PINK1)–Parkin pathway is central to this process. Upon mitochondrial depolarization, PINK1 accumulates on the OMM, recruiting and activating Parkin to ubiquitinate membrane proteins, targeting the organelle for autophagosome-mediated degradation [2].

An alternative and increasingly recognized MQC route involves mitochondria-derived vesicles (MDVs). These small vesicles bud from the OMM and/or IMM and selectively package damaged or oxidized cargo for delivery to lysosomes, peroxisomes, or the extracellular space without whole organelle degradation [7]. MDV biogenesis occurs via at least two constitutive pathways: the first involves the formation of electron-dense mitochondrial portions that bud off as vesicles, while the second proceeds through the elongation of thin membrane protrusions along microtubules, which are subsequently pinched off at their tips [7]. These mechanisms operate under steady-state conditions and are largely dependent on the mitochondrial dynamics regulator DRP1 and mitochondrial Rho GTPases MIRO1 and MIRO2, which facilitate mitochondrial tubulation, cargo segregation, and membrane scission [7]. In addition to constitutive MDV generation, cells can enact MDV production in response to changing metabolic conditions. Under mild mitochondrial stress MDVs are formed via PINK1–Parkin-dependent pathway [7]. This stress-adaptive pathway may act as an early defense, maintaining mitochondrial integrity without wholesale turnover.

Distinct MDV populations have been identified depending on cellular metabolic conditions. For instance, oxidative stress can instigate the generation of vesicles enriched in mitochondrial matrix proteins such as pyruvate dehydrogenase (PDH) but lacking OMM proteins like TOM, whereas steady-state MDVs often show an opposite composition [7]. Upon generation, MDVs are sorted along different intracellular and extracellular trafficking routes. Intracellularly, they can be directed to lysosomes or peroxisomes for degradation, with pathway selection guided by signaling proteins including syntaxin-17, Tollip, PINK1, Parkin, and vacuolar protein sorting 35 (VPS35) [7]. Alternatively, MDVs can be packaged into multivesicular bodies and released into the extracellular environment, a process regulated by factors such as CD38, sorting nexin 9, and optic atrophy 1 (OPA1). Recently, a novel class of extracellular vesicles, termed mitovesicles, has been described. Mitovesicles carry mitochondrial proteins such as voltage-dependent anion channel (VDAC), cytochrome C oxidase subunit 4, and PDH-E1α, but unlike other vesicle populations, lack typical structural components of mitochondria, suggesting a distinct biogenesis mechanism and release [8].

The complexity of MDV pathways underscores their vital roles in mitochondrial surveillance, interorganelle communication, and cellular adaptation to metabolic and oxidative stress. However, their heterogeneity also complicates classification and isolation, presenting challenges for standardizing extracellular vesicle research [3▪]. Clarifying MDV biogenesis and signaling in the context of aging and frailty may open new venues for biomarker discovery and targeted mitochondrial therapeutics [3▪,9▪].

MITOCHONDRIA IN THE FRAILTY CONTINUUM

Mitochondrial derangements in frailty

Age-related alterations in mitochondrial cristae architecture and network organization have been linked to ADP insensitivity, impaired respiratory capacity, elevated oxidative stress, and accumulation of mtDNA mutations. Nuclear genome instability, mostly resulting from inefficient repair, further compromises mitochondrial function, given that most mitochondrial proteins are nuclear encoded, including those required for biogenesis, mitophagy, apoptosis, and other MQC processes.

Declining physical function is a hallmark of frailty, reflected in the physical frailty model that underpins most clinical assessment tools. Sarcopenia, defined as quantitative (muscle mass) and qualitative (strength and/or function) losses of skeletal muscle, shares core clinical manifestations with frailty, including muscle wasting, dynapenia, and reduced physical function. As such, sarcopenia is increasingly viewed as a biological substratum of physical frailty, with mitochondrial dysfunction emerging as a unifying mechanism.

Recent evidence underscores the pivotal role of MQC signaling and bioenergetics in maintaining muscle integrity and functional resilience in aging. Transcriptomic analyses revealed marked downregulation of mitochondrial genes in the skeletal muscle of prefrail older adults, indicating that mitochondrial dysfunction may precede measurable performance

declines [10]. In older human skeletal muscle, expression of autophagy and mitophagy genes strongly correlates with mitochondrial function, muscle mass, and physical performance [11]. Furthermore, enhanced transcription of mitochondrial oxidative stress defense genes, such as superoxide dismutase 2, thioredoxin 2, peroxiredoxin 3, and glutaredoxin, has been associated with better mitochondrial respiration and physical function [12], highlighting the integration of redox control and bioenergetics in muscle health.

Deficits in skeletal muscle mitochondrial energetics have been identified as potential biological drivers of frailty [13▪▪]. Recent studies have shown lower mitochondrial energetics in older women compared with men, which helps explain the higher prevalence of mobility impairment observed in women [14▪]. Sex-specific associations with mitochondrial bioenergetics have also been described for perceived fatigability [15]. Finally, recent findings in humans highlight a decline in mitochondrial biogenesis and autophagic processes as a central mechanism contributing to sarcopenia progression and metabolic dysregulation [11].

Although diminished mitochondrial capacity is often interpreted as an intrinsic defect limiting ATP production, the responsiveness of sarcopenic muscle to exercise suggests that mitochondrial bioenergetics can be restored upon appropriate stimulation [16,17]. This supports the idea that reduced oxidative capacity in aging muscle may represent an adaptive downscaling to chronically low energy demand rather than irreversible failure. Decreased mitochondrial protein synthesis likely contributes to reduced ATP availability, creating a self-reinforcing cycle. Anabolic resistance, alongside with chronic inflammation and oxidative stress, further contributes to reduced mitochondrial protein synthesis and ATP availability [17]. Of note, these mechanisms can also mirror processes described in wasting conditions. Targeted exercise modalities, including resistance training, can restore mitochondrial coupling and oxidative capacity in aged skeletal muscle, supporting the concept of structured, progressive training as a mitochondria-directed strategy in frailty [16,17].

Frailty reflects a multisystem dysregulation in which coordinated musculoskeletal, metabolic, and stress-response networks progressively deteriorate [18]. Once this integrated regulation falls below a critical threshold, frailty manifests as reduced physiological reserve and resilience. Within this framework, inflammaging is acknowledged as a central driver linking immune dysregulation, mitochondrial decline, and muscle dysfunction. Transcriptomic profiling of the CD4/Treg axis (helper and regulatory T cells) in frail older adults has identified a dysfunctional Treg subtype characterized by reduced mitochondrial protein expression, impaired oxidative phosphorylation, and activation of the tumor necrosis factor (TNF)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, perpetuating inflammation [19]. Altered cytokine expression with age further perturbs the balance between pro- and anti-inflammatory responses, impairing mitochondrial function and hampering skeletal muscle regeneration.

Immune–mitochondrial crosstalk appears to be bidirectional and therapeutically relevant. In aged mice, T cell-specific overexpression of the antiapoptotic protein B-cell lymphoma-extra-large (Bcl-xL) enhanced adaptive immunity, reduced systemic inflammation, and preserved mitochondrial ultrastructure and bioenergetics in skeletal muscle, thereby preventing frailty [20▪]. These findings reinforce the concept that interventions targeting immune–mitochondrial interactions through metabolic, nutritional, or pharmacological means could help maintain muscle function and delay the onset of frailty and sarcopenia.

Mitochondria as a source of frailty biomarkers

Owing to the multifactorial nature of frailty, it is unlikely that a single biomarker can fully capture its biological complexity. Instead, multivariate biomarker approaches, integrating measures across molecular, metabolic, inflammatory, and functional domains, offer greater potential to reflect underlying pathophysiology and predict clinical outcomes. Given the central role of mitochondrial dysfunction in aging biology, mitochondria represent a rich source of candidate frailty biomarkers (Table 1).

The BIOSPHERE (BIOmarkers associated with Sarcopenia and Physical frailty in ElderRly pErsons) study evaluated 74 serum analytes spanning inflammation, muscle remodeling, neuromuscular junction integrity, and amino acid metabolism in older adults with and without physical frailty and sarcopenia (PF&S) [21]. Using sequential and orthogonalized covariance selection modeling, researchers identified a seven-biomarker panel that classified PF&S status with ~80% accuracy [21]. PF&S individuals exhibited elevated asparagine, aspartic acid, and citrulline, indicative of disrupted nitrogen and glutamine metabolism, processes tightly coupled to mitochondrial function. In contrast, non-PF&S participants had higher levels of platelet-derived growth factor BB (PDGF-BB), heat shock protein 72 (HSP72), myeloperoxidase (MPO), and α-aminobutyric acid, which are linked to muscle regeneration, immune activity, oxidative stress buffering, and mitochondrial redox homeostasis. Sex-stratified analyses revealed a conserved biomarker

Table 1. Summary of key human studies reporting the contribution of mitochondrial derangements to frailty

Main findings	Reference
Frailty is associated with reduced mitochondrial bioenergetics in skeletal muscle	[13▪▪]
Dysfunctional Tregs are marked by impaired oxidative phosphorylation via TNF/NF-κB activation in frail older people	[19]
Overexpression of Bcl-xL in T cells maintains mitochondrial integrity and function in muscle tissue, preventing age-related frailty in mice	[20▪]
An increase in EVs containing mitochondrial components indicates an attempt to eliminate malfunctioning organelles in physical frailty and sarcopenia	[22]
Frail older adults show low mtDNA, altered mitochondrial dynamics, reduced respiration, and elevated ROS in PBMCs	[24,25]
The FRAMITO project seeks to identify mitochondrial biomarkers in frail individuals	[26▪]

Bcl-xL, B-cell lymphoma-extra-large; EVs, extracellular vesicles; mtDNA, mitochondrial DNA; NF-κB, nuclear factor-κB; PBMCs, peripheral blood mononuclear cells; ROS, reactive oxygen species; TNF, tumor necrosis factor.

"core" in PF&S characterized by elevated aspartic acid, reduced HSP72, and lower macrophage inflammatory protein 1β (MIP-1β), pointing to both conserved and sex-specific molecular signatures, also converging on mitochondrial pathways [21]. Reduced circulating MPO levels reflect immune senescence, while diminished PDGF-BB and MIP-1β levels signal impaired muscle regenerative capacity and disrupted macrophage polarization, respectively. Lower α-aminobutyric acid implicates compromised glutathione biosynthesis and oxidative stress, processes closely regulated by mitochondrial function. HSP72 reduction suggests hormetic imbalance and mitochondrial protein stress. These alterations underscore the systemic nature of frailty and the utility of multivariate biomarker panels in its detection [21].

Recent findings point to MDVs as an additional source of frailty-related biomarkers [22]. These vesicles carry mitochondrial components altered under stress, contributing molecules that align with PF&S biomarker profiles. MDVs may thus provide real-time signatures of MQC and mitochondrial signaling in aging and frailty [22].

The MetaboFrail (metabolic biomarkers of frailty in older people with type 2 diabetes mellitus) study extended the multivariate approach used in BIOSPHERE to metabolomics, identifying specific metabolic signatures in frail or prefrail older adults with type 2 diabetes [23▪]. Notably, several markers converge on mitochondrial pathways, further supporting the relevance of mitochondrial health to frailty even in its early stages. This suggests that mitochondrial dysfunction may be detected before overt frailty. Taken as a whole, results from these studies highlight amino acid and other metabolite profiles as relevant to mitochondrial function that may also instruct plausible nutrition-informed targets [21,23▪]. However, dedicated nutrition trials in frail older adults remain limited and warrant evaluation.

Circulating peripheral blood mononuclear cells (PBMCs) are increasingly explored as an accessible window into systemic mitochondrial health. In older adults, frailty has been associated with lower PBMC mtDNA content, altered dynamics, reduced respiratory capacity, and elevated reactive oxygen species production [24]. Furthermore, mitochondrial oxygen consumption rate in PBMCs is significantly lower in frail individuals than in age-matched nonfrail controls, supporting its potential as a frailty biomarker [25].

The FRAMITO project is an ongoing initiative aiming to identify and validate mitochondrial dysfunction-associated biomarkers in frail individuals, both with and without chronic comorbidities [26▪]. Its integrative approach, combining molecular, metabolic, and functional assays, may advance the development of diagnostic tools and targeted interventions to preserve mitochondrial health, slow frailty progression, and improve quality of life in vulnerable older adults.

CONCLUSION

Mitochondrial dysfunction is emerging as a central driver in the complex biological network underlying frailty. Evidence from preclinical and human studies highlights the critical role of MQC, bioenergetics, redox homeostasis, and immunometabolic signaling in sustaining muscle integrity and functional resilience during aging. The interplay between inflammation, immune senescence, and mitochondrial pathways underscores the multisystem nature of frailty and supports the need for integrative biomarker discovery strategies. Multidimensional signatures, encompassing circulating metabolites, MDVs, and measures of PBMC respiration, offer promise for early detection and targeted intervention. While existing observations support exercise and nutritional interventions as promising mitochondria-

directed strategies, they remain still under-tested avenues for intervention. Longitudinal and mechanistic studies are essential to establish causality, define sex-specific patterns, and advance precision medicine approaches aimed at preserving mitochondrial health, slowing frailty progression, and improving quality of life in aging populations.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the Università Cattolica del Sacro Cuore (D1.2024 and D1.2025), the Italian Ministry of Health (Ricerca Corrente 2025), and the nonprofit research foundation "Centro Studi Achille e Linda Lorenzon" (N/A). E.M. received support from the European Union's Next Generation EU PRIN (2022YNENP3). E.M. also acknowledges co-funding from Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment PE8—Project Age-It: "Ageing Well in an Ageing Society". This resource was co-financed by the Next Generation EU (DM 1557 11.10.2022). The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Conflicts of interest

There are no conflicts of interest.

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The article describes the protocol of an ongoing study investigating mitochondrial dysfunction as a biomarker of frailty. By combining metabolomics and functional analyses, the research may uncover mechanisms linking cellular bioenergetics, oxidative stress, and frailty.