



From adaptation to exhaustion: defining exposure-related malnutrition as a bioenergetic phenotype of aging

Torsak Tippairote · Pruettithada Hoonkaew ·
Aunchisa Suksawang · Prayfan Tippairote

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Abstract Aging is increasingly understood not as the passive accumulation of molecular damage, but as the cumulative cost of unresolved physiological adaptation under bioenergetic constraint. This review introduces *Exposure-Related Malnutrition (ERM)* as a mechanistically grounded and clinically actionable phenotype of early maladaptation. ERM arises from sustained metabolic strain during chronic stress exposure and manifests not through overt weight loss or nutrient deficiency, but through subtle, multisystem declines in physical, cognitive, and regenerative capacity. These include fatigue, impaired recovery, cognitive slowing, immune dysregulation, chronic pain, anabolic resistance, and reproductive decline—features often missed by classical malnutrition criteria. We propose a unifying framework—*Respond* → *Adapt* → *Resolve*—to model the trajectory

of stress response and resolution, emphasizing the critical role of bioenergetic availability in shaping divergent outcomes. When metabolic substrates are insufficient, resolution fails and the system defaults to a trade-off state, prioritizing immediate survival over long-term maintenance. ERM represents this inflection point: a reversible, energy-constrained condition that precedes frailty and chronic disease. We review interconnected mechanisms—including neuroendocrine activation, immune reprogramming, skeletal muscle catabolism, translational suppression, and mitochondrial distress—that create a self-perpetuating loop of maladaptive adaptation. We map ERM onto key hallmarks of aging, propose a multidimensional staging model, and outline clinical strategies to detect and reverse ERM using dynamic biomarkers, functional assessments, and circadian-aligned lifestyle interventions. By reframing aging as a failure of adaptive resolution, this framework offers a novel lens to extend healthspan—via early detection of metabolic compromise and restoration of resilience before functional decline becomes irreversible.

Graphical abstract This model illustrates the trajectory of stress adaptation and resolution, highlighting how divergent outcomes—hormesis, homeostasis, or maladaptation—are shaped by energy and substrate availability. Exposure-Related Malnutrition (ERM) represents a subclinical, reversible state of unresolved adaptation under chronic bioenergetic strain. As allostatic load increases and nutrient support declines,

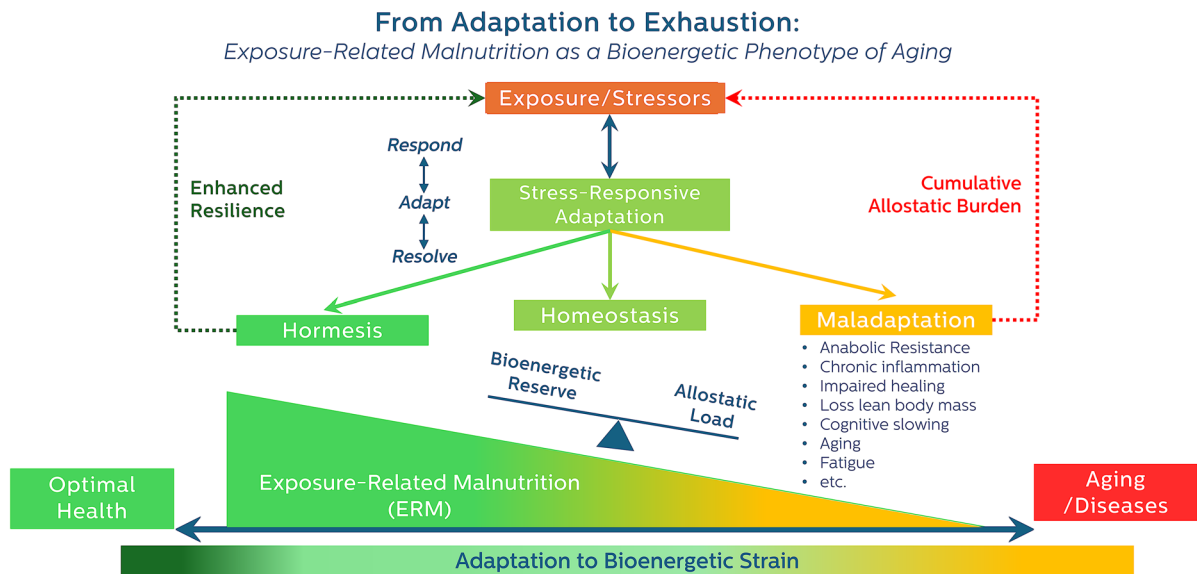
T. Tippairote (✉)
School of Health Sciences, Sukhothai Thammathirat Open
University, Pak Kret District, Nonthaburi 11120, Thailand
e-mail: torsak@healingpassion-asia.com

T. Tippairote · P. Hoonkaew · A. Suksawang · P. Tippairote
Thailand Initiatives for Functional Medicine,
Bangkok 10540, Thailand

T. Tippairote · P. Hoonkaew · A. Suksawang · P. Tippairote
HP Medical Centre, 19/73 Bangna, Bangkok 10260,
Thailand

P. Hoonkaew
Department of Diagnostic Imaging, Mahachai 2 Hospital,
Samut Sakorn 74130, Thailand

ERM may progress toward maladaptation and age-related disease. Early recognition and restoration of resolution capacity may preserve resilience and delay dysfunction.



Keywords Aging · Stress · Physiological · Malnutrition · Energy Metabolism · Biomarkers · Hormesis

Abbreviations

AMPK	AMP-activated Protein Kinase
ATF4	Activating Transcription Factor 4
ATP	Adenosine Triphosphate
BEC	Brain–Body Energy Conservation
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
cGAS–STING	Cyclic GMP–AMP synthase–stimulator of interferon genes
CED	Chronic Energy Deficiency
CHOP	C/EBP Homologous Protein
CRP	C-Reactive Protein
DHEA	Dehydroepiandrosterone
DRM	Disease-Related Malnutrition
eIF2 α	Eukaryotic Initiation Factor 2 Alpha
ERM	Exposure-Related Malnutrition
FGF21	Fibroblast Growth Factor 21
GDF15	Growth Differentiation Factor 15

GLIM

Global Leadership Initiative on Malnutrition

HPA

Hypothalamic–Pituitary–Adrenal (axis)

IGF-1

Insulin-like Growth Factor 1

ISR

Integrated Stress Response

MBSR

Mindfulness-Based Stress Reduction

mTORC1

Mechanistic Target of Rapamycin Complex 1

mt-ISR

Mitochondrial Integrated Stress Response

mtDNA

Mitochondrial DNA

MPS

Muscle Protein Synthesis

NLRP3

NOD-like receptor family pyrin domain-containing 3

PhA

Phase Angle

RED-S

Relative Energy Deficiency in Sport

ROS

Reactive Oxygen Species

SAM

Sympathetic–Adrenal–Medullary

SASP

Senescence-Associated Secretory Phenotype

SCENITH	Single-Cell Energetic metabolism by Translation Inhibition
scRNA-seq	Single-cell RNA sequencing
UPR	Unfolded Protein Response

Introduction

Despite the unprecedented rise in global life expectancy, healthspan—the proportion of life spent in good functional health—has not kept pace (Crane et al. 2022; WHO 2025). This disparity between longer survival and earlier onset of functional decline underscores a key paradox of modern aging: while we are living longer, we are not necessarily living better. Increasingly, evidence suggests that this gap may be rooted not in isolated disease processes, but in a systemic failure of the body's adaptive capacity to meet the cumulative demands of modern stress exposure (McEwen 2022; Monzel et al. 2023).

Central to this emerging perspective is the concept of stress adaptation as a metabolically governed trajectory, in which the ability to resolve, rather than merely respond to, stress determines long-term resilience. Classical models, such as Selye's *General Adaptation Syndrome*, framed stress as a linear sequence of alarm, resistance, and exhaustion (Selye 1950). Contemporary refinements—such as the concepts of *allostasis* and *the integrated stress response*—emphasize the dynamic, resource-dependent nature of this process (Costa-Mattioli & Walter 2020; McEwen & Wingfield 2003). These models converge on a common insight: chronic or unresolved stress imposes a persistent bioenergetic cost that progressively undermines system integrity, accelerating biological aging and predisposing to chronic disease (Bobba-Alves et al. 2023; Ryan & Ryznar 2022).

This burden is further magnified by *the exposome*—the totality of exposures an individual accumulates across the lifespan, spanning both external and internal domains (Rappaport et al. 2014; Vermeulen et al. 2020). External exposures include pollutants, pathogens, dietary factors, psychosocial stressors, and circadian disruption, while internal exposures arise from endogenous processes such as inflammation, oxidative stress, metabolic byproducts, and microbiome activity.

These factors interact continuously with the body, shaping health trajectories over time. The exposome captures not only the environment we live in but also how our biology responds to and is shaped by these influences—emphasizing the dynamic interplay between context and physiology that governs resilience and vulnerability. Even in well-nourished individuals living under relatively low external stress, biological systems are never free from the cumulative pressure of adaptation. Chronic interaction with the internal and external exposome imposes ongoing bioenergetic demands that, over time, contribute to functional aging—even in the absence of overt malnutrition or pathology.

We do not inhabit a clean or neutral world; rather, our systems are constantly navigating a complex and evolving landscape of challenges that intersect with genetic, epigenetic, and metabolic susceptibilities. In this context, equilibrium is not a fixed state (*homeostasis*), but a dynamic process (*homeodynamics*) requiring ongoing adaptation and resource reallocation to preserve function (Demirovic & Rattan 2013; Rattan 2020). When adaptive capacity is strained—whether through depletion, inefficiency, or chronic overload—this resilience erodes, giving rise to adaptive failure phenotypes that often precede or underlie clinical disease and contribute to the progressive acceleration of biological aging (Kivimäki et al. 2023; Wu et al. 2024).

Within this framework, *Exposure-Related Malnutrition (ERM)* is proposed as a mechanistically distinct, early-stage phenotype of stress maladaptation, marking the tipping point between successful resolution and unresolved, energy-intensive adaptation. Unlike classical malnutrition, which is typically characterized by overt nutritional deficits, weight loss, or insufficient intake, ERM reflects a state of functional undernourishment, where the ongoing energetic demands of unresolved stress deplete available resources, forcing a trade-off that deprioritizes essential housekeeping functions—including cellular maintenance, repair, and long-term regenerative processes. This may occur despite seemingly adequate—or even excessive—caloric intake (Cederholm & Bosaeus 2024).

The foundational logic of ERM draws on *Bruce Ames' nutrient triage theory*, which proposed that during periods of limited micronutrient availability, the body preferentially allocates resources to

short-term survival functions at the expense of long-term health maintenance (Ames 2006). ERM extends this concept to the broader bioenergetic landscape, highlighting how chronic stress can drive substrate misallocation not only in micronutrient pathways but across major energy-requiring systems.

While conceptually closer to *Disease-Related Malnutrition (DRM)*—in which illness-driven metabolic demands exceed nutritional supply—ERM may arise earlier, during a phase when adaptive systems are still actively compensating, albeit at escalating energetic cost (Muscaritoli et al. 2023). Unlike DRM, which typically presents with recognizable clinical and biomarker signs of classical malnutrition, ERM can remain silent, occurring in individuals who appear outwardly well-nourished. It reflects a subtle, progressive decline in resilience that precedes overt malnutrition, organ dysfunction, or clinical disease.

ERM reflects a state of *energy and substrate rationing*, in which declining availability, coupled with persistent adaptive demands, drives systematic misallocation of resources across neuroendocrine, immune, muscular, and mitochondrial systems. These covert trade-offs suppress anabolism, immune surveillance, and cellular turnover—while sustaining low-grade inflammation, mitochondrial dysfunction, fatigue, and early functional decline (Paulussen et al. 2021). They reflect a physiological state in which the body has responded and adapted but failed to resolve the stressor—resulting in unfinished resolution or maladaptation. Critically, these shifts represent adaptive strategies that become progressively unsustainable, ultimately eroding resilience and predisposing to chronic dysfunction. When identified early, they may be reversible, offering a vital window for intervention before irreversible dysfunction or structural disease emerges (Picard et al. 2018; Shaulson et al. 2024).

The purpose of this review is to synthesize current evidence across biological systems to propose a bioenergetic model of stress adaptation in aging. We introduce ERM as a unifying early-stage phenotype marked by declining energy availability, substrate misallocation, and failure to resolve prolonged adaptation. We trace how these unresolved adaptive processes give rise to maladaptive consequences across multiple levels of biological organization—including mitochondrial

dysfunction, impaired cellular turnover, organ-level decline, and neuroendocrine disruption—positioning ERM as a critical contributor to the molecular basis of aging. This model reframes aging not as a passive or predetermined process, but as an energetically governed trajectory—shaped by cumulative stress exposure and potentially modifiable through early detection and targeted intervention.

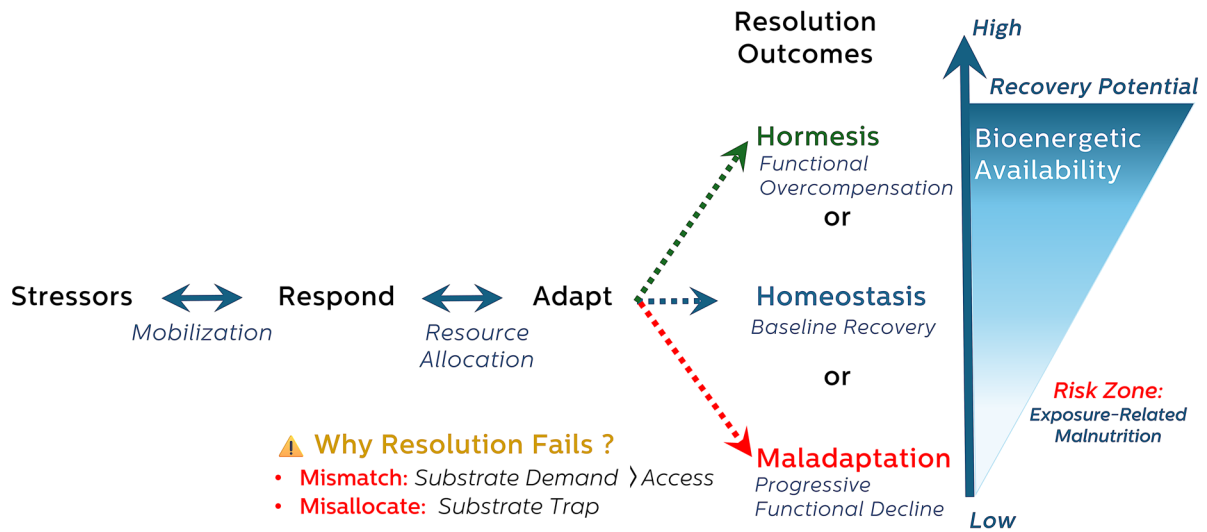
Conceptual model

"Respond → Adapt → Resolve: A Bioenergetic Trajectory of Stress and Aging"

To move beyond fragmented views of aging, we propose a unifying trajectory—*Respond → Adapt → Resolve*—that conceptualizes aging as the cumulative outcome of unresolved physiological adaptation. Rather than emphasizing acute stress responses or isolated damage pathways, this model centers on the critical role of energy and substrate availability in determining whether adaptation leads to resolution or maladaptation. When recovery is incomplete, bioenergetic costs accumulate, triggering covert trade-offs that progressively degrade resilience (Harrell et al. 2016). This framework highlights a critical inflection point—failure to resolve—as a key determinant of biological aging and a precursor to early dysfunction, exemplified by transitional states such as ERM.

Structured around three metabolically demanding phases, the *Respond → Adapt → Resolve* model emphasizes that it is not the presence of stress alone, but the effectiveness of resolution that determines long-term outcomes. In the *Respond phase*, acute stress activates emergency systems, mobilizing energy and suppressing non-essential functions to ensure immediate survival. The *Adapt phase* involves sustained physiological adjustments, including neuroendocrine, immune, organ-level, cellular, and mitochondrial reprogramming to maintain function under constraint. The *Resolve phase* governs recovery and restoration, requiring sufficient energy and coordination to reverse adaptive changes and restore homeodynamic balance. When resolution fails—due to depleted bioenergetic reserves or chronic exposure—maladaptive consequences ensue,

Resolution Outcomes of Stress Adaptation: A Bioenergetic Framework for ERM



Adaptive outcomes following stress are contingent on energy and substrate sufficiency. The resolution phase can lead to hormesis, homeostasis, or maladaptation.

Fig. 1 Resolution Outcomes of Stress Adaptation: A Bioenergetic Framework for Exposure-Related Malnutrition (ERM). Adaptive responses to stress follow a trajectory from *Response* (mobilization) to *Adaptation* (resource allocation), culminating in one of three resolution outcomes: *Hormesis* (functional overcompensation), *Homeostasis* (baseline recovery), or *Maladaptation* (progressive decline). These outcomes are contingent on the sufficiency and allocation of *energy and metabolic substrates*, represented by the vertical gradient on the right. *Hormesis* occurs when energy is sufficient and optimally allocated, supporting repair and strengthening. *Homeosta-*

sis reflects adequate but not surplus recovery. *Maladaptation* arises when resolution fails due to either (1) *substrate mismatch* (demand exceeds access) or (2) *substrate misallocation* (resources are diverted to short-term survival at the expense of long-term repair). ERM is depicted as a syndrome that emerges under low energy and substrate availability—where chronic, unresolved adaptation leads to covert trade-offs and progressive loss of systemic resilience. This framework highlights the critical role of bioenergetic sufficiency in determining long-term health trajectories following stress

including persistent inflammation, mitochondrial dysfunction, and accelerated biological decline (Bobb-Alves et al. 2023; Paulussen et al. 2021).

This adaptive trajectory is visually summarized in Fig. 1, which maps resolution outcomes as a function of energy and substrate availability and highlights ERM as an early phenotype of failed resolution.

Within this model, ERM is conceptualized as an early and distinct phenotype of impaired stress resolution. This covert trade-off can occur even in individuals with adequate or excessive caloric intake, rendering it undetectable by conventional assessments. Clinically, ERM may manifest as features that frequently precede the onset of frailty or overt chronic disease (Arron et al. 2024; Cabre et al.

2022; National Academies of Sciences & Medicine, 2024).

This *Respond*→*Adapt*→*Resolve* reframes aging as a dynamic, resource-sensitive trajectory in which the outcome of stress exposure is determined not solely by the magnitude of the stressor, but by the organism's capacity to complete resolution. Divergent resolution outcomes emerge based on bioenergetic availability: when energetic and substrate resources are abundant, transient stress exposures may trigger *hormetic strengthening* through overcompensatory adaptive responses; when resources are merely sufficient, *homeostasis* may be restored without gain; whereas chronic insufficiency drives unresolved adaptation and *maladaptive remodeling* (Calabrese et al. 2024). ERM marks a critical threshold—a metabolically constrained state in which adaptive

processes are initiated but remain energetically unsupported and unresolved. Recognizing ERM as a reversible, subclinical phenotype of maladaptation offers a vital opportunity for early intervention—shifting the clinical focus from managing downstream dysfunction to restoring upstream resolution capacity (Ryan & Ryznar 2022).

Mechanistic pathways underlying ERM

From central command to cellular collapse: the bioenergetic logic of maladaptive adaptation

The failure to resolve chronic physiological stress is evident across tightly interlinked systems, beginning with central neuroendocrine regulation and extending through immune and muscular function to cellular signaling networks and mitochondrial energetics. At each level, a common pattern emerges: a metabolic phenotype characterized by substrate rationing and resource allocation under persistent bioenergetic strain. Critically, these systems operate as dynamic, feedback-regulated loop—where signals originating from mitochondria, cells, and peripheral organs ultimately shape central control. This bidirectional communication determines whether the organism adapts, recovers, or progressively declines. The ERM phenotype, therefore, reflects not isolated dysfunction but a systemic failure of resolution across the bioenergetic hierarchy.

Neuroendocrine axis: central command of substrate allocation

The hypothalamic–pituitary–adrenal (HPA) axis serves as the central regulator of systemic energy allocation in response to stress. Activation of the HPA and *sympathetic–adrenal–medullary (SAM)* systems initiate the Respond phase, rapidly mobilizing glucose and fatty acids while downregulating energy-intensive processes such as reproduction, growth, and digestion (Tsigos & Chrousos 2002). Under conditions of chronic stress, sustained activation imposes bioenergetic strain that disrupts hormonal homeostasis—flattening the diurnal cortisol rhythm and skewing the cortisol: DHEA ratio toward a catabolic profile. These changes, commonly observed

with aging, reflect a shift from adaptive flexibility to maladaptive rigidity (McEwen 2007; Yiallouris et al. 2019).

The *Selfish Brain Theory* posits that the brain prioritizes its access to glucose and oxygen over peripheral tissues, especially under conditions of systemic energy scarcity (Peters 2004; Peters et al. 2022). This neurocentric substrate allocation becomes maladaptive over time, diverting resources away from essential processes such as tissue repair, immune tolerance, and muscle maintenance—hallmarks of *the Adapt phase* trade-offs. The *Brain–Body Energy Conservation (BEC)* model expands this concept by identifying the brain as the central broker of the organism’s finite energy budget (Shaulson et al. 2024). As molecular damage accumulates, somatic cells may enter a state of senescence, adopting a *senescence-associated secretory phenotype (SASP)*—a hypersecretory program marked by the sustained release of pro-inflammatory cytokines, chemokines, growth factors, and proteases (Coppé et al. 2008). While the SASP plays a role in signaling cellular stress and coordinating tissue repair and immune surveillance, its chronic activation imposes substantial metabolic demands and contributes to systemic inflammation. Over time, this persistent low-grade inflammatory state may evolve into *inflammaging*—a distinct, age-associated phenotype of chronic immune activation that contributes to tissue dysfunction and age-related disease. These hypermetabolic signals are sensed by the brain, which responds with energy-conservation strategies that suppress non-essential physiological processes. This includes downregulation of anabolic hormones, reduced voluntary activity, and simplification of immune and endocrine functions. Chronically elevated cortisol and sympathetic tone further reinforce this adaptive trade-off, promoting insulin resistance, visceral adiposity, and circadian disruption—hallmarks of allostatic load and declining systemic flexibility (Ryan & Ryznar 2022; Sapolsky 2004). Over time, these adaptations, though protective in the short term, contribute to the erosion of physiological resilience and the emergence of the ERM phenotype as a bioenergetically compromised state of accelerated aging. This neuroendocrine-driven substrate misallocation contributes to the ERM phenotype by creating an apparent paradox: energy is present but inaccessible to systems that need it

most—undermining cellular repair and systemic resilience.

Immune reprogramming and inflammaging: energy-intensive surveillance

In response to stress, the immune system rapidly adopts a pro-inflammatory phenotype, shifting macrophages, neutrophils, and T cells toward aerobic glycolysis—a metabolically costly state that supports cytokine production, phagocytosis, and rapid cell proliferation (Olenchok et al. 2017). While this reprogramming is essential for acute host defense, it becomes maladaptive under conditions of chronic stress and limited metabolic resources. Immune cells fail to revert to oxidative metabolism, locking into a glycolytic phenotype that sustains low-grade inflammation and impairs resolution (Franceschi et al. 2018; Willmann & Moita 2024).

This loss of metabolic flexibility reflects a broader bioenergetic trade-off characteristic of ERM: when energy and substrate availability are constrained, immune surveillance is maintained at the expense of tissue regeneration, neuroprotection, and systemic homeostasis. Chronically activated or aging immune cells exhibit mitochondrial dysfunction and impaired mitochondrial quality control—including reduced mitophagy and elevated oxidative stress. These disturbances lead to the release of mitochondrial *damage-associated molecular patterns (DAMPs)*, such as *mitochondrial DNA (mtDNA)*, which may be oxidized depending on the cellular context. Once released into the cytosol, mtDNA activates innate immune pathways including the *NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome*—particularly when oxidized—and the *cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) axis*, thereby amplifying cytokine production and sustaining chronic inflammatory signaling (Wu et al. 2025).

As a result, immune cells shift from being metabolically flexible responders to chronically activated drivers of tissue injury, fibrosis, and energetic collapse—hallmarks of *immunosenescence* and *inflammaging* (Fulop et al. 2018). Persistent immune activation also depletes micronutrients critical to systemic resilience—such as zinc, selenium, and iron—compromising antioxidant defenses, mitochondrial function, and epithelial repair

(Alack et al. 2019; Gulhar et al. 2024). This creates a self-reinforcing loop of micronutrient insufficiency, metabolic stress, and immune dysfunction.

Emerging technologies, such as *Single-Cell Energetic metabolism by Translation Inhibition (SCENITH)* and *single-cell RNA sequencing (scRNA-seq)*, have revealed that aged immune cells display distinctive metabolic signatures—marked by diminished oxidative capacity and exaggerated inflammatory output (Wu et al. 2025). These findings align with ERM-associated metabolic adaptations, where immune vigilance is preserved while anabolic and reparative systems—such as skeletal muscle, neural tissue, and intestinal epithelium—are systematically deprioritized. Immune reprogramming under chronic metabolic strain thus exemplifies a maladaptive resolution phase of stress adaptation: energy is persistently funneled into defense and surveillance at the cost of long-term functional integrity and resilience.

Skeletal muscle and anabolic resistance: the energetic reservoir depleted

Skeletal muscle serves as the body's primary amino acid reservoir, mobilized during physiological stress to support gluconeogenesis, immune activation, and the hepatic acute-phase response (Cahill 2006). While this catabolic mobilization is adaptive in the short term, persistent stress drives a chronic depletion of muscle mass—transforming a protective mechanism into a source of dysfunction. In the Adapt phase of prolonged stress exposure, elevated catabolic hormones, such as cortisol, and pro-inflammatory cytokines promote proteolysis, while simultaneously impairing *muscle protein synthesis (MPS)* even in the presence of adequate protein intake (Ferreira & Duarte 2023; Paulussen et al. 2021).

This impaired responsiveness to anabolic stimuli—termed *anabolic resistance*—reflects a systemic energy trade-off in which substrate allocation is redirected away from tissue maintenance and regeneration. Key anabolic pathways, including *mechanistic target of rapamycin complex 1 (mTORC1)* and *insulin-like growth factor-1 (IGF-1)* signaling, are suppressed under metabolic strain. Additionally, muscle stem cells (*satellite cells*) fail to initiate proper regeneration in the absence of

sufficient energetic and micronutrient support (Bian et al. 2020; Langston & Mathis 2024).

Over time, these deficits contribute to muscle atrophy and the development of *sarcopenia*—a progressive loss of muscle mass and function that is both a hallmark of biological aging and a potential clinical endpoint of undiagnosed ERM (Cederholm & Bosaeus 2024; Walrand et al. 2021). Importantly, this decline in muscle integrity is not merely structural; it underpins a wide spectrum of clinical phenotypes, including fatigue, poor exercise tolerance, and delayed recovery following physical activity. These features reflect the energetic exhaustion of skeletal muscle as both an effector and a victim of chronic metabolic trade-offs—where maintaining defense and immune activation takes precedence over repair, performance, and resilience.

Cellular integrated stress response: translational triage under strain

The *Integrated Stress Response (ISR)* is a highly conserved mechanism that regulates cellular adaptation to stress by modulating protein synthesis. In response to nutrient deprivation, redox imbalance, or proteotoxic stress, ISR is activated through phosphorylation of *eukaryotic initiation factor 2 alpha (eIF2 α)*, which attenuates global protein translation while selectively enhancing the synthesis of adaptive transcription factors such as *activating transcription factor 4 (ATF4)* and *C/EBP homologous protein (CHOP)* (Costa-Mattioli & Walter 2020; Pakos-Zebrucka et al. 2016). This selective translational reprogramming enables cells to conserve resources and temporarily shift priorities toward stress mitigation and survival.

The ISR is functionally integrated with the *endoplasmic reticulum (ER) stress response* and the *Unfolded Protein Response (UPR^{ER})*, particularly through the PERK–eIF2 α –ATF4 signaling axis. These systems converge on shared nodes to coordinate cellular responses to proteostatic disruption and nutrient imbalance. When misfolded proteins accumulate in the ER, the UPR^{ER} is activated to restore folding capacity or trigger apoptosis if damage is beyond repair (Hetz & Saxena 2017).

This interplay exemplifies the principle of interorganelle collaboration, wherein stress signals from the ER, cytoplasm, and nutrient-sensing

pathways are integrated to determine cellular fate. Importantly, the outcome of this collaboration is not fixed, but context dependent. According to the *catabolic–anabolic cycling hormesis (CACH) model*, adaptive responses to stress occur in two phases: an initial catabolic phase characterized by autophagy, translational suppression, and metabolic reallocation, followed by an anabolic recovery phase involving biosynthesis, growth, and repair (Calabrese & Mattson 2024). The adaptive value of stress responses such as the ISR and UPR^{ER} depends on sufficient energy and substrates to sustain both the stress response and its recovery phase.

In *C. elegans*, targeted non-cell-autonomous activation of the UPR^{ER} through *xbp-1s* expression in specific neurons has been shown to enhance systemic proteostasis, increase ER stress resistance, and extend lifespan—largely through coordinated gut-directed signaling (Coakley et al. 2024; Higuchi-Sanabria et al. 2020; Taylor & Dillin 2013). These benefits, however, appear contingent on spatiotemporal control and adequate metabolic buffering. By contrast, chronic or unresolvable stress, particularly under conditions of metabolic insufficiency, can lead to maladaptive persistence of catabolic signaling. Prolonged ISR or UPR^{ER} activation in this context disrupts proteostasis, impairs regenerative signaling, and may culminate in senescence or apoptosis, especially in high-turnover tissues such as intestinal epithelium and immune cells (Hetz & Papa 2018). Similar mechanisms may also affect skeletal muscle, although this requires further empirical clarification.

Thus, while interorganelle stress signaling pathways can be central to resilience, their effects depend on duration, localization, and metabolic context. When the catabolic phase is prolonged without anabolic resolution, adaptive responses may collapse into degenerative trade-offs, exhausting cellular reserves and accelerating vulnerability. This stress-induced shift—marked by sustained translational suppression and impaired renewal, characterizes early-stage ERM, in which the capacity for repair is sacrificed to preserve immediate survival.

Mitochondrial stress response and mitokines: the energetic fulcrum and feedback signal

Mitochondria are increasingly recognized not only as producers of *adenosine triphosphate (ATP)* but

also as central signal transduction hubs that integrate metabolic status, oxidative stress, immune activation, and intercellular communication (Picard & Shirihi 2022). These organelles coordinate cellular responses to stress by modulating ATP output, redox balance, reactive oxygen species (ROS) generation, and the supply of metabolic intermediates. In response to mild or transient energetic stress, mitochondria engage in *mitohormesis*—a process in which low-level ROS production triggers adaptive signaling pathways that enhance mitochondrial biogenesis, repair, and overall resilience (Ristow & Schmeisser 2014).

However, when energy demands exceed capacity over time, these adaptive processes fail. Mitochondrial dysfunction leads to excess ROS, loss of membrane potential, and the release of mitochondrial DNA (mtDNA) into the cytosol—activating inflammatory signaling via the *NLRP3 inflammasome* and *cGAS–STING pathway* (Ni et al. 2015; Qi et al. 2025). Beyond fueling inflammation, these mitochondrial disturbances also contribute to the induction of cellular senescence and SASP, creating a self-perpetuating cycle of immune activation, tissue damage, and bioenergetic decline (Martini & Passos 2023; Vettorelli et al. 2023). This cascade amplifies systemic inflammation and accelerates the progression of ERM phenotypes, senescence, and chronic disease.

In addition to local signaling, dysfunctional mitochondria produce mitokines—circulating stress signals such as *fibroblast growth factor 21 (FGF21)* and *growth differentiation factor 15 (GDF15)*. These mitokines act on the central nervous system, particularly the hypothalamus and area postrema, to suppress appetite, reduce activity, and recalibrate energy expenditure (Lockhart et al. 2020; Zhang et al. 2024). GDF15, in particular, has been linked to anorexia, fatigue, and muscle catabolism, effectively informing the brain of peripheral energetic crisis and reinforcing systemic energy conservation (Shaulson et al. 2024).

Importantly, mitochondria also participate in intercellular rescue mechanisms through mitochondrial transfer—a process in which healthy mitochondria are transferred from donor cells (such as mesenchymal stem cells or astrocytes) to stressed or energy-depleted recipient cells via tunneling nanotubes, extracellular vesicles, or cell fusion (Diaz-Meco

et al. 2025; Dong et al. 2023). This transfer restores oxidative capacity, reverses bioenergetic failure, and promotes tissue recovery, particularly in metabolically active or injured environments such as the brain, heart, and immune system (Islam et al. 2012; Spees et al. 2006). Mitochondrial transfer thus exemplifies a critical resilience mechanism—extending stress adaptation beyond the individual cell to a community-level response.

Together, these processes illustrate that mitochondria are not passive power plants, but energetic sentinels and signaling nodes that regulate both local and systemic adaptation. Through mitohormesis, mitokine signaling, and intercellular mitochondrial transfer, they act as the fulcrum of the stress response—balancing survival, repair, and functional decline across the trajectory of resilience and exhaustion.

Closing the loop: from peripheral strain to central reprogramming

Collectively, these mechanistic pathways form a closed, self-reinforcing circuit of maladaptive stress adaptation. The loop begins with neuroendocrine activation, redirecting energy away from long-term maintenance toward immediate survival. This shift is reinforced by immune reprogramming that sustains inflammation, skeletal muscle catabolism that depletes physical capacity, translational triage that suppresses cellular renewal, and mitochondrial signaling that conveys energetic distress to the central nervous system. As resolution fails, this interconnected network transitions from adaptive to degenerative—locking the body into a chronically depleted, energy-conserving, and catabolic state.

The result is ERM—a subtle yet systemic bioenergetic phenotype that reflects the failure to resolve chronic physiological stress. This functional malnourishment is not characterized by overt starvation, but by persistent substrate rationing and misallocation, impaired anabolic signaling, and the chronic prioritization of immune and neural defense over cellular turnover and tissue repair. It represents the convergence of central command and peripheral exhaustion—a dynamic imbalance in which energy conservation becomes maladaptive, and the capacity for recovery is no longer energetically sustained.

By tracing this loop—from central regulation to peripheral strain and back—we recognize ERM as a *bioenergetic signature of unresolved adaptation*. It manifests as the metabolic cost of sustained defenses, the silent erosion of physiological plasticity, and the gradual loss of systemic resilience. Recognizing this loop presents a critical opportunity: to identify ERM early, disrupt its trajectory, and restore the bioenergetic balance essential for repair, recovery, and renewal—before chronic strain culminates in irreversible dysfunction.

Defining ERM as a preclinical aging phenotype

Rather than repeating the definition of ERM, this section builds on the earlier conceptualization by outlining how ERM differs from classical malnutrition syndromes and how it serves as an early biomarker of resilience loss. ERM may occur despite normal or excessive caloric intake and arises in response to sustained stress exposure, bioenergetic strain, and substrate misallocation. The hallmark is not nutrient depletion per se, but maladaptive energy trade-offs that compromise long-term physiological functions.

ERM vs. classical malnutrition syndromes

Unlike classical demand-driven syndromes—such as *DRM*, *Chronic Energy Deficiency (CED)*, or *Relative Energy Deficiency in Sport (REDs)*—ERM may occur despite normal or even excessive caloric intake (Cederholm & Bosaeus 2024; Mountjoy et al. 2018; Prisabela et al. 2023). DRM is typically characterized by inflammation-induced catabolism in the context of acute or chronic illness; CED often results from increased physiological demands such as pregnancy without sufficient intake; and REDs reflects chronic energy imbalance in athletes.

In contrast, ERM develops insidiously in response to sustained physiological stressors—including chronic inflammation, environmental toxicant burden, circadian misalignment, and psychosocial strain—that progressively elevate metabolic demand. These exposures challenge adaptive capacity over time, necessitating covert energy trade-offs that impair long-term resilience despite preserved or excessive energy intake.

ERM results from a chronic *mismatch* between metabolic demands and substrate availability, compounded by persistent *misallocation* of available resources. These demands are frequently amplified by prolonged inflammation, psychosocial stress, circadian disruption, and environmental exposures, all of which impose sustained strain on adaptive systems. In this context, neuroendocrine stress responses—particularly elevations in cortisol, insulin, and sympathetic activity—redirect metabolic substrates away from anabolic and regenerative pathways. A key feature of this maladaptive shift is the “*insulin-induced substrate trap*,” in which glucose and lipids are preferentially routed into storage compartments despite unresolved cellular energy needs (Friedman et al. 2024). While core survival systems remain supported, peripheral processes—such as skeletal muscle integrity, immune surveillance, and tissue repair—experience persistent energetic shortfall, undermining systemic resilience (Shaulson et al. 2024).

The hallmark of ERM is not overt nutrient depletion, but a characteristic pattern of maladaptive bioenergetic trade-offs—where physiological systems increasingly prioritize immediate survival at the expense of long-term functions such as repair, regeneration, and reproduction (Bobbá-Alves et al. 2023; Ryan & Ryznar 2022). ERM may precede, overlap with, or predispose individuals to later-stage malnutrition syndromes, including sarcopenia and frailty. Often clinically silent in its early stages, it represents a critical window for preventive detection and intervention.

ERM as the early metabolic signature of resilience loss in aging

ERM represents a transitional phase in which chronic activation of stress-adaptive systems gradually erodes physiological resilience, even in the absence of overt disease. In this context, chronic exposure to the exposure can be understood as a universal driver of adaptive demand. ERM may represent the early, maladaptive intersection between cumulative environmental and internal exposures, bioenergetic trade-offs, and declining physiological resilience. As an early metabolic hallmark of aging, it is characterized by substrate misallocation, diminished anabolic signaling,

Table 1 Phenotypic and mechanistic distinctions between exposure-related malnutrition (ERM), normative aging, and disease-related malnutrition (DRM)

Feature	ERM (Exposure-related malnutrition)	Normative aging	DRM (Disease-related malnutrition)
Definition	A stress-adapted, potentially reversible phenotype of unresolved bioenergetic and physiological adaptation	Intrinsic, time-dependent biological decline involving both reversible and irreversible processes	Malnutrition driven by inflammatory or disease-related catabolic burden exceeding nutritional intake
Primary triggers	Chronic psychosocial, inflammatory, environmental, or metabolic stress	Telomere attrition, genomic instability, epigenetic drift, stem cell exhaustion	Acute or chronic disease, systemic inflammation, illness-induced catabolism
Typical onset pattern	Gradual, subclinical, often early in life under chronic stress exposure	Progressive and cumulative over decades	Subacute or acute during illness or hospitalization
Reversibility	Potentially reversible if identified before senescence or tissue degeneration	Partially reversible in early stages; largely irreversible in advanced aging	Partially reversible with nutritional and anti-inflammatory treatment
Clinical phenotype	Functional decline: fatigue, cognitive slowing, impaired recovery, anabolic resistance, subtle loss of resilience	Gradual decline in strength, endurance, repair capacity, cognition, and stem cell activity	Weight loss, poor wound healing, immune dysfunction, frailty in late stages
Nutritional profile	Often normal or elevated BMI; masked by central adiposity or preserved weight	Highly variable; may show gradual decline in lean mass and nutrient absorption	Low BMI, weight loss, or muscle wasting often evident
Biomarker pattern	Trade-off signature with prioritized stress survival (e.g., acute-phase proteins), suppressed maintenance markers (e.g., nutrient transport, protein synthesis), and impaired long-term repair—indicative of progressive substrate misallocation	Gradual decline in both anabolic and stress-response pathways without prioritized misallocation	Overt catabolic state with marked inflammation, suppressed repair, and visible nutrient depletion
Common diagnostic oversights	Attributed to stress, aging, or mood disorder; often missed due to normal appearance	Considered “normal” aging even when early functional decline signals underlying stress load	Misdiagnosed as aging or cachexia; underrecognized in stable-weight patients
Response to intervention	Responsive to metabolic, circadian, and resilience-focused therapies; improvement possible before irreversible decline	Slower or limited response to intervention; focus on maintenance and delay of decline	Requires combined nutrition and medical care; may reverse weight loss and inflammation

and impaired recovery—marking the shift from adaptive flexibility to cumulative vulnerability.

This perspective aligns with models that frame aging as the biological toll of chronic adaptation demands and allostatic load accumulation (Seeman et al. 2001), as well as with emerging views of mitochondria as central hubs that integrate and propagate cellular stress signals across systems (Picard & Shirihai 2022; Seeman et al. 2001). Just as prediabetes signals metabolic dysfunction before the onset of diabetes, ERM reflects subclinical energy imbalance that, if left unresolved, increases vulnerability to chronic disease, immune decline, and accelerated aging.

Table 1 summarizes the key phenotypic distinctions between ERM, normative aging, and DRM, highlighting ERM as a distinct, stress-adapted phenotype shaped by cumulative adaptive trade-offs rather than overt nutrient deficiency or chronological age alone.

Fig. 2 Characteristic Constellation of Exposure-Related Malnutrition (ERM): Functional Symptoms, Physical Signs, and Biomarker Trade-Offs. ERM is an early-stage maladaptive state marked by subtle but systemic bioenergetic compromise. It manifests as a patterned triad of functional symptoms (e.g., fatigue, slowed recovery, anabolic resistance), physical performance signs (e.g., grip strength, gait speed, calf circumference), and distinctive biochemical trade-offs. Biomarker patterns reflect adaptive substrate prioritization: preservation of acute-phase reactants, decline in housekeeping proteins and cellular repair capacity, and suppression of anabolic and reproductive functions

Recognizing ERM phenotypes

ERM rarely presents with overt clinical signs in its early stages. Individuals often maintain a normal or elevated body mass index (BMI), masking underlying physiological compromise. Yet, they may exhibit subtle but functionally significant and progressive patterns of decline—including *chronic fatigue, delayed physical recovery, increased susceptibility to infections, cognitive slowing, declining reproductive capacity, and persistent or unexplained chronic pain such as myofascial pain syndromes*. These symptoms reflect sustained bioenergetic strain, impaired tissue repair, and neuromuscular inefficiency—hallmarks of maladaptive stress physiology.

Crucially, these features do not occur in isolation but rather as part of a recognizable constellation—a patterned signal of systemic compromise resulting from chronic substrate misallocation. Under conditions of persistent psychosocial stress, low-grade inflammation, and neuroendocrine dysregulation, energy allocation is progressively reprogrammed away from long-term maintenance toward short-term survival, often before classical signs of malnutrition

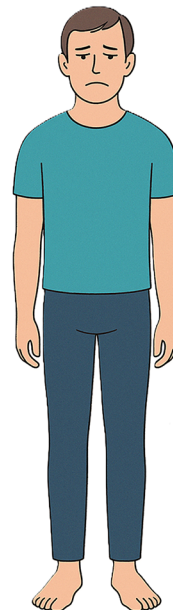
Constellation of Exposure-Related Malnutrition (ERM): Characteristic Phenotype of Early-Stage Maladaptation

Functional Symptoms

- Chronic fatigue
- Poor physical recovery
- Frequent infections
- Cognitive slowing
- Persistent pain
- Anabolic resistance
- Declined reproductive health

Functional Signs

- Reduced strength e.g., grip strength
- Slow gait
- Decreased stamina e.g., 6-minute walk test, one leg standing
- Low muscle mass e.g., calf circumference
- Central obesity



Biomarker Trade-Off Patterns

Preservation

- Acute Phase reactants such as hsCRP, ESR, ferritin, fibrinogen etc.

Decline

- Housekeeping proteins such as Transport proteins, e.g., transferrin, albumin
- Slow cell turnover/repair with elevated intracellular enzymes such as ALT, AST, CPK

Suppression

- Growth such as IGF-1, lean body mass, bone mass
- Suppressed reproductive markers such as testosterone and estrogen

appear (Fülöp et al. 2025). Yet, such early-stage dysfunction is frequently misattributed to aging, lifestyle, or mood disorders—leading to clinical underrecognition and missed opportunities for preventive intervention.

A recent case series of three Thai men with late-onset idiopathic Parkinson's disease offers a compelling example of how ERM phenotypes may be present and clinically silent for decades (Tippairote et al. 2025). These individuals exhibited persistently elevated mercury levels due to lifelong fish and seafood consumption, compounded by chronic vitamin D insufficiency. Long before clinical diagnosis, they demonstrated functional ERM characteristics—fatigue, cognitive slowing, anabolic resistance, and elevated markers of oxidative stress, inflammation, and metabolic dysregulation. This trajectory exemplifies a “*functional ERM*” state: one in which apparent homeostasis is maintained through hidden energy trade-offs and micronutrient depletion, quietly eroding resilience.

Importantly, these bioenergetic compromises are not readily captured by conventional assessments. Instead, they manifest as emergent physiological patterns—integrating functional symptoms, signs, compositional shifts, and biochemical trade-offs—that signal maladaptive adaptation under chronic stress. Recognizing ERM as a distinct, stress-mediated malnutrition phenotype requires moving beyond isolated markers toward a systems-level interpretation of early resilience loss.

Functional biomarkers: the first line of ERM detection

Emerging consensus emphasizes the value of functional tests—such as handgrip strength, gait speed, one-leg standing time, and calf circumference—as early, accessible indicators of systemic decline. These tests reflect neuromuscular performance, metabolic reserve, and organ system coordination. In fact, they outperform many molecular biomarkers in predicting mortality and frailty across populations (Furrer & Handschin 2025a, 2025b). Figure 2 summarizes the early phenotype of ERM, integrating functional symptoms, physical signs, and measurable biochemical trade-offs. This visualization supports clinical recognition of ERM beyond traditional malnutrition criteria.

- *Handgrip strength and muscle power* (dynapenia/powerpenia) have stronger associations with morbidity and mortality than muscle mass alone, and reflect early disruption in anabolic signaling and mitochondrial energy metabolism.
- *Gait speed and balance tests* capture neuromuscular coordination and are sensitive to cognitive and central nervous system compromise.
- *Calf circumference*, particularly in the context of preserved BMI, serves as a practical surrogate for declining peripheral muscle mass and functional reserve.

These physical assessments should not be interpreted as isolated values, but as part of an integrated functional pattern that reflects ERM's early-stage bioenergetic erosion.

From structure to cellular function: compositional and biophysical markers

In addition to performance-based tests, *bioelectrical impedance analysis (BIA)* provides insight into the body's internal reallocation of resources:

- *Progressive decline in skeletal muscle mass and bone mineral content* signals a shift away from long-term structural investment, consistent with catabolic resource diversion.
- *Accumulation of visceral fat*, particularly in the presence of stable or rising BMI, reflects a maladaptive redistribution of energy stores—often sustained by hyperinsulinemia and glucose-driven metabolic programming under stress.
- *Reduction in phase angle (PhA)*, a marker of cell membrane integrity and intracellular water balance, reflects impaired cellular vitality and bioenergetic efficiency. Rather than relying on a single cutoff, declining trends in PhA may indicate cumulative stress effects and loss of physiological plasticity. Reduced PhA is also linked to anabolic resistance, sarcopenia, and increased frailty (Akamatsu et al. 2022; Norman et al. 2012).

Recent findings indicate that PhA is particularly sensitive in women, where it correlates not only with global cognitive function but also with specific

domains such as memory, executive function, and attention—suggesting its potential as an early marker of physiological vulnerability prior to the development of overt malnutrition or dementia (Ikeue et al. 2025).

Patterns over points: the ERM signature

ERM is best recognized not by single diagnostic thresholds, but by emergent physiological patterns over time. This concept aligns with recent findings showing that hematologic and metabolic biomarkers exhibit stable, individualized setpoints in healthy individuals. Deviations from personal baselines—even within population-normal ranges—can signal early adaptation failure (Foy et al. 2024).

These changes occur within the broader context of the integrated stress response (ISR), nutrient triage, and brain–body energy conservation, which prioritize short-term survival over long-term maintenance and repair (Ames 2006; Shaulson et al. 2024; Wang & Zhang 2025).

Pattern of biochemical trade-offs: systemic signals of strain

The underlying biochemical constellation reinforces the pattern-based signature of ERM:

- *Preservation or elevation of acute-phase reactants* (e.g., CRP, ferritin), coagulation factors, and stress

proteins indicate active immune prioritization (Cederholm & Bosaeus 2024; Sganga et al. 1985).

- *Decline in housekeeping proteins* such as transthyretin and transferrin marks hepatic reprioritization away from maintenance functions (Evans et al. 2021; Paulussen et al. 2021).
- *Suppression of long-term anabolic markers*, including IGF-1, sex hormones, and proteins related to muscle, bone, and reproductive function, reflects deeper systemic sacrifice in favor of short-term homeostasis (Bian et al. 2020; Payea et al. 2024; Ryan & Ryznar 2022).

These physiological and biochemical trends are often amplified by mitochondrial dysfunction and redox imbalance. Recognizing these patterns allows for a more precise clinical understanding of early resilience loss (Brzezniakiewicz-Janus et al. 2025).

ERM and the GLIM criteria: a missing middle

The Global Leadership Initiative on Malnutrition (GLIM) provides an internationally accepted framework for diagnosing malnutrition in clinical and aging populations. Diagnosis requires the presence of at least one phenotypic criterion, e.g., non-volitional weight loss, low BMI, reduced muscle mass, and one etiologic criterion, e.g., reduced food intake, disease burden, or inflammation (Cederholm et al. 2025). While GLIM represents a major advance in standardizing clinical nutrition assessment, it may overlook a biologically significant but

Table 2 Conceptual comparison between GLIM* and ERM** frameworks for malnutrition recognition and intervention

Domain	GLIM malnutrition framework	ERM malnutrition framework
Focus	Observable malnutrition	Subclinical bioenergetic exhaustion
Phenotypic Criteria	Weight loss, low BMI, low muscle mass	Fatigue, immune dysfunction, reduced phase angle, anabolic resistance
Etiologic Criteria	Inflammation, reduced intake, disease burden	Chronic adaptation to physiological stress, environmental burden, and cumulative lifestyle exposures
Detection sensitivity	Moderate-to-late-stage malnutrition	High; based on emerging biomarkers and functional pattern recognition
Intervention window	Post-functional decline	Early, targets reversible physiological compromise before functional decline
Biomarker use	Optional; not central to diagnosis	Central to detection; includes acute phase reactants, cellular turnover, anabolic and stress-response markers

*GLIM Global leadership initiative on malnutrition

**ERM Exposure-related malnutrition

subclinical stage of nutrient misallocation and bioenergetic exhaustion.

This is where the concept of ERM offers critical complementary insight. Unlike GLIM-defined malnutrition, ERM can present in individuals who do not meet GLIM criteria, yet are experiencing metabolic compromise due to chronic stress adaptation, systemic inflammation, and substrate misallocation (Bobba-Alves et al. 2023; Ryan & Ryznar 2022). The hallmark phenotypes of ERM—such as chronic fatigue, cognitive dysfunction, physical intolerance, immune dysregulation, shifts in body composition, and coordinated biomarker trade-off patterns—are not captured by the static thresholds defined in the GLIM criteria.

ERM may therefore be conceptualized as either:

- a “*pre-GLIM*” phenotype, representing an earlier, subclinical stage of adaptation failure, or
- a *parallel subtype of functional malnutrition*, primarily driven by maladaptive stress physiology rather than overt intake deficiency.

This distinction is especially relevant in older adults and individuals with chronic illness or psychosocial stress exposure, where conventional indicators—such as BMI or body weight—may remain within normal ranges even as *physiological reserve and resilience quietly erode*. These differences are further clarified in Table 2, which contrasts the GLIM and ERM frameworks across key domains—highlighting how ERM expands malnutrition recognition to include earlier, subclinical phases of bioenergetic compromise.

As shown, GLIM prioritizes observable structural loss, whereas ERM focuses on functional and metabolic vulnerability under stress. The two are not mutually exclusive: ERM may precede GLIM-defined malnutrition or persist in parallel. Recognizing this distinction allows for *earlier, resilience-preserving interventions*—particularly in aging populations where *intake remains stable but physiological reserve is already compromised*.

ERM and the hallmarks of aging: reframing aging as a failure to resolve adaptation

This section builds upon the earlier definition of ERM and maps it onto the established hallmarks of aging (Lopez-Otin et al. 2013; López-Otín et al. 2023). ERM exemplifies a reversible phase of stress maladaptation that converges with features such as mitochondrial dysfunction, impaired autophagy, and altered nutrient sensing—traditionally considered hallmarks of aging (Lopez-Otin et al. 2013). Rather than redefining ERM again, we focus on how its bioenergetic characteristics align with aging mechanisms and present opportunities for targeted intervention (Bobba-Alves et al. 2023; Schmauck-Medina et al. 2022).

This evolving perspective aligns closely with the concept of ERM, which characterizes a metabolically constrained but potentially reversible state of chronic adaptation failure. In ERM, the body reallocates limited energy and substrates toward short-term survival functions at the expense of maintenance, repair, and regeneration. This systemic triage can activate features classically associated with aging—such as mitochondrial inefficiency, anabolic suppression, immune dysregulation, and impaired tissue renewal—*not because of biological age, but because of unresolved stress*.

ERM thus reframes aging as a *dynamic consequence of adaptation failure* rather than a fixed outcome of time. Crucially, many of the functional changes observed in ERM—such as suppressed IGF-1 signaling, mitochondrial stress, reduced autophagy, and stem cell dormancy—are not necessarily irreversible. With timely intervention to restore nutrient availability, redox balance, and anabolic signaling, biological aging trajectories may be interrupted, and resilience potentially recovered.

Mitochondrial dysfunction → bioenergetic reversibility

Mitochondrial dysfunction is a central hallmark of aging, characterized by impaired oxidative phosphorylation, increased reactive oxygen species (ROS), mitochondrial DNA instability, and defective mitophagy. These changes reduce cellular energy availability and contribute to inflammatory signaling

and tissue degeneration (Picard & Shirihi 2022; Qi et al. 2025).

However, such impairments are not always irreversible. In the context of chronic metabolic stress—such as that seen in ERM—mitochondrial fragmentation, redox imbalance, and ATP insufficiency may reflect adaptive energy reallocation rather than permanent failure. The *mitochondrial integrated stress response (mt-ISR)* downregulates energetically costly processes to preserve core functions under resource scarcity.

Importantly, when substrate availability and redox conditions are restored, mitochondrial dynamics and ATP production can often recover. This suggests that mitochondrial dysfunction in ERM represents a *reversible metabolic bottleneck*, offering a window to restore bioenergetic function and interrupt decline before structural damage becomes entrenched.

Altered nutrient sensing → adaptive metabolic flexibility

Disruption of nutrient-sensing pathways—including *insulin-like growth factor 1 (IGF-1)*, *mechanistic target of rapamycin (mTOR)*, *AMP-activated protein kinase (AMPK)*, and *insulin signaling*—is another hallmark of aging. These disruptions impair anabolic signaling, autophagy, and metabolic flexibility, undermining the capacity to balance growth and maintenance under fluctuating conditions (Chrousos 2009).

A similar pattern is observed in ERM, where chronic energy insufficiency and stress induce systemic downregulation of these pathways. Suppressed IGF-1 signaling, insulin resistance, and impaired mTOR activity reflect an energy-conserving response to prolonged substrate scarcity. In skeletal muscle, this contributes to anabolic resistance—a reduced responsiveness to anabolic stimuli such as amino acids or mechanical loading—closely mirroring sarcopenia (Paulussen et al. 2021).

Unlike irreversible endocrine failure, these adaptations may be functionally reversible. When energetic capacity is restored and chronic stress resolved, nutrient-sensing pathways can recover their regulatory flexibility. ERM thus represents a state of *adaptive metabolic plasticity*, not permanent breakdown.

Cellular senescence: metabolically driven vulnerability

Cellular senescence is canonically defined as a state of irreversible cell cycle arrest, typically triggered by DNA damage, telomere attrition, oncogenic signaling, or oxidative stress (López-Otín & Kroemer 2024; Wiley & Campisi 2021). Senescent cells undergo distinctive metabolic remodeling and adopt a SASP that promotes chronic inflammation, tissue remodeling, and age-related pathology. Importantly, senescence is not merely a loss of proliferative capacity—it reflects a hyperfunctional, pro-inflammatory state with substantial bioenergetic demands.

In the context of ERM, chronic metabolic stress, including mitochondrial dysfunction, redox imbalance, and AMP/ATP depletion, may not directly induce senescence but may predispose cells to enter or maintain the senescent state. Metabolic factors such as NAD⁺/NADH ratios, AMPK activation, and ROS signaling are known to modulate the SASP and influence the inflammatory output of senescent cells (Wiley & Campisi 2021). These shifts may determine whether a stressed cell proceeds toward full senescence or can recover from metabolic arrest. However, once the senescent state is established, it is generally considered irreversible, and metabolic modulation—though it may attenuate the SASP—is unlikely to restore proliferative capacity (Blagosklonny 2011).

Rather than causing senescence directly, ERM may induce transient, non-proliferative states driven by nutrient deprivation, ISR activation, and translational repression (Costa-Mattioli & Walter 2020; Wek 2018). These metabolically adaptive responses—such as quiescence or ISR-induced dormancy—are distinct from senescence in that they retain the potential for recovery. However, persistent stress or failure to resolve the bioenergetic deficit may result in loss of proliferative potential and transition into true senescence. ERM may initially present as a reversible, stress-adaptive state such as cellular quiescence or ISR-induced dormancy. However, once cells undergo irreversible senescence, reversing ERM is unlikely to restore regenerative or proliferative function, and thus cannot reverse established aging-related decline.

Stem cell exhaustion → resource-dependent dormancy

Stem cell exhaustion is a hallmark of aging, marked by reduced self-renewal, differentiation, and tissue maintenance across systems such as muscle, immune, and hematopoietic lineages (López-Otín & Kroemer 2021). This decline arises from accumulated genomic damage, disrupted niche signaling, and chronic inflammatory environments, contributing to impaired regeneration and frailty.

However, not all stem cell dysfunction stems from irreversible depletion. Under prolonged stress or energy scarcity, stem cells can enter a quiescent state—a protective dormancy that suppresses proliferation to conserve energy and reduce damage risk (Cheung & Rando 2013; Ryall et al. 2015). This response is particularly relevant in ERM, where inflammation, mitochondrial stress, and downregulated mTORC1/IGF-1 signaling create a hostile metabolic environment.

In this context, stem cells may remain metabolically silenced rather than lost—preserved in dormancy until conditions improve. Restoration of nutrient flow, redox balance, and growth signaling can reactivate regenerative function. This concept of resource-dependent dormancy positions ERM as a reversible stage within the trajectory of stem cell exhaustion.

Bioenergetic inadequacies: a hidden cost of chronic adaptation

Daily adaptation to internal and external exposomes—ranging from chronic inflammation and environmental toxicants to psychological stress and circadian disruption—sustains a state of low-grade metabolic activation. This persistent activation places ongoing demands not only on macronutrient reserves, but also on micronutrients essential for enzymatic activity, redox homeostasis, and mitochondrial function (Alack et al. 2019; Raiten et al. 2015). Over time, this sustained pressure may result in subtle but cumulative bioenergetic inadequacy, where nutrient availability fails to keep pace with the prolonged demands of adaptation and repair.

Population-based studies reveal widespread nutrient insufficiencies, particularly among older adults, individuals with chronic illnesses, and those

exposed to sustained psychosocial or environmental stressors (Kiani et al. 2022). While overt deficiency syndromes are relatively rare in developed countries, chronic functional depletion and physiological misallocation of essential micronutrients—such as magnesium, zinc, selenium, B vitamins, iron, and vitamin D—are common and frequently underrecognized (Bailey et al. 2015; Han et al. 2022; Wessells & Brown 2012).

Macronutrients provide the foundational substrates for energy production, protein synthesis, and membrane integrity, while micronutrients serve as catalytic cofactors, coenzymes, and regulators across all domains of cellular metabolism. Under chronic stress, however, a mismatch emerges between rising metabolic demands and the body's ability to supply and allocate resources. Stress-induced neuroendocrine signals also favor substrate storage and active acute-phase responses while suppressing longer-term regenerative and anabolic functions. This substrate trapping creates a hidden trade-off: nutrients may be present, but are rendered functionally unavailable to systems responsible for repair and resilience (Friedman et al. 2024).

This stress-induced reallocation reflects Bruce Ames' nutrient triage hypothesis, which proposes that when resources are limited, the body prioritizes short-term survival at the expense of long-term maintenance (Ames 2006). Even modest degree of nutrient insufficiencies—if chronically diverted—can undermine tissue repair, immune regulation, and mitochondrial integrity, contributing to the emergence of ERM as a systemic energy-constrained state of maladaptive adaptation.

These nutrient-based trade-offs do not operate in isolation; rather, they converge with the core hallmarks of aging—fueling mitochondrial dysfunction, impairing nutrient-sensing pathways, and disrupting regenerative signaling. By undermining the biochemical foundations of repair and resolution, chronic bioenergetic inadequacy accelerates the transition from adaptive stress response to maladaptive exhaustion. In this light, ERM may be understood as a nutrient-sensitive phenotype of early aging—subclinical yet mechanistically aligned with canonical hallmarks, and potentially reversible if identified and addressed in time.

From irreversibility to intervention: ERM as a critical inflection point

By mapping the functional features of ERM onto canonical hallmarks of aging, this framework reconceptualizes biological aging not as an inevitable outcome of time, but as an accumulation of unresolved adaptation. ERM represents a critical inflection point—where physiological strain has begun to compromise resilience, yet functional systems remain responsive to intervention.

ERM thus reframes aging as a dynamic consequence of adaptation failure (Ryan & Ryznar 2022). Many functional changes observed in ERM—such as suppressed IGF-1 signaling or mitochondrial stress—are not necessarily irreversible (Picard & Shirihaï 2022; Wang & Zhang 2025). With timely intervention, biological aging trajectories may be interrupted (Calabrese & Mattson 2024; Shaulson et al. 2024).

Translational and clinical relevance: reframing healthspan through adaptive recovery

ERM challenges the traditional view of aging as a passive, time-driven decline. Instead, it reframes many hallmarks of aging—such as mitochondrial dysfunction, anabolic resistance, and immune dysregulation—as the downstream effects of unresolved physiological adaptation. ERM represents a chronic shift in bioenergetic priorities, where sustained stress redirects substrates away from maintenance and repair toward immediate survival, progressively compromising immune integrity, tissue regeneration, and neuroendocrine balance (Martel et al. 2024; Yiallouris et al. 2019).

A Window for preventive intervention

Despite its clinical relevance, ERM often remains invisible to conventional diagnostics. Individuals may fall within normal ranges for weight and laboratory values, yet present with signs of declining resilience—fatigue, brain fog, chronic pain, impaired recovery, immune susceptibility, and anabolic resistance. These early indicators often precede structural decline and mirror preclinical frailty (Arron et al. 2024; Walrand et al. 2021).

Japan's national health model illustrates how early-stage metabolic compromise can be identified and mitigated. Since 2008, routine metabolic syndrome screening has included waist circumference—highlighting central adiposity as an early marker of energy misallocation driven by chronic glucose, insulin, and cortisol exposure. This simple anthropometric indicator reflects a core feature of ERM: substrate accumulation in visceral fat at the expense of lean tissue and repair capacity. Japan's model, which integrates personalized lifestyle guidance into workplace and community health systems, has led to measurable improvements in metabolic outcomes (Shirai & Tsushita 2024).

While the Japanese model provides a particularly integrated example, it is not the only cultural tradition supporting resilience and healthy aging. The Mediterranean lifestyle—characterized by plant-based dietary patterns, social meal rituals, and moderate physical activity—has also been associated with reduced allostatic load and improved metabolic health. These traditions, though geographically distinct, share key features: nutrient density, circadian-aligned behaviors, and community integration—each contributing to sustained adaptive capacity across the lifespan.

This proactive framework aligns with the clinical potential of ERM. By recognizing functional symptoms and biomarker trade-offs—before irreversible damage occurs—interventions can be deployed to restore bioenergetic availability, reactivate regenerative pathways, and preserve long-term physiological resilience.

Strategies to restore metabolic governance

Because ERM stems from chronic resource misallocation and maladaptive stress responses, recovery requires a systems-level approach targeting both upstream causes and downstream consequences.

- Lifestyle-Circadian Synchronization:** Synchronizing daily behaviors with circadian rhythms—through structured sleep, timed meals, and light exposure—plays a vital role in restoring metabolic tempo, optimizing insulin sensitivity, and recalibrating neuroendocrine function (Ryan & Ryznar 2022; Shaulson et al. 2024; Tippirote et al. 2021). Central to this process

is the alignment of the cortisol rhythm, a core output of the circadian system that governs energy mobilization, immune modulation, and stress response. Disruptions to this rhythm—whether through irregular sleep patterns, nighttime eating, or insufficient light exposure—can desynchronize the HPA axis, promoting metabolic dysfunction. Traditional Japanese lifestyle patterns, such as early dinners, seasonal meal timing, and exposure to natural light, inherently support circadian alignment. These culturally embedded practices may contribute to Japan's exceptional longevity by sustaining hormonal rhythms and reducing bioenergetic strain (Shirai & Tsushita 2024).

- Mitochondrial and Nutritional Support for Resilience:** Mitochondrial resilience and nutritional sufficiency are tightly intertwined. Essential cofactors—magnesium, zinc, selenium, B vitamins, alpha-lipoic acid—are critical for mitochondrial redox balance and energy production. Subclinical deficiencies often manifest as low alkaline phosphatase, elevated homocysteine, or reduced transport proteins (e.g., prealbumin, transferrin), signaling the need for targeted repletion and consistent protein intake (Beck & Rosenthal 2002; Ray et al. 2017). Complementary mitohormetic stimuli—such as moderate exercise, thermal stress, and intermittent fasting—enhance mitochondrial biogenesis and adaptive signaling. These effects are reinforced by polyphenols like quercetin and epigallocatechin gallate (EGCG), which reduce senescent cell burden and promote tissue repair (Martel et al. 2024; Ristow & Schmeisser 2014). Japan's traditional diet offers a real-world validation: nutrient-dense, anti-inflammatory, and phytonutrient-rich, it supports immune competence, muscle integrity, and systemic recovery. This dietary pattern has been associated with reduced chronic disease burden and sustained physical and cognitive function into advanced age (Li et al. 2024; Shirai & Tsushita 2024). Improving dietary quality is a critical foundation in addressing ERM. Strategies such as reducing refined carbohydrate and sugar intake may help modulate insulin and stress hormone dynamics, while adequate protein intake supports tissue repair and regeneration. Repletion of specific micronutrients—particularly vitamin D, a

key regulator of counter-regulatory immune responses—is essential to reduce the risk of sustained inflammation and impaired resolution in individuals with high metabolic demand. However, nutritional repletion alone may be insufficient in the presence of unresolved stress, inflammation, or toxicant exposure, which can impair nutrient utilization and reinforce maladaptive metabolic states. Therefore, dietary strategies should be implemented as part of a broader integrative approach. Ultimately, successful reversal of ERM requires not just the availability of nutrients, but the physiological capacity to utilize them—highlighting the importance of synchronized, resilience-informed interventions.

- Neuroendocrine and Stress Axis Modulation:** The capacity to dynamically regulate stress through the HPA and SAM axes is essential for survival and healthy aging. In ERM, chronic overactivation of these axes leads to persistent catabolism, inflammation, and autonomic imbalance. Mind-body interventions—such as mindfulness-based stress reduction (MBSR), yoga, and vagal breathing—help restore parasympathetic tone, lower cortisol output, and improve neuroendocrine flexibility (Chrousos 2009; Srouf & Keyes 2025). These practices support systemic recovery and energy conservation. Cultural constructs also matter. In Japan, *ikigai*—a sense of meaning and purpose—has been linked to lower allostatic load and longer lifespan, highlighting the role of psychosocial integration in sustaining adaptive capacity (Shirai & Tsushita 2024). Targeting these neuroendocrine hubs—where emotion, metabolism, and inflammation intersect—can help reverse the maladaptive cycle of ERM and reestablish the physiological adaptability required for resilience.

Toward resilience-informed healthspan strategies

ERM reframes healthcare goals—from treating disease to preserving adaptive potential. A resilience-informed approach emphasizes:

- *Monitoring of functional reserve*
- *Recognition of dynamic biomarker constellations* rather than reliance on static thresholds

- *Restoration of energy availability and systemic plasticity*

This model is not aspirational—it is already being implemented. Japan's Health Promotion Law, *Smart Life Project*, and community-based integrated care prioritize functional maintenance and social participation. These policies have contributed to Japan's status as a global leader in healthy life expectancy (Shirai & Tsushita 2024).

ERM provides a practical framework to apply similar principles in clinical settings. By identifying reversible patterns of depletion and intervening before overt disease, we can extend healthspan, delay frailty, and support aging as a process of sustained adaptation—not inevitable decline.

Conclusion

Aging is not merely the passive accumulation of molecular damage over time—it is increasingly recognized as the *cumulative cost of chronic adaptation* under conditions of bioenergetic constraint. This review introduces ERM as a mechanistically grounded and clinically actionable phenotype of early maladaptation. ERM reflects a persistent state of stress-induced substrate misallocation, manifesting as a distinct constellation of metabolic trade-offs and progressive physiological inefficiency. Unlike classical forms of malnutrition, ERM does not result from overt nutrient deprivation but emerges from *chronic bioenergetic compromise* that prioritizes short-term survival at the expense of long-term maintenance and repair.

By aligning ERM with the established hallmarks of aging, this framework positions ERM as a potentially reversible driver of biological aging. It provides a new lens through which to detect early functional decline and metabolic fragility, often preceding the clinical onset of frailty, immune dysfunction, or sarcopenia.

To translate this concept into clinical and research practice, a phased and multidisciplinary strategy is essential:

- *A systematic review*, registered with PROSPERO (ID: CRD420251033154), is currently underway to consolidate evidence across stress physiology, metabolic adaptation, and malnutrition domains.

This review aims to identify converging biomarker constellations and physiological trade-offs that define ERM and support the development of pattern-based recognition criteria.

- In parallel, *a retrospective analysis of clinical data* is in progress. This study will identify real-world ERM phenotypes, validate functional and biomarker signatures, and inform the development of a robust ERM staging model.
- With phenotype recognition and staging in place, *intervention trials* can be designed to target the mechanisms underpinning ERM. These may include strategies to restore mitochondrial function, rebalance micronutrient and amino acid status, synchronize circadian and neuroendocrine rhythms, and promote recovery following sustained stress exposure.

Together, these research phases aim to establish ERM as *a measurable, pattern-defined, and clinically meaningful constellation*—a modifiable inflection point along the continuum of aging and chronic disease.

Reframing healthspan through the lens of adaptive recovery and metabolic flexibility offers a compelling new direction for preventive aging care. By detecting ERM in its earliest stages—and restoring the physiological conditions necessary for repair, regeneration, and energy balance—we may preserve systemic resilience, prolong functional independence, and intervene before chronic dysfunction becomes entrenched or irreversible.

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