Review

A Conceptual Framework of Bioenergetic Trade-Offs in Stress Adaptation, Aging, and Chronic Disease

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The Metabolic Cost of Resilience: A Conceptual Framework of Bioenergetic Trade-Offs in Stress Adaptation, Aging, and Chronic Disease

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Highlights

- Introduces *Exposure-Related Malnutrition (ERM)* as a reversible stress adaptation failure
- Proposes a three-phase model: *Respond* → *Adapt* → *Resolve* → 3 metabolic outcomes
- Links *early substrate misallocation* to aging and chronic disease progression
- Integrates mitochondrial, immune, and endocrine stress responses into *a unified model*
- Supports *pattern-based biomarkers* for early detection of metabolic resilience loss

Abstract: While global lifespan continues to rise, healthspan—the period of life spent in good health—remains stagnant or in decline. This widening gap reflects more than chronic disease burden; it signals the hidden metabolic cost of prolonged stress adaptation. Under sustained physiological strain, the body reallocates energy and nutrients away from maintenance and repair toward short-term survival priorities such as immune defense and glucose mobilization. Although initially protective, these trade-offs progressively impair recovery, erode resilience, and accelerate biological aging. Current stress and aging frameworks, including allostatic load, describe cumulative burden but lack the resolution to detect early, reversible stages of metabolic compromise—especially in individuals without weight loss or intake deficiency. To address this, we propose *Exposure-Related Malnutrition (ERM)*: a subclinical condition marked by chronic substrate misallocation under stress, despite adequate caloric intake or BMI. ERM represents an early inflection point of adaptive failure with implications for aging, resilience, and chronic disease. This thematic narrative review integrates findings from endocrinology, immunometabolism, mitochondrial biology, and systems physiology. We present a unifying three-phase model of stress response—*Respond* → *Adapt* → *Resolve*—and show how bioenergetic constraints during the resolution phase shape divergent outcomes: homeostasis, hormesis, or maladaptation. Clinically, ERM reframes unexplained fatigue, anabolic resistance, or immune dysfunction as signs of early metabolic imbalance. Recognizing ERM enables earlier detection and supports biomarker-guided, resilience-informed interventions aimed at preserving healthspan by addressing the energetic cost of unresolved adaptation.

Keywords: energy metabolism; stress adaptation; aging; resilience; malnutrition; mitochondrial dysfunction

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1. Introduction

1.1. The Paradox of Longevity: Rising Lifespan, Declining Healthspan

Advances in medicine and public health have extended the human lifespan dramatically over the past century. Yet this progress has exposed a paradox: while people are living longer, they are not necessarily living healthier (Crane et al., 2022). The gap between lifespan and healthspan—the portion of life spent in good functional health—continues to widen. Chronic, non-communicable diseases (NCDs) such as diabetes, cardiovascular disease, and neurodegeneration are now the dominant causes of morbidity and mortality, often manifesting decades before death (WHO, 2025).

1.2. A Critical Gap in Stress and Aging Models

Many aging theories emphasize molecular damage, telomere attrition, mitochondrial dysfunction, or cellular senescence (Polidori, 2024). Yet these models often overlook a key transitional process: the *cumulative energetic cost of sustained stress adaptation*. Classical frameworks such as Selye's General Adaptation Syndrome (GAS) and McEwen's concept of allostatic load have been instrumental in describing how the body responds to stress and the physiological toll of prolonged strain (McEwen & Wingfield, 2003; Selye, 1950). However, these models fall short in explaining *early, subclinical declines in adaptive capacity* that occur without weight loss, overt disease, or measurable intake deficiency—particularly in individuals who appear metabolically normal by conventional standards.

Emerging evidence suggests that persistent stress, inflammation, and metabolic strain can lead to a silent diversion of substrates away from regeneration, repair, and resilience maintenance (Bobba-Alves et al., 2023; Shaulson et al., 2024). This hidden cost of adaptation is not adequately captured by current stress or aging models, leaving clinicians and researchers without a clear framework to recognize or intervene in early maladaptation. Moreover, while concepts such as allostatic load and mitochondrial dysfunction have contributed valuable insights into the biology of aging, they do not adequately account for the bioenergetic decision points or systemic substrate trade-offs that precede functional decline.

1.3. Purpose and Scope: Introducing ERM as a Conceptual Bridge

This review introduces the concept of *Exposure-Related Malnutrition (ERM)*— a proposed subclinical, pre-diagnostic state of bioenergetic insufficiency that arises not from food scarcity, but from *chronic substrate misallocation under sustained stress exposure*. Unlike previously described forms of subclinical malnutrition, ERM is defined not by intake or anthropometry, but by persistent diversion of metabolic substrates away from long-term maintenance and toward short-term survival functions

Drawing from immunometabolism, systems biology, mitochondrial signaling, and stress physiology, we synthesize classical and emerging frameworks—including the integrated stress response (ISR), mitochondrial ISR (ISR^{mt}), brain-body energy conservation, and metabolic triage—to propose ERM as a unifying construct that links adaptation failure to aging and chronic disease (Ames, 2006; Larabee et al., 2020; Payea et al., 2024; Shaulson et al., 2024; Wang & Zhang, 2025). ERM also offers a framework for interpreting early, pattern-based signals of maladaptation—such as slowed recovery, anabolic resistance, low-grade inflammation, or fatigue—even in the absence of overt nutritional deficits. It highlights the need to move beyond static thresholds and embrace dynamic pattern recognition in clinical evaluation.

In summary, ERM advances the current literature by:

- Identifying a reversible stage of adaptation failure that precedes traditional disease markers;
- Integrating energy availability and substrate allocation as central regulators of stress resolution and resilience;
- Bridging molecular stress models with clinical presentations; and

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- Providing a systems-level framework for early detection and intervention before irreversible aging-related decline.

This review therefore builds on existing stress and aging paradigms but moves beyond descriptive burden models by offering a mechanistically grounded, energetically framed, and clinically actionable concept: ERM as the metabolic cost of unresolved adaptation.

1.4. Structure of the Review

This review is organized into three thematic sections:

1. *Energetic adaptation:* We describe the trajectory of stress response using the *Respond → Adapt → Resolve* framework and outline how this process may lead to homeostasis, hormesis, or maladaptation.
2. *System-level trade-offs:* We examine how neuroendocrine, immune, muscular, mitochondrial, and cellular networks navigate energetic constraints and reallocate resources under stress.
3. *Clinical implications:* We outline the presentation, staging, and early biomarkers of ERM and propose practical strategies for detection, intervention, and prevention of chronic disease rooted in adaptive energy failure.

By recognizing ERM as a preclinical expression of unresolved adaptation, this framework reframes healthspan as an energetically governed capacity—one that can be measured, supported, and ultimately preserved.

2. Methodology: A Thematic Narrative Review

This review employs a *thematic narrative synthesis* to explore how chronic stress adaptation imposes metabolic trade-offs that shape the trajectory of aging and chronic disease. A narrative approach was selected to integrate mechanistic insights across disciplines—including physiology, endocrinology, immunometabolism, systems biology, and mitochondrial research— where the complexity and interdependence of processes are not easily captured by systematic or quantitative methods. The goal is not to exhaustively catalog studies, but to conceptually synthesize evidence across domains and develop a unifying framework for metabolic adaptation failure.

Relevant literature was identified through purposive searches of PubMed, Scopus, and Web of Science using combinations of terms such as “chronic stress,” “energy metabolism,” “resilience,” “immune aging,” “mitochondrial dysfunction, and “adaptive trade-offs.” Inclusion was guided by conceptual relevance rather than study design, prioritizing peer-reviewed studies from 2000–2025, foundational models, and recent interdisciplinary advances.

The synthesis was guided by an iterative, concept-driven approach. We mapped recurring patterns of substrate reallocation, recovery failure, and physiological trade-offs, which were then distilled into a conceptual model (Figure 1) that outlines a three-phase adaptive trajectory: *Respond → Adapt → Resolve*, with outcomes of *homeostasis, hormesis, or maladaptation*. Within this arc, *Exposure-Related Malnutrition (ERM)* is positioned as a *subclinical inflection point* where energy availability becomes insufficient to sustain recovery.

As *a narrative review*, this work is intended to conceptually integrate existing knowledge rather than provide an exhaustive or systematic appraisal of literature. The goal is to offer a transdisciplinary synthesis that supports hypothesis generation, model development, and clinical translation in the context of metabolic resilience and early-stage malnutrition.

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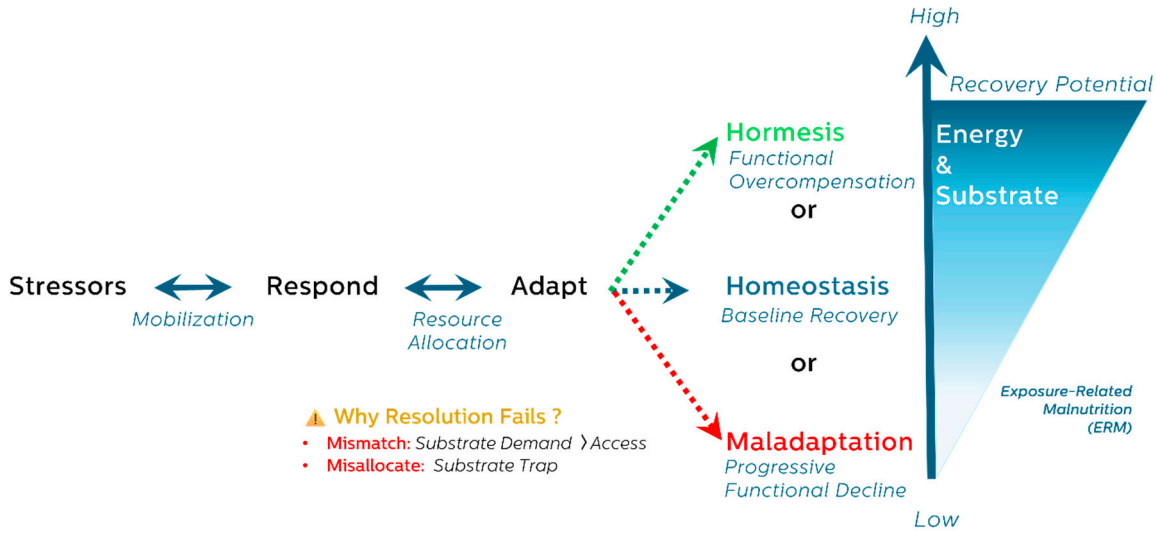

Figure 1. Energetic Adaptation Arc: Respond → Adapt → Resolve outcomes shaped by energy availability. Adaptive outcomes following stress are contingent on energy and substrate sufficiency. The resolution phase can lead to hormesis, homeostasis, or maladaptation. See Table 2 for comparative system outcomes.

3. The Energetic Trajectory of Stress Adaptation: From Response to Resolution

Stress adaptation is not a static or purely biochemical process—it is an *energetically expensive trajectory* that unfolds across systems, requiring continuous reallocation of substrates to balance survival, repair, and resilience (Monzel et al., 2023). At every level—organismal, cellular, and subcellular—outcomes hinge on energy availability, substrate prioritization, and the capacity to resolve stress efficiently. When demands exceed available resources, physiological systems invoke trade-offs that may preserve immediate function but compromise long-term integrity.

3.1. General Adaptation and the Cost of Resolution

GAS, proposed by Hans Selye, remains foundational for understanding systemic stress responses. It outlines three stages: *Alarm* (emergency mobilization), *Resistance* (sustained adaptation), and *Exhaustion* (breakdown from prolonged strain) (Selye, 1950). Contemporary models such as allostasis refine this view, emphasizing dynamic resource reallocation to maintain stability through change (McEwen & Wingfield, 2003). Crucially, the "*Resistance*" phase is not a static holding pattern—it can resolve in one of three ways:

- Restored homeostasis
- Adaptive overcompensation (hormesis)
- Progressive maladaptation and decline (exhaustion)

This triad reflects a nonlinear and reversible path, contingent on bioenergetic reserve and recovery capacity. *Exhaustion is not inevitable—but neither is resilience free.*

3.2. Hormesis: A Metabolic Bet on Adaptive Remodeling

Hormesis illustrates how *low-dose or transient stress*, if resolved, can strengthen resilience (Calabrese & Agathokleous, 2019). Initially observed in toxicology, it is now recognized across contexts like exercise, caloric restriction, and thermal exposure. These stressors impose *short-term metabolic costs* in exchange for durable *gains* in tolerance, repair, or capacity.

However, this benefit is then *conditional*: when stress exceeds recovery capacity, the same stimulus may lead to dysfunction. Hormesis, then, is a *conditional investment*—a metabolic gamble whose return depends on the ability to resolve stress efficiently.

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3.3. Substrate Limitation and Trade-Offs

All stress responses require core substrates—ATP, amino acids, glucose, fatty acids, and micronutrients. Under stress, these are diverted from maintenance processes (e.g., neurogenesis, tissue repair, immune surveillance) to immediate survival priorities (Zera & Harshman, 2001). When stress is chronic, this becomes a zero-sum game: systems are forced to *triage functions* in ways that preserve critical operations while deferring or degrading others.

The *nutrient triage hypothesis* proposes that even mild, sustained substrate limitations can suppress longevity pathways in favor of short-term survival (Ames, 2006). Over time, this results in functional erosion—manifesting as fatigue, inflammation, anabolic resistance, and poor repair capacity—hallmarks of what we term *subclinical adaptation failure*.

These functional trade-offs signal an early decline in adaptive efficiency—what we propose to recognize as the earliest stage of ERM. They represent a critical turning point in the adaptive arc, where unresolved substrate mismatch and reallocation may tip physiological systems toward maladaptation.

3.4. A Unifying Trajectory: Respond → Adapt → Resolve

Despite diversity in mechanisms, a consistent three-phase trajectory underlies most physiological stress responses:

- **Phase 1: Respond** – Emergency mobilization of energy and substrate.
- **Phase 2: Adapt** – Resource reallocation, stress programming, and metabolic reprioritization.
- **Phase 3: Resolve** – Withdrawal of stress programs, restoration of balance, or collapse into dysfunction.

At each phase, the availability of metabolic substrates and the flexibility of regulatory networks determine whether systems recover, overcompensate, or deteriorate. This shared arc is explored in depth across five systems below and visualized conceptually in Figure 1.

4. The Energetic Architecture of Adaptation: Substrate Reallocation in Systemic Stress Responses

Physiological systems vary in their stress signaling, but they converge on a common energetic logic: *adaptation requires prioritized substrate allocation under constraint*. The trajectory—*Respond → Adapt → Resolve*—is not merely descriptive, but *energetically governed.*

This section explores how this trajectory manifests across five key systems: *neuroendocrine, immune, muscular, cellular integrated stress responses (ISR), and mitochondrial networks*. Outcomes—homeostasis, hormesis, or maladaptation—depend on the interplay of substrate availability, regulatory capacity, and stress duration. These dynamics are summarized in Table 1 and visually represented in Figure 2.

Table 1. Comparative features of adaptive stress responses across key physiological systems. Resolution potential reflects each system's capacity to recover following stress exposure, which depends on energy substrate availability, regulatory flexibility, and the timely deactivation of stress programs. Vulnerabilities describe the characteristic dysfunctions that emerge when resolution is impaired, or adaptation is prolonged.

System	Primary Adaptive Role Under Stress	Preferred Energy Substrates	Recovery Potential (if Stress Resolves)	Vulnerabilities Under Deficit
Neuroendocrine	Glucose mobilization, survival triage	Gluconeogenesis, lipolysis	Moderate (via HPA feedback and cortisol tapering)	HPA overactivation, insulin resistance
Immune	Inflammation, defense coordination	Glycolysis (pro-inflammatory), OXPHOS (resolution)	High (if inflammatory–resolving balance restored)	Chronic inflammation, immune senescence

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Muscle	Amino acid reservoir, metabolic buffering	Glycogen, fatty acids, protein catabolism	High (if nutrient repletion and anti-inflammatory signaling occur)	Anabolic resistance, sarcopenia
Cellular ISR	Proteostasis, autophagy, stress signaling	Internal recycling, selective translation	Moderate to high (if ATP/redox status is restored)	Persistent translation block, proteostasis failure, apoptosis
Mitochondria	Energy production, redox balance, mitokine release	OXPHOS, glycolysis, fatty acids	High (if mitophagy and fission/fusion are restored)	ROS overload, mitokine dysfunction

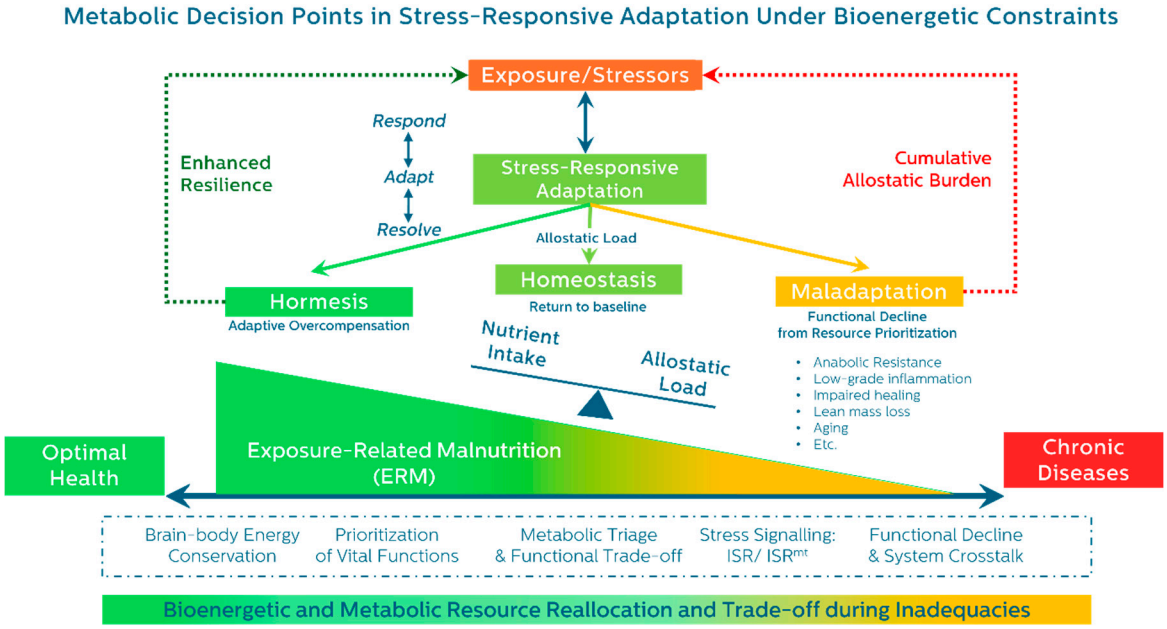

Figure 2. Metabolic Decision Points in Stress-Responsive Adaptation Under Bioenergetic Constraints. Stress adaptation follows a three-phase trajectory—*Respond* → *Adapt* → *Resolve*—in which outcomes are shaped by bioenergetic capacity and substrate allocation. Depending on nutrient availability and allostatic regulation, the resolution phase may lead to: • *Homeostasis (baseline recovery),* • *Hormesis (adaptive overcompensation), or* • *Maladaptation (functional decline from unresolved stress).* These outcomes represent a *metabolic decision point* governed by cumulative allostatic load and substrate sufficiency. The green arc reflects successful resolution and resilience; the yellow arc reflects unresolved stress and risk of chronic disease. Energy reallocation and trade-offs occur at each stage, with patterns of metabolic triage, function prioritization, and stress regulatory signaling (e.g., ISR/ISR^{mt}) determining long-term outcomes.

4.1. Phase 1—Respond: Emergency Signaling and Energy Mobilization

In the initial *Response* phase, each system activates defense mechanisms that divert energy from growth and maintenance toward survival:

- *Neuroendocrine System:* The *hypothalamic-pituitary-adrenal (HPA) axis* and *sympathetic-adrenal-medullary (SAM) system* initiate a coordinated stress response, rapidly mobilizing glucose while suppressing growth and reproduction (Tsigos & Chrousos, 2002).
- *Immune System:* Pattern recognition receptors (PRRs) activate acute inflammation and drive metabolic polarization toward glycolysis, supporting cytokine production (e.g., TNF-α, IL-6) (Alack et al., 2019; Straub, 2017).
- *Skeletal muscle:* Acts as a metabolic reservoir, supplying gluconeogenic substrates through proteolysis (Cahill, 2006; Wolfe, 2006).

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- *Cellular ISR* halts general protein synthesis via eIF2α phosphorylation while promoting selective translation of stress-resilient genes (Pakos-Zebrucka et al., 2016).
- *Mitochondria* toward ATP generation, activate antioxidant pathways, and initiate the mitochondrial unfolded protein response (UPR^{mt}) (Picard & Shirihai, 2022).

This phase reflects *catabolic triage*—substrates are mobilized to preserve critical function at the expense of repair. If the stressor is short-lived, systems may return to baseline. If not, adaptation ensues.

4.2. Phase 2— Adapt: Metabolic Prioritization and Stress Programming

In the *Adapt* phase, systems implement energy-saving, resource-redistributing programs to cope with sustained demands:

- *Neuroendocrine System:* Cortisol orchestrates systemic prioritization, supporting cerebral glucose supply while suppressing insulin, growth, and reproduction (McEwen & Wingfield, 2003).
- *Immune cells* undergo metabolic polarization: pro-inflammatory cells rely on glycolysis, while regulatory or reparative cells depend on oxidative phosphorylation (Olenchock et al., 2017; Willmann & Moita, 2024) (Geric et al., 2019; Olenchock et al., 2017). Chronic stress can trap cells in inflammatory states.
- *Skeletal muscle*, a major metabolic sink, attempts to transition from catabolism to repair. This shift requires amino acid availability and immune–muscle coordination, both of which are impaired under conditions of anabolic resistance. Anabolic resistance is not only a consequence but also a signal of unresolved adaptation, a state in which substrates and signaling are insufficient to restore muscle regeneration (Paulussen et al., 2021).
- *Cellular ISR*, when energetically supported, transitions from acute translation suppression to remodeling via autophagy, stress granule formation, and selective translation of repair-promoting factors (Gambardella et al., 2020). This metabolic reprioritization also drives epigenetic remodeling that accelerates cellular aging, especially under persistent stress (Gambardella et al., 2020).
- *Mitochondria* undergo remodeling, including mitophagy, fission/fusion dynamics, and shifts in substrate utilization to meet tissue-specific energy demands (Lockhart et al., 2020).

This phase is *energetically constrained but potentially reversible*. Systems remain functional, but operate below baseline. Whether they recover or decline depends on resolution dynamics.

4.3. Phase 3—Resolve: Transitioning from Adaptation to Outcome

The *Resolution* phase determines whether systems return to baseline, rebuild capacity, or collapse into dysfunction. It marks a pivotal inflection point: recovery is possible, but only if energy and regulatory balance are restored.

- *Neuroendocrine system* downregulates HPA activity and reinstates circadian and metabolic rhythms. Persistent flattening of cortisol indicates impaired resolution (McEwen, 2007; Sapolsky, 2004).
- *Immune systems* transition from inflammation to repair, with M1 macrophages converting to M2 phenotypes and resolution pathways (e.g., resolvins, lipoxins) facilitating tissue remodeling (Olenchock et al., 2017). Micronutrient sufficiency—particularly zinc, selenium, and iron—is critical to this process.

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- *Skeletal muscle* resumes protein synthesis and regeneration, but only if inflammation resolves and energy/nutrient levels support mTORC1 and satellite cell activation. Without adequate support, fibrosis or sarcopenia may ensue (Paulussen et al., 2021).
- *Cellular ISR mechanisms*, such as GADD34-mediated dephosphorylation of eIF2α, permit selective restoration of protein synthesis. This reactivation depends on sufficient ATP, proteostasis, and redox control (Gambardella et al., 2020).
- *Mitochondria* stabilize through restored fission/fusion dynamics and mitophagy, allowing redox homeostasis and efficient energy production. Transient mitokine signaling subsides as systemic demands normalize (Picard & Shirihai, 2022).

These recovery programs are not automatic. They require sufficient energy, nutrient cofactors, and cessation of the primary stressor. In their absence, resolution stalls, leading to maladaptation—a theme further explored in Section 5.

5. Resolution and Its Consequences: Divergent Outcomes Shaped by Energy and Resource Allocation

The final stage of the stress adaptation cascade—Resolve—is where systems either recover, remodel, or decline. Crucially, outcomes are not determined by stress exposure alone but by *the availability and distribution of metabolic resources*, the *flexibility of regulatory systems*, and the *duration of unresolved strain*.

Three principal outcomes emerge across physiological systems:

1. *Homeostasis* – restoration of baseline function
2. *Hormesis* – adaptive overcompensation and enhanced resilience
3. *Maladaptation* – incomplete resolution and functional deterioration

These outcomes reflect a branching decision point within the adaptive trajectory, influenced by energy sufficiency, recovery dynamics, and systemic reserve. Resolution is not uniform across tissues; one system (e.g., immune) may successfully recover, while others (e.g., muscle or mitochondria) remain maladaptive—reflecting differences in energetic thresholds and prior burden.

5.1. Homeostasis: Energetic Recovery and Structural Recalibration

Homeostasis represents a return to equilibrium, where stress programs are deactivated and metabolic balance restored. This outcome requires adequate energy and substrates to downregulate catabolic signaling, resolve inflammation, and reinstate long-term maintenance.

Key features across systems include:

- *Neuroendocrine recovery:* HPA axis normalization and restored circadian rhythm with cortisol and sympathetic output declining. Parasympathetic tone is restored, and insulin sensitivity improves (Bobba-Alves et al., 2022).
- *Immune recalibration:* Immune resolution involves clearance of apoptotic cells, matrix remodeling, and macrophage transition from M1 to M2 phenotypes—processes that rely on mitochondrial OxPhos, redox regulation, and micronutrients like zinc, iron, and selenium (Alack et al., 2019; Laurent et al., 2017; Olenchock et al., 2017).
- *Muscle regeneration:* Recovery depends on satellite cell activation and nutrient-sensitive pathways such as mTORC1, supported by leucine, vitamin D, and redox cofactors (Beaudart et al., 2017; Careccia et al., 2023; Paulussen et al., 2021).
- *Cellular ISR* resolves through GADD34-mediated dephosphorylation of eIF2α, enabling proteostasis and selective translation restoration (Gambardella et al., 2020; Novoa et al., 2001).

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- *Mitochondrial recovery* via mitophagy and biogenesis restores ATP production and oxidative balance; transient ROS bursts activate adaptive pathways via NRF2 and FOXO, while sustained oxidative stress impairs recovery (Picard & Shirihai, 2022).

Homeostasis is energetically efficient, but not passive—it depends on successful substrate repletion, resolution of the initiating stressor, and intact signaling loops.

5.2. Hormesis: Energetic Overcompensation and Adaptive Remodeling

Hormesis occurs when *moderate, time-limited stress*, paired with adequate recovery, induces adaptive remodeling that enhances system capacity beyond baseline (Calabrese & Agathokleous, 2019). It is metabolically costly but offers long-term resilience benefits and improved future adaptability.

Examples of hormetic outcomes include:

- *Trained immunity*: Monocytes, macrophages, and NK cells undergo glycolytic and epigenetic reprogramming via mTOR–HIF-1α signaling, increasing responsiveness and tolerance (Netea et al., 2016; Ochando et al., 2023; Vuscan et al., 2024).
- *Immune resolution and tolerance*: Regulatory T cells and M2 macrophages mediate inflammation resolution and tissue repair via mitochondrial metabolism (Vuscan et al., 2024).
- *Exercise-induced muscle remodeling:* IL-13–producing ILC2s, IL-33–expressing stromal cells, and macrophage–Treg signaling coordinate mitochondrial biogenesis and type 2 immunity in recovery (Langston & Mathis, 2024; Metallo & Vander Heiden, 2013).
- *Mild ISR activation:* Transient eIF2α phosphorylation enhances redox balance, proteostasis, and metabolic flexibility via ATF4/CHOP signaling (Costa-Mattioli & Walter, 2020; Sparkenbaugh et al., 2011).
- *Mitohormesis:* Low-level ROS from mitochondrial stress induces biogenesis, antioxidant upregulation, and mitokine release (e.g., FGF21, MOTS-c) for systemic coordination (Lockhart et al., 2020; Ristow & Schmeisser, 2014).

Hormetic remodeling occurs only when the energy required for overcompensation is available. Without it, the same stressor may lead to maladaptation.

5.3. Maladaptation: Energetic Collapse and Structural Degeneration

Maladaptation represents a failure to resolve stress—a condition in which catabolic programs remain active, repair is stalled, and structural decline accelerates. It is not simply an overwhelmed system, but one *trapped in unresolved adaptation* due to substrate insufficiency or regulatory dysfunction.

System-level manifestations include:

- *Neuroendocrine:* Sustained cortisol, insulin resistance, hippocampal atrophy, and central fatigue due to prolonged stress signaling (Chrousos, 2009; Meeusen et al., 2006; Shaulson et al., 2024).
- *Immune*: Inflammaging and immunosenescence from persistent IL-6, TNF-α, SASP signaling, and impaired clearance of senescent cells(Franceschi et al., 2018; Fulop et al., 2018; Wang et al., 2024).
- *Skeletal muscle:* Anabolic resistance, mitochondrial dysfunction, and catabolism lead to sarcopenia and frailty, compounded by aging, nutrient deficits, and inflammation(Cruz-Jentoft et al., 2023; Walrand et al., 2021).
- *Cellular ISR:* Chronic eIF2α phosphorylation impairs translation, promotes apoptosis, and drives redox imbalance and mitochondrial damage (Hetz & Papa, 2018; Wek, 2018).

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- *Mitochondria:* PGAM5-driven mitochondrial fragmentation, ROS generation, and mtDNA-triggered inflammasome activation fuel a cycle of mitophagy failure, pyroptosis, and degeneration (Qi et al., 2025; Youle & van der Bliek, 2012; Yuk et al., 2020)

Maladaptation represents the energetic tipping point beyond which resilience cannot spontaneously re-emerge without targeted recovery support.

5.4. Interpreting Resolution as a Metabolic Decision Point

The resolution phase is not a passive return to baseline—it is *a metabolic decision point* that determines whether the adaptive process results in recovery, remodeling, or degeneration.

Outcomes are influenced by:

- *Stressor burden and duration*
- *Substrate availability and recovery efficiency*
- *System-specific thresholds for adaptation or collapse.*

We propose that resolution represents a metabolic decision point—one visualized and detailed in Figure 2 and Table 2, where the *Respond* → *Adapt* → *Resolve* cascade branches toward homeostasis, hormesis, or maladaptation based on energetic sufficiency, recovery support, and system-specific thresholds.

Early recognition of stalled resolution offers a critical opportunity for intervention—before functional decline becomes entrenched. Restoring substrate flow, resolving inflammation, and rebalancing regulatory signals may still redirect adaptation toward recovery, even in later stages.

Table 2. Divergent Outcomes of Stress Resolution: Comparative Features of Homeostasis, Hormesis, and Maladaptation. Each resolution pathway—homeostasis, hormesis, or maladaptation—emerges from the intersection of energy availability, regulatory recovery, and system-specific adaptability. This table compares outcome-specific features across domains commonly affected during prolonged or repeated stress exposure. ISR: Integrated Stress Response; ROS: Reactive Oxygen Species; OXPHOS: Oxidative Phosphorylation.

Feature	✔ **Homeostasis "Return to Baseline"**	✚ **Hormesis "Adaptive Overcompensation"**	⚠ **Maladaptation "Chronic Dysregulation"**
Energy Availability	Restored baseline levels	Sufficient with transient surplus	Depleted or misallocated
Functional Outcome	Functional recovery	Enhanced resilience or capacity	Progressive dysfunction
Immune Response	Inflammation resolves	Trained immunity and regulatory tolerance	Chronic inflammation, immune exhaustion
Muscle Remodeling	Repair of damaged fibers	Functional hypertrophy, mitochondrial gains	Catabolism, fibrosis, loss of regenerative signaling, sarcopenia
ISR Recovery	Reinstated proteostasis	Increased stress resilience, adaptive proteostatic memory	Persistent translation block, apoptosis
Mitochondrial Dynamics	Normalized bioenergetics	Improved redox balance, adaptive signaling	ROS overload, mitophagy failure, fragmentation, fission–fusion imbalance
Recovery Prerequisites	Energy repletion, stress withdrawal	Surplus energy, time, micronutrient support	Insufficient recovery, chronic demand

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6. Recognizing the Spectrum of Malnutrition: From Demand to Distribution Dysfunction

Malnutrition is traditionally associated with insufficient intake or overt nutrient loss. However, a growing body of evidence shows that malnutrition can also arise from *elevated demand, inefficient distribution*, or *chronic misallocation of metabolic substrates*. These distinct but overlapping mechanisms give rise to *well-characterized clinical phenotypes.* Together, they form a conceptual foundation for understanding the broader adaptive failure proposed in ERM.

6.1. Demand-Driven Malnutrition: Elevated Needs, Silent Deficits

Several classical conditions demonstrate that energy and nutrient insufficiency can occur even in the presence of adequate intake, driven instead by heightened metabolic demands:

- *Disease-Related Malnutrition (DRM): Triggered* by inflammation-induced hypermetabolism and catabolism in acute or chronic disease, even when feeding is maintained (Cederholm & Bosaeus, 2024; Muscaritoli et al., 2023).
- *Chronic Energy Deficiency (CED): Seen* in conditions like pregnancy or undernutrition in low-resource settings, where demand outpaces supply despite normal or near-normal BMI (Prisabela et al., 2023; Taylor-Baer & Herman, 2018).
- *Relative Energy Deficiency in Sport (REDs):* Affects athletes with chronic low energy availability, leading to multisystem compromise despite preserved weight or caloric intake (Cabre et al., 2022; Mountjoy et al., 2018).

These phenotypes reveal that *malnutrition can be functional, stress-driven, and demand-driven*, often independent of caloric scarcity. Table 3 compares core features of these high-demand malnutrition syndromes.

Table 3. Comparative Features of Classical Demand-Driven Malnutrition Syndromes. While differing in context and onset, all three conditions reflect a functional mismatch between metabolic demand and substrate availability. This mismatch often occurs in the absence of overt dietary deficiency, underscoring the limitations of intake- and weight-based assessments of nutritional sufficiency. DRM: Disease-Related Malnutrition, CED: Chronic Energy Deficiency, REDs: Relative Energy Deficiency in Sport.

Feature	DRM	CED	REDs
Predominant Affected Populations	Hospitalized or chronically ill patients or elderly patients	Pregnant women, children, low-resource settings	Endurance athletes, dancers, military recruits
Typical Onset Pattern	Insi	Gradual under chronic physiological strain (e.g., pregnancy)	Subacute with high training load
Primary Triggers	Inflammation, disease burden	Increased physiological need, low intake, low protein quality, micronutrient dilution	Prolonged mismatch between training intensity and caloric intake
Common Nutritional Biomarker Patterns	Often abnormal (e.g., prealbumin ↓)	Subclinical changes; may appear normal in standard labs	May have normal BMI, hormonal suppression, low leptin, low T3
Typical Misinterpretation	Mistaken for cachexia or age-related wasting; underrecognized in patients with stable weight but ongoing inflammation	Often overlooked due to normal BMI; perceived as low priority unless accompanied by weight loss or overt signs of undernutrition	Frequently missed due to normal or athletic appearance; symptoms attributed to overtraining,

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			psychological stress, or lifestyle choice
Characteristic Clinical Features	Weight loss, immune dysfunction, poor healing	Maternal fatigue, micronutrient depletion, fetal risk, growth restriction	Performance decline, bone loss, menstrual irregularity
Response to Nutritional Intervention	Requires nutritional support alongside anti-inflammatory therapy	Improves with energy/nutrient repletion	Requires coordinated refeeding and training load recalibration

6.2. Substrate Trapping: When Energy Is Present but Misallocated

Beyond mismatch, malnutrition can also result from a *distribution failure*—a state where metabolic substrates are abundant but *fail to reach the tissues that need them*. This phenomenon is best illustrated by *insulin resistance* (Ludwig, 2023).

Insulin plays a central role in coordinating nutrient flow—promoting glucose uptake, lipid storage, and protein synthesis. In insulin-resistant states, however, this coordination breaks down. *Skeletal muscle and liver become desensitized*, while adipose tissue often retains partial insulin sensitivity, favoring fat storage over energy mobilization (Friedman et al., 2024). As a result, glucose and amino acids are sequestered in storage rather than delivered to active tissues (Chen & Kahn, 2024).

This *substrate trapping* impairs mitochondrial function, promotes chronic inflammation, and fuels energy-sensing stress responses. Defend and repair systems become substrate-starved, contributing *to anabolic resistance, immune dysfunction, and system rigidity*. Over time, this persistent misallocation undercuts systemic resilience, laying the groundwork for chronic disease (Kalinkovich & Livshits, 2017; Speakman & Hall, 2021).

The *Fructose Survival Hypothesis* extends this idea, proposing that fructose—whether ingested or endogenously produced—activates a conserved metabolic program designed to maximize energy storage and suppress non-survival functions (Johnson et al., 2024). This same metabolic logic underlies insulin-induced substrate partitioning with depleted circulating fuel despite caloric sufficiency. Fructose metabolism triggers ATP depletion, impairs mitochondrial function, elevates oxidative stress, and shifts energy away from processes like reproduction, cognition, and muscle maintenance. Repeated activation—via dietary fructose or stress-induced glucocorticoid pathways—drives a *"storage-locked" state*, amplifying insulin resistance and reinforcing substrate misallocation across systems. While adaptive during food scarcity, this response becomes maladaptive in chronic modern exposure.

6.3. Type 5 Diabetes: A Visible Phenotype of Stress-Driven Reallocation

An atypical pattern of diabetes has long been observed among individuals with *low body mass index (BMI <19 kg/m²)*, particularly in low- and middle-income countries (Hugh-Jones, 1955). *Type 5 Diabetes* exemplifies a distinct clinical endpoint of *maladaptive substrate reallocation*. These individuals often present with preserved insulin secretion but paradoxical insulin resistance, especially in the liver, alongside a lack of ketosis, absence of autoimmune markers, and a history of early-life malnutrition, infection, or socioeconomic deprivation (Lontchi-Yimagou et al., 2022). Unlike classical forms of Type 1 or Type 2 diabetes, these patients require high doses of insulin to maintain glycemic control despite their lean phenotype and normocaloric intake

This syndrome is not solely explained by energy deficit, but by *chronic metabolic misallocation under stress*—particularly glucocorticoid-driven substrate mobilization that impairs insulin sensitivity. Prolonged exposure to elevated glucocorticoids such as *cortisol*, triggered by persistent psychosocial or environmental stress, promotes *sustained glucose mobilization* and metabolic reprogramming. Over time, sustained stress reprograms energy allocation toward survival priorities, impairing glycemic regulation despite adequate or even high caloric input.

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Recent expert consensus has endorsed this phenotype as Type 5 Diabetes, reframing it as a form of malnutrition-related diabetes mellitus (MRDM) (IDF, 2025). This reinforces the clinical relevance of ERM, which describes a broader, systemic form of energy misallocation—of which Type 5 Diabetes may be one organ-specific manifestation.

6.4. ERM: A Preclinical Framework of Bioenergetic Adaptation Failure

ERM builds upon these phenotypes to describe a silent, reversible stage of adaptation failure that precedes overt malnutrition. It arises not from food scarcity, but from prolonged exposure to *metabolic, inflammatory, or environmental stressors* that disrupt substrate availability and allocation—long before weight loss or laboratory abnormalities appear.

Key Features of ERM:

1. *No overt intake deficit* – energy intake may appear normal, and BMI may be stable or elevated.
2. *Triggered by cumulative exposome burden* – including inflammation, toxin exposure, psychosocial stress, circadian disruption, or chronic low-grade infections (Pizzorno, 2020; Vermeulen et al., 2020).
3. *Manifests through the metabolic trade-offs pattern* – such as impaired muscle recovery, fatigue, immunosuppression, or anabolic resistance, often before clinical thresholds of dysfunction are met.

ERM marks the *front end of the malnutrition trajectory*—a critical tipping point in which *recovery is still possible*, but system flexibility is beginning to erode. It helps explain why individuals with normal labs and body composition may experience sarcopenia, infections, or poor healing—*hallmarks of bioenergetic constraint* rather than overt deficiency (Ames, 2006; Sganga et al., 1985; Wang & Zhang, 2025).

Recognizing ERM opens a window for early intervention—before DRM, CED, REDs, or Type 5 Diabetes fully manifest. With timely substrate support and stressor reduction, *metabolic resilience can be restored*.

7. Recognizing ERM in Clinical Practice: From Substrate Trade-Offs to Resilience-Informed Care

ERM reflects a subclinical and reversible state of bioenergetic compromise, in which metabolic substrates are persistently redirected from long-term maintenance toward immediate survival. Unlike classical malnutrition, ERM often arises in individuals with normal weight, caloric intake, and lab values, making it invisible to standard diagnostic tools. Over time, this silent metabolic reallocation undermines resilience and impairs recovery capacity, especially in the context of sustained exposome burden.

Recognizing ERM in clinical practice requires a paradigm shift—from snapshot biomarkers and anthropometry to dynamic, pattern-based interpretation of physiological trade-offs.

7.1. Functional Clues: Detecting ERM Beyond Deficiency

ERM does not present as overt malnutrition but as a constellation of functional impairments consistent with energy mismatch and substrate misallocation. Early clinical clues include:

- Chronic fatigue despite adequate sleep and nutrition
- Poor exercise recovery or delayed wound healing
- Frequent mild infections or persistent low-grade inflammation
- Difficulty maintaining or building lean mass despite sufficient intake
- Subtle shifts in lab values suggesting nutrient redistribution

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These features are early warnings of energetic insufficiency, especially when they co-occur with known stressors or inflammatory exposure.

7.2. Drivers of ERM: The Cumulative Exposome

ERM arises not from a single cause, but from the accumulated burden of internal and external stressors that disrupt metabolic equilibrium. These include:

- *External triggers*: air pollution, persistent organic pollutants (POPs), heavy metals (e.g., lead, arsenic, mercury), microplastics, endocrine-disrupting chemicals, and circadian rhythm disruption
- *Internal triggers*: chronic inflammation, dysbiosis, latent infections, psychosocial stress, and trauma

These exposures divert metabolic resources toward defense, suppress repair programs, and impair recovery, even when caloric supply appears adequate (Pizzorno, 2020; Vermeulen et al., 2020). In ERM, nutrition alone is not enough—restoration requires reducing the underlying burden and rebalancing substrate allocation.

7.3. Staging ERM: A Functional Continuum of Decline

ERM unfolds along a spectrum of metabolic compromise. Identifying its stage informs prognosis and guides intervention:

- *Mild ERM*: Slight reductions in stamina, cognition, or stress recovery. Reversible with timely substrate support and stress mitigation.
- *Moderate ERM*: Onset of measurable trade-offs—low-grade inflammation, anabolic resistance, suppressed protein turnover, hormonal shifts.
- *Severe ERM*: Entrenched catabolism, immune dysfunction, sarcopenia, and system rigidity—often preceding overt disease.

Markers of progression include rising inflammatory signals, decreasing regenerative capacity, and blunted adrenal output. *Timely recognition of these shifts* enables targeted intervention before irreversible damage occurs.

7.4. Biomarkers of Trade-Offs: Functional Patterns over Static Values

Rather than isolated nutrient levels, ERM is characterized by biomarker patterns reflecting nutrient triage:

- Positive acute-phase proteins (e.g., CRP, ferritin, fibrinogen) increase in response to inflammation.
- Negative acute-phase proteins (e.g., albumin, prealbumin, transferrin) decrease as the liver reallocates amino acids (Cederholm & Bosaeus, 2024; Gulhar et al., 2024; Sganga et al., 1985).

This trade-off is adaptive in the acute phase but becomes maladaptive when sustained, contributing to impaired recovery and long-term functional decline (Bresnahan & Tanumihardjo, 2014). Importantly, these biomarkers fluctuate based on the phase of adaptation. For example, prealbumin may transiently increase during early resolution if substrate availability is sufficient but will decline if metabolic reserves are not restored. As highlighted in the ASPEN guidelines, these proteins are best interpreted as indicators of inflammatory protein redistribution rather than standalone measures of nutritional status (Evans et al., 2021).

Similarly, increased activity of glycolytic enzymes—such as lactate dehydrogenase (LDH) and neuron-specific enolase (NSE) —may signal a shift toward glycolytic predominance or impaired OXPHOS. These changes reflect a broader metabolic reprogramming under sustained stress, favoring

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rapid ATP generation at the cost of mitochondrial efficiency and long-term resilience (Donnelly & Finlay, 2015; Fang et al., 2024; Olcay Güngör et al., 2018).

Despite widespread clinical use, serum and plasma nutrient levels are limited in their ability to detect subtle or early nutrient insufficiencies. These levels primarily reflect short-term intake and systemic circulation, which may appear normal despite intracellular depletion or increased demand under chronic stress. While valuable for population-level trends—such as in NHANES—these markers lack the sensitivity to identify individual functional deficits, such as ERM (Adams et al., 2020; Peeri et al., 2021).

Rather than relying on isolated values, clinicians should interpret *shifts across systems*—patterns of redistribution, not absolute deficiency.

7.5. Hidden Catabolism: Intracellular Proteins and Cellular Turnover

A less commonly recognized sign of maladaptive stress is the elevation of intracellular proteins and enzymes—such as alanine transaminase (ALT), aspartate transaminase (AST), and creatine phosphokinase (CPK)—without clear organ-specific pathology or causes. These elevations may also indicate slow cell turnover, impaired proteostasis, or early signs of catabolic stress, accompanying by gradual stage of ERM. When persistent, these elevations may reflect insufficient support of bioenergetic and metabolic substrates to sustain normal cellular turnover under metabolic strain, rather than overt tissue injury (Aujla et al., 2025; Nakajima et al., 2022).

7.6. Body Composition: Bioimpedance as an Early Warning Tool

Bioelectrical impedance analysis (BIA) provides a non-invasive, early detection tool for identifying subclinical changes associated with ERM. A declining *phase angle* indicates compromised cellular membrane integrity and reduced cellular health (Lee et al., 2014). A stable or increasing BMI accompanied by a loss of lean mass suggests covert nutrient redistribution and a shift toward catabolic dominance. Additionally, elevated *extracellular water* may reflect low-grade inflammation, edema, or protein loss (Branco et al., 2023). When interpreted alongside clinical symptoms and biochemical markers, BIA enhances early recognition, staging, and monitoring of ERM before overt dysfunction appears.

7.7. Endocrine Clues: Adrenal Reserve and HPA Flexibility

Another essential dimension of physiological adaptation is adrenal reserve—the capacity of the adrenal glands to sustain glucocorticoid output under chronic or repeated stress. The HPA axis is central to coordinating systemic stress responses, regulating glucose metabolism, inflammation, protein turnover, and circadian synchrony (Herman, 2013). In the context of ERM, the functionality of this axis plays a decisive role in determining whether the body can successfully adapt and recover or begins to decompensate.

In early ERM, adrenal output generally supports stability, enabling sufficient cortisol-mediated mobilization of substrates. However, as adaptive demands accumulate, the HPA axis may become dysregulated. Clinical signs of this shift include flattened diurnal cortisol rhythms, exaggerated fatigue, stress intolerance, and delayed recovery from illness or exertion (Herman, 2013). Aging compounds this burden: while basal cortisol may remain stable or rise slightly, dynamic responsiveness often declines. Decreased DHEA production and a higher cortisol to DHEA ratio reflect a catabolic endocrine profile associated with frailty and immune senescence (Yiallouris et al., 2019).

In this context, elevated cholesterol may serve as an indirect marker of adrenal demand, as it is the precursor for cortisol and DHEA. Similarly, sustain elevation of glycated hemoglobin level despite adequate diet may reflect cortisol-driven gluconeogenesis and emerging insulin resistance—both signs of stress-induced substrate mobilization (Bar-Ziv et al., 2020; Seiler et al., 2020; Yiallouris et al., 2019).

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Functional adrenal assessments—such as morning cortisol and DHEA-S, or ACTH stimulation testing—can help evaluate adrenal reserve, particularly in patients with unexplained fatigue, poor recovery, or paradoxically elevated lipids despite lifestyle intervention (Warde et al., 2023). When interpreted alongside inflammatory markers, BIA trends, and clinical history, these assessments contribute to a broader picture of stress-related endocrine and metabolic burden.

7.8. Clinical Implication: Interpreting Patterns, Not Points

To recognize ERM before it progresses to overt dysfunction, clinicians must move beyond interpreting individual lab values in isolation and instead focus on identifying meaningful patterns over time. For example:

- Persistent elevation of CRP alongside declining prealbumin or transferrin
- Declining phase angle and lean body mass, even with preserved or rising body weight
- Elevated intracellular enzymes (e.g., ALT, AST, CPK) without clear organ-specific pathology
- Persistent hypercholesterolemia or hyperglycemia despite appropriate dietary and lifestyle interventions

These trends suggest systemic metabolic trade-offs—hallmarks of adaptation under constraint—and can help differentiate functional compensation from emerging maladaptation.

The most important clinical questions shift from asking *"Is this patient malnourished?"* to:

- *"What phase of adaptation is this patient in?"*
- *"What exposures, stressors, or nutritional deficits are sustaining this trade-off—and what interventions could restore metabolic balance?"*

This perspective emphasizes dynamic evaluation, enabling earlier and more effective intervention to preserve resilience and prevent the progression toward irreversible dysfunction

7.9. Timeliness and Reversibility: Catching ERM Early

The window to reverse ERM is greatest in its early stages. When substrate flow is restored and stressors are reduced, recovery is possible. Physiological resilience can be rebuilt through targeted intervention—restoring immune tolerance, mitochondrial flexibility, and protein turnover.

This underscores the need for vigilance: *the earlier ERM is recognized and addressed, the greater the potential for recovery.* Timely intervention not only halts progression to disease but reestablishes resilience before deeper dysfunction takes hold.

7.10. Toward Resilience-Informed Healthspan Care

Preserving healthspan requires a fundamental shift in clinical strategy—from treating disease endpoints to proactively supporting the body's adaptive capacity. The goal is not merely to correct deficiencies, but to maintain or restore the metabolic flexibility essential for responding to stress, repairing damage, and sustaining long-term resilience.

Intervention strategies include:

- *Targeted Dietary support*: Emphasize high-quality protein and healthy fats, with controlled and context-specific carbohydrate intake
- *Micronutrient repletion*: Address subclinical deficiencies in protein and their critical cofactors for metabolic and immune functions such as zinc, selenium, magnesium, and iron
- *Exposome reduction:* Minimize environmental and dietary stressors through clean air and water, toxin avoidance, and anti-inflammatory, nutrient-dense foods
- *Circadian and metabolic tempo optimization:* align light exposure, sleep-wake cycles, and feeding-fasting windows to support hormonal and metabolic coherence

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- *Lifestyle-based resilience building:* Encourage regular physical activity, stress reduction techniques, restorative sleep, and social connectedness
- *Functional monitoring tools:* utilize technologies such as *BIA and AI-powered wearables* to track recovery and adaptation capacity in real time

Together, this approach supports resilience-informed medicine—not just treating malnutrition, but preventing its subclinical progression through early detection and strategic intervention.

8. Conclusion: The Metabolic Cost of Resilience

This review reframes aging and chronic disease as the *cumulative metabolic cost of unresolved adaptation*. Under chronic or repeated stress—whether inflammatory, environmental, psychological, or metabolic—the body prioritizes immediate survival by reallocating energy and substrates away from long-term repair, regeneration, and resilience. While initially protective, these adaptive trade-offs come at the expense of repair, regeneration, and long-term resilience.

Over time, persistent substrate diversion leads to *anabolic resistance, immune dysfunction, mitochondrial inefficiency, and progressive tissue degradation*. These are not isolated dysfunctions, but systemic outcomes of a body caught in a state of *chronic metabolic triage*—prioritizing the urgent at the expense of the essential.

In this framework, resilience is not a static attribute but a *dynamic, energetically expensive state*—one that must be actively sustained. When substrate availability becomes insufficient—or when allocation is chronically misdirected through inflammation, insulin resistance, or hormonal disruption—adaptive responses begin to falter. What begins as functional compensation eventually transitions into maladaptation and decline.

The introduction of ERM provides a critical framework for recognizing this process in its early, reversible stage. ERM describes a silent, subclinical phase of energetic constraint in which adaptive systems remain operational, but increasingly compromised. It offers a lens to detect and interpret patterns of functional decline—*not as isolated deficiencies, but as coordinated signals of energetic misallocation under stress*.

By recognizing ERM, clinicians can *move from diagnosing deficiency to managing resilience*. This shift reframes clinical care—not as a binary search for disease, but as an effort to preserve and restore adaptive capacity before it fails.

Importantly, ERM is not a fixed state—it is *dynamic and reversible*. With timely intervention, resilience can be rebuilt through substrate restoration, exposome reduction, and regulation of stress-response systems. The goal is not merely to correct imbalances, but to *sustain the energetic architecture of adaptation itself*.

Ultimately, this perspective calls for a shift in clinical strategy—from reactive, symptom-driven diagnostics to *proactive, pattern-based recognition of energetic trade-offs*. From treating endpoints to supporting the energetic architecture that sustains adaptation. From managing diseases to cultivating resilience.

Future Directions

The ERM model provides a conceptual foundation for advancing research into early-stage stress adaptation failure. Future research may focus on the following priorities:

1. *Validation of ERM-related biomarker clusters* (e.g., patterns of acute phase proteins, mitochondrial stress markers, and metabolic flexibility indicators) to *predict risk for sarcopenia, frailty, or chronic disease*.
2. *Prospective trials of resilience-informed nutritional interventions*—targeting protein quality, micronutrient cofactors, and circadian alignment—to reverse ERM and improve recovery in high-stress populations.

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3. *Development of ERM staging algorithms* based on dynamic, cross-system biomarker trends and clinical phenotypes for early detection and monitoring.
4. *Exploration of ERM phenotypes in specific clinical contexts*, such as long COVID, environmental exposure syndromes, or post-intensive care recovery, where metabolic misallocation is suspected.
5. *Integration of digital health technologies* (e.g., bioimpedance, wearables, AI-based recovery tracking) to monitor real-time adaptation and substrate sufficiency in outpatient or preventive care settings.

These directions support the development of a new clinical paradigm—one that moves beyond nutrient replacement toward metabolic pattern recognition, functional recovery, and the active preservation of healthspan.

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List of Abbreviations

Abbreviation	Full Term
ACE	Adverse Childhood Experiences
ACTH	Adrenocorticotropic Hormone
ALT	Alanine Transaminase
AMPK	AMP-Activated Protein Kinase
APP	Acute Phase Proteins
AST	Aspartate Transaminase
ATP	Adenosine Triphosphate
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CED	Chronic Energy Deficiency
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
DHEA	Dehydroepiandrosterone
DRM	Disease-Related Malnutrition

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eIF2α	Eukaryotic Initiation Factor 2 Alpha
ERM	Exposure-Related Malnutrition
FGF21	Fibroblast Growth Factor 21
GADD34	Growth Arrest and DNA Damage-Inducible Protein 34
GAS	General Adaptation Syndrome
GDF15	Growth Differentiation Factor 15
HIF-1α	Hypoxia-Inducible Factor 1-Alpha
HPA axis	Hypothalamic–Pituitary–Adrenal Axis
IL	Interleukin (e.g., IL-6, IL-13, IL-33)
ISR	Integrated Stress Response
ISR^{mt}	Mitochondrial Integrated Stress Response
LDH	Lactate Dehydrogenase
M1/M2	Macrophage Polarization States (Pro-inflammatory / Anti-inflammatory)
mTORC1	Mechanistic Target of Rapamycin Complex 1
mtDNA	Mitochondrial DNA
NK cells	Natural Killer Cells
NCDs	Non-Communicable Diseases
NRF2	Nuclear Factor Erythroid 2–Related Factor 2
OxPhos	Oxidative Phosphorylation
POPs	Persistent Organic Pollutants
PRR	Pattern Recognition Receptor
REDs	Relative Energy Deficiency in Sport
ROS	Reactive Oxygen Species
SAM system	Sympathetic–Adrenal–Medullary System
SASP	Senescence-Associated Secretory Phenotype
Treg	Regulatory T Cells
TNF-α	Tumor Necrosis Factor Alpha
UPR^{mt}	Mitochondrial Unfolded Protein Response

References

Adams, S. H., Anthony, J. C., Carvajal, R., Chae, L., Khoo, C. S. H., Latulippe, M. E.,…Yan, W. (2020). Perspective: Guiding Principles for the Implementation of Personalized Nutrition Approaches That Benefit Health and Function. *Adv Nutr*, *11*(1), 25-34. https://doi.org/10.1093/advances/nmz086

Alack, K., Pilat, C., & Krüger K*Shared, a. (2019). Current Knowledge and New Challenges in Exercise Immunology. *Deutsche Zeitschrift für Sportmedizin*, *Volume 70*(No. 10), 250-260. https://doi.org/10.5960/dzsm.2019.391

Ames, B. N. (2006). Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. *Proc Natl Acad Sci U S A*, *103*(47), 17589-17594. https://doi.org/10.1073/pnas.0608757103

Aujla, R. S., Zubair, M., & Patel, R. (2025). Creatine Phosphokinase. In *StatPearls*. StatPearls Publishing.

Bar-Ziv, R., Bolas, T., & Dillin, A. (2020). Systemic effects of mitochondrial stress. *EMBO reports*, *21*(6), e50094. https://doi.org/https://doi.org/10.15252/embr.202050094

Beaudart, C., Dawson, A., Shaw, S. C., Harvey, N. C., Kanis, J. A., Binkley, N.,…Dennison, E. M. (2017). Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. *Osteoporos Int*, *28*(6), 1817-1833. https://doi.org/10.1007/s00198-017-3980-9

Bobba-Alves, N., Juster, R.-P., & Picard, M. (2022). The energetic cost of allostasis and allostatic load. *Psychoneuroendocrinology*, *146*, 105951. https://doi.org/https://doi.org/10.1016/j.psyneuen.2022.105951

Bobba-Alves, N., Sturm, G., Lin, J., Ware, S. A., Karan, K. R., Monzel, A. S.,…Picard, M. (2023). Cellular allostatic load is linked to increased energy expenditure and accelerated biological aging. *Psychoneuroendocrinology*, *155*, 106322. https://doi.org/https://doi.org/10.1016/j.psyneuen.2023.106322

Branco, M. G., Mateus, C., Capelas, M. L., Pimenta, N., Santos, T., Mäkitie, A.,…Ravasco, P. (2023). Bioelectrical Impedance Analysis (BIA) for the Assessment of Body Composition in Oncology: A Scoping Review. *Nutrients*, *15*(22), 4792. https://www.mdpi.com/2072-6643/15/22/4792

Bresnahan, K. A., & Tanumihardjo, S. A. (2014). Undernutrition, the acute phase response to infection, and its effects on micronutrient status indicators. *Adv Nutr*, *5*(6), 702-711. https://doi.org/10.3945/an.114.006361

 doi:10.20944/preprints202504.1142.v2

Cabre, H. E., Moore, S. R., Smith-Ryan, A. E., & Hackney, A. C. (2022). Relative Energy Deficiency in Sport (RED-S): Scientific, Clinical, and Practical Implications for the Female Athlete. *Dtsch Z Sportmed*, *73*(7), 225-234. https://doi.org/10.5960/dzsm.2022.546

Cahill, G. F., Jr. (2006). Fuel metabolism in starvation. *Annu Rev Nutr*, *26*, 1-22. https://doi.org/10.1146/annurev.nutr.26.061505.111258

Calabrese, E. J., & Agathokleous, E. (2019). Building Biological Shields via Hormesis. *Trends Pharmacol Sci*, *40*(1), 8-10. https://doi.org/10.1016/j.tips.2018.10.010

Careccia, G., Mangiavini, L., & Cirillo, F. (2023). Regulation of Satellite Cells Functions during Skeletal Muscle Regeneration: A Critical Step in Physiological and Pathological Conditions. *Int J Mol Sci*, *25*(1). https://doi.org/10.3390/ijms25010512

Cederholm, T., & Bosaeus, I. (2024). Malnutrition in Adults. *New England Journal of Medicine*, *391*(2), 155-165. https://doi.org/doi:10.1056/NEJMra2212159

Chen, W., & Kahn, C. R. (2024). Insulin. *Trends in Endocrinology & Metabolism*. https://doi.org/10.1016/j.tem.2024.09.001

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nat Rev Endocrinol*, *5*(7), 374-381. https://doi.org/10.1038/nrendo.2009.106

Costa-Mattioli, M., & Walter, P. (2020). The integrated stress response: From mechanism to disease. *Science*, *368*(6489), eaat5314. https://doi.org/doi:10.1126/science.aat5314

Crane, P. A., Wilkinson, G., & Teare, H. (2022). Healthspan versus lifespan: new medicines to close the gap. *Nature Aging*, *2*(11), 984-988. https://doi.org/10.1038/s43587-022-00318-5

Cruz-Jentoft, A. J., Gonzalez, M. C., & Prado, C. M. (2023). Sarcopenia ≠ low muscle mass. *European Geriatric Medicine*, *14*(2), 225-228. https://doi.org/10.1007/s41999-023-00760-7

Donnelly, R. P., & Finlay, D. K. (2015). Glucose, glycolysis and lymphocyte responses. *Mol Immunol*, *68*(2 Pt C), 513-519. https://doi.org/10.1016/j.molimm.2015.07.034

Evans, D. C., Corkins, M. R., Malone, A., Miller, S., Mogensen, K. M., Guenter, P.,…Committee, A. M. (2021). The Use of Visceral Proteins as Nutrition Markers: An ASPEN Position Paper. *Nutr Clin Pract*, *36*(1), 22-28. https://doi.org/10.1002/ncp.10588

Fang, Y., Li, Z., Yang, L., Li, W., Wang, Y., Kong, Z.,…Zeng, L. (2024). Emerging roles of lactate in acute and chronic inflammation. *Cell Communication and Signaling*, *22*(1), 276. https://doi.org/10.1186/s12964-024-01624-8

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., & Santoro, A. (2018). Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology*, *14*(10), 576-590. https://doi.org/10.1038/s41574-018-0059-4

Friedman, M. I., Sørensen, T. I. A., Taubes, G., Lund, J., & Ludwig, D. S. (2024). Trapped fat: Obesity pathogenesis as an intrinsic disorder in metabolic fuel partitioning. *Obesity Reviews*, *n/a*(n/a). https://doi.org/https://doi.org/10.1111/obr.13795

Fulop, T., Larbi, A., Dupuis, G., Le Page, A., Frost, E. H., Cohen, A. A.,…Franceschi, C. (2018). Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? [Review]. *Front Immunol*, *8*(1960). https://doi.org/10.3389/fimmu.2017.01960

Gambardella, G., Staiano, L., Moretti, M. N., De Cegli, R., Fagnocchi, L., Di Tullio, G.,…di Bernardo, D. (2020). GADD34 is a modulator of autophagy during starvation. *Science Advances*, *6*(39), eabb0205. https://doi.org/doi:10.1126/sciadv.abb0205

Geric, I., Schoors, S., Claes, C., Gressens, P., Verderio, C., Verfaillie, C. M.,…Baes, M. (2019). Metabolic Reprogramming during Microglia Activation. *Immunometabolism*, *1*(1), e190002, Article e190002. https://doi.org/10.20900/immunometab20190002

Gulhar, R., Ashraf, M. A., & Jialal, I. (2024). Physiology, Acute Phase Reactants. In *StatPearls*. StatPearls Publishing.

Herman, J. P. (2013). Neural control of chronic stress adaptation. *Front Behav Neurosci*, *7*, 61. https://doi.org/10.3389/fnbeh.2013.00061

Hetz, C., & Papa, F. R. (2018). The Unfolded Protein Response and Cell Fate Control. *Molecular Cell*, *69*(2), 169-181. https://doi.org/10.1016/j.molcel.2017.06.017

 doi:10.20944/preprints202504.1142.v2

Hugh-Jones, P. (1955). DIABETES IN JAMAICA. *The Lancet*, *266*(6896), 891-897. https://doi.org/https://doi.org/10.1016/S0140-6736(55)92530-7

IDF. (2025, 2025 Apr 8). *IDF Endorses New Classification of Type 5 Diabetes at World Diabetes Congress*. International Diabetes Federation. Retrieved 2025 Apr 18 from https://idf.org/news/new-type-5-diabetes-working-group

Johnson, R. J., Sánchez-Lozada, L. G., & Lanaspa, M. A. (2024). The fructose survival hypothesis as a mechanism for unifying the various obesity hypotheses. *Obesity*, *32*(1), 12-22. https://doi.org/https://doi.org/10.1002/oby.23920

Kalinkovich, A., & Livshits, G. (2017). Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. *Ageing Res Rev*, *35*, 200-221. https://doi.org/10.1016/j.arr.2016.09.008

Langston, P. K., & Mathis, D. (2024). Immunological regulation of skeletal muscle adaptation to exercise. *Cell Metab*. https://doi.org/10.1016/j.cmet.2024.04.001

Larabee, C. M., Neely, O. C., & Domingos, A. I. (2020). Obesity: a neuroimmunometabolic perspective. *Nature Reviews Endocrinology*, *16*(1), 30-43. https://doi.org/10.1038/s41574-019-0283-6

Laurent, P., Jolivel, V., Manicki, P., Chiu, L., Contin-Bordes, C., Truchetet, M.-E., & Pradeu, T. (2017). Immune-Mediated Repair: A Matter of Plasticity [Mini Review]. *Front Immunol*, *8*. https://doi.org/10.3389/fimmu.2017.00454

Lee, S. Y., Lee, Y. J., Yang, J. H., Kim, C. M., & Choi, W. S. (2014). The Association between Phase Angle of Bioelectrical Impedance Analysis and Survival Time in Advanced Cancer Patients: Preliminary Study. *Korean J Fam Med*, *35*(5), 251-256. https://doi.org/10.4082/kjfm.2014.35.5.251

Lockhart, S. M., Saudek, V., & O'Rahilly, S. (2020). GDF15: A Hormone Conveying Somatic Distress to the Brain. *Endocr Rev*, *41*(4). https://doi.org/10.1210/endrev/bnaa007

Lontchi-Yimagou, E., Dasgupta, R., Anoop, S., Kehlenbrink, S., Koppaka, S., Goyal, A.,…Hawkins, M. (2022). An Atypical Form of Diabetes Among Individuals With Low BMI. *Diabetes Care*, *45*(6), 1428-1437. https://doi.org/10.2337/dc21-1957

Ludwig, D. S. (2023). Carbohydrate-insulin model: does the conventional view of obesity reverse cause and effect? *Philosophical Transactions of the Royal Society B: Biological Sciences*, *378*(1888), 20220211. https://doi.org/doi:10.1098/rstb.2022.0211

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*, *87*(3), 873-904. https://doi.org/10.1152/physrev.00041.2006

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, *43*(1), 2-15. https://doi.org/https://doi.org/10.1016/S0018-506X(02)00024-7

Meeusen, R., Watson, P., Hasegawa, H., Roelands, B., & Piacentini, M. F. (2006). Central fatigue: the serotonin hypothesis and beyond. *Sports Med*, *36*(10), 881-909. https://doi.org/10.2165/00007256-200636100-00006

Metallo, Christian M., & Vander Heiden, Matthew G. (2013). Understanding Metabolic Regulation and Its Influence on Cell Physiology. *Molecular Cell*, *49*(3), 388-398. https://doi.org/10.1016/j.molcel.2013.01.018

Monzel, A. S., Levin, M., & Picard, M. (2023). The energetics of cellular life transitions. *Life Metabolism*, *3*(3). https://doi.org/10.1093/lifemeta/load051

Mountjoy, M., Sundgot-Borgen, J. K., Burke, L. M., Ackerman, K. E., Blauwet, C., Constantini, N.,…Budgett, R. (2018). IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. *Br J Sports Med*, *52*(11), 687-697. https://doi.org/10.1136/bjsports-2018-099193

Muscaritoli, M., Imbimbo, G., Jager-Wittenaar, H., Cederholm, T., Rothenberg, E., di Girolamo, F. G.,…Molfino, A. (2023). Disease-related malnutrition with inflammation and cachexia. *Clin Nutr*, *42*(8), 1475-1479. https://doi.org/10.1016/j.clnu.2023.05.013

Nakajima, K., Yuno, M., Tanaka, K., & Nakamura, T. (2022). High Aspartate Aminotransferase/Alanine Aminotransferase Ratio May Be Associated with All-Cause Mortality in the Elderly: A Retrospective Cohort Study Using Artificial Intelligence and Conventional Analysis. *Healthcare (Basel)*, *10*(4). https://doi.org/10.3390/healthcare10040674

Netea, M. G., Joosten, L. A., Latz, E., Mills, K. H., Natoli, G., Stunnenberg, H. G.,…Xavier, R. J. (2016). Trained immunity: A program of innate immune memory in health and disease. *Science*, *352*(6284), aaf1098. https://doi.org/10.1126/science.aaf1098

 doi:10.20944/preprints202504.1142.v2

Novoa, I., Zeng, H., Harding, H. P., & Ron, D. (2001). Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2alpha. *J Cell Biol*, *153*(5), 1011-1022. https://doi.org/10.1083/jcb.153.5.1011

Ochando, J., Mulder, W. J. M., Madsen, J. C., Netea, M. G., & Duivenvoorden, R. (2023). Trained immunity — basic concepts and contributions to immunopathology. *Nature Reviews Nephrology*, *19*(1), 23-37. https://doi.org/10.1038/s41581-022-00633-5

Olcay Güngör, Oya Kıreker Köylü, Tahir Dalkıran, Serkan Kırık, Elif Tepe, Derya Cevizli,…Dilber, C. (2018). Evaluation of blood neuron specific enolase and S-100 beta protein levels in acute mercury toxicity. *Trace Elements and Electrolytes*, *35*(131-136.). https://doi.org/10.5414/TEX01505.

Olenchock, B. A., Rathmell, J. C., & Vander Heiden, M. G. (2017). Biochemical Underpinnings of Immune Cell Metabolic Phenotypes. *Immunity*, *46*(5), 703-713. https://doi.org/10.1016/j.immuni.2017.04.013

Pakos-Zebrucka, K., Koryga, I., Mnich, K., Ljujic, M., Samali, A., & Gorman, A. M. (2016). The integrated stress response. *EMBO reports*, *17*(10), 1374-1395. https://doi.org/https://doi.org/10.15252/embr.201642195

Paulussen, K. J. M., McKenna, C. F., Beals, J. W., Wilund, K. R., Salvador, A. F., & Burd, N. A. (2021). Anabolic Resistance of Muscle Protein Turnover Comes in Various Shapes and Sizes. *Front Nutr*, *8*, 615849. https://doi.org/10.3389/fnut.2021.615849

Payea, M. J., Dar, S. A., Anerillas, C., Martindale, J. L., Belair, C., Munk, R.,…Maragkakis, M. (2024). Senescence suppresses the integrated stress response and activates a stress-remodeled secretory phenotype. *Molecular Cell*, *84*(22), 4454-4469.e4457. https://doi.org/10.1016/j.molcel.2024.10.003

Peeri, N. C., Chai, W., Cooney, R. V., & Tao, M. H. (2021). Association of serum levels of antioxidant micronutrients with mortality in US adults: National Health and Nutrition Examination Survey 1999-2002. *Public Health Nutr*, *24*(15), 4859-4868. https://doi.org/10.1017/s1368980020004619

Picard, M., & Shirihai, O. S. (2022). Mitochondrial signal transduction. *Cell Metab*, *34*(11), 1620-1653. https://doi.org/10.1016/j.cmet.2022.10.008

Pizzorno, J. (2020). Thoughts on a Unified Theory of Disease. *Integrative medicine (Encinitas, Calif.)*, *19*(6), 8-17.

Polidori, M. C. (2024). Aging hallmarks, biomarkers, and clocks for personalized medicine: (re)positioning the limelight. *Free Radical Biology and Medicine*. https://doi.org/https://doi.org/10.1016/j.freeradbiomed.2024.02.012

Prisabela, M., Nadhiroh, S. R., & Isaura, E. R. (2023). Characteristics of Pregnant Woman with Chronic Energy Deficiency in Puskesmas Gesang, Lumajang on 2020: Descriptive Analysis. *Media Gizi Kesmas*, *12*(2), 643-648. https://doi.org/10.20473/mgk.v12i2.2023.643-648

Qi, Y., Rajbanshi, B., Hao, R., Dang, Y., Xu, C., Lu, W.,…Zhang, X. (2025). The dual role of PGAM5 in inflammation. *Exp Mol Med*, *57*(2), 298-311. https://doi.org/10.1038/s12276-025-01391-7

Ristow, M., & Schmeisser, K. (2014). Mitohormesis: Promoting Health and Lifespan by Increased Levels of Reactive Oxygen Species (ROS). *Dose-Response*, *12*(2), dose-response.13-035.Ristow. https://doi.org/10.2203/dose-response.13-035.Ristow

Sapolsky, R. M. (2004). *Why zebras don't get ulcers: The acclaimed guide to stress, stress-related diseases, and coping (3rd ed.)*. Henry Holt.

Seiler, A., Fagundes, C. P., & Christian, L. M. (2020). The Impact of Everyday Stressors on the Immune System and Health. In A. Choukèr (Ed.), *Stress Challenges and Immunity in Space: From Mechanisms to Monitoring and Preventive Strategies* (pp. 71-92). Springer International Publishing. https://doi.org/10.1007/978-3-030-16996-1_6

Selye, H. (1950). Stress and the General Adaptation Syndrome. *British Medical Journal*, *1*(4667), 1383-1392. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2038162/

Sganga, G., Siegel, J. H., Brown, G., Coleman, B., Wiles, C. E., 3rd, Belzberg, H.,…Placko, R. (1985). Reprioritization of hepatic plasma protein release in trauma and sepsis. *Arch Surg*, *120*(2), 187-199. https://doi.org/10.1001/archsurg.1985.01390260051008

Shaulson, E. D., Cohen, A. A., & Picard, M. (2024). The brain–body energy conservation model of aging. *Nature Aging*, *4*(10), 1354-1371. https://doi.org/10.1038/s43587-024-00716-x

 doi:10.20944/preprints202504.1142.v2

Sparkenbaugh, E. M., Saini, Y., Greenwood, K. K., LaPres, J. J., Luyendyk, J. P., Copple, B. L.,…Roth, R. A. (2011). The Role of Hypoxia-Inducible Factor-1α in Acetaminophen Hepatotoxicity. *J Pharmacol Exp Ther*, *338*(2), 492-502. https://doi.org/https://doi.org/10.1124/jpet.111.180521

Speakman, J. R., & Hall, K. D. (2021). Carbohydrates, insulin, and obesity. *Science*, *372*(6542), 577-578. https://doi.org/10.1126/science.aav0448

Straub, R. H. (2017). The brain and immune system prompt energy shortage in chronic inflammation and ageing [Perspective]. *Nat Rev Rheumatol*, *13*, 743–751 https://doi.org/10.1038/nrrheum.2017.172

Taylor-Baer, M., & Herman, D. (2018). From Epidemiology to Epigenetics: Evidence for the Importance of Nutrition to Optimal Health Development Across the Life Course. In N. Halfon, C. B. Forrest, R. M. Lerner, & E. M. Faustman (Eds.), *Handbook of Life Course Health Development* (pp. 431-462). Springer International Publishing. https://doi.org/10.1007/978-3-319-47143-3_18

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, *53*(4), 865-871. https://doi.org/https://doi.org/10.1016/S0022-3999(02)00429-4

Vermeulen, R., Schymanski, E. L., Barabási, A. L., & Miller, G. W. (2020). The exposome and health: Where chemistry meets biology. *Science*, *367*(6476), 392-396. https://doi.org/10.1126/science.aay3164

Vuscan, P., Kischkel, B., Joosten, L. A. B., & Netea, M. G. (2024). Trained immunity: General and emerging concepts. *Immunological Reviews*, *323*(1), 164-185. https://doi.org/https://doi.org/10.1111/imr.13326

Walrand, S., Guillet, C., & Boirie, Y. (2021). Nutrition, Protein Turnover and Muscle Mass. In *Sarcopenia* (pp. 45-62). https://doi.org/https://doi.org/10.1002/9781119597896.ch5

Wang, L., Hong, W., Zhu, H., He, Q., Yang, B., Wang, J., & Weng, Q. (2024). Macrophage senescence in health and diseases. *Acta Pharm Sin B*, *14*(4), 1508-1524. https://doi.org/10.1016/j.apsb.2024.01.008

Wang, X., & Zhang, G. (2025). The mitochondrial integrated stress response: A novel approach to anti-aging and pro-longevity. *Ageing Res Rev*, *103*, 102603. https://doi.org/https://doi.org/10.1016/j.arr.2024.102603

Warde, K. M., Smith, L. J., & Basham, K. J. (2023). Age-related Changes in the Adrenal Cortex: Insights and Implications. *Journal of the Endocrine Society*, *7*(9), bvad097. https://doi.org/10.1210/jendso/bvad097

Wek, R. C. (2018). Role of eIF2α Kinases in Translational Control and Adaptation to Cellular Stress. *Cold Spring Harb Perspect Biol*, *10*(7). https://doi.org/10.1101/cshperspect.a032870

WHO. (2025). *Noncommunicable diseases*. WHO. Retrieved March 25 from https://www.who.int/health-topics/noncommunicable-diseases#tab=tab_1

Willmann, K., & Moita, L. F. (2024). Physiologic disruption and metabolic reprogramming in infection and sepsis. *Cell Metab*. https://doi.org/10.1016/j.cmet.2024.02.013

Wolfe, R. R. (2006). The underappreciated role of muscle in health and disease. *Am J Clin Nutr*, *84*(3), 475-482. https://doi.org/https://doi.org/10.1093/ajcn/84.3.475

Yiallouris, A., Tsioutis, C., Agapidaki, E., Zafeiri, M., Agouridis, A. P., Ntourakis, D., & Johnson, E. O. (2019). Adrenal Aging and Its Implications on Stress Responsiveness in Humans [Review]. *Frontiers in Endocrinology*, *10*(54). https://doi.org/10.3389/fendo.2019.00054

Youle, R. J., & van der Bliek, A. M. (2012). Mitochondrial Fission, Fusion, and Stress. *Science*, *337*(6098), 1062-1065. https://doi.org/doi:10.1126/science.1219855

Yuk, J.-M., Silwal, P., & Jo, E.-K. (2020). Inflammasome and Mitophagy Connection in Health and Disease. *Int J Mol Sci*, *21*(13), 4714. https://www.mdpi.com/1422-0067/21/13/4714

Zera, A. J., & Harshman, L. G. (2001). The Physiology of Life History Trade-Offs in Animals. *Annual Review of Ecology, Evolution, and Systematics*, *32*(Volume 32, 2001), 95-126. https://doi.org/https://doi.org/10.1146/annurev.ecolsys.32.081501.114006