Review

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

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

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Abstract: While life expectancy has risen, healthspan—the period of life spent in good functional health—has not kept pace. Age-related and chronic diseases are often seen as inevitable decline, but more accurately reflect the cumulative cost of chronic stress adaptation under conditions of bioenergetic and substrate depletion. This review presents a systems-level framework that links aging and chronic disease to prolonged energy and nutrient trade-offs across physiological systems. We introduce the concept of Exposure-Related Malnutrition (ERM)—a subclinical state in which metabolic resources are silently diverted from maintenance and repair toward stress response. Drawing on classical stress models and evidence from immunometabolism, endocrinology, and systems biology, we describe how persistent stress drives resource reallocation across neuroendocrine, immune, muscular, and mitochondrial systems. We outline a shared adaptive trajectory—Respond → Adapt → Resolve—with outcomes shaped by both exposure intensity and metabolic availability. Progressive ERM manifests as anabolic resistance, low-grade inflammation, impaired healing, and lean mass loss—despite adequate intake. Clinical recognition of ERM using tools like pattern-based biomarkers, bioelectrical impedance, and adrenal reserve testing may allow early intervention. By identifying ERM as a reversible precursor to maladaptation, this framework reframes resilience as a metabolically costly process and highlights opportunities to preserve healthspan through upstream strategies.

Keywords: energy metabolism; adaptation; chronic disease; malnutrition; aging, resilience

1. Introduction

The paradox of modern resilience: longer life, less health

Human longevity has increased dramatically over the past century. Yet this achievement has revealed a troubling paradox: lifespan has outpaced healthspan—the portion of life spent in good functional health (Crane et al., 2022). Non-communicable diseases (NCDs) such as cardiovascular disease, diabetes, obesity, and neurodegeneration now account for over 70% of global deaths, with prevalence continuing to rise (WHO, 2025).

This growing gap raises fundamental questions about resilience: the body's ability to withstand and recover from stress. In this review, we examine how responses to chronic stress follow a trajectory first outlined in Hans Selye's *General Adaptation Syndrome (GAS)—Alarm, Resistance,*

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Exhaustion—now reframed through the lens of energy availability and recovery potential. We explore how the distribution of metabolic substrates across systems shapes whether stress resolves in recovery or decline.

The Exposome and Adaptive Responses: Drivers of Metabolic Burden

The body exists in continuous interaction with a dynamic *exposome*—encompassing diet, inactivity, psychosocial stress, circadian disruption, toxins, and infections (Vermeulen et al., 2020). While short-term exposures can trigger beneficial adaptations, chronic exposures impose a cumulative metabolic toll. These persistent demands drain energy reserves and force biological trade-offs that may not cause immediate dysfunction but gradually erode resilience.

Crucially, health outcomes are not determined by exposure alone, but by the individual's capacity to adapt. For example, Baldwin et al. (2021) found that higher adverse childhood experience (ACE) scores correlate with disease risk at a population level but fail to predict individual trajectories. This underscores a critical insight: *resilience is shaped by how energy and substrates are triaged across competing priorities*—respond, adapt, and recover (Baldwin et al., 2021). When adaptive capacity is exceeded—due to limited metabolic reserves or inefficient allocation, maladaptation leads to arise of chronic dysfunction and disease: *not from failure to respond, but from failure to resolve*.

Healthspan as a Function of Adaptive Capacity

According to the World Health Organization, health is *"a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity"* (WHO, 1948)." In this context, healthspan reflects the body's sustained ability to restore balance under stress, across multiple systems (Calabrese & Agathokleous, 2019). This ability hinges not only on energy availability but also on how efficiently it is allocated to meet fluctuating physiological demands.

The GAS provides a useful model. During the Alarm phase, resources are mobilized for defense, and performance often declines. In the Resistance phase, the body attempts to restore stability. Recovery depends on whether energy and substrates are sufficient—and properly directed—for repair. Successful adaptation may restore baseline or even enhance capacity (hormesis); if not, persistent stress leads to maladaptation and decline (Selye, 1950).

This trajectory parallels athletic training, where initial performance dips under load but may rebound with proper recovery or worsen if demands outpace regeneration (West, 2008). These outcomes reveal a critical insight: resilience is not a passive capacity but a metabolically expensive investment. It requires continuous investment of energy, often at the expense of long-term maintenance (Ryan & Ryznar, 2022).

Aging and Chronic Disease as the Cost of Adaptation

Aging and chronic disease are not simply the result of isolated system failures but reflect the accumulated toll of energy-conserving trade-offs. Under sustained stress, the body prioritizes short-term survival over long-term maintenance—diverting resources from repair, immunity, and regeneration.

This persistent triage drives functional decline over time. For example, skeletal muscle catabolism, inflammation, and mitochondrial dysfunction all reflect energetic reallocations made during chronic adaptation (Shaulson et al., 2024). At the cellular level, stress impairs mitochondrial efficiency, increases reliance on glycolysis, and accelerates epigenetic aging (Bobba-Alves et al., 2023). These changes represent not just damage but a biological reprogramming that favors short-term adaptation at the expense of long-term resilience.

Toward a systems view of metabolic trade-offs

This review adopts a systems-level framework to examine chronic stress triggers, energy availability, and substrate allocation shape adaptive outcomes across physiological domains—including neuroendocrine, immune, muscular, and mitochondrial networks. We propose reframing aging and chronic disease as the cumulative metabolic cost of unresolved adaptation to stress.

In the final sections, we introduce the concept of *Exposure-Related Malnutrition (ERM)*—a proposed early-stage, subclinical energetic deficit that arises from chronic stress adaptation—highlighting its role as a precursor to overt dysfunction and a potential target for preventive

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intervention. By identifying early signs of subclinical maladaptation, we aim to inform strategies that preserve adaptive capacity, improve recovery potential, and extend healthspan through timely intervention and support of metabolic resilience.

2. Methodology: A Thematic Narrative Review

This review uses a thematic narrative synthesis to investigate how chronic stress, energy availability, and metabolic resource allocation shape resilience, aging, and disease across multiple levels of biological organization—from systemic and organ-level processes to cellular mechanisms. The aim is to identify recurring adaptive patterns and the determinants that shift outcomes toward recovery, compensation, or decline.

Literature Selection

We used *purposive sampling* to identify relevant peer-reviewed studies and conceptual frameworks across physiology, aging research, systems biology, molecular signaling, immunometabolism, and exposomics. Priority was given to work that addressing:

- energy availability and substrate partitioning,
- adaptive stress responses across biological levels,
- chronic stress or allostatic load,
- aging mechanisms and chronic disease progression.

Sources were identified through targeted searches in PubMed, Web of Science, and Scopus, complemented by backward citation tracking. While not systematic, this approach emphasized conceptual depth and interdisciplinary integration.

Thematic Synthesis

We employed a three-phase thematic coding strategy:

1. *Open coding* identified recurrent concepts such as metabolic trade-offs, substrate reallocation, and hormesis.
2. *Axial coding* mapped relationships among energy dynamics, stress adaptation, and physiological outcomes.
3. *Narrative integration* constructed a coherent, system-level framework that reflects a consistent adaptive trajectory: Respond → Adapt → Recover, culminating in either homeostasis, hormesis, or maladaptation.

Cross-Domain Conceptual Integration

This model emerged inductively through repeated analysis cycles across diverse domains and was cross-compared with established frameworks such as the GAS and hormesis theory, and emerging models including immunometabolic reprogramming, integrated stress response (ISR and ISR^{mt}), brain–body energy conservation, and insulin-regulated substrate dynamics to ensure conceptual coherence and validity. These perspectives, drawn from molecular to whole-organism levels, reveal a common stress trajectory shaped by energetic and substrate availability and prioritization. The model is visually represented in **Figure 1**, which synthesizes the energetic trajectory of adaptation and its divergent outcomes:

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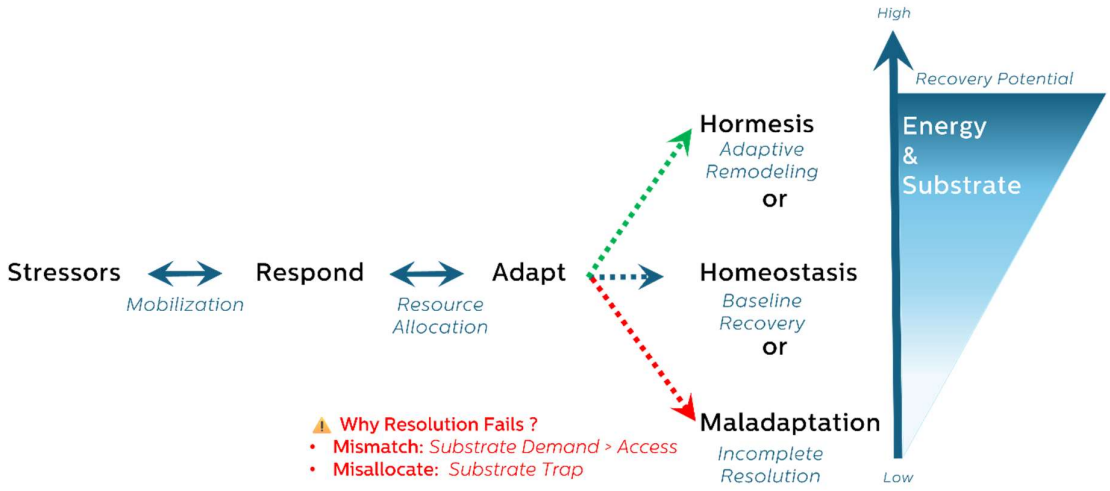

Figure 1. Energetic Adaptation Arc: Respond → Adapt → Resolve outcomes shaped by energy availability

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 merely a biochemical or hormonal cascade—it is an energetically expensive process requiring the coordinated mobilization, prioritization, and allocation of metabolic resources (Monzel et al., 2023). Across organismal, cellular, and subcellular levels, adaptive outcomes hinge on substrate availability and distribution efficiency. When demands exceed energy supply, systems are forced into trade-offs that preserve immediate function at the expense of long-term health.

General Adaptation Syndrome and Allostatic Load

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).

The Resistance phase may lead not only to delay of collapse but to one of three outcomes:

- Restored homeostasis
- Adaptive overcompensation (hormesis)
- Maladaptation and decline (exhaustion)

This non-linear, reversible trajectory underscores that exhaustion is not inevitable—given sufficient resources and recovery capacity, systems may recover or even strengthen.

Hormesis: Adaptive Activation and Thresholds of Strain

Hormesis describes how low-dose or transient stress can activate adaptive responses that enhance long-term 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, the hormetic response depends on dose, timing, and recovery. The same exposure that promotes adaptation under one condition can trigger dysfunction in another. Hormesis is thus best understood as an energetic gamble—one that pays off only if recovery is supported.

Energy and Substrates as Limiting Factors in Resilience

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All stress responses require substrates—ATP, amino acids, glucose, lipids, and micronutrients. These are reallocated to meet immediate demands, often diverting resources from longer-term processes like growth, cognition, and immune surveillance (Zera & Harshman, 2001). Under chronic or cumulative stress, this redistribution becomes a zero-sum game.

The Concept of Metabolic Triage and Functional Trade-Offs

When resources are constrained, the body activates conserved survival hierarchies—prioritizing critical functions while deferring regeneration and maintenance. This is captured by the nutrient triage hypothesis, which posits that even marginal deficits prompt protection of short-term survival at the expense of longevity-promoting pathways (Ames, 2006). Over time, this results in degradation of systems like skeletal muscle, reproductive health, and neuroplasticity.

We introduce the idea of *subclinical adaptation failure*—early physiological inefficiency where resilience erodes before overt disease manifests. Fatigue, low-grade inflammation, anabolic resistance, and poor recovery may reflect this hidden cost. Detecting such trade-offs offers a window for preclinical intervention.

Unifying System-Specific Adaptation: Respond, Adapt, Resolve

A consistent stress trajectory emerges across physiological systems:

- Phase 1: Respond – Emergency activation and energy mobilization.
- Phase 2: Adapt – Metabolic prioritization and reprogramming.
- Phase 3: Resolve – Transition toward recovery or dysfunction.

At each phase, outcomes depend on energetic capacity and regulatory flexibility. Systems that restore balance may regain function (homeostasis) or strengthen (hormesis); those that fail to resolve may enter a maladaptive state marked by dysfunction, inflammation, or degeneration.

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

This section explores how the energetic economy of stress adaptation plays out across five key systems: neuroendocrine, immune, muscular, mitochondrial, and cellular integrated stress response (ISR) networks. Despite differing mechanisms, all follow the shared trajectory outlined earlier: *Respond* → *Adapt* → *Resolve*, culminating in one of three outcomes—*Homeostasis, Hormesis,* or *Maladaptation.* The quality and direction of this resolution depend on substrate availability, system-specific regulatory capacity, and the degree of sustained stress.

Phase 1: Respond — Emergency Signaling and Energy Mobilization

In the initial response phase, systems activate high-priority defense mechanisms, diverting energy from non-essential functions to immediate survival needs:

- Neuroendocrine System activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) system, rapidly mobilizing glucose and suppressing growth and reproduction (Tsigos & Chrousos, 2002).
- Immune System initiates acute inflammation via pattern recognition receptors (PRRs), releasing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and shifting immune metabolism toward glycolysis (Alack et al., 2019; Straub, 2017).
- Muscle tissue supplies gluconeogenic substrates by breaking down amino acids via proteolytic pathways (Cahill, 2006; Wolfe, 2006).
- Cellular ISR halts general protein synthesis via eIF2α phosphorylation while promoting selective translation of stress-resilient genes (Pakos-Zebrucka et al., 2016).
- Mitochondria shift metabolic output and activate antioxidant signaling and the mitochondrial unfolded protein response (UPRmt), increase ATP production, and activate antioxidant signaling (Picard & Shirihai, 2022).

This phase reflects acute catabolic triage: stress overrides baseline priorities, rerouting energy toward preservation of core functions.

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Phase 2: Adapt — Metabolic Prioritization and Stress Programming

If stress persists, systems enter an adaptive phase, reallocating resources to optimize survival under constraint:

- 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).

At this stage, systems are not yet failing, but function is constrained. Sustained imbalance may entrench dysfunction or promote resilience—depending on recovery support.

Table 1. provides a comparative overview of how different systems prioritize, adapt, and resolve under stress conditions, based on their energetic thresholds and functional roles.

System	Stress Priority Function	Energy Source Preference	Resolution Potential	Vulnerabilities Under Deficit
Neuroendocrine	Glucose mobilization, survival triage	Gluconeogenesis, lipolysis	Moderate (via cortisol tapering)	HPA overactivation, insulin resistance
Immune	Inflammation, defense	Glycolysis (pro-inflammatory), OXPHOS (repair)	High if balance restored	Chronic inflammation, immune senescence
Muscle	Amino acid reservoir, repair coordination	Glycogen, fatty acids, structural protein	High if nutrients available	Anabolic resistance, sarcopenia
Cellular ISR	Proteostasis, autophagy	Internal recycling, selective translation	Moderate tohigh	Persistent translation block, apoptosis
Mitochondria	Energy production, redox signaling	OXPHOS, glycolysis, fatty acids	High if fission/fusion restored	ROS overload, mitokine dysfunction

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Table 1. Comparative features of adaptive stress responses across physiological systems. Resolution capacity depends on energy substrate availability and the ability to deactivate stress programs. Vulnerabilities reflect common outcomes of unresolved or prolonged adaptation.

Phase 3: Resolve — Transitioning from Adaptation to Outcome

The *Resolve phase* marks a pivotal point in the stress response—where systems either recover, overcompensate, or deteriorate. Unlike the rapid mobilization of Phase 1 or the constrained remodeling of Phase 2, this phase involves deactivating stress programs and restoring metabolic balance. Crucially, resolution is *not binary*. Outcomes are contingent on energy availability, substrate reallocation, and system-specific capacity for repair.

When recovery is successful, systems withdraw catabolic signals—cortisol declines, parasympathetic tone increases, and inflammatory responses resolve. Tissue remodeling, mitochondrial recalibration, and restoration of anabolic processes follow—*but only if metabolic reserves are sufficient* (McEwen, 2007; Sapolsky, 2004).

In this phase:

- Neuroendocrine systems reduce HPA axis activity and re-establish circadian rhythm and metabolic homeostasis. Flattened or delayed cortisol recovery signals impaired resolution.
- 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.
- 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 transitions are *dynamic and reversible.* Systems can shift toward recovery—or regress toward dysfunction—based on fluctuations in substrate availability and stressor duration. Even partially stalled recovery can be redirected if energetic and regulatory conditions improve.

Outcomes fall into one of three categories:

1. *Homeostasis* – Return to pre-stress function and balance.
2. *Hormesis* – Functional overcompensation and increased resilience.
3. *Maladaptation* – Incomplete resolution, leading to persistent dysfunction.

These are not uniform across systems. As shown in **Table 1**, resolution pathways vary in efficiency and vulnerability depending on tissue type, stress history, and energetic flexibility. This variability explains why stress recovery may be complete in one domain (e.g., immune) but incomplete or pathological in another (e.g., muscle or mitochondrial networks) (McEwen & Wingfield, 2003; Sapolsky, 2004).

To visualize how stress responses unfold through these stages, we reintroduce the broader energetic trajectory of adaptation in **Figure 2** below. This model illustrates how *Respond* → *Adapt* → *Resolve* leads to divergent outcomes, shaped by metabolic availability and trade-offs at each stage.

Ultimately, the Resolve phase offers a critical window for intervention—*the point at which resilience can be reinforced or decline accelerated.* Early detection of stalled resolution, paired with targeted substrate support and stressor mitigation, may shift outcomes from maladaptive to restorative.

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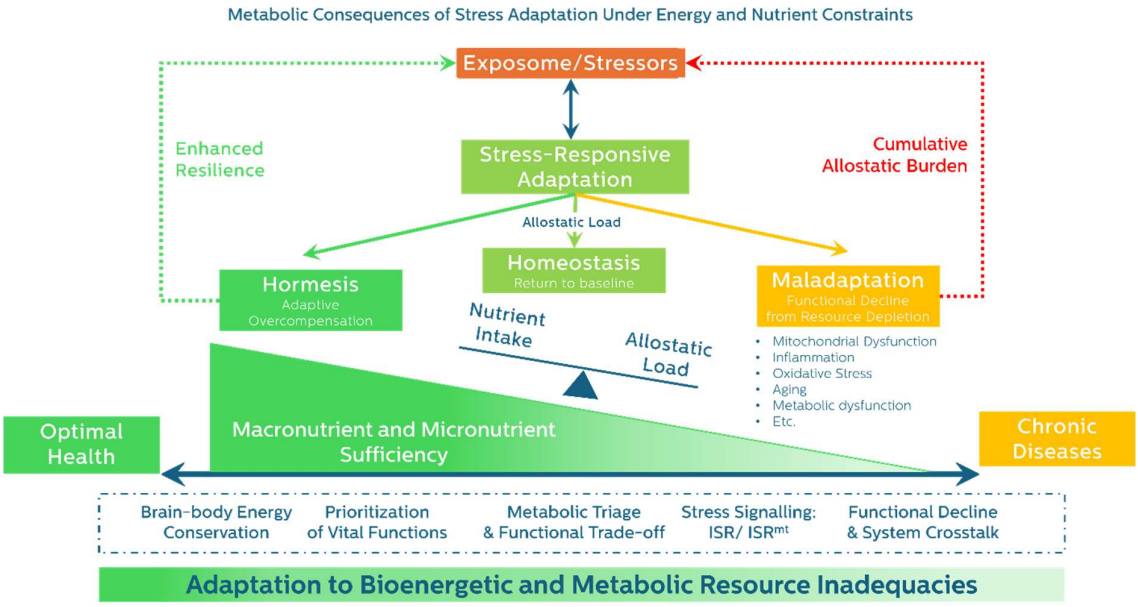

Figure 2. Metabolic Outcomes of Stress-Responsive Adaptation Under Bioenergetic Constraints.

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

Following the adaptive phase, stress resolution proceeds along one of three general paths: *Homeostasis, Hormesis, or Maladaptation*. These outcomes depend not on exposure alone, but on energy status, substrate distribution, and system-specific flexibility. While all systems share basic resolution pathways, their capacity to complete this process varies depending on metabolic reserve and prior stress burden.

5.1. Homeostasis — Energetic Recovery and Structural Recalibration

Homeostasis reflects a return to pre-stress equilibrium. This requires sufficient energy and nutrients to downregulate catabolic pathways, restore baseline signaling, and re-engage long-term maintenance.

Shared features across systems:

- Cortisol and inflammatory cytokines decline, parasympathetic tone is restored, and insulin sensitivity improves (Bobba-Alves et al., 2022).
- 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).
- In skeletal muscle, 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).

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- Cellular ISR resolves through GADD34-mediated dephosphorylation of eIF2α, enabling proteostasis and selective translation restoration (Gambardella et al., 2020; Novoa et al., 2001).
- 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).

These changes re-establish systemic integrity but depend heavily on substrate sufficiency and stress program withdrawal.

5.2. Hormesis — Energetic Overcompensation and Adaptive Remodeling

Hormesis occurs when moderate, transient stress paired with adequate recovery produces adaptive overcompensation—resulting in enhanced function and resilience (Calabrese & Agathokleous, 2019). Hormesis is not a reward but a cost-paid outcome—it emerges only when the energetic investment required for overcompensation is met and recovery pathways are intact.

Examples of hormetic remodeling:

- *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).

These adaptations are metabolically expensive and depend on sufficient ATP, intact signaling, and micronutrient availability.

5.3. Maladaptation — Energetic Collapse and Structural Degeneration

Maladaptation reflects failed recovery—where energy reserves are insufficient or misdirected, and stress programs remain chronically active. This outcome is not a failure to respond, but a failure to resolve.

Key system manifestations:

- *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).

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- *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).
- *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)

This phase marks the *energetic and structural tipping point* beyond which spontaneous recovery is unlikely without targeted intervention. Maladaptation arises not from insufficient signaling, but from a systemic failure to allocate energy and substrates toward recovery—a breakdown in bioenergetic governance.

To synthesize and compare these divergent outcomes,

Table 2. summarizes the key physiological and metabolic characteristics of *Homeostasis, Hormesis, and Maladaptation,* highlighting how energy status and adaptive resolution differ across systems. This table encapsulates the core thesis of the review: *that resilience, while biologically attainable, carries a metabolic cost*—and that outcome hinges not just on the presence of stress but on *the energetic resources available* to recover from it.

Feature	✔ Homeostasis	✚ Hormesis	⚠ Maladaptation
Energy Availability	Restored baseline levels	Sufficient with transient surplus	Depleted or misallocated
Functional Outcome	Re-equilibration	Enhanced resilience or capacity	Persistent 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, sarcopenia
ISR Recovery	Reinstated proteostasis	Increased stress resilience, adaptive memory	Persistent translation block, apoptosis
Mitochondrial Dynamics	Normalized bioenergetics	Improved redox balance, adaptive signaling	ROS overload, mitophagy failure
Recovery Dependency	Energy repletion, stress withdrawal	Surplus energy, time, micronutrient support	Insufficient recovery, chronic demand

Table 2. Comparative features of adaptive resolution outcomes across systems.

Each outcome—homeostasis, hormesis, or maladaptation—reflects differences in energy availability, recovery quality, and system-specific plasticity.

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6. Energy and Substrate Insufficiency in High-Demand States

Across a wide range of physiological and clinical conditions, nutrient insufficiency often arises not from inadequate intake, but from *elevated metabolic demand*. In such states, energy and substrates may be diverted toward acute survival functions at the expense of long-term maintenance, gradually undermining resilience.

Three classical syndromes illustrate how *malnutrition can be demand-driven*, even in the presence of apparently adequate intake:

- *Disease-Related Malnutrition (DRM)* occurs in patients with acute or chronic disease where inflammation increases resting energy expenditure and protein breakdown, often despite ongoing feeding (Cederholm & Bosaeus, 2024; Muscaritoli et al., 2023).
- *Chronic Energy Deficiency (CED)* reflects persistent nutritional insufficiency during states of heightened need—such as pregnancy—where energy and nutrient reallocation can compromise maternal and fetal health even when BMI appears normal (Prisabela et al., 2023; Taylor-Baer & Herman, 2018).
- *Relative Energy Deficiency in Sport (REDs)* results from chronic low energy availability in athletes, leading to impaired endocrine, immune, bone, and cognitive function, often with normal or low-normal body weight (Cabre et al., 2022; Mountjoy et al., 2018).

Each reflects a state where high demand, rather than insufficient supply, drives a critical mismatch between energy needs and availability. These conditions demonstrate that energy deficiency can be demand-driven, even in nutrient-replete environments.

Table 3. compares features of these classical high-demand malnutrition.

Feature	DRM	CED	REDs
Primary Affected Populations	Hospitalized or chronically ill patients	Pregnant women, children, low-resource settings	Endurance athletes, dancers, military recruits
Onset	Acute or chronic illness	Gradual under chronic stress (e.g., pregnancy)	Subacute with high training load
Triggers	Inflammation, disease burden	Increased physiological need, low intake	Prolonged mismatch between training intensity and caloric intake
Nutritional Markers	Often abnormal (e.g., prealbumin ↓)	Subclinical changes; may appear normal in standard labs	May have normal BMI, altered hormones
Clinical Presentation	Weight loss, immune dysfunction, poor healing	Maternal fatigue, micronutrient depletion, fetal risk	Performance decline, bone loss, endocrine suppression

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Feature	DRM	CED	REDs
Response to Nutrition	Requires nutritional support alongside anti-inflammatory therapy	Improves with energy/nutrient repletion	Requires coordinated refeeding and training balance

Table 3. Comparative features of classical high-demand energy deficiency syndromes.

While differing in onset and context, all reflect a mismatch between energy demand and metabolic availability—often in the absence of overt undernutrition.

These syndromes illustrate how substrate insufficiency can develop independently of food scarcity—an insight that underpins the emerging concept of *Exposure-Related Malnutrition*.

Exposure-Related Malnutrition: The Preclinical Cost of Chronic Stress Adaptation

We propose the term *Exposure-Related Malnutrition (ERM)* to describe a *subclinical, early-stage form of nutrient insufficiency* that emerges in response to prolonged metabolic and environmental stress.

ERM differs from traditional malnutrition in three key ways:

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 represents the *front end of the malnutrition trajectory.* It is the physiological *cost of prolonged adaptation* under constraint, when substrates are increasingly diverted from maintenance and repair toward stress-response and immune activation. Over time, this hidden deficit can fuel *the transition to maladaptation* and eventual disease.

Clinically, ERM helps explain why individuals with normal labs and anthropometrics may still present with chronic fatigue, sarcopenia, frequent infections, or poor healing—hallmarks of *compromised metabolic resilience* (Ames, 2006; Sganga et al., 1985; Wang & Zhang, 2025).

By identifying and intervening during this early stage—before DRM, CED, or REDs develop—clinicians have a window to preserve adaptive capacity and restore metabolic flexibility.

7. Metabolic Substrate Misallocation, Aging, and the Modern Disease Burden

Modern chronic diseases are often attributed to caloric excess. But beneath this lies a deeper dysfunction: the *misallocation of metabolic substrates*. This process—driven by chronic stress, insulin resistance, and hormonal signaling errors—leads to energy being sequestered in storage rather than delivered to tissues that need it most(Ludwig, 2023).

Insulin Signaling and Substrate Trapping

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 fail to reach active tissues, even amid nutrient abundance (Chen & Kahn, 2024).

This mismatch—known as *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 cellular rigidity.

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Over time, this persistent misallocation undercuts systemic resilience, laying the groundwork for chronic disease (Kalinkovich & Livshits, 2017; Speakman & Hall, 2021).

Fructose Survival Hypothesis: A Maladaptive Energy Lock-In

The *Fructose Survival Hypothesis* proposes 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. While adaptive during food scarcity, this response becomes maladaptive in modern environments of caloric surplus and chronic stress. Repeated activation—via dietary fructose or stress-induced glucocorticoid pathways—drives a "storage-locked" state, amplifying insulin resistance and reinforcing substrate misallocation across systems.

This energy-locking phenomenon contributes to systemic metabolic rigidity—a hallmark of aging and chronic disease—driven in part by impaired nutrient-sensing pathways such as mTOR–AMPK imbalance and SIRT1 downregulation. These regulatory disruptions further suppress adaptive flexibility, hindering the body's ability to shift from survival metabolism to repair, growth, or recovery.

Chronic Maladaptation and the Progression of Aging and NCDs

This metabolic rigidity mirrors the broader theme of maladaptation: the collapse of flexible energy allocation in favor of chronic survival signaling. In this framework, *NCDs reflect not only nutrient overload, but the chronic failure to deliver substrates to where they are needed most*—a breakdown in energetic governance across the body's most adaptive systems.

8. Recognizing ERM as the Cost of Adaptation in Clinical Practice

ERM represents the early, subclinical consequence of prolonged stress adaptation, in which metabolic substrates are continuously diverted toward immediate survival functions at the expense of repair, regeneration, and long-term resilience. Unlike classical malnutrition, ERM often arises in individuals with normal caloric intake and body weight, making it difficult to detect using conventional anthropometric or laboratory markers. Rather than reflecting nutrient scarcity, ERM is defined by persistent bioenergetic trade-offs. Over time, this silent reallocation erodes physiological reserve and impairs recovery capacity, especially when exposure burdens are sustained and unresolved.

Recognizing ERM Through Functional Patterns

Early detection of ERM requires a shift from static diagnostic thresholds to recognition of dynamic shifts in metabolism, recovery, and stress-response efficiency. Key features reflect subtle metabolic compromises across systems:

Clinical clues of ERM:

1. *Chronic fatigue* despite adequate sleep and nutrition
2. *Poor exercise recovery* or delayed wound healing
3. *Frequent mild infections* or persistent low-grade inflammation
4. *Difficulty maintaining or gaining lean mass* despite adequate intake and physical activity
5. *Biomarker patterns* suggesting inflammation-driven nutrient diversion

When these signs co-occur—particularly in the context of known exposome stressors—ERM should be suspected, even in the absence of weight loss or overt nutritional deficiency.

Drivers of ERM: The Cumulative Exposome

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ERM emerges from chronic exposure to a wide range of environmental, lifestyle, and internal stressors that challenge metabolic regulation and repair capacity. 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 stressors interact with metabolic and immune systems, shifting nutrient allocation toward short-term defense and away from tissue maintenance (Pizzorno, 2020; Vermeulen et al., 2020). Without addressing underlying exposures, nutrition alone is often insufficient to restore resilience.

Staging ERM: A Continuum of Energetic Decline

ERM unfolds along a progressive trajectory of adaptive compromise, characterized by increasing metabolic inefficiency and loss of recovery capacity:

- *Mild ERM*: Subtle reductions in physical performance, cognitive clarity, or recovery from exertion; typically reversible with adequate substrate support and removal of stressors
- *Moderate ERM*: Emergence of functional trade-offs, including low-grade inflammation, anabolic resistance, downregulated housekeeping and transport proteins, or early hormonal imbalances
- *Severe ERM*: Entrenched catabolism, sarcopenia, immune dysfunction, and metabolic rigidity, often accompanied by structural decline and reduced adaptability

Each stage is marked by measurable physiological changes, including elevated inflammatory markers, reprioritization of protein synthesis, slowed cellular turnover, and blunted adrenal output. Recognizing these patterns across systems enables timely, targeted intervention—potentially preventing irreversible dysfunction and the transition to overt disease.

Biomarkers of Nutrient Triage and Trade-Offs

ERM reflects an altered hepatic protein synthesis profile in response to inflammation. Positive acute-phase proteins (APPs)—such as C-reactive protein (CRP), ferritin, and fibrinogen—rise to support immune defense, while negative APPs—albumin, prealbumin, transferrin, and retinol-binding protein— decline as the liver reallocates amino acids away from homeostatic functions (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).

In addition, 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 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

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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 functional deficits in individuals (Adams et al., 2020; Peeri et al., 2021).

Moreover, comprehensive serum testing for all nutrients is costly and impractical in clinical practice. Emerging tools like urine organic acid profiling provide insights into intermediary metabolism but are expensive, not standardized, and lack reference ranges for early-stage dysfunction. Variability in sample preparation and metabolite recovery further reduces reliability in mild cases (Carling et al., 2025).

In contrast, recognizing trade-off patterns in standard clinical biomarkers offers a more practical and cost-effective strategy for detecting ERM (Foy et al., 2024). These changes provide an actionable window into physiological compromise, enabling earlier intervention to restore resilience before irreversible dysfunction develops.

Cellular Turnover and Intracellular Proteins

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).

Bioimpedance: A Window into Subclinical Body Composition Changes

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.

Endocrine Clues: Adrenal Reserve and Allostatic Load

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.

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

Reversibility of ERM and the Importance of Timing

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.

Toward Resilience-Informed Healthspan Interventions

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, these interventions help shift the clinical paradigm from reactive care to proactive resilience—supporting the body's ability to adapt, repair, and thrive across the lifespan.

9. Conclusion: The Metabolic Cost of Resilience

This review reframes aging and chronic disease as the *cumulative metabolic cost of unresolved adaptation*. Under conditions of chronic or repeated stress—whether inflammatory, psychological, environmental, or metabolic—the body reallocates limited energy and substrates toward immediate survival functions, including immune activation, neural vigilance, and glucose mobilization. While initially protective, these shifts come at the expense of long-term maintenance, regeneration, and repair.

Over time, this persistent triage leads to anabolic resistance, immune dysfunction, impaired mitochondrial function, and structural decline across systems. These are not isolated failures, but systemic outcomes of energetic reallocation under constraint. Resilience, in this framework, is not a default state—it is an energetically costly, actively maintained capacity.

When substrate availability is inadequate or allocation becomes dysregulated—through mechanisms such as insulin resistance, inflammation, or substrate trapping—adaptive processes stall. What begins as a healthy stress response transitions into a trajectory of progressive maladaptation and subclinical dysfunction.

By introducing the concept of *ERM*, this review offers a unifying framework to recognize and intervene in the early, reversible stages of this trajectory. ERM reflects a state in which the body's adaptive systems remain intact but are operating under silent energy constraints. Identifying ERM opens a new window for restoring resilience—before sarcopenia, immune failure, or chronic metabolic disease emerge.

Ultimately, this perspective calls for a transformation in clinical thinking: from *static diagnostics* to *dynamic pattern recognition*; from treating symptoms to *tracking substrate trade-offs;* from reactive care to *resilience-informed, bioenergetically aware prevention.*

Aging and chronic illness are not inevitable endpoints. They represent the long-term cost of unrecognized and unaddressed energy and substrate imbalance. Preserving healthspan will require that we learn to recognize—and repay—that metabolic debt before critical systems begin to fail.

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

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Abbreviation	Full Term
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
eIF2α	Eukaryotic Initiation Factor 2 Alpha
ERM	Exposure-Related Malnutrition
FGF21	Fibroblast Growth Factor 21
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
ISRmt	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
UPRmt	Mitochondrial Unfolded Protein Response

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