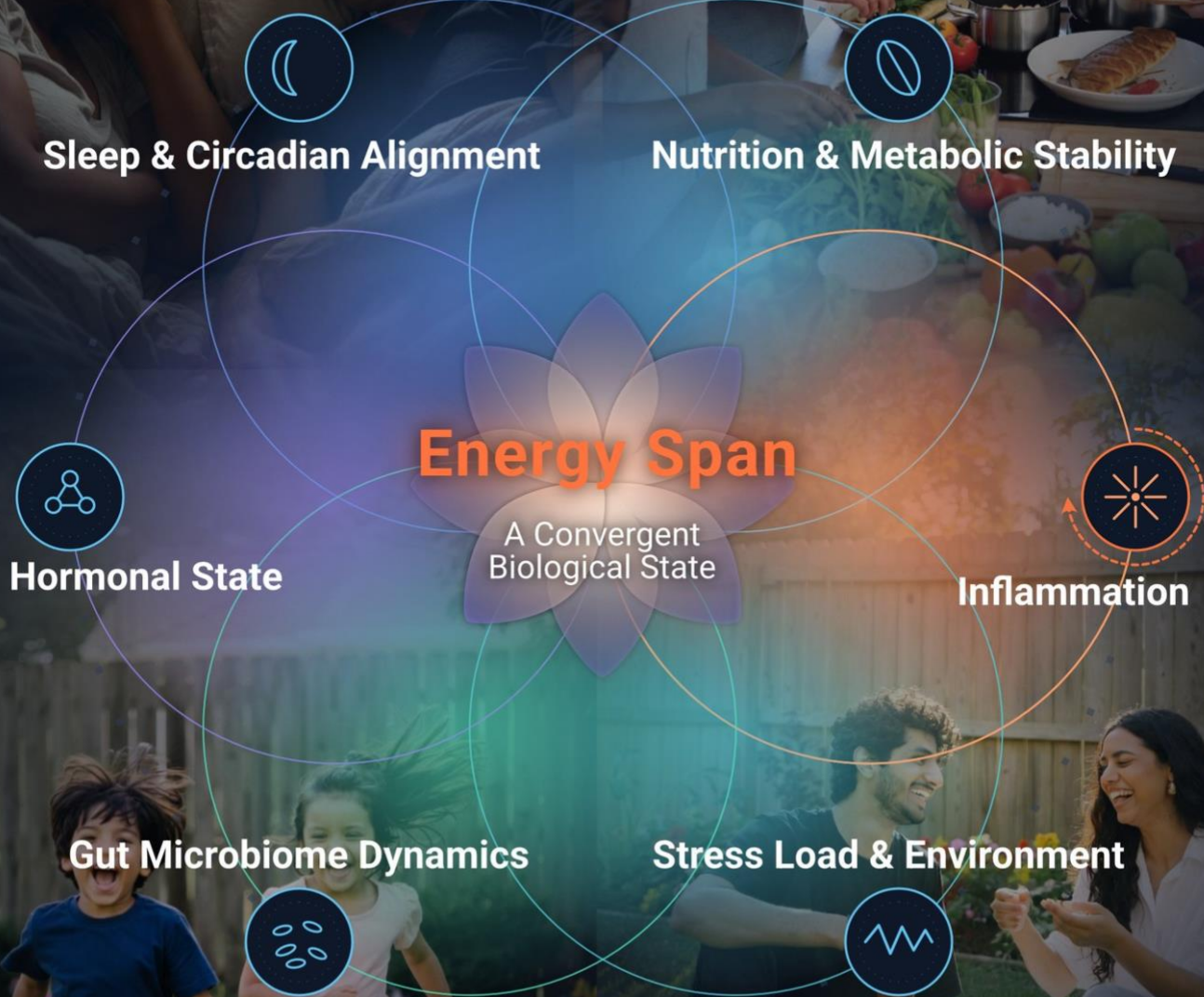


# Energy Span: An Early Signal of Healthspan Decline

What your mitochondria and metabolism reveal about resilience, fatigue, and measurable health



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C O N T E N T S

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## Defining Energy Span

Energy is one of the earliest dimensions of health to change, and one of the least rigorously measured. Long before people receive diagnoses and long before biomarkers cross clinical thresholds, they notice something subtler and more personal: effort costs more than it used to, recovery takes longer, focus fades earlier in the day. These changes are rarely dramatic. They accumulate slowly, often remaining invisible to healthcare systems that are designed to detect disease rather than drift (Rappaport et al., 2026). Yet for individuals, this erosion of energy is often the first signal that something in their biology is no longer operating optimally.



**Figure 1.** Energy Span emerges from the coordinated function of multiple biological systems anchored by mitochondrial energy production. Metabolic flexibility, neuroenergetics, autonomic balance, and hormonal rhythms interact continuously to generate and regulate both physical and cognitive energy. No single biomarker defines this system-level output.

Within Healthspan Horizons, we refer to this capacity as the Energy Span. Energy Span is not a symptom and not a diagnosis. It is the capacity to generate, sustain, and regulate physical and mental energy across daily life, under variable demands and stressors, over time. It is not synonymous with fitness, sleep quality, mood, or motivation, although it depends on all of them. Instead, Energy Span represents an intermediate functional phenotype emerging from the coordinated performance of mitochondrial bioenergetics, metabolic flexibility, neuroenergetics,

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autonomic regulation, endocrine rhythms, and recovery biology. When these systems remain resilient, people experience stable energy and cognitive clarity.

This framing reflects a core principle of the Healthspan Horizons SPANS system: health is not experienced as a binary state but as the evolution of functional capacity across domains that matter in daily life. Healthspan, as traditionally defined, is difficult to operationalize precisely because it collapses multiple biological systems into a single abstract outcome. As we separate out healthspan into Spans, such as Energy, Strength, Recovery, Attention, Intelligence, Confidence, and others, we gain the ability to observe how health changes before disease appears in a way that is the most meaningful to daily life, and where intervention is still tractable.

Energy Span is foundational among these domains. Declines in energy often precede measurable losses in strength, cognition, or resilience, while improvements in energy frequently accompany recovery across systems. This makes Energy Span not only a lived experience but also a sensitive early indicator of healthspan trajectories.

## SECTION 02

# The Biology of Energy Span

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## Mitochondrial Decline and Aging

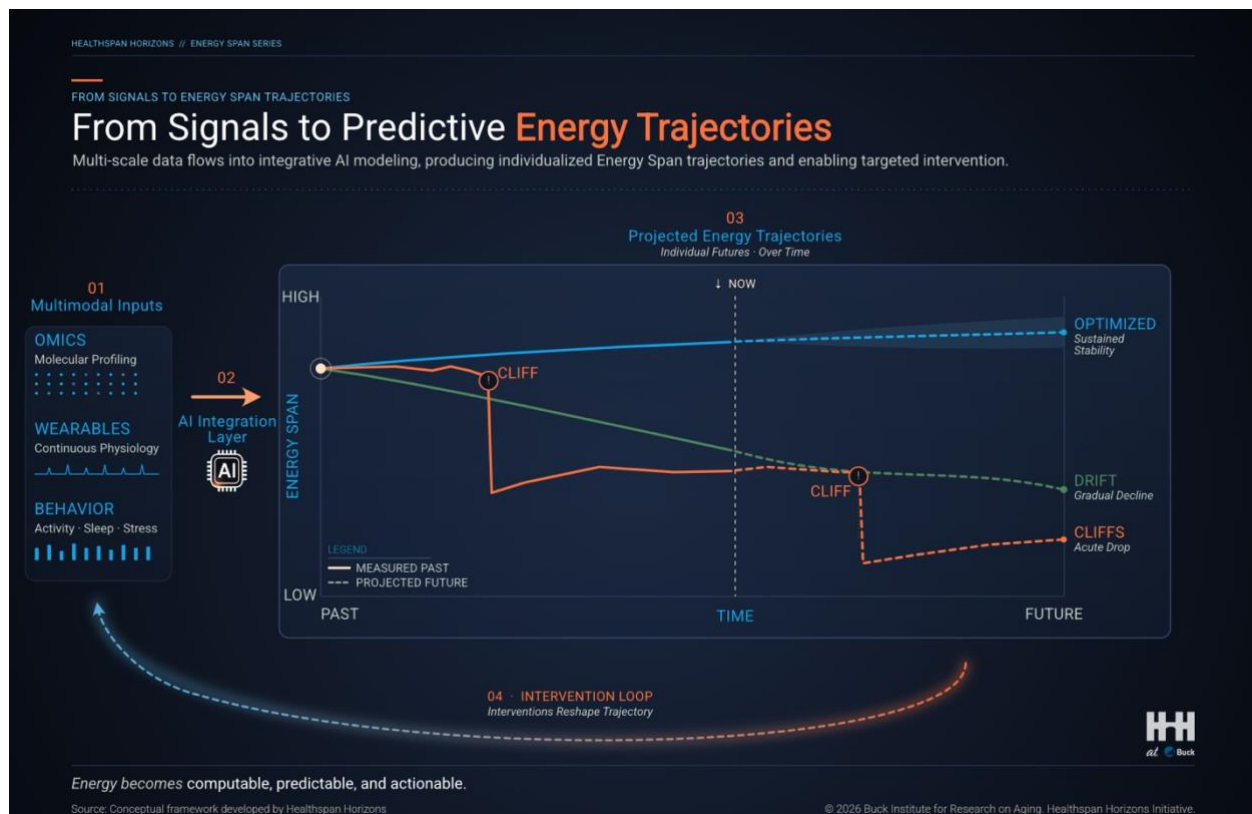
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At the biological level, energy is inseparable from mitochondrial function. Mitochondria generate ATP through oxidative phosphorylation, but they also regulate redox balance, metabolic signaling, and inflammatory tone (Martínez-Reyes & Chandel, 2020; Hamanaka & Chandel, 2010; Billingham et al., 2022). Age-associated declines in mitochondrial efficiency, increased reactive oxygen species, altered mitochondrial dynamics, and impaired biogenesis have been repeatedly linked to fatigue and reduced endurance, even in individuals without overt disease (Srivastava, 2017; López-Otín et al., 2023). The quantitative trajectory of this decline is now well characterized. Skeletal muscle mass decreases at a rate of 3 to 8 percent per decade after age 30, accelerating after age 60 (Volpi et al., 2004). Mitochondrial oxidative capacity, measured through phosphocreatine recovery kinetics or muscle biopsy enzyme assays, declines approximately 5 percent per decade in sedentary adults (Short et al., 2005). NAD<sup>+</sup> levels in human tissues show progressive reduction with age, though the magnitude varies across tissues and measurement methods; recent clinical reviews emphasize that evidence for universal age-related NAD<sup>+</sup> decline in humans remains less definitive than animal data suggest, highlighting the need for tissue-specific and longitudinal measurement (Vinten et al., 2025).

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## Drift and Cliff Events

Mitochondrial DNA copy number in muscle decreases with age, and accumulation of mitochondrial DNA mutations correlates with reduced ATP synthesis capacity (Goulding et al., 2025). These changes do not occur linearly. Major physiological stressors can trigger accelerated decline: critical illness, prolonged immobilization, chemotherapy, and sustained psychological stress each produce measurable drops in mitochondrial function that may take months or years to recover, if recovery occurs at all. The practical implication is that Energy Span erosion has both a slow background drift and episodic “cliff events” that accelerate the trajectory. Importantly, subclinical mitochondrial inefficiency is common in otherwise healthy adults and correlates with lower energy capacity long before clinical pathology emerges. Low levels of mitochondrial cofactors such as coenzyme Q10 or carnitine, impaired fatty acid transport, and altered NAD<sup>+</sup> availability can all reduce ATP production and accelerate perceived fatigue (Covarrubias et al., 2021; Castro-Marrero et al., 2021; Kim et al., 2022).



**Figure 2.** By integrating multimodal biological and behavioral data, AI models can generate individualized Energy Span trajectories. These trajectories reveal patterns of stability, gradual decline, or acute disruption, and enable targeted interventions that reshape future outcomes.

## Energy Is Trainable

Crucially, mitochondria are not static. Exercise-induced activation of PGC-1 $\alpha$  and related pathways stimulates mitochondrial biogenesis and improves oxidative capacity, providing one of the most robust biological explanations for why regular physical activity reliably improves energy

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in daily life (Lira et al., 2010; Memme et al., 2021; Pilegaard et al., 2003). From an Energy Span perspective, this means that energy is not simply consumed, but it is trained. Declines in Energy Span often reflect lost adaptive capacity rather than irreversible damage (López-Otín et al., 2023; Melov et al., 2007; Grevendonk et al., 2021; Lima et al., 2022).

## Inflammation and the Biology of Fatigue

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Chronic low-grade inflammation provides another mechanistic link between biology and perceived energy. Elevated interleukin-6 and C-reactive protein are associated with fatigue in older adults, even after adjustment for depression, sleep, and body composition. Longitudinal data from the Whitehall II cohort found that high CRP and IL-6 at baseline predicted new-onset fatigue over the following three years (Cho et al., 2013). The relationship appears bidirectional: inflammation predicts future fatigue, and fatigue predicts future inflammation, suggesting a self-reinforcing cycle.

Exercise interrupts this cycle; a 2025 umbrella review confirmed that physical activity reduces circulating CRP, TNF- $\alpha$ , and IL-6 in older adults (Mathot et al., 2025). From an Energy Span perspective, subclinical inflammation represents a measurable contributor to energy erosion that responds to lifestyle intervention.

## The Gut Microbiome and Energy Regulation

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The gut microbiome contributes to this inflammatory landscape. Microbial fermentation of dietary fiber produces short-chain fatty acids, particularly butyrate, which serve as energy substrates for colonocytes and help regulate systemic inflammation. Aging is associated with reduced microbial diversity, decreased abundance of SCFA-producing bacteria, and expansion of pro-inflammatory species (Aldriwesh et al., 2026). Centenarians, by contrast, often retain microbial profiles enriched in taxa associated with metabolic balance and anti-inflammatory activity, suggesting that microbial composition may actively support resilience rather than merely reflecting it (Pang et al., 2023; Sato et al., 2021). For Energy Span, these findings imply that dietary fiber intake and gut microbial health represent underappreciated modulators of energy availability, particularly in aging populations where both tend to decline together.

## Hormonal Influences on Energy Span

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Hormonal transitions represent another category of cliff events that reshape Energy Span. Estrogen regulates mitochondrial biogenesis, electron transport chain efficiency, and oxidative

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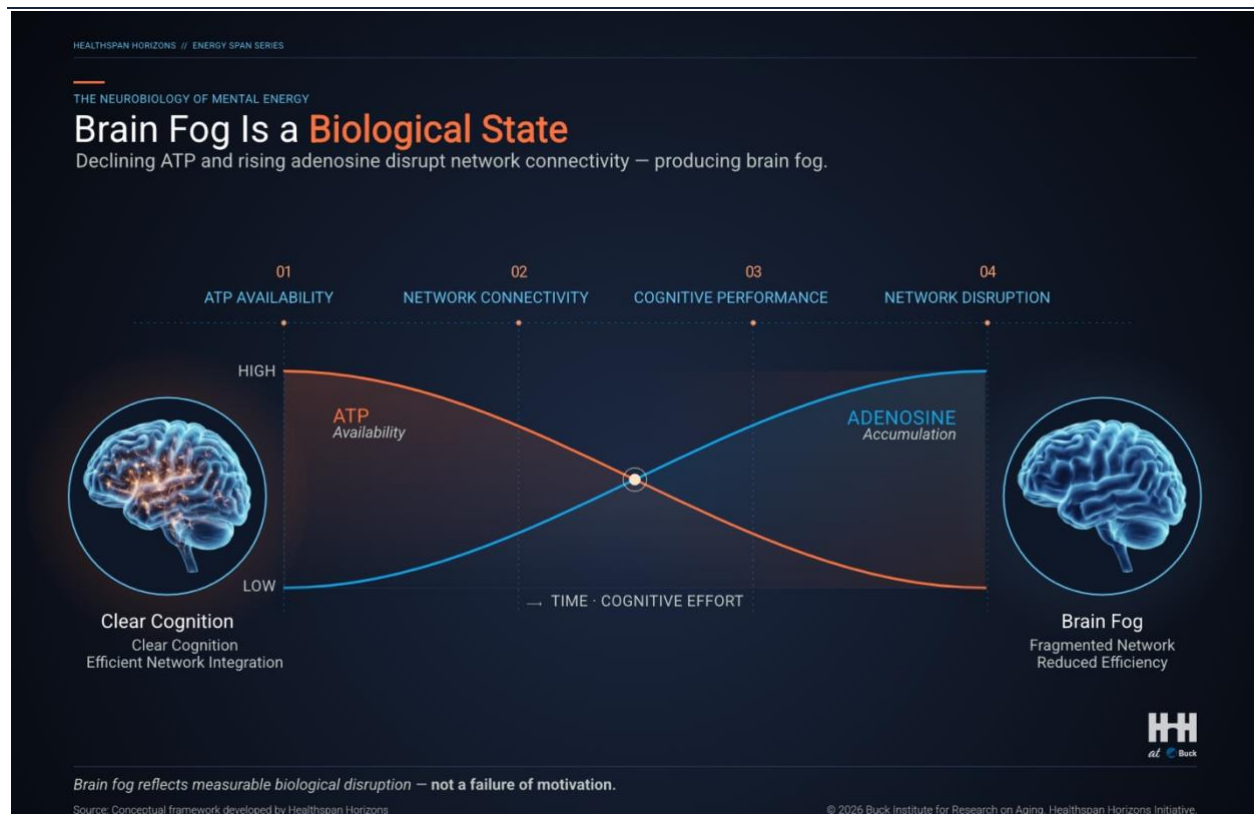
stress defense in multiple tissues including brain and skeletal muscle. During perimenopause, the decline in estradiol removes this mitochondrial protection, contributing to the fatigue, brain fog, and metabolic shifts that many women experience during this transition (Yu et al., 2025). Postmenopausal women receiving hormone therapy had higher skeletal muscle mitochondrial respiratory capacity than untreated women, suggesting that estrogen status directly affects muscle bioenergetics (Kleis-Olsen et al., 2024). In men, gradual testosterone decline affects muscle mass, recovery capacity, and subjective energy, though the trajectory is less abrupt. These hormonal influences underscore that Energy Span is not sex-neutral; interventions and expectations must account for where individuals stand in their reproductive life course.

## The Neurobiology of Mental Energy and Brain Fog

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Mental energy follows the same logic, but the brain's vulnerability is more acute. The brain constitutes roughly 2 percent of body mass yet consumes 20 percent of resting oxygen and glucose. This metabolic demand is non-negotiable; neurons lack significant energy reserves and depend on continuous substrate delivery. Prolonged cognitive effort depletes local ATP and elevates extracellular adenosine, a metabolic byproduct that accumulates during sustained neural activity. Adenosine acts on A1 and A2A receptors in prefrontal and striatal circuits, producing the subjective experience of mental fatigue and reduced willingness to exert further effort (Reichert et al., 2022). This is why caffeine, an adenosine receptor antagonist, temporarily restores subjective alertness.

The phenomenon commonly described as “brain fog” now has a clearer neurobiological basis, and is characterized as a syndrome of attention and memory complaints, overlapping substantially with mental fatigue, and appearing across conditions ranging from post-viral syndromes to menopause to autoimmune disease (Denno & Hampshire, 2025). Functional neuroimaging studies in individuals reporting brain fog demonstrate altered connectivity and reduced efficiency in frontoparietal networks responsible for executive control. Brain fog severity correlated with decreased global efficiency and altered information flow patterns, suggesting that subjective cognitive cloudiness reflects measurable disruption in how brain regions communicate (Kesler et al., 2024). The metabolic underpinning appears consistent: when energy supply to prefrontal circuits becomes unstable or insufficient, whether from sleep loss, glucose dysregulation, inflammation, or chronic stress, the result is the same constellation of symptoms people describe as foggy thinking, difficulty concentrating, and mental slowness. Neuroimaging studies in fatigue-related conditions demonstrate altered cerebral perfusion and metabolic patterns, reinforcing that mental fatigue is a biological state, not a motivational failure (Shan et al., 2020; Darnai et al., 2023; Pessiglione et al., 2025).



**Figure 3.** Brain fog reflects a biological shift in energy availability and neural function. As ATP declines and adenosine accumulates, network connectivity becomes less efficient, leading to measurable declines in cognitive performance. This is a physiological state, not a psychological failure.

## Autonomic Regulation and Wearable Measurement

### Heart Rate Variability as a Signal

The autonomic nervous system acts as a real-time governor of energy allocation. Healthy Energy Span requires the ability to flexibly transition between sympathetic activation and parasympathetic recovery. Reduced heart rate variability, reflecting autonomic inflexibility, is consistently associated with fatigue across medical and non-medical populations (Csathó et al., 2024; Escorihuela et al., 2020). Chronic sympathetic dominance produces a paradoxical state in which physiology remains activated while subjective energy collapses. In this sense, fatigue often reflects failed recovery rather than insufficient effort.

### Consumer Wearables as Measurement Tools

Wearable-derived autonomic metrics now make this imbalance visible in daily life, revealing how sustained stress, poor sleep, or excessive training erode energy capacity even when individuals feel they are “coping”. Consumer wearable devices have reached sufficient accuracy to make autonomic monitoring practical outside clinical settings. Comparing five commercial devices

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against electrocardiogram reference found that the Oura Ring (Generation 3 and 4) achieved concordance correlation coefficients above 0.97 for both resting heart rate and heart rate variability (HRV), with mean absolute percentage errors under 8 percent (Dial et al., 2025). WHOOP showed acceptable agreement, while other devices demonstrated more variable performance. These validation data matter because HRV, specifically the root mean square of successive R-R interval differences (RMSSD), serves as a proxy for parasympathetic tone and recovery capacity. Longitudinal HRV tracking can identify when recovery is incomplete, when stress load exceeds adaptive capacity, and when interventions such as sleep optimization or training reduction produce measurable physiological shifts. A comprehensive guide to consumer wearables for cardiovascular monitoring reviewed devices from Apple, Fitbit, Garmin, Oura, Polar, Samsung, Withings, and WHOOP, finding that while accuracy varies, the category as a whole now supports meaningful health tracking when used consistently (Jamieson et al., 2025). For Energy Span assessment, nocturnal HRV trends offer a window into the autonomic recovery processes that determine next-day energy availability.

## Circadian Rhythms and Energy Regulation

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Endocrine rhythms add a temporal dimension to Energy Span. The circadian pattern of cortisol, peaking in the morning and declining at night interacts with patterns of recovery. Flattened or phase-shifted cortisol rhythms, common in shift workers, chronic stress, and burnout, are strongly associated with persistent fatigue (Adam et al., 2017; Oosterholt et al., 2015; Andreadi et al., 2025; Nijhof et al., 2014). Thyroid hormones regulate basal metabolic rate, and even subclinical deviations can meaningfully affect energy availability. Catecholamines provide short-term boosts that, when chronically overused, increase allostatic load and accelerate energy collapse rather than sustain performance (Mullur et al., 2014; Harper & Seifert, 2008; Juster et al., 2010). Together, these findings reinforce that energy loss may reflect dysregulated timing rather than absolute deficiency.

Lifestyle and environment modulate these biological systems continuously. Sleep is not simply restorative; it is regulatory. Fragmented sleep architecture and circadian misalignment disrupt mitochondrial efficiency, glucose regulation, autonomic balance, and hormonal rhythms, producing fatigue that does not resolve with a single night of rest (Potter et al., 2016; Saner et al., 2021; Chai et al., 2020). Nutrition shapes energy stability through glycemic control and substrate availability. Acute hyperglycemia and reactive hypoglycemia both reduce perceived energy and cognitive performance, while stable glucose dynamics support sustained mental and physical output (Chi et al., 2023; Arshad et al., 2025; Frier, 2001).

Continuous glucose monitoring (CGM), originally developed for diabetes management, is increasingly used in non-diabetic populations to characterize individual glycemic patterns. CGM data from thousands of non-diabetic individuals demonstrated substantial inter-individual variation in postprandial glucose responses to identical foods, confirming that generalized dietary

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advice fails to account for metabolic individuality (Keshet et al., 2023). For Energy Span, this finding has direct implications: two people eating the same breakfast may experience entirely different glucose trajectories, and with them, different patterns of energy stability and cognitive performance through the morning. Combining CGM with ecological momentary assessment found that blood glucose fluctuations and insulin resistance status affected working memory performance assessed in real-world conditions throughout the day (Gruber et al., 2024).

## Metabolic Flexibility and Energy Stability

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Metabolic flexibility, the capacity to efficiently switch between glucose and fatty acid oxidation depending on substrate availability and energy demand, declines with age and sedentary behavior. Healthy individuals transition smoothly from fat oxidation during fasting to glucose oxidation after meals; this adaptability characterizes efficient energy regulation (Goodpaster & Sparks, 2017). Insulin resistance, chronic overnutrition, and physical inactivity each impair this switching capacity, producing a state where mitochondria become less responsive to changing fuel conditions. Aging itself alters glucose kinetics and reduces the dynamic range of substrate oxidation in response to oral glucose challenge (Curl et al., 2024). For Energy Span, metabolic inflexibility means less resilience to dietary variation and fasting states, contributing to the energy fluctuations many people experience as they age. Physical activity, paradoxically, increases Energy Span by improving mitochondrial capacity, cardiovascular efficiency, inflammatory tone, and psychological resilience (Abrego-Guandique et al., 2025; Puetz et al., 2008; Petersen & Pedersen, 2005). Chronic psychosocial stress, digital overload, and poorly designed work environments act in the opposite direction, flattening recovery signals and fragmenting attention.

### SECTION 03

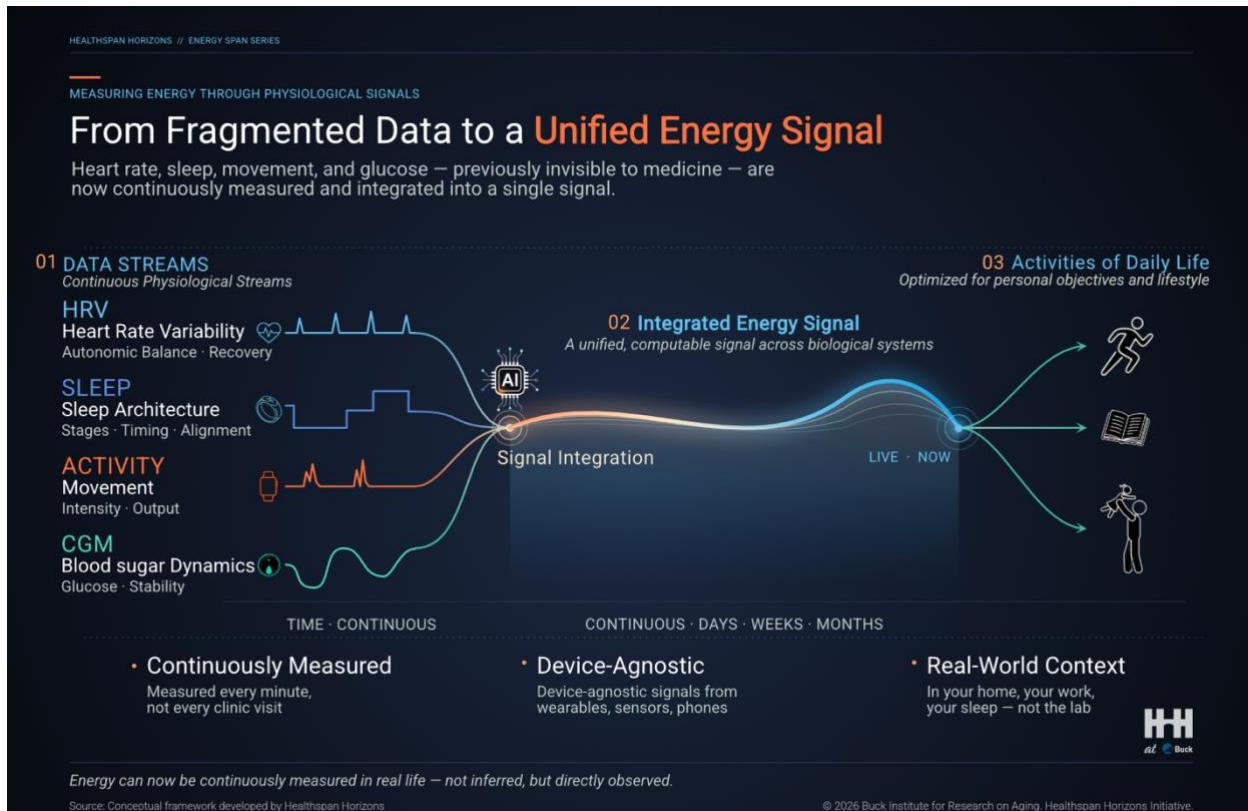
## From Measurement to Energy Span Trajectories

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A central perspective in healthspan optimization overall, and specifically as it pertains to bioenergetics, is that studying energy only in sick populations misses the biology that matters most (Rappaport et al., 2026). Fatigue research has historically focused on late-stage failure: chronic fatigue syndrome, cancer-related fatigue, depression. These states are informative, but they represent collapse, not early deviation. Healthspan Horizons instead emphasizes deep, longitudinal data from healthy individuals, where Energy Span erosion is still reversible. This approach aligns with the Scientific Wellness paradigm articulated by Leroy Hood and Nathan Price, which prioritizes dense biological measurement, personal baselines, and early detection of deviation rather than population thresholds (Hood & Price, 2023).

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Longitudinal multi-omic profiling, wearable-derived physiology, and cognitive performance metrics allow Energy Span to be modeled as a trajectory rather than a score. No single biomarker defines energy. Actionable possibilities will be derived from patterns and tradeoffs of mitochondrial efficiency, autonomic balance, sleep architecture, cognitive vigilance, recovery kinetics as well as stress exposure. Within-person change matters more than cross-sectional comparison. Two individuals with identical “average energy” may differ radically in resilience, recovery, and long-term outcomes.



**Figure 4.** Continuous physiological data streams – including heart rate variability, sleep architecture, activity, and glucose dynamics – can now be integrated into a unified Energy Signal. This enables real-time, real-world measurement of human energy across daily life.

Digital phenotyping extends this measurement capacity beyond periodic assessments to continuous behavioral and physiological streams. Smartphones and wearables can passively capture sleep patterns, activity levels, mobility, and interaction patterns that correlate with subjective energy states. Combining passive sensor data from smartphones and fitness trackers with brief ecological momentary assessments could predict patient-reported fatigue and sleep quality over months of monitoring, using machine learning on features extracted from location patterns, screen use, heart rate, and step count (Yi et al., 2025). For Energy Span, digital phenotyping offers the possibility of detecting drift in energy-related behaviors before individuals consciously notice decline. The practical question shifts from “how do you feel today” to “what do your patterns reveal about your trajectory.” This approach also identifies which behavioral

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signatures, such as sleep timing consistency, activity distribution, or recovery periods, most strongly predict next-day energy availability in each individual.

## SECTION 04

### The Social and Cultural Dimensions of Energy Span

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Energy Span is shaped by society and culture in ways that operate above individual behavior. Work schedules misaligned with circadian biology, chronic caregiving stress, socioeconomic insecurity, and digital overstimulation all shorten Energy Span at population scale. Cultural factors are embedded in these patterns: norms around productivity and rest, attitudes toward sleep as either essential recovery or expendable time, food environments that prioritize convenience over metabolic health, and social expectations that reward visible busyness over sustainable performance. In some cultural contexts, fatigue carries stigma, discouraging acknowledgment of energy limits until collapse becomes unavoidable. In others, rest is valued but structurally inaccessible.

The Energy Span framework does not separate culture from biology; rather, it recognizes that cultural and economic structures create the conditions under which biological systems either thrive or deteriorate. Interventions at the individual level matter, but population-level Energy Span will require changes in how societies organize work, value rest, and distribute the burdens that deplete human energy. Many changes once attributed to aging alone, such as loss of endurance, mental fatigue or slow recovery, are modifiable through targeted interventions, even late in life (Huang et al., 2005; Lai et al., 2024; Kalapotharakos et al., 2010). Energy Span therefore represents both a biological and societal challenge.

## SECTION 05

### Making Energy Span Measurable and Actionable

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The biological systems underlying Energy Span respond to intervention. For individuals seeking to measure and improve their energy capacity, several evidence-based approaches deserve attention.

#### Exercise

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Exercise remains the most robust intervention for mitochondrial health. Meta-analysis of randomized trials found that endurance exercise training produced large effect sizes for PGC-

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1alpha expression (Hedges'  $g = 1.17$ ), the master regulator of mitochondrial biogenesis (Abrego-Guandique et al., 2025). Resistance training preserves muscle mass and complements aerobic work; a randomized trial in older adults with obesity found that combined aerobic and resistance exercise was the most effective approach for improving functional status (Villareal et al., 2017). The recommendation is not extreme volume but consistency: regular sessions that challenge both cardiovascular and musculoskeletal systems.

## Sleep

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Sleep optimization addresses both recovery and circadian alignment. The goal is not merely duration but architecture: sufficient slow-wave sleep for physical restoration and REM sleep for cognitive consolidation (Dattilo et al., 2011; Rasch & Born, 2013). Wearable devices now provide sleep stage estimates that, while imperfect, can guide behavioral adjustments. Morning light exposure, consistent sleep timing, and evening light restriction all support circadian alignment, which in turn supports cortisol rhythms and autonomic recovery.

## Nutrition

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Glycemic stability can be pursued through dietary composition and timing. Prioritizing fiber, protein, and fat alongside carbohydrates slows glucose absorption and reduces postprandial spikes. For those willing to experiment, short-term CGM use can identify personal trigger foods that produce disproportionate glycemic excursions. The patterns are often surprising and highly individual.

## Stress Regulation

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Stress management directly affects HRV and autonomic balance. Techniques with evidence for HRV improvement include slow-paced breathing (around six breaths per minute), which shifts autonomic tone toward parasympathetic dominance (Laborde et al., 2022). Some wearable devices now incorporate HRV biofeedback training. The principle is straightforward: practices that improve HRV reflect improved autonomic flexibility, which supports energy regulation.

These interventions interact. Exercise improves sleep; sleep improves glucose regulation; stable glucose supports consistent energy for exercise. The goal is not perfection in any single domain but directional improvement across the system.

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Within Healthspan Horizons, Energy Span serves three functions. It is an early and sensitive signal of declining resilience. It is a translational bridge between deep biology and lived experience. And it is a measurable target for extending healthy, functional years.

*Energy is not a slogan for wellness. It is a computable dimension of healthspan. Treating it as such reframes aging not as an inevitable loss of vitality, but as a dynamic process that can be measured, understood, and shaped long before disease speaks loudly enough to demand attention.*

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## A B O U T   T H I S   R E S E A R C H

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This keynote perspective was developed by Healthspan Horizons, an initiative based at the Buck Institute for Research on Aging. The work reflects a unified research and systems design effort to make healthspan measurable, computable, and actionable. Healthspan Horizons advances a federated, AI-enabled framework for integrating multi-omic, clinical, behavioral, and environmental data to support long-term resilience and healthy aging.

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