HEALTHSPAN HORIZONS

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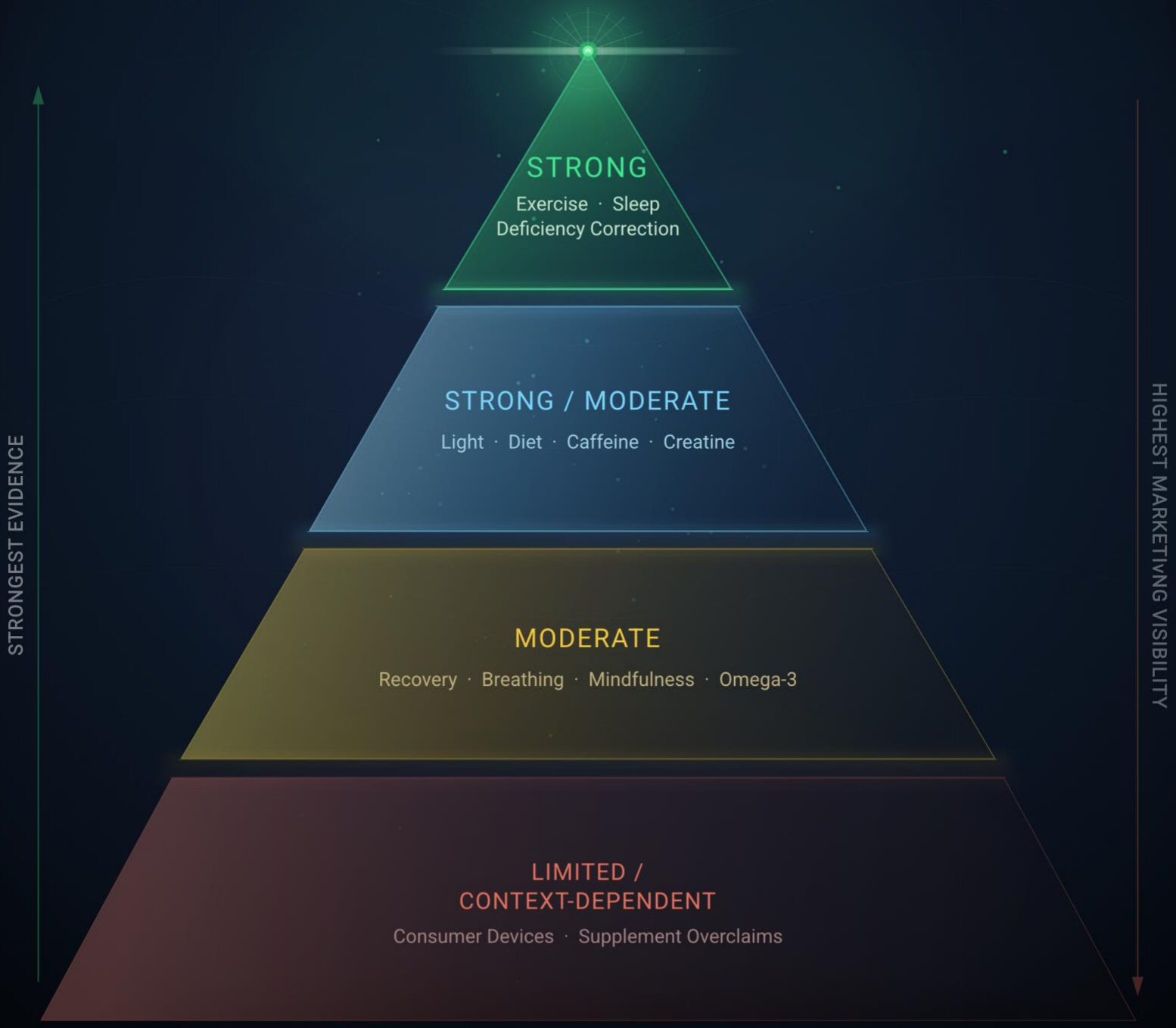
ENERGY SPAN · PART 2

What Actually Moves Energy Span

A critical evaluation of the evidence across six dimensions



16 SOLUTIONS · 6 DIMENSIONS · 7 SYSTEMS

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What's inside

SECTION 01

Introduction

This is Part 2 of a two-part series on Energy Span. Part 1 established the definition and biological framework: Energy Span is the capacity to generate, sustain, and regulate physical and mental energy across daily life, under variable demands and stressors, over time — an emergent functional capacity shaped by seven interacting biological systems (Rappaport, 2026).

Part 2 shifts from concept to evaluation: what the evidence actually supports, what it does not, and where most people should start.

> EDITORIAL NOTE
>
> This is not only an evaluation of interventions. It is a step toward making Energy Span computable — translating heterogeneous evidence into structured signals that can ultimately be modeled, personalized, and acted upon at the individual level. Energy Span is one of several measurable Spans within the Healthspan Horizons framework — alongside Strength, Recovery, Attention, and others — each representing a distinct, computable dimension of healthspan.

Note: Several important Energy Span drivers — including inflammatory burden, gut–metabolic signaling, and hormonal transitions — operate across multiple systems rather than as isolated dimensions. Rather than treating them as stand-alone consumer categories, their most evidence-based interventions are incorporated within the relevant solution cards below (nutrition, sleep, exercise, clinical evaluation, and metabolic care).

1.1 From Concept to Evaluation

Part 1 established that Energy Span is a biological capacity — not a symptom and not a subjective state. It is shaped by seven interacting systems, each measurable and modifiable. It cannot be reduced to sleep alone, mitochondria alone, or any single wearable metric. This framing reflects a broader shift in healthspan science toward functional capacity as it is lived, consistent with the World Health Organization's emphasis on intrinsic capacity in healthy aging (Beard et al., 2016; Cesari et al., 2018).

Understanding this architecture immediately raises a harder, more practical question: of the many interventions, devices, and products marketed for energy, fatigue, and performance — which ones actually hold up?

The answers are less tidy than the market suggests. Strong, replicated evidence exists for structured exercise, sleep extension, circadian anchoring, and clinical correction of deficiencies such as iron deficiency and hypothyroidism. But that evidence coexists with:

- consumer products supported by small, manufacturer-funded studies
- supplements built on plausible mechanisms without demonstrated outcomes in healthy adults
- measurement tools marketed as if tracking a signal were equivalent to improving it

Healthspan Horizons evaluates solutions through:

- explicit evidence tiers
- a validity versus utility distinction
- direct identification of where marketing claims exceed demonstrated evidence

This is consistent with formal evidence-grading frameworks such as GRADE (Grading of Recommendations Assessment, Development and Evaluation): confidence in an intervention should reflect quality, consistency, and applicability of evidence — not the appeal of its mechanism (Guyatt et al., 2008).

The goal is not to catalogue solutions. The goal is to enable calibrated judgment — the prerequisite for making Energy Span actionable and, ultimately, computable.

1.2 Why Most Solutions Reviews Get This Wrong

Most wellness content approaches solutions with a single evaluative question: does it work? It is a binary question applied to a non-binary evidence base, producing a landscape where a Cochrane systematic review and a manufacturer-funded pilot of 30 participants are treated as the same type of information — differentiated mainly by marketing reach rather than epistemic weight (Sackett et al., 1996).

Two specific failures recur. The first is conflating measurement with intervention: consumer wearables measure HRV, sleep staging, and glucose but improve none of these metrics. Improvement requires behaviour change, and behaviour change requires consistent action on what the data reveals — which in practice often does not follow data exposure alone (Baron et al., 2017). The second is treating biological plausibility as demonstrated benefit: a mechanism that is real at the cellular level is not evidence that a consumer product produces the same effect at consumer-grade parameters in healthy adults (Bekelman et al., 2003; Ioannidis, 2005). Photobiomodulation is instructive: a real cellular mechanism and legitimate dermatological evidence, neither of which establishes systemic energy improvement from a consumer panel (Vanin et al., 2018).

HH's approach separates validity from utility, evidence quality from marketing confidence, and population-level findings from individual applicability. These are not semantic distinctions. They are what allow a solutions review to produce actual judgment rather than curated commentary.

SECTION 02

How HH Evaluates Solutions

The landscape evaluated here spans behavioural interventions, measurement tools, supplements, and clinician-guided treatments — categories routinely discussed as though they were comparable. They are not. A wearable tracking HRV, a structured exercise programme, and a prescription correction for iron deficiency all get described as supporting energy, but they operate through different mechanisms, carry different qualities of evidence, and make different demands on the person using them. Without a framework that surfaces these differences, comparison is unreliable.

2.1 The Validity / Utility Distinction

These two concepts are frequently conflated. They are not the same thing.

- Validity asks: does a tool measure what it claims, reliably and in context?
- Utility asks: does that measurement enable meaningful action for a specific person?

The two often diverge. A consumer HRV wearable may achieve acceptable nocturnal measurement validity while offering low utility to someone who will not consistently act on the data. For devices in particular, physiological signal validity must be kept separate from algorithmic summary scores: a wearable may record resting heart rate accurately while producing a 'readiness score' that is a proprietary composite with no validation against any clinical outcome (de Zambotti et al., 2019). Both things can be true simultaneously.

2.2 Evidence Tiers

The evidence tier reflects the strength of evidence for outcomes — not safety or plausibility. A plausible mechanism does not elevate the evidence tier. Manufacturer-funded studies alone do not support moderate or strong classification (Lundh et al., 2017).

TIER	WHAT IT MEANS
STRONG	Multiple RCTs, systematic reviews, or meta-analyses; endorsed by major clinical guidelines (AASM, ATA, AHA, ACP, WHO, NICE, Cochrane). Consistent findings across populations and study designs.
MODERATE	RCTs or large cohort studies; consistent direction of effect; some limitations in sample size, generalisability, or follow-up. Guideline-level support may be partial or context-specific.

TIER	WHAT IT MEANS
LIMITED	Small trials, mechanistic data, or inconsistent findings. Signal may be real but not yet replicated at sufficient scale or in appropriate populations.
EMERGING	Plausible biological mechanism; preliminary human data; insufficient evidence for broad confidence. Worth tracking; insufficient for population-level recommendation.

2.3 Solution Types

Not all solutions are the same kind of intervention. A wearable and an exercise protocol are fundamentally different: one generates data that may or may not prompt behaviour change; the other is the behaviour change itself. The type label on each card is not a quality judgment — it defines what a solution is and the role it can realistically serve.

TYPE	WHAT IT IS	ROLE
Measurement Tool	Generates data about a biological signal	Informs decisions; does not cause improvement directly
Behavioral	Evidence-backed lifestyle or cognitive intervention	Directly modifies one or more Energy Span dimensions
Supplement	Orally consumed compound	May support a specific dimension; evidence quality varies widely
Medical / Rx	Requires clinical evaluation or prescription	Addresses a deficiency or disorder; not self-managed
Device	Physical tool delivering a stimulus	Delivers a behavioral or physiological effect; validity varies by product
Environment	Physical or social context modification	Removes stressors or supports recovery; often undervalued

2.4 What This Framework Is For

This framework is not designed for static evaluation.

It is designed to feed into a longitudinal model of Energy Span, where interventions are evaluated not only by evidence tier, but by:

- their impact on trajectories over time
- their interaction across systems
- and their relevance to individual constraints (Hood and Price, 2023; Rappaport et al., 2026)

2.5 How to Read the Solution Cards

Each card covers the same fields in the same order: mechanism, evidence tier, validity, utility, failure modes, how to use it, the overclaim (the specific gap between what is marketed and what evidence supports), and a systems signal indicating cross-dimensional interactions. One caveat throughout: the evidence reviewed describes population-level findings, not guaranteed individual responses. Age, baseline health, and which dimensions are currently limiting a person's energy all affect how much any given solution is likely to matter.

SECTION 03

Solutions — 16 Cards Across 6 Dimensions

NOTE ON DIMENSIONS VS. SYSTEMS

The six dimensions used to organize the solution cards are reader-facing groupings designed to simplify navigation across the intervention landscape. Underneath these groupings, Energy Span is still governed by the seven interacting biological systems introduced in Part 1. The Systems Signal in each card therefore references these underlying systems (Sys 1–7), not the six section headers.

As a result, some cards will reference system numbers that do not map one-to-one onto the section they appear in. This is intentional: the dimension structure organizes solutions; the systems structure reflects biological reality and cross-system effects.

DIMENSION 1 OF SIX

Bioenergetics & Physical Capacity

The foundation of Energy Span. Mitochondria set the ceiling for sustainable energy — and that ceiling is trained, not fixed.

01

Structured Aerobic and Resistance Exercise Training

BEHAVIORAL · EVIDENCE STRONG

WHAT IT IS

A planned programme combining progressive aerobic exercise (≥150 min/week at moderate intensity) with resistance training (2–3×/week), sustained over weeks to months.

MECHANISM

Activates the AMPK → PGC-1α cascade — the master regulator of mitochondrial biogenesis — increasing mitochondrial density, oxidative capacity, and skeletal muscle ATP production (Hood et al., 2019).

Resistance training reverses age-related mitochondrial gene expression toward younger profiles (Melov et al., 2007).

EVIDENCE

g = 0.42
ENERGY EFFECT (META-ANALYSIS)

81 RCTs
N = 7,050 PARTICIPANTS

STRONG — the strongest evidence base in this landscape. Wender, Manninen and O'Connor (2022) meta-analysed 81 RCTs (N = 7,050): chronic exercise reduces fatigue (g = −0.37), increases energy (g = 0.42), and vitality (g = 0.54). WHO guidelines provide highest-level global endorsement (Bull et al., 2020). A 2025 meta-regression of 353 studies confirmed 23–27% increases in skeletal muscle mitochondrial content across age groups (Mølmen et al., 2025).

VALIDITY

Convergent across biopsy studies (mitochondrial enzyme activity), VO_2max (predicts all-cause mortality; Kodama et al., 2009), and validated fatigue scales (POMS, SF-36). Key limit: trials cannot be blinded, introducing expectation effects.

UTILITY

Universally applicable; largest gains in previously sedentary individuals. Subjective energy improves within 2–4 weeks; VO_2max gains at 6–12 weeks; mitochondrial adaptation at 8–12 weeks. Gains persist even in adults aged 80–88 (Kalapotharakos et al., 2010).

⚠ FAILURE MODES

- Short-term fatigue in weeks 1–2 is normal — the benefit requires outlasting this phase.
- Excessive volume without recovery produces overtraining syndrome: paradoxical energy decline and chronic sympathetic dominance (Kreher and Schwartz, 2012). Persistent resting HR elevation over 2+ weeks is the early warning signal.

OVERCLAIM THE GAP

Exercise is marketed as producing an immediate energy boost.

▶ **The Energy Span benefit is a trajectory outcome over weeks of sustained physiological adaptation. No proprietary modality has demonstrated a mitochondrial advantage over standard moderate-to-vigorous exercise.**

SYSTEMS SIGNAL

SYS 1 | SYS 3 | SYS 5 | SYS 6 | SYS 7

The most multi-dimensional intervention in this landscape: simultaneously improves mitochondrial quality (Sys 1), autonomic recovery and HRV (Sys 3), sleep architecture (Sys 5), insulin sensitivity via GLUT4 translocation (Sys 6), and HPA axis reactivity (Sys 7).

HOW TO USE IT

- 150–300 min/week moderate intensity (RPE 4–6/10) + 2–3 resistance sessions/week — the dose with the strongest RCT support (Bull et al., 2020).
- Deconditioned or older adults: start at 75–100 min/week and progress. Even 15 min/day produces VO_2max gains in previously sedentary older adults (Huang et al., 2005).

02 Creatine Monohydrate Supplementation

◆ SUPPLEMENT · EVIDENCE STRONG

WHAT IT IS

Creatine monohydrate at 3–5 g/day taken with food, combined with resistance training to maximise physical performance benefits.

MECHANISM

Increases intramuscular phosphocreatine (PCr) stores by 20–40% (over 3–4 weeks at 3–5 g/day, or 5–7 days with a loading dose of ~20 g/day), enabling rapid ATP regeneration via the creatine kinase shuttle during high-intensity effort. Brain uptake is constrained by blood-brain barrier transport via the SLC6A8 creatine transporter, which appears to operate near saturation at typical dietary intake. Standard supplementation produces small or inconsistent increases in brain PCr in rested, well-nourished adults; however, high acute doses (~0.35 g/kg) under metabolic stress such as sleep deprivation have been shown in small trials to measurably raise cerebral PCr and improve cognitive performance (Gordji-Nejad et al., 2024; McMorris et al., 2024).

EVIDENCE

+11.3 kg
LOWER-BODY 1RM vs PLACEBO

23 RCTs
STRENGTH META-ANALYSIS

STRONG for physical performance. Wang et al. (2024) meta-analysed 23 RCTs in adults under 50 (predominantly male): upper-body strength increased WMD 4.43 kg ($p < 0.001$) and lower-body WMD 11.35 kg ($p < 0.001$) versus placebo. Chilibeck et al. (2017) meta-analysed 22 RCTs (n=721) in older adults, showing creatine plus resistance training increased lean tissue mass by 1.37 kg and improved upper- and lower-body strength versus resistance training alone. The ISSN endorses creatine monohydrate as the most effective legal ergogenic supplement (Kreider et al., 2017; Antonio et al., 2025). LIMITED but promising for cognitive function. Evidence is heterogeneous overall but converging toward context-dependent benefits. Gordji-Nejad et al. (2024, Scientific Reports) demonstrated via ^{31}P-MRS that a single high dose (0.35 g/kg) raised brain phosphocreatine and improved processing speed, memory, and subjective fatigue during 21-hour sleep deprivation. Stronger signals also appear in older adults and in those with low baseline creatine intake (vegetarians, vegans). EFSA's 2024 health claim review nonetheless concluded that a cause-and-effect relationship in the general healthy adult population has not yet been established at typical doses (EFSA NDA Panel, 2024). The current best characterization is a real but conditional signal — most evident under metabolic stress, in older adults, or where baseline status is low.

VALIDITY

Physical outcomes (1RM, lean mass via DEXA) are well validated. Cognitive outcomes rely on heterogeneous neuropsychological batteries across small samples; most trials do not measure brain PCr directly.

UTILITY

Physically active adults, older adults with declining muscle mass, and those with lower dietary creatine intake (vegetarians, vegans). Strength gains emerge within 4–8 weeks of creatine plus resistance training at 3–5 g/day.

⚠ FAILURE MODES

- Does not address general daily fatigue — mechanism operates under high metabolic demand, not chronic tiredness.
- Alternative forms (HCl, ethyl ester, buffered) show no superiority over monohydrate and cost substantially more (Kreider et al., 2017).

OVERCLAIM THE GAP

Marketed sometimes as a general 'brain fuel' producing reliable cognitive enhancement in healthy adults at standard 3–5 g/day doses.

- **EFSA declined to authorize a population-level cognitive health claim in 2024 based on the submitted evidence. The best-supported cognitive benefits are conditional — under sleep deprivation (at higher acute doses), in older adults, or where baseline creatine is low — rather than a routine cognitive enhancement effect in well-rested young adults at typical doses.**

SYSTEMS SIGNAL

SYS 1 SYS 2

Bioenergetics (direct — PCr buffer during high-intensity effort — Sys 1); neuroenergetics (context-dependent — measurable cerebral PCr and cognitive effects under sleep deprivation or in low-baseline populations — Sys 2).

HOW TO USE IT

- 3–5 g monohydrate daily, any time. Combine with resistance training — creatine without training produces substantially smaller gains (Kreider et al., 2017).
- For cognitive benefits in specific contexts (sleep deprivation, demanding cognitive load), early evidence suggests higher acute doses may be required — Gordji-Nejad et al. (2024) used 0.35 g/kg (~20–25 g for most adults); the optimal protocol for sustained use has not yet been established.
- Choose Creapure-sourced or NSF Certified for Sport products.

DIMENSION 2 OF SIX

Neuroenergetics & Cognitive Performance

The brain consumes 20 percent of resting energy while representing 2 percent of body mass (Raichle and Gusnard, 2002). Mental fatigue is a biological state — the accumulation of adenosine and

glutamate under sustained cognitive demand — not a failure of motivation (Reichert et al., 2022; Wiehler et al., 2022).

03 Strategic Caffeine Timing

BEHAVIORAL • EVIDENCE STRONG

WHAT IT IS

Caffeine (≤400 mg/day) timed to maximise alertness while enforcing a hard curfew of at least 6 hours before bedtime to protect sleep architecture.

MECHANISM

Competitive antagonism at adenosine A_1 and A_2A receptors, disinhibiting dopaminergic and noradrenergic neurotransmission and reducing perceived fatigue (McLellan, Caldwell and Lieberman, 2016). With a plasma half-life of 5–6 hours, late intake directly suppresses slow-wave sleep even when users feel subjectively unaffected (Drake et al., 2013).

EVIDENCE

≤ 400 mg
DAILY INTAKE CEILING

6 hr
EVENING CURFEW BEFORE SLEEP

STRONG for acute alertness. McLellan, Caldwell and Lieberman (2016), reviewing hundreds of controlled studies, confirmed 40–300 mg reliably improves alertness, vigilance, and reaction time. No RCT evidence for the 90-minute delay protocol. Antonio et al. (2024, ISSN) explicitly evaluated this claim and concluded it is unsupported: habitual consumers develop cortisol tolerance minimising CAR interaction, and adenosine clears during sleep, not progressively after waking. The curfew is evidence-based: Drake et al. (2013) demonstrated 400 mg at 6 hours before bed significantly disrupted sleep ($p < 0.05$), reducing total sleep time by over one hour without users detecting the effect.

VALIDITY

PVT reaction time is the gold-standard alertness outcome, consistently responsive across populations. Key limit: CYP1A2 metaboliser variation meaningfully affects caffeine half-life — rarely controlled in general recommendations (Cornelis et al., 2006).

UTILITY

All habitual consumers. The highest-value change is enforcing the evening curfew, not adjusting morning timing. Sleep quality improvement is detectable within 5–10 nights.

⚠ FAILURE MODES

- Doses above 400 mg/day increase anxiety and may impair rather than enhance performance — dose-response is not linear beyond this threshold (McLellan, Caldwell and Lieberman, 2016).
- Caffeine masks adenosine signalling without resolving the underlying sleep debt. Pregnancy: limit to <200 mg/day per ACOG guidance (ACOG, 2010).

OVERCLAIM THE GAP

'Delay caffeine 90 minutes after waking to protect your cortisol awakening response'

▶ **a mechanistically plausible hypothesis that has never been tested in a single RCT. The evidence-based priority is the evening curfew, not morning delay timing.**

SYSTEMS SIGNAL

SYS 3 | SYS 4 | SYS 5

Sleep (most consequential — late caffeine disrupts slow-wave architecture without subjective detection — Sys 5); circadian/endocrine (mild HPA activation — Sys 4); autonomic (modest sympathetic stimulation at high doses — Sys 3).

HOW TO USE IT

- ≤400 mg/day. Hard curfew: no caffeine within 6 hours of target sleep time (Drake et al., 2013).
- For anxiety-prone users: 200 mg caffeine + 200 mg L-theanine attenuates jitteriness without reducing alertness benefit (Haskell et al., 2008).

04 Structured Work-Rest Cycles / Cognitive Recovery Breaks

◐ BEHAVIORAL / DEVICE · EVIDENCE MODERATE

WHAT IT IS

Deliberate alternation between focused cognitive work blocks (typically 60–90 minutes) and short recovery intervals (5–15 minutes), repeated across the day to preserve sustained mental performance and reduce cognitive fatigue accumulation.

MECHANISM

Sustained cognitively demanding work progressively increases local metabolic strain in frontoparietal control networks, with accumulation of glutamate and adenosine linked to mental fatigue signals (Wiehler et al., 2022). Periodic disengagement restores attentional control, reduces error rates, and preserves executive performance.

EVIDENCE

60–90 min
FOCUS BLOCK LENGTH

5–15 min
RECOVERY INTERVAL

MODERATE. Experimental literature consistently shows declining vigilance, increased error rates, and slower reaction times during prolonged continuous cognitive effort, partially mitigated by structured breaks and task switching (Boksem and Tops, 2008; Lim and Dinges, 2010). Precise optimal timing varies by task and individual.

VALIDITY

Psychomotor Vigilance Task (PVT), reaction time, error rates, and subjective fatigue scales are validated outcomes. Real-world knowledge work performance is harder to standardize.

UTILITY

High-value for knowledge workers, students, clinicians, executives, and anyone performing prolonged mentally demanding tasks. Benefits often detectable the same day.

⚠ FAILURE MODES

- Breaks filled with additional cognitively taxing screen activity may not restore attention.
- Excessively frequent interruptions impair deep work and task continuity.

OVERCLAIM THE GAP

"Productivity hacks"

- **often market one ideal interval (e.g., Pomodoro) as universally optimal. Evidence supports periodic recovery, not a single magic schedule.**

SYSTEMS SIGNAL

SYS 2 | SYS 5 | SYS 7

Neuroenergetics (Sys 2 direct); stress load (Sys 7 via reduced cognitive strain); sleep (Sys 5 indirectly when late-night compensatory work is reduced).

HOW TO USE IT

- Use 60–90 min focused work blocks followed by 5–15 min movement, daylight, hydration, or non-screen recovery.
- During high fatigue periods, shorten blocks to 45–60 min.
- Track afternoon error rate, irritability, or attention drift as personal signals.

DIMENSION 3 OF SIX

Autonomic Balance & Recovery

The autonomic nervous system governs the transition between effort and recovery. Fatigue often reflects failed recovery rather than insufficient effort — and HRV is the most accessible window into that balance (Thayer et al., 2012; Csathó et al., 2024).

05

Paced Breathing and HRV Biofeedback

BEHAVIORAL / DEVICE · EVIDENCE MODERATE

WHAT IT IS

Slow, rhythmic breathing at approximately 6 breaths per minute, optionally guided by real-time HRV feedback from a validated sensor, practised for 10–20 minutes daily.

MECHANISM

Breathing at ~0.1 Hz stimulates arterial baroreceptors at their cardiovascular resonance frequency, amplifying beat-to-beat heart rate oscillations 4–10 times above baseline and progressively strengthening baroreflex gain and vagal efferent tone via the nucleus tractus solitarius (Lehrer and Gevirtz, 2014). HRV biofeedback devices reinforce resonance-frequency breathing in real time.

EVIDENCE

g = 0.83
STRESS / ANXIETY EFFECT

24 studies
N = 484 META-ANALYSED

MODERATE. Goessl, Curtiss and Hofmann (2017) meta-analysed 24 studies (N = 484): between-group Hedges' g = 0.83 for stress and anxiety reduction. Key limitations: most RCTs lack adequate sham controls; sustained resting HRV improvements in healthy adults are less consistently demonstrated than during-session increases inflated by the breathing protocol itself (Lehrer et al., 2020). Methodological heterogeneity limits generalisability.

VALIDITY

RMSSD and HF-HRV are the most valid autonomic outcome measures (Shaffer and Ginsberg, 2017) . Critical limit: HRV recorded during slow breathing is inflated by respiratory artefact - the meaningful outcome is resting HRV change post-training, which is harder to demonstrate and less consistently reported.

UTILITY

Adults with chronically low resting HRV, high-stress occupations, or poor recovery from training. Acute calming within 5–10 minutes of a session; sustained resting HRV improvements at 4–8 weeks of daily practice.

⚠ FAILURE MODES

- Monitoring HRV without acting on it confers no benefit — measurement is not intervention.
- 'Coherence scores' (HeartMath, similar apps) measure breathing compliance, not independent clinical biomarkers (Lehrer and Gevirtz, 2014).

OVERCLAIM THE GAP

Consumer apps market readiness and coherence scores as independent health biomarkers.

- **These are proprietary algorithmic composites — directionally useful over weeks, not diagnostic measures of autonomic health (de Zambotti et al., 2019).**

SYSTEMS SIGNAL

SYS 2 | SYS 5 | SYS 7

Stress reactivity (Sys 7 — direct); sleep via parasympathetic pre-sleep activation (Sys 5); neuroenergetics via vagal afferent projections to prefrontal cortex (Sys 2) (Lehrer and Gevirtz, 2014).

HOW TO USE IT

- 10–20 min daily at ~6 breaths/min — free, no device required. This is the evidence-based core (Lehrer and Gevirtz, 2014).
- Device guidance: Polar H10 + Elite HRV (gold-standard beat-to-beat accuracy); HeartMath Inner Balance (validated resonance-frequency biofeedback); Oura Ring Gen 3 (reliable for nocturnal HRV trend tracking only); Apple Watch (insufficient sampling frequency for systematic HRV work).

06 Consumer Vagus Nerve Stimulation Wearables

■ DEVICE • EVIDENCE LIMITED

WHAT IT IS

Wrist-worn or chest-applied consumer devices marketed as vagus nerve stimulators, delivering vibrotactile or low-current electrical stimulation at consumer-grade parameters.

MECHANISM

Clinical taVNS delivers electrical stimulation to the auricular branch of the vagus nerve at the cymba conchae, modulating the nucleus tractus solitarius and downstream autonomic pathways (Gerber et al., 2024). Consumer devices diverge fundamentally: Apollo Neuro delivers vibrotactile wrist stimulation — activating cutaneous mechanoreceptors, not vagal afferents. Pulsetto applies cervical transcutaneous stimulation at unvalidated parameters. None stimulate confirmed vagal afferent targets at clinically validated parameters.

EVIDENCE

LIMITED. The clinical taVNS literature comprises 109 studies (N = 3,231) across 21 populations — genuine neuromodulation evidence that must not be extrapolated to consumer wrist and chest devices (Gerber et al., 2024). Apollo Neuro's primary evidence consists of studies (N = 22–40) conducted by the device's co-founders with manufacturer funding — high bias risk per GRADE standards (Lundh et al., 2017). No adequately powered independent RCT demonstrates sustained autonomic improvement for any consumer VNS device.

VALIDITY

2–3 minute HRV windows are insufficient to demonstrate clinically meaningful autonomic remodelling (Shaffer and Ginsberg, 2017). Self-report outcomes are highly susceptible to placebo from wearing a vibrating device.

UTILITY

Tactile relaxation cue at best. Paced breathing at ~6 breaths/min achieves better-documented vagal tone changes at zero cost (Lehrer and Gevirtz, 2014). This is not a priority purchase on current evidence.

⚠ **FAILURE MODES**

- Clinical taVNS evidence is routinely cited to imply consumer device equivalence — the delivery mechanisms are entirely different (Gerber et al., 2024).
- ⚠ Primary Apollo Neuro evidence is manufacturer-funded and co-founder-authored — explicit high bias risk per GRADE standards (Lundh et al., 2017).

OVERCLAIM THE GAP

Apollo Neuro markets itself as a 'vagus nerve stimulator' while delivering vibrotactile wrist stimulation that does not contact the vagus nerve. 'Scientifically validated' is claimed from small, short-duration, manufacturer-funded studies.

▶ **This is the clearest mechanism-to-marketing extrapolation in this landscape.**

SYSTEMS SIGNAL

SYS 5 SYS 7

Stress reactivity (Sys 7) and sleep (Sys 5) — both proposed, neither established in adequately powered independent trials.

HOW TO USE IT

- If already owned: may serve as a relaxation anchor for some users — do not expect clinical-grade autonomic remodelling.
- Default: paced breathing (Card 5) achieves better-documented vagal effects at zero cost. Behavioural approaches — slow exhalation, humming, cold face immersion — carry more biological plausibility and require no purchase (Lehrer and Gevirtz, 2014).

DIMENSION 4 OF SIX

Sleep & Circadian Alignment

Sleep is not simply restorative — it is regulatory. Circadian misalignment disrupts every other dimension simultaneously, producing fatigue that does not resolve with a single night of rest (Potter et al., 2016; Chai et al., 2020).

07

Morning Bright-Light Exposure and Circadian Anchoring

BEHAVIORAL / DEVICE · EVIDENCE STRONG

WHAT IT IS

Morning bright-light exposure (≥2,500 lux, optimally 10,000 lux) within 30–60 minutes of waking, combined with a fixed wake time maintained ±30 minutes across 7 days.

MECHANISM

Morning bright light activates melanopsin in intrinsically photosensitive retinal ganglion cells (ipRGCs), projecting via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), phase-advancing the central circadian clock, suppressing melatonin, and augmenting the cortisol awakening response (Czeisler and Gooley, 2007). Consistent wake timing is independently the most potent circadian anchor - more powerful than any device (Roenneberg et al., 2012).

EVIDENCE

10,000 lux
SAD LAMP STANDARD

1–3 days
PHASE SHIFT ONSET

STRONG for SAD and circadian rhythm sleep disorders (AASM practice parameters endorsed). Van Maanen et al. (2016) meta-analysed 53 studies (N = 1,154): light therapy effective for sleep problems overall (g = 0.39) and circadian disorders (g = 0.41). MODERATE for healthy adults — acute alerting effects are physiologically established; large RCTs in non-clinical populations are fewer. Blue-blocking glasses: no meaningful benefit. Singh et al. (2023, Cochrane, 17 RCTs) found no clinically meaningful difference for visual fatigue or sleep; screen blue light is ~1/1,000th of natural daylight.

VALIDITY

Dim-light melatonin onset (DLMO) is the gold-standard circadian phase marker. Key limit: few studies control for total daily light exposure — a major confounder that may inflate apparent effect sizes of light therapy.

UTILITY

Adults with delayed sleep phase, seasonal energy fluctuation, shift work, or jetlag. Acute alerting within 20–30 min; phase shift within 1–3 days. Outdoor morning light (10,000–100,000 lux) is the first-line, zero-cost approach.

⚠ **FAILURE MODES**

- Contraindicated in bipolar disorder — bright-light therapy may precipitate mania (Terman and Terman, 2005). Clinician consultation required.
- Social jetlag (sleeping >1 hour later at weekends) undermines any weekday circadian anchoring protocol (Roenneberg et al., 2012).

OVERCLAIM THE GAP

'Blue-blocking glasses improve sleep'

▶ **directly contradicted by Singh et al. (2023, 17 RCTs). The most impactful evening change is reducing screen use, not the glasses worn while using screens.**

SYSTEMS SIGNAL

SYS 2 | SYS 3 | SYS 5 | SYS 6

Sleep architecture (Sys 5); circadian insulin sensitivity rhythms (Sys 6); autonomic HRV modulation (Sys 3); ascending arousal system activation and alertness (Sys 2).

HOW TO USE IT

- Fix wake time ±30 min, 7 days/week. Within 30–60 min of waking: 10–20 min outdoors or 20–30 min at a 10,000-lux SAD lamp (e.g. Carex Day-Light Classic) — strongest device evidence (van Maanen et al., 2016).
- Evening: dim overhead lighting 90 min before bed. f.lux or Apple Night Shift are sufficient. Blue-blocking glasses are not recommended on current evidence.

08 Sleep Extension and Sleep Hygiene

BEHAVIORAL · EVIDENCE STRONG

WHAT IT IS

Extending nightly sleep to ≥7 hours through earlier bedtimes, consistent wake timing, and a caffeine curfew, supported by evidence-based sleep hygiene practices.

MECHANISM

Adequate sleep enables adenosine clearance, glymphatic metabolite removal, synaptic homeostasis, and HPA axis normalisation (Xie et al., 2013). Individuals chronically sleeping 6 hours perform as poorly on objective tests as those acutely sleep-deprived for 24 hours while reporting only mild sleepiness (Van Dongen et al., 2003).

EVIDENCE

≥ 7 hr
AASM / SRS MINIMUM

9 domains
SYSTEMATIC REVIEW BASE

STRONG for duration. Watson et al. (2015) AASM/SRS consensus, from systematic review across nine health outcome categories, recommends ≥7 hours/night. Sleeping ≤6 hours associates with obesity, diabetes, and all-cause mortality (Cappuccio et al., 2010; N = 1,382,999). MODERATE for sleep extension; LIMITED for sleep hygiene as monotherapy (Irish et al., 2015).

VALIDITY

Actigraphy and sleep diary (SOL, WASO, TST) are validated outcomes. Self-reported TST overestimates by ~30 minutes. PVT reaction time is the gold-standard objective performance marker (Dinges et al., 1997).

UTILITY

All adults, especially habitual short sleepers. Performance benefits within 2–3 recovery nights; insulin sensitivity improves within ~2 weeks (Saner et al., 2021) .

⚠ FAILURE MODES

- Sleep hygiene alone cannot treat clinical insomnia — refer to CBT-I (Card 9).
- Napping partially restores alertness but not the hormonal and metabolic deficits from chronic restriction (Faraut et al., 2011).

OVERCLAIM THE GAP

'8 hours is optimal for everyone'

▶ **AASM recommends ≥7 hours minimum; individual need varies. No supplement or device protocol substitutes for duration.**

SYSTEMS SIGNAL

SYS 1 | SYS 2 | SYS 3 | SYS 4 | SYS 6 | SYS 7

The most cross-dimensional card: mitochondrial repair (Sys 1), adenosine clearance and cognitive restoration (Sys 2), sympathovagal normalisation (Sys 3), cortisol and melatonin rhythm restitution (Sys 4), insulin sensitivity (Sys 6), allostatic load reduction (Sys 7).

HOW TO USE IT

- Target ≥7 hours/night. Consistent wake time ±30 min, 7 days/week — the most evidence-based single hygiene behaviour (Irish et al., 2015).
- Hard curfew: no caffeine within 6 hours of bed; no alcohol within 3 hours (Ebrahim et al., 2013).

09 CBT-I for Chronic Insomnia

✚ MEDICAL / RX · EVIDENCE STRONG

WHAT IT IS

A structured psychological treatment for chronic insomnia delivered in 6–8 sessions, comprising sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relaxation training.

MECHANISM

Targets the perpetuating factors of chronic insomnia — cognitive hyperarousal and conditioned wakefulness — rather than sedating the patient. Sleep restriction consolidates sleep drive; stimulus control re-associates bed with sleep; cognitive restructuring addresses dysfunctional beliefs (Morin et al., 2006).

EVIDENCE

70%
RESPONSE RATE

−26 min
WAKE AFTER SLEEP ONSET

STRONG — one of the most robustly evidenced interventions in sleep medicine. Trauer et al. (2015) meta-analysed 20 RCTs (N = 1,162): SOL improved −19 min, WASO −26 min, sleep efficiency +9.9 percentage points — gains maintained at follow-up. ACP: strong recommendation as first-line treatment (Qaseem et al., 2016). AASM: strong recommendation based on 66 RCTs (Edinger et al., 2021). NICE endorsed Sleepio (MTG70, 2022). CBT-I produces outcomes comparable to hypnotics acutely with superior durability. Treatment response rate up to 70% (Trauer et al., 2015).

VALIDITY

ISI and PSQI are validated clinical scales. Sleep diary (SOL, WASO, TST, efficiency) is the gold-standard monitoring tool — more diagnostically useful than consumer wearable scores for insomnia. Key limit: TST improvement is modest (+7.6 min); gains are primarily in sleep efficiency and daytime function.

UTILITY

Adults with chronic insomnia disorder (≥3 nights/week for ≥3 months). Digital: Sleepio (NICE-recommended, FDA-cleared 2024); Somryst (FDA-authorised). Meaningful improvement typically by weeks 4–6 after an initial worsening during sleep restriction.

⚠ FAILURE MODES

- Sleep restriction temporarily worsens daytime fatigue — the most common reason for early dropout before benefit is reached.
- CBT-I is routinely bypassed for supplements and wearables; none approach its effect size or durability (Trauer et al., 2015).

OVERCLAIM THE GAP

'CBT-I is just sleep hygiene.'

▶ **Sleep hygiene is the least active component; sleep restriction and stimulus control drive efficacy. Supplement blends marketed for insomnia have no RCT evidence at the blend level.**

SYSTEMS SIGNAL

SYS 2 | SYS 3 | SYS 4 | SYS 7

Autonomic regulation (sympathovagal normalisation — Sys 3); circadian/endocrine (sleep schedule alignment — Sys 4); neuroenergetics (adenosine clearance and memory consolidation — Sys 2); stress (directly addresses cognitive hyperarousal — Sys 7).

HOW TO USE IT

- First-line before any pharmacotherapy for chronic insomnia (Qaseem et al., 2016).
- Digital delivery: Sleepio (NICE-endorsed, FDA-cleared) is the most accessible evidence-based entry point.
- Track ISI at weeks 0, 4, and 8. If no improvement by week 8, reassess for OSA or periodic limb movement disorder.

DIMENSION 5 OF SIX

Nutrition, Metabolic Stability & Body Composition

Energy stability depends on what fuels are available and how efficiently they are used. Glycaemic variability, substrate availability, and micronutrient sufficiency each constrain Energy Span in ways that are measurable, correctable, and frequently missed (Benton and Owens, 1993; Goodpaster and Sparks, 2017).

10

Low-Glycaemic Diet and Protein-Anchored Meals

● BEHAVIORAL · EVIDENCE MODERATE

WHAT IT IS

Meals structured around low-glycaemic-index carbohydrates and 25–35 g of protein per eating occasion, to reduce postprandial glucose excursions and attenuate post-meal energy dips.

MECHANISM

Low-GI foods slow carbohydrate digestion, attenuating postprandial glucose excursions. Protein co-ingestion amplifies this via GLP-1 secretion from intestinal L-cells and delayed gastric emptying, collectively reducing glucose AUC substantially (Wolever et al., 2024).

EVIDENCE

25–35 g
DAILY FIBER TARGET

Pattern
NOT INDIVIDUAL FOODS

MODERATE for glycaemic control. Wolever et al. (2024) meta-analysed 154 trial comparisons: dairy and plant protein co-ingestion reduced postprandial glucose AUC by 52–55% in non-diabetic adults ($p < 0.05$). ICQC consensus endorses low-GI/GL diets for metabolic disease risk reduction (Augustin et al., 2015). LIMITED for subjective energy in healthy adults — most fatigue evidence derives from diabetic populations; the link between normoglycaemic variability and perceived energy is inadequately tested in healthy individuals.

VALIDITY

Postprandial glucose AUC and GI/GL are well-validated dietary metrics (ISO 26642). CGM sensor accuracy in the normoglycaemic range (70–120 mg/dL) is weaker — small absolute differences may fall within sensor error (Hengist et al., 2024).

UTILITY

Adults experiencing frequent post-meal energy crashes, prediabetes, or metabolic syndrome. Post-meal energy changes detectable within days of dietary modification.

⚠ FAILURE MODES

- Real-world GI responses are highly variable depending on preparation, ripeness, and co-ingestion context (Augustin et al., 2015).
- CGM readings in the normoglycaemic range may be within sensor noise — small values should not drive rigid dietary decisions (Hengist et al., 2024).

OVERCLAIM THE GAP

'CGM will reveal your personal glucose responses and optimize your energy'

▶ **in normoglycaemic adults, measured excursions may fall within sensor error, and the link between these excursions and subjective energy is unproven. CGM is best positioned as a 2-week observational tool, not a permanent monitoring behaviour.**

SYSTEMS SIGNAL

SYS 2 | SYS 4 | SYS 5

Sleep (late high-GI meals impair architecture — Sys 5); circadian insulin sensitivity rhythms (Sys 4) (Saad et al., 2012); neuroenergetics (extreme variability may impair cognition; routine excursions in healthy adults probably do not — Sys 2).

HOW TO USE IT

- Anchor every meal with 25–35 g protein — the most evidence-supported single dietary change for post-meal energy stability (Wolever et al., 2024).
- Use Dexcom Stelo (OTC, FDA-cleared 2024, ~$89/2wk) to identify personal trigger meals — then modify diet; do not continue indefinite monitoring.
- Self-rate post-meal energy (1–10 at 90 min) as a free proxy before purchasing a CGM.

11 Mediterranean / High-Fiber Whole-Food Dietary Pattern

BEHAVIORAL · EVIDENCE STRONG

WHAT IT IS

A dietary pattern emphasizing vegetables, legumes, fruit, whole grains, nuts, olive oil, seafood, fermented foods, and minimally processed protein sources, with high total fiber intake and low ultra-processed food exposure.

MECHANISM

Improves glycaemic stability, insulin sensitivity, micronutrient sufficiency, endothelial function, and gut-derived short-chain fatty acid production. Collectively these support mitochondrial function, metabolic flexibility, and lower inflammatory burden.

EVIDENCE

−52 to −55%
POSTPRANDIAL GLUCOSE AUC

p < 0.001
PROTEIN CO-INGESTION (n = 154)

STRONG for cardiometabolic risk reduction and chronic disease prevention (Estruch et al., 2018; Martínez-González et al., 2019). MODERATE for energy-related outcomes through improved metabolic stability, reduced postprandial crashes, and better long-term vitality, though fatigue is rarely the primary endpoint.

VALIDITY

Diet quality indices, HbA1c, triglycerides, waist circumference, inflammatory markers, and longitudinal event outcomes are validated metrics. Self-reported intake remains imperfect.

UTILITY

Broadly applicable population-level intervention with particularly high utility in metabolic syndrome, overweight, poor diet quality, and fluctuating daytime energy.

⚠ **FAILURE MODES**

- "Mediterranean" branding can mask calorie-dense processed foods.
- Benefits depend on sustained pattern quality, not isolated ingredients.

OVERCLAIM THE GAP

Single "superfoods," powders, or microbiome products are often marketed as substitutes for dietary pattern quality.

▶ **No supplement replicates a whole-pattern effect.**

SYSTEMS SIGNAL

SYS 1 | SYS 2 | SYS 6 | SYS 7

Metabolic stability (Sys 6 direct); bioenergetics (Sys 1); inflammation/stress load (Sys 7); neuroenergetics via glycaemic steadiness (Sys 2).

HOW TO USE IT

- Target ≥25–35 g fiber/day.
- Anchor meals around plants + protein + healthy fats.
- Replace ultra-processed snacks with nuts, yogurt, legumes, fruit.
- Think pattern, not perfection.

12 Iron Deficiency Screening and Correction

✚ MEDICAL / RX · EVIDENCE STRONG

WHAT IT IS

Clinician-ordered ferritin and CBC testing in symptomatic adults, followed by oral iron supplementation if iron deficiency (with or without anaemia) is confirmed.

MECHANISM

Iron is an essential cofactor for mitochondrial ETC complexes (iron-sulfur clusters in Complexes I-III; cytochrome c oxidase in Complex IV), oxygen transport via haemoglobin, and tyrosine hydroxylase — the rate-limiting enzyme for dopamine synthesis (Beard, 2001). Depletion impairs cellular energy production and neurotransmitter synthesis before anaemia manifests, making iron deficiency one of the most commonly missed reversible causes of fatigue.

EVIDENCE

SMD −0.38
FATIGUE (IRON-DEFICIENT NON-ANAEMIC)

< 30 ng/mL
FERRITIN THRESHOLD

STRONG for iron-deficient non-anaemic (IDNA) adults with fatigue. Houston et al. (2018) systematically reviewed 18 RCTs (N = 1,170): iron supplementation significantly reduced fatigue (SMD −0.38; 95% CI −0.52 to −0.23; I^2 = 0%) but did not improve VO_2max (SMD 0.11, NS). Vaucher et al. (2012, CMAJ): 198 non-anaemic women with ferritin <50 µg/L showed significant fatigue improvement at 12 weeks. Evidence is specific to iron-deficient populations; no benefit in iron-replete individuals.

VALIDITY

Serum ferritin is the most sensitive iron stores marker but is an acute-phase reactant — interpret alongside CRP. Threshold for IDNA: ferritin <30 ng/mL symptomatic, or <15 ng/mL regardless. A ferritin + CBC panel is low-cost and rules out one of the most common reversible causes of fatigue.

UTILITY

At-risk groups: premenopausal women, vegetarians and vegans, endurance athletes, frequent blood donors. Fatigue improvement with oral iron at 6–12 weeks (Houston et al., 2018).

⚠ FAILURE MODES

- Supplementing without confirmed deficiency carries overload risk, particularly in men and postmenopausal women; hereditary haemochromatosis affects 1 in 200–300 Northern Europeans (Bacon et al., 2011).
- Identifying deficiency without treating the underlying cause (menorrhagia, GI blood loss) leads to recurrence.

OVERCLAIM THE GAP

'Everyone who is tired should supplement.'

▶ **Iron benefits only confirmed deficient individuals. Supplementing without testing is potentially harmful. 'Iron tonic' and 'thyroid support' blends are often marketed without evidence and carry iodine overload risk in autoimmune thyroid disease.**

SYSTEMS SIGNAL

SYS 1 | SYS 2 | SYS 3 | SYS 5

Bioenergetics (iron-sulfur clusters essential for ETC — Sys 1); neuroenergetics (tyrosine hydroxylase is iron-dependent for dopamine synthesis — Sys 2); sleep (iron deficiency linked to restless legs syndrome — Sys 5) (Allen and Earley, 2001); autonomic regulation (compensatory tachycardia in deficiency — Sys 3).

HOW TO USE IT

- Test ferritin + CBC when fatigue is unexplained and clinical features are consistent — do not supplement without testing.
- If IDNA confirmed: oral ferrous sulfate 100–200 mg elemental iron daily; retest ferritin at 3 months (WHO, 2001).
- Identify and treat the underlying cause of deficiency to prevent recurrence.

13 GLP-1-Based Anti-Obesity Medications

✚ MEDICAL / RX • EVIDENCE STRONG

WHAT IT IS

Injectable or oral GLP-1 receptor agonists (semaglutide, tirzepatide) prescribed for weight management in adults with obesity or metabolic disease, administered weekly at clinician-titrated doses.

MECHANISM

GLP-1 receptor agonists (semaglutide, tirzepatide, liraglutide) act on receptors in the gut, pancreas, and CNS: slowing gastric emptying, stimulating glucose-dependent insulin secretion, and suppressing reward-driven food-seeking via hypothalamic and nucleus accumbens signalling (Müller et al., 2019). Their relationship to Energy Span is conditional: by improving glycaemic stability (Sys 6), reducing obesity-associated inflammation (Sys 7), and reducing metabolic burden on mitochondrial function (Sys 1), GLP-1 agonists may improve the conditions that constrain Energy Span - but will initially worsen subjective

energy in individuals who do not actively protect muscle mass, protein intake, hydration, and physical activity during treatment.

EVIDENCE

−14.9%
BODY WEIGHT vs −2.4% PLACEBO

STEP 1
N = 1,961 RCT

STRONG for weight reduction and glycaemic control in obesity and T2DM. Wilding et al. (2021, STEP 1, N = 1,961): semaglutide 2.4 mg reduced body weight 14.9% versus 2.4% placebo ($p < 0.001$). Jastreboff et al. (2022, SURMOUNT-1, N = 2,539): tirzepatide achieved up to 22.5% weight reduction — the largest pharmacological weight loss demonstrated to date. Neither trial measured any direct Energy Span dimension as a primary endpoint. LIMITED for Energy Span specifically - patient-reported energy improvements exist as secondary outcomes but are confounded by psychological effects of weight loss and have not been disaggregated by whether protective co-interventions were maintained.

VALIDITY

Weight loss, HbA1c, and fasting glucose are well-validated trial outcomes but are proxies for Energy Span, not direct measures of it; patient-reported fatigue improvements are confounded by the psychological effects of weight loss and are not disaggregated by whether protective co-interventions were maintained.

UTILITY

Most relevant for adults with obesity, metabolic syndrome, or T2DM where downstream Energy Span constraints are demonstrably present. The Energy Span benefit is conditional on actively maintaining resistance training, adequate protein intake (≥1.2 g/kg/day), hydration, and physical activity throughout treatment - without these, subjective energy is likely to worsen before it improves. Not supported for metabolically healthy individuals seeking an energy intervention.

⚠ FAILURE MODES

- 25–40% of weight lost can be lean tissue without resistance training and adequate protein - directly worsening Sys 1 bioenergetic capacity (Rubino et al., 2022).
- Early nausea, reduced intake, and dehydration can acutely worsen subjective energy in weeks 1–12; the subjective energy trajectory is frequently U-shaped before metabolic benefits compound.

OVERCLAIM THE GAP

Marketed as metabolic reset tools and energy optimizers for non-obese individuals - trial evidence is entirely in overweight, obese, or T2DM populations; no evidence supports use for Energy Span improvement in metabolically healthy adults.

SYSTEMS SIGNAL

SYS 1 | SYS 2 | SYS 6 | SYS 7

Glucose stability (Sys 6 - direct); bioenergetics (Sys 1 - potentially bidirectional: fat mass reduction improves mitochondrial efficiency, lean mass loss worsens it); allostatic load (Sys 7); neuroenergetics via food-reward pathway attenuation (Sys 2 - proposed, not directly measured).

HOW TO USE IT

- Indicated for BMI ≥30, or ≥27 with a weight-related comorbidity; requires prescribing clinician and monitoring.
- Mandatory co-interventions: resistance training 2–3×/week and ≥1.2 g/kg/day protein to limit lean mass loss; monitor fatigue trajectory and adjust dose titration pace accordingly.

14 Omega-3 Fatty Acid Supplementation

◆ SUPPLEMENT • EVIDENCE MODERATE

WHAT IT IS

EPA/DHA supplementation, typically fish oil or algae-derived omega-3 products, used to improve triglycerides and support inflammatory regulation where dietary intake is low.

MECHANISM

EPA and DHA incorporate into cell membranes, alter eicosanoid signaling, and may reduce pro-inflammatory mediator production while improving lipid metabolism.

EVIDENCE

MODERATE. Strong evidence for triglyceride lowering and selected cardiovascular contexts; mixed evidence for general fatigue, mood, or energy in healthy adults (Abdelhamid et al., 2020; Nicholls et al., 2020). Benefit is most plausible where baseline intake is low or inflammatory burden elevated.

VALIDITY

Triglycerides, omega-3 index, and cardiovascular endpoints are validated outcomes. “energy boost” claims are weakly supported.

UTILITY

Useful in individuals with low seafood intake, elevated triglycerides, or specific clinician-guided indications.

⚠ **FAILURE MODES**

- Low-dose underpowered products may deliver negligible benefit.
- Oxidized poor-quality oils reduce usefulness.
- Not a substitute for whole dietary improvement.

OVERCLAIM THE GAP

Often marketed as universal brain-energy or anti-fatigue support.

▶ **Evidence is population- and context-dependent.**

SYSTEMS SIGNAL

SYS 2 | SYS 6 | SYS 7

Inflammatory load (Sys 7 direct); metabolic health (Sys 6); neuroenergetics (Sys 2 possible but inconsistent).

HOW TO USE IT

- Prioritize fatty fish intake first.
- If supplementing, choose third-party tested EPA/DHA products.
- Use clinician guidance when treating hypertriglyceridemia.

DIMENSION 6 OF SIX

Stress Load, Hormonal Transitions & Environment

Chronic stress imposes a biological tax across every other dimension — elevating allostatic load, fragmenting recovery, and flattening the adaptive signals that all other interventions depend on. It is the

dimension most likely to make everything else underperform (McEwen, 1998; Juster, McEwen and Lupien, 2010).

15 MBSR and Structured Mindfulness

BEHAVIORAL • EVIDENCE MODERATE

WHAT IT IS

An 8-week structured mindfulness programme (~2.5 hours/week) combining body scan, seated meditation, and mindful movement, delivered in person or via a validated digital format.

MECHANISM

Strengthens top-down prefrontal cortex regulation of the stress response by modifying prefrontal-amygdala functional connectivity, reducing HPA axis reactivity and cortisol output (Creswell, 2017). Standard MBSR delivers ~2.5 hours/week for 8 weeks. The mechanism is well-characterised; evidence for energy and fatigue specifically as a primary outcome is limited.

EVIDENCE

ES 0.38
ANXIETY (ACTIVE-CONTROLLED)

47 RCTs
N = 3,515 META-ANALYSIS

MODERATE for stress and anxiety. Goyal et al. (2014, JAMA Internal Medicine) meta-analysed 47 RCTs (N = 3,515) with active controls: moderate evidence for anxiety (ES 0.38), depression (ES 0.30), and pain (ES 0.33). Critically: insufficient evidence for fatigue as a primary outcome, and no evidence that meditation outperformed exercise or pharmacotherapy. Khoury et al. (2015) found comparable effects in healthy populations (Hedges' g = 0.53, highly heterogeneous).

VALIDITY

PSS-10, DASS, and STAI are validated stress outcome measures. Salivary cortisol provides an objective marker. Key limits: blinding is impossible; against active controls (rather than waitlist), effect sizes shrink to d ~0.2–0.3 (Goyal et al., 2014). Structural brain change claims derive from cross-sectional studies — causation is not established.

UTILITY

Adults under chronic stress or burnout risk; those with anxiety-driven fatigue. PSS-10 improvement typically detectable at 4 weeks; benefits maintained at ~19-week follow-up (Khoury et al., 2015).

⚠ FAILURE MODES

- Requires a sustained 8-week commitment; dropout rates are significant and shorter programmes show substantially smaller effects (Parsons et al., 2017).
- App-based mindfulness (Calm, Headspace) has substantially weaker evidence than programme-delivered MBSR (Linardon and Fuller-Tyszkiewicz, 2020).

OVERCLAIM THE GAP

'MBSR rewires your brain'

- **effect sizes (~0.3) are meaningful but comparable to antidepressants for mild depression, not transformative (Cipriani et al., 2018). Structural brain change claims are based on cross-sectional studies and do not establish causation (Van Dam et al., 2018) .**

SYSTEMS SIGNAL

SYS 2 | SYS 3 | SYS 4 | SYS 5

Autonomic regulation (improved vagal tone — Sys 3) (Kok et al., 2013); circadian/endocrine (cortisol normalisation — Sys 4) (Turakitwanakan et al., 2013); sleep (indirect improvement via stress reduction — Sys 5); neuroenergetics (attention regulation may reduce cognitive fatigue accumulation — Sys 2).

HOW TO USE IT

- 8-week structured MBSR programme — in-person or Palouse Mindfulness (free, evidence-based online format).
- Track PSS-10 at weeks 0, 4, and 8 to quantify progress.
- App-based: Waking Up or Ten Percent Happier are better aligned to programme structure than ambient relaxation apps.

16 Perimenopause / Menopause Evaluation and Targeted Management

✚ MEDICAL / RX · EVIDENCE STRONG

WHAT IT IS

Clinical evaluation of fatigue, sleep disruption, mood change, thermoregulatory symptoms, and cognitive complaints during perimenopause or menopause, with individualized treatment that may include hormone therapy, sleep interventions, exercise, and metabolic support.

MECHANISM

Declining and fluctuating estrogen affects thermoregulation, sleep continuity, mood signaling, autonomic balance, body composition, and insulin sensitivity. These changes can materially constrain Energy Span.

EVIDENCE

STRONG for hormone therapy reducing vasomotor symptoms and improving sleep in appropriate candidates (NAMS, 2023; NICE Menopause Guideline). MODERATE for downstream improvements in daytime energy, cognition, and quality of life, though Energy Span itself is rarely directly measured.

VALIDITY

Validated symptom scales, sleep quality measures, hot flash frequency, body composition trends, and metabolic markers.

UTILITY

High utility for midlife women with new fatigue, fragmented sleep, mood shifts, exercise intolerance, or unexplained changes in body composition.

⚠ FAILURE MODES

- Symptoms normalized as “just aging” and left untreated.
- Direct-to-consumer hormone approaches without proper risk review.
- Ignoring exercise, sleep, and protein needs during transition.

OVERCLAIM THE GAP

Neither “everyone needs HRT” nor “no one should use hormones” reflects evidence.

▶ **Appropriate use is individualized risk-benefit medicine.**

SYSTEMS SIGNAL

SYS 2 | SYS 3 | SYS 4 | SYS 5 | SYS 6 | SYS 7

Sleep/circadian (Sys 4/5); metabolic stability/body composition (Sys 6); stress/autonomic regulation (Sys 3/7); neuroenergetics (Sys 2).

HOW TO USE IT

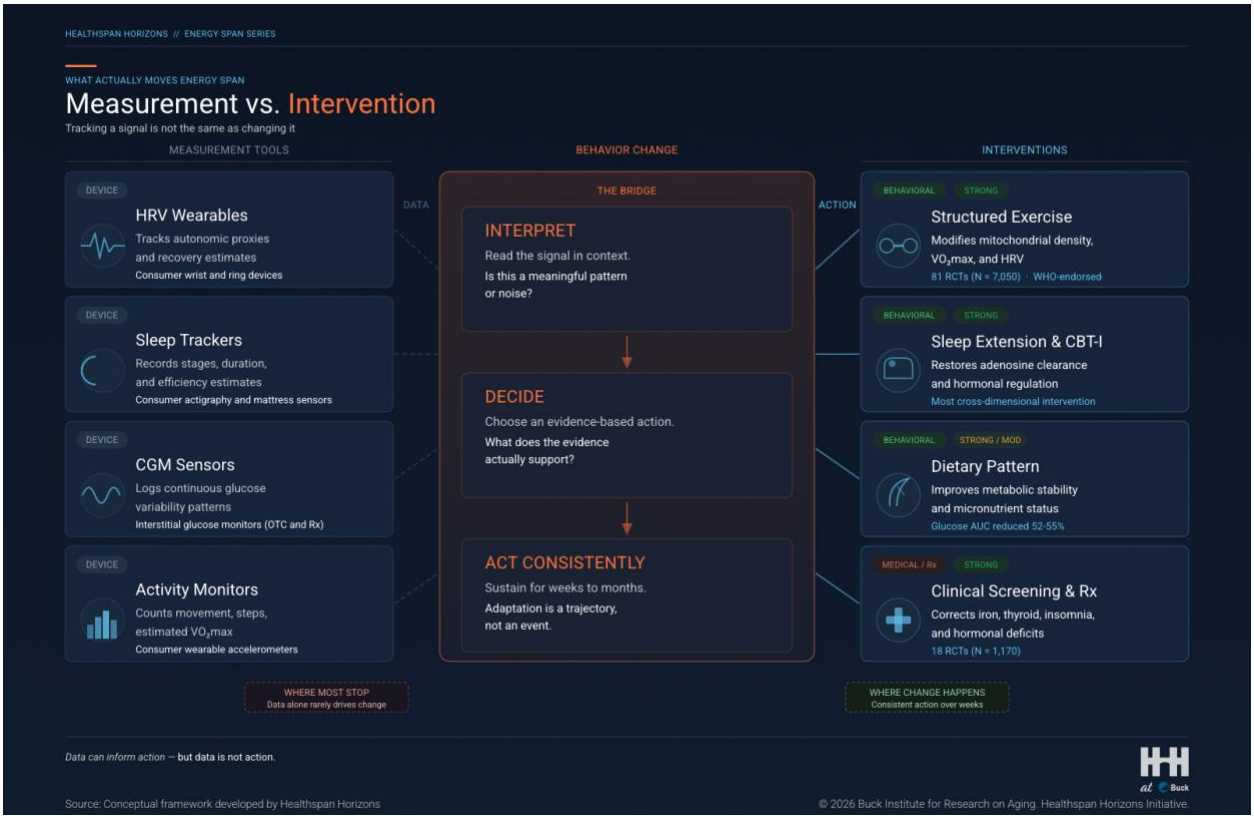
- Seek clinician evaluation when symptoms affect daily function.
- Combine symptom treatment with resistance training, protein adequacy, sleep optimization, and cardiometabolic screening.

SECTION 04

What the Landscape Shows

Looking across all sixteen solutions, several patterns emerge — not only about what works, but about how interventions propagate across the seven interacting systems that define Energy Span.

FIGURE 2 *Tracking a signal is not the same as changing it.*



Source: Conceptual framework developed by Healthspan Horizons (2026).

1 The strongest evidence clusters in behavioural and clinical interventions

Structured exercise (Wender, Manninen and O'Connor, 2022), sleep extension (Watson et al., 2015), CBT-I for insomnia (Trauer et al., 2015; Qaseem et al., 2016), circadian anchoring (van Maanen et al., 2016), and iron deficiency correction (Houston et al., 2018) carry the most replicated evidence. Not one requires a novel device or premium supplement. The least commercially exciting solutions produce the most reliable and durable outcomes.

2 Most consumer devices are measurement tools, not interventions

Wearables, CGMs, and HRV apps generate data; their value is entirely conditional on the behaviour change they prompt (Baron et al., 2017).

3 Clinical solutions are routinely bypassed

CBT-I has a 70% response rate and three major guideline endorsements (ACP, AASM, NICE) yet is consistently skipped in favour of supplement blends with no blend-level RCT evidence (Trauer et al., 2015; Qaseem et al., 2016; Edinger et al., 2021; NICE, 2022). A ferritin and CBC panel costs less than one month of a CGM subscription. These inversions are structural, not accidental — they reflect a solutions market shaped by commercial incentives rather than evidence hierarchies (Lundh et al., 2017; Bekelman et al., 2003).

4 Over-marketing follows a predictable template

Plausible cellular mechanism — small manufacturer-funded study — systemic clinical claim (Lundh et al., 2017; Ioannidis, 2005). This sequence repeats across consumer vagus nerve devices, red-light panels, caffeine timing protocols, and cognitive supplementation. Recognising the template is more informative than evaluating each instance in isolation.

5 Time horizon mismatch drives premature abandonment

The strongest interventions operate on biological adaptation timescales — weeks to months (Hood et al., 2019). Most marketed solutions promise immediate effects. This mismatch drives early dropout, perceived failure, and unnecessary switching before any intervention has had time to produce a measurable effect (Puetz, Flowers and O'Connor, 2008).

6 Cost does not correlate with impact

High-cost solutions tend to produce narrower or indirect effects. Low-cost behavioural interventions — consistent sleep timing, paced breathing, morning light exposure — produce multi-system effects with stronger evidence than most premium alternatives (Wender, Manninen and O'Connor, 2022; Watson et al., 2015; Lehrer and Gevirtz, 2014).

TABLE 1

Solutions Summary Matrix

SOLUTION	TYPE	EVIDENCE	PRIMARY OVERCLAIM
01 Structured Aerobic and Resistance Exercise Training	BEHAVIORAL	STRONG	*Exercise is marketed as producing an immediate energy boost.*
02 Creatine Monohydrate Supplementation	SUPPLEMENT	STRONG	*Marketed sometimes as a general 'brain fuel' producing reliable cognitive enhancement in healthy adults at standard 3–5 g/day doses.*
03 Strategic Caffeine Timing	BEHAVIORAL	STRONG	*'Delay caffeine 90 minutes after waking to protect your cortisol awakening response'*
04 Structured Work-Rest Cycles / Cognitive Recovery Breaks	BEHAVIORAL / DEVICE	MODERATE	*"Productivity hacks"*
05 Paced Breathing and HRV Biofeedback	BEHAVIORAL / DEVICE	MODERATE	*Consumer apps market readiness and coherence scores as independent health biomarkers.*
06 Consumer Vagus Nerve Stimulation Wearables	DEVICE	LIMITED	*Apollo Neuro markets itself as a 'vagus nerve stimulator' while delivering vibrotactile wrist stimulation that does not contact the vagus nerve. 'Scientifically validated' is claimed from small, short-duration, manufacturer-funded studies.*
07 Morning Bright-Light Exposure and Circadian Anchoring	BEHAVIORAL / DEVICE	STRONG	*'Blue-blocking glasses improve sleep'*
08 Sleep Extension and Sleep Hygiene	BEHAVIORAL	STRONG	*'8 hours is optimal for everyone'*
09 CBT-I for Chronic Insomnia	MEDICAL / RX	STRONG	*'CBT-I is just sleep hygiene.'*
10 Low-Glycaemic Diet and Protein-Anchored Meals	BEHAVIORAL	MODERATE	*'CGM will reveal your personal glucose responses and optimize your energy'*
11 Mediterranean / High-Fiber Whole-Food Dietary Pattern	BEHAVIORAL	STRONG	*Single "superfoods," powders, or microbiome products are often marketed as substitutes for dietary pattern quality.*
12 Iron Deficiency Screening and Correction	MEDICAL / RX	STRONG	*'Everyone who is tired should supplement.'*
13 GLP-1-Based Anti-Obesity Medications	MEDICAL / RX	STRONG	*Marketed as metabolic reset tools and energy optimizers for non-obese individuals - trial evidence is entirely in overweight, obese, or T2DM populations; no evidence supports use for Energy Span improvement in metabolically healthy adults.*
14 Omega-3 Fatty Acid Supplementation	SUPPLEMENT	MODERATE	*Often marketed as universal brain-energy or anti-fatigue support.*
15 MBSR and Structured Mindfulness	BEHAVIORAL	MODERATE	*'MBSR rewires your brain'*
16 Perimenopause / Menopause Evaluation and Targeted Management	MEDICAL / RX	STRONG	*Neither "everyone needs HRT" nor "no one should use hormones" reflects evidence.*

SECTION 05

Practical Playbook

The practical question is not which interventions exist. It is which to act on first, in what sequence, and under what conditions.

FIGURE 3 *The Bottleneck Principle — Energy Span cannot exceed its weakest system.*

Source: Conceptual framework developed by Healthspan Horizons (2026).

This sequencing reflects a biological dependency structure: later-stage interventions often fail, stall, or underperform when foundational systems are not yet in place. A supplement cannot compensate for chronic sleep restriction. A wearable cannot substitute for movement. A glucose trace cannot overcome persistent circadian disruption.

CORE PRINCIPLE

Energy Span is constrained by the most limiting system at a given time. The goal is not to apply every available intervention. It is to identify and address the current bottleneck.

For one person, the limiting factor may be chronic sleep debt. For another, poor fitness, iron deficiency, post-meal glucose instability, untreated insomnia, chronic stress, or menopause-related sleep disruption. The same recommendation will not fit each case equally well.

Most individuals do not need more data. They need higher adherence to the fundamentals already supported by the strongest evidence.

In practice, the highest-return first moves are usually consistent sleep timing, adequate sleep duration, structured exercise, morning light exposure, stable meal quality, and reduction of obvious physiological drains such as excessive alcohol, late caffeine, or unmanaged stress.

Population-level frameworks remain useful, but they cannot substitute for individual calibration. The right entry point varies by which systems are most limiting, by baseline health status, by life stage, and by clinical history.

Identifying which systems are rate-limiting for a specific person, at a specific point in time, is precisely the problem that HH's personalisation infrastructure is designed to solve.

What follows is therefore a starting point grounded in evidence—not a prescription, and not a substitute for clinical care where appropriate.

STAGE 1

FOUNDATION

Sleep · Circadian · Movement

- ≥7 hours/night; fixed wake time ±30 min, 7 days/week
- 10–20 min outdoor light within 60 min of waking
- ≥150 min/week aerobic exercise + 2–3× resistance training

TIME-TO-SIGNAL

Energy: 2–4 wks. VO_2max / fitness: 6–12 wks. Sleep quality: days–2 wks.

STAGE 2

OPTIMIZATION

Caffeine · Glucose · Breathing · Cognitive pacing

- Hard caffeine curfew ≥6 h before sleep
- 25–35 g protein per meal
- 10–20 min paced breathing daily
- Structured work-rest cycles during demanding mental work

TIME-TO-SIGNAL

Sleep: 5–10 nights. Post-meal energy: days. Focus / calm: same day–2 wks.

STAGE 3

CLINICAL / PRECISION

Deficiencies · Hormonal transitions · Sleep disorders · Metabolic disease

- Ferritin + CBC when clinically indicated
- CBT-I for chronic insomnia
- TSH/fT4 when symptom pattern supports testing
- Perimenopause / menopause evaluation when sleep, fatigue, mood, or body composition shift
- GLP-1 care when obesity / metabolic criteria are met

TIME-TO-SIGNAL

Iron: 6–12 wks. CBT-I: 4–8 wks. Menopause symptom relief: variable. GLP-1 metabolic benefits: weeks–months.

STAGE 4

SELECTIVE / SITUATIONAL

Supplements · Devices · Data tools

- Creatine if physically active / older / vegetarian
- Omega-3 when intake low or triglycerides elevated
- CGM or wearables only when paired with a behaviour-change plan
- Consumer VNS devices not priority on current evidence

TIME-TO-SIGNAL

Creatine: 4–8 wks. Omega-3 labs: weeks–months. Device value depends on adherence.

SECTION 06

Conclusion

The opening question of this piece was straightforward: of the many interventions marketed for energy and fatigue, which ones actually hold up?

Across sixteen solutions spanning six interacting biological dimensions, the answer is clear. The landscape is uneven, and that unevenness follows predictable patterns. The strongest evidence is concentrated in behavioural and clinical interventions. These are often low-cost, biologically coherent, and systematically underused. By contrast, many of the most aggressively marketed solutions rely on plausible mechanisms without robust outcome-level evidence, or confuse measurement with intervention.

This is not accidental. Much of the wellness market rewards novelty, visibility, and narrative confidence more than evidentiary strength (Sackett et al., 1996; Bekelman et al., 2003). Biological plausibility is valuable for generating hypotheses. It is not a substitute for demonstrated benefit. The market does not lack solutions. It lacks prioritisation grounded in evidence, systems thinking, and biological timescales.

What this review offers is therefore not a protocol or a ranked list. It is a framework for calibrated judgment, applied consistently across all sixteen solutions:

- validity before utility
- evidence before marketing confidence
- systems before single interventions
- explicit identification of overclaim

Using that lens, the strongest evidence in this landscape belongs to structured exercise (Wender et al., 2022), sleep extension (Watson et al., 2015), circadian anchoring (van Maanen et al., 2016), CBT-I for chronic insomnia (Trauer et al., 2015; Qaseem et al., 2016), targeted correction of genuine deficiencies such as iron deficiency (Houston et al., 2018), and dietary patterns centered on whole foods, fiber quality, and metabolic stability. None require a premium consumer product. Most require consistency, time, and correct sequencing.

Most devices, by contrast, are measurement tools. Their value depends entirely on what the user does next (Baron et al., 2017). Data can inform action, but data is not action.

Part 1 established that Energy Span is a computable dimension of healthspan: the capacity to generate, sustain, and regulate physical and mental energy over time across interacting biological systems (Hood and Price, 2023; Rappaport et al., 2026). This piece extends that

foundation by evaluating interventions at the population level: what tends to work, under which conditions, and with what degree of confidence.

That is necessary. But it is not sufficient.

The next step — and the core of HH's work — is individual-level calibration:

- Which systems are currently limiting?
- At what point in time?
- Under what constraints, exposures, and behaviours?
- Which intervention comes first, and which can wait?

Healthspan Horizons is not building another layer of generic recommendations. It is building the infrastructure to translate longitudinal biological data into personalised understanding of which systems matter, for whom, and when. Population-level evidence tells us what works on average. A true healthspan platform should help determine what matters most for the individual in front of it.

The landscape reviewed here will continue to evolve. Evidence will strengthen or fail. Devices will be validated or exposed. New therapies will emerge. What should remain constant is the framework: validity before utility, evidence before marketing confidence, systems before isolated solutions.

> THE CLOSING THOUGHT
>
> The future of Energy Span is not a better product. It is a better model — one that integrates biology, behaviour, environment, and time into a coherent, computable system.

SECTION 07

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ABOUT THIS RESEARCH

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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