



The Longevity Stack

Creatine · cold exposure · fasting · aerobic training · resistance training · melatonin

Mechanisms, human evidence, and hypotheses about what they do together

Research brief · 12 October 2026

Evidence is graded; speculation is labeled as speculation.

At a glance

Six interventions, one question: what does each actually do, how good is the evidence in humans, and what might they do *together*? The short version is that the stack is not six equal pillars. Two of the six carry almost all of the hard-outcome evidence; the other four are better understood as modulators, each with a specific job and a specific way to go wrong.

Five things worth knowing

- 1. Aerobic fitness and resistance training are the foundation.** Cardiorespiratory fitness has the steepest, most consistent mortality gradient in preventive medicine with no observed ceiling^[1,2]; any resistance training is associated with roughly 15% lower all-cause mortality, with most of the benefit at only 30–60 minutes a week^[3,4].
- 2. Creatine is the best-evidenced supplement here, mostly for muscle.** The brain effects are real at the level of phosphocreatine, but the cognitive benefits in healthy adults are modest and mixed; the clearest signal is under energetic stress such as sleep loss^[5--9].
- 3. Cold and fasting are mostly metabolic and subjective stories.** Cold produces a large, brief nora-drenaline surge and small metabolic adaptations^[10,13,14]. Time-restricted eating matches ordinary calorie restriction when calories are equated^[19--21], with a mechanistic case for more.
- 4. Melatonin is a clock signal, not a vitamin.** It has a clear job (timing), a plausible secondary job (mitochondrial antioxidant at higher doses), and an unresolved long-term safety signal in observational data^[22].
- 5. The interactions matter as much as the effects.** Post-lifting cold blunts hypertrophy^[12]; antioxidant-dose melatonin near training may blunt training signals; and intensity, not fasting, drives the BDNF response^[18]. Sequencing is a bigger lever than adding a seventh intervention.

	Hard outcomes (mortality)	Cardiometabolic	Muscle & function	Cognition & mood	Sleep & circadian
Aerobic training	Strong cohorts	RCTs + cohorts	Modest	Moderate	Moderate
Resistance training	Cohorts ~15%	Good	Strong	Modest	Modest
Creatine	No data	Limited	Strong	Small / mixed	Stress / preclinical
Fasting / TRE	Mostly mechanistic	≈ calorie restriction	Lean-mass risk	Limited	Limited
Cold exposure	No data	Small; acclimation	Blunts hypertrophy*	Acute mood, short-lived	Anecdotal
Melatonin	Safety signal (observational)	Limited	Next-day perf. (small)	Limited	Timing / onset

none / unknown
mechanistic or sparse human data
modest / mixed

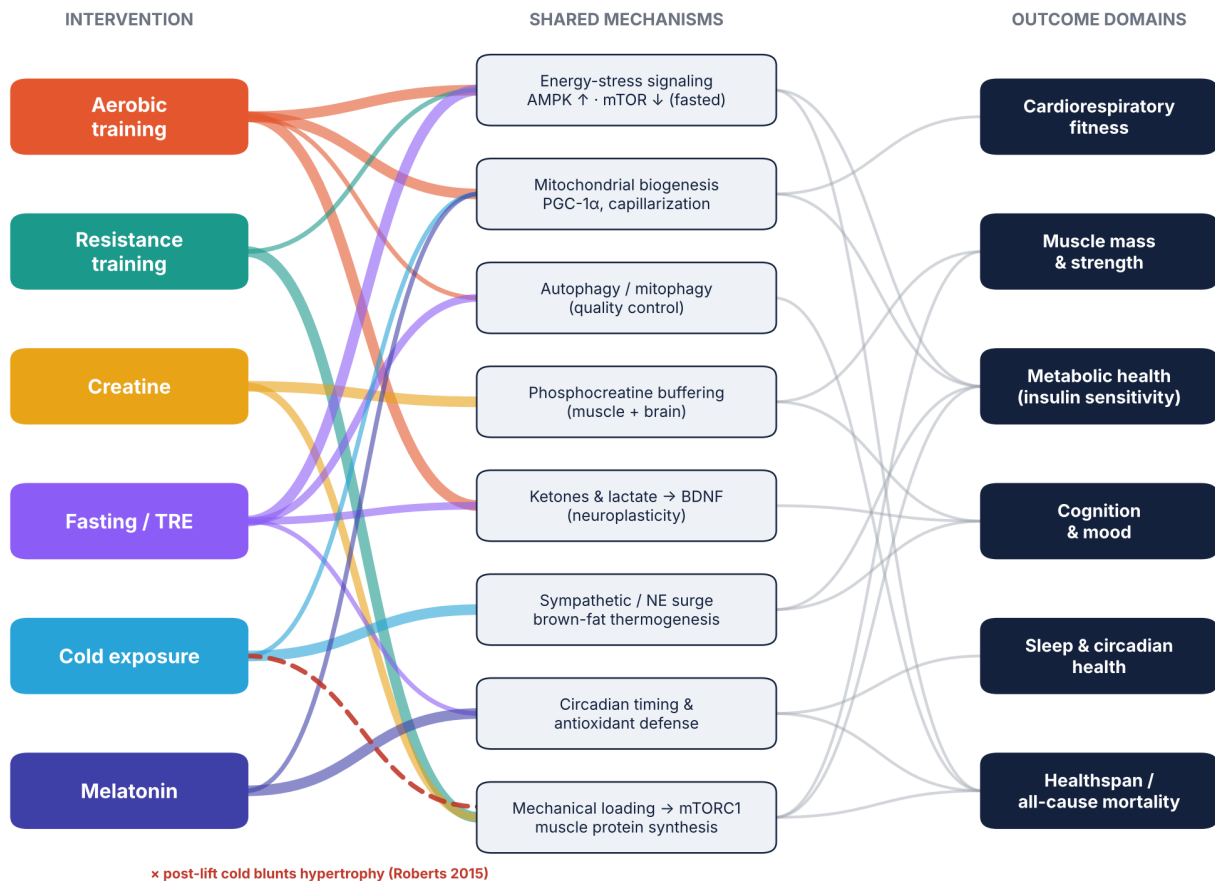
good (RCTs or large cohorts)
strong, consistent
antagonism or safety signal

Figure 1. Evidence scorecard by outcome domain. Scores are my qualitative judgment of *human* evidence quality from the sources reviewed here, not a formal grading. *Cold blunts hypertrophy specifically when applied after lifting.

How to read this report. Chapters 2--7 summarize each intervention and cite sources in square brackets (numbered in the reference list at the end; items marked † are cited second hand: I did not re-read the primary paper while writing this). Chapter 9 is deliberately speculative; each hypothesis carries two ratings: *mechanistic plausibility* and *human evidence for the combination*. The second is almost always low, because almost nobody has tested these combinations.

1 The shared mechanism map

The interventions look unrelated, but they converge on a small number of cellular and neural switches. Energy stress activates AMPK and, downstream, PGC-1 α , which drives mitochondrial biogenesis. Mechanical loading activates mTORC1 for muscle protein synthesis. Exercise and fasting both produce metabolites (lactate, β -hydroxybutyrate) that signal to the brain. Cold recruits the noradrenergic system, and melatonin sets the timing of the whole sequence. Figure 2 traces these paths.



Line thickness = strength of the mechanistic/human support (my qualitative judgment). Dashed red = antagonistic interaction.

Figure 2. From interventions to shared mechanisms to outcomes. Where several colored lines land on the same mechanism box, the interventions share that pathway, which is where synergy (and redundancy) is most likely to arise.

Two readings of this map are useful. First, **convergence cuts both ways**: inputs to a saturating node (AMPK/PGC-1 α is the obvious candidate) are likely to be sub-additive, so stacking several energy-stress signals will probably not multiply benefit. Second, the **one dashed line** (cold applied after lifting) is a reminder that some pairings are antagonistic at the level of a single pathway.

2 Aerobic training

Aerobic training

Builds the engine: stroke volume, capillaries, mitochondria. The strongest hard-outcome evidence in the stack.

Mechanism. Muscle contraction raises the AMP:ATP ratio and calcium flux, activating AMPK, p38 MAPK and CaMK. These converge on PGC-1 α , the master regulator of mitochondrial biogenesis, and promote capillarization. Centrally, repeated high cardiac output remodels the heart (stroke volume), the component of VO₂max that declines most with age. In the brain, high-intensity exercise raises lactate, which signals through MCT transporters and SIRT1 to PGC-1 α /FNDC5 and hippocampal *Bdnf* (rodent)^[31]; prolonged exercise also raises β -hydroxybutyrate, which inhibits HDAC2/3 at the *Bdnf* promoter^[17].

Human evidence.

- In 122,007 patients undergoing treadmill testing, all-cause mortality fell stepwise with fitness, with **no upper limit of benefit**: elite versus low fitness adjusted HR 0.20 (0.16–0.24), elite versus high 0.77 (0.63–0.95). The risk of being in the lowest fitness group was comparable to or greater than smoking (aHR 1.41), coronary disease (1.29) and diabetes (1.40)^[1].
- A meta-analysis of 33 studies (102,980 participants) found each +1 MET of fitness (about +1 km/h running speed) was associated with 13% lower all-cause mortality and 15% lower CHD/CVD events; the low-fitness group (below about 7.9 METs) had a 70% higher risk of death than the high-fitness group^[2].
- Fitness is modifiable: a longitudinal cohort found that a 1 mL/kg/min higher change in VO₂max over 11 years was associated with 9% lower mortality^[34].

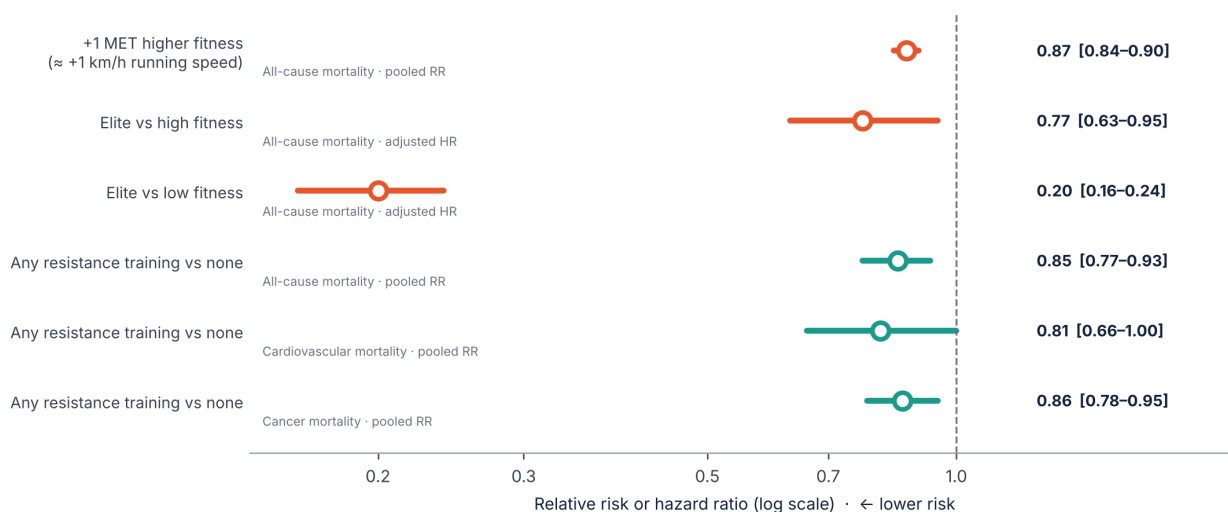


Figure 3. Mortality associations for aerobic fitness (orange) and resistance training (green). These are observational associations from different comparisons (per-unit, extreme-vs-reference, any-vs-none), so rows are not directly comparable. Confounding (healthier people are fitter) is the standing caveat.

Intensity versus volume. Matched for total work, PGC-1 α induction was greater with higher intensity (Egan 2010^[28]), and single-leg interval training beat continuous training for mitochondrial adaptation in the same subjects (MacInnis 2017^[29]). But the dose-response is an inverted U: at the highest weekly volume of HIIT, healthy volunteers showed impaired mitochondrial function and glucose tolerance that partly recovered with tapering (Flockhart 2021^[30]). Intensity is the more potent signal per minute, and the one that damages if overdosed; low-intensity volume is the way to add stimulus without paying that cost. This is the physiological logic of the polarized, roughly 80/20 pattern: most sessions at conversational pace (zone 2), one or two high-intensity sessions a week.

Practical parameters from the literature (synthesis)

3–4 zone-2 sessions of 45–90 min below the first lactate threshold; 1 session of VO₂max intervals (for example 4×4 min at 90–95% HRmax); hard cap of about 2 high-intensity sessions per week. Intervals are better done fed, because session quality is the point of them.

3 Resistance training

Resistance training

Protects the organ that actually fails with age: skeletal muscle. Small dose, large return.

Mechanism. Mechanical tension and stretch activate mTORC1 (through PI3K/Akt and mechanosensors), satellite cells and ribosome biogenesis; the result is muscle protein synthesis that, repeated, becomes hypertrophy. High-force work is the only stimulus that reliably recruits type II fibres, which are preferentially lost with ageing. Muscle is also the largest insulin-stimulated glucose sink, so preserving it protects insulin sensitivity^[4].

Human evidence.

- A systematic review of 10 studies found any resistance training was associated with 15% lower all-cause mortality (RR 0.85, 0.77–0.93), 19% lower cardiovascular mortality (0.81, 0.66–1.00) and 14% lower cancer mortality (0.86, 0.78–0.95)^[3].
- A dose-response meta-analysis of 16 cohort studies found 10–17% lower risk of all-cause mortality, CVD, total cancer, diabetes and lung cancer, *independent of aerobic activity*. The relationship was J-shaped, with the largest reduction at about 30–60 minutes a week; the effect of much higher volumes was unclear^[4].
- Combined muscle-strengthening and aerobic activity was associated with a lower risk of all-cause, CVD and cancer mortality than either alone^[4].

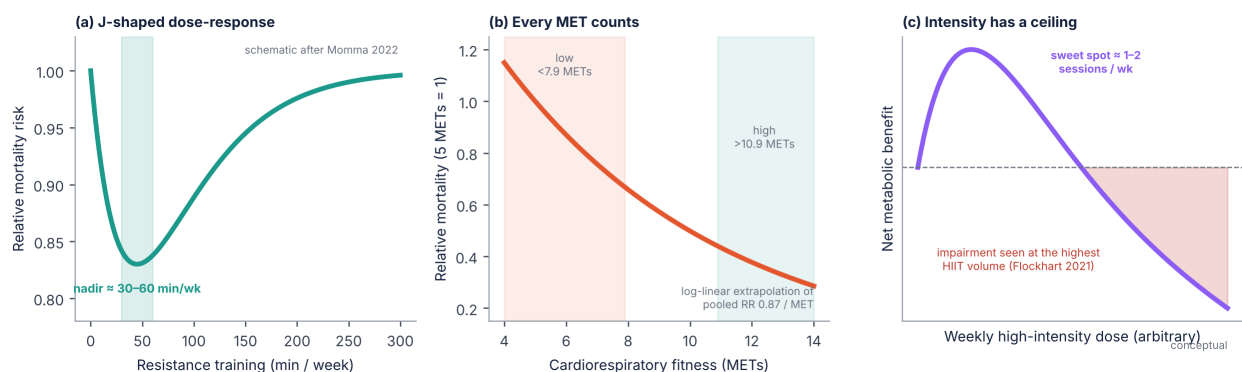


Figure 4. Dose-response shapes. (a) and (c) are schematic illustrations of published findings (Momma 2022; Flockhart 2021), not data plots. (b) extrapolates the pooled risk ratio per MET log-linearly; the true curve is uncertain at the extremes.

Caveats. All of this is observational; people who lift are different from people who do not, and the J-shape rests on few studies. Nevertheless, the dose is small enough, and the biological rationale strong enough, that the asymmetry favors doing it: two sessions a week covering all major muscle groups is the standard guideline.

4 Creatine

Creatine

An energy buffer for muscle and brain. Strong for strength and lean mass; modest, context-dependent for cognition.

Mechanism. Phosphocreatine (PCr) regenerates ATP from ADP in milliseconds via creatine kinase and acts as a spatial shuttle between mitochondria and ATP-consuming sites (Figure 5). The brain uses the same system and synthesizes its own creatine, but uptake across the blood–brain barrier is transporter-limited (SLC6A8), which caps how far oral supplementation can raise brain levels.

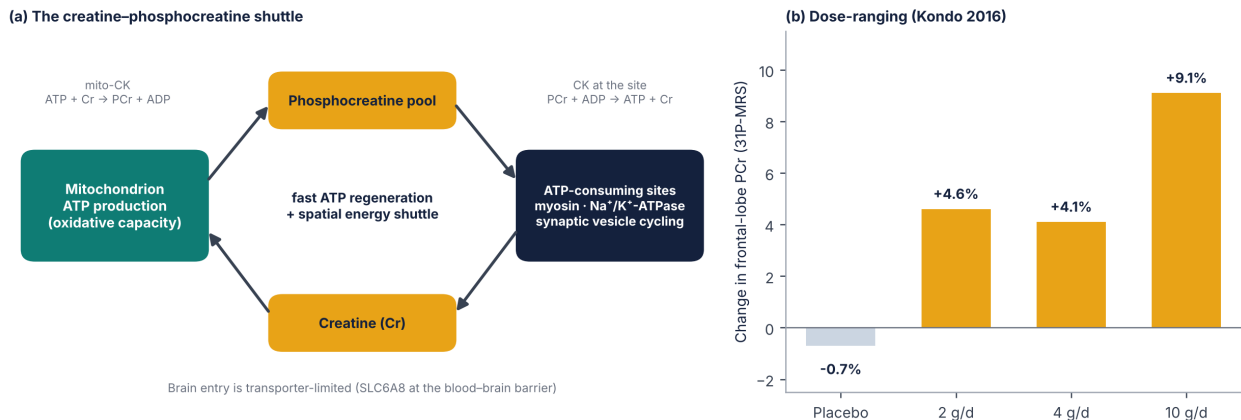


Figure 5. (a) The creatine–PCr shuttle. (b) Change in frontal-lobe PCr by 31P-MRS across doses in the only randomized dose-ranging study (Kondo 2016†, adolescent females with treatment-resistant depression; small sample).^[9]

Human evidence.

- **Muscle and function.** A 2025 narrative review concluded that creatine monohydrate, primarily combined with exercise training, is safe and improves lean mass, regional muscle size, strength, bone area and thickness, and functional ability in older adults; it also reports effects on glucose kinetics, cognition and memory^[5].
- **Cognition, aging.** A systematic review of older adults found 5 of 6 studies reported a positive association with cognition, especially memory and attention, though the samples were small and mostly healthy^[6].
- **Cognition, mixed.** A Frontiers in Nutrition meta-analysis found benefit for memory, attention time and processing speed, with effects significant at ages 18–60 but not above 60^[7]. Later commentary has flagged double-counting in some of the pooled meta-analyses, and the European Food Safety Authority rejected a cognitive claim in 2024 (second hand†); treat the healthy-adult cognition literature as small effects of uncertain size.
- **Under stress.** The most consistent signal is energetic stress. A single high dose (0.35 g/kg) during a night of sleep deprivation protected brain PCr/Pi and pH and improved processing speed (Gordji-Nejad 2024)^[8].
- **Brain dose.** Oral monohydrate raises brain total creatine roughly 5–10%; at 10 g/day, frontal PCr rose 9.1% versus a 0.7% fall on placebo^[9]. Most protocols use 3–5 g/day for muscle; the brain studies above used 10–20 g/day.

Caveats and open questions. Serum creatinine rises with supplementation without implying kidney injury (cystatin C is the cleaner marker if renal function matters). A 2026 mouse study reported that creatine promoted metastasis through a megakaryocyte–CKB–STAT5B pathway†^[33]; this is preclinical and unreplicated in humans but is worth tracking. In rodents, creatine reduced sleep need and homeostatic sleep pressure (Dworak 2017†^[32]); whether this matters in humans is unknown.

5 Fasting and time-restricted eating

Fasting and time-restricted eating

Metabolic switching: lower insulin, higher ketones, an AMPK-leaning state. The mechanism is richer than the human outcome data.

Mechanism. As feeding stops, insulin falls, liver glycogen is drawn down, and ketone production rises (Figure 6a). Reduced glucose and amino acids lower mTOR activity and raise the AMP:ATP ratio, activating AMPK and autophagy. β -Hydroxybutyrate is both a neuronal fuel and a signaling molecule that induces *Bdnf*. The review that framed this as “intermittent metabolic switching” proposed BDNF, SIRT3 and PGC-1 α as key genes for neuroplasticity and stress resistance^[16].

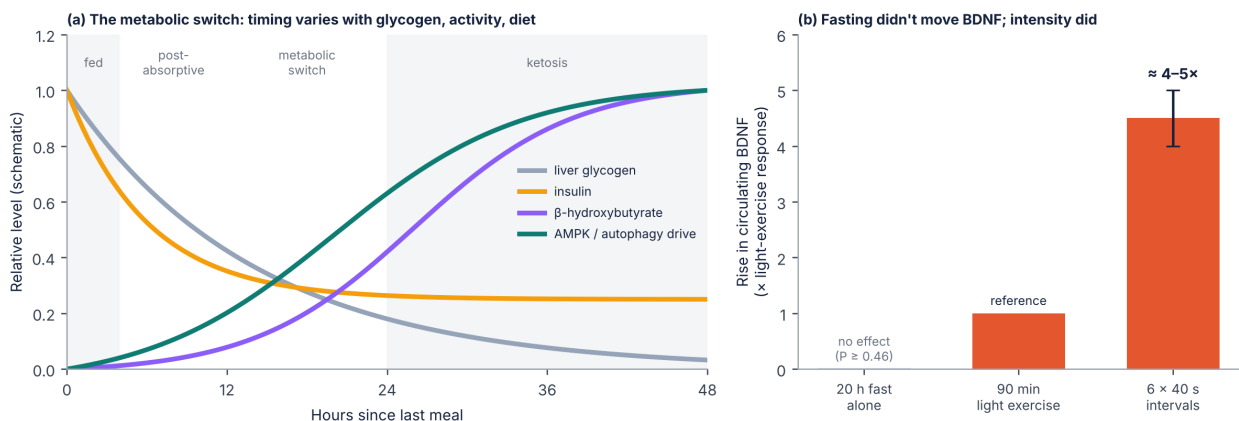


Figure 6. (a) Schematic of the fasting transition; timing varies by person. (b) In 12 volunteers, 20 h of fasting raised ketones (about 9-fold more ketone delivery to the brain) but did not change circulating BDNF; six 40-second intervals raised it 4–5-fold more than light exercise did^[18].

Human evidence.

- In a trial of 8-hour eating windows (early, late, or self-selected), all time-restricted groups lost more weight than habitual eaters at 12 weeks, and early and late groups maintained greater weight loss at 12 months, though only about 26% reported still practicing TRE at follow-up^[19].
- When calories were equated, time-restricted eating was no more effective than calorie restriction alone for weight loss in a randomized trial^[20], and a review of intermittent fasting versus calorie restriction concluded that both give similar cardiometabolic benefit^[21]. The metabolic gain appears to track overall energy reduction more than timing.
- Neuroprotection and longevity claims rest mainly on animal studies and short human trials; reviews are explicit that animal mechanisms are not assumed to translate^[16].

Caveats. Lean-mass preservation requires adequate protein inside the feeding window and resistance training. Fasting is inappropriate with a history of disordered eating, and needs medical input with insulin or sulfonylurea use, pregnancy, or low body weight.

6 Cold exposure

Cold exposure

A sympathetic jolt and a small thermogenic adaptation. Good for alertness; antagonistic to lifting adaptations when mistimed.

Mechanism. Skin cold receptors drive sympathetic activation: noradrenaline rises sharply, vessels constrict, and shivering and non-shivering (brown-fat, UCP1-mediated) thermogenesis increase. Immersion at 14 °C for an hour raised metabolic rate 350%, plasma noradrenaline 530% and dopamine 250% without raising cortisol^[10] (Figure 7a). The same group's earlier work found no significant dopamine rise, and these are peripheral plasma values, not brain dopamine, so brain-level claims go beyond the data.

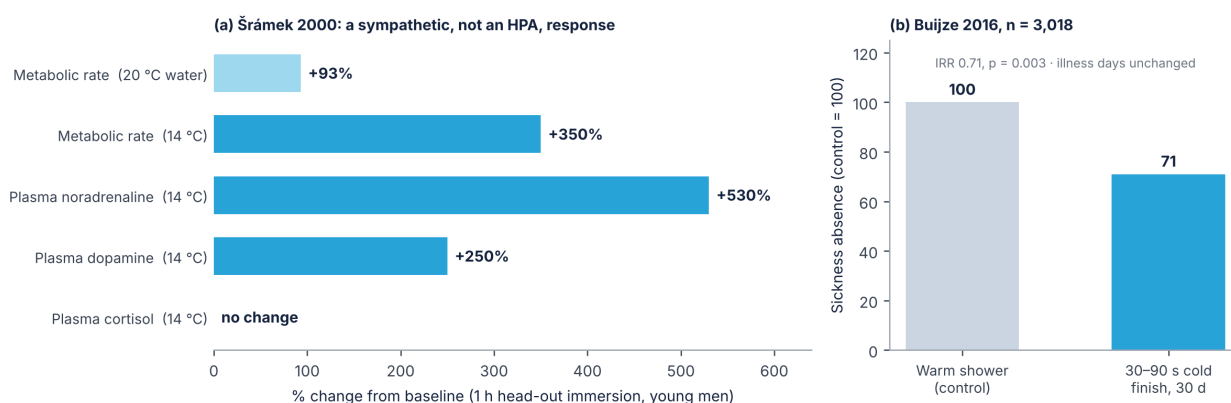


Figure 7. (a) Acute physiological response to 1 h head-out immersion^[10]. (b) The only large randomized trial of cold showering: 30, 60 or 90 s of cold at the end of a daily shower for 30 days reduced sickness absence 29%; there was no dose-response and illness days did not change^[11].

Human evidence.

- **Illness and energy.** Participants in the shower trial felt ill just as often but missed less work, which the authors attributed to the invigorating effect; a small quality-of-life gain at 30 days faded by 90^[11].
- **Mood and stress.** A 2025 meta-analysis of 11 RCTs (n = 3,177) found stress was reduced only at 12 h after immersion, null at other timepoints, and inflammatory markers were acutely higher^[15].
- **Metabolism.** In people with active brown fat, 5–8 h of cold raised energy expenditure, glucose disposal and insulin sensitivity^[13]; a 10-day mild-cold acclimation improved postprandial insulin sensitivity^[14]. The brown-fat contribution is small, probably 1–5% of basal metabolic rate even after acclimation^[34], so cold is not a weight-loss tool.
- **Habituation.** After about 4–8 immersions the heart-rate and breathing response to the initial shock falls sharply^[35], which is the main safety adaptation.

The recovery–adaptation paradox. In a 12-week trial, 21 men who sat in 10 °C water after each lifting session gained less muscle mass and strength than those who did active recovery, with reduced p70S6K phosphorylation and satellite-cell activity^[12]. Hot-water immersion did not show this penalty in the review literature. Cold is therefore best used away from lifting, or when speed of recovery matters more than growth.

Risks. The cold-shock response (gasp, hyperventilation, arrhythmia) is most dangerous in the first minutes and in cold open water; people with cardiovascular disease should be cautious. Showers carry far less risk than immersion.

7 Melatonin

Melatonin

A timing signal first, an antioxidant second, and a long-term safety question mark.

Mechanism. At low doses (about 0.3–0.5 mg) melatonin acts as a chronobiotic through MT1 and MT2 receptors, shifting the phase of the circadian clock according to when it is taken; it is a timing cue rather than a sedative. At higher doses it accumulates in mitochondria, scavenges reactive oxygen and nitrogen species, and is reported to support electron-transport function^[26]. The two ranges are different pharmacologies (Figure 8b).

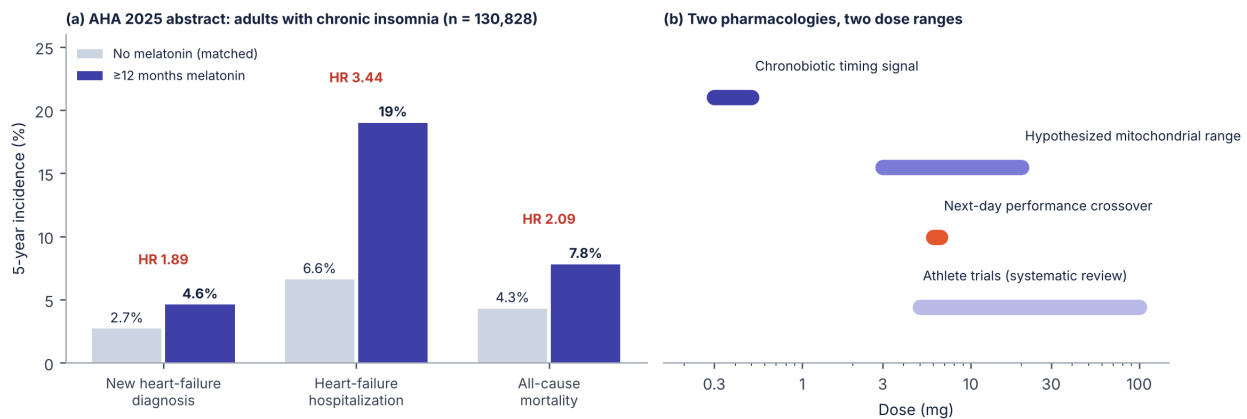


Figure 8. (a) Observational data from the AHA 2025 abstract (TriNetX electronic records, 65,414 users matched to 65,414 non-users)^[22]. (b) Dose ranges used in different literatures; the hypothesized mitochondrial range is a second-hand figure†.

Human evidence.

- **Exercise performance.** A meta-analysis of 19 RCTs (266 participants) found evening melatonin, with a gap of more than 6 hours before exercise, improved endurance and explosive power and reduced muscle damage markers^[23]. In one crossover study, 6 mg at night improved next-day high-intensity performance and perceived recovery for up to 72 h^[24]. A separate systematic review of highly trained athletes (doses 5–100 mg) found no improvement in strength, power or speed^[25].
- **Circadian effects of exercise.** One hour of evening exercise advanced circadian phase by about 30 minutes versus a delay of 25 minutes without exercise, so training time and melatonin time interact^[27].
- **Safety signal.** In adults with insomnia taking melatonin for 12 months or longer, 5-year incidence of heart failure was 4.6% versus 2.7% (HR 1.89), heart-failure hospitalization 19% versus 6.6% (HR 3.44), and all-cause mortality 7.8% versus 4.3% (HR 2.09)^[22]. The authors stressed the study cannot show causation; likely confounders include insomnia severity and over-the-counter use of melatonin among controls, which electronic records cannot capture. An industry group's response noted decades of experience with low-dose, short-term use. This is a signal to track, not a verdict.

Practical implication. Low-dose, well-timed use matches the mechanism and the benign short-term record. Indefinite high-dose use in the evening is the pattern with the least supporting evidence and the one the new observational signal concerns.

8 Pairwise interactions

Fifteen pairs, color-coded. Only two earn the label “synergy” on current evidence (aerobic with resistance, resistance with creatine); one is a clear conflict (cold after lifting). Most of the remainder are timing problems, which are solvable.

	Aerobic training	Resistance training	Creatine	Fasting / TRE	Cold exposure	Melatonin
Aerobic training		Concurrent training +	Interval / sprint support ~	Fasted Z2: more turnover ~	Cold after endurance: mixed !	Evening exercise shifts clock ~
Resistance training	Concurrent training +		Best-evidenced pairing +	Protein timing, lean mass !	Post-lift cold blunts growth x	Antioxidant timing !
Creatine	Interval / sprint support ~	Best-evidenced pairing +		Dose inside feeding window ~	No data ?	Sleep effects unknown ?
Fasting / TRE	Fasted Z2: more turnover ~	Protein timing, lean mass !	Dose inside feeding window ~		Hypoglycemia / shivering !	Keep away from meals !
Cold exposure	Cold after endurance: mixed !	Post-lift cold blunts growth x	No data ?	Hypoglycemia / shivering !		Late cold = arousal !
Melatonin	Evening exercise shifts clock ~	Antioxidant timing !	Sleep effects unknown ?	Keep away from meals !	Late cold = arousal !	

■ + synergy
 ■ ~ complementary / neutral
 ■ ! timing or safety caution
 ■ x conflict
 ? no data

Figure 9. Interaction matrix (my synthesis). Symbols repeat the colors for black-and-white printing.

Resistance + creatine	Best-evidenced pairing: lean mass and strength gains exceed training alone, especially in older adults ^[5] .
Aerobic + resistance	Concurrent training is associated with lower mortality than either alone ^[4] ; interference is real but modest, and sequencing manages it.
Resistance + cold	Post-lift cold blunts hypertrophy and anabolic signaling ^[12] . Separate by several hours or skip.
Resistance + melatonin	Antioxidant doses near training may blunt the oxidative signals that drive adaptation (theoretical); keep melatonin away from training.
Fasting + melatonin	Circadian-phase effects on glucose handling are proposed ^[22] ; avoid taking melatonin close to meals.
Fasting + cold	Plausibly additive metabolic stress, with hypoglycemia, dizziness and shivering risks; untested.
Creatine + fasting	Calorie-free, so timing is flexible; taking it with the first meal is a convenient default.

9 Hypotheses: what might they do together?

A caution before the speculation

Hazard ratios do not multiply. The fitness, strength, fasting and cold effects above come from different populations, outcomes and study types; stacking them arithmetically ($“0.85 \times 0.87 \times …”$) would double-count shared pathways and confounding. Treat every hypothesis below as a testable guess, not a forecast. Ratings: left dots = mechanistic plausibility, right dots = human evidence for the *combination*.

H1. Foundation plus modulators

PLAUSIBILITY ●●●●● COMBINATION EVIDENCE ●●●○○

Aerobic fitness and muscle set the *ceilings* (VO₂max, lean mass, strength) that dominate mortality data. Creatine, fasting, cold and melatonin act on the *approach to the ceiling*: training volume and recovery, metabolic flexibility, arousal, timing. **Prediction:** a person who adds all four modulators but under-trains the foundation will do worse than one who trains well and adds none. This is the hypothesis best supported by the effect-size comparison in this report.

H2. Pulsatile signaling: alternate catabolic and anabolic states

PLAUSIBILITY ●●●●○ COMBINATION EVIDENCE ●●○○○

Fasting and zone-2 work push the cell toward AMPK, autophagy and mitochondrial turnover; feeding plus lifting (with creatine supporting training capacity) pushes toward mTORC1 and tissue building. Cycling the two within a day may give more of both than a constant fed state gives of either (Figure 10). **Prediction:** on a time-restricted schedule with adequate protein and lifting, lean mass is preserved while insulin sensitivity and markers of mitochondrial quality improve. **Against:** time-restricted eating alone does not beat calorie restriction when calories are matched^[20].

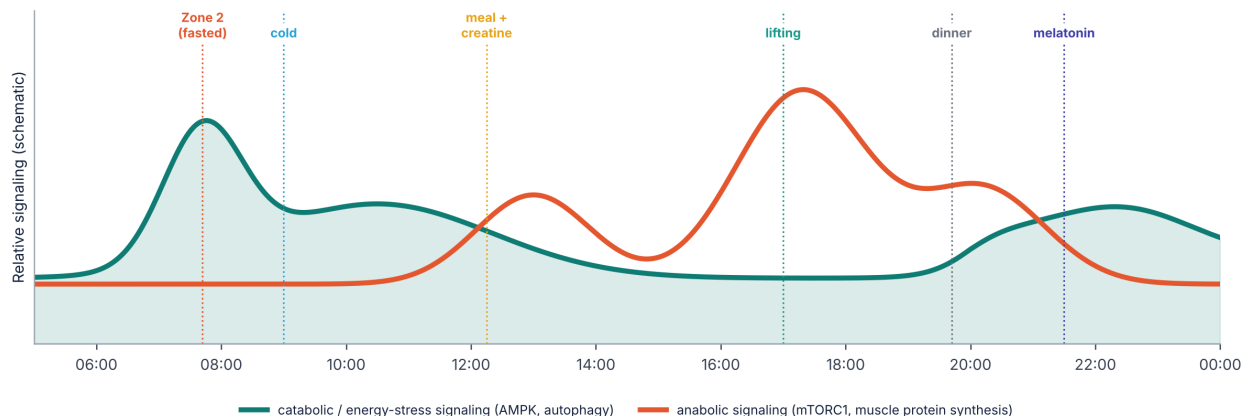


Figure 10. Conceptual signaling profile across a day (not measured data). Fasted low-intensity work lengthens the catabolic phase; the feeding window and lifting create the anabolic pulse.

H3. Brain plasticity convergence

PLAUSIBILITY ●●●○○ COMBINATION EVIDENCE ●○○○○

Four inputs reach the same neural machinery by different routes: exercise intensity (lactate → BDNF), prolonged exercise or fasting (β -hydroxybutyrate → HDAC inhibition at *Bdnf*)^[17,31], noradrenergic arousal from cold, and a larger energetic reserve from creatine under stress^[8], with melatonin-protected sleep to consolidate. **Prediction:** learning scheduled shortly after intense exercise and followed by good sleep improves more than learning alone. **Against:** 20 h of fasting alone did not change circulating BDNF^[18]; creatine effects in healthy adults are small^[7]; cold's attention effects are mixed. Serum BDNF is also a poor proxy for brain BDNF. The convergence may mostly mean redundancy rather than addition.

H4. Thermo-metabolic additivity

PLAUSIBILITY ●●●●○ COMBINATION EVIDENCE ●○○○○

Cold acclimation recruits brown fat and improves insulin sensitivity modestly^[13,14]; time-restricted eating improves glycemic control; aerobic training raises mitochondrial capacity. **Prediction:** the combination improves glucose disposal more than any one alone, with cold contributing the smallest share given brown fat's small energetic footprint^[34]. **Test:** OGTT or clamp after 8–12 weeks.

H5. A circadian scaffold

PLAUSIBILITY ●●●●○ COMBINATION EVIDENCE ●●○○○

Three of the interventions are zeitgebers: timed exercise shifts the clock^[27], restricted feeding anchors peripheral clocks, and low-dose melatonin shifts phase by its timing. Aligned, they may reinforce each other; scattered, they may fight (late hard exercise delays; late cold arouses; late meals plus melatonin impair glucose handling). **The missing zeitgeber is morning light**, which is the strongest of all and is not on the list. **Prediction:** a consistent daily sequence beats the same interventions at random times.

H6. The hormesis budget

PLAUSIBILITY ●●●●○ COMBINATION EVIDENCE ●●○○○

Cold, fasting, hard intervals and antioxidant dosing are all stressors that are beneficial in a window and harmful beyond it. The inverted U seen for HIIT volume^[30] may apply to the *total* stress load. **Prediction:** resting heart rate, heart-rate variability and sleep quality drift before performance does, so they work as early warnings. **Rule of thumb:** place different stressors on different days or hours rather than stacking them.

10 A worked example: one possible day

The chart applies the interaction rules from Chapters 8–9. It is a template to adapt, not a prescription. Resistance and aerobic sessions are placed on separate occasions; cold is kept away from lifting; creatine rides with the first meal; melatonin is taken low-dose, well after the last meal and training.



Figure 11. Hypothetical lift-day template (16:8 eating window). On interval days the zone-2 slot would move to the afternoon, fed.

Measuring whether it works

Each hypothesis predicts something measurable. A small dashboard turns the stack into an experiment:

Domain	Measure	Why
Aerobic capacity	VO ₂ max or 12-min test; resting HR	Strongest mortality gradient; every MET counts
Muscle	Grip strength; DEXA lean mass; a fixed lift	Function, not appearance, predicts outcomes
Metabolic	Fasting glucose, insulin, HbA1c; ApoB	Tests H2 and H4
Recovery / load	HRV, sleep duration and regularity	Early warning for H6; tests H5
Brain	A repeatable cognitive test at a fixed time	Tests H3 (noisy; use trends)
Safety	Blood pressure, cystatin C if on creatine, symptoms	Catches the failure modes above

11 Limits of this report

- **Observational dominance.** Most hard-outcome data (fitness, resistance training, melatonin) are cohort studies; healthy-user bias and reverse causation apply in both directions.
- **Rodent dominance in the mechanisms.** Brain BDNF routes, creatine's signaling effects, and melatonin's mitochondrial actions are mostly animal or in vitro findings.
- **Combinations are untested.** Chapter 9 is reasoning, not evidence. The correct summary of the combined benefit is: plausible, probably partly redundant, probably more sensitive to timing than to inclusion.
- **Scores and diagrams are qualitative.** Scorecard grades, line thicknesses and schematic curves are my judgment, and several secondary sources were used where primary papers were paywalled.
- **Medical context.** Individual risks (cardiovascular disease, medications, history of eating disorders, mood

disorders, kidney disease) change the calculus; a clinician who knows the patient should have the final say.

References

- [1] Mandsager K et al. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw Open* 2018. jamanetwork.com/journals/jama/fullarticle/2707428
- [2] Kodama S et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;301:2024--35. doi:10.1001/jama.2009.681
- [3] Resistance training and mortality risk: a systematic review and meta-analysis. *Am J Prev Med* 2022. research.usq.edu.au/item/z02v2
- [4] Momma H et al. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. *Br J Sports Med* 2022.
- [5] Candow DG et al. Creatine monohydrate supplementation for older adults and clinical populations. *J Int Soc Sports Nutr* 2025. doi:10.1080/15502783.2025.25341
- [6] Creatine and cognition in aging: a systematic review of evidence in older adults. *Nutr Rev* 2025. PMID 40971619.
- [7] The effects of creatine supplementation on cognitive function in adults: a systematic review and meta-analysis. *Front Nutr* 2024.
- [8] Gordji-Nejad A et al. Single dose creatine improves cognitive performance and induces changes in cerebral high energy phosphates during sleep deprivation. *Sci Rep* 2024.
- [9] Kondo DG et al. Creatine target engagement with brain bioenergetics: a dose-ranging phosphorus MRS study of adolescent females with SSRI-resistant depression. *Amino Acids* 2016.†
- [10] Šrámek P, Šimečková M, Janský L et al. Human physiological responses to immersion into water of different temperatures. *Eur J Appl Physiol* 2000. doi:10.1007/s004210050065
- [11] Buijze GA et al. The effect of cold showering on health and work: a randomized controlled trial. *PLOS ONE* 2016;11:e0161749. doi:10.1371/journal.pone.0161749
- [12] Roberts LA et al. Post-exercise cold water immersion attenuates acute anabolic signalling and long-term adaptations in muscle to strength training. *J Physiol* 2015;593:4285--301.
- [13] Chondronikola M et al. Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. *Diabetes* 2014;63:4089--99.
- [14] Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. *Diabetes* 2014. PMC4207391.
- [15] Cain et al. Cold-water immersion and stress, mood and inflammation: meta-analysis of 11 RCTs. *PLOS ONE* 2025.†
- [16] Mattson MP et al. Intermittent metabolic switching, neuroplasticity and brain health. *Nat Rev Neurosci* 2018;19:63--80. PMC5913738
- [17] Sleiman SF et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β -hydroxybutyrate. *eLife* 2016. elifesciences.org/articles/15092
- [18] Fasting for 20 h does not affect exercise-induced increases in circulating BDNF in humans. *J Physiol*. pure.cardiffmet.ac.uk
- [19] Time-restricted eating (early, late, self-selected) with 12-month follow-up. *Clin Nutr*. theeducatedpatient.com
- [20] Liu D et al. Calorie restriction with or without time-restricted eating in weight loss. *N Engl J Med* 2022.
- [21] Review of intermittent fasting versus calorie restriction on ageing-related outcomes. *Nutrients*. menshealth.com.au/intermittent-fasting-diets-longevity
- [22] Nnadi E et al. Long-term melatonin use for insomnia and heart failure risk. AHA Scientific Sessions 2025, abstract MP2306 (HealthDay coverage, 6 Nov 2025).
- [23] Timing-dependent effects of melatonin supplementation on exercise performance and exercise-induced muscle damage: systematic review and meta-analysis. *Front Nutr* 2026. doi:10.3389/fnut.2026.1742464
- [24] Melatonin supplementation enhances next-day high-intensity exercise performance and recovery in trained males. *J Funct Morphol Kinesiol* 2025;13(6):190. mdpi.com/2075-4663/13/6/190
- [25] Impact of melatonin supplementation on sports performance and circulating biomarkers in highly trained athletes. *Nutrients* 2024;16:1011. PMC11013451
- [26] Kruk J et al. Exercise-induced oxidative stress and melatonin supplementation: current evidence. *J Physiol Sci* 2021;71:27.
- [27] Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. *Am J Physiol*. pure.psu.edu
- [28] Egan B et al. Exercise intensity-dependent regulation of PGC-1 α mRNA abundance. *J Physiol* 2010.†
- [29] MacInnis MJ et al. Superior mitochondrial adaptations in human skeletal muscle after interval compared to continuous single-leg cycling matched for total work. *J Physiol* 2017.†
- [30] Flockhart M et al. Excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in healthy volunteers. *Cell Metab* 2021.†
- [31] El Hayek L et al. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal BDNF. *J Neurosci* 2019.†
- [32] Dworak M et al. Creatine supplementation reduces sleep need and homeostatic sleep pressure in rats. *J Sleep Res* 2017.†
- [33] Xie et al. Creatine promotes metastasis via megakaryocyte CKB--STAT5B signaling in mice. *Nat Commun* 2026.†
- [34] Long-term change in cardiorespiratory fitness and all-cause mortality: a population-based study (VO₂max measured by gas exchange). *Mayo Clin Proc* 2016. PMID 27444976. Also: Human brown adipose tissue: a decade later. PMC8360096.
- [35] Barwood MJ et al. Habituation to cold-water immersion: meta-analysis. 2024.†

† Cited second hand: I did not re-read the primary paper. Several secondary sources (news summaries, trade press) were used where primary articles were paywalled; verify exact figures against the primary papers before citing.