Longevity Research Brief

A Proco research brief — what the published evidence describes about extending healthy years

Compiled by the Proco editorial team Last reviewed: 2 June 2026

What this brief is

This brief describes what well-conducted human research has measured about interventions associated with longer healthspan and lower all-cause mortality. It does not recommend a regimen, advise on supplements, or claim therapeutic effects. It describes what trials and large-scale observational studies have found — effect sizes, study designs, and the methodological limits readers should be aware of when reading "longevity" content elsewhere.

A note on the word **longevity**. In the consumer wellness space, "longevity" gets used loosely to cover everything from caloric restriction to NAD+ infusions to compression boots. In peer-reviewed research it usually means one of three things: (1) reductions in all-cause mortality (the most robust endpoint), (2) extension of healthspan — years lived without major chronic disease, or (3) changes in biological-age markers like DNA methylation clocks. These are not interchangeable. A finding for one is not a finding for the others. This brief flags which is which throughout.

A note on translation. Almost everything that produces dramatic lifespan extension in mice (caloric restriction, rapamycin, metformin) produces much smaller and less consistent effects in non-human primates and humans. Effects that look enormous in *C. elegans* often disappear entirely in mammals. Be cautious of "longevity" claims that rest on model-organism data without human follow-through.

What this brief is not

Not advice. Not a recommended protocol. Not personalised guidance. Not a substitute for a clinician. Decisions about exercise, diet, medication, or supplementation should involve a qualified professional who can account for personal medical history, current conditions, medications, and goals.

Vulnerable populations — please read first

The interventions described in this brief have meaningful contraindications. Specifically:

- **People with a history of disordered eating** should be especially cautious about content describing caloric restriction or fasting. The research literature on caloric restriction is studied under controlled conditions; consumer adoption of "fasting for longevity" has been associated with disordered eating onset and relapse in vulnerable individuals.

- **People over 65** have different evidence bases — caloric restriction and prolonged fasting carry sarcopenia and frailty risks that change the risk-benefit calculation substantially. Most caloric-restriction research is on middle-aged adults.
- **Pregnancy and lactation** alter the safety profile of most interventions discussed below. Discuss any changes with an obstetric or primary-care clinician.
- **Type 1 and insulin-dependent type 2 diabetes** make fasting protocols medically inappropriate without close clinical supervision.
- **People on medications** — particularly cardiovascular, psychiatric, immunosuppressant, or anticoagulant — should expect that exercise intensity changes, dietary changes, or any supplement decision interacts with their treatment. Consult the prescribing clinician.

Proco does not recommend any of the interventions described in this brief for any individual reader.

How interventions are ordered

We've organised them roughly by **strength of evidence in humans**, with the most rigorously studied at the top. This is not a ranking of "most powerful" or "most worth doing." It's a ranking of "best understood" — the interventions where multiple high-quality human studies converge on a consistent finding.

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1. Smoking cessation

What research describes: This is the single most impactful longevity intervention in the entire literature. Doll and colleagues' 50-year British Doctors Study found that smoking cessation before age 40 restored most of the lost life expectancy; cessation at older ages restored progressively less but always more than continuing. Lifetime smokers lose approximately 10 years of life expectancy on average compared with never-smokers; quitting at 30 recovers nearly all of it, at 50 recovers around 6 years, at 60 around 3 years.

Study type: Multiple large prospective cohorts, decades-long follow-up, consistent across populations.

Key caveat: Effect size is so large and so consistent that it can crowd out smaller interventions in discussion. Most "longevity protocols" sold to non-smokers omit this because it doesn't apply — but in the literature, no other intervention comes close.

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2. Cardiorespiratory fitness (VO2 max)

What research describes: Mandsager and colleagues (JAMA Network Open, 2018) analysed 122,000 patients tested on treadmill protocols and found that all-cause mortality scaled almost monotonically with cardiorespiratory fitness. Moving from "below average" to "above average" fitness was associated with substantially lower mortality (hazard ratio ~0.40). The dose-response continues into elite fitness ranges; there is no clear upper limit at which more fitness stops being associated with lower mortality.

Study type: Large prospective observational. Mendelian randomisation studies (using genetic variants associated with fitness as instruments) support a causal interpretation.

Key caveats: VO2 max is largely modifiable through training. The association may overstate the modifiable component because some VO2 max variation is genetic. Effect estimates in studies are adjusted for the major confounders but residual confounding from healthy-user bias remains plausible.

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3. Regular physical activity (any kind)

What research describes: Pooled meta-analyses (Ekelund et al., BMJ 2019; Saint-Maurice et al., JAMA 2020) describe a dose-response between physical activity and all-cause mortality. Moving from sedentary (<5,000 steps/day, no structured exercise) to moderately active (~7,000–10,000 steps/day or 150 minutes of moderate-intensity activity per week) is associated with hazard ratios around 0.50–0.65 for all-cause mortality. The curve flattens above ~10,000 steps but does not reverse.

Study type: Multiple large observational cohorts with accelerometer-measured activity (which is more reliable than self-report).

Key caveats: The "10,000 steps" figure is a useful benchmark but the actual research suggests benefit accrues well below that level — meaningful mortality reductions start around 5,000–7,000 steps/day in older adults. Reverse causation (sick people move less) is partially addressed by sensitivity analyses but cannot be fully eliminated.

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4. Resistance training and muscle mass

What research describes: Saeidifard and colleagues (American Journal of Preventive Medicine, 2019) meta-analysed 11 cohorts and found that resistance training participation 30–60 minutes per week was associated with ~17% lower all-cause mortality, independent of aerobic activity. Grip strength — a proxy for whole-body muscle function — is one of the strongest single-variable predictors of all-cause mortality in older adults (Leong et al., Lancet 2015), with each 5 kg decrement associated with measurably higher mortality.

Study type: Observational cohorts. Mechanistic literature is strong (sarcopenia → falls, metabolic dysfunction, frailty); randomised trials of resistance training in older adults show consistent functional benefits.

Key caveats: Independent contribution of resistance training over and above aerobic activity is harder to isolate. Combined exercise (resistance plus aerobic) has the strongest evidence for older adult populations.

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5. Diet quality (Mediterranean-pattern diets)

What research describes: The PREDIMED trial (Estruch et al., New England Journal of Medicine, 2013, with reanalysis in 2018) randomised over 7,000 high-cardiovascular-risk participants to a Mediterranean-pattern diet (supplemented with extra-virgin olive oil or mixed nuts) versus a low-fat control. The Mediterranean groups showed approximately 30% lower incidence of major cardiovascular events over a median 4.8 years. Long-term cohort data (Trichopoulou et al., NEJM 2003; multiple subsequent cohorts) describe consistent inverse associations between Mediterranean-diet adherence and all-cause mortality.

Study type: Large randomised trial (rare in nutrition research) plus consistent observational cohort evidence.

Key caveats: PREDIMED had some randomisation issues that were re-analysed and the conclusions held but the original trial design had limitations. "Mediterranean diet" is a heterogeneous pattern, not a single regimen — exact components vary by study. Adherence in real-world settings is far lower than trial conditions.

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6. Sleep duration and quality

What research describes: Meta-analyses describe a U-shaped relationship between sleep duration and all-cause mortality, with lowest mortality typically associated with 7 hours of sleep and increased mortality below 6 or above 9 hours (Cappuccio et al., Sleep 2010; Yin et al., Journal of the American Heart Association 2017). Effect sizes for the short-sleep tail (HR ~1.10–1.15) are smaller than for physical activity or smoking but are consistent across populations. Sleep apnea, where present, has a much larger association with mortality and cardiovascular outcomes.

Study type: Observational cohort meta-analyses; mechanistic evidence from sleep-restriction studies is robust.

Key caveats: The long-sleep tail (>9 hours) likely reflects underlying illness rather than long sleep causing mortality. Self-reported sleep duration is unreliable; the few studies using polysomnography or actigraphy show somewhat different patterns. See Proco's Sleep Research Brief for fuller treatment.

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7. Caloric restriction and time-restricted eating

What research describes: This is the area where consumer "longevity" content most diverges from the research. The CALERIE trial (Ravussin et al., 2015; Kraus et al., Lancet Diabetes & Endocrinology 2019) randomised 220 non-obese adults to 25% caloric restriction or ad-libitum eating over 2 years. The CR group achieved about 12% restriction in practice (not 25%) and showed measurable improvements in cardiometabolic risk markers — lower blood pressure, lower LDL, improved insulin sensitivity. CR also produced sustained changes in some biomarkers of biological aging.

The trial **did not** measure lifespan or mortality, because the follow-up was too short. The mortality and lifespan claims associated with caloric restriction in humans rest on mechanistic extrapolation, not direct measurement.

For **time-restricted eating** (eating within a defined daily window, often 8–10 hours), short-term trials show modest weight loss and metabolic improvements but no convincing additional benefit beyond what total-calorie reduction would explain. Liu et al. (NEJM 2022) compared time-restricted eating to calorie-restriction-only over 12 months and found no significant difference in weight loss or metabolic outcomes.

Study type: A few good randomised trials (mostly short duration), supplemented by extensive animal-model work that does not necessarily translate.

Key caveats: Outsized claims in the consumer space. The CR animal lifespan extension is dramatic in mice (~30%) and minimal-to-absent in non-human primates. The Wisconsin and NIA monkey trials disagreed on whether CR extended life at all; the consensus is small effects at most, dependent on diet composition. Caloric restriction also carries identifiable risks in older adults (muscle loss, bone density loss, fertility effects) that are not always disclosed in consumer content.

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8. Alcohol consumption

What research describes: Recent re-analyses (Zhao et al., JAMA Network Open, 2023; GBD 2020) have substantially revised earlier J-curve findings that suggested moderate drinking was protective. The current best interpretation: any apparent benefit of moderate drinking is largely explained by methodological problems with the comparison group (former drinkers, who tend to be sicker than lifelong abstainers, were often pooled with non-drinkers). Once that is corrected, the risk curve is essentially flat or slightly upward at low intake levels and clearly upward above ~10 g/day of pure ethanol (about one standard drink).

Study type: Large observational meta-analyses with methodological corrections.

Key caveats: The cardiovascular literature is genuinely mixed; some specific outcomes (e.g. ischemic heart disease) may show small protective associations at low intake. But all-cause mortality and cancer risk show no protective effect of moderate drinking when methodological adjustments are made. The earlier "red wine is good for you" framing does not survive current methodology.

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9. Pharmacological geroscience (metformin, rapamycin)

What research describes: Two repurposed drugs have generated the most attention. **Metformin**, a first-line type 2 diabetes drug, has shown reduced all-cause mortality in observational comparisons of diabetic patients on metformin versus other diabetes treatments — but this is a comparison within a sick population, not evidence that metformin extends life in healthy adults. The TAME trial (Targeting Aging with Metformin), designed to test this directly, has been in funding/planning for years and not yet reported.

Rapamycin extends lifespan in mice (~10–15% in median lifespan in the ITP studies). Human data is limited to short-term immune and metabolic biomarker studies. The PEARL trial (low-dose rapamycin in healthy adults) has reported preliminary safety data but no longevity outcomes. Side effect profiles in chronic use (immunosuppression, glucose dysregulation, mouth ulcers) are non-trivial.

Study type: For metformin: large observational data in diabetic populations, no completed RCT in healthy adults. For rapamycin: strong animal data, very limited human data.

Key caveats: Both are prescription medications. Off-label use for "longevity" is widespread in some communities and is not supported by completed clinical trials. The geroscience field is genuinely promising; the evidence base does not yet support consumer adoption.

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10. NAD+ precursors, senolytics, and other consumer supplements

What research describes: NAD+ precursors (nicotinamide riboside, NMN) increase circulating NAD+ levels in humans (Martens et al., Nature Communications 2018; Yoshino et al., Science 2021). Whether this translates into longevity, healthspan, or any meaningful clinical outcome is unresolved — short trials have shown some metabolic improvements but no clear functional benefits in otherwise-healthy adults. Senolytic compounds (dasatinib + quercetin, fisetin) have promising early data in animals and very small human trials in specific disease contexts. Resveratrol — once heavily marketed — has not held up in larger human trials.

Study type: Short-duration human trials measuring biomarkers, not clinical endpoints. Animal data ranges from suggestive to strong depending on the molecule.

Key caveats: The consumer supplement market for "longevity" compounds is large and largely outpaces the evidence. Claims of "biological age reduction" are typically based on DNA methylation clocks that are themselves still being validated as health-relevant. Independent human trials of consumer-purchased product quality, dose, and outcome are mostly absent.

What the brief deliberately does not include

- **Specific supplement recommendations.** This is content scope: Proco describes what the research literature reports, not which products to take.

- **Personalised regimens.** Tailoring depends on individual context that no general content piece can address.
- **Biomarker-target charts.** Optimal levels for individuals depend on age, sex, medical history, and clinical context.
- **Anti-aging clinic protocols.** Many proprietary protocols sold direct-to-consumer rest on heterogeneous and often weak evidence; we don't catalogue them.

How to read longevity content elsewhere

A few tests you can apply to any longevity claim:

Did the study measure mortality, or a biomarker? Biomarkers are useful but they're a proxy, not the outcome. "Reduces biological age by 3 years" usually means a methylation clock changed; whether that translates to actual longer life is not established.

Was the study in humans? Mouse, worm, and yeast longevity data is foundational but does not reliably translate. Translation rates from animal model to human are low across all medical research domains.

What was the follow-up? Longevity is a long-time-horizon outcome. A 12-week trial cannot meaningfully test life-extension claims; it can only test short-term biomarker changes.

Who funded the study? Supplement industry funding is widespread in the longevity space and is associated with reporting bias.

What was the comparison group? Was it the right control? In nutrition and supplement research, the choice of comparator dramatically changes apparent effect sizes.

How Proco approaches longevity content

Our editorial position: most of what's described as "longevity science" in the consumer space conflates three distinct things — extending lifespan, extending healthspan, and changing biological-age biomarkers. The research on extending all-cause mortality in healthy adults converges on a small number of well-evidenced interventions (don't smoke, maintain cardiorespiratory fitness, eat a Mediterranean-pattern diet, sleep 7–8 hours, maintain muscle mass, limit alcohol). Most of the rest is more uncertain than the consumer presentation suggests.

We publish citation-dense content describing what the research actually says, including the uncertainty. We do not market protocols, regimens, supplements, or "longevity stacks." If a Proco piece tells you what to do, it's failing our internal compliance standards and you should send us a correction.

Citations

Selected. Full reference list available on request to hello@procohq.com.

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• Saeidifard F, et al. The association of resistance training with mortality. American Journal of Preventive Medicine. 2019;57(2):232–240.

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• Kraus WE, et al. 2 years of calorie restriction and cardiometabolic risk (CALERIE). Lancet Diabetes & Endocrinology. 2019;7(9):673–683.

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• Zhao J, et al. Association between daily alcohol intake and risk of all-cause mortality. JAMA Network Open. 2023;6(3):e236185.

• Martens CR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. Nature Communications. 2018;9:1286.

About Proco

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