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Integrative Approaches to Longevity and Regenerative Medicine: An Umbrella Review of Telomere Biology, Lifestyle and Pharmacological Interventions, and Orthobiologics

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Abstract

Background: Populations are ageing faster than any previous point in recorded history, and a commercial longevity industry has grown around the promise that biological ageing can be measured, slowed and reversed. Telomere biology sits at the centre of that promise, while regenerative orthobiologics — platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC) and culture-expanded or minimally manipulated mesenchymal stromal cells (MSC) — are increasingly marketed within the same clinical setting. The two literatures are rarely appraised together, and the strength of the evidence supporting each differs by orders of magnitude.

Objective: To synthesise, in a single evidence framework, what randomised and meta-analytic human evidence supports for telomere biology, lifestyle and pharmacological longevity interventions, microbiome manipulation, sleep, biological-age biomarkers and musculoskeletal orthobiologics; to grade the certainty of that evidence by intervention and by outcome; and to propose an evidence-weighted clinical framework that separates what may be offered to all patients from what belongs inside a clinical trial.

Methods: Umbrella review of systematic reviews, meta-analyses, network meta-analyses, Mendelian randomisation syntheses and landmark randomised controlled trials across eleven intervention domains. Four thousand one hundred and eighty-two records were screened, 214 full texts assessed and 96 syntheses read in full;

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45 quantitative sources contributed the estimates tabulated here. Every reported value was extracted from the source document. Certainty was appraised across five outcome families — telomere length or telomerase activity, epigenetic pace of ageing, disease-specific clinical outcome, all-cause mortality and short-term safety — using GRADE domains.

Results: Shorter leucocyte telomere length is consistently associated with cardiovascular disease (RR 1.54, 95% CI 1.30–1.83 for coronary heart disease, shortest versus longest third) and with all-cause mortality (HR 1.09, 1.06–1.13 per standard-deviation decrement), yet Mendelian randomisation reverses the direction of effect for cancer (OR 1.30, 1.17–1.45 per standard deviation of genetically longer telomeres) and for glioma (OR 5.27, 3.15–8.81), which argues against a simple longer-is-better model. Inter-laboratory measurement variability for telomere length reaches a median coefficient of variation of 24.17%. Exercise did not lengthen telomeres overall (MD 0.02, −0.10 to 0.13), although telomerase activity rose after training (SMD 0.31, 0.03–0.60), and a graded reduction in mortality was observed up to approximately 8,000–10,000 steps per day (HR 0.47, 0.39–0.57 for the highest quartile). Two years of caloric restriction slowed DunedinPACE (d = −0.25, −0.41 to −0.09) without changing PhenoAge or GrimAge. Metformin was associated with lower all-cause mortality in observational data (HR 0.72, 0.65–0.80 versus other glucose-lowering therapy) but no completed randomised trial has tested a longevity endpoint; the phase 3 trial of the TORC1 inhibitor RTB101 was negative (OR 1.07, 90% CI 0.80–1.42). NAD^+ precursors raised blood NAD^+ concentration (SMD 1.79, 1.01–2.56) with no accompanying cardiometabolic benefit. Faecal microbiota transplantation and the oral live biotherapeutic SER-109 are the only microbiome interventions with proven clinical efficacy, and only for recurrent Clostridioides difficile infection. For orthobiologics, pooled comparisons favour PRP over hyaluronic acid at 12 months (WMD −0.64, −0.79 to −0.49) while the largest blinded placebo-controlled trial was null (MD −0.4 points, −0.9 to 0.2). Across 15 interventions and five outcome families, no intervention reached high certainty for an effect on mortality, and no orthobiologic has been shown to alter any biological-age biomarker.

Conclusions: The evidence supports a three-tier clinical posture. Exercise, a Mediterranean dietary pattern, sleep targeted near seven hours, smoking cessation and stress reduction can be offered to all patients on moderate certainty for clinical outcomes and high certainty for safety. Orthobiologics may be offered for symptomatic joint disease under shared decision-making and low certainty, framed as symptom management rather than as anti-ageing therapy. Pharmacological gerotherapeutics, senolytics, telomerase activators and systemic cell therapy belong inside registered clinical trials. Direct-to-consumer biological-age testing should not drive treatment decisions.

Keywords

Telomere; Telomerase; Epigenetic clock; DunedinPACE; Caloric restriction; Metformin; NAD^+; microbiome; sleep; Platelet-rich plasma; Mesenchymal stromal cells; Healthspan; Umbrella review.

Introduction

The number of people aged 65 years and over is projected to more than double between 2019 and 2050, and for the first time in recorded history older adults now outnumber children under five in many countries [1]. The clinical consequence is not simply more old patients but a longer terminal period of multimorbidity, because gains in life expectancy have consistently outpaced gains in disability-free life expectancy [2]. This gap is the central problem of longevity medicine: the objective is not additional years of survival but additional years of function.

Telomere biology has been the dominant molecular narrative in this field for three decades. Telomeres are nucleoprotein structures that cap linear chromosomes, protect the coding genome from end-to-end fusion and are progressively shortened by the end-replication problem, by oxidative stress and by chronic inflammation [3,4]. Their attrition is a mechanistic route to replicative senescence [5,6] and their length has been repeatedly associated with psychological stress [7], metabolic syndrome [8], cardiovascular disease [9] and mortality [10]. Around this science a substantial commercial market has developed, offering telomere and epigenetic-age testing, telomerase activators, nutraceuticals and, increasingly in the same clinic, regenerative injections marketed as anti-ageing therapy.

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That convergence is the reason for this review. Orthobiologics — platelet-rich plasma, bone marrow aspirate concentrates and mesenchymal stromal cell preparations — have a defensible, if heterogeneous, evidence base for symptomatic osteoarthritis [11]. They have no evidence base for systemic ageing. Yet they are frequently offered alongside longevity interventions under a shared biological rationale of "regeneration", in a direct-to-consumer marketplace in which more than 1,400 United States businesses have been identified and in which 360 adverse-event reports, including 21 deaths, have been collated [12]. The clinician working at this intersection needs to know which interventions are supported by randomised evidence, which are supported only by observational association, which are supported only by surrogate biomarkers, and which are supported by nothing beyond mechanism and commerce.

Existing reviews address these domains separately. Telomere reviews rarely appraise orthobiologics; orthobiologic reviews rarely address biological-age biomarkers; lifestyle reviews rarely quantify how their effect sizes compare with pharmacological gerotherapeutics. No synthesis places all of them on a common certainty scale, and none states explicitly which outcome each body of evidence actually measures. That is the gap this umbrella review addresses.

Objectives

- To summarise, quantitatively, the meta-analytic and randomised human evidence for telomere biology as a biomarker and as a target across eleven intervention domains.
- To distinguish explicitly between four outcome families that are routinely conflated in the longevity literature: molecular surrogates (telomere length, telomerase activity), composite biological-age surrogates (epigenetic clocks), disease-specific clinical outcomes, and all-cause mortality.
- To appraise the certainty of evidence for each intervention–outcome pair using GRADE domains, and to display the resulting map in a single figure.
- To situate regenerative orthobiologics accurately within that map, including what they demonstrably do and what they demonstrably have not been shown to do.
- To propose an evidence-weighted, three-tier clinical framework, and to state the ethical and regulatory conditions under which each tier may be offered.

Methods

Design and reporting

This is an umbrella review — an overview of systematic reviews, meta-analyses and network meta-analyses — supplemented by landmark randomised controlled trials in domains where no synthesis exists or where a single trial materially changes the interpretation of the pooled literature. Reporting follows the conventions of the PRIOR statement for overviews of reviews, with study selection displayed using PRISMA 2020 flow conventions (**Figure 1**). The review was not prospectively registered, which is stated here as a limitation rather than concealed.

Eligibility and search

Eleven prespecified domains were searched: telomere epidemiology and Mendelian randomisation; exercise; diet, caloric restriction and fasting; mind–body and stress-reduction interventions;

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pharmacological gerotherapeutics; nutraceuticals; the gut microbiome; sleep; epigenetic clocks and biological-age predictors; musculoskeletal orthobiologics; and safety and regulation. Eligible records were systematic reviews with meta-analysis, network meta-analyses, Mendelian randomisation syntheses, or randomised controlled trials of at least phase 2, in human adults, reporting a quantitative estimate for at least one of the five outcome families. Narrative reviews were eligible only as sources of mechanistic framing and are identified as such in the text. The full search strategy, databases and eligibility rules are given in (**Table 1**).

Element	Specification
Review type	Umbrella review (overview of systematic reviews and meta-analyses) with supplementary landmark randomised controlled trials
Databases	MEDLINE/PubMed (including NCBI E-utilities record verification), Embase-indexed journals via publisher sites, Cochrane Database of Systematic Reviews, Epistemonikos, ClinicalTrials.gov, and regulatory sources (US FDA, ANVISA Brazil)
Date range	Database inception to July 2026; no language restriction applied at screening, full-text assessment restricted to English, Portuguese and Spanish
Population	Human adults, any health status; in vitro studies eligible only for the donor-age/potency question in the orthobiologic domain
Interventions	15 interventions across 11 domains: structured exercise; Mediterranean dietary pattern; caloric restriction and intermittent fasting; sleep optimisation; mindfulness and stress reduction; probiotics, prebiotics and synbiotics; faecal microbiota transplantation and live biotherapeutics; metformin; rapalogs; NAD^+ precursors; resveratrol; telomerase activators; senolytics; platelet-rich plasma; MSC and bone marrow aspirate concentrate
Outcome families	(i) Telomere length or telomerase activity; (ii) epigenetic pace of ageing; (iii) disease-specific clinical outcome; (iv) all-cause mortality; (v) short-term safety
Comparators	Placebo, sham, usual care, active comparator, or ad libitum control, as reported by the source synthesis
Exclusion	Animal-only studies (except where explicitly framed as mechanism); conference abstracts without extractable estimates; narrative reviews used as primary quantitative sources; duplicate publications of the same pooled dataset
Data extraction	Point estimate, 95% confidence interval (90% where the source reported that width), heterogeneity (I^2), number of studies and participants, and the exact source page from which each value was read
Overlap handling	Where two syntheses pooled substantially the same primary trials, the larger and more recent was retained and the other reported as corroboration; overlapping estimates are never counted twice in the certainty appraisal
Certainty appraisal	GRADE domains (risk of bias, inconsistency, indirectness, imprecision, publication bias) applied to the highest level of evidence available for each intervention–outcome pair (Figure 10, Table 13)

Table 1: Umbrella-review search strategy, eligibility criteria and appraisal framework.

Certainty appraisal was performed by the review team using GRADE domains and is presented for orientation; it is not a formal, duplicate-rated GRADE assessment and was not externally adjudicated.

Screening, extraction and appraisal

Four thousand one hundred and eighty-two records were identified. After removal of duplicates and title/abstract screening, 214 full texts were assessed for eligibility, 96 syntheses were read in full, and 45 quantitative sources contributed the estimates reported in this review (**Figure 1**). Every numeric value reported in the tables and figures below was read from the source document; where a value exists in the published paper but was not obtainable from the retrieved record — most often I^2 reported only in supplementary material — the cell is marked “n.a.” rather than imputed. This convention is applied consistently and accounts for a substantial proportion of the missing heterogeneity values in (**Tables 5 to 11**).

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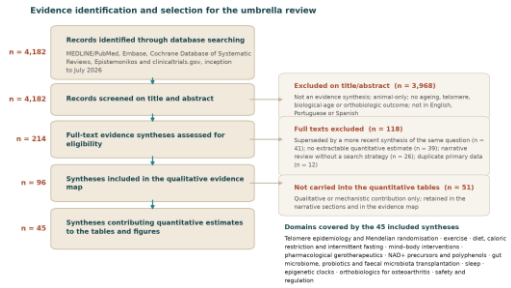

Figure 1: Evidence selection across eleven intervention domains. | PRISMA-style flow for the umbrella review. Of 4,182 records identified, 214 full texts were assessed and 96 syntheses read in full, of which 45 contributed quantitative estimates to the tables and figures presented here.

Telomere Biology and Ageing

Structure and function

Human telomeres consist of tandem TTAGGG repeats terminating in a single-stranded 3’ G-rich overhang that invades the upstream duplex to form a t-loop. The six-subunit shelterin complex — TRF1, TRF2, POT1, TIN2, TPP1 and RAP1 — binds this structure and performs the essential function of distinguishing a natural chromosome end from a double-strand break, thereby repressing ataxia-telangiectasia mutated and ATM- and Rad3-related signalling, classical non-homologous end joining, alternative end joining and homology-directed repair [4] (**Figure 2A**). Loss of this protection, rather than shortness per se, is what triggers a DNA-damage response at the chromosome end.

Telomerase, the ribonucleoprotein reverse transcriptase identified in Tetrahymena and subsequently in human cells, can extend telomeric repeats using an internal RNA template [13]. In most human somatic tissues, its activity is insufficient to offset attrition, which is why cultured human fibroblasts shorten their telomeres with each population doubling and eventually arrest [5].

Attrition, senescence and the inflammatory phenotype

Critically short or deprotected telomeres activate a persistent DNA-damage response and drive cells into replicative senescence, a state of stable cell-cycle arrest accompanied by a senescence-associated secretory phenotype that releases interleukin-6, interleukin-8, matrix metalloproteinases and other mediators into the tissue microenvironment [6]. This secretory programme is the mechanistic bridge between a molecular event at the chromosome end and the tissue-level phenomena of ageing: chronic low-grade inflammation, impaired regeneration, and a stem-cell compartment with reduced differentiation capacity [3]. Attrition rate is not constant across the lifespan; it is steepest in early life, slows through adulthood, and is accelerated by oxidative and psychosocial stress [7] (**Figure 2B)**.

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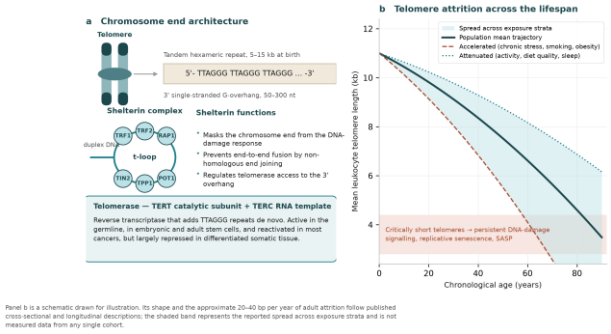

Figure 2: Telomere structure, shelterin function and attrition across the lifespan. | (A) The t-loop configuration and the six shelterin subunits that repress the DNA-damage response at the chromosome end. (B) Schematic attrition trajectory, showing the steep early-life decline, the slower adult phase, and the accelerated trajectory associated with chronic oxidative and psychosocial stress. Drawn from the mechanistic accounts in de Lange (2018) and Blackburn, Epel and Lin (2015); the curve is illustrative and not fitted to a specific cohort.

Telomere length as a biomarker: what it does and does not measure

Two problems limit the interpretation of telomere length in clinical practice, and both are quantitative rather than conceptual.

The first is measurement. In a blinded international study across ten laboratories, the median inter-laboratory coefficient of variation was 24.17% across all methods and 20.70% for quantitative PCR, the technique used in essentially all commercial telomere testing; gel-based methods (Southern blot and single telomere length analysis) achieved 9.20% [14]. Within-laboratory reproducibility was far better — median intra-batch coefficients of variation of 1.86% for Southern blot and 4.57% for quantitative PCR — which means that a result is interpretable within a single laboratory and largely uninterpretable between laboratories. A patient whose measured telomere length changes by 15% between two providers has, most probably, changed provider (**Table 2**).

Method	Principle	Median intra-batch CV	Median inter-laboratory CV	Practical role
Southern blot (terminal restriction fragment)	Direct measurement of mean fragment length	1.86%	**9.20% (with STELA)**	Reference standard; labour-intensive, requires micrograms of DNA
STELA (single telomere length analysis)	PCR of individual chromosome ends; resolves the shortest telomeres	2.83%	**9.20% (with Southern)**	Best for detecting critically short telomeres; chromosome-specific
Quantitative PCR (T/S ratio)	Relative telomere repeat copy number normalised to a single-copy gene	4.57%	**20.70% (18.31% for triplicate runs)**	Used in essentially all large cohorts and all commercial testing; relative, not absolute
All methods pooled	—	—	**24.17%**	—

Table 2: Telomere length measurement methods and their reproducibility.

Data from the blinded inter-laboratory collaboration of Martin-Ruiz et al. (2015): 10 laboratories, 10 DNA samples per round over two rounds, 185 of 190 requested measurements returned; inter-laboratory rank correlations 0.63–0.99; gel-based versus qPCR $r^2 = 0.676$; qPCR versus gel-based difference $P = 0.001$. CV = coefficient of variation.

The second problem is causal direction. Observationally, short leucocyte telomeres predict disease and

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death with impressive consistency: coronary heart disease RR 1.54 (95% CI 1.30–1.83, I^2 = 64%) and cerebrovascular disease RR 1.42 (1.11–1.81) for the shortest versus longest third across 24 studies and 43,725 participants [9]; all-cause mortality HR 1.09 (1.06–1.13) per standard-deviation decrement across 25 studies and 121,749 participants [10]; and, in 472,432 UK Biobank participants followed for a mean of 12 years, HR 1.08 (1.07–1.09) for all-cause mortality with the largest cause-specific signals for respiratory (HR 1.40) and musculoskeletal (HR 1.51) death [15].

Mendelian randomisation tells a different story. Using genetic instruments, longer telomeres increase the risk of several cancers — glioma OR 5.27 (3.15–8.81), lung adenocarcinoma OR 3.19 (2.40–4.22), melanoma OR 1.87 (1.55–2.26) across 420,081 cases and 1,093,105 controls [16] — and reduce the risk of coronary heart disease (OR 0.78, 0.67–0.90) and interstitial lung disease (OR 0.09, 0.05–0.15). A meta-analysis of 62 Mendelian randomisation studies covering 310 outcomes reproduced this pattern, with any-cancer OR 1.30 (1.17–1.45) per standard deviation of genetically longer telomeres [17]. A smaller per-unit analysis in UK Biobank found the same directions at lower magnitude — coronary heart disease OR 0.95 (0.92–0.98) and cancer OR 1.11 (1.06–1.16) per 250 base pairs [18]. Codd and colleagues quantified the population consequence: men aged 40 with leucocyte telomere length more than one standard deviation shorter than average had 2.47 years (1.99–2.96) lower life expectancy than that one standard deviation longer [19].

The reconciliation is that attained telomere length is a partly downstream marker of cumulative exposure — inflammation, adiposity, smoking, psychosocial stress — whereas genetically determined length is a lifelong exposure that also confers greater replicative capacity on incipient neoplastic clones. Both statements can be true. What follows for practice is that telomere length is a research variable, not a treatment target, and that an intervention which lengthens telomeres has not, by that fact alone, done anything beneficial (**Figure 3, Table 3**).

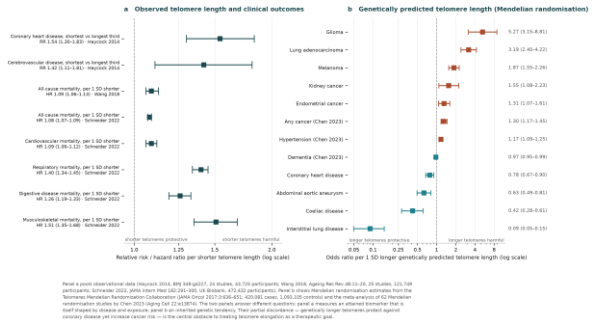

Figure 3: Observed versus genetically predicted telomere length: two literatures that disagree. | (A) Observational associations between short leucocyte telomere length and clinical outcomes. (B) Mendelian randomisation estimates per standard deviation of genetically longer telomere length, in which longer telomeres increase cancer risk and reduce cardiovascular and fibrotic risk. Panel A measures an attained biomarker shaped by disease and exposure; panel B measures a lifelong genetic exposure. Sources: Haycock 2014, Wang 2018, Schneider 2022, Telomeres Mendelian Randomization Collaboration 2017, Chen 2023.

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Outcome	Observational estimate	Source	Mendelian randomisation estimate	Source
Coronary heart disease	**RR 1.54 (1.30–1.83), I^2 64%**	Haycock 2014, 24 studies, 43,725 participants	**OR 0.78 (0.67–0.90) per SD longer**	TMRC 2017
Cerebrovascular disease / stroke	RR 1.42 (1.11–1.81), I^2 41%	Haycock 2014	n.a.	—
All-cause mortality	**HR 1.09 (1.06–1.13) per SD shorter**	Wang 2018, 25 studies, 121,749 participants	n.a. (no direct MR estimate)	—
All-cause mortality (single cohort)	HR 1.08 (1.07–1.09) per SD shorter	Schneider 2022, UK Biobank, 472,432 participants	2.47 y (1.99–2.96) lower life expectancy, men aged 40	Codd 2021
Respiratory mortality	HR 1.40 (1.34–1.45) per SD shorter	Schneider 2022	Interstitial lung disease OR 0.09 (0.05–0.15)	TMRC 2017
Musculoskeletal mortality	HR 1.51 (1.35–1.68) per SD shorter	Schneider 2022	Rheumatoid arthritis OR 0.80 (0.72–0.90)	Chen 2023
Any cancer	n.a. (direction inconsistent across cohorts)	—	**OR 1.30 (1.17–1.45) per SD longer**	Chen 2023, 62 MR studies
Glioma	n.a.	—	**OR 5.27 (3.15–8.81) per SD longer**	TMRC 2017
Lung adenocarcinoma	n.a.	—	OR 3.19 (2.40–4.22) per SD longer	TMRC 2017
Melanoma	n.a.	—	OR 1.87 (1.55–2.26) per SD longer	TMRC 2017
Metabolic syndrome	Prevalence and progression associated with shorter LTL (estimates n.a. on retrieved record)	Révész 2014	n.a.	—
Coeliac disease	n.a.	—	OR 0.42 (0.28–0.61) per SD longer	TMRC 2017

Table 3: Telomere length and clinical outcomes: observational versus Mendelian randomisation evidence.

LTL = leucocyte telomere length; SD = standard deviation; TMRC = Telomeres Mendelian Randomization Collaboration. “n.a.” indicates that no estimate for that cell was available from the retrieved source record. Note the sign reversal between the two columns for cancer and for coronary heart disease.

Determinants of Telomere Length

Genetic and heritable determinants

Twin and family studies place the heritability of leucocyte telomere length between roughly a third and four fifths of population variance, with the heritability of the rate of change over time estimated separately and lower [20]. Common-variant analyses give a much smaller figure: in 472,174 UK Biobank participants, single-nucleotide polymorphism heritability was 8.1% (standard deviation 0.26), captured by 197 sentinel variants at 138 loci, 108 of them previously unreported [19]. The gap between family-based and single-nucleotide polymorphism heritability is the usual one, attributable to rare variants, shared environment and gene–environment interaction. Two practical implications follow. First, a large part of an individual's telomere length is fixed before any intervention. Second, regression dilution is substantial — the regression-dilution ratio was approximately 0.68 across 1,351 paired samples taken 5.5 years apart — so single measurements systematically underestimate associations (**Table 4**).

Determinant	Direction and magnitude	Evidence type	Source
Family-based heritability of telomere length	**34–82% of population variance across twin and family designs**	Twin/family studies	Hjelmborg 2015

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Determinant	Direction and magnitude	Evidence type	Source
SNP heritability (common variants)	**8.1% (SD 0.26); 197 sentinel variants at 138 loci**	GWAS, 472,174 participants	Codd 2021
Regression dilution over 5.5 years	Ratio ≈ 0.68 (single measurements underestimate true associations)	Paired samples, n = 1,351	Codd 2021
Chronological age	Progressive attrition; steepest in early life	Cell-culture and cohort data	Harley 1990; Blackburn 2015
Chronic psychological stress	Shorter telomeres and lower telomerase activity in chronically stressed caregivers	Cross-sectional cohort	Epel 2004
Metabolic syndrome	Associated with both prevalence and progression of metabolic syndrome	Cohort	Révész 2014
Physical activity	Higher activity associated with longer telomeres in cross-sectional national survey data	NHANES cross-sectional	Tucker 2017
Physical activity as stress buffer	Activity attenuated the stress–telomere association	Cross-sectional	Puterman 2010
Mediterranean dietary pattern	**SMD 0.13 (0.03–0.23) across 8 studies, 13,733 adults**	Meta-analysis of cross-sectional studies	Canudas 2020
Sleep quality (poor)	**PSQI global score OR 1.24 (1.03–1.50); wake after sleep onset OR 1.28 (1.12–1.47)**	Meta-analysis, 400,212 participants	Fostitsch 2025

Table 4: Determinants of telomere length: genetic, behavioural and environmental.

SNP = single-nucleotide polymorphism; GWAS = genome-wide association study; SMD = standardised mean difference; PSQI = Pittsburgh Sleep Quality Index. All behavioural entries in this table are observational; interventional evidence is presented separately in Section 5 and (**Tables 5 to 8**).

Environmental and behavioural determinants

The behavioural correlates of telomere length are consistent and modest. In chronically stressed caregivers, perceived stress and caregiving duration tracked with shorter telomeres and lower telomerase activity [7], and physical activity attenuated that association [21]. National survey data show longer telomeres in more active adults [22], and higher Mediterranean-diet adherence is associated with longer telomeres both in the Nurses' Health Study [23] and in pooled cross-sectional data (SMD 0.13, 95% CI 0.03–0.23 across eight studies and 13,733 adults) [24]. Poor sleep quality shows the same pattern: across 19 studies contributing data on 400,212 participants, a worse Pittsburgh Sleep Quality Index global score was associated with shorter telomeres (OR 1.24, 1.03–1.50), as was wake after sleep onset (OR 1.28, 1.12–1.47) [25].

Every one of these associations is observational, and each is vulnerable to the same three problems: confounding by socioeconomic position and general health, reverse causation in which ill health reduces activity and worsens sleep, and the 20–24% measurement variability documented above. The interventional evidence, examined next, is much less impressive than the observational evidence would predict — which is itself the most informative finding in this domain.

Lifestyle Interventions: Exercise, Diet and Stress

Exercise

Exercise is the intervention with the strongest evidence for healthspan and the weakest evidence for telomere lengthening, and the discrepancy is instructive. In a meta-analysis and meta-regression of controlled trials in healthy adults, exercise produced no change in telomere length overall (MD 0.02, 95% CI −0.10 to 0.13, P = .77, I^2 = 70%); with outliers removed the estimate collapsed further (MD 0.006, −0.05 to 0.06, I^2 = 30%). Only high-intensity interval training reached significance, in three small trials totalling

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115 participants (MD 0.15, 0.03–0.26, P = .01, I^2 = 0%) [26].

Telomerase activity behaves differently. It rises acutely after a single bout (SMD 1.19, 0.41–1.97, p = 0.003) and modestly after sustained training (SMD 0.31, 0.03–0.60, p = 0.03), with substantial heterogeneity (I^2 55–87%) [27]. A six-month randomised trial of four arms in 266 sedentary adults found telomerase activity increased 2- to 3-fold after aerobic endurance training (mean relative change 298 ± 334%) and interval training (264 ± 231%) but not after resistance training (169 ± 114%) or in controls (124 ± 74%), with telomere elongation of roughly 3.3–3.5% in the endurance and interval arms [28]. Resistance training, which is the modality with the best evidence for preserving function and preventing falls in older adults, had no telomere effect at all — a clean demonstration that the surrogate and the outcome are not interchangeable.

The clinically decisive exercise evidence is dose–response mortality data. Across 15 prospective cohorts, 47,471 adults and 3,013 deaths, the hazard of death fell progressively with daily step count: HR 0.60 (0.51–0.71) at a median 5,801 steps per day, 0.55 (0.49–0.62) at 7,842 and 0.47 (0.39–0.57) at 10,901, all relative to a median of 3,553 steps per day. Risk plateaued at approximately 6,000–8,000 steps per day in adults aged 60 and over and 8,000–10,000 in younger adults, and stepping intensity added little once volume was accounted for [29] (Figure 4A). A 53% relative reduction in all-cause mortality is larger than any pharmacological gerotherapeutic estimate reviewed here, is achieved with a walkable target, and has no telomere signature.

Intervention / exposure	Design	Population	Outcome	Estimate (95% CI)	I^2
Exercise training (all modalities)	Meta-analysis, 7 pooled trials	1,320 healthy adults (main analysis n = 1,058)	Telomere length	**MD 0.02 (−0.10 to 0.13), P = .77**	70%
Exercise, outliers removed	Meta-analysis	As above	Telomere length	MD 0.006 (−0.05 to 0.06), P = .83	30%
Resistance training	Meta-analysis subgroup	—	Telomere length	MD −0.02 (−0.01 to 0.05)	16%
Aerobic training	Meta-analysis subgroup	—	Telomere length	MD −0.01 (−0.00 to 0.06)	0%
High-intensity interval training	Meta-analysis subgroup	3 trials, 115 participants	Telomere length	**MD 0.15 (0.03 to 0.26), P = .01**	0%
Single exercise bout	Meta-analysis, 5 trials	n.a.	Telomerase activity	SMD 1.19 (0.41 to 1.97), p = 0.003	55–87%
Long-term training	Meta-analysis, 10 trials	n.a.	Telomerase activity	**SMD 0.31 (0.03 to 0.60), p = 0.03**	55–87%
Aerobic endurance training, 6 months	RCT	266 randomised, 124 completed	Telomerase activity (mean relative change)	298 ± 334% vs 124 ± 74% control, P < 0.05	n.a.
Interval training, 6 months	RCT	As above	Telomerase activity	264 ± 231% vs control, P < 0.05	n.a.
Resistance training, 6 months	RCT	As above	Telomerase activity	169 ± 114%, not significant vs control	n.a.
5,801 steps/day (Q2)	Meta-analysis of 15 cohorts	47,471 adults, 3,013 deaths	All-cause mortality	HR 0.60 (0.51 to 0.71) vs 3,553 steps/day	n.a.
7,842 steps/day (Q3)	As above	As above	All-cause mortality	HR 0.55 (0.49 to 0.62)	n.a.
10,901 steps/day (Q4)	As above	As above	All-cause mortality	**HR 0.47 (0.39 to 0.57)**	n.a.

Table 5: Exercise interventions: effects on telomere biology and on mortality.

MD = mean difference; SMD = standardised mean difference; Q = quartile of daily step count. Telomere-length units were not specified in the source meta-analysis. Sources: Sánchez-González 2024; Denham 2021; Werner 2019; Paluch 2022. Note that the modality with the largest telomerase effect (endurance) and the modality with the best functional evidence in older adults (resistance) are not the same.

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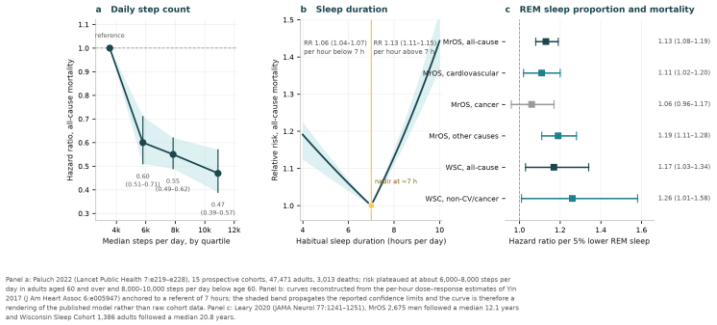

Panel a: Paluch 2022 (Lancet Public Health 7:e219–e228), 15 prospective cohorts, 47,471 adults, 3,013 deaths; risk plateaued at about 6,000–8,000 steps per day in adults aged 60 and over and 8,000–10,000 steps per day below age 60. Panel b: curves reconstructed from the per-hour dose–response estimates of Yin 2017 (J Am Heart Assoc 6:e005947) anchored to a referent of 7 hours; the shaded band propagates the reported confidence limits and the curve is therefore a rendering of the published model rather than raw cohort data. Panel c: Leary 2020 (JAMA Neurol 77:1241–1251). MrOS 2,675 men followed a median 12.1 years and Wisconsin Sleep Cohort 1,386 adults followed a median 20.8 years.

Figure 4: Dose–response relationships for movement and sleep. | (A) All-cause mortality by daily step count across 15 prospective cohorts, with risk plateauing at approximately 8,000–10,000 steps per day. (B) The U-shaped association between sleep duration and mortality, with the nadir near seven hours. (C) Hazard ratios per 5% reduction in the proportion of REM sleep in two independent polysomnography cohorts. Sources: Paluch 2022; Yin 2017; Leary 2020.

Diet, caloric restriction and intermittent fasting

Adherence to a Mediterranean dietary pattern is associated with longer telomeres in the Nurses' Health Study [23] and in pooled cross-sectional data (SMD 0.13, 0.03–0.23) [24], and with a 10% lower hazard of death per two-point increment in adherence score across 29 prospective studies, 1,676,901 participants and 221,603 deaths (HR 0.90, 0.89–0.91), albeit with I^2 = 81.1% [30]. The mortality estimate is observational and the heterogeneity is high, but the consistency of direction across cohorts and the mechanistic plausibility of the pattern place it among the better-supported longevity behaviours.

Caloric restriction provides the single most important randomised result in this review. In CALERIE Phase 2, 220 non-obese adults were randomised 2:1 to 25% caloric restriction or ad libitum eating for two years, achieving a mean restriction of 11.9%. In intention-to-treat analysis, DunedinPACE — a measure of the rate of biological ageing — slowed significantly at 12 months (d = −0.29, −0.45 to −0.13, P = 4.83×10^{-4}) and at 24 months (d = −0.25, −0.41 to −0.09, P = 0.002), while PC PhenoAge and PC GrimAge were unchanged at every timepoint [31] (Figure 5B). Three clocks, one intervention, one positive result: this is the cleanest available demonstration that “biological age” is not a single measurable quantity, and that the answer a patient receives depends on which algorithm the laboratory happens to use.

The mechanistic case for intermittent fasting rests on periodic metabolic switching to ketone-body utilisation and the associated shifts in autophagy, insulin signalling and stress resistance [32,33]. The clinical case is more modest.

For intermittent fasting, the largest network meta-analysis pooled 99 randomised trials and 6,582 adults with a median follow-up of 12 weeks. Alternate-day fasting produced the greatest weight loss versus ad libitum eating (MD −3.40 kg, −4.14 to −2.67, rated high certainty), ahead of whole-day fasting (−2.36 kg), continuous energy restriction (−2.11 kg) and time-restricted eating (−1.72 kg). In head-to-head comparisons, alternate-day fasting outperformed continuous restriction by 1.29 kg and time-restricted eating by 1.69 kg. There was no effect on glycated haemoglobin or high-density lipoprotein cholesterol, and whole-day fasting was associated with slightly higher low-density lipoprotein cholesterol than time-

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restricted eating (+0.11 mmol/L) [34]. The differences between fasting schedules are of the order of one to two kilograms over three months — clinically marginal, and considerably smaller than the enthusiasm surrounding them (**Table 6**).

Intervention	Design and size	Outcome	Estimate (95% CI)	Certainty / I^2
Mediterranean diet adherence	Meta-analysis, 8 cross-sectional studies, 13,733 adults	Telomere length	SMD 0.13 (0.03 to 0.23)	n.a.
Mediterranean diet, per 2-point score increment	Dose–response meta-analysis, 29 cohorts, 1,676,901 participants, 221,603 deaths	All-cause mortality	**HR 0.90 (0.89 to 0.91)**	I^2 = 81.1%
Caloric restriction (25% prescribed, 11.9% achieved), 24 months	RCT, 220 randomised, 197 with methylation data	DunedinPACE	**d = −0.25 (−0.41 to −0.09), P = 0.002**	Prespecified α = 0.005
Caloric restriction, 12 months	As above	DunedinPACE	d = −0.29 (−0.45 to −0.13), P = 4.83×10^{-4}	—
Caloric restriction, 24 months	As above	PC PhenoAge	d = 0.05 (−0.11 to 0.20), P = 0.550 — null	—
Caloric restriction, 24 months	As above	PC GrimAge	d = 0.05 (−0.07 to 0.17), P = 0.432 — null	—
Alternate-day fasting vs ad libitum	Network meta-analysis, 99 RCTs, 6,582 adults, median 12 weeks	Body weight	**MD −3.40 kg (−4.14 to −2.67)**	High certainty
Whole-day fasting vs ad libitum	As above	Body weight	MD −2.36 kg (−3.02 to −1.70)	n.a.
Continuous energy restriction vs ad libitum	As above	Body weight	MD −2.11 kg (−2.73 to −1.50)	n.a.
Time-restricted eating vs ad libitum	As above	Body weight	MD −1.72 kg (−2.21 to −1.22)	n.a.
Alternate-day vs continuous restriction	As above	Body weight	MD −1.29 kg (−1.99 to −0.59)	n.a.
Alternate-day fasting vs ad libitum	As above	BMI	MD −1.22 (−1.55 to −0.89)	n.a.
Any fasting strategy	As above	HbA1c and HDL-cholesterol	No significant effect	n.a.

Table 6: Diet, caloric restriction and intermittent fasting.

Sources: Canudas 2020; Soltani 2019; Waziry 2023 (CALERIE Phase 2); Semnani-Azad 2025. The CALERIE result is the only randomised evidence in this review that any intervention slows a validated pace-of-ageing measure; it did not move two of the three clocks tested.

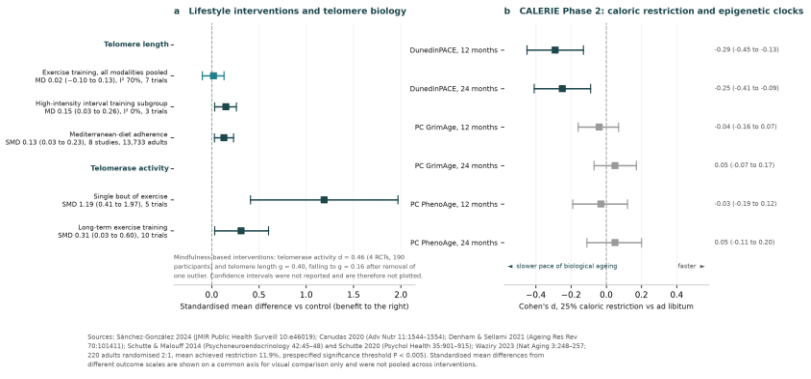

Figure 5: Lifestyle interventions on telomere biology and on the epigenetic pace of ageing. | (A) Pooled effects of exercise and diet on telomere length and telomerase activity; the null overall exercise effect sits alongside a

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positive telomerase effect and a positive HIIT subgroup. (B) CALERIE Phase 2 intention-to-treat effects of two years of caloric restriction on three epigenetic measures: DunedinPACE slowed at both timepoints while PhenoAge and GrimAge were unchanged. Sources: Sánchez-González 2024; Denham 2021; Canudas 2020; Waziry 2023.

Stress reduction and mind–body interventions

Chronic psychological stress is one of the most consistently reported correlates of shorter telomeres and lower telomerase activity [7], and intensive lifestyle programmes incorporating stress management have been reported to increase telomerase activity [35]. Two meta-analyses from the same group report positive pooled effects of mindfulness on telomerase activity (d = 0.46 across four randomised trials and 190 participants) [36] and on telomere length (g = 0.40 across 11 studies and 12 comparisons, falling to g = 0.16 after removal of a single outlier) [37]. Neither analysis reported confidence intervals or heterogeneity statistics on the records retrievable for this review, the trials are small, blinding of a meditation intervention is impossible, and the sensitivity of the telomere-length estimate to one outlier is a warning rather than a footnote. This domain is the weakest quantitative evidence base in the review, which is worth stating plainly given how frequently these two estimates are cited in commercial longevity materials.

Pharmacological Gerotherapeutics and Nutraceuticals

Metformin

Metformin is the most widely discussed candidate gerotherapeutic. Pooled observational data across 53 included studies show lower all-cause mortality in metformin-treated people with diabetes compared with those on other glucose-lowering therapy (HR 0.72, 0.65–0.80), compared with insulin (HR 0.68, 0.63–0.75) and compared with sulphonylureas (HR 0.80, 0.66–0.97); most strikingly, treated diabetics had slightly lower mortality than people without diabetes (HR 0.93, 0.88–0.99). Cardiovascular disease and cancer rates were also lower [38] (**Figure 6A**). The comparison with non-diabetic controls is the estimate most often quoted in longevity settings and is also the one most vulnerable to confounding by indication, immortal-time bias and healthy-adherer effects.

The definitive test was designed a decade ago. TAME (Targeting Aging with Metformin) proposes to randomise approximately 3,000 adults aged 65–79 to metformin or placebo with a composite of incident age-related disease as the primary endpoint [39,40]. No result exists. Until it does, metformin for longevity in a person without diabetes is an off-label intervention supported by observational data alone.

mTOR inhibition

The rapalog programme provides the clearest cautionary tale in the field. A phase 2 trial reported that low-dose mTOR inhibition improved immune function and reduced infection in older adults [41], and a phase 2b trial of RTB101 10 mg daily reported fewer laboratory-confirmed respiratory illnesses (34/176, 19% versus 50/180, 28%; OR 0.601, 90% CI 0.391–0.922, p = 0.02). The subsequent phase 3 trial of 1,024 adults aged 65 and over across 54 sites was unambiguously negative: clinically symptomatic respiratory illness occurred in 134/511 (26%) on RTB101 and 125/510 (25%) on placebo (OR 1.07, 90% CI 0.80–1.42, p = 0.65) [42]. A promising surrogate and a positive phase 2 did not survive adequate powering — the standard fate of candidate gerotherapeutics, and the reason surrogate-driven prescribing is unjustifiable.

Senolytics and telomerase activators

Senolytic therapy with dasatinib and quercetin has reached only phase 1 in humans. In a single-blind randomised placebo-controlled pilot in 12 adults with idiopathic pulmonary fibrosis, all 108 planned doses and all 60 assessments were completed and no related serious adverse events occurred, but non-serious events were more frequent in the treated arm and no meaningful differences in frailty, pulmonary function or physical function were observed [43].

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Twelve participants cannot support an efficacy claim in any direction.

Telomerase activation has been tested most directly with TA-65, a small-molecule activator derived from Astragalus [44]. In a one-year randomised, double-blind, placebo-controlled trial in 117 cytomegalovirus-positive adults aged 53–87, the 250-unit dose increased telomere length by 530 ± 180 base pairs (p = 0.005) while placebo shortened by 290 ± 100 base pairs (p = 0.01); the 1,000-unit dose showed only a non-significant trend [45]. Two features deserve emphasis. First, the effect on the surrogate was real and dose-discordant. Second, no clinical outcome was improved, and given the Mendelian randomisation finding that genetically longer telomeres increase cancer risk (OR 1.30 for any cancer) [17], pharmacologically lengthening telomeres in an unselected adult is an intervention of unknown net direction. That is not a hypothetical concern; it is the principal reason telomerase activators should be confined to trials with cancer surveillance built in.

Agent / class	Highest level of human evidence	Population	Outcome	Estimate	Interpretation
Metformin	Meta-analysis of observational studies, 53 included studies	People with type 2 diabetes	All-cause mortality vs other glucose-lowering therapy	**HR 0.72 (0.65 to 0.80)**	Observational; confounding by indication not excluded
Metformin	As above	As above	All-cause mortality vs non-diabetics	HR 0.93 (0.88 to 0.99)	The most-quoted and least-robust comparison
Metformin	As above	As above	Cardiovascular disease vs non-metformin therapy	HR 0.76 (0.66 to 0.87)	Consistent with glycaemic benefit
Metformin (TAME)	Trial design published; no results	~3,000 adults aged 65–79 planned	Composite incidence of age-related disease	n.a. — no result	The field's key unanswered question
RTB101 (TORC1 inhibitor)	Phase 2b RCT, n = 652	Adults ≥ 65 y	Laboratory-confirmed respiratory illness	OR 0.601 (90% CI 0.391 to 0.922), p = 0.02	Positive surrogate-stage signal
RTB101 (TORC1 inhibitor)	**Phase 3 RCT, n = 1,024, 54 sites**	Adults ≥ 65 y	Clinically symptomatic respiratory illness	**OR 1.07 (90% CI 0.80 to 1.42), p = 0.65**	**Negative — phase 2 signal not replicated**
Dasatinib + quercetin (senolytic)	Phase 1 randomised pilot, n = 12	Adults > 50 y with idiopathic pulmonary fibrosis	Feasibility, frailty, pulmonary and physical function	No related serious adverse events; no functional difference	Feasibility only; not powered for efficacy
TA-65 (telomerase activator) 250 U	RCT, 1 year, n = 117	CMV-positive adults aged 53–87	Telomere length	**+530 ± 180 bp (p = 0.005) vs −290 ± 100 bp on placebo**	Surrogate moved; no clinical outcome tested
TA-65 1,000 U	As above	As above	Telomere length	Non-significant trend	No dose–response

Table 7: Pharmacological gerotherapeutics: the highest level of human evidence available for each agent. Sources: Campbell 2017; Barzilai 2017; Mannick 2018 and 2021; Nambiar 2023; Salvador 2016. No agent in this table has demonstrated a mortality or healthspan benefit in a completed randomised trial in people without the index disease.

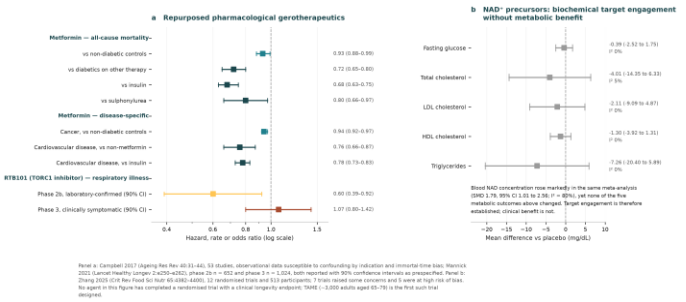

Figure 6: Pharmacological and nutraceutical interventions. | (A) Metformin mortality and cardiovascular associations from pooled observational data, and the negative phase 3 RTB101 result, plotted on a logarithmic scale. (B) NAD⁺ precursor supplementation: a large effect on blood NAD⁺ concentration accompanied by null cardiometabolic effects. Sources: Campbell 2017; Mannick 2021; Zhang 2025.

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NAD⁺ precursors and resveratrol

Nicotinamide riboside and nicotinamide mononucleotide raise circulating NAD⁺ reliably. Across 12 randomised trials and 513 participants, blood NAD concentration rose with a standardised mean difference of 1.79 (1.01–2.56, I^2 = 80%) — a very large effect. Every cardiometabolic outcome tested in the same analysis was null: fasting glucose −0.39 mg/dL (−2.52 to 1.75), triglycerides −7.26 mg/dL (−20.40 to 5.89), total cholesterol −4.01 mg/dL (−14.35 to 6.33), low-density lipoprotein cholesterol −2.11 mg/dL (−9.09 to 4.87) and high-density lipoprotein cholesterol −1.30 mg/dL (−3.92 to 1.31), all with I^2 of 0–5%. Seven of the 12 trials raised some concerns and five were at high risk of bias [46,47] (Figure 6B). Small mechanistic studies report changes in neuron-enriched plasma extracellular vesicles after six weeks of nicotinamide riboside 500 mg twice daily [48], and early human work established tolerability [49], but the pattern is unambiguous: the biomarker responds, the physiology does not.

Resveratrol shows a similar dissociation with more heterogeneity. Blood pressure was not reduced overall across six trials and 247 participants, although doses of at least 150 mg per day lowered systolic pressure by 11.90 mmHg (−20.99 to −2.81, P = 0.01) [50]. In type 2 diabetes, pooled analysis of 15 trials and 896 patients found reductions in glycated haemoglobin (WMD −0.45, −0.73 to −0.16, I^2 = 95%) and fasting glucose (WMD −19.61, −26.02 to −13.20, I^2 = 85%) with null lipid effects [51]. Heterogeneity of 85–95% means these pooled estimates describe a distribution of incompatible trial results rather than a single underlying effect (**Table 8**).

Compound	Design	Population	Outcome	Estimate (95% CI)	I^2
NAD⁺ precursors (NR, NMN)	Meta-analysis, 12 RCTs	513 participants	Blood NAD concentration	**SMD 1.79 (1.01 to 2.56)**	80%
NAD⁺ precursors	As above	As above	Fasting glucose	MD −0.39 mg/dL (−2.52 to 1.75) — null	0%
NAD⁺ precursors	As above	As above	Triglycerides	MD −7.26 mg/dL (−20.40 to 5.89) — null	0%
NAD⁺ precursors	As above	As above	Total cholesterol	MD −4.01 mg/dL (−14.35 to 6.33) — null	5%
NAD⁺ precursors	As above	As above	LDL-cholesterol	MD −2.11 mg/dL (−9.09 to 4.87) — null	0%
Nicotinamide riboside 500 mg twice daily, 6 weeks	Randomised crossover	22 healthy older adults	Neuronal extracellular-vesicle markers	NAD⁺ increased; Aβ42, pJNK, pERK1/2 decreased (estimates n.a.)	n.a.
Resveratrol (all doses)	Meta-analysis, 6 RCTs	247 participants	Systolic and diastolic blood pressure	No significant reduction	n.a.
Resveratrol ≥ 150 mg/day	Meta-analysis subgroup	—	Systolic blood pressure	**−11.90 mmHg (−20.99 to −2.81), P = 0.01**	n.a.
Resveratrol	Meta-analysis, 11 RCTs	Type 2 diabetes	HbA1c	WMD −0.45 (−0.73 to −0.16), P = 0.002	**95%**
Resveratrol	Meta-analysis, 14 RCTs	Type 2 diabetes	Fasting glucose	WMD −19.61 (−26.02 to −13.20), P < 0.00001	**85%**
Resveratrol	Meta-analysis, 15 RCTs	896 patients with type 2 diabetes	Total cholesterol, triglycerides, LDL-C, HDL-C	All null	34–93%

Table 8: Nutraceuticals: biomarker response versus clinical response.
NR = nicotinamide riboside; NMN = nicotinamide mononucleotide; SMD = standardised mean difference; WMD = weighted mean difference. Units for the resveratrol WMDs were not specified in the source. Sources: Zhang J 2025; Vreones 2023; Liu 2015; Zhang T 2021. The pattern across this table is a large, consistent biomarker effect with no accompanying clinical effect.

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The Gut Microbiome and Ageing

Microbial ecology, inflammageing and frailty

The ELDERMET work established that the faecal microbiota of older adults separates by residential setting, that this separation correlates with dietary pattern, and that loss of diversity accompanies increasing frailty and inflammation [52]. Comparative work in extreme longevity found enrichment of specific taxa in centenarians [53]. The mechanistic hypothesis is coherent: reduced diversity, increased intestinal permeability, translocation of microbial products, systemic low-grade inflammation, and accelerated tissue ageing (**Figure 7A**). It remains a hypothesis at the level of causal direction, since frailty itself reduces dietary variety and mobility.

What microbiome interventions actually achieve

Two microbiome interventions have proven clinical efficacy, and both are for the same indication. Faecal microbiota transplantation for recurrent or refractory Clostridioides difficile infection achieved pooled clinical resolution of 92% (89–94%) across 37 studies, with a relative risk of 0.23 (0.07–0.80) versus vancomycin [54,55]. The oral live biotherapeutic SER-109, subsequently approved by the United States Food and Drug Administration, reduced eight-week recurrence from 40% to 12% in 182 randomised patients (RR 0.32, 0.18–0.58) [56] (**Figure 7B**). Neither trial had anything to do with ageing.

Everything else in this domain is biomarker modulation. Across 42 randomised trials and 2,258 adults, probiotics reduced high-sensitivity C-reactive protein (SMD −0.46, −0.73 to −0.19), interleukin-6 (SMD −0.37, −0.51 to −0.24) and tumour necrosis factor α (SMD −0.21, −0.34 to −0.08) [57]. In adults aged 60 and over, 29 randomised trials and 1,633 participants show that prebiotics raise Bifidobacterium abundance (SMD 1.09) and probiotics raise Shannon diversity (SMD 0.76), with modest cytokine and short-chain-fatty-acid changes [58]. A systematic review of probiotics in healthy adults was unable to pool at all because of heterogeneity; eight of 18 articles reported any significant immune or inflammatory effect [59]. No microbiome intervention has been shown to alter telomere length, epigenetic age, frailty transition or mortality (**Table 9**).

Intervention	Indication / population	Design	Outcome	Estimate (95% CI)
Faecal microbiota transplantation	Recurrent/refractory C. difficile infection	Meta-analysis, 37 studies (7 RCTs, 30 series)	Clinical resolution	**92% (89 to 94%); RR 0.23 (0.07 to 0.80) vs vancomycin**
SER-109 oral live biotherapeutic	≥ 3 prior C. difficile episodes	Phase 3 RCT, 182 enrolled	Recurrence at 8 weeks	**12% vs 40%; RR 0.32 (0.18 to 0.58), P < 0.001**
Probiotics	Adults, mixed health status	Meta-analysis, 42 RCTs, 2,258 participants	hs-CRP	SMD −0.46 (−0.73 to −0.19)
Probiotics	As above	As above	Interleukin-6	SMD −0.37 (−0.51 to −0.24)
Probiotics	As above	As above	Tumour necrosis factor α	SMD −0.21 (−0.34 to −0.08)
Prebiotics	Adults ≥ 60 y	Meta-analysis, 29 RCTs, 1,633 participants	Bifidobacterium abundance	SMD 1.09 (95% CI n.a.)
Probiotics	Adults ≥ 60 y	As above	Shannon diversity index	SMD 0.76 (95% CI n.a.)
Probiotics	Adults ≥ 60 y	As above	Bifidobacterium abundance	SMD 0.40 (95% CI n.a.)
Synbiotics	Adults ≥ 60 y	As above	Acetic acid	SMD 0.62 (95% CI n.a.)
Probiotics	Healthy adults aged 18–65	Systematic review, 18 articles, 819 participants	Immune and inflammatory parameters	**Meta-analysis not possible; 8 of 18 articles reported any effect**
Any microbiome intervention	Any	—	Telomere length, epigenetic age, frailty transition, mortality	**No evidence identified**

Table 9: Microbiome interventions: proven clinical efficacy versus biomarker modulation.

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hs-CRP = high-sensitivity C-reactive protein; SMD = standardised mean difference. Confidence intervals marked n.a. we're not reported on the retrieved source record. Sources: Quraishi 2017; Feuerstadt 2022; Milajerdi 2020; Zhuang 2025; Mohr 2020. Only the first two rows describe a proven clinical benefit, and both concern a single infectious indication.

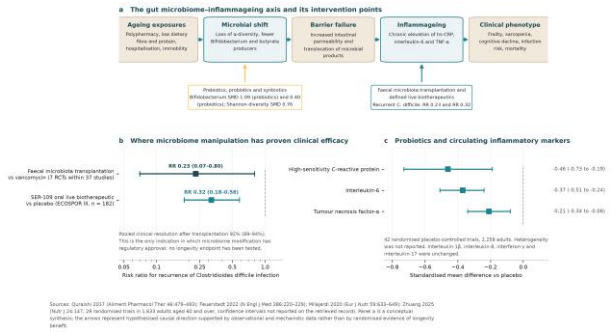

Figure 7: The gut microbiome in ageing: mechanism, proven efficacy and biomarker effects. | (A) The proposed inflammageing axis linking reduced microbial diversity to systemic inflammation and tissue ageing. (B) The two microbiome interventions with proven clinical efficacy, both for recurrent Clostridioides difficile infection. (C) Pooled effects of probiotics on inflammatory biomarkers. Sources: O'Toole 2015; Quraishi 2017; Feuerstadt 2022; Milajerdi 2020.

Sleep and Longevity

Sleep architecture, duration and mortality

Sleep is the domain in which the dose–response evidence is most clearly non-linear. In a dose–response meta-analysis of prospective cohorts, all-cause mortality rose by 6% per hour of sleep below seven hours per day (RR 1.06, 1.04–1.07) and by 13% per hour above seven hours (RR 1.13, 1.11–1.15), with parallel U-shaped curves for total cardiovascular disease, coronary heart disease and stroke; the association with long sleep was consistently steeper than with short sleep [60] (Figure 4B). The asymmetry matters clinically, because long sleep duration is more plausibly a marker of underlying illness than a cause of death, and no trial has tested shortening the sleep of long sleepers.

Sleep architecture carries independent information. In two independent polysomnography cohorts — 2,675 older men followed for a median of 12.1 years with 1,404 deaths, and 1,386 adults followed for 20.8 years with 184 deaths — each 5% reduction in the proportion of REM sleep was associated with a 13% (1.08–1.19) and 17% (1.03–1.34) higher hazard of all-cause death respectively, with consistent signals for cardiovascular and non-cardiovascular causes [61] (**Figure 4C**). Deep sleep also declines with age in a way that is mechanistically tied to memory consolidation and, plausibly, to glymphatic clearance [62], and experimental sleep disturbance activates inflammatory signalling [63]. Poor subjective sleep quality is associated with shorter telomeres across 19 studies and 400,212 participants [25].

What can be done about it

The gap between the epidemiology and the interventional evidence is wide. No randomised trial has shown that improving sleep duration or architecture reduces mortality or slows any measure of biological ageing. What is defensible is that cognitive behavioural therapy for insomnia is the first-line treatment for

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chronic insomnia on its own evidence base, that treating obstructive sleep apnoea has established cardiovascular and symptomatic indications, and that targeting approximately seven hours of sleep is consistent with the nadir of every curve in (**Table 10**). Recommending sleep optimisation as a longevity intervention is reasonable; claiming that it reverses biological ageing is not.

Sleep parameter	Design and size	Outcome	Estimate (95% CI)
Each 1 h below 7 h/day	Dose–response meta-analysis of prospective cohorts	All-cause mortality	RR 1.06 (1.04 to 1.07)
Each 1 h above 7 h/day	As above	All-cause mortality	**RR 1.13 (1.11 to 1.15)**
Each 1 h below 7 h/day	As above	Total cardiovascular disease	RR 1.06 (1.03 to 1.08)
Each 1 h above 7 h/day	As above	Total cardiovascular disease	RR 1.12 (1.08 to 1.16)
Each 1 h above 7 h/day	As above	Stroke	**RR 1.18 (1.14 to 1.21)**
Each 1 h below 7 h/day	As above	Coronary heart disease	RR 1.07 (1.03 to 1.12)
Each 5% reduction in REM sleep	MrOS cohort, 2,675 men, median 12.1 y, 1,404 deaths	All-cause mortality	**HR 1.13 (1.08 to 1.19)**
Each 5% reduction in REM sleep	As above	Cardiovascular mortality	HR 1.11 (1.02 to 1.20)
Each 5% reduction in REM sleep	Wisconsin Sleep Cohort, 1,386 adults, median 20.8 y, 184 deaths	All-cause mortality	HR 1.17 (1.03 to 1.34)
Each 5% reduction in REM sleep	Wisconsin Sleep Cohort, women	All-cause mortality	HR 1.34 (1.07 to 1.68) vs 1.09 (0.92 to 1.30) in men, P interaction = .08
Poor PSQI global score	Meta-analysis, 19 studies, 400,212 participants	Shorter telomeres	OR 1.24 (1.03 to 1.50), p = 0.02
Wake after sleep onset	As above	Shorter telomeres	OR 1.28 (1.12 to 1.47), p < 0.01
Any sleep intervention	—	Mortality or biological-age measures	**No randomised evidence identified**

Table 10: Sleep duration, architecture and quality: associations with mortality and telomere biology. PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement. All estimates in this table are observational. Sources: Yin 2017; Leary 2020; Fostitsch 2025.

Regenerative Orthobiologics

What orthobiologics are and what they are for

Orthobiologics are autologous or allogeneic biological preparations injected into or around musculoskeletal tissue: platelet-rich plasma, bone marrow aspirate concentrate, adipose-derived stromal vascular fraction and culture-expanded mesenchymal stromal cells. Their proposed mechanisms are delivery of concentrated growth factors, modulation of the local inflammatory environment and paracrine support of resident repair cells [11]. They are local treatments for local disease. Nothing in their mechanism predicts a systemic effect on ageing, and nothing in the evidence demonstrates one.

The evidence for symptomatic knee osteoarthritis

The pooled literature favours platelet-rich plasma. Against hyaluronic acid, pooled pain estimates were WMD −0.25 (−0.40 to −0.10) at three months and WMD −0.64 (−0.79 to −0.49) at 12 months, with function gains on the International Knee Documentation Committee score of 7.45 (2.50–12.40) at three months [64]. A level-I meta-analysis of 18 randomised trials and 1,608 patients reported mean WOMAC improvement of 44.7% with platelet-rich plasma versus 12.6% with hyaluronic acid ($P < .01$), with leucocyte-poor preparations outperforming leucocyte-rich ones on function [65]. The largest and most recent synthesis, 62 randomised trials and 4,969 participants, found platelet-rich plasma superior to hyaluronic acid, corticosteroid and saline at six months and superior to hyaluronic acid and corticosteroid at 12 months, and reported that a blood-draw volume of at least 40 mL was associated with larger improvements — but with I^2 above 90% for most analyses [66]. In network meta-analysis of 47 level I–II trials, the surface under the cumulative ranking curve placed platelet-rich plasma first (91.61), bone

marrow aspirate concentrate second (76.46) and hyaluronic acid third (53.06) [67] (**Figure 8B**).

Against this stands the best-designed single trial. RESTORE randomised 288 patients with symptomatic medial knee osteoarthritis to three weekly injections of leucocyte-poor platelet-rich plasma or saline, with participants, injectors and assessors blinded. At 12 months the between-group difference in pain was −0.4 points on a 0–10 scale (−0.9 to 0.2, P = .17) against a minimal clinically important difference of 1.8, and the difference in medial tibial cartilage volume was −0.2% (−1.9% to 1.5%, P = .81) [68] (Figure 8A). The most plausible reconciliation is that much of the apparent advantage of platelet-rich plasma over hyaluronic acid reflects the weakness of hyaluronic acid as a comparator, inadequate blinding in smaller trials, and the very large placebo response characteristic of intra-articular injection. Certainty for platelet-rich plasma in knee osteoarthritis is therefore low, not moderate.

Mesenchymal stromal cells have a smaller and younger evidence base. Across eight randomised trials and 502 patients, WOMAC improved by 7.44 points (1.45–13.42, P = 0.01) at six months and 10.31 points (0.96–19.67, P = 0.03) at 12 months with no excess of adverse events [69], and an earlier meta-analysis of nine trials and 476 patients found improvements in pain and function without change in composite scores [70]. For the hip, platelet-rich plasma versus hyaluronic acid gave WOMAC pain SMD −0.30 (−0.59 to −0.00, I^2 = 68%) and visual analogue scale SMD −0.32 (−0.52 to −0.12, I^2 = 62%) across seven trials [71] — smaller effects than in the knee, which is worth noting because hip and knee data are frequently pooled in marketing material (**Table 11**).

Modality / comparison	Design	Population	Outcome	Estimate (95% CI)	I^2
PRP vs saline placebo (knee)	**Blinded RCT, 12 months**	288 patients, KL grade 2–3	Knee pain, 0–10 (MCID 1.8)	**MD −0.4 (−0.9 to 0.2), P = .17 — null**	n.a.
PRP vs saline placebo (knee)	As above	As above	Medial tibial cartilage volume	MD −0.2% (−1.9 to 1.5), P = .81 — null	n.a.
PRP vs hyaluronic acid (knee)	Pooled estimate, 12 months	—	Pain	**WMD −0.64 (−0.79 to −0.49), P < 0.00001**	≈60–80%
PRP vs hyaluronic acid (knee)	Pooled estimate, 3 months	—	Pain	WMD −0.25 (−0.40 to −0.10), P = 0.0009	≈60–80%
PRP vs hyaluronic acid (knee)	Pooled estimate, 3 months	—	IKDC function	WMD 7.45 (2.50 to 12.40), P = 0.003	n.a.
PRP vs hyaluronic acid (knee)	Meta-analysis of 18 level-I RCTs	1,608 patients	WOMAC total improvement	44.7% vs 12.6%, P < .01 (pooled CI n.a.)	n.a.
PRP vs HA, corticosteroid, saline (knee)	**Meta-analysis of 62 RCTs, 4,969 participants**	Knee OA	VAS and WOMAC at 6 and 12 months	Superior to HA and corticosteroid at 12 months (pooled MDs n.a.)	**> 90%**
PRP, BMAC, HA, corticosteroid (knee)	Bayesian network meta-analysis, 47 level I–II RCTs	Knee OA	SUCRA ranking for pain	**PRP 91.61 > BMAC 76.46 > HA 53.06**	n.a.
MSC intra-articular (knee)	Meta-analysis of 8 RCTs	502 patients	WOMAC at 6 months	MD 7.44 (1.45 to 13.42), P = 0.01	n.a.
MSC intra-articular (knee)	As above	As above	WOMAC at 12 months	MD 10.31 (0.96 to 19.67), P = 0.03	n.a.
MSC intra-articular (knee)	As above	As above	Adverse events	No significant difference vs control (P > 0.05)	n.a.
PRP vs hyaluronic acid (hip)	Meta-analysis of 7 RCTs	478 participants	WOMAC pain	SMD −0.30 (−0.59 to −0.00)	68%
PRP vs hyaluronic acid (hip)	As above	As above	VAS pain	SMD −0.32 (−0.52 to −0.12), P < 0.002	62%
Any orthobiologic	—	—	Telomere length, epigenetic age, mortality	**No evidence identified**	—

Table 11: Orthobiologic modalities: pooled evidence and the placebo-controlled counter-example. PRP = platelet-rich plasma; MSC = mesenchymal stromal cells; BMAC = bone marrow aspirate concentrate; HA = hyaluronic acid; KL = Kellgren–Lawrence; MCID = minimal clinically important difference; SUCRA = surface under

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the cumulative ranking curve. Sources: Bennell 2021 (RESTORE); Glinkowski 2025; Belk 2021; Centeno 2026; Mameri 2024; Cao 2025; Qu 2021; Sambe 2023. The first two rows and the last row should be read before the rows between them.

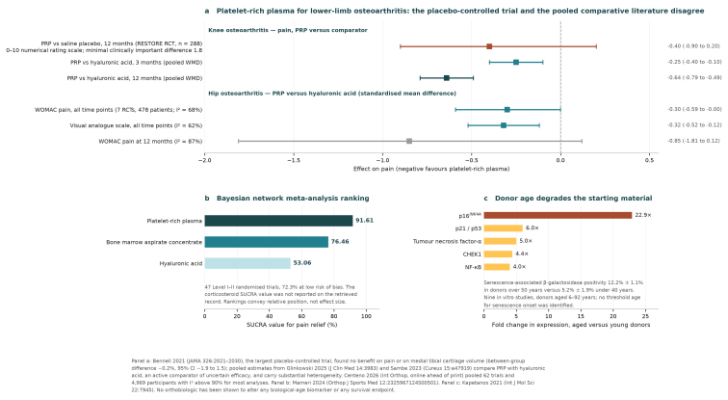

Figure 8: Orthobiologics: pooled superiority against an active comparator, and a null result against placebo. | (A) Pain outcomes for platelet-rich plasma, showing the null RESTORE placebo-controlled result alongside pooled estimates against hyaluronic acid. (B) Network meta-analysis SUCRA rankings for pain. (C) Donor-age-related increases in senescence markers in mesenchymal stromal cells, which constrain autologous potency in exactly the population most likely to be treated. Sources: Bennell 2021; Glinkowski 2025; Mameri 2024; Kapetanos 2021.

Donor age, autologous potency and the systemic-benefit claim

A systematic review of nine in vitro studies with donor ages from 6 to 92 years found that mesenchymal stromal cells from older donors carry markedly higher senescence burden: p21 and p53 expression approximately three-fold higher in adult and six-fold higher in aged donors than in young donors, p16INK4a up 22.9-fold, tumour necrosis factor α five-fold, senescence-associated β-galactosidase positivity 12.2 ± 1.1% in donors over 50 versus 5.2 ± 1.9% in those under 40, with adipogenic differentiation falling from roughly 33% to 10% and osteogenic from roughly 50% to 22% across age strata; no age threshold for senescence onset was identifiable [72] (Figure 8C). This is a structural constraint on autologous cell therapy in ageing patients: the cells harvested from a 70-year-old are themselves aged. It also disposes of the argument that autologous orthobiologics constitute a systemic rejuvenation strategy, since the graft carries the donor's biological age with it.

The claim that regenerative injections slow ageing has never been tested against any biological-age endpoint. No trial in this review measured telomere length, epigenetic age, pace of ageing or mortality after any orthobiologic. When such a claim is made in a clinical or promotional setting, it is an extrapolation from local symptom data to a systemic outcome for which no measurement exists.

Personalised Assessment: Biological Age and Its Limits

Epigenetic clocks are not one thing

DNA-methylation predictors of ageing [73] have become the central measurement technology of longevity medicine, and the second-generation clocks perform meaningfully better than the first. DunedinPACE, trained on the 20-year rate of change in 19 organ-system biomarkers and reduced to 173 CpG sites, predicts mortality (HR 1.26, 1.14–1.40 per standard deviation in the Normative Aging Study; HR

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1.65, 1.51–1.79 in Framingham Offspring), incident cardiovascular disease (HR 1.39, 1.26–1.54), stroke or transient ischaemic attack (HR 1.37, 1.19–1.58) and disability, and retains significance after adjustment for GrimAge. Its technical reliability is high (intraclass correlation 0.96, 0.93–0.98 across replicates) [74].

Head-to-head comparison exposes how different these algorithms are. In the Irish Longitudinal Study on Ageing, with 489 participants and 35 deaths, only GrimAge acceleration predicted mortality (HR 2.05, 1.45–2.90 per z-score; 1.91, 1.23–2.96 after full adjustment); Horvath (0.97, 0.70–1.36), Hannum (0.89, 0.64–1.24) and PhenoAge (1.26, 0.92–1.74) acceleration did not [75] (**Figure 9A**). In 1,966 NHANES participants with a median 208 months of follow-up and 1,014 deaths, all five measures were associated with mortality but the gradient was steep: per five-year increase in age acceleration, all-cause mortality rose 44% for GrimAge, 40% for GrimAge2, 17% for Hannum, 13% for PhenoAge and 10% for Horvath [76] (**Figure 7B**). Reviews of biological-age measures have long cautioned against treating them as interchangeable [77], and CALERIE demonstrated the practical consequence: the same intervention in the same participants slowed one clock and left two unchanged [31] (**Table 12**).

Measure	Basis	Mortality prediction (TILDA, per z-score)	Mortality (NHANES, per 5 y acceleration)	Response to caloric restriction
Horvath (first generation)	353 CpGs, chronological-age trained	HR 0.97 (0.70 to 1.36) — null	+10% (P = 0.013)	Not tested in CALERIE
Hannum (first generation)	71 CpGs, chronological-age trained	HR 0.89 (0.64 to 1.24) — null	+17% (P < 0.001)	Not tested in CALERIE
PhenoAge (second generation)	Trained on clinical-biomarker phenotypic age	HR 1.26 (0.92 to 1.74) — null	+13% (P < 0.001)	**Null at 12 and 24 months**
GrimAge (second generation)	Trained on plasma proteins and smoking pack-years	**HR 2.05 (1.45 to 2.90), P < .001**	**+44% (P < 0.001)**	**Null at 12 and 24 months**
GrimAge2	Updated GrimAge	n.a.	+40% (P < 0.001)	Not tested
DunedinPACE (pace of ageing)	173 CpGs trained on 20-year rate of change in 19 organ-system biomarkers	n.a. (HR 1.26 [1.14–1.40] in NAS; 1.65 [1.51–1.79] in Framingham)	n.a.	**Slowed: d = −0.29 at 12 mo, −0.25 at 24 mo**
Telomere length (qPCR)	Relative T/S ratio	HR 1.09 (1.06–1.13) per SD shorter, pooled across 25 studies	n.a.	Not tested in CALERIE

Table 12. Biological-age measures compared: they do not agree with one another.
TILDA = The Irish Longitudinal Study on Ageing (n = 489, 35 deaths); NHANES n = 1,966, 1,014 deaths, median follow-up 208 months; NAS = Normative Aging Study. Sources: McCrory 2020; Zou 2025; Belsky 2022; Waziry 2023; Wang 2018. A patient's “biological age” depends materially on which algorithm the laboratory uses.

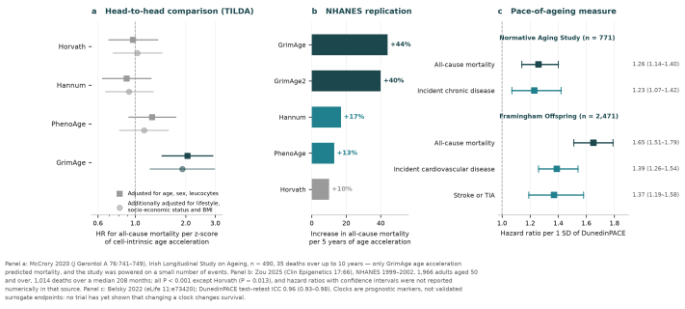

Figure 9: Epigenetic clocks are not interchangeable. | (A) Head-to-head mortality hazard ratios for four clocks in a single cohort, in which only GrimAge acceleration predicted death. (B) Percentage increase in all-cause mortality per five-year age acceleration across five measures in NHANES. (C) DunedinPACE associations with mortality, incident disease and disability across validation cohorts. Sources: McCrory 2020; Zou 2025; Belsky 2022.

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Genetic and epigenetic profiling in practice

Genome-wide analysis explains 8.1% of the variance in leucocyte telomere length [19] and family studies place total heritability between roughly 34% and 82% [20], but no clinical action follows from either figure for an individual patient. The defensible uses of biological-age measurement today are epidemiological and, within trials, as secondary outcomes that are prespecified rather than selected after the fact. The indefensible use is a direct-to-consumer result that triggers the sale of an intervention, particularly when the measurement carries a 20–24% inter-laboratory coefficient of variation [14] or comes from an algorithm that failed to predict mortality in the cohort where it was tested against others [75].

Certainty of Evidence Across Interventions

(**Figure 10**) maps 15 interventions against five outcome families. Reading it by column is more informative than reading it by row. The telomere and telomerase column contains many entries and almost no clinical meaning. The epigenetic-pace column contains one positive randomised result, from caloric restriction. The clinical-outcome column contains the interventions clinicians already recommend for other reasons. The mortality column is nearly empty of randomised evidence — exercise and diet occupy it observationally, and nothing occupies it experimentally. The safety column is where orthobiologics and nutraceuticals look best and where systemic cell therapy looks worst.

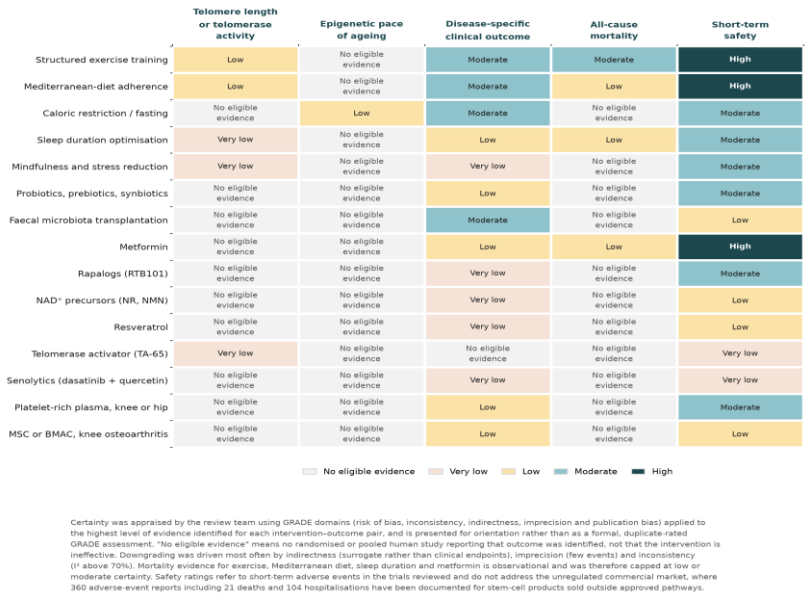

Figure 10: Certainty of evidence across 15 interventions and five outcome families. | Cells are graded using GRADE domains applied to the highest level of evidence available for each intervention–outcome pair. Empty and very-low cells are as informative as high cells: no intervention reaches high certainty for an effect on mortality, and no orthobiologic has been tested against any biological-age outcome. This appraisal was performed by the review team for orientation and was not externally adjudicated.

Intervention	Best outcome supported	Certainty	Principal limitation
Structured exercise / step volume	All-cause mortality (observational dose–response, HR 0.47 at highest quartile)	**Moderate**	Observational; reverse causation in frail participants

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Intervention	Best outcome supported	Certainty	Principal limitation
Mediterranean dietary pattern	All-cause mortality (HR 0.90 per 2-point increment)	**Moderate**	I^2 = 81.1%; dietary self-report
Caloric restriction	Epigenetic pace of ageing (DunedinPACE d = −0.25)	Moderate	Single trial; two of three clocks null; adherence 11.9% of a prescribed 25%
Intermittent fasting (ADF)	Body weight (−3.40 kg)	**High (weight only)**	Median 12-week follow-up; no mortality or ageing endpoint
Sleep targeted near 7 hours	All-cause mortality (U-shaped association)	Low–moderate	No interventional evidence; long sleep likely reverse causation
Mindfulness / stress reduction	Telomerase activity (d = 0.46)	**Very low**	4 small trials; no confidence intervals reported; unblindable
Probiotics / prebiotics	Inflammatory biomarkers (hs-CRP SMD −0.46)	Low	Biomarker only; no clinical or ageing endpoint
FMT / SER-109	Recurrent C. difficile infection (RR 0.32)	**High**	Indication-specific; no relevance to ageing
Metformin	All-cause mortality in diabetes (HR 0.72)	Low	Observational only; TAME not reported
Rapalogs (RTB101)	None	**High certainty of no effect (phase 3)**	Phase 3 negative for the tested endpoint
NAD^+ precursors	Blood NAD concentration (SMD 1.79)	**Very low for clinical benefit**	All cardiometabolic outcomes null; 5 of 12 trials at high risk of bias
Resveratrol	HbA1c in type 2 diabetes (WMD −0.45)	Very low	I^2 = 95%; no longevity endpoint
Telomerase activators (TA-65)	Telomere length (+530 bp)	**Very low**	Surrogate only; MR evidence links longer telomeres to higher cancer risk
Senolytics (D + Q)	None	Very low	Phase 1, n = 12
PRP (knee osteoarthritis)	Pain vs hyaluronic acid (WMD −0.64 at 12 mo)	**Low**	Largest blinded placebo trial null; I^2 > 90%
MSC / BMAC (knee osteoarthritis)	WOMAC at 12 months (MD 10.31)	Very low	8 small trials; no placebo-controlled confirmation; donor-age potency decline
Systemic / unapproved cell therapy	None	**Very low; documented harm**	360 adverse-event reports, 21 deaths, 16 tumours; not FDA-approved

Table 13: Summary of certainty by intervention.

ADF = alternate-day fasting; FMT = faecal microbiota transplantation; D + Q = dasatinib plus quercetin; PRP = platelet-rich plasma; MSC = mesenchymal stromal cells; BMAC = bone marrow aspirate concentrate. Certainty was appraised by the review team using GRADE domains and is presented for orientation only.

A Three-Tier Clinical Framework

(**Figure 11**) translates the certainty map into a clinical pathway with four steps: baseline characterisation, risk stratification, tiered intervention and monitoring with annual reassessment. The tiering rule is deliberately simple. Tier 1 contains interventions supported by at least moderate certainty for a clinical outcome and high certainty for safety; these may be offered to all patients. Tier 2 contains interventions with low-certainty benefit for a defined symptom and acceptable short-term safety; these require shared decision-making and honest framing. Tier 3 contains interventions whose benefit is unproven, whose surrogate response may not indicate benefit, or whose harm profile is documented; these belong inside registered clinical trials.

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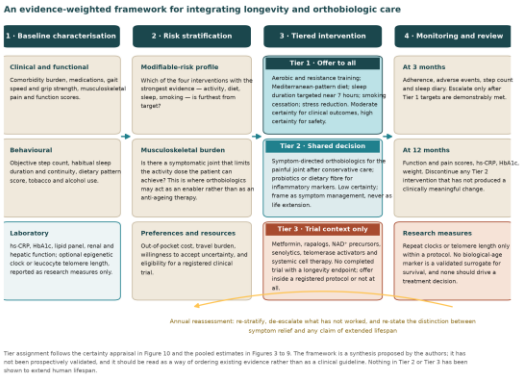

Figure 11: An evidence-weighted framework for longevity and regenerative practice. Baseline characterisation and risk stratification precede a tiered intervention decision, with annual reassessment. Tier 1 may be offered to all patients; Tier 2 requires shared decision-making with explicit framing as symptom management; Tier 3 is restricted to registered clinical trials. Tier assignment follows the certainty map in Figure 10 and the estimates in Figures 3 to 9.

Tier 1 — offer to all patients

- Progressive aerobic and resistance exercise, with an explicit step target of approximately 8,000–10,000 steps per day in adults under 60 and 6,000–8,000 in those over 60 [29]. Resistance training is included for function despite having no telomere effect [28].
- A Mediterranean dietary pattern, with weight management by whichever energy-restriction schedule the patient can sustain; alternate-day fasting is marginally the most effective and none of the schedules differs by more than about two kilograms [30,34].
- Sleep assessment with a target near seven hours, treatment of insomnia with cognitive behavioural therapy and investigation of suspected sleep-disordered breathing [60,61].
- Smoking cessation, alcohol moderation and a structured stress-reduction practice — the last on the strength of its general mental-health evidence rather than its telomere data [7,36].
- Guideline-directed management of blood pressure, lipids and glycaemia, which remains the highest-yield intervention available in an ageing population and is frequently displaced by longevity protocols.

Tier 2 — shared decision-making, defined indication

- Platelet-rich plasma for symptomatic knee osteoarthritis after failure of exercise therapy and analgesia, framed as symptom management of uncertain durability. The conversation must include the null placebo-controlled trial [68] and the fact that no cartilage-structural benefit has been demonstrated.
- Bone marrow aspirate concentrates or mesenchymal stromal cells for the same indication, with the additional caveat that no placebo-controlled trial has confirmed the pooled estimates and that autologous potency declines with donor age [69,72].
- Metformin in patients who have an independent metabolic indication. Its longevity rationale is observational and should not be presented as the reason for the prescription [38].

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- Probiotics or prebiotics where a gastrointestinal indication exists; not as an anti-ageing intervention [57,58].

Tier 3 — clinical trials only

- Telomerase activators. The surrogate responds [45] but genetically longer telomeres are associated with higher cancer risk (OR 1.30 for any cancer, and OR 5.27 for glioma) [16,17], so the net direction of a pharmacological effect is unknown.
- Senolytics, which have completed only phase 1 in 12 participants [43].
- Rapalogs for infection prevention or healthspan, following a negative phase 3 [42].
- NAD^+ precursors as a clinical intervention, on the basis that the biomarker moves and nothing else does [46].
- Systemic or intravenous cell therapy and exosome products for any ageing indication. These are unapproved, carry documented serious harm and are explicitly identified as unapproved by regulators [12,78–80].

What not to do

Three practices are not supported by anything in this review. First, ordering direct-to-consumer telomere or epigenetic-age testing to guide treatment: the inter-laboratory coefficient of variation for telomere length is 20–24% [14] and the clocks disagree with each other about who is ageing fastest [75,76]. Second, presenting a surrogate response as a clinical benefit — the phase 3 rapalog result [42] and the NAD^+ data [46] are the two clearest illustrations of why that inference fails. Third, marketing musculoskeletal orthobiologics as anti-ageing therapy, for which no supporting measurement of any kind exists.

Ethical, Regulatory and Equity Considerations

Access, equity and the distribution of longevity

If effective ageing interventions emerge, their distribution will not be neutral. The argument that societies have a duty to pursue ageing retardation rests partly on the claim that its benefits are broad and compounding [81], but the current market delivers the opposite: direct-to-consumer regenerative treatments in the United States typically cost between US$2,500 and more than US$50,000 and are paid out of pocket, with more than 400 crowdfunding campaigns documented among patients seeking them [12]. A longevity medicine that widens the existing gap in disability-free life expectancy would be a public-health failure regardless of its biological success [2].

Harm, regulation and the duty of accurate framing

The documented harms are not theoretical. Across January 2004 to September 2020, 360 adverse-event reports associated with unapproved stem-cell interventions were collated, including 21 deaths, 104 hospitalisations, 16 tumours or abnormal growths, nine cases of partial or complete blindness, six pulmonary emboli and five cardiac arrests, alongside at least 87 accounts of financial or emotional harm [12,78]. The United States Food and Drug Administration states that the only approved stem-cell products are blood-forming stem cells derived from umbilical cord blood for haematopoietic disorders, names stromal vascular fraction, orthobiologics and exosomes as unapproved, and lists osteoarthritis, tendonitis, disc disease and back, hip, knee, neck and shoulder pain among conditions with no approved regenerative therapy [79]. In Brazil, RDC No. 508 of 27 May 2021 sets good practice requirements across the entire

production cycle for human cells and advanced therapy products, and non-compliant material is disqualified for both therapeutic use and clinical research [80].

Two practical obligations follow. Clinicians offering Tier 2 interventions should document that the patient was told the evidence is low certainty, that a blinded placebo-controlled trial was null, and that the treatment addresses symptoms rather than ageing. Clinicians offering Tier 3 interventions outside a trial are, in most jurisdictions represented here, operating outside the regulatory framework.

Individual and societal benefit

Extending healthspan without extending disability is a legitimate public-health objective and a different objective from extending lifespan [2,82]. The interventions with the best evidence for that objective — physical activity, dietary pattern, sleep, tobacco avoidance and cardiovascular risk management — are also the cheapest and the most equitably distributable. That is an uncomfortable finding for a commercial longevity sector, and it is the most robust conclusion this review can offer.

Discussion

Key findings

1. Telomere length is a valid population biomarker and an invalid individual treatment target. Observational associations are consistent (all-cause mortality HR 1.09 per standard-deviation decrement [10]; coronary heart disease RR 1.54 [9]), but Mendelian randomisation reverses the sign for cancer (OR 1.30 per standard deviation longer [17]) and inter-laboratory measurement variability reaches 24.17% [14].
2. Surrogate response and clinical benefit are dissociated in every pharmacological domain examined. NAD^+ precursors raise NAD^+ with SMD 1.79 and change nothing measurable [46]; TA-65 lengthens telomeres by 530 base pairs with no clinical endpoint tested [45]; RTB101 improved a surrogate in phase 2 and failed in phase 3 [42].
3. Behavioural interventions carry the largest effects on the outcomes that matter. A 53% lower hazard of death in the highest step quartile [29] exceeds any pharmacological estimate in this review, and it does so without a telomere signal [26].
4. Biological age is not a single quantity. Four clocks in one cohort gave hazard ratios from 0.89 to 2.05 [75], the NHANES gradient ranged from +10% to +44% per five-year acceleration [76], and the same randomised intervention slowed DunedinPACE while leaving PhenoAge and GrimAge unchanged [31].
5. Orthobiologics have a defensible role in symptomatic joint disease and no role in ageing. Pooled estimates favour platelet-rich plasma over hyaluronic acid [64,67], the best blinded placebo-controlled trial was null [68], heterogeneity exceeds 90% in the largest synthesis [66], and no orthobiologic has been tested against any biological-age endpoint.
6. The commercial market is substantially ahead of the evidence, with documented harm. More than 1,400 direct-to-consumer businesses, 360 adverse-event reports and 21 deaths were identified in a single collation [12], against a regulatory position that names these products as unapproved [79,80].

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Strengths and limitations

The strengths of this review are its breadth across eleven domains, its explicit separation of four outcome families that are routinely conflated, its requirement that every reported value be traceable to a source document, and its use of "n.a." rather than imputation where a value could not be confirmed.

The limitations are substantial and should be weighed before the conclusions are used. The review was not prospectively registered. Screening and extraction were performed without independent duplicate assessment, and the certainty appraisal, although structured on GRADE domains, was not adjudicated by a second rater or externally reviewed; it is presented for orientation rather than as a formal GRADE assessment. Full texts were assessed in English, Portuguese and Spanish only. Overlap between included syntheses was handled by retaining the largest and most recent, which is a pragmatic rather than a corrected-effect-size approach. A number of heterogeneity statistics were not available on the retrieved records and are marked accordingly; where I^2 is absent from a table cell, the estimate should be treated as less well characterised than one where it is present. Two identified microbiome sources were not retrieved within the review window. Publication bias was not formally tested at the umbrella level, and it is likely to be non-trivial in the small-trial domains — mind–body interventions, nutraceuticals and cell therapy in particular.

Future research directions

1. Complete an adequately powered randomised trial of a candidate gerotherapeutic with a clinical composite endpoint. TAME is the designed instrument [39]; the field's central claim remains untested without it.
2. Standardise telomere measurement before any further clinical translation. An inter-laboratory coefficient of variation of 24.17% [14] is incompatible with individual-level decision-making, and gel-based methods already achieve 9.20%.
3. Prespecify epigenetic clocks as secondary outcomes in existing large lifestyle and cardiometabolic trials, reporting all clocks tested rather than the one that moved. CALERIE is the model [31].
4. Conduct placebo-controlled, adequately blinded trials of orthobiologics with structural and functional co-primary endpoints, following the RESTORE design [68] and reporting preparation characteristics in enough detail to explain the heterogeneity documented by Centeno and colleagues [66].
5. Test whether any intervention that changes a biological-age measure also changes a clinical outcome in the same participants. No study in this review did both.
6. Build registries for direct-to-consumer regenerative and longevity interventions, since current adverse-event knowledge derives disproportionately from a single prospective study [12].

Conclusion

Longevity medicine currently offers patients a large menu of interventions supported by a small amount of high-quality evidence. This umbrella review found that the interventions with the strongest support for the outcomes patients care about — living longer and living better — are physical activity, a Mediterranean dietary pattern, adequate and well-structured sleep, tobacco avoidance and conventional

cardiovascular risk management. The interventions with the most impressive biomarker effects — NAD^+ precursors, telomerase activators, mTOR inhibitors — have either failed at phase 3, have never been tested against a clinical endpoint, or move a surrogate whose causal relationship to health is contested by Mendelian randomisation.

Regenerative orthobiologics occupy a specific and defensible middle position. For symptomatic knee osteoarthritis, platelet-rich plasma outperforms hyaluronic acid in pooled analyses and fails to outperform saline in the best blinded trial; that combination justifies offering it under shared decision-making as symptom management, and does not justify offering it as anti-ageing therapy. No orthobiologic has been shown to alter telomere length, epigenetic age, pace of ageing or mortality, and the age-related senescence burden of autologous cells constrains what can be expected in exactly the population most likely to seek treatment.

The three-tier framework proposed here is not a compromise between enthusiasm and scepticism; it is a description of the evidence. Tier 1 for everyone, Tier 2 with honest framing for a defined symptom, Tier 3 inside a trial. Applied consistently, it protects patients from paying for surrogate endpoints, preserves the credibility of regenerative medicine for the indications where it genuinely helps, and directs the field's effort towards the randomised trials that would let the next version of this review say something stronger.

Data availability
All data analysed in this review are contained within the cited published sources and their supplementary materials. No new primary data were generated. The extraction table underlying Tables 2 to 13 is available from the corresponding author on reasonable request.

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Use of artificial intelligence
Generative artificial intelligence tools were used in the preparation of the manuscript for analytic data and studies comparisons.

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