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Perspective

Chronogeroprotection: Circadian Action Bundles for Healthy Aging

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ABSTRACT: Aging is a multidimensional biological process characterized by a progressive decline in physiological resilience to stressors, shaped by molecular dysregulation and cumulative behavioral and environmental challenges, and accompanied by an increased risk of disease. Despite advances in geroscience, biological time remains underused in prevention, clinical care, and public-health strategy. Here we propose chronogeroprotection as a novel circadian-informed perspective on the preservation of physiological resilience across the life span. We synthesize evidence showing that circadian regulation coordinates near-24-hour rhythms in metabolism, immune function, DNA repair, and sleep-wake regulation, thereby influencing vulnerability to age-related diseases. We then translate these insights into a prevention-oriented model for healthy aging. We suggest that chronogeroprotective action bundles, which consist of interventions, properly synchronized to light exposure, sleep, meal timing, physical activity, pharmacology, diagnostics, and patient care workflows according to biological time, will help bridge the hallmarks of aging and healthcare system redesign. Through integration of circadian principles into diagnostic procedures, electronic health records, clinical workflows, educational programs, research networks, and public-health policy, biological time can become a tangible preventive and therapeutic factor relevant for healthy aging consistent with the WHO Decade of Healthy Ageing priorities.

Keywords: chronogeroprotection, circadian rhythm, healthy aging, longevity, geroscience, preventive medicine

Global aging and the need for scalable prevention

The pace of population ageing is accelerating worldwide, ushering societies into an unprecedented era (https://cdn.who.int/media/docs/default-source/decade-of-healthy-ageing/decade-proposal-final-apr2020-en.pdf). Globally, the share of adults aged 65 or older is projected to rise from about 10 % in 2022 to 16 % by 2050 (https://www.un.org/development/desa/pd/content/World-Population-Prospects-2022).

Aging is a complex multidimensional biological process characterized by a gradual decline in physiological functions and increased risk of diseases such as cancer, cardiovascular disease, metabolic disorders, and neurodegenerative conditions [1]. As populations age globally, accessible, scalable, and effective preventive strategies are urgently needed to extend healthy lifespan, which can significantly reduce the "burden of aging" on the individual, their caregivers, and society at large.

Two key intervention paradigms can be distinguished: *anti-aging* and *geroprotection*. Although often used interchangeably, the terms imply distinct mechanisms and strategies. Anti-aging, often used commercially, refers to products and treatments claiming to reverse or conceal visible signs of aging but often lacking biological and clinical validation [2]. In contrast, geroprotective strategies target fundamental aging mechanisms like oxidative stress, DNA damage, and

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cellular senescence through pharmacological, dietary, and genetic interventions [1, 3].

Why chronogeroprotection?

In this Perspective, we define chronogeroprotection as the use of circadian-informed approaches for preserving or restoring physiological resilience in the context of aging. It refers mainly to a conceptual and translational framework, rather than to a single intervention, biomarker, or even a separate clinical specialty. It is based on the central premise that biological time is a modifiable factor of health span and that age-related vulnerability may be decreased by stabilizing rhythm robustness, reducing circadian misalignment, enhancing synchrony between central and peripheral clocks, and integrating timing information into prevention, medical practice and healthcare organization.

Thus, chronogeroprotection can be implemented through several approaches. At the clinical level, it would include chronocounseling, timed light exposure, sleep-wake stabilization, timing of meals and activities, rhythm assessment, and, where appropriate, pharmacological support of circadian resilience. At the healthcare-system level, it would include chronodiagnostics, time-stamped laboratory interpretation, circadian lighting, and time-sensitive clinical workflows. At the public-health level, it would include rhythm-supportive workplace design, shift work policies, light hygiene, and education on circadian health. These characteristics are assessable via indicators such as sleep-wake rhythm consistency, circadian phase markers, light-exposure profiles, timing of food intake and activity, medication timing, and biological-time metadata in diagnostic methods.

This framework differs from related disciplines by its explicit focus on aging and resilience. Chronomedicine and circadian medicine broadly address the role of biological rhythms in health and disease, chronotherapy and chronopharmacology focus mainly on the therapeutic timing, chrononutrition addresses the timing of food intake, sleep medicine focuses on sleep and sleep-wake disorders, while geroscience targets biological mechanisms of aging. Chronogeroprotection combines selected principles from all these areas but organizes them around a distinct preventive goal: preserving health span by aligning geroprotective mechanisms, clinical care, diagnostics, and public-health strategies with biological time [1, 2, 4–8].

The concept of chronogeroprotection arises from growing evidence that circadian rhythms are fundamental to maintaining resilience and healthy aging, and that their disruption accelerates vulnerability to age-related disease. The circadian system is an ancient, highly conserved mechanism that evolved to align physiology and behavior with daily geophysical cycles such as the 24-hour light-dark cycle. Its origins can be traced to the "Great Oxygenation Event" ~2.5 billion years ago, when rising atmospheric oxygen and reactive oxygen species (ROS) created selective pressure for internal clocks to temporally organize metabolism and DNA repair, thereby limiting oxidative stress and improving survival [9–11]. Over evolutionary time, circadian regulation expanded to encompass sleep-wake cycles, metabolism, cognition, hormone release, and emotion [12]. Fundamental principles of chronobiology, i.e., endogeneity, entrainment, hierarchical organization, and adaptive value, highlight why circadian rhythms are integral to organismal function [13, 14]. By aligning physiological cycles with one another and with external cycles, circadian clocks enhance efficiency, protect genomic integrity, and preserve homeostasis. In this context, physiological resilience can be understood as the capacity to adapt to stressors and restore balance after perturbation [4].

With advancing age, circadian rhythms lose robustness, characterized by weakened amplitude, increased phase variance, and decreased synchrony between rhythms, due to both intrinsic and environmental factors [15]. This weakening of circadian control contributes to oxidative stress, chronic inflammation, and increased susceptibility to age-related disease. Beyond natural, age-related deterioration in the molecular components (such as clock gene dysregulation), behavioral and environmental stressors further exacerbate circadian vulnerability. Modern lifestyle conditions, particularly exposure to artificial light at night and night-shift work, can alter the phase of human circadian rhythms, primarily by shifting the timing of internal clocks relative to the external light-dark cycle. In humans, nocturnal light exposure and night-work are associated with altered melatonin rhythms and delayed circadian phase relative to solar time. Although other factors such as irregular meal timing, sedentary activity and sleep patterns are hypothesized to influence circadian physiology, the direct evidence for their effects on entrainment in humans remains limited compared with the robust data on light-induced phase shifts. Psychosocial stress and social isolation may perturb daily rhythms, such as those in sleep, mood, and metabolic function, through inflammatory and neuroendocrine pathways [16, 17]. While circadian rhythms generally remain robust under constant conditions, these stressors can influence diurnal rhythms (patterns that follow a daily cycle but may not be fully endogenous) by affecting factors like sleep-wake timing, cortisol levels, and other physiological markers.

Chronically disrupted circadian rhythms have been associated with changes in immune regulation and increased inflammatory signaling, and may contribute to

aspects of inflamm-aging, the chronic low-grade inflammation that develops with age [18]. In animal models, long-term circadian misalignment accelerates markers of immune senescence and chronic inflammation, suggesting a mechanistic link between circadian disruption and age-related inflammatory phenotypes [19]. However, in humans, while sleep and circadian irregularities are associated with elevated inflammatory markers, direct evidence that circadian disruption drives systemic inflamm-aging per se remains limited and is an active area of investigation.

Although direct causal evidence remains limited, such maladaptive signaling likely weakens coupling among central and peripheral clocks, reducing overall circadian stability and function [20–22]. Chronodisruption, or the misalignment between the internal circadian clock and external time cues, can exacerbate changes in circadian period, amplitude, and acrophase, particularly when there is persistent disconnection from natural light-dark cues [23, 24]. These lifelong influences act in concert with developmental factors established before birth, when maternal environment and nutrition imprint epigenetic programs with enduring effects on health [25–27]. Human premature-aging disorders further illustrate that pathways involved in genomic maintenance, nuclear architecture, and circadian regulation may intersect. In Hutchinson-Gilford progeria, LMNA mutations disturb chromatin architecture and lead to the loss of function and increased degradation of circadian regulators such as BMAL1, accelerating biological aging [28].

Together, these findings highlight that circadian integrity is deeply embedded with broader molecular networks involved in genomic stability, metabolic regulation, stress responses, and physiological resilience. Reinforcing these interacting pathways may therefore represent a key chronogeroprotective strategy to preserve cellular homeostasis and support health span. This perspective provides the basis for the next step of the framework: understanding how age-related weakening of circadian organization emerges across the central and peripheral clock systems.

Age-related changes of the circadian system

The circadian system coordinates the timing of physiological processes with external environmental cycles, supporting homeostasis, and longevity [29–32]. With age, however, this circadian coordination is weakened, which may be related to biological and behavioral changes associated with aging.

Typical age-related changes in circadian rhythms include a reduction in amplitude, observed as weaker oscillations in body temperature rhythms, and hormone secretion [33–35]. While changes in sleep-wake patterns are an output of the circadian clock, they are also influenced by homeostatic (internal) and social (external) factors, making them not solely driven by circadian changes. Older adults also tend to show an advance in circadian phase, reflected in earlier sleep and wake times and a stronger preference for morning activity [36, 37]. Aging is further associated with impaired phase shifting and entrainment, with diminished responsiveness of the circadian system to zeitgebers such as light, feeding, and social cues [35, 38]. A debated change in circadian rhythms concerns the intrinsic circadian period (tau), while some animal studies have suggested a shortening of tau with age, human studies, including forced desynchrony studies in both young and older adults, have found no evidence for age-related changes in circadian period [31, 38, 39]. Thus, the functional significance of period changes with age remains unresolved.

The suprachiasmatic nucleus (SCN), the central circadian clock, serves as the body's principal circadian pacemaker and coordinates peripheral clocks throughout the organism [40]. During aging, the SCN deteriorates structurally and functionally, showing neuronal loss, reduced neurotransmission, and decreased plasticity, impairing temporal precision and reducing circadian amplitude [35, 41]. Declining light perception due to melanopsin-expressing retinal ganglion cell loss further weakens synchronization to the external light-dark cycle [42, 43].

On a molecular level, core clock genes, e.g., CLOCK, BMAL1, PER1-3, and CRY1/2 become vulnerable to oxidative stress and epigenetic alterations, weakening circadian gene expression [44, 45]. Reduced early growth response protein 1 (EGR1), for example, diminishes PER1 activation, impairing hepatic regeneration and metabolic function [46, 47]. Peripheral clocks in tissues like liver, heart, and kidney progressively desynchronize from the SCN, promoting systemic dysregulation [15, 48, 49].

Aging also alters circadian regulation through intertwined molecular and metabolic mechanisms. Declining melatonin secretion and reduced sirtuin-1 (SIRT1) activity impair the transcriptional regulation of clock genes and DNA-repair processes, potentially linking circadian dysfunction with genomic instability [50]. While melatonin's effects are primarily chronobiotic, and SIRT1 is a key player in circadian regulation, its role in this context is likely part of a broader network influencing both circadian rhythms and DNA repair mechanisms. The insulin/IGF-1 (Insulin-like growth factor 1) and mTOR (Mammalian Target of Rapamycin) signaling pathways, key nutrient-sensing regulators of aging, also interact with circadian timing networks,

influencing metabolism, autophagy, and proteostasis [32, 51].

Together, these alterations may weaken circadian integrity by disrupting the molecular machinery of the circadian clock, reducing synchrony between central and peripheral clocks, and impairing alignment with external light-dark and behavioral cycles time. This loss of temporal coordination may reduce physiological resilience to age-related challenges and provides the clinical rationale for linking circadian disruption to disease vulnerability and aging-relevant outcomes in the following section (Fig. 1).

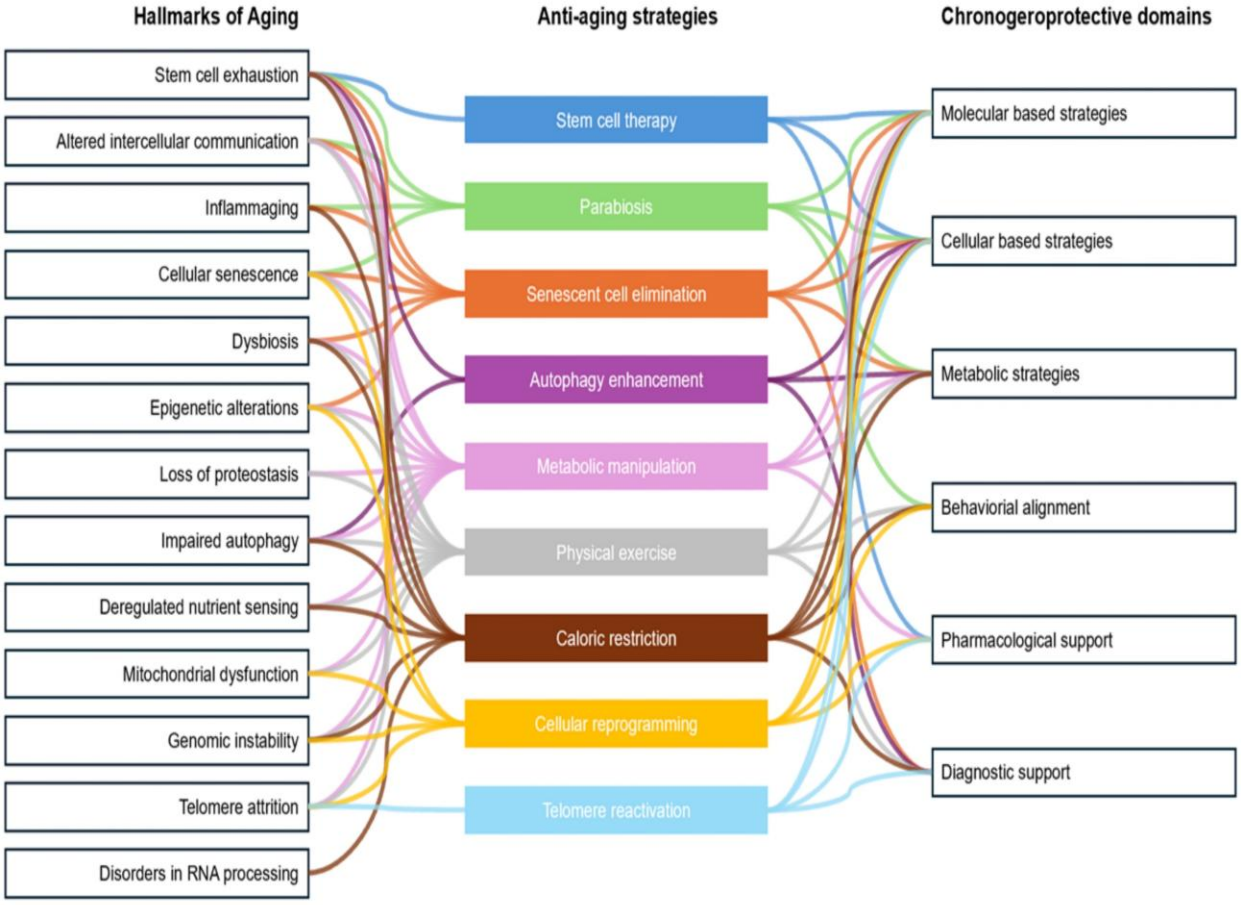

Figure 1. Translational continuum from biological hallmarks to chronogeroprotective strategies. The hallmarks of aging (left) denote molecular and cellular processes contributing to physiological decline. The intermediate layer depicts mechanistic and therapeutic interventions that target circadian, metabolic, and repair pathways—ranging from cellular reprogramming and autophagy enhancement to behavioral entrainment and caloric restriction. These mechanisms converge into six chronogeroprotective domains (right): molecular-, cellular-, and metabolic-based strategies, behavioral alignment, pharmacological support, and diagnostic integration. Flows indicate conceptual linkages only; their thickness and curvature carry no quantitative meaning. Together, the diagram illustrates how circadian and metabolic regulation provide an actionable bridge from fundamental aging biology to chronogeroprotective healthcare design.

Impact of circadian disruption on health

Chronic circadian disruption, a term encompassing both circadian misalignment (when the internal clock remains functional but is desynchronized from behavioral or environmental cycles) and breakdown of clock machinery (intrinsic weakening or loss of rhythmicity within the circadian system), contributes to a wide range of adverse outcomes, including circadian rhythm sleep-wake disorders, cardiovascular disease, metabolic dysfunction (e.g., metabolic dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes), and neuropsychiatric conditions including depression, cognitive impairment, and sleep apnea [52–54].

Historical comparisons, such as those involving individuals in highly structured and low-stress environments (e.g., monastic populations), suggest that regularity in daily routines can be associated with improved health outcomes and lower mortality rates [55]. While the benefits of these routines may stem from

multiple factors, including circadian stability, reduced stress, social support, and consistent physical activity, emerging literature highlights the importance of cycle regularity in maintaining metabolic, immune, and cardiovascular health, as well as reducing disease risk.

Disorders like Non-24-Hour-Sleep-Wake-Disorder (N24SWD) and Delayed-Sleep-Wake-Phase-Disorder (DSWPD) underscore the clinical impact of circadian misalignment. N24SWD affects 55-70% of totally blind individuals, who are unable to entrain their circadian rhythms to a 24-hour cycle, leading to poor sleep, chronic fatigue, cognitive decline, and metabolic disorders such as MASLD [56]. Treatment with melatonin or tasimelteon, a melatonin receptor-1 agonist, has demonstrated efficacy in restoring circadian entrainment in this population [57].

In the context of aging, these effects are clinically relevant because circadian disruption does not only influence intermediate biological processes, such as metabolic dysfunction, inflammation, sleep-wake disturbance, and failure in DNA repair, but may also contribute to outcomes that determine resilience, recovery, and autonomy in later life. In older adults, weakened rhythm robustness and irregular daily timing may contribute to vulnerability across several geriatric domains. Sleep-wake disruption, nocturnal light exposure, reduced daytime activity, and misaligned care routines may increase the risk of cognitive decline, delirium, falls, impaired recovery, and loss of functional independence, particularly in hospitalized, frail, or institutionalized populations [58–65]. Circadian disruption may also interact with multimorbidity by amplifying metabolic, cardiovascular, psychiatric, and neurodegenerative vulnerability, thereby increasing the cumulative burden of disease across the life course [52, 66–72].

Indeed, the pertinent consequences that could result from enhancing circadian function for the purpose of chronogeroprotection include decreased frailty, fall risk, susceptibility to delirium, cognitive impairment, multimorbidity burden, and institutionalization, as well as preserved functional independence. Similarly, biomarkers of biological aging, which include epigenetic, transcriptional, metabolic, inflammatory, and functional biomarkers, might be used to determine whether enhancement of circadian function alters biological aging. Ultimately, from a population-health perspective, besides the expected reduction in morbidity and mortality due to such interventions, health span and freedom from disability are among the end points to consider.

Pharmacological support of circadian resilience

Circadian disruption has been associated with metabolic dysfunction, inflammation, and cognitive decline, making restoration of rhythmic robustness a potential preventive target [35, 73]. Nonetheless, the pharmacologic support of circadian resilience still appears to be an evolving field wherein different levels of evidence exist for various agents. Pharmacological interventions need to be recognized as adjuncts that are indication-based, as opposed to being well-established chronogeroprotective treatments. While behaviors and environmental factors like light-exposure, sleep-wake schedules, timing of meals, exercise, and social activities, are the primary and best-established measures that have been shown to support circadian organization, some pharmacological agents have also proven useful in stabilizing or potentiating circadian organization.

Melatonin and melatonin-receptor agonists currently have the strongest clinical evidence, especially where circadian rhythm sleep-wake disorders and sleep-wake consolidation are concerned in certain patient groups, such as older adults and totally blind individuals with N24SWD [57, 74, 75]. Their role in chronogeroprotection is therefore best framed as chronobiotic and symptom- or disorder-directed. Evidence that melatonin broadly slows biological aging or preserves health span in humans remains indirect and should not be inferred solely from its effects on sleep or circadian phase.

Preclinical research has demonstrated that metformin impacts clock-metabolism interactions, AMPK/SIRT1-mediated mechanisms, and mitochondrial/redox circadian rhythms [76–78]. These findings have biological relevance to chronogeroprotection due to overlapping signaling between AMPK/SIRT1 metabolism-nutrient-sensing mechanisms and circadian/cellular aging processes [32, 78]. Nevertheless, there is a dearth of clinical data supporting any circadian effects of metformin on circadian robustness, healthy aging, or resilience. Analogously, pharmacologic modulation of SIRT1 enzymes also holds biological relevance to chronogeroprotection due to its involvement in clock regulation, mitochondrial function, and metabolic adaptation, but its clinical relevance in humans remains speculative.

In aging tissues, mTOR inhibition (e.g., rapamycin) has been associated in experimental models with the recovery of circadian gene programs in the stem-cell niche and metabolic pathways [79]. Nonetheless, there is currently no scientific basis for the application of rapamycin in the clinical setting to enhance circadian reorganization in humans. The potential role of NAD^+ precursors in improving human health is related to the fact that NAD^+ is associated with the activities of sirtuins, mitochondria, and circadian transcriptional programs. However, the link between NAD^+ precursor supplementation and the restoration of circadian

organization remains preclinical or at least lacks direct human evidence.

Accordingly, pharmacological agents should be introduced as candidates rather than proven components of routine circadian protection practice. Future studies must clarify whether such measures improve circadian endpoints, including circadian phase stability, rhythm amplitude, rest-activity cycle, metabolome rhythms, inflammatory profiles, physical capacity, and health-span-related outcomes, and assess safety, tolerability, adherence, drug interactions and regulatory feasibility. Until such evidence is available, pharmacological approaches should be integrated cautiously and only in combination with established behavioral, environmental, and clinical indications [6, 80].

Integrating chronogeroprotection across healthcare and institutional levels

Beyond individual pharmacological and behavioral measures, the sustainable implementation of chronogeroprotection depends on how healthcare systems integrate circadian principles into routine clinical practice.

Chronogeroprotection requires translation from molecular principles into coordinated healthcare delivery. Because circadian dysregulation cuts across metabolic, psychiatric, oncologic, and geriatric domains, implementation must extend beyond single specialties toward multilevel, cross-sector coordination [7, 73].

Existing clinical pathways often address only overt sleep-wake disorders, while the broader continuum of subclinical rhythm disruption is largely ignored or undiagnosed because insurance does not cover rhythm assessment [81–83]. Effective prevention therefore depends on embedding time-aware approaches throughout the continuum of care rather than creating separate programs.

For chronodiagnostics and timestamped laboratory analytics to become operational, biological-time information must be captured in a standardized but feasible manner. As an initial step, a minimum metadata set could be incorporated into laboratory requests, EHRs, or research protocols, particularly for analytes or clinical situations in which circadian variation is known or suspected to be relevant.

Core metadata:

- Clock time and date of sampling
- Time zone
- Fasting status and timing of last meal
- Sleep timing, including bedtime, wake time, and sleep duration before sampling
- Medication timing, especially timing of last dose
- Recent light exposure, particularly bright light exposure and nocturnal light exposure
- Shift work or night work status
- Chronotype, where available

Contextual metadata:

- Physical activity timing before sampling
- Inpatient versus outpatient setting
- Posture during or before sampling
- Acute illness, stress, or recent hospitalization
- Menstrual or hormonal status where relevant
- Sample type, processing delay, storage, and transport conditions.

These metadata should initially support interpretation, quality control, and research comparability rather than replace established reference ranges or clinical judgment. A stepwise approach may begin with universal timestamping of sampling and medication administration, followed by structured capture of selected contextual variables for circadian-sensitive analytes, and later integration of biological-time estimates, or wearable-derived data once validated. This laboratory example illustrates a broader implementation principle: chronogeroprotection can be introduced gradually into existing healthcare structures by adding time-aware information, workflows, and decision points where they are most clinically relevant.

Five healthcare service levels provide natural entry points for this stepwise implementation:

(i) *Laboratory diagnostics* can integrate timestamped sampling and selected biological-time metadata into analytic workflows, establishing *chronodiagnostics* for phase-resolved interpretation and research standardization [8, 84] (see Table 1).

(ii) *Primary and preventive care* can incorporate structured chronocounseling, linking lifestyle advice with circadian timing [97, 98].

(iii) *Hospitals and specialized care* can adopt timed medication, circadian lighting, and digital tools for rhythm monitoring [63, 99].

(iv) *Rehabilitation and long-term care* can stabilize daily activity, light exposure, and nutrition schedules to reinforce synchronization [100].

(v) *Public-health services* can promote societal rhythm alignment through education, workplace standards, and environmental design [101].

Achieving this integration depends on *institutional frameworks* that align scientific, clinical, and regulatory responsibilities. Academic centers generate evidence, clinical and laboratory networks translate findings into protocols, public-health and policy bodies establish standards, education systems ensure competency, and industry partners provide time-aware technologies

(https://wellcomeopenresearch.org/documents/10-381) [102].

Coordinated across these layers, chronogeroprotection becomes an operational model rather than a theoretical construct, linking laboratory data, clinical action, and public policy within a cohesive framework that prioritizes the timing of interventions. This multilevel foundation enables the *action bundles* described in the next section.

Table 1. Diagnostic Tools for Circadian Rhythm Disorders: The Crucial First Step Before Advancing to Chronogeroprotection.

Diagnostic Tool	**Description**	**Purpose**	**Advantages**	**Limitations**	**Ref.**
Sleep questionnaires	Standardized surveys (e.g., Morningness-Eveningness Questionnaire [MEQ], the Pittsburgh Sleep Quality Index [PSQI]).	Screen for circadian preference and sleep quality, detecting the full range of disorder types and quantifying quality.	Quick, easy to administer, cost-effective, informs treatment decisions, good reliability.	Subjective reporting, limited precision.	[85]
Sleep diary	Self-reported daily record of sleep patterns, bedtimes, wake times, and perceived sleep quality.	Identify sleep patterns and irregularities.	Cost-effective, easy to use, supports treatment planning.	Relies on patient accuracy and recall, subject to bias.	[86]
Polysomnography (PSG)	Overnight study measuring brain waves (electroencephalography [EEG], eye movements (electrooculography [EOG]), oxygen levels, heart rate, and muscle activity.	Assess sleep architecture and exclude other disorders.	Gold standard for objective sleep assessment, especially in patients with sleep apnea.	Expensive, requires overnight stay, may not reflect habitual sleep patterns, limited resources.	[87]
Melatonin assay	Salivary, blood, or urinary assessment (e.g., dim-light melatonin onset [DLMO]).	Evaluate circadian phase and melatonin secretion timing.	Gold standard for assessment of core-clock function, direct measurement of circadian phase.	Requires controlled lighting, multiple sample collections in the evening, time-intensive, laboratory analysis.	[88]
Actigraphy and Light Dosimeters	Wearable devices tracking movement and light exposure over time.	Estimate patterns and activity levels in natural settings.	Non-invasive, objective, suitable for long-term monitoring, supports light therapy interventions.	Limited accuracy, cannot reliably distinguish quiet wakefulness from sleep.	[89, 90]
Core body temperature monitoring	Continuous measurement of temperature fluctuations by auricular, rectal or intestinal sensor.	Assess circadian phase and amplitude.	Objective biological marker of internal rhythm.	May be uncomfortable or invasive, requires specialized equipment.	[91]
Wearable tools	Devices combining sleep diaries, actigraphy, light sensors, temperature, oxygen saturation and pulse monitoring.	Assess environmental and behavioral impacts on rhythm.	Non-invasive, comprehensive data on circadian influences, suitable for epidemiological studies and big data analyses.	Requires compliance, data interpretation, data transfer and interoperability with clinical/research systems remain challenging, privacy concerns.	[92, 93]
Circadian phase markers	Biomarkers such as cortisol rhythm profiles.	Indirect marker of central circadian pacemaker activity via the Hypothalamic-pituitary-adrenal axis.	Objective biological insight into circadian misalignment.	Time-intensive, stress- and drug-sensitive, standardized conditions needed.	[94]
RNA-expression of clock genes	RNA-based analysis from hair follicles or peripheral mononuclear blood cells to determine individual gene expression patterns to	Characterize individual internal clock and classify chronotype, calibrated on DLMO as a reference.	No serial testing, freely available, home sampling, no DNA sequencing.	Expensive, limited availability, requires sample return within a specific timeframe,	[95]

	determine circadian phase and chronotype using single-sample testing.			not yet established in medical care.	
Genetic testing	Detection of polymorphisms and mutations.	Sequencing of genes with known mutations linked to sleep disorders and senescence.	Enables identification of rare diseases and inherited risk factors.	Expensive, complex interpretation of genotype/phenotype interrelation.	[96]

Chronogeroprotection: approach and strategies - action bundles

The WHO *Decade of Healthy Ageing* (2021–2030) emphasizes that longevity must coincide with extended functional health span and autonomy (https://cdn.who.int/media/docs/default-source/decade-of-healthy-ageing/decade-proposal-final-apr2020-en.pdf). Chronogeroprotection translates this vision into practice by addressing circadian misalignment and rhythm weakening as modifiable contributors to age-related vulnerability, while coupling circadian stabilization with established geroprotective principles. Rather than isolated measures, chronogeroprotective *action bundles* represent coordinated, circadian-informed interventions acting synergistically on biological, behavioral, clinical, institutional and public-health levels [7, 73]. Because these proposed chronogeroprotective strategies differ substantially in their current level of evidence, feasibility, safety, cost, and scalability, they should not be interpreted as equally ready for implementation. To avoid overinterpretation and provide clearer prioritization, the approaches can be separated into three groups.

First, high-confidence recommendations ready for clinical use include established sleep and circadian-health practices that are already part of clinical care when indicated. These include assessment of sleep-wake timing, chronotype, sleep quality, shift work exposure, and rhythm irregularity; use of sleep diaries, validated questionnaires, actigraphy, and light-exposure monitoring when appropriate; diagnosis and treatment of circadian rhythm sleep-wake disorders; timed light-exposure or light avoidance; sleep-wake stabilization; and the use of melatonin or melatonin-receptor agonists for selected circadian indications. General counseling on regular sleep-wake schedules, daytime light exposure, reduced nocturnal light exposure, and alignment of daily routines with the light-dark cycle also belongs to this category. These approaches are clinically usable when linked to established indications or low-risk behavioral counseling, but they should not be interpreted as proven anti-aging therapies.

Second, promising strategies requiring pilot testing include structured chronocounseling programs for older adults or individuals at risk of metabolic, cognitive, psychiatric, or functional decline; circadian lighting interventions in hospitals, rehabilitation facilities, nursing homes, and long-term care settings; time-aware scheduling of meals, physical activity, rehabilitation, diagnostics, and medication administration; integration of wearable-derived sleep, activity, and light-exposure data into preventive-care workflows; and chronodiagnostic interpretation of selected laboratory parameters using biological-time metadata. These strategies are biologically plausible and supported by mechanistic, observational, or limited interventional evidence, but they require feasibility studies, implementation trials, cost-effectiveness analyses, and validation of clinically meaningful outcomes before broad adoption.

Third, speculative research directions include the use of the pharmacological geroscience candidates, such as metformin, rapamycin, SIRT1-targeting compounds, or NAD^+ precursors, specifically as chronogeroprotective therapies; pharmacological manipulation of clock genes or clock-controlled pathways; transcriptomic, epigenetic, metabolomic, or multi-omic circadian biomarkers for individualized aging-prevention strategies; circadian dashboards estimating internal biological time and rhythm robustness; and longitudinal trials testing whether improving circadian robustness delays frailty, multimorbidity, cognitive decline, or biological aging. These approaches remain hypothesis-generating and are mainly supported by animal studies, cellular models, mechanistic reasoning, or early translational research. They should therefore be framed as future research priorities rather than current clinical recommendations.

This graded structure provides a practical prioritization pathway. Chronogeroprotection should begin with low-risk, high-feasibility measures that can already be integrated into clinical assessment, counseling, and treatment of established circadian rhythm sleep-wake disorders. The next priority is pilot testing of scalable interventions, while more complex approaches should currently be treated as longer-term research and implementation priorities.

Building on this stepwise readiness and prioritization framework for integrating biological time into healthy aging prevention, chronogeroprotection action bundles can be grouped into four complementary domains corresponding to the green layer of the conceptual framework (Fig. 2):

- Personalized clinical chronocare integrates evidence-based lifestyle timing (sleep, meals, light exposure) with targeted nutrient supplementation and, where appropriate, chronopharmacology.
- Time-aware healthcare systems apply circadian lighting, rhythm-based scheduling, and temporal data integration in hospitals and laboratories to enhance recovery, diagnostic precision, and staff performance [63, 102].
- Education and research networks foster literacy and innovation in chronobiology across professions, supported by initiatives such as the Wellcome Sleep and Circadian Health Programme (https://wellcomeopenresearch.org/documents/10-381).
- Public-health and policy frameworks promote circadian rhythm stability across populations by implementing evidence-informed workplace design, protecting shift workers from excessive circadian burden, improving light environments in long-term care and dementia care, supporting caregivers, and planning urban environments to ensure adequate daylight and night-time light exposure [97, 101].

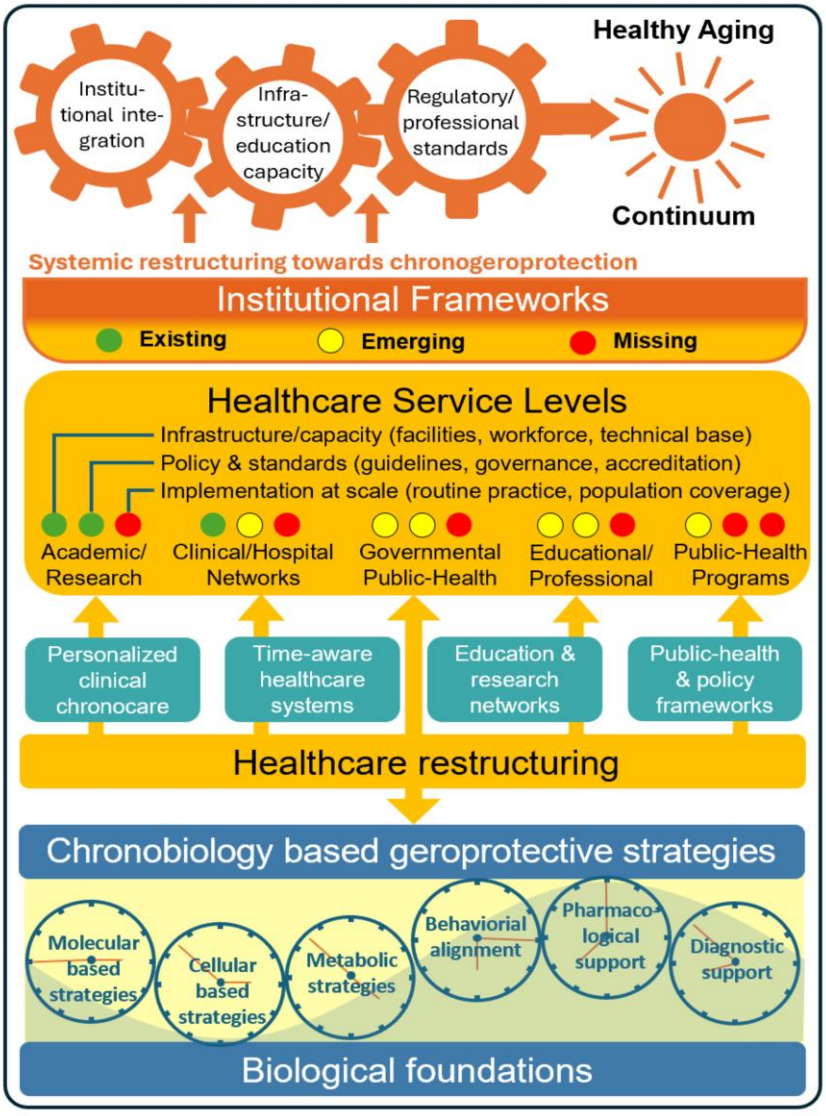

Figure 2. From molecular clocks to healthy aging: a multilevel framework for chronogeroprotection. Chronogeroprotection provides a multilevel framework linking the biological hallmarks of aging to systemic healthcare transformation. The lower tier depicts molecular and circadian mechanisms that underline geroprotective strategies. These strategies converge into four chronogeroprotective action bundles: personalized clinical chronocare, time-aware healthcare systems, public-health and policy frameworks, and education and research networks. The central tiers illustrate the healthcare and institutional levels where implementation must occur, highlighting existing (●), emerging (●), and missing (●) structures. The upper tier summarizes the systemic restructuring required - conceptual, organizational, infrastructural, and regulatory - to embed biological time as a dimension of preventive and protective care.

For example, in an older adult undergoing rehabilitation after a fall, chronogeroprotection would not require a separate clinical program, but could be integrated into routine care. Sleep-wake timing, chronotype, light exposure, meal timing, medication timing, cognitive status, and fall risk could be assessed together. Low-risk interventions might include strengthening daytime light exposure and activity, protecting night-time sleep from unnecessary disruption, regularizing meals, reviewing the timing of sedating or activating medication, and scheduling rehabilitation at times when the patient is most alert. This example illustrates how biological-time principles can be translated into practical care while remaining within established clinical practice and avoiding premature use of speculative interventions.

Implementation therefore requires cross-sector translation: scientists define molecular targets and biomarkers; clinicians integrate timing into prescriptions and counseling; communities and digital platforms support adherence; and policymakers create enabling infrastructure.

Together, these bundles form the operational foundation of chronogeroprotection. Their integration across healthcare, research, and policy initiates systemic restructuring.

Risks, safeguards, vulnerable populations, and ethical considerations

Despite the preventive and resilience-based approach that chronogeroprotection is intended to take, there are still risks associated with it. First, chronogeroprotective strategies should not be implemented in a way that would overmedicalize the natural variability in chronotypes. Morningness, eveningness, and interindividual differences in preferred sleep-wake timing are not pathological per se, except when such chronotypic variability leads to distress or problems with functioning, poses safety hazards or misalignment with required social or occupational schedules. Chronogeroprotection should therefore support adaptive rhythm alignment rather than impose a single ideal daily schedule.

Second, pharmacotherapy necessitates special care. Although effective in certain types of circadian rhythm disorders, the use of melatonin and its receptor agonists can be hindered by improper timing, overuse, prolonged unsupervised treatment, differences in product quality, interactions with other drugs, and next-day sleepiness. Moreover, the regulation of their availability varies across jurisdictions, with melatonin treated as a dietary supplement in some countries and as a prescription medicine or regulated drug in others [103, 104]. The application of metformin, rapamycin, SIRT1-targeting compounds, and NAD^+ precursors should not be considered established chronogeroprotection strategies either. Their use for circadian or healthy aging purposes remains investigational and requires attention to safety, contraindications, monitoring requirements, and regulatory approval.

The third potential concern involves misinterpretation and health inequities that might arise from new technologies. The use of consumer wearables may allow for long-term analysis of sleep, activity, and light exposure. However, the predictions made by these devices regarding sleep stages, circadian timing, and rhythmicity are not identical to clinically validated measurements. Overreliance on wearable data may generate anxiety, inappropriate self-medication, or false reassurance. Furthermore, new circadian diagnostics, biomarkers of biological time, and EHR-based circadian health monitoring may be accessible only to better-equipped healthcare institutions, potentially widening disparities in preventive care.

Lastly, chronogeroprotection must explicitly consider vulnerable populations and the social determinants of circadian health. Circadian rhythms are shaped not only by individual behavior, but also by occupation, housing, income, caregiving responsibilities, neighborhood light exposure, institutional routines, and work schedules. Older adults in long-term care and people with dementia may be exposed to insufficient daytime light, excessive nocturnal light and noise, fragmented sleep, limited daytime activity, and care routines that disrupt rest-activity cycles. In these settings, chronogeroprotective strategies should prioritize environmental light-dark contrast, daytime activity, meal regularity, protected sleep periods, and staff workflows that minimize unnecessary night-time disruption.

Visually impaired individuals, especially totally blind individuals, also constitute a susceptible population since they can develop N24SWD, recurrent circadian misalignment of their biological clock, disruption of sleep, fatigue, and impairment in their daily functioning. There is also the potential for chronically disrupted circadian rhythms in caregivers of patients owing to nocturnal caregiving, disrupted sleep, emotional stress, and unpredictable daily routines. Night-shift and rotating-shift workers are exposed to socially induced circadian disruption and should not be expected to carry the burden of adaptation alone. Chronogeroprotection for these groups requires occupational measures such as evidence-informed shift scheduling, adequate recovery periods, controlled light exposure, and avoidance of excessive cumulative night work burden.

Finally, socioeconomically disadvantaged groups may have less control over work schedules, housing conditions, light exposure, sleep opportunity, safe outdoor

activity, and access to circadian diagnostics or specialist care. Recommendations should therefore be accompanied by workplace, policy, and environmental interventions that reduce circadian burden rather than simply instructing individuals to adapt. Overall, ethical implementation must be guided by principles of proportionality, accessibility, occupational protection, data privacy, and a clear distinction between clinically indicated care, preventive counseling, and speculative research.

Concluding remarks

Chronogeroprotection reframes healthy aging as a temporal systems approach, drawing parallels with how sleep was integrated into Life's Essential 8 [105]. Just as sleep has become a critical component of cardiovascular and metabolic health, chronogeroprotection emphasizes the timing of biological processes, advocating for a holistic approach that connects molecular geroscience, clinical care, and public-health through biological time. By aligning nutrition, pharmacology, and lifestyle with circadian regulation, it can move beyond isolated anti-aging strategies toward a coordinated, evidence-based resilience promotion approach.

Realizing this vision requires systemic restructuring along four interdependent axes that underpin the framework's red-orange tier (Fig. 2):

- Conceptual reframing, viewing aging as a circadian time-dependent loss of adaptability and resilience;
- Organizational redesign, embedding circadian timing into clinical and laboratory workflows;
- Infrastructural modernization, integrating temporal metadata into electronic health records and analytics;
- Regulatory and educational reform, accrediting, incentivizing, and sustaining circadian-informed practice.

Several domains remain underdeveloped, the red-dot areas in the framework where chronogeroprotection is still missing:

- Translational research linking circadian biology and geroscience is needed to operationalize molecular findings in real-world populations.
- Circadian-informed infrastructures, including circadian dashboards for real-time tracking of biological rhythms, timestamped laboratory analytics that account for the circadian phase in test interpretation, and biologically informed scheduling, must be established to scale implementation.
- Policy frameworks should recognize circadian health as a measurable public-health target, comparable to nutrition or physical activity indicators.
- Education and certification pathways are required to build chronobiological competence across medical, nursing, and laboratory professions.
- Population-level prevention programs promoting light hygiene, rhythm stability, and temporal nutrition remain virtually absent.

Aligning progress in these areas with the *WHO Decade of Healthy Ageing* agenda could transform circadian science into a pillar of preventive health systems. Future longitudinal, interventional, and implementation studies should define candidate outcomes across several domains. These include circadian and sleep-related endpoints, such as sleep-wake regularity, circadian phase stability, rhythm amplitude, chronotype stability, and light exposure patterns; geriatric and functional endpoints, such as frailty index, falls, delirium incidence, cognitive performance, quality of life, functional independence, institutionalization, disability-free survival, and health span; cardiometabolic and inflammatory endpoints, such as glycemic control, blood pressure variability, lipid rhythmicity, and inflammatory markers; healthcare-system endpoints such as hospital length of stay, readmissions, rehabilitation progress, and care dependency; and long-term outcomes, including biological age measures, multimorbidity burden, and mortality.

Even modest improvements in health span and functional independence could have meaningful social, economic and healthcare implications by reducing frailty, dependency, and care needs and healthcare utilization. More fundamentally, chronogeroprotection restores autonomy, cognitive performance, and participation throughout later life; however, the magnitude of these benefits requires evaluation in longitudinal and implementation studies.

Viewed through this lens, aging is no longer a passive decline but a dynamic process of adaptive capacity. By embedding biological time into prevention, medicine can convert the rhythm of aging from a liability into an opportunity, making time itself a therapeutic ally.

Author contributions

J.W.: conceptualization, writing, and preparation of the figures. S.R., M.Ö.: review, comments, and further additions. All authors contributed to discussions of the scope of this perspective article and approved the final revised version of the manuscript.

Conflict of interest

All authors state no conflict of interest.

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