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Perspective

# Delphi-derived Framework for Healthspan-Oriented Care: The Cardiometabolic Health Perspective

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**ABSTRACT: This Delphi-derived expert consensus provides a clinical framework to optimize and maintain healthspan along the lifespan from the cardiometabolic health perspective in both healthy individuals and individuals with well-controlled cardiometabolic diseases. The framework guides the shaping of the evidence base in the clinical approach for assessing and targeting intrinsic capacity and healthspan. This approach integrates well-established cardiometabolic guidelines with the innovative and rapidly developing field of healthspan medicine. Recommendations were developed through a literature review and structured Delphi consensus. To ensure methodological rigor, recommendations were developed using a grading framework adapted from AHA/ESC guidelines. This system applied standardized Classes of Recommendation (I, IIa-c, III) and added novel Class IIc to designate interventions with uncertain or minimal benefit, supported by limited or inconclusive evidence. Evidence levels ranged from multiple RCTs/meta-analyses (A) to single RCTs or non-**

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**RCT studies (B) to expert consensus (C). Such an approach is a crucial step toward building both evidence and credibility for clinical strategies aimed at preserving healthspan—specifically by preventing cardiometabolic pathological aging and the associated decline in intrinsic capacity. The healthspan-oriented care framework defines healthy aging from a cardiometabolic perspective, classifying individuals into "healthy aging without CMD" and "healthy aging with well-controlled CMD" based on clinical, laboratory, and functional criteria. The framework also evaluates emerging diagnostic tools and their role in risk stratification. While emerging approaches show considerable promise, their clinical translation requires further validation, standardization, and large-scale evidence. This Delphi-derived expert consensus outlines a comprehensive framework for the cardiometabolic healthspan-oriented model of care by integrating evidence-based clinical criteria, functional assessments, and emerging geroscience insights**

***Keywords:*** healthspan-oriented care, cardiometabolic diseases, intrinsic capacity, delphi-derived consensus, geroscience, aging

## Introduction

Despite growing interest in promoting healthspan, the field of healthy longevity medicine currently lacks standardized clinical guidelines. As highlighted in a recent international survey of aging researchers, there is no consensus on a unified definition of aging that would be translatable into clinical practice. Scientific opinions offer suggestions on the drivers of aging, primarily characterized by damage accumulation, functional decline, loss of homeostasis, or evolutionary trade-offs. This landscape might thus lead to a fragmented approach, with varying definitions and strategies that rely on empirical methods. Recent efforts to include aging as a diagnosis within the International Classification of Diseases (ICD-11) highlight the importance of establishing a common framework, as formal recognition would have major implications for research prioritization, clinical coding, and therapeutic development.

Despite some conceptual differences across the scientific and medical communities, aging research provides valuable insights into the management of cardiometabolic disease (CMD). Advances in aging biomarkers and biological age assessment open new possibilities for early risk stratification, targeted prevention, and healthspan-oriented interventions within cardiometabolic care. Aging and cardiometabolic dysfunction are intimately linked via shared mechanisms, including chronic low-grade inflammation (inflammaging), oxidative stress, mitochondrial decline, epigenetic drift, and cellular and immunosenescence. These hallmarks of aging not only drive functional decline but are also intimately connected to the pathophysiology of CMDs, including type 2 diabetes (T2DM), hypertension, dyslipidemia, and others. Thus, aging and CMDs share common biological underpinnings, making CMDs both a consequence and an accelerant of biological aging.

In this context, healthy longevity medicine, as an emerging branch of geroscience and a personalized disease-prevention approach, focuses on extending individuals' healthspan using modern technologies, including artificial intelligence (AI) techniques. Preventive strategies, lifestyle modifications, and personalized interventions are key strategies in healthy longevity medicine to improve health outcomes and quality of life for all individuals.

Recent advances in geroscience have accelerated the fundamental concepts in age-related disease diagnostics and therapeutics [1]. Aging is now recognized as the major risk factor for CMDs [2], yet conventional CMD management often focuses on symptom control rather than addressing the underlying biological drivers.

Therefore, assessing patients' intrinsic capacity (IC), a key concept in geroscience, through clinical and biological markers (biomarkers of aging) is crucial in the study of aging [3, 4]. A study using UK Biobank data found that lower IC was associated with a higher risk of cardiovascular disease and even death over 10 years [5].

Evaluating intrinsic capacity is resource-intensive, and its molecular and cellular bases remain poorly understood. For this reason, research groups are investigating the correlation between intrinsic capacity and surrogate measures, such as epigenetic clocks that predict mortality [6]. It is also crucial that epigenetic clocks have been extensively studied to evaluate the risk of major adverse cardiac events (MACE), mortality, CVD incidence, and frailty [7, 8].

Translation of geroscience research data and innovative approaches into modern, evidence-based, healthspan-oriented care requires a fundamental background to integrate urgently needed technologies into clinical practice [9]. For instance, incorporating healthy longevity principles such as biological aging clocks [10], multi-omics profiling [11], and geroprotective therapies [12] may offer a transformative approach to mitigating CMD risk and extending healthspan.

It is worth noting that there is currently no clinical evidence supporting radical lifespan extension, and the term "longevity interventions" is often misinterpreted. Therefore, the proposed healthspan-oriented care framework defines *healthy longevity interventions* as those that focus primarily on extending healthspan (based on MACE, incidence of age-related diseases, or by indirect surrogate biomarker data) and only secondarily on lifespan extension (based on disease-specific and all-cause mortality research data).

This delphi-derived expert consensus aims to define clear clinical criteria for evaluating and supporting healthy aging from a cardiometabolic function perspective, in the absence or presence of at least well-controlled CMDs, grounded in emerging biological and functional models of aging. Within this delphi-derived expert consensus, we define healthy aging as the preservation of functional capacity, physiological resilience, and well-being across the lifespan - with a particular emphasis on the absence or at least well-controlled presence of chronic diseases such as cardiovascular disease (CVD), heart failure (HF), T2DM, hypertension (HTN), and dyslipidemia. These age-related CMDs significantly accelerate biological aging and are among the most modifiable drivers of morbidity in older adults.

Please note that this Delphi-derived expert consensus does not cover other chronic diseases, such as chronic obstructive pulmonary disease (COPD), neurodegenerative disorders, or chronic kidney disease. Our focus is specifically on cardiometabolic healthspan-oriented care, enabling a targeted, in-depth exploration of this important area and potentially advancing its clinical use in close collaboration with well-respected clinical associations.

The delphi-derived expert consensus is intended as a basis for guidance for health professionals and scientists, assisting in tailoring clinical decisions to each patient's health condition. These recommendations are intended to complement, not replace, regional regulatory and clinical guidelines. Implementation should follow local approval status and legal frameworks. Health professionals are also responsible for ensuring compliance with the relevant rules and regulations regarding drugs and devices in their country at the time of prescription, as well as for upholding the ethical standards of their profession.

## Methods

Relevant evidence was identified through targeted PubMed and major guideline repository searches from 2010 to 2025, focusing on interventions and diagnostics relevant to cardiometabolic health and aging. Evidence appraisal was performed in pairs, with disagreements resolved by group discussion. To ensure methodological rigor and transparency, the recommendations presented in this manuscript were developed using a structured, two-round Delphi consensus process involving a multidisciplinary panel of international experts in cardiometabolic medicine, aging research, and related fields. This Delphi-derived expert consensus represents the position statement of the writing committee and the expert Delphi panel.

Recommendations were graded using a modified framework of Classes of Recommendation (I, IIa, IIb, IIc, III) and Levels of Evidence (A, B, C), aligned with AHA/ACC and ESC methodologies (Table 1–2). However, given the specific challenges inherent to the field of healthspan and geroscience, a modification was introduced through the addition of a Class IIc category.

In this adapted framework, Class I indicates strong evidence and clear benefit, Class IIa denotes moderate evidence with benefit likely, and Class IIb reflects limited evidence with uncertain benefit. However, existing AHA/ACC and ESC classification systems do not explicitly distinguish between interventions supported by weak but suggestive evidence and those for which evidence is insufficient or inconclusive. For this reason Class IIc was added to classify interventions with evidence indicating no meaningful clinical benefit, primarily due to a lack of validated scientific data or inconclusive results. This distinction allows separation from Class IIb (where some clinical signal of benefit exists) and from Class III (where evidence suggests lack of benefit or potential harm).

The type of supporting data further qualified the levels of evidence. Interventions supported by multiple randomized controlled trials or meta-analyses were assigned Level A; single RCTs or large non-randomized studies, Level B; and expert consensus, mechanistic, or early-phase data, Level C. If direct evidence was limited (Class IIb–C recommendations), the strength of recommendations was informed by expert consensus using a structured Delphi process.

A multidisciplinary panel of experts, represented by the authors' group, participated in the panel review to develop the consensus statements (N=21). The panel was intentionally multidisciplinary and geographically diverse, including participants from Europe, North America, and the Middle East. This diversity was designed to ensure broad representation of clinical perspectives, healthcare systems, and research approaches, thereby enhancing the generalizability and applicability of the consensus framework. The expert Delphi panel consisted of experts represented within the authorship group, selected based on predefined criteria including:

(i) a publication record in cardiometabolic diseases, geroscience, or related disciplines;

(ii) strong clinical or research expertise in relevant domains such as cardiology, endocrinology, internal diseases, aging biology, or preventive medicine; and

(iii) active engagement in academic, clinical, or translational research settings.

**Table 1.** Modified version of the AHA/ESC recommendations classes and level of evidence.

| Recommendation Classes (Criteria) | Modified version of the AHA/ESC recommendations classes (Description) |
|---|---|
| **Class I (Strong)** | Interventions are unequivocally recommended – evidence indicates that the benefits significantly outweigh the risks. In this class, diagnostic tests and drugs have a proven effect on cardiometabolic health and healthy aging. Multiple randomized clinical trials or meta-analyses support recommendations.<br><br>Suggesting wording to use: The intervention is recommended. |
| **Class II** | Interventions may be helpful, but the evidence needs to be more definitive. Class II is further divided into subclasses: |
| **Class IIa (Moderate)** | The benefits outweigh the risks – the intervention is likely effective, but available studies indicate a need for further confirmation. For Class IIa, evidence should ideally come from at least one well-designed randomized controlled trial (RCT) or from robust observational studies that provide consistent findings supporting the intervention's efficacy.<br>**Clinical use:** Can be used in clinical practice.<br><br>Suggesting wording to use: The intervention should be considered. |
| **Class IIb (Weak)** | Benefits may be present, but the evidence is less specific – the intervention can be used in specific conditions, but current scientific data do not fully confirm its broader use. For Class IIb, evidence can be derived from smaller RCTs, non-randomized studies, or observational data that suggest a potential benefit, but with greater uncertainty due to limitations in study design or sample size.<br>**Clinical use:** Not FDA- or EMA-approved interventions for healthy aging. Only in clinical trial settings/ defined FDA-or EMA-approved clinical indications, or off-label use in specific conditions.<br><br>Suggesting wording to use: The intervention may be considered. |
| **Class IIc (No proven benefit yet)** | Benefits may be present on the animal model. Still, the evidence is less specific or ambiguous – the intervention may potentially be used in the future, but current scientific data do not fully confirm it. For Class IIc, evidence can be derived from smaller RCTs, non-randomized studies, or observational data that suggest a potential benefit, but with greater uncertainty due to limitations in study design and sample size.<br>**Clinical use:** Not FDA- or EMA-approved for healthy aging. Use is restricted to clinical trial settings and considered experimental.<br><br>Suggesting wording to use: The intervention is not yet recommended. |
| **Class III (Harmful)** | Interventions are not recommended – available evidence suggests they do not confer benefits or may be harmful. Therapies in this class may increase the risk of adverse effects or have a neutral impact on health.<br><br>Suggesting wording to use: The intervention is not recommended. |
| **Levels of Evidence** | **Modified version of the AHA/ESC levels of evidence (Description)** |
| **Level A** | Data derived from multiple randomized clinical trials or meta-analyses. The evidence for the drug's geroprotective or senolytic effect is high quality, supported by multiple studies involving large patient groups. Drugs with Level A evidence have a solid scientific foundation. |
| **Level B** | Data derived from a single randomized trial or a large non-randomized study. The evidence is of moderate quality – there are not many studies, but the results of the available studies are promising. |
| **Level C** | Evidence derived from expert opinion, small studies, registries, or case series. The evidence for the healthy longevity intervention is limited and requires further studies to verify its efficacy. |

The Delphi procedure consisted of two iterative rounds administered via the ISO-certified data management platform *Longenesis Engage* (Longenesis Ltd). In the first round, panelists (N=21) independently evaluated a predefined set of 16 statements derived from a structured literature review. Participants rated each statement using a standardized agreement scale and were encouraged to provide qualitative comments and suggestions for modification. Following round one, responses were analyzed both quantitatively (agreement levels) and qualitatively (thematic analysis of comments). Based on this feedback, 16 statements were revised, refined, and expanded where appropriate, resulting in a total of 18 statements that were presented in the second round.In the second round, panelists (N=21) were presented with anonymized group feedback (statistical distributions and qualitative summaries) and asked to re-rate each statement, with revisions incorporated when appropriate. Consensus was defined as a priori at least 75% agreement among panelists (Supplementary Material 1). If statements that did not reach consensus those were flagged as areas of ongoing uncertainty. The number of participants and response rates were monitored across both rounds to assess engagement and potential attrition. Attrition between rounds was minimal and did not materially affect the robustness of the consensus process.

All panel members were required to disclose potential conflicts of interest in accordance with standard academic and journal policies. Any identified conflicts were reviewed and managed to minimize potential bias in the consensus process. Panelists with relevant conflicts were not excluded but were expected to evaluate statements objectively within the structured Delphi framework.

Direct type of evidence refers to findings from randomized controlled trials, meta-analyses, or large prospective cohort studies reporting clinical outcomes. Indirect type of evidence encompassed biomarker or surrogate endpoint analyses (epigenetic clocks), which were used to inform recommendations when direct clinical outcome data were unavailable. A complete summary of all recommendations, presented as evidence tables, is provided in Supplementary Material 2 (Supplementary Tables 1–5).

**Table 2.** Direct/indirect types of evidence used in the expert consensus to evaluate healthspan/lifespan.

| Type of evidence | Definition of the evidence | Description |
|---|---|---|
| **Direct** | Direct evidence pertains to measurable clinical outcomes that reflect the impact of an intervention on healthspan or lifespan. | **All-Cause Mortality**: Reduction in death from any cause.<br><br>**Cause-Specific Mortality**: Reduction in death from specific causes, such as cardiovascular disease.<br><br>**Major Adverse Cardiovascular Events (MACE)**: Reduction in myocardial infarction, stroke, or cardiovascular death.<br><br>**Incidence of Age-Related Diseases**: Decrease in the occurrence of diseases such as dementia, cancer, or T2DM. |
| **Indirect** | Indirect evidence involves surrogate markers associated with aging processes but that do not directly measure clinical outcomes. These biomarkers can provide insights into the biological age and the effectiveness of interventions on aging-related pathways. | **Epigenetic Clocks:** Epigenetic clocks estimate biological age based on patterns of DNA methylation (DNAm). They are increasingly used in clinical trials to assess the impact of interventions on biological aging.<br>● **GrimAge**: Currently, the most accurate epigenetic predictor of mortality risk. It has been associated with various age-related diseases and used in many studies, including exercise, weight loss, omega-3 supplementation, and aspirin studies, to measure slowed biological aging.<br>● **DunedinPACE**: Measures the pace of aging and has shown responsiveness to caloric restriction (CALERIE trial), physical activity, and diet interventions.<br>● **PhenoAge**: Similar to GrimAge, it is strongly correlated with chronic disease risk and mortality; it is used to demonstrate the benefits of the Mediterranean diet, omega-3 fatty acids, weight loss, and caloric restriction.<br>● **Hannum mAge:** Outdated DNAm clock applied in nutraceutical and drug RCTs (e.g., metformin, rapamycin).<br>**Horvath Clock:** Outdated multi-tissue DNAm clock foundational to aging trials; used in CALERIE and pharmacological RCTs. The Horvath clock is the best clock for detecting Clonal Hematopoiesis of Indeterminate Potential and is also valuable for studying the effect of HIV infection. |

| | | |
|---|---|---|
| | | • **Li mAge:** Intervention-sensitive DNAm clock; lowered in polyphenol supplementation studies.<br>**Telomere-Based Biomarker (Telomere Length):** Proxy for replicative aging; used in exercise and weight loss interventions as a supportive biomarker (not a primary clock). |

## 1. Redefining Healthy Aging Through a Cardiometabolic Lens

Healthy aging has traditionally been described as aging free of chronic disease or disability. However, this binary concept is increasingly recognized as overly simplistic, particularly in populations where chronic conditions, such as CMDs, are highly prevalent with advancing age.

Recognizing the substantial public health burden of CMDs, both European and U.S. professional societies have called for a paradigm shift from reactive disease treatment to proactive, integrated prevention strategies. In Europe, leadership has come from the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), the European Association for the Study of Obesity (EASO), the European Society of Endocrinology (ESE), and the European Association for the Study of Diabetes (EASD).

In parallel, major U.S. bodies - including the American Heart Association (AHA), American College of Cardiology (ACC), American Diabetes Association (ADA), American Association of Clinical Endocrinology (AACE), and Obesity Society - have emphasized guideline-directed, risk-based care with increasing attention to age-specific needs.

In the context of geroscience and healthspan-oriented care, healthy aging is better conceptualized as a spectrum defined not solely by the absence of disease but by the preservation of previously mentioned intrinsic capacity, functionality, and physiological resilience. Declines in IC, especially when multidomain, strongly predict frailty, cardiovascular events, and mortality. CMDs can accelerate this decline, but timely and targeted interventions, including lifestyle, pharmacologic, and digital monitoring strategies, can mitigate or even reverse such trajectories.

Therefore, redefining healthy aging through a cardiometabolic lens involves moving away from purely disease-absent models toward function-oriented and resilience-based paradigms (Fig.1). This approach supports the current set of realistic goals of healthy longevity medicine as a healthspan-oriented care, not merely extending life, but also ensuring that additional years are lived with vitality, autonomy, and purpose - whether or not CMDs are present.

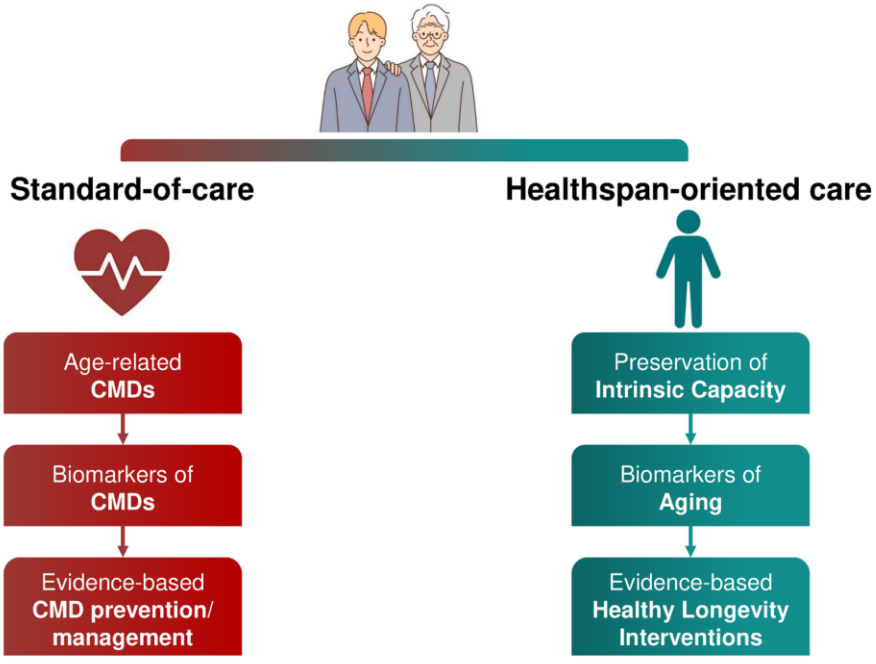


**Figure 1. Comparison of standard-of-care and healthspan-oriented care approaches to healthy aging.** The paradigm is shifting from disease-centered models toward function-oriented, resilience-based strategies.

To redefine healthy aging, it is essential to adopt terminology that reflects functional trajectories and clinical realities:

**1) Healthy Aging without CMDs:** Refers to individuals who have reached older age without clinical manifestations of major chronic diseases, including cardiometabolic diseases. These individuals maintain stable metabolic, vascular, and cognitive function and demonstrate preserved intrinsic capacity across domains such as locomotion, cognition, sensory ability, vitality, and emotional well-being. They represent an optimal aging trajectory, often shaped by favorable genetics, lifestyle, and environmental exposures.

**2) Healthy Aging with Well-Controlled CMDs:** Recognizes that many older adults live with CMDs but are aging healthily due to successful disease management. In this context, "well-controlled CMDs" means the condition is:

- Diagnosed and monitored under evidence-based clinical guidelines,
- Not associated with significant complications or end-organ damage,
- Managed in a way that maintains independence and functional ability,
- Free from frequent hospitalizations or major adverse events.
- No clinically evident progression

This inclusive definition acknowledges that healthy aging can coexist with chronic disease, provided the disease does not significantly impair function or quality of life. For example, an individual with T2DM who maintains glycemic control (e.g., HbA1c <7.0%), exhibits no cardiovascular complications, and leads an active, independent life may be considered as aging healthily.

### 1.1. Selection criteria for healthspan-oriented care: healthy aging individuals with absence or well-controlled cardiometabolic diseases:

In defining eligibility for healthy longevity interventions, it is essential to establish clear criteria distinguishing individuals without or with well-controlled CMDs from those with insufficiently controlled CMDs. Recent guidelines, such as the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice which introduced SCORE2 and SCORE2-OP, have recalibrated cardiovascular risk prediction across regions and age strata, promoting a life-course prevention model in Europe. Similarly, U.S. guidelines, including the 2025 ACC/AHA Hypertension Guidelines [13], 2018 AHA/ACC Guideline on the Management of Blood Cholesterol, and 2023 ADA Standards of Care, propose PREVENT equations (for total CVD, atherosclerotic CVD (ASCVD) and HF) and underscore intensive early intervention and precision-based management, reinforcing the potential integration of biological aging concepts into CMD care [13]. This evolution supports the integration of risk-based, life-course approaches to CMD management, aligning with goals of biological age reduction and healthspan-oriented care.

**A. Arterial hypertension:** In the management of hypertension, guidelines recommend a personalized approach to blood pressure control, especially in older adults [14]. Based on EU guidelines, systolic blood pressure should generally be reduced to below 140 mmHg, with lower treatment targets (120–129 mmHg) appropriate for many, depending on tolerability. A new category called 'Elevated BP' is introduced and is defined as an office systolic blood pressure of 120–139 mmHg or diastolic BP of 70–89 mmHg. U.S. guidelines define hypertension as ≥130/80 mmHg [13]. Lifestyle interventions, including salt restriction, regular physical activity, and weight loss, are recognized as central components of blood pressure control and cardiovascular risk reduction. Pharmacological treatment is typically initiated with a two-drug combination: commonly a renin-angiotensin system inhibitor with a calcium channel blocker or diuretic.

**B. Dyslipidemia.** For dyslipidemia, the ESC and EAS provide updated guidelines (2019 with 2025 focused update) that align lipid management with individual cardiovascular risk [15], while the AHA/ACC cholesterol guidelines (2018) adopt a risk- and threshold-based approach [16]. In low CV risk individuals considered to be aging healthily without dyslipidemia, lipid profiles are typically within optimal ranges: LDL cholesterol <2.6 mmol/L (100 mg/dL), HDL cholesterol >1.0 mmol/L (40 mg/dL) in men and >1.3 mmol/L (50 mg/dL) in women, triglycerides <1.7 mmol/L (150 mg/dL), and total cholesterol <5.0 mmol/L (190 mg/dL, U.S. guidelines generally consider <150 mg/dL desirable). For those with diagnosed dyslipidemia, well-controlled disease in the EU and U.S. frameworks is guided by risk stratification. In both systems, statins remain the cornerstone of LDL-C lowering, with adjunctive options such as ezetimibe, bempedoic acid, or PCSK9 inhibitors recommended when statin therapy alone is inadequate or not tolerated. Both guidelines emphasize comprehensive cardiovascular risk assessment, considering lipid levels in the context of comorbidities, inflammation, and metabolic status, rather than isolated laboratory values.

**C. T2DM:** For T2DM, the 2023 guidelines from the ESC, in collaboration with the EASD, emphasize a structured approach to cardiovascular risk management. A key innovation is the use of the SCORE2-Diabetes calculator, which combines traditional cardiovascular risk factors with diabetes-specific variables to classify patients with diabetes into different risk categories. Similar

guidelines are provided in ADA Standards of Care 2025. The guidelines highlight the value of SGLT2 inhibitors and GLP-1 receptor agonists in reducing cardiovascular events in individuals with T2DM and either established ASCVD or high cardiovascular risk, regardless of baseline glycemic control. This is also in line with the consensus statement of the EASD and the ADA 2022 [17].

These therapies represent a paradigm shift from glucose-centered treatment to a holistic approach. Importantly, the concept of healthy aging in this context distinguishes between individuals without T2DM, defined as the absence of a clinical diagnosis, normal fasting glucose and HbA1c levels (<5.7%, 39 mmol/mol), and no evidence of insulin resistance - and those with *well-controlled T2DM*. The latter refers to individuals whose T2DM is managed according to evidence-based clinical standards, with HbA1c typically maintained below 7.0% (or individualized targets, including frail/comorbid patients), absence of acute complications (such as severe hypoglycemia or diabetic ketoacidosis), and no significant microvascular or macrovascular damage. Such patients may be considered as aging healthily if they maintain functional independence and quality of life.

It should be noted, however, that achieving guideline-based control of cardiometabolic risk factors does not necessarily equate to preserved biological healthspan, as individuals may still exhibit underlying biological aging, frailty, or functional decline not captured by conventional clinical metrics.

**D. Obesity**: Absence of obesity is defined by maintaining a body mass index (BMI) within the normal range of 18.5 to 24.9 kg/m², together with measures of central adiposity. Traditionally, waist circumference cut-offs (<94 cm in men, <80 cm in women) have been applied as thresholds for lower cardiometabolic risk. However, contemporary guidelines increasingly recommend waist-to-height ratio (WHtR <0.5) as a more robust and age-independent indicator of central obesity and cardiometabolic risk [18]. A particularly interesting notion from the CMD point of view is a combination of both overweight based on BMI (>25) and WHtR (>0,5), indicating high-risk adipose tissue accumulation, which identifies people with a higher risk of CMD [19].

Well-controlled obesity refers to individuals who have achieved and sustained a weight reduction of at least 10%, accompanied by measurable improvements in key metabolic parameters, including blood pressure, lipid profile, and glycemic control. Effective management also requires ongoing engagement in structured lifestyle interventions, including tailored dietary modifications, regular physical activity, and behavioral strategies aimed at long-term adherence and relapse prevention [18, 20].

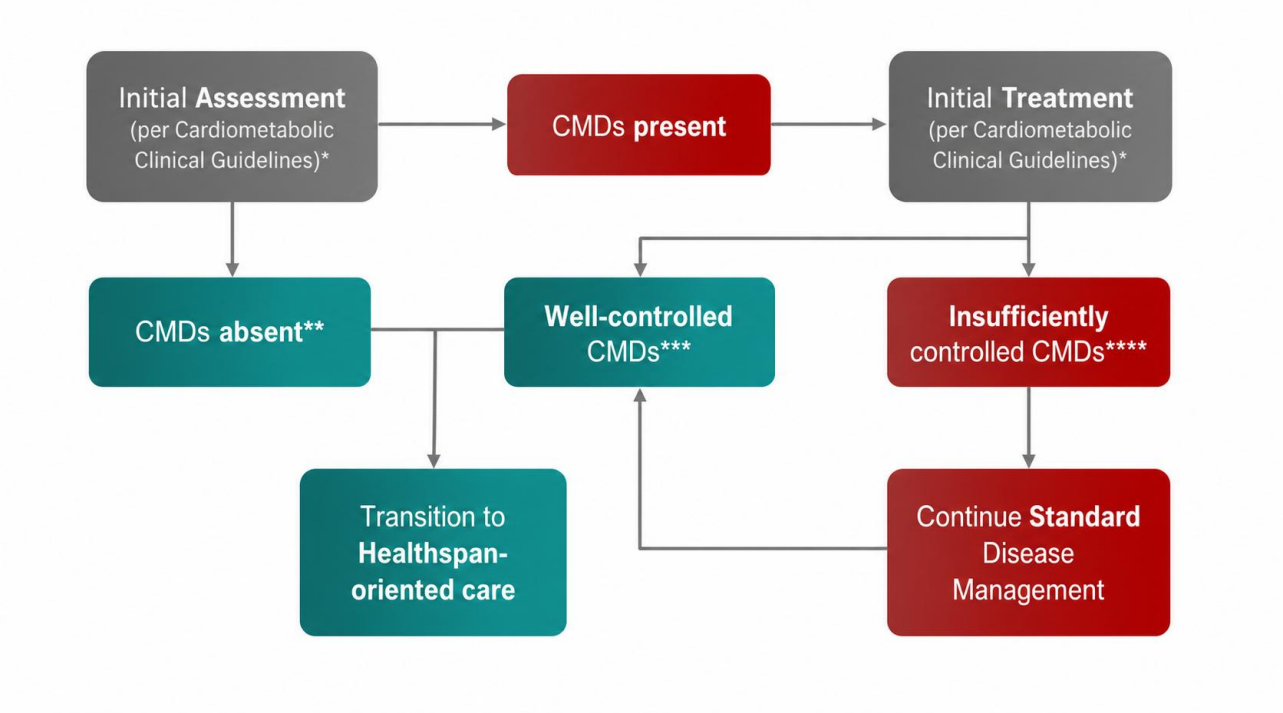


**Figure 2. Criteria to Transition from Disease Management to Healthspan Focus.** *Screen and treat patients for cardiometabolic diseases using evidence-based protocols. **The patient has no signs of CMD. ***CMD is under optimal control. ****CMD is diagnosed, and disease markers are insufficiently managed.

**E. Heart Failure:** Absence of heart failure is defined by the lack of any history or clinical symptoms of heart failure, alongside a normal left ventricular ejection fraction (LVEF) and no evidence of structural heart disease on imaging or clinical evaluation. Well-controlled heart failure refers to patients who are in New York Heart Association (NYHA) functional class I or II, indicating no or only mild limitations in physical activity. These individuals maintain stable symptoms under optimized, guideline-directed medical therapy and have no recent hospitalizations or clinical decompensation, reflecting effective disease management and reduced risk of progression [21].

## 2. Cardiometabolic Disease Management for Aging Populations

### 2.1. Established Cardiometabolic Care

To establish well-controlled CMD, effective and individualized management is essential to support healthy aging and extend healthspan. Given the multifactorial nature of CMDs, their management requires a personalized, multidisciplinary approach that addresses metabolic, cardiovascular, and inflammatory dimensions simultaneously. Comprehensive CMD management requires standardized diagnostic workflows integrating laboratory testing (lipid profile, glucose metrics, renal and metabolic panels) with instrumental assessments (ECG, echocardiography, imaging modalities).

These evaluations enable early disease detection, risk stratification, and therapeutic tailoring to facilitate the transition of individuals to healthspan-oriented care (Fig. 2). A curated overview of guideline-based diagnostic and therapeutic standards for major CMDs is provided in Table 3, with direct links to EU- and U.S.-based clinical society resources.

### 2.2. From Disease Control to Healthspan-Oriented Care: Gaps and Opportunities

Despite these advancements, there remains a need to more comprehensively integrate aging-related factors into cardiometabolic health management by establishing a cardiometabolic healthspan-oriented model of care. The heterogeneity of the older population, characterized by varying degrees of frailty, comorbidities, and functional status, necessitates more nuanced guidelines that address these complexities. Furthermore, the underrepresentation of individuals aged ≥75 years in clinical trials limits the evidence base for this demographic, underscoring the importance of developing tailored recommendations that address the unique challenges of aging.

**Table 3.** Selected Guidelines for Diagnosis and Management of Major Cardiometabolic Conditions.

| Chronic disease | Guidelines (year) | References |
|---|---|---|
| Arterial Hypertension management | EU: 2024 ESC Guidelines for the management of elevated blood pressure and hypertension | [14] |
| | USA: 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adult | [13] |
| Dyslipidemia management | EU: 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias (with updates in 2025 Position Papers) | [15] |
| | US: 2018 AHA/ACC/Multi-society Cholesterol Guideline | [16] |
| T2DM management | EU: EASD/ADA 2024 Consensus; 2023 ESC Guidelines on Diabetes, Prediabetes, and Cardiovascular Diseases | [22, 23] |
| | US: 2025 ADA Standards of Care | [23] |
| Obesity management | EU: EASO 2024 | [24] |
| | US: 2025 AACE/ACE Guidelines | [25] |
| Heart failure management: | EU: 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (with 2023 updates) | [21] |
| | US: 2022 AHA/ACC/HFSA Heart Failure Guideline | [26] |

Integrating assessments of intrinsic capacity, cognitive function, and functional status into CMD management protocols may improve the precision and personalization of care in older adults. Within this framework, IC is assessed across five domains: locomotion, cognition, sensory function, vitality, and psychological well-being. Practical tools appropriate for standard clinical settings include: (i) Locomotion: grip strength dynamometry (normative cut-offs: <27 kg in men, <16 kg in women), gait speed (usual pace <0.8 m/s signals significant decline), and the Short Physical Performance Battery (SPPB, score ≤9/12); (ii) Cognition: Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA, score <26/30 for screening); (iii) Vitality/Nutritional status: Mini Nutritional Assessment Short Form (MNA-SF) and BMI; (iv) Sensory: standardized visual acuity and hearing screening; (v) Psychological: validated depression screening (e.g., PHQ-9) and quality-of-life measures [27]. IC assessment within this framework adds incremental value over conventional CMD management in the following specific clinical scenarios: (a) In patients with guideline-concordant CMD control but declining IC, IC findings should prompt consideration of deprescribing, fall-risk review, and intensification of functional support interventions, even in the absence of conventional clinical deterioration [28]. (b) When IC decline co-exists with well-controlled CMDs, this signals the need for more intensive lifestyle intervention (supervised exercise, nutritional support) and re-evaluation of whether pharmacotherapy burden may be contributing to functional decline [29]. (c) IC assessment is designed to stratify patients according to their risk of intervention-related adverse outcomes.

Importantly, achieving current guideline target control defines entry into the well-controlled CMD tier of this framework but does not constitute evidence of preserved healthspan. Disease control and preserved biological healthspan are related but not equivalent constructs. Patients meeting conventional targets may still exhibit accelerated biological aging, functional decline, or reduced IC not reflected by standard biomarkers. The healthspan-oriented framework is designed specifically to address this residual gap.

Additionally, integrating emerging biomarkers of biological aging may provide deeper insights into an individual's health status beyond chronological age, facilitating more targeted interventions. Aging biomarkers, including DNA methylation clocks and metabolic signatures, may potentially provide predictive insights into CMD risk and treatment response. However, their clinical utility outside clinical and epidemiological studies remains limited due to variability and lack of standardization. Multi-omics precision medicine, by integrating genomics, proteomics, and metabolomics, may support risk stratification in research settings, but its clinical utility remains unproven. It could also include the new concept of precision geromedicine, with a theoretical foundation for future gene-targeted preventive interventions [30].

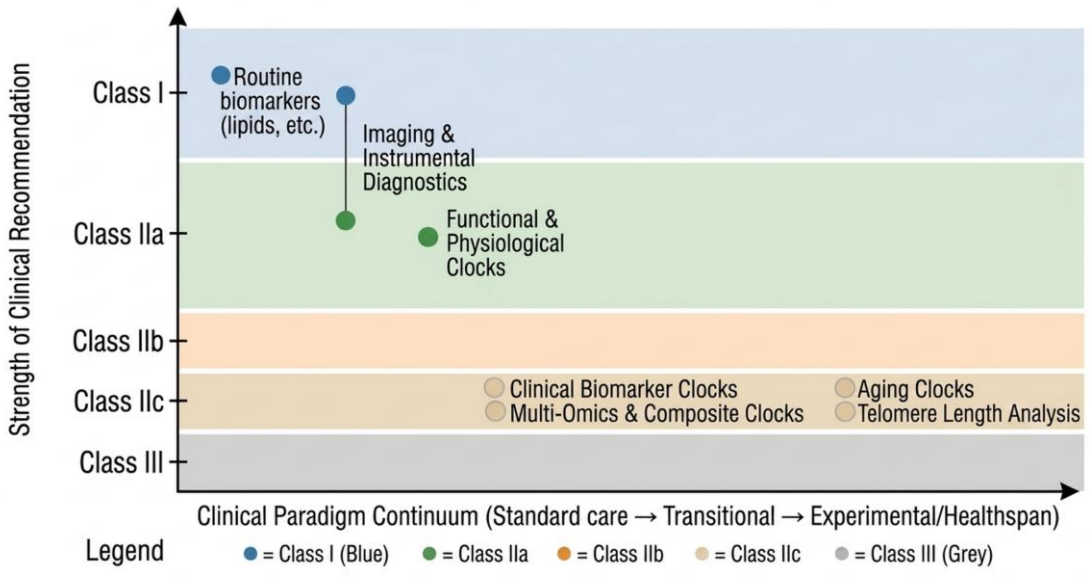


**Figure 3. The stratification of Bimarker-based healthspan Diagnostics according to the Classes of Recommendations**. Aging research has generated a greater diversity of biomarkers including epigenetic, transcriptomic, proteomic, metabolomic, glycomic, telomere length, gerogenes, but the still remain in research and/or early validation stages (based on Supplementary material 2, Supplementary Table 1).

However, these approaches are in the validation phase, so their clinical use is limited by the existing evidence.

### 3. Biomarker-Based Healthspan Diagnostics: From Routine Metrics through Biological Clocks to Intrinsic Capacity

Advances in biomolecular and functional diagnostics are transforming how clinicians assess biological age and stratify CMD risk. This section reviews both established CMD-related biomarkers and emerging diagnostic biomarkers of aging (BOA), categorized by their biological modality and clinical use (Fig. 3). Clinical utility, the level of evidence, and current use are summarized in Supplementary Table 1 in the Supplementary Material 2. The recommendation statements are summarized in Table 4.

**Table 4.** Biomarker-Based Healthy Longevity Diagnostics.

| Nr | Recommendation Statements |
|---|---|
| 1 | The continued and routine use of both traditional CMD-related biomarkers (lipid profile, fasting glucose, HbA1c, hs-CRP, creatinine, liver enzymes), and select functional and imaging diagnostics, including ECG, Echocardiography, abdominal USG is recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. These measures are well-established, widely accessible, and supported by strong clinical evidence forming the foundation of CMD risk assessment and management. Their integration into preventive and therapeutic care pathways enables effective risk stratification and monitoring of disease progression. |
| 2 | The use of additional functional biomarkers, including Cardiopulmonary Exercise Testing (CPET), grip strength and frailty indices, as well as imaging modalities like DEXA scan and carotid intima-media thickness (CIMT) should be considered in specific clinical contexts, for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. These tools offer practical insights into systemic aging, musculoskeletal integrity, and subclinical atherosclerosis and are particularly valuable in geriatric and preventive cardiology for personalized risk profiling and early detection of functional decline. |
| 3 | While growing evidence shows that epigenetic clocks, particularly GrimAge, are promising prognostic biomarkers for cardiometabolic diseases and mortality, their routine clinical use remains premature and is not yet recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. Current data suggest that next-generation DNA methylation-based biomarkers (GrimAge, PhenoAge, and DunedinPACE) may provide greater predictive insight than traditional measures like telomere length or single-omics markers. As research progresses, the refinement and validation of multi-omics aging clocks could further improve risk assessment and personalization of care. For now, however, their main value lies in research and exploratory clinical applications until large-scale studies confirm their practical and actionable benefits. |

Traditional CMD-related biomarkers, such as lipid profiles, fasting glucose, HbA1c, hs-CRP, and renal and liver function markers, remain the cornerstone of routine CMD risk stratification and are fully integrated into clinical practice with high levels of evidence (Class I, Level A). Functional biomarkers ($VO_2$max, grip strength, frailty indices) and imaging diagnostics (ECG, DEXA, CIMT) offer practical insights into organ-specific and systemic aging and are increasingly used.

In contrast, emerging biomarkers of aging should be interpreted within a different framework, as their clinical applicability remains limited and largely confined to research settings. Even though BOA have potential clinical use in understanding, monitoring, and potentially intervening in the aging process and age-related diseases, their clinical application is still under development and requires further validation. According to the Biomarkers of Aging Consortia perspective article [31], biomarkers intended for future use in healthspan-oriented practice must follow several essential criteria to ensure their relevance and reliability. These biomarkers should correlate strongly with chronological age and accurately predict important outcomes such as all-cause mortality, survival, frailty, healthspan, and the incidence of multiple age-related diseases. They must reflect the underlying causal mechanisms of aging and respond sensitively to factors that accelerate aging as well as to interventions known as geroprotectors. Additionally, these biomarkers require rigorous validation across diverse populations to confirm their broad applicability and robustness. Only by meeting these criteria biomarkers can become trustworthy tools to guide personalized interventions that promote healthy aging and lifespan. At present, researchers still debate for and against inclusion of all evaluation criteria and also the scope of the use for diagnostic, prognostic, responsive purposes [32, 33].

Epigenetic clocks like GrimAge, PhenoAge, and DunedinPACE estimate biological age and are associated with disease risk and intervention response in clinical trials, though they are not yet standardized (Class IIc, Level B) for clinical use [6, 34]. Despite their currently low class of recommendation for direct clinical application, their role in clinical research remains pivotal. Among these, the DNAm–based GrimAge (DNAm GrimAge) clock is the most relevant for evaluating cardiometabolic aging.

DNAm GrimAge represents a promising integrative biomarker for cardiometabolic risk, derived from DNA methylation surrogates of plasma proteins and smoking exposure. GrimAge Acceleration (GrimAA) shows robust associations with cardiovascular mortality and major adverse cardiovascular events, independent of traditional risk factors [35], suggesting that it captures biological processes not reflected by standard clinical metrics. However, epigenetic clocks are not validated for individual-level clinical decision-making and remain primarily research tools. Supporting their biological relevance, a six-month exercise intervention demonstrated an inverse association between improvements in $VO_2$max and reductions in GrimAge [36], while longitudinal increases in GrimAge have been linked to higher mortality risk [37]. Therefore, although further clinical validation is required, GrimAge is currently used primarily as a research tool, and its usefulness in clinical settings remains uncertain.

Complementary approaches, including transcriptomic, proteomic, metabolomic, and glycan clocks, provide insights into systemic inflammation, metabolic health, and immune aging, primarily within research or educational contexts but still do not meet the criteria for clinical use (Class IIc, Level B) [38, 39, 40, 41, 42]. Telomere length, while widely studied, also lacks clinical precision and is largely limited to observational use (Class IIc, Level B) [43].

Composite biomarker clocks, such as phenotypic or functional age estimators, combine physiological and clinical data to predict adverse outcomes and are beginning to be incorporated into digital health platforms. Advanced imaging modalities will also provide additional information to improve functional age estimation, in the very near future [44–46]. More advanced approaches, such as multi-omics clocks and AI-driven digital biomarkers from wearables or imaging, represent an emerging area of personalized aging research, but still lack robust clinical data (IIc, Level B) [31, 47, 48, 49].

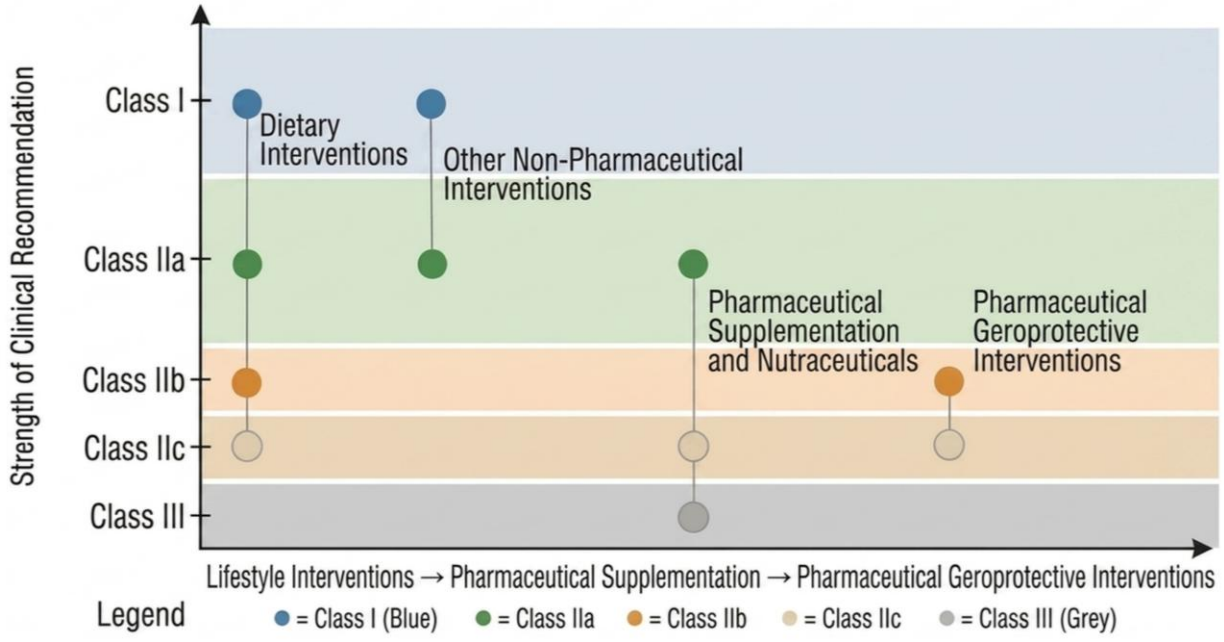


**Figure 4. The stratification of tiers of healthspan interventions according to the Classes of Recommendations**. For interventions, the situation is reversed. CMD interventions recommended by medical societies are strongly validated by outcome trials and meta-analyses. However, only a limited subset of these CMD interventions show clinical evidence of healthspan improvement. Most proposed geroprotective agents remain exploratory, with insufficient validation in well-controlled trials of non-diseased cohorts (based on Supplementary material 2, Supplementary Tables 2-5).

Although BOA shows potential in research settings, their clinical application remains under development and requires further validation.

## 4. Healthspan interventions in cardiometabolic health: from non-pharmacological to geroprotectors

The management of CMDs in aging individuals has traditionally focused on controlling risk factors and mitigating end-organ complications. However, emerging evidence from geroscience and precision medicine reveals that CMDs share common biological pathways with the aging process itself. This overlap provides an opportunity to shift clinical strategies from disease-specific treatment toward interventions that target fundamental aging mechanisms to preserve functional capacity and extend healthspan.

This section provides a structured overview of healthy longevity-promoting interventions with relevance to cardiometabolic health. Interventions are classified into four tiers:

**(1)** dietary interventions,

**(2)** other non-pharmacological lifestyle-based strategies (e.g., exercise, sleep, stress management, weight management),

**(3)** pharmaceutical supplements and nutraceuticals with emerging clinical data,

**(4)** pharmacological agents, referred to as *geroprotectors*, that may modulate biological aging and CMD progression.

Each intervention is evaluated for clinical utility, class and level of evidence, and readiness for integration into routine practice. Detailed description is available in the Supplementary Material 2 (Supplementary Tables 2-S5). The goal is to offer a practical, tiered cardiometabolic healthspan-oriented care framework to guide prevention and personalized care in individuals aging without or with well-controlled CMDs.

### 4.1 Non-Pharmacological Approaches

Non-pharmacological strategies remain the foundational interventions for cardiometabolic healthspan-oriented care. These include evidence-backed dietary patterns, physical activity, sleep optimization, and body weight regulation. These interventions not only target traditional risk factors but also influence molecular hallmarks of aging such as inflammation, mitochondrial dysfunction, insulin resistance, and biological age markers.

#### 4.1.1. Dietary Patterns

Among non-pharmacological strategies, dietary interventions represent a cornerstone for cardiometabolic healthspan-oriented care. The Mediterranean diet remains the most robustly validated pattern, consistently endorsed by major societies (ESC/EAS, ESC/EASD) with Class I, Level A evidence for reducing cardiovascular morbidity and mortality, improving metabolic parameters, and modulating pathways of biological aging [50, 51]. Alternative approaches such as the Nordic diet and plant-based diets (Class IIa, Level A), as well as low-carbohydrate or ketogenic patterns (Class IIc, Level A) show variable evidence, with some demonstrating short-term metabolic benefits but lacking long-term safety or outcome validation [52–57]. Emerging models, including intermittent fasting, calorie restriction (Class IIb, Level A) and personalized nutrition based on genetic or microbiome profiling (Class IIc, Level C), are promising but remain largely investigational.

A comparative overview of these dietary strategies, including their strengths, limitations, and supporting guidelines is summarized in Supplementary Table 2 in the Supplementary Material 2. This structured presentation helps clinicians differentiate dietary recommendations ready for immediate use in cardiometabolic healthspan–oriented care from those best confined to research or specialized clinical contexts. The recommendation statements are summarized in Table 5.

**Table 5.** Dietary Patterns as healthy longevity interventions.

| Nr | Recommendation Statements |
|---|---|
| 1 | The Mediterranean diet is recommended as a foundational dietary intervention for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. It consistently reduces cardiovascular mortality, improves metabolic markers, and supports healthy aging pathways. |
| 2 | The Nordic diet and plant-based diets should be considered for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs and are also supported in clinical contexts for reducing CMD risk and systemic inflammation, though their impact on aging biomarkers is less defined. |

| | |
|---|---|
| 3 | In specific clinical settings, intermittent fasting and caloric restriction strategies may be considered for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. Intermittent fasting and caloric restriction strategies are under investigation and may show promise in modulating aging pathways including autophagy, insulin sensitivity, and effect on epigenetic aging clocks. However, these approaches should be individualized and monitored, as long-term adherence, metabolic effects, and impacts on aging remain under investigation. Their use may be most appropriate within structured programs and under clinical supervision due to an increased risk of frailty and sarcopenia in those over 65 y.o. As such, chronological age should be considered in the decision-making process. |
| 4 | The routine clinical use of personalized nutrition strategies based on genetic, microbiome, or metabolic profiling is not yet recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. While these approaches have strong theoretical grounding and encouraging early data, they remain investigational due to the absence of validated algorithms, heterogeneous results, and lack of outcome-based evidence. We support their continued evaluation within clinical research settings to determine their future role in precision aging and nutrition care. |
| 5 | Low-carbohydrate or ketogenic diets are not yet recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs and must be also restricted without according to indication for long-term use. |

### 4.1.2. Physical Activity and Exercise.

Physical activity and exercise are also cornerstones of both CMD prevention and healthy aging. Aerobic and resistance training improve cardiovascular fitness, insulin sensitivity, lipid metabolism, and muscle mass, which are key factors in reducing CMD risk and functional decline. Regular exercise mitigates low-grade chronic inflammation, enhances mitochondrial efficiency, and preserves vascular elasticity. Mechanistically, it influences key aging biomarkers including telomere length, DNA methylation clocks, and heart rate variability (HRV). Evidence from large-scale cohort studies and interventional trials confirms that even moderate daily activity substantially lowers all-cause and cardiovascular mortality. Exercise also improves mental health, cognitive function, and mobility, making it integral not only for disease prevention but also for maintaining independence and quality of life in older age [58]. Despite these benefits, physical activity remains underutilized, particularly in aging populations, highlighting the need for individualized exercise prescriptions within clinical care. The recommendation statements are summarized in Table 6.

### 4.1.3. Sleep Hygiene

High-quality sleep is increasingly recognized as a fundamental pillar of both CMD prevention and healthy aging [59]. Poor sleep, whether due to short duration, fragmentation, or circadian misalignment, disrupts hormonal regulation (e.g., cortisol, melatonin, insulin), impairs glucose metabolism, increases sympathetic tone, and contributes to hypertension, obesity, and depression [60, 61]. These effects cumulatively accelerate biological aging via mechanisms such as increased oxidative stress, reduced telomerase activity, and adverse changes in DNA methylation [62]. Epidemiologic and interventional studies have shown that improving sleep quality and duration can normalize blood pressure, improve insulin sensitivity, and reduce inflammatory cytokines like CRP and IL-6. Moreover, aligning sleep-wake patterns with circadian rhythms supports mitochondrial function and DNA repair processes, potentially influencing aging trajectories. While robust evidence supports sleep's importance, it remains under-addressed in routine clinical practice. Increasing use of wearables, sleep tracking, and cognitive behavioral therapies may help bridge this gap in the context of precision aging care. The recommendation statements are summarized in Table 6.

### 4.1.4. Stress Management

Chronic psychological stress is a powerful driver of cardiometabolic disease and biological aging, acting through the hypothalamic-pituitary-adrenal axis and autonomic nervous system. Sustained elevations in cortisol and reductions in vagal tone lead to systemic inflammation, impaired glucose regulation, endothelial dysfunction, and increased oxidative damage. Stress-related pathophysiology is also linked with shorter telomeres, accelerated epigenetic aging, and higher risk of CMD and neurodegenerative disease [63]. Interventions such as mindfulness-based stress reduction (MBSR), cognitive behavioral therapy (CBT), HRV biofeedback, and exposure to natural environments ("green space") have demonstrated efficacy in lowering blood pressure, reducing inflammatory markers, and improving emotional regulation [64]. These approaches can modulate biological age markers, enhance resilience, and improve quality of life, especially when integrated into holistic care plans. While evidence is growing, routine implementation in CMD and aging clinics is limited, though digital tools and wearables are expanding access

to guided stress management interventions. The recommendation statements are summarized in Table 6.

#### 4.1.5. Weight Management

Maintaining a healthy body weight, particularly through reduction of excess visceral adiposity, is essential in preventing and managing CMD and supporting healthy aging. Obesity worsens insulin resistance, hypertension, dyslipidemia, and systemic inflammation. Those factors that accelerate biological aging and heighten the risk of T2DM, cardiovascular disease, and cognitive decline. Evidence shows that intentional weight loss of ≥10% in overweight or obese individuals produces measurable improvements in blood pressure, glycemic control, lipid profiles, and markers of inflammation [18]. These physiological changes may contribute to slower biological aging through pathways involving reduced oxidative stress, improved mitochondrial function, and enhanced autophagy. While direct effects on epigenetic clocks are still under investigation, indirect markers such as CRP, IL-6, and adipokines (e.g., adiponectin, leptin) show favorable shifts [65]. Weight management strategies including behavioral interventions and pharmacotherapy, and are standard in CMD care, with growing relevance in longevity and healthy aging frameworks [66–69]. The recommendation statements are summarized in Table 6.

**Table 6.** Other Lifestyle interventions as healthy longevity interventions.

| Nr | **Recommendation Statements** |
|---|---|
| 1 | Incorporation of regular physical activity including both aerobic and resistance exercise, is recommended as a standard component of cardiometabolic healthspan-oriented care, both in individuals without or with well-controlled CMDs, regardless of age. The following targets are advised i) aerobic activity: at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity exercise per week; (ii) resistance training: ≥2 sessions per week, engaging all major muscle groups. For adults aged 65 years and older, balance and flexibility exercises should be performed 2–3 times per week to support mobility, coordination, and fall prevention. Regular adherence to these recommendations helps preserve muscle mass and function, improves insulin sensitivity and cardiovascular fitness, and supports longevity through better metabolic and cognitive resilience. |
| 2 | Assessment and improvement of sleep duration and quality including optimizing circadian alignment, ensuring ≥7 hours of restorative sleep, and addressing sleep disorders is recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. |
| 3 | Evidence-based stress reduction strategies including mindfulness-based stress reduction, Heart Rate Variability (HRV)-guided biofeedback, and psychotherapy should be considered for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. These interventions may support autonomic balance, inflammation reduction, and aging modulation. |
| 4 | Intentional weight loss of ≥10% is recommended for cardiometabolic healthspan-oriented care for patients with obesity or overweight, particularly in those with metabolic syndrome or T2DM. In parallel, efforts should focus on optimizing healthy body composition, with appropriate preservation of lean mass and reduction of excess fat mass, as both underweight and obesity are associated with increased cardiometabolic risk. |

### 4.2. Pharmacological supplements and nutraceuticals

A variety of nutraceuticals are being evaluated for their potential roles in supporting cardiometabolic health and modulating biological aging, though their clinical utility varies widely based on available evidence. A major limitation of nutraceuticals is the lack of standardization in formulation, purity, and bioavailability, which makes it difficult to provide consistent recommendations. Importantly, a large epidemiological study analyzing data from over 390,000 adults in U.S. cohorts found that daily multivitamin use did not extend lifespan and was associated with a modest but statistically significant 4% increase in mortality risk during the first 12 years of follow-up [70]. Therefore, in this statement, we restrict our focus to only a few well-characterized nutraceuticals with relatively stronger clinical evidence, while underscoring the pressing need for rigorous randomized trials and biomarker validation prior to their integration into preventive cardiometabolic care. Clinical utility, the level of evidence, and current use of several potential healthspan-oriented nutraceuticals are summarized in the Supplementary Table 3 in the Supplementary Material 2. The recommendation statements are summarized in Table 7.

Among the better studied compounds, omega-3 fatty acids and vitamin D stand out as the most evidence-based. Pharmaceutical omega-3 supplementation with

eicosapentaenoic acid (EPA) ethyl esters (Icosapent ethyl) is already integrated into the ESC guidelines for cardiovascular prevention in patients with hypertriglyceridemia [15]. The evidence for non-pharmaceutical omega-3 supplementation containing EPA and docosahexaenoic acid (DHA) in cardiometabolic disease prevention remains limited and controversial. EPA has reduced myocardial infarction in randomized trials (HR 0.72, p = 0.003) [71–73]. Marine Omega-3 supplementation (EPA/DHA) has demonstrated cardioprotective effects in metaanalysis of 13 RCTs (127 477 participants), including significant reductions in myocardial infarction (RR 0.92, 95% CI 0.86–0.99; p = 0.02), coronary heart disease death, and total cardiovascular events, with a dose-dependent relationship [74]. Non-pharmaceutical omega-3 supplementation also slowed DNA methylation–derived aging trajectories such as GrimAge2 and DunedinPACE ($p < 0.05$) in the DO-Health trial ([71–73]). However, large-scale evidence summarized by the Cochrane Review (79 RCT, 112,059 participants) suggests that marine-derived omega-3 exerts little or no effect on overall cardiovascular or all-cause mortality [75]. It is also worth noting that high-dose supplementation of Omega-3 Fatty Acids and their derivatives may be a risk factor for atrial fibrillation [76].

Vitamin D, though mixed in primary outcomes, showed an additive effect with omega-3 and exercise in slowing PhenoAge (difference -0.24) [71–73]. Another study shows that participants with vitamin D deficiency who started taking supplements had a 7-CpG DNAmAA that was 2.6 years lower (p = 0.011) and a Horvath DNAmAA that was 1.3 years lower (p = 0.042) compared to those who didn't get treatment and still had low vitamin D [71].

However, according to a Systematic Review Supporting the Endocrine Society Clinical Practice Guidelines on Vitamin D [77], the supplementation with Vitamin D was not associated with a significant effect on cardiovascular events, mortality, fracture, stroke and MI in population age 50-74 and below. At the same time in the group of adults ages ≥ 75 years there was a trend with vitamin D to reduce the risk of mortality (RR 0.96 [0.93, 1.00], high certainty) and the supplementation was associated with a decreased incidence of falls (IRR 0.91, 95% CI [0.81, 0.99]) [77].

**Table 7.** Pharmacological supplements and nutraceuticals as healthy longevity interventions.

| Nr | **Recommendation Statements** |
|---|---|
| 1 | Selective use of omega-3 fatty acids and vitamin D supplementation should be considered for cardiometabolic healthspan-oriented care in patients with well-controlled CMDs only when supported by evidence and patient-specific indications. Pharmaceutical formulations of icosapent ethyl and cholecalciferol are regulatory-approved agents with demonstrated benefits in defined clinical settings,when used within clinically accepted dose ranges, including patients with hypertriglyceridemia or vitamin D deficiency. Non-standardized nutraceutical formulations of omega-3 and vitamin D should therefore be used cautiously, as variability in content and bioavailability limits reproducibility of outcomes. Their clinical use of non-standardized nutraceutical formulations is limited by the existing evidence and should remain adjunctive to evidence-based lifestyle and pharmacologic therapies. |
| 2 | Magnesium, DHEA, creatine, and folate/B12, as well as various experimental compounds, lack robust clinical validation and standardized dosing guidelines. Polyphenols such as resveratrol and curcumin demonstrate promising anti-inflammatory and antioxidant effects in preclinical and small clinical studies; however, large, well-controlled trials are needed to establish their clinical relevance. Thus those compounds are not yet recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. Until more conclusive data become available, their use should be limited to research settings. Evidence-based lifestyle interventions and proven medical therapies remain the foundation of cardiometabolic healthspan-oriented care. |
| 3 | The routine clinical use of multivitamins is not recommended for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs without strong evidence of efficacy and safety: Multivitamin supplements lack robust clinical validation and show signs of harm. |

Magnesium and folic acid/vitamin B12 are also clinically relevant, particularly in aging adults with subclinical deficiencies as magnesium intake was associated with lower PhenoAge acceleration ($\beta = -1.13$, p = 0.016) [78]. Meta-analysis of 21 RCTs (n≈115k) shows ~10% stroke risk reduction with folic acid supplementation [79]. At the same time folate/B12 supplementation increased global DNA methylation ($\Delta\beta = +0.003$, p = 0.01) and modulated specific epigenetic loci, although Horvath DNAmAge itself remained unchanged (p = 0.60) [80]. Polyphenols such as green tea catechins, resveratrol, and curcumin show considerable mechanistic promise, and in the DIRECT-PLUS trial a polyphenol-rich diet attenuated aging signatures (Li

mAge β = −0.41, p = 0.004; Hannum mAge β = −0.38, p = 0.03), though inconsistent bioavailability and lack of strong RCTs limits their routine use [81]. Creatine intake correlated with lower GrimAge mortality predictors (r ≈ −0.04, p < 0.05) [82] and even shows an inverse association with all-cause mortality (B = -0.094; P = 0.04) [83], but lacks strong RCTs. In a small pilot trial (n=10) Dehydroepiandrosterone (DHEA) supplementation combined with Metformin and rhGH showed reduction in biological age accessed by Horvath (p = 0.0009) and GrimAge (p = 0.0049) clocks, although the effect cannot be attributed to DHEA alone [84].

Although these emerging compounds are increasingly used in wellness and longevity settings, they should be regarded as exploratory and not yet part of standard, evidence-based healthspan-oriented care protocols. A limited number of pharmaceutical-grade supplements can be recommended with a defined level of confidence in cardiometabolic healthspan-oriented care; however, most nutraceuticals remain investigational and require further validation in well-designed human studies before they can be considered for routine clinical use.

### 4.3 Pharmacological Geroprotection

Geroprotectors are a potential class of pharmacological agents that aim to target the biological hallmarks of aging, with the ultimate goal of delaying age-related diseases, preserving physiological function, and extending healthspan. Current clinical guidelines do not recognize geroprotective agents as a distinct pharmacological category, and no formal geroprotective indications have been established to date. Therefore, we classify these pharmacological interventions with geroprotective effect as Class IIb, reflecting their investigational status and lack of FDA or EMA approval. Clinical utility, the level of evidence, and current use of geroprotectors are summarized in Supplementary Table 4 in the Supplementary Material 2. The recommendation statements are summarized in Table 8.

**Table 8.** Pharmacological Geroprotectors.

| Nr | **Recommendation Statements** |
|---|---|
| 1 | Selective, evidence-based use of pharmacological agents with geroprotective effects may be considered within their approved clinical indications: hormonal replacement therapy (HRT), when appropriately prescribed in women within 10 years of menopause onset, may be considered as a geroprotective agent both for patients without or with well-controlled CMDs. Similarly, metformin, SGLT2 inhibitors, and GLP-1/GIP receptor agonists, according to their clinically approved use, may be considered as pharmacological agents with geroprotective effects in patients with well-controlled CMDs, recognizing their possible indirect effects on aging pathways. |
| 2 | The routine clinical use of pharmacological agents as geroprotectors is not yet recommended for cardiometabolic healthspan-oriented care in individuals without concrete indications: Although agents such as metformin, SGLT2 inhibitors, and GLP-1 receptor agonists demonstrate clear benefits for managing specific cardiometabolic conditions like T2DM, obesity, chronic kidney disease (excluding metformin) or heart failure, their off-label use purely for aging delay lacks regulatory approval and definitive evidence. These drugs should be reserved for their approved indications while research continues to clarify their geroprotective potential in healthy individuals. |
| 3 | The use of rapalogs, senolytics, and other novel geroprotectors is not yet recommended for cardiometabolic healthspan-oriented care in individuals without or with well-controlled CMDs without clear FDA and EMA approval in particular fields. These emerging agents should remain within the domain of controlled clinical trials and experimental research. While promising in preclinical models—demonstrating lifespan extension and improved healthspan—they currently lack sufficient human safety and efficacy data. Until rigorous evidence from randomized controlled trials becomes available, their use outside of research protocols is premature and not advised. |

These compounds act on pathways such as inflammation, oxidative stress, cellular senescence, and nutrient sensing (e.g., mTOR, AMPK), and include both repurposed medications (e.g., metformin, SGLT2 inhibitors, GLP-1 receptor agonists) and emerging therapies (e.g., rapalogs, senolytics). Their potential for broad preventive impact on CMDs, frailty, and cognitive decline has generated growing interest in the field of healthy longevity medicine. However, despite promising preclinical data and some clinical signals, none of the commonly cited geroprotectors are currently approved by regulatory bodies like the FDA or EMA for aging-related indications.

At present, pharmacological agents may be considered as *geroprotectors* only within their approved clinical indications, in individuals with well-controlled CMDs, and when supported by clear evidence of healthspan-related benefits. In contrast, particularly in individuals without established cardiometabolic disease, their use remains investigational and is not supported by

outcome-based evidence. At present, we do not recommend the off-label or routine clinical use of potential geroprotectors in patients without a formal indication (insulin resistance, obesity, menopause, etc). Although medications such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors show benefits in specific patient groups (e.g., individuals with insulin resistance, T2DM or obesity) their application solely for the purpose of slowing biological aging remains investigational in individuals without CMDs. It is also essential to assess patient frailty, given the increased risk of falls associated with certain pharmacologic interventions [85].

Hormone Replacement Therapy (HRT), currently used mainly for managing menopausal symptoms, may also offer geroprotective benefits when initiated early in healthy women, typically before age 60 or within 10 years of menopause. Evidence suggests that early perimenopausal HRT initiation leads to a reduction of atherosclerosis and cardiac events [86–88], enhancement of bone density [89]) and possibly slower biological aging [89, 90]. Most current guidelines recommend HRT only for symptom relief and osteoporosis prevention, not for general healthspan purposes [91, 92]. However, based on evidence supporting the geroprotective effects of HRT on cardiometabolic parameters, there are voices recommending a change of these guidelines and the initiation as a geroprotector outside the symptomatic thresholds [93]. At the same time HRT should be individualized, avoiding use in women with atherosclerosis or thromboembolic risk [94], with transdermal forms preferred over oral due to lower adverse risk [95].

Finally, agents like rapalogs and senolytics have shown lifespan-extending effects in animal models but lack robust human data and carry safety concerns. As such, the current use of these agents should be limited to controlled clinical research or targeted therapeutic indications [96]. Ongoing interventional trials [96]. and biomarker-driven studies will be critical in defining their future role in evidence-based healthspan-oriented care. The levels of evidence are summarized in Supplementary Table 5.

## 5. Challenges, Controversies, Gaps, and Perspectives

The integration of geroscience into cardiometabolic clinical practice represents a promising but complex paradigm shift. While the concept of healthspan-oriented care is gaining momentum, several conceptual and translational challenges remain.

A key challenge lies in the heterogeneity of aging itself. The absence of a universally accepted clinical definition of biological aging complicates the development of standardized diagnostic and therapeutic frameworks. As a result, current approaches rely on a combination of functional, clinical, and emerging molecular markers, which may differ in their interpretability and applicability across populations.

Another important consideration is the integration of multi-omics and artificial intelligence–driven approaches into clinical workflows. While these technologies offer unprecedented opportunities for precision risk stratification and individualized care, their complexity poses challenges in data interpretation, clinical integration, and physician training.

From a translational perspective, the shift from disease-centered care toward function- and resilience-based models requires reorganization of healthcare systems. This includes the need for multidisciplinary collaboration, incorporation of digital health tools, and alignment with existing clinical guidelines.

Looking forward, advancing healthspan-oriented care will require harmonization of definitions, development of standardized clinical frameworks, and expansion of interdisciplinary research. Integration of geroscience principles into large-scale clinical trials and real-world data platforms will be essential to bridge the gap between experimental findings and routine clinical application.

Additionally, threshold-based definitions of disease control may not fully capture the multidimensional nature of biological aging and functional capacity.

In addition to these conceptual and translational challenges, several important limitations and implementation constraints warrant dedicated consideration.

## 6. Limitations and Implementation Challenges

Despite the comprehensive and integrative nature of this Delphi-derived framework, several important limitations and implementation challenges must be acknowledged.

First, although biomarkers of biological aging, particularly epigenetic clocks and multi-omics signatures, represent a promising advancement in precision medicine, their clinical utility remains limited. Most of these markers lack large-scale validation, standardization, and reproducibility across diverse populations, restricting their applicability outside research settings.

Second, a significant gap in the current evidence base relates to the underrepresentation of older adults, particularly those aged ≥75 years, in randomized clinical trials. This limits the generalizability of many clinical trial results, while the cardiometabolic and geroscience-based recommendations are to the highest relevance in this population.

Third, there is ongoing regulatory uncertainty surrounding the use of interventions targeting aging processes. Many proposed geroprotective therapies are

used off-label or lack formal approval for "healthy longevity" indications, creating ambiguity in clinical decision-making and limiting their integration into routine practice.

Fourth, the implementation of advanced diagnostics and personalized interventions raises concerns regarding health equity. High costs, limited availability of multi-omics technologies, and unequal access to specialized care may exacerbate existing disparities, particularly across different socioeconomic and healthcare system contexts.

Finally, the practical feasibility of implementing a healthspan-oriented model of care remains a major challenge. Comprehensive assessment of intrinsic capacity, integration of multi-domain interventions (lifestyle, pharmacological, and digital), and the need for multidisciplinary coordination may be difficult to achieve in standard clinical workflows, especially in resource-constrained settings.

Taken together, these limitations highlight the need for further validation studies, inclusive clinical trial designs, clearer regulatory frameworks, and scalable implementation strategies to ensure that healthspan-oriented care can be translated into equitable and effective clinical practice.

## 7. Conclusions and Future Perspective

This Delphi-derived expert consensus outlines a framework for redefining healthy aging through a cardiometabolic lens, distinguishing between individuals without CMDs and those with well-controlled diseases. By integrating evidence-based clinical criteria, functional assessments, and geroscience insights, it provides a pathway toward healthspan-oriented models of care.

From a clinical perspective, this framework supports the immediate implementation of established strategies, including guideline-directed cardiometabolic risk management, lifestyle interventions, and functional assessment. In contrast, emerging approaches, such as biological aging biomarkers, multi-omics profiling, and pharmacological geroprotectors, should remain within research settings until further validated.

Future progress will require large-scale, longitudinal, and interventional studies linking biological aging measures with clinical outcomes, alongside the development of standardized and scalable frameworks for implementation. Ensuring equitable access, appropriate infrastructure, and multidisciplinary training will be essential for translating these advances into routine practice.

By combining scientific rigor with responsible and equitable implementation, healthspan-oriented care has the potential to evolve into a sustainable clinical paradigm. Given the rapid pace of discovery, this position statement will require periodic re-evaluation as new evidence emerges.

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## Competing interests

MP, SK, ANS, AE, UK, DB, IS, JR, MSK, VNG, BV, GAK, EB declare no conflict of interest related to this work. KK has received lecture fees and travel grants from Eli Lilly, Novo Nordisk, Pfizer, Boehringer Ingelheim, AstraZeneca, ProMed, MSD. OM has received lecture fees from Medtronic, Eli Lilly, Novo Nordisk, Sanofi, TAD Pharma, Theras, Diatec, Ypsomed, Dexcom, AstraZeneca, Insulet and Perfood; and is on the advisory board for Sanofi, TAD Pharma, Glaice, Perfood, Medtronic and Dexcom. ES is the CEO and cofounder of Longenesis Ltd. The Regents of the University of

California are the sole owner of patents and patent applications directed at epigenetic biomarkers for which Steve Horvath is a named inventor; SH is a founder and paid consultant of the non-profit Epigenetic Clock Development Foundation that licenses these patents. SH is a Principal Investigator at the Altos Labs, Cambridge Institute of Science. HS has received lecture fees or is on the advisory board of Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, NovoNordisk, Novartis, Sanofi and Sobi. AZ is the CEO and shareholder of generative AI longevity company, Insilico Medicine. AFHP has received honoraria from Sanofi, Lilly, Novo-Nordisk, Astra-Zeneca, Abbott. SDR has received lecture fees and/or has been involved in advisory boards for Amarin, Amgen, AstraZeneca, Aurora Biopharma, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, General Electric, Novartis, Philips, Sandoz, SANOFI, Viatris.

## Author Contributions

Writing - original draft preparation, MP, SK, ANS, SD, KK, UK, HS, AFHP; writing - review and editing, MP, SK, ANS, SDR, KK, AE, UK, OM, DB, IS, ES, JR, MSK, AZ, VNG, SH, BV, GAK, HS, EB, AFHP; visualization, SK, ES; literature search, MP, SK, ANS, SD, KK, UK, AFHP; supervision, AFHP. All authors have read and agreed to the published version of the manuscript.

## Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2026.0279.

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