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Brief Report

Building a roadmap to nutrition for Healthy Ageing: a brief report on the ILSI Europe Healthy Ageing Task Force

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ABSTRACT

At the end of October 2024, ILSI Europe brought together industry and academic experts from different fields to identify research gaps and challenges in nutritional interventions supporting healthy ageing. The objectives of the Healthy Ageing Working Group workshop were to address the urgent need to define ageing outcomes and associated biomarkers, determine the trajectory of functional ageing across the lifespan, and leverage technology to tailor nutritional and lifestyle interventions for healthy ageing. This brief report presents the key points highlighted during this workshop.

1. Introduction

An unprecedented increase in life expectancy has been noted worldwide due to medical advances, improved living conditions, and effective public health policies [1,2]. This improvement is accompanied by a significant rise in the number of years spent with disability, chronic diseases, and multi-morbidities [3,4]. These factors strain healthcare systems globally and contribute to a reduced quality of life. It is estimated that the gap between life expectancy and health-adjusted life expectancy (HALE) worldwide is around 10 years, with the largest

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disparity observed in the United States (12.4 years) and has increased by more than 1 year in the last two decades [5]. It is highly likely that this gap will widen further in the future, with potentially significant socio-economic repercussions, making it necessary to take urgent measures to reduce the burden of disease among older people. By 2050, it is estimated that the number of adults over 65 will increase to 16 % of the global population [6]. To mitigate the load of functional decline and chronic diseases throughout the lifespan, it is crucial to explore possible interventions that promote healthy ageing, and, as importantly, it is essential to structure age groups.

Ageing, defined as the progressive decline in physiological function and the accumulation of biological changes over time, is a primary risk factor for chronic diseases and functional decline. Recognising this, the field of geroscience has emerged as an interdisciplinary approach with a central focus: to highlight which biological mechanisms can be targeted to slow down the ageing process, and to understand their fluctuations across the lifespan [7]. This paradigm shift calls for the optimisation of geroscience through specifically designed and refined clinical studies, the careful selection of markers of healthy ageing, and the identification of an ideal study population. Healthy ageing is about maintaining an individual's functional ability, or their capacity to continue their day-to-day activities and independence, for as long as possible [8]. In addition to improving personal well-being, healthy ageing can alleviate the economic and social burden on society [9–11]. At the core of this approach is a focus on 'modifiable' parameters which can potentially counterbalance the effects of 'non-modifiable' factors such as genetics, sex, ethnicity, socio-economic status and family history. Nutrition, due to its considerable influence in various areas related to ageing, is a pillar of longevity strategies across the lifespan. Effective dietary patterns for longevity have the potential to influence longevity and health span by modulating biological ageing processes, reducing chronic disease risks, and preserving cognitive and physical health [12]. To identify the relevant information on the contribution of nutrition to healthy ageing, on 21 and 22 October 2024, the European branch of the International Life Sciences Institute (ILSI Europe) held a workshop in Brussels, bringing together experts from research, clinical practice, academia and industry. This brief report provides an overview of the gaps and challenges identified in research on nutritional interventions in the context of supporting and promoting healthy ageing, and offers recommendations and reflections on the topic. Overall, the workshop discussions focused on identifying key biological and functional markers of ageing and the challenges they pose, understanding how these markers evolve across the lifespan, highlighting which nutritional intervention strategies and research approaches are (still) needed in this context, and exploring ways in which technological advances can monitor and promote healthy ageing. In the following sections, we will start by presenting potential biomarkers related to ageing that can be used in nutritional studies on healthy longevity. We will then highlight intervention strategies and challenges in nutritional research on ageing, followed by future directions for research in this field, with an emphasis on available technological tools that can help address these challenges. An overview of the currently available (bio)markers, challenges, and future research directions discussed in the following sections is provided in Table 1.

2. Research priority: defining and selecting (bio)markers related to ageing

Ageing is characterised by a consistent decline in physical and mental abilities, an increased risk of disease and, ultimately, death [13]. Although ageing is inevitable and multifaceted, wellbeing and the maintenance of functional capacities into older age are essential to ensure a good quality of life, and independence. This is encapsulated in the concept of 'healthy ageing', which focuses on extending health span and is influenced by the ongoing interaction between individuals and their environments. Nutrition is a critical component of this interaction and can assist the preservation of functional ability and the prevention of cognitive decline, whereby a better-quality diet is linked to greater odds of healthy ageing [12]. Consequently, one way of achieving this is to intervene in lifestyle, including dietary patterns, to maintain or even improve the trajectory of an individual's overall functional ability and health as they age. In this effort, it is essential to characterise ageing and define subgroups throughout life that can be reflected by specific markers that respond to nutritional interventions. The challenge here is to identify markers that are sensitive to nutritional changes that are non-invasive, inexpensive and accurate. That said, it is now well understood that an individual's chronological age (CA) does not accurately reflect their physiological health, which is better captured by their biological age (BA) [14]. Nonetheless, biological ageing is heterogeneous, not only between individuals but also across the organs within the body [7], raising the question of how to accurately measure ageing and identify meaningful biophysiological markers [13,15].

Although BA is a complex phenomenon, it may offer a more meaningful insight into an individual's health status at any given point. Unlike CA, BA can be modified, offering the opportunity to influence the trajectory of ageing. For example, the evaluation of a diverse range of markers that emerge with increasing entropy from representative population data, from the cellular to the organism level, will aid in the development of new geroprotection strategies and offer predictive insights into the likelihood of the individual's rate of ageing and the likelihood of transitioning to a pathological state. These opportunities involve various temporary or reversible measures reflecting homeostatic dysregulations, multidimensional approaches in cohort studies and mixed models, with the need to focus on measurable outcomes that do not require (only) extremely long follow-ups, and the measurement of innovative biomarkers within the context of 'stratified medicine' or 'precision medicine'. Recent scientific advances are helping us move away from our genetic blueprint determinism, with the establishment of several biological clocks to quantify the BA of an individual, considering a variety of different factors [16]. It is equally important to account not only for markers that indicate changes over time, but also those that reflect differences in risk and physiological status between individuals of the same CA. Thus, to evaluate real-life functional ability and decline, it is needed to mix markers with complementary applications. In the following sections, we make the case for functional markers, which can be measured directly (performance-based) and are clinically relevant, and for biomarkers that might lack clinical translatability [17] but that still have the potential to predict ageing trajectory before the manifestation of functional decline, as they focus on molecular aspects [18].

2.1. *Functional markers*

Maintaining good physical and functional capacities as we age are determinants for longevity. Preserving mobility is unquestionably of benefit for independence, vitality, quality of life and overall intrinsic capacities in older adults. When physiological resilience declines, there is an increase in vulnerability to stressors that is paralleled by a decrease in metabolic functions, with repercussions for biological homeostasis. The biological foundations of functional capacity focus on the inherent abilities to maintain physical and mental capabilities and are encompassed within the aspect of intrinsic capacity, which is firmly recognised (and used) in the field to predict health risks and healthy ageing [19,20]. Some physiological markers, such as cardiorespiratory fitness, have excellent predictive power on morbidity and mortality, even in heterogeneous groups (different age groups, sex, ethnicities or health backgrounds) [21]. Markers of physical function such as VO_2 max and grip strength [22], or gait speed [23], are crucial indicators of health-related functional health or decline. These also contribute to changes in frailty and related frailty indices, which combine assessments of physical activity, weight loss or exhaustion, and are also valuable markers to predict vulnerability to stressors and assess the aging phenotype [24]. Frailty and malnutrition have related risk factors and share similar

Table 1
Overview of (bio)markers related to nutrition for healthy ageing: a summary of multistakeholder workshop highlights. This table aims to present a summary of the distinct (bio)markers described in the text and to add further elements related to their evaluation. It also provides a backbone for further reports to guide the scientific community in upcoming work. Sampling constrains are refereeing to time, frequency, storage issues, and data privacy issues; and impacts of non-nutritional confounding factors are refereeing to drugs and medical interventions.

(Bio)marker category	Marker examples	Area and focus	(Bio)matrix/(Bio) fluid type	Assessment type	Limitations and challenges
Functional	- VO2 max, - Grip strength, - Gait speed, - Frailty indices	- Physical function and resilience, - Mobility, vitality, - Independence, - Quality of life, - Prediction of morbidity/ mortality	- Whole body, - Muscle and standard fitness tests - Mastication capability and xerostomia	- Maximal exercise capacity test, - Maximal grip strength and hand dynamometer test, - Timed walking test	- In-person visits required for physical ability assessment, - Calibration is necessary for respective populations, - Long term interventions may be required
Genetic	- Single Nucleotide Polymorphisms (SNPs) and Polygenic Scores	- Disease risk, - Family links/risks - Longevity, disability - Adjusted life years (DALYs), - Personalised nutrition/ stratification, - Phenotypes	- Blood, saliva, urine, semen, pleural	- Next-gen sequencing - Genotyping assay, - Enzymatic based methods, - Bioinformatics pipeline, - Genome Wide Association Studies (GWAS)	- Inability to capture gene-environment interactions, - Limited clinical trials with stratification and targeted prevention, - Impact on phenotype often not clear, - High inter-individual variations, - Lack of standard databases
Epigenetic	- DNA methylation clocks (PhenoAge, GrimAge), - Telomere length	- Biological age, - Ageing progression and trajectory, - Family links/risks	- Blood, saliva, urine, semen, pleural	- Bisulphite sequencing, - qPCR and - Methylation arrays	- Long-term changes affected by cell type (intra-individual variation), - Limited clinical trials with stratification and targeted prevention, - Impact on phenotype often not clear, - High inter-individual variations, - Lack of standard databases
Metabolomic	- Metabolomic profiles, - Trimethylamine N-oxide (TMAO), - Bile acids - Short-chain fatty acids (SCFAs), - Imidazole propionate	- Metabolic health, nutrition - Cellular health, cardiometabolic health, - Metabotypes	-Blood, urine, faeces, breath	- Mass spectrometry, - Nuclear magnetic resonance spectroscopy (NMR)	- Technical, analytical and bioinformatical complexity, - Technique-dependent, - Rapid fluctuations post-nutritional intervention, - High inter-individual variability, - Sampling constrains, - Limited clinical trials with stratification and targeted prevention, - Overall lack of standardisation, - Impact of non-nutritional confounding factors
Microbiome	- Gut, oral, vaginal, skin microbiome	- Gut, oral, vaginal, skin microbiome composition, - Microbiome interaction with exercise, diet and drugs, - Enterotypes - Metabolic potential	- Stool samples, biopsies, swaps, …	- 16 s rRNA amplicon sequencing - Other metagenetic analysis - Shotgunmetagenomics - Transcriptomics (RNA-seq) - Proteomics	- Technical, analytical and bioinformatical complexity, - Lack of standardisation of the complete pipeline - Completeness of relevant DNA databases - High inter-individual variability, - Sampling constrains, - Limited clinical trials with stratification and targeted prevention, - Impact of non-nutritional confounding factors, - Quantification remains difficult, - Stool sample not representative for total GI Tract
Inflammatory/ Immunity	- Pro-inflammatory cytokines and markers (CRP, TMAO,…) - Regulatory cytokines - Immune cell profiles, - Immunoglobulins - 'Immunity clocks' - Vaccination efficacy	- Disease risk (infection), - Autoimmunity risk, - Immunosenescence, - Inflammageing, - Frailty, - Resilience,	- Blood, plasma, stool samples, saliva	- ELISA, - Flow cytometry, - Immune cell panels, - Vaccination response	- Intra-individual fluctuations, - Seasonal variations, - Potential confounding factors, such as illnesses, - Lack of standardised profiles

(*continued on next page*)

Table 1 (*continued*)

(Bio)marker category	Marker examples	Area and focus	(Bio)matrix/(Bio) fluid type	Assessment type	Limitations and challenges
Vascular/Cardiac	- Pulse Wave Velocity (PWV), - Flow-Mediated Dilation (FMD), - Troponin	- Vascular health, - Cardiac function and clinical risk assessment	- Blood, ultrasound	- Tonometry, - Ultrasound based-assessments, - Immunoassays	- Technique-dependent, - Episodic measurements and in-person visit requirements

prevention strategies. Improving and maintaining good nutritional status in older adults (via nutritional education and interventions such as oral nutrition support, or protein-energy supplementation [25]) is crucial to restore functional capacities, which can be challenging in a population who often have reduced chewing capacity (mastication) and xerostomia (hyposalivation) [26,27]. Consequently, new assessment methods focusing on oral functional abilities and oral health, are increasingly recognised in gerontological studies, as they play an important role in nutritional status (e.g., changes in food choices based on alterations in saliva production and dental integrity). As functional capacities, for example those related to muscle power and strength, start to decline in midlife, it is equally important to preserve the functional reserve capacities in younger adults [28].

Additionally, other complementary biological markers may elucidate underlying mechanisms and provide valuable information about individual susceptibilities that accompany functional changes. These markers can provide a better understanding of the progression of ageing, and some of them can help develop early intervention strategies such as lifestyle and dietary changes.

2.2. Biological markers

2.2.1. Genetic and epigenetic biomarkers

Although, while some genetic susceptibilities have profound effects on health and longevity and cannot be modified (e.g. genetic disorders), other genetic variations influence modifiable risk factors and the ageing process, as captured by disability-adjusted life years (DALYs; 'lost healthy life years' [1]). For example, the use of a single nucleotide polymorphism (SNP) analysis can offer insights into nutritional interventions and help clarify the interconnections between individual needs and inter-variable responses [29]. However, it has notable limitations, such as not incorporating the exposome,i.e., the interactions between the genome and environmental exposures throughout the life course [15]. Polygenic scores (PGS) can also be used to understand individual risk of common diseases [30], though metabolomic profiles may supersede PGS in future [31]. Both SNPs and PGS offer options for stratifying the population for targeted prevention or early intervention. Plus, these might offer the potential to minimise or correct deficiencies via micronutrient optimisation, for example vitamin intakes such as vitamin D or folate, or those related to lipid metabolism or insulin signalling, which are important for inflammation and even DNA damage [32].

Epigenetic markers, particularly DNA methylation patterns (affecting gene expression), have emerged as indicators of BA. The rate of DNA methylation, described as the epigenetic clock (e.g., CpG sites with PhenoAge [33] and GrimAge [34]), indicates consistent age-related changes in cellular/gene expression in individuals. A global epigenetic biomarker of ageing might have the potential to be developed by replacing the prediction of CA with the prediction of a proxy measure of 'phenotypic age' [33]. Another epigenetic marker is telomere length [35], which could be considered as a 'mitotic clock' and is used to detect immunosenescence and biological ageing patterns. Although this marker is recognized, it is an imperfect marker of ageing and can, to date, only explain a small fraction of ageing-related health risks compared to the functional or epigenetic markers mentioned above. Interestingly, telomere length has recently been proposed as a way of predicting cancer risk, correlating with the number of stem cell divisions over a lifetime, with relevant models already suggested (e.g., Horvath's clock [36], EpiTOC, EpiTOC2 [37,38], and MiAge clocks [39]). In the same way, the characterisation of biological ageing has also appeared in the context of skin ageing, with a skin ageing clock developed to predict the progression of visual age (e.g., VisAgeX) [40].

The most salient point here is that these epigenetic markers (beside telomere length that is insensitive to short-term changes, limiting its use as a biomarker in interventional ageing research) can be influenced by long-term dietary patterns and specific nutrients. Diets rich in antioxidants, such as the Mediterranean diet, or with caloric restrictions are associated with longer telomeres, while pro-inflammatory and high-glycaemic-load diets can accelerate telomere attrition [35]. Specific nutrients such as choline, B vitamins such as folate (B9) or cobalamin (B12), among others, influence DNA methylation patterns directly (providing methyl groups), or indirectly (via enzymatic activities). Similarly, gut microbiome-derived by-products such as short-chain fatty acid (SCFAs) can also participate in epigenetic modulations [41].

2.2.2. Metabolomic and microbiomic biomarkers

Metabolomic biomarkers, i.e., the use of small molecules detected in biofluids (urine, blood) to reflect physiological functions, provide a detailed systemic assessment of ageing [42]. The gut microbiota and the metabolites it produces can be used both as a marker of metabolic health and inflammation, and as a guide in disease phenotypes. As such, the microbiome and its metabolic products are emerging as potential biomarkers for ageing [43]. Gut dysbiosis, an imbalance of microbes in the gut, can be linked to pathological ageing [44], while specific microbial communities have been associated with ageing [45]. Indeed, an extensive analysis of 21,000 gut microbiomes (18–107 years) showed microbiome diversity and uniqueness correlated with ageing, but not healthy ageing [46]. As such, in microbiome studies, the consideration of confounders (e.g. diet, BMI, medication status, sex) is of paramount importance. Moreover, microbes present in the gastrointestinal tract (GIT), not only influence immune function but as mentioned above, can also promote epigenetic mechanisms such as DNA methylation. The role of nutrition is cardinal in healthy ageing, with diet being a major driver of microbial composition [47,48] and functional capacity. SCFAs (most notably acetate, propionate and butyrate) are produced by microbial fermentation of dietary fibre in the large intestine, yet the microbes responsible for these bioconversions are depleted in older individuals consuming low-fibre diets [49]. Availability of aromatic amino acids, phenolic compounds, cresols, indoles, branched-chain amino acids and methylamine derivatives is also dependent on diet, microbiome and health status of an individual [50], with their effects ranging from beneficial to detrimental depending on context and levels [51,52].

2.2.3. Inflammatory markers and markers of vascular ageing

While both healthy and pathological ageing involve a certain degree of inflammation, excessive or persistent inflammation, known as 'inflammageing', is a predictor of BA and the trajectory of ageing. For example, specific pro-inflammatory cytokines are used to reflect frailty, which is a powerful predictor of several health-related outcomes and often outperforms CA in predicting individual mortality [53]. The development of approaches with the use of immune variables and the analysis of the changes between naïve and memory immune cells is also proposed as 'immunity clock' to determine BA [54]. Efforts in this domain of research might also provide valuable insights into the

characterisation of phenotypic age, as already proposed (Immunity Clock [33], IMMClock, Immunosenescence clock [55]). In addition, it is important to mention other markers, for example those of vascular health, such as Pulse Wave Velocity (PWV), Flow-Mediated Dilation (FMD), or cardiac biomarkers, such as troponin [56], a widely recognised marker of heart muscle damage following myocardial infarction, as they have valuable clinic relevance in relation to ageing [57].

BA markers such as the ones presented here, have been reported to be more accurate for assessing ageing-related health risks (for example frailty or mortality) than markers used to define CA [58].

3. Research priority: selection and harmonisation of (bio) markers

Selecting appropriate biomarkers to reflect individual ageing processes requires a tailored approach. Ideally, researchers and clinicians should be working together towards creating a comprehensive catalogue of biomarkers that reflect known mechanisms of action across different medical disciplines, and different segments of the population. Given the complexity of ageing, ranking biomarkers based on their strength (proven / strong / medium / weak) may vary depending on the research context, as pointed out in a prior report [59]. For that reason, to achieve consensus on the selection of appropriate (bio)markers, we also need to consider their transferability. This raises the (challenging) question of the compatibility of biobanks (cells, fluids, etc.) and the acquisition of similar data worldwide, given the differences in regulations, protocols, databases or even infrastructures, besides cultural, technical, and socioeconomic differences.

As the number of biomarkers increases, so does the complexity of data analysis. This does pose the question of how best to manage the interconnectivity between biomarkers and translate them into a single measure of BA. This multidisciplinary challenge might require innovative models and international collaboration to ensure the accuracy and relevance in defining BA.

4. Research priority: define key points and trajectory of ageing across the lifespan

Biomarkers are not static; they fluctuate across the lifespan [54], emphasising the need to define baselines for healthy ageing at different life stages. Lifespan adversity and baseline health may already differ significantly across populations. Understanding these fluctuations requires longitudinal studies to stratify biomarkers by age group and identify different dietary lifestyle interventions, capable of redirecting individuals towards healthier ageing trajectories. For example, anti-inflammatory diets rich in fibre and fermented foods, such as the Mediterranean diet, and/or incorporating probiotics or prebiotics, support balanced metabolic pathways and an overall healthier lifestyle. Conversely, diets high in sodium and refined carbohydrates are potentially associated with increased inflammation and an increased risk of chronic disease [60]. More in-depth research is necessary to establish and validate already suggested causal links between diet and clinical outcomes, particularly to understand the effects on cellular mechanisms impacting the gut-brain axis, mitochondrial responses or systemic inflammation.

Future research is also required to identify the most important (bio) markers of ageing and understand how they interact, focusing on dynamic markers that can also reflect individual resilience to different stressors [61,62]. Environmental factors such as stress (cortisol levels), physical activity, sedentariness and sleep quality can also modulate the effects of dietary and lifestyle interventions, or attenuating their protective or destructive effects, which complicates the interpretation of current markers.

In parallel, there is a fundamental need to select appropriate endpoints for ageing-related clinical trials with multi-domain responder indices [63]. Distinguishing between healthy age-related decline and accelerated unhealthy degradation of functional capacity is crucial, as it may indicate an underlying health condition. For example, markers such as glomerular filtration rate for kidney function, when linked to biomarkers like trimethylamine *N*-oxide (TMAO), may show different patterns depending on the rate of decline [64]. Additionally, it is vital to select the right confounders when assessing these markers. This includes considering various 'modifiable' and 'non-modifiable' factors that contribute to the exposome [65] and how they interact with the biological processes. For instance, butyrate which can indicate gut health [66], may not be detected in the blood serum [67], emphasising the need to consider the specific biofluids when evaluating markers.

In this respect, it is essential to strike a balance between scientific rigor, feasibility, patient relevance and economic considerations, to design interventions that promote healthy ageing, and which can be effectively translated into clinical and nutritional practices. Having insight in the underlying mode of action of the intervention, might help to promote its application in a well-defined context that considers the above mentioned "modifiable" and "unmodifiable" confounders.

5. Research priority: integrating analytical techniques

To better understand healthy ageing and its biomarkers, there is an undeniable need to develop complex analytical models that integrate diverse datasets and guide meaningful interventions [68]. Wearable or 'smart' devices offer continuous monitoring and tracking of biomarkers as they fluctuate across the day, as well across longer periods of time [69]. These changes in biomarkers reflect both the individual's normal behaviour and any deviation from said norm, such as reduced physical activity or changes in dietary intake [70]. These devices complement laboratory measurements by capturing real-time fluctuations, which is not possible in a laboratory that produces only a biomarker 'snapshot' during each visit. However, ensuring specificity, reliability in data collected across different manufacturers is crucial for effective data integration. Identifying 'black spots' in biomarker measurement will further advance the development of comprehensive monitoring systems. However, it should be noted that close monitoring of personal activity may not be exempt of ethical considerations and may require a well-defined regulatory framework.

Here, health technology and artificial intelligence could also play a critical role in public health, encouraging physical activities and motivating healthier dietary choices in younger generations, while enhancing diagnosis, treatments and patient care. In effect, these advances bring closer the possibility of personalised advice and nutrition while reducing the variability in responses, as demonstrated by encouraging results obtained in a recent trial [71], showing that in older and care-dependent populations, technology offers dynamic monitoring and stratification capabilities, enabling tailored interventions and allowing longer maximal independence.

There is a need to establish task forces for training and knowledge transfer between the fields of nutrition, data acquisition, data science and bioinformatics, to develop robust tools that promote healthy ageing and avoid misinterpretation in patient care. This collaboration will enable nutrition specialists, clinicians and technology companies to develop products and interventions which translate the innovations and developments in geroscience into public health and nutrition benefits.

6. Conclusion

As the population continues to age, maintaining life-long health and functional capacity becomes a critical priority. This workshop and report highlighted the pressing need to define normal ageing through standardized biological reference ranges and to prioritise the discovery and validation of robust, reproducible biomarkers with established sensitivity and specificity that can guide targeted nutritional and lifestyle interventions. To fully map the biological trajectory of ageing, longitudinal studies across all age groups are essential to better

understand the ageing progression and to design both clinical and nutritional interventions that promote healthy and resilient ageing. Therefore, upcoming research needs to enable the integration of biomarker data into the design of clinical and nutritional strategies that promote health, resilience, and functional capacity over the life course. Furthermore, the integration of advanced technologies such as wearables and artificial intelligence offers transformative potential for personalised nutrition and health monitoring. However, significant challenges remain, including the need for regulatory frameworks for personalized (nutritional) interventions, ethical considerations around predictive biomarkers, and ensuring equitable access to these technologies.

To achieve these goals, the development of interdisciplinary collaborations across nutrition scientists, clinicians, technologists, and policymakers is paramount. Establishing dedicated task forces for these collaborations will accelerate knowledge exchange and drive innovation in the field of geroscience. Future work should prioritize the development of intervention trials with robust clinical endpoints to translate biomarker discoveries into actionable health strategies. By addressing these challenges, we pave the way for healthier, longer lives, while reducing the economic and societal burden of ageing.

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