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Scientific News
7th of June 2025
Sven Bulterijs

Business/Conferences/ General news

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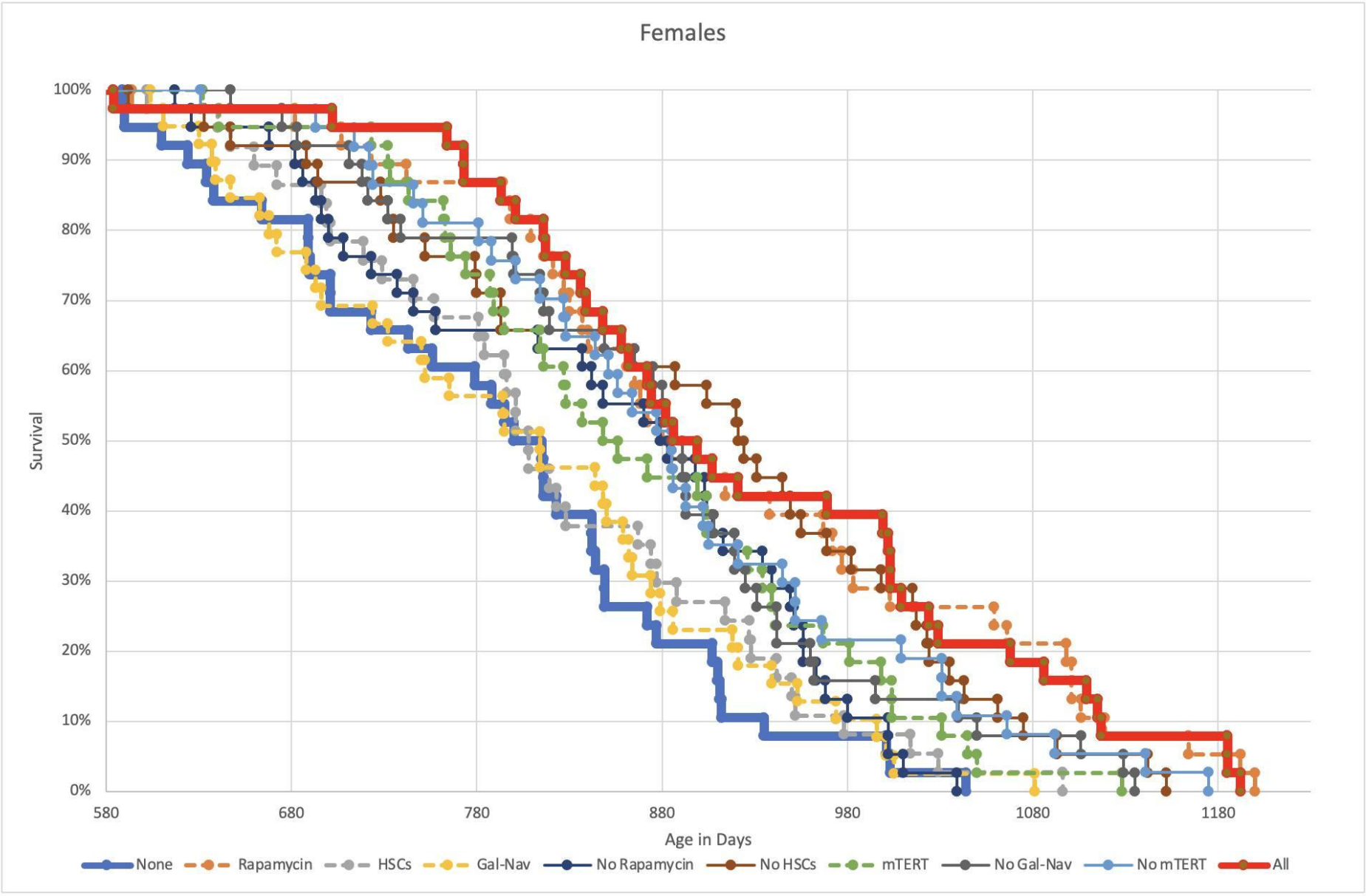
MRM1 study results



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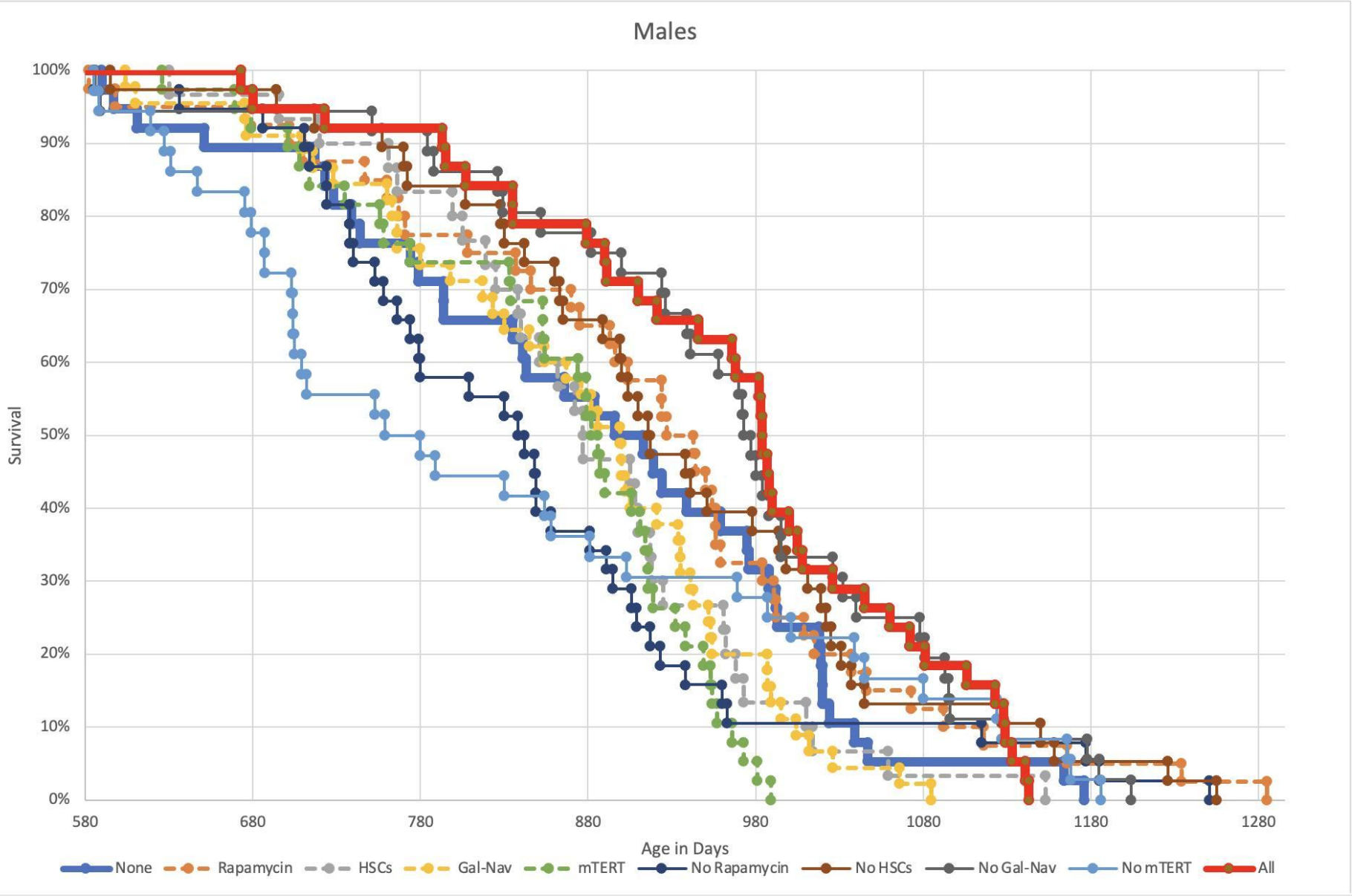

Interview with Victor Björk

The Trust Factor: Inside the World of Longevity Concierge Services

Wednesday, May 21, 2025 AntiAging LongevityTech LongevityConcierge

What if the future of healthcare wasn't in hospitals—but in personal science advisors? As the field of longevity evolves rapidly, a new role is emerging: the longevity concierge. In this exclusive interview, Victor Björk, a biomedical scientist and longevity concierge, shares how he helps clients navigate cutting-edge treatments, avoid pseudoscience, and make evidence-based choices in a landscape filled with both opportunity and noise.

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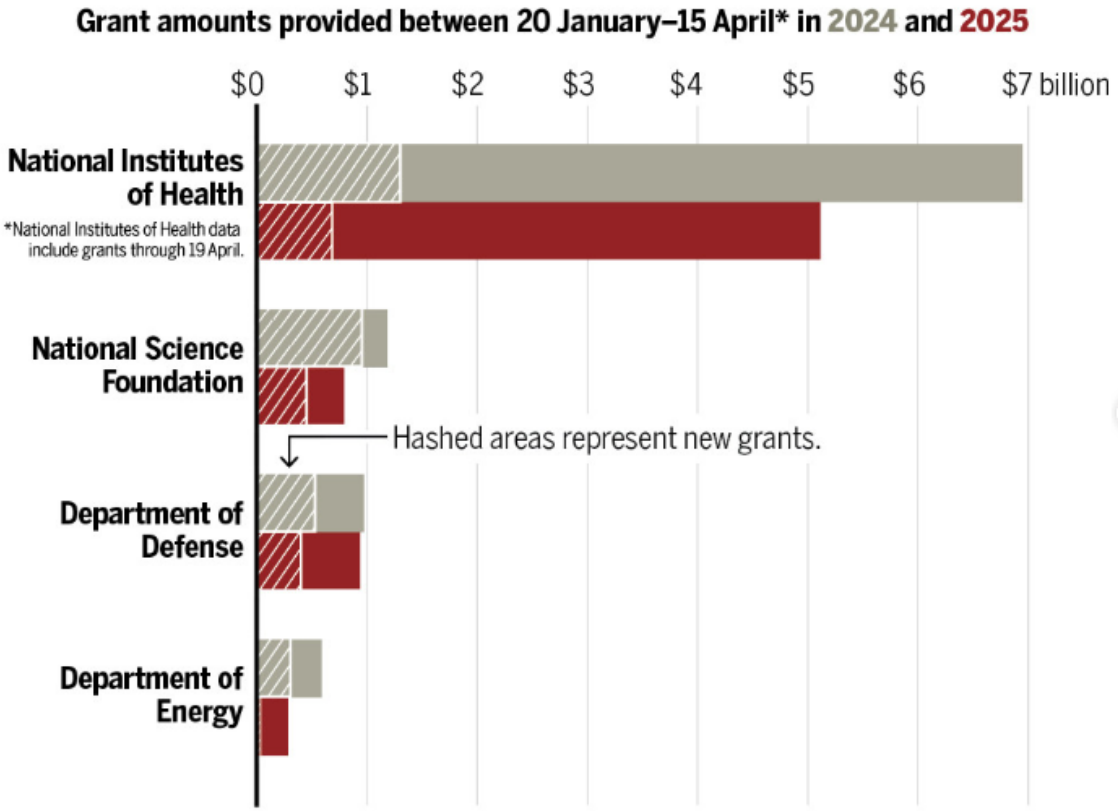
Science spending plummets

Since Donald Trump was inaugurated as president on 20 January, the largest federal agency funders of research have spent billions less on grants, compared with the same 3-month period in 2024. Causes include a freeze on federal spending and administration reviews to root out and terminate grants on topics banned by Trump's executive orders on diversity and "gender ideology."



New grant spending has plummeted

53%

since Trump took office in January, on average, across **four science agencies.**

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Gene editing leaders call for 10-year suspension of heritable human genome editing

By **Darren Incorvaia** · May 28, 2025 7:00am

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CRISPR Therapeutics sees 80% fall in LDL, triglycerides after in vivo liver editing

By **Nick Paul Taylor** · May 7, 2025 10:00am

CRISPR Therapeutics has reported reductions in triglycerides and LDL cholesterol of more than 80% after a single dose of its in vivo liver editing prospect CTX310, encouraging the company to forge ahead with dose escalation.

CTX310 targets ANGPTL3, a gene that encodes for a protein involved in the regulation of LDL cholesterol. Drug developers are coming at the target from a variety of angles. Regeneron's antibody Evkeeza hits ANGPTL3, as do siRNA therapies in development at Arrowhead Pharmaceuticals/Eli Lilly. CRISPR Tx and Verve Therapeutics are leading efforts to knock out hepatic ANGPTL3 expression through in vivo editing.

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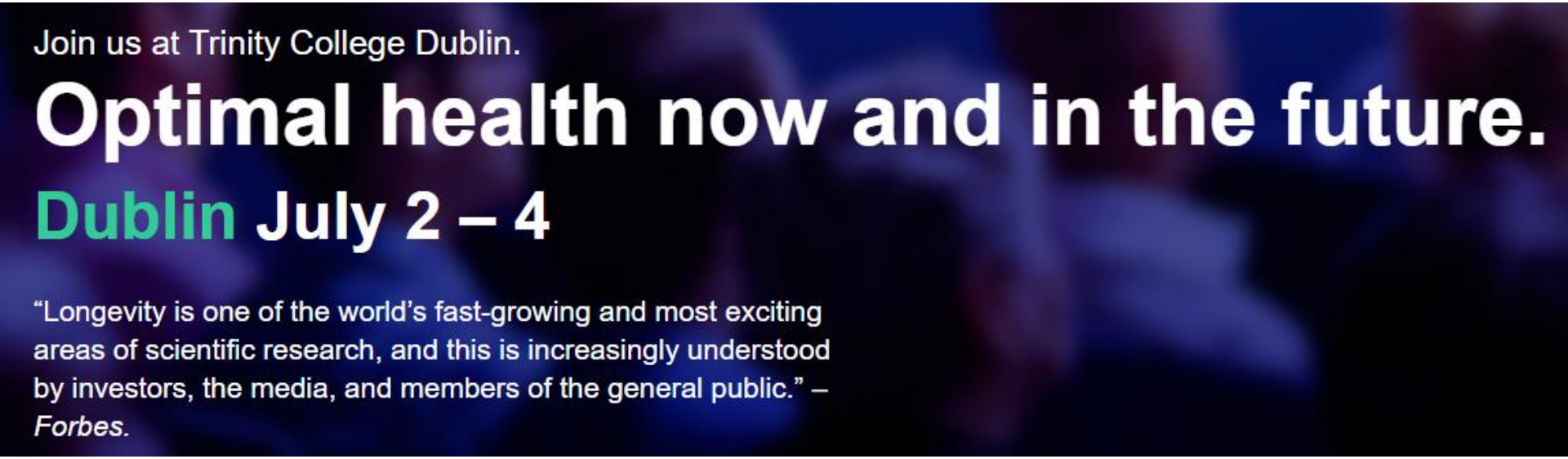
Nieuwe studie bewijst nut van strenge maatregelen en coronavaccins: “Tienduizenden extra sterfgevallen vermeden”

HASSELT - **Zonder vaccins en zonder gedragsaanpassingen waren er tijdens de coronapandemie in België mogelijk tot 62.000 extra coronadoden gevallen. Dat blijkt uit een nieuwe studie van de UHasselt. “Dit toont nog maar eens het belang van vaccinatie”, zegt prof. Niel Hens (UHasselt).**

Upcoming conferences

I'll be there!



Aging research articles

Feasibility of intravenous injection of pig plasma extracellular particles into rats: an acute study

Extracellular particles (EPs), especially small extracellular vesicles (EVs), extracted from young animals are increasingly being studied in animal models as agents for regeneration and rejuvenation, with studies using EPs from one species injected into another showing no immune reaction. In this study, we aimed to investigate if the injection of Pig Plasma Extracellular Particles (PPEPs) into rats would produce an acute immune or toxic reaction. Blood from a young pig was collected, PPEPs were isolated by size exclusion chromatography and injected into young male Sprague-Dawley rats, while the control group received a sterile saline injection. After 9 days, the animals were euthanized and their organs were histologically analyzed for signs of cellular damage or immune infiltration. The treated rats showed no signs of acute immunological reaction, behaving normally immediately after the injections and during the 9 days since the first injection. Throughout the trial period, the animals continued gaining weight normally and the histological analysis of their liver, kidney and spleen showed no signs of acute toxicity. PPEPs from young animals do not cause an acute immune or toxic response when injected intravenously into young male Sprague-Dawley rats.

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Global incidence trends and projections of Alzheimer disease and other dementias: an age–period–cohort analysis 2021

Background: Alzheimer disease (AD) is a growing global health issue, with incidence varying by gender, age, and region. Understanding these trends is essential for developing effective prevention strategies as the population ages. Unlike previous Global Burden of Disease (GBD) studies that primarily focussed on prevalence and mortality, we offer a novel perspective by examining historical incidence trends and projecting future patterns of AD and other dementias using advanced analytical approaches.

Methods: We used data from 204 countries and 21 global regions from the GBD 2021 database. We applied the age-period-cohort (APC) model to analyse historical incidence trends, and the Bayesian APC (BAPC) model to forecast future incidence from 2022-36. These models help reveal changes related to age, period, and birth cohort and enable forecasting of future trends - analytical perspectives not provided in the original GBD data sets or their supplementary documents.

Results: Between 1992-2021, global AD cases increased from 4.078 million to 9.837 million, while the global age-standardised incidence rate (ASIR) remained relatively stable, rising slightly from 117.7 to 119.8 per 100 000. ASIR increased significantly in high-middle and middle-sociodemographic index regions, but declined in the low-sociodemographic index regions. Women consistently exhibited higher incidence rates than men across all regions. Projections indicate that 2036 global AD cases will reach 19.117 million, with an ASIR of 418.92 per 100 000.

Conclusions: While global ASIR has remained stable, the number of AD cases continues to rise due to population ageing, particularly in middle- and high-income regions. Low-income regions face additional challenges due to limited health care resources. Gender disparities and unequal access to health care contribute to the variations in disease burden. These findings emphasise the need to prioritise early diagnosis and implement targeted interventions to reduce future disease burdens and address global health care inequalities.

Changing Story of the Dementia Epidemic

P. J. Eric Stallard, BS[1]; Svetlana V. Ukraintseva, PhD[1]; P. Murali Doraiswamy, MBBS[2,3]

The common perception that little progress has been made in stemming the expected tsunami of dementia in the US may be incorrect. The increase is expected because the large baby boom generation, born in 1946 to 1964, will soon reach the ages at which the risks of dementia are highest. The population aged 80 years or older will double between 2025 and 2050, with the population aged 85 years or older 2.5 times larger and that aged 95 years or older 3.0 times larger than they are today.[1] If age-specific dementia prevalence rates do not change, then the number of persons with dementia at these ages will be 2.0, 2.5, and 3.0 times larger, respectively, in just 25 years, justifying the tsunami metaphor.

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Global, regional, and national burden of ischemic stroke in older adults (≥60 years) from 1990 to 2021 and projections to 2030

Background: Ischemic stroke is a leading cause of disability and mortality among adults worldwide, particularly in the older population (≥60 years). With the accelerating global aging population, it is crucial to analyze the trends and influencing factors of the global, regional, and national burden of ischemic stroke and forecast future trends. These insights are essential for informing the formulation of public health policies.

Methods: Using data from the Global Burden of Disease (GBD) 2021 database, this study examined the age-standardized incidence, age-standardized prevalence, age-standardized mortality, and age-standardized disability-adjusted life years (DALYs) of ischemic stroke in individuals aged 60 years and above from 1990 to 2021. A combination of variables, including the socio-demographic index (SDI), sex, and age groups, was applied in regression analyses and Bayesian predictive models to examine trends and forecast the burden of ischemic stroke up to 2030.

Results: From 1990 to 2021, despite global population growth among older adults, the age-standardized incidence, age-standardized prevalence, age-standardized mortality, and age-standardized disability-adjusted life years of ischemic stroke demonstrated an overall declining trend (all EAPCs were negative). The decline in disease burden was most pronounced in high-SDI regions, while low-SDI regions faced a significantly higher disease burden and exhibited notable regional disparities. The overall burden of ischemic stroke was higher in males than in females; however, in the 80-84 age group, females exceeded males in disease burden. Projections indicate that by 2030, the burden of ischemic stroke in older adults globally will continue to decline. Nevertheless, due to the aging population, the absolute number of patients is expected to increase.

Conclusion: The global burden of ischemic stroke has significantly decreased, particularly in high-SDI regions with abundant healthcare resources. However, low-SDI regions face more substantial public health challenges. It is recommended to enhance the control of high-risk factors such as hypertension, smoking, and high BMI, and to optimize healthcare services in low-income regions to further reduce the burden of ischemic stroke and improve the quality of life for older adults.

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Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease

V. Tabar ✉, H. Sarva, A. M. Lozano, A. Fasano, S. K. Kalia, K. K. H. Yu, C. Brennan, Y. Ma, S. Peng, D. Eidelberg, M. Tomishima, S. Irion, W. Stemple, N. Abid, A. Lampron, L. Studer & C. Henchcliffe

Parkinson's disease is a progressive neurodegenerative condition with a considerable health and economic burden[1]. It is characterized by the loss of midbrain dopaminergic neurons and a diminished response to symptomatic medical or surgical therapy as the disease progresses[2]. Cell therapy aims to replenish lost dopaminergic neurons and their striatal projections by intrastriatal grafting. Here, we report the results of an open-label phase I clinical trial (NCT04802733) of an investigational cryopreserved, off-the-shelf dopaminergic neuron progenitor cell product (bemdaneprocel) derived from human embryonic stem (hES) cells and grafted bilaterally into the putamen of patients with Parkinson's disease. Twelve patients were enrolled sequentially in two cohorts—a low-dose (0.9 million cells, $n = 5$) and a high-dose (2.7 million cells, $n = 7$) cohort—and all of the participants received one year of immunosuppression. The trial achieved its primary objectives of safety and tolerability one year after transplantation, with no adverse events related to the cell product. At 18 months after grafting, putaminal ^{18}Fluoro-DOPA positron emission tomography uptake increased, indicating graft survival. Secondary and exploratory clinical outcomes showed improvement or stability, including improvement in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III OFF scores by an average of 23 points in the high-dose cohort. There were no graft-induced dyskinesias. These data demonstrate safety and support future definitive clinical studies.

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Phase I/II trial of iPS-cell-derived dopaminergic cells for Parkinson's disease

Parkinson's disease is caused by the loss of dopamine neurons, causing motor symptoms. Initial cell therapies using fetal tissues showed promise but had complications and ethical concerns[1,2,3,4,5]. Pluripotent stem (PS) cells emerged as a promising alternative for developing safe and effective treatments[6]. In this phase I/II trial at Kyoto University Hospital, seven patients (ages 50–69) received bilateral transplantation of dopaminergic progenitors derived from induced PS (iPS) cells. Primary outcomes focused on safety and adverse events, while secondary outcomes assessed motor symptom changes and dopamine production for 24 months. There were no serious adverse events, with 73 mild to moderate events. Patients' anti-parkinsonian medication doses were maintained unless therapeutic adjustments were required, resulting in increased dyskinesia. Magnetic resonance imaging showed no graft overgrowth. Among six patients subjected to efficacy evaluation, four showed improvements in the Movement Disorder Society Unified Parkinson's Disease Rating Scale part III OFF score, and five showed improvements in the ON scores. The average changes of all six patients were 9.5 (20.4%) and 4.3 points (35.7%) for the OFF and ON scores, respectively. Hoehn–Yahr stages improved in four patients. Fluorine-18-L-dihydroxyphenylalanine (^{18}F-DOPA) influx rate constant (K_i) values in the putamen increased by 44.7%, with higher increases in the high-dose group. Other measures showed minimal changes. This trial (jRCT2090220384) demonstrated that allogeneic iPS-cell-derived dopaminergic progenitors survived, produced dopamine and did not form tumours, therefore suggesting safety and potential clinical benefits for Parkinson's disease.

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PREPRINT

A single factor for safer cellular rejuvenation

Ageing is a key driver of the major diseases afflicting the modern world. Slowing or reversing the ageing process would therefore drive significant and broad benefits to human health. Previously, the Yamanaka factors (OCT4, SOX2, KLF4, with or without c-MYC: "OSK(M)") have been shown to rejuvenate cells based on accurate predictors of age known as epigenetic clocks. Unfortunately, OSK(M) induces dangerous pluripotency pathways, making it unsuitable for therapeutic use. Recent work has focused on minimising the danger of the cocktail, but safety concerns remain. Here we present "SB000", the first single gene intervention to rejuvenate cells from multiple germ layers with efficacy rivalling the Yamanaka factors. Cells rejuvenated by SB000 retain their somatic identity, without evidence of pluripotency or loss of function. These results reveal that decoupling pluripotency from cell rejuvenation does not remove the ability to rejuvenate multiple cell types. This discovery paves the way for cell rejuvenation therapeutics that can be broadly applied across age-driven diseases.

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PREPRINT

Increased Genetic Protection Against Alzheimer's Disease in Centenarians

We constructed a polygenic protective score specific to Alzheimer's disease (AD PPS) based on the current literature among the participants enrolled in five studies of healthy aging and extreme longevity in the US, Europe, and Asia. This AD PPS did not include variants on Apolipoprotein E (APOE) gene. Comparisons of AD PPS in different data sets of healthy agers and centenarians showed that centenarians have stronger genetic protection against AD compared to individuals without familial longevity. The current study also shows evidence that this genetic protection increases with increasingly older ages in centenarians (centenarians who died before reaching age 105 years, semi-supercentenarians who reached age 105 to 109 years, and supercentenarians who reached age 110 years and older). However, the genetic protection was of modest size: the average increase in AD PPS was approximately one additional protective allele per 5 years of gained lifetime. Additionally, we show that the higher AD PPS was associated with better cognitive function and decreased mortality. Taken together, this analysis suggests that individuals who achieve the most extreme ages, on average, have the greatest protection against AD. This finding is robust to different genetic backgrounds with important implications for universal applicability of therapeutics that target this AD PPS.

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Signatures of Nonlinear Aging: Molecular Stages of Life

Sudden Changes During Aging as Potential Biomarkers for an Age Classification System

Maja Olecka, Helen Morrison, Steve Hoffmann

The traditional view of aging as a gradual, progressive process is increasingly being challenged. A growing body of evidence suggests the existence of abrupt transitions in the aging process, marked by sudden molecular shifts. Interestingly, the data indicates that such transitions occur not only in late life but also throughout the entire lifespan. Further research on the nature of such events could enhance our understanding of aging and pave the way for novel therapeutic strategies, including personalized medicine. We propose that these abrupt molecular shifts could serve as biomarkers, dividing the lifespan into distinct stages and providing the foundation for a much-needed staging system for aging. Furthermore, we argue that the sudden changes may be the hallmarks of aging tipping points, that is, points in time where aging processes are quickly amplified after surpassing critical biological thresholds.

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PREPRINT

How Can I Stay Healthy? – Benchmarking Large Language Models for Personalized and Biomarker-Based Intervention Recommendations

Background The integration of large language models (LLMs) into clinical workflows for diagnostics and intervention recommendations has gained interest due to their strong performance on various medical benchmarks. However, we lack benchmarks that assess their applicability for personalized interventions, specifically in geroscience and longevity medicine. **Methods** We extended the BioChatter framework for developing biomedical benchmarks for LLMs with the primary aim of assessing the ability of LLMs to generate personalized intervention recommendations based on biomarker profiles, while ensuring compliance with predefined validation requirements. We created 25 medically relevant personal profiles across three age groups, where people seek advice on interventions such as caloric restriction, intermittent fasting, exercise, and selected supplements and drugs. We then used these profiles to construct 1,000 test cases in a combinatorial fashion, simulating real-world user prompt variability. We evaluated multiple proprietary and open-source models using an LLM-as-a-judge approach, assessing 48,000 primary responses against expert-validated ground truths. **Results** Proprietary models outperformed open-source ones, particularly with respect to comprehensiveness. While LLMs largely succeed in providing explainable suggestions, their limited comprehensiveness may hinder informed decision-making. LLMs respond positively to more concrete instructions in the system prompt but remain vulnerable to overall prompt variability. Responses account well for the safety of interventions, potentially at the cost of lower utility. Moreover, LLM performance is heterogeneous across different age groups, displaying age-related biases, which may, however, be due to differential disease prevalence. **Conclusion** Our findings indicate that LLMs are not generally suitable for unsupervised preventive intervention recommendations due to inconsistent performance across key validation requirements, but proprietary models mostly perform well when evaluated by automated judgments assisted by expert commentaries. Our open-source benchmarking and evaluation framework provides a blueprint for advancing LLM evaluation in other medical contexts, enabling better AI-driven healthcare applications.

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Is taurine an aging biomarker?

MARIA EMILIA FERNANDEZ, MICHEL BERNIER, NATHAN L. PRICE, SIMONETTA CAMANDOLA, MIGUEL A. AON, KELLI VAUGHAN, JULIE A. MATTISON, JOSHUA D. PRESTON, DEAN P. JONES, [...], AND RAFAEL DE CABO +4 authors Authors Info & Affiliations

RESULTS

Measurement of taurine concentration was performed on longitudinally collected plasma of human subjects (26 to 100 years old) from the Baltimore Longitudinal Study of Aging (BLSA), longitudinally collected serum from rhesus monkeys (3 to 32 years old), and C57BL/6J mice (9 to 27 months old) from the Study of Longitudinal Aging in Mice (SLAM). Taurine concentrations exhibited a sex-specific increase with age in all cohorts except male mice, in which taurine remained unchanged. These longitudinal analyses also revealed that the interindividual variability contributes more to the differences in taurine concentrations than age. Similar age-related changes in taurine concentrations were observed in two cross-sectional studies of geographically distinct human populations. The relation between taurine and muscle strength or body weight was inconsistent within and across cohorts.

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The geroprotectors trametinib and rapamycin combine additively to extend mouse healthspan and lifespan

Suppression of the insulin–IGF–mTORC1–Ras network ameliorates aging in animals. Many drugs have targets in the network because of its roles in cancer and metabolic disease and are candidates for repurposing as geroprotectors. Rapamycin, an established geroprotective drug, blocks mTORC1 signaling, and trametinib inhibits the Ras–MEK–ERK pathway. In this study, we assessed survival and health of male and female mice treated with trametinib, rapamycin or their combination. We show here that trametinib treatment extended lifespan in both sexes and that its combination with rapamycin was additive. Combination treatment reduced liver tumors in both sexes and spleen tumors in male mice, blocked the age-related increase in brain glucose uptake and strongly reduced inflammation in brain, kidney, spleen and muscle and circulating levels of pro-inflammatory cytokines. We conclude that trametinib is a geroprotector in mice and that its combination with rapamycin is more effective than either drug alone, making the combination a candidate for repurposing as a gerotherapy in humans.

NAD depletion in skeletal muscle does not compromise muscle function or accelerate aging

Nicotinamide adenine dinucleotide (NAD) is a ubiquitous electron carrier essential for energy metabolism and post-translational modification of numerous regulatory proteins. Dysregulations of NAD metabolism are widely regarded as detrimental to health, with NAD depletion commonly implicated in aging. However, the extent to which cellular NAD concentration can decline without adverse consequences remains unclear. To investigate this, we generated a mouse model in which nicotinamide phosphoribosyltransferase (NAMPT)-mediated NAD^+ biosynthesis was disrupted in adult skeletal muscle. The intervention resulted in an 85% reduction in muscle NAD^+ abundance while maintaining tissue integrity and functionality, as demonstrated by preserved muscle morphology, contractility, and exercise tolerance. This absence of functional impairments was further supported by intact mitochondrial respiratory capacity and unaltered muscle transcriptomic and proteomic profiles. Furthermore, lifelong NAD depletion did not accelerate muscle aging or impair whole-body metabolism. Collectively, these findings suggest that NAD depletion does not contribute to age-related decline in skeletal muscle function.

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PREPRINT

A nucleic acid prodrug that activates mitochondrial respiration, promotes stress resilience, and prolongs lifespan

Mitochondrial dysfunction caused by aging leads to decreased energy metabolism, resulting in functional decline and increased frailty in multiple tissues. Strategies for protecting and activating mitochondria under stressful conditions are required to suppress aging and age-related diseases. However, it is challenging to develop drugs capable of boosting mitochondrial respiration and compensating for the reduced intracellular adenosine triphosphate (ATP) levels. In this study, we developed a prodrug that stimulates the metabolism of intracellular adenine nucleotides (AXP: adenosine monophosphate (AMP), adenosine diphosphate (ADP), and ATP). It enhances AMP-activated protein kinase activity, fatty acid oxidation, oxidative stress resistance, and mitochondrial respiration, thereby increasing the intracellular ATP levels. Furthermore, this prodrug markedly extended the lifespan of *Caenorhabditis elegans*. AXP-driven stimulation of cellular energy metabolism proposed herein represents a novel geroprotective strategy and paves the way for the development of bioenergetic-molecule therapeutics.

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Sex-specific insights into drug-induced lifespan extension and weight loss in mice

Aleksey V. Belikov, Angelo Talay & João Pedro de Magalhães

The DrugAge database serves as a comprehensive resource for studying compounds that increase lifespan in model organisms. In the latest version of DrugAge, we implemented multiple updates, predominantly focusing on mouse studies to enhance data accuracy and consistency. Key improvements include re-recording of mouse data from original sources, standardization of drug dosages to parts per million, and recording of administration routes, treatment initiation ages, and lifespans of controls. The user interface was also upgraded. Additionally, weight change data were included to address the potential impact of caloric restriction induced by drug administration on lifespan. Our analysis revealed significant correlations between weight loss and lifespan extension in male mice, particularly in studies conducted by the Interventions Testing Program, highlighting the importance of considering weight changes in lifespan studies. We also observed notable sex-related differences in lifespan and weight change responses, underscoring the need for sex-specific analyses in aging research.

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PREPRINT

Deep Learning of Cellular Metabolic Flux Distributions Predicts Lifespan

It is a common observation that individuals within a species age at different rates. Variation in both genetics and environmental interaction are generally thought responsible. Surprisingly, even genetically identical organisms cultured under environmentally homogeneous conditions age at different rates, implying a more fundamental cause of aging. Here we have examined the basis for lifespan variance in haploid, single-celled yeast of *Saccharomyces cerevisiae*. The probabilistic nature of metabolism means metabolites often, but not always, follow the same route through the metabolic network. We speculate redundancy in metabolic pathway choice is sufficient to explain lifespan variance. To interrogate the reaction flux space of *S. cerevisiae* we used a model of its intermediary metabolism, comprising 1,150 genes, 4,058 reactions, and 2,742 metabolites (yeast GEM_v8.5.0). We restricted traffic through the metabolic network by knocking out each of the 1,150 genes, then generated a total of 406,500 flux distributions spanning the solution space of the resulting 812 viable mutants. We used replicative life span (RLS) data for the 812 viable mutants, corresponding to 66,400 individual cells. Four approaches were then employed to test whether reaction flux configuration could be used to predict lifespan: Principal Component Analysis (PCA) in conjunction with non-linear modeling of RLS; deep learning of RLS using either a Regression Neural Network (RNN) or a Classification Neural Network (CfNN); and deep learning using a convolutional neural network (CNN) following conversion of flux distributions to pixelated images. The four approaches reveal a core network of highly correlated reactions controlling aging rate that is sufficient to explain all lifespan variance. It includes biosynthetic pathways encompassing ceramides, monolysocardiolipins, phosphoinositides, porphyrin and glycerolipids. Our data lead to two novel conclusions. First, variance in the replicative lifespan of *S. cerevisiae* is an emergent property of its metabolic network. Second, there is convergence among metabolic configurations toward three meta-stable flux states – one associated with extended life, another with shortened life, and a third with wild type life span.

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Late Life Supplementation of 25-Hydroxycholesterol Reduces Aortic Stiffness and Cellular Senescence in Mice

Sophia A. Mahoney, Mary A. Darrah, Ravinandan Venkatasubramanian, Serban Ciotlos, Matthew J. Rossman, Judith Campisi, Douglas R. Seals, Simon Melov, Zachary S. Clayton

Stiffening of the aorta is a key antecedent to cardiovascular diseases (CVD) with aging. Age-related aortic stiffening is driven, in part, by cellular senescence—a hallmark of aging defined primarily by irreversible cell cycle arrest. In this study, we assessed the efficacy of 25-hydroxycholesterol (25HC), an endogenous cholesterol metabolite, as a naturally occurring senolytic to reverse vascular cell senescence and reduce aortic stiffness in old mice. Old (22–26 months) p16-3MR mice, a transgenic model allowing for genetic clearance of p16-positive senescent cells with ganciclovir (GCV), were administered vehicle, 25HC, or GCV to compare the efficacy of the experimental 25HC senolytic versus genetic clearance of senescent cells. We found that short-term (5d) treatment with 25HC reduced aortic stiffness in vivo, assessed via aortic pulse wave velocity ($p = 0.002$) to a similar extent as GCV. Ex vivo 25HC exposure of aorta rings from the old p16-3MR GCV-treated mice did not further reduce elastic modulus (measure of intrinsic mechanical stiffness), demonstrating that 25HC elicited its beneficial effects on aortic stiffness, in part, through the suppression of excess senescent cells. Improvements in aortic stiffness with 25HC were accompanied by favorable remodeling of structural components of the vascular wall (e.g., lower collagen-1 abundance and higher α-elastin content) to a similar extent as GCV. Moreover, 25HC suppressed its putative molecular target CRYAB, modulated CRYAB-regulated senescent cell anti-apoptotic pathways, and reduced markers of cellular senescence. The findings from this study identify 25HC as a potential therapy to target vascular cell senescence and reduce age-related aortic stiffness.

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Clonal tracing with somatic epimutations reveals dynamics of blood ageing

Current approaches used to track stem cell clones through differentiation require genetic engineering[1,2] or rely on sparse somatic DNA variants[3,4], which limits their wide application. Here we discover that DNA methylation of a subset of CpG sites reflects cellular differentiation, whereas another subset undergoes stochastic epimutations and can serve as digital barcodes of clonal identity. We demonstrate that targeted single-cell profiling of DNA methylation[5] at single-CpG resolution can accurately extract both layers of information. To that end, we develop EPI-Clone, a method for transgene-free lineage tracing at scale. Applied to mouse and human haematopoiesis, we capture hundreds of clonal differentiation trajectories across tens of individuals and 230,358 single cells. In mouse ageing, we demonstrate that myeloid bias and low output of old haematopoietic stem cells[6] are restricted to a small number of expanded clones, whereas many functionally young-like clones persist in old age. In human ageing, clones with and without known driver mutations of clonal haematopoieis[7] are part of a spectrum of age-related clonal expansions that display similar lineage biases. EPI-Clone enables accurate and transgene-free single-cell lineage tracing on hematopoietic cell state landscapes at scale.

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Association of clonal hematopoiesis of indeterminate potential with cardiometabolic multimorbidity progression and mortality: a prospective study of UK Biobank

Methods: We included UK Biobank participants without CMD at baseline. The primary outcomes were the first CMD, CMM, and death. We evaluated associations between any CHIP (variant allele fraction [VAF] ≥ 2%), large CHIP (VAF ≥ 10%), and gene-specific CHIP subtypes (DNMT3 A, TET2, ASXL1, JAK2, PPM1D/TP53 [DNA damage genes], and SF3B1/SRSF2/U2 AF1 [spliceosome genes]) with CMD transitions via multistate model analyses. We estimated multivariable-adjusted hazard ratios (HRs) and 95% CIs with age as the time scale, and adjusted for sex, race, Townsend Deprivation Index, body mass index (BMI), smoking, alcohol, physical activity, sleep duration, and hypertension.

Results: The study included 371,544 participants, with a mean age of 56.60 (± 8.03) years, and 44.2% of whom were male (CHIP: n = 11,570 [3.1%]; large CHIP: n = 7156 [1.9%]). During a median follow-up period of 14.49 years, 54,805 individuals developed at least one CMD, 8090 experienced CMM, and 26,218 died. In the fully adjusted multistate models, CHIP and large CHIP were associated with adjusted hazard ratios (HR) of 1.11 (95% CI 1.07-1.16) and 1.14 (95% CI 1.08-1.20), respectively, for transitioning from a CMD-free condition to a single CMD. The mortality risk associations were strongest, with adjusted HR of 1.45 (95% CI 1.36-1.55) and 1.64 (95% CI 1.52-1.77) for those without CMD, 1.39 (95% CI 1.26-1.54) and 1.59 (95% CI 1.41-1.79) for individuals with single CMD, and 1.58 (95% CI 1.31-1.91) and 1.61 (95% CI 1.29-2.02) for those with CMM. No significant association was observed with CMM development. Gene-specific analyses identified DNMT3 A, TET2, DNA damage genes, and spliceosome genes as the primary contributors to increased CMD risk. While CHIP showed no association with CMM progression, spliceosome genes were linked to a 1.72-fold higher risk (adjusted HR 1.72, 95% CI 1.14-2.59) of recurrent CMD events. All CHIP subtypes were strongly related to a heightened risk of mortality, with JAK2 presenting the highest adjusted odds ratio at 6.79 (95% CI 4.12-11.2).

Conclusions: CHIP serves as an independent risk factor for transitioning to the first CMD incidence and for mortality but is not associated with CMM development. CHIP-targeted management may represent a promising strategy for the primary prevention of CMD and for reducing mortality risk.

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Ndufs4$^{-/-}$ mice: a testing ground for longevity interventions

Mice missing the complex I subunit Ndufs4 of the electron transport chain are widely used as a leading animal model of Leigh syndrome, a pediatric neurodegenerative disorder that leads to premature death. More broadly, this animal model has enabled a better understanding of the pathophysiology of mitochondrial disease and mitochondrial dysfunction in sporadic disorders. Intriguingly, longevity interventions are very effective at treating symptoms of disease in this model. Herein, we introduce the model and its notable features that may help provide insights in longevity research. We performed a retrospective analysis of historical data from our laboratories over the past 10 years regarding the use of this animal model in aging studies, the manifestation and progression of mitochondrial disease, and factors that influence their premature death. We observed a correlation between weight and lifespan in female animals and a sex-independent correlation between the onset of clasping, a typical neurodegenerative symptom, and overall survival. We observed a sexual dimorphism in lifespan with female mice being more resilient despite a similar age of onset of disease symptoms. Lastly, we report increased lifespan and delayed onset of disease symptoms following treatment with 17-alpha-estradiol, a non-feminizing estrogen which can extend lifespan in genetically heterogeneous mice. This analysis serves as a useful guide for researchers utilizing this animal in the discovery of effective interventions for longevity and to prevent the onset of disease. It suggests there may be unprecedented underlying sex-specific differences in patients with Leigh syndrome and further strengthens the connection between normative aging and mitochondrial dysfunction.

Long-Term High-Altitude Exposure, Accelerated Aging, and Multidimensional Aging-Related Changes

Yuwei Wu, MD[1]; Yuming Jin, MD[1]; Linghui Deng, MD[2]; et al

Exposure The participants' altitudes were determined using the global Shuttle Radar Topography Mission 4 data based on residential addresses. High-altitude areas refer to regions with altitudes of greater than or equal to 1500 m (4921 feet) above the mean sea level.

Main Outcomes and Measures Biological aging (BA) and aging acceleration (AA) were measured through the Klemera-Doubal Biological Age (KDM-BA) and PhenoAge methods. Multidimensional aging-related metrics were based on questionnaire, measurement, and self-report.

Results A total of 9846 participants from the WCNPCS cohort (mean [SD] age, 55.73 [11.06] years; 6730 women [68.35%]) and 3593 participants from the WCHAT cohort (mean [SD] age, 62.27 [8.40] years; 2253 women [62.71%]) were included. The participants living at high altitudes presented increased KDM-BA acceleration by 0.85 years for the WCNPCS cohort and 0.71 years for the WCHAT cohort. The PhenoAge results were similar, with even larger effect sizes (WCNPCS, β, 2.08 years; 95% CI, 1.77-2.39 years; WCHAT, β, 2.23 years; 95% CI, 1.91-2.54 years). The association between high-altitude exposure and biologically accelerated aging was particularly pronounced among smokers. Associations between high-altitude exposure and various multidimensional aging-related metrics were also observed.

Conclusions and Relevance These findings suggest that extended periods at high altitudes may hasten BA and contribute to the onset of aging-related illnesses. Implementing public health interventions for individuals residing in high-altitude regions may aid in alleviating the disease burden within these communities.

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Cross-sectional associations of epigenetic clocks with intrinsic capacity and functional ability in older adults with frailty and cognitive impairment: the COGFRAIL study

Functional ability and intrinsic capacity (IC) have been proposed as determinants of healthy aging, but the extent to which these indicators are affected by biological aging remains unknown. We explored the association of biological age acceleration (BAA) with functional ability and IC in older adults with physical and cognitive impairments. This cross-sectional study used data from 163 individuals (84.0 ± 5.2 years [range 72–99], 61.8% women) of the COGFRAIL cohort. Functional ability on basic (BADL-Katz Index) and instrumental activities of daily living (IADL-Lawton Index) was assessed. IC was measured as a composite score (0–100, higher is better) including the locomotion, cognition, psychology, sensory, and vitality domains. BAA was assessed by Horvath's, Hannum's, PhenoAge, and GrimAge epigenetic clocks. In the fully adjusted model, higher $BAA_{PhenoAGe}$ was associated to lower functional ability in BADLs (β = − 0.021, 95% confidence interval = − 0.038 to − 0.003, p = 0.022), with no significant results observed for the remaining clocks. No significant association was found between BAA and IC, but some associations were found with specific IC domains. Particularly, $BAA_{GrimAge}$ was associated with lower locomotion scores (β = − 1.179, 2.286 to − 0.072, p = 0.037), while $BAA_{PhenoAge}$ tended to be associated with lower scores in vitality (β = − 0.257, − 0.539 to 0.025, p = 0.073). Higher $BAA_{Phenoage}$ was associated with lower functional ability in very old adults with frailty and cognitive impairment. Although no biological clock was associated with a composite IC score, some associations were found between second-generation epigenetic clocks and specific IC domains.

Intrinsic Capacity Across 15 Countries in the Survey of Health, Aging, and Retirement in Europe

Meimei Chen, MRes[1,2]; Katja Hanewald, PhD[3,4]; Yafei Si, PhD[3,4,5]; et al

Main Outcomes and Measures Changes in activities of daily living (ADL) and instrumental activities of daily living (IADL). Methods included structural equation modeling, bifactor analysis, and path analysis. Construct validity was tested through multiple linear regression and validity of estimates through mediation analysis. Centile curves were established using the generalized additive models for location, scale, and shape.

Results The sample included 64 872 eligible participants aged 50 to 104 years, with a mean (SD) age of 67.24 (10.01) years, of whom 35 976 (55.46%) were women. The bifactor confirmatory factor analysis model achieved good fit (comparative fit index, 0.986; Tucker-Lewis index, 0.981), suggesting an IC structure consisting of 1 general factor and 5 subdomains. Mediation analysis indicated that IC was associated with subsequent declining performance in ADL (standard coefficient [SD], −0.213 [0.002]; $P<.001$) and IADL (standard coefficient [SD], −0.209 [0.002]; $P<.001$) after adjusting for age, gender, educational attainment, socioeconomic status, and country. Socioeconomic status was associated with IC both within and between countries. Centile curves for IC by gender and country (5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles) were constructed.

Conclusions and Relevance Results of this cohort study of older adults suggest that IC was a valid and reliable measure that effectively captured individual-level aspects of functional ability. The centile curves developed during the study suggest that IC has the potential to serve as a benchmark for health status in older populations.

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PREPRINT

Multiomic clocks to predict phenotypic age in mice

Daniel L. Vera, Patrick T. Griffin, David Leigh, Jason Kras, Enrique Ramos, Isaac Bishof, Anderson Butler, Karolina Chwalek, David S. Vogel, Alice E. Kane, David A. Sinclair

Biological age refers to a person's overall health in aging, as distinct from their chronological age. Diverse measures of biological age, referred to as "clocks", have been developed in recent years and enable risk assessments, and an estimation of the efficacy of longevity interventions in animals and humans. While most clocks are trained to predict chronological age, clocks have been developed to predict more complex composite biological age outcomes, at least in humans. These composite outcomes can be made up of a combination of phenotypic data, chronological age, and disease or mortality risk. Here, we develop the first such composite biological age measure for mice: the mouse phenotypic age model (Mouse PhenoAge). This outcome is based on frailty measures, complete blood counts, and mortality risk in a longitudinally assessed cohort of male and female C57BL/6 mice. We then develop clocks to predict Mouse PhenoAge, based on multi-omic models using metabolomic and DNA methylation data. Our models accurately predict Mouse PhenoAge, and residuals of the models are associated with remaining lifespan, even for mice of the same chronological age. These methods offer novel ways to accurately predict mortality in laboratory mice thus reducing the need for lengthy and costly survival studies.

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Multi-Omic Associations of Epigenetic Age Acceleration Are Heterogeneously Shaped by Genetic and Environmental Influences

Connections between the multi-ome and epigenetic age acceleration (EAA), and especially whether these are influenced by genetic or environmental factors, remain underexplored. We therefore quantified associations between the multi-ome comprising four layers—the proteome, metabolome, external exposome (here, sociodemographic factors), and specific exposome (here, lifestyle)—with six different EAA estimates. Two twin cohorts were used in a discovery-replication scheme, comprising, respectively, young (N = 642; mean age = 22.3) and older (N = 354; mean age = 62.3) twins. Within-pair twin designs were used to assess genetic and environmental effects on associations. We identified 40 multi-omic factors, of which 28 were proteins, associated with EAA in the young twins while adjusting for sex, smoking, and body mass index. Within-pair analyses revealed that genetic confounding influenced these associations heterogeneously, with six multi-omic factors —matrix metalloproteinase 9, complement component C6, histidine, glycoprotein acetyls, lactate, and neighborhood percentage of nonagenarians—remaining significantly associated with EAA, independent of genetic effects. Replication analyses showed that some associations assessed in young twins were consistent in older twins. Our study highlights the differential influence of genetic effects on the associations between the multi-ome and EAA and shows that some, but not all, of the associations persist into adulthood.

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A blood-based epigenetic clock for intrinsic capacity predicts mortality and is associated with clinical, immunological and lifestyle factors

Matías Fuentealba, Laure Rouch, Sophie Guyonnet, Jean-Marc Lemaitre, Philipe de Souto Barreto, Bruno Vellas, Sandrine Andrieu & David Furman

Age-related decline in intrinsic capacity (IC), defined as the sum of an individual's physical and mental capacities, is a cornerstone for promoting healthy aging by prioritizing maintenance of function over disease treatment. However, assessing IC is resource-intensive, and the molecular and cellular bases of its decline are poorly understood. Here we used the INSPIRE-T cohort (1,014 individuals aged 20–102 years) to construct the IC clock, a DNA methylation-based predictor of IC, trained on the clinical evaluation of cognition, locomotion, psychological well-being, sensory abilities and vitality. In the Framingham Heart Study, DNA methylation IC outperforms first-generation and second-generation epigenetic clocks in predicting all-cause mortality, and it is strongly associated with changes in molecular and cellular immune and inflammatory biomarkers, functional and clinical endpoints, health risk factors and lifestyle choices. These findings establish the IC clock as a validated tool bridging molecular readouts of aging and clinical assessments of IC.

How does biological age acceleration mediate the associations of obesity with cardiovascular disease? Evidence from international multi-cohort studies

Results

In CHARLS, the median follow-up period was 9.00 years, with a baseline age of 58 (52, 65) years. Obesity, KDM-BAacc, and CVD were all significantly associated with each other. For each 1-year increase in KDM-BAacc, the risk of incident stroke, heart disease and CVD increased by 68% (*OR* 1.68, 95% *CI* 1.35–2.09), 35% (*OR* 1.35, 95% *CI* 1.15–1.59), and 44% (*OR* 1.44, 95% *CI* 1.25–1.65), respectively. KDM-BAacc mediated the associations between BMI, WC, WtHR, BRI, CVAI, LAP, TyG-BMI, TyG-WC, TyG-WtHR, with CVD, with the mediation proportions ranging from 10.03 to 25.46%. However, the mediating effect was significant mostly in middle-aged individuals aged 45–65 years. Furthermore, sex differences existed in the mediation mechanisms. Biological age acceleration strongly mediated body shape indices and incident CVD in males, whereas in females, it predominantly mediated visceral fat accumulation and metabolic function dimensions with incident CVD. Similar main results were found in UKB and HEHEC.

Conclusions

Biological age acceleration partially mediates the relationship between obesity and incident CVD. This temporal evidence firstly validated the mediation pathway based on international cohorts, emphasizing the importance of addressing biological aging processes in population aged 45–65 years while providing sex-specific obesity intervention strategies to prevent CVD.

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PREPRINT

Pasta, an age-shift transcriptomic clock, maps the chemical and genetic determinants of aging and rejuvenation

Jerome Salignon, Maria Tsiokou, Patricia Marques, Enriqueta Rodriguez-Diaz, Hazel Ang, Federico Pietrocola, Christian G. Riedel

As the prevalence of age-related diseases rises, understanding and modulating the aging process is becoming a priority. Transcriptomic aging clocks (TACs) hold great promise for this endeavor, yet most are hampered by platform or tissue specificity and limited accessibility. Here, we introduce Pasta, a robust and broadly applicable TAC based on a novel age-shift learning strategy. Pasta accurately predicts relative age from bulk, single-cell, and microarray data, capturing senescent and stem-like cellular states through signatures enriched in p53 and DNA damage response pathways. Its predictions correlate with tumor grade and patient survival, underscoring clinical relevance. Applied to the CMAP L1000 dataset, Pasta identified known and novel age-modulatory compounds and genetic perturbations, and highlighted mitochondrial translation and mRNA splicing as key determinants of the cellular propensity for aging and rejuvenation, respectively. Supporting Pasta's predictive power, we validated pralatrexate as a potent senescence inducer and piperlongumine as a rejuvenating agent. Strikingly, chemotherapy drugs were highly enriched among pro-aging hits. Taken together, Pasta represents a powerful and generalizable tool for aging research and therapeutic discovery, distributed as an easy-to-use R package on GitHub.

Nuclear Import Defects Drive Cell Cycle Dysregulation in Neurodegeneration

Jonathan Plessis-Belair, Taylor Russo, Markus Riessland, Roger B. Sher

Neurodegenerative diseases (NDDs) and other age-related disorders have been classically defined by a set of key pathological hallmarks. Two of these hallmarks, cell cycle dysregulation (CCD) and nucleocytoplasmic transport (NCT) defects, have long been debated as being either causal or consequential in the pathology of accelerated aging. Specifically, aberrant cell cycle activation in post-mitotic neurons has been shown to trigger neuronal cell death pathways and cellular senescence. Additionally, NCT has been observed to be progressively dysregulated during aging and in neurodegeneration, where the increased subcellular redistribution of nuclear proteins, such as TAR DNA-Binding Protein-43 (TDP-43), to the cytoplasm is a primary driver of disease. However, the functional significance of NCT defects as either a causal mechanism or consequence of pathology, and how the redistribution of cell cycle machinery contributes to neurodegeneration, remains unclear. Here, we describe that pharmacological inhibition of importin-β nuclear import is capable of perturbing cell cycle machinery both in mitotic neuronal cell lines and post-mitotic primary neurons in vitro. Our *Nemf*^{R86S} mouse model of motor neuron disease, characterized by nuclear import defects, further recapitulates the hallmarks of CCD we observed in mitotic cell lines and in post-mitotic primary neurons in vitro, and in spinal motor neurons in vivo. The observed CCD is consistent with the transcriptional and phenotypical dysregulation commonly associated with neuronal cell death and senescence-like features in NDDs. Together, this evidence suggests that impairment of nuclear import pathways resulting in CCD may be a common driver of pathology in neurodegeneration.

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The pace and shape of ant ageing

Luisa M. Jaimes-Nino ✉, Jan Oettler

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ABSTRACT

Ants have been proposed as good models to study ageing and the effects of extrinsic mortality because of their long lifespans and plasticity of ageing within species. We discuss how age-dependent extrinsic mortality might influence queen lifespan, and how the effect of age-independent extrinsic mortality needs further study, accounting for different density-dependence scenarios. Based on a critical review of the available demographic data, we discuss the selective forces underlying ant ageing. We discuss differences and similarities between the life-history strategy of ants and the reproductive strategies iteroparity and semelparity. We consider how late-life fitness gains for the "superorganism" select for a delay of actuarial, and reproductive senescence, and we suggest future research directions.

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Variable Gene Copy Number in Cancer-Related Pathways Is Associated With Cancer Prevalence Across Mammals

Sophie Matthews , Vahid Nikoonejad Fard , Marc Tollis , Cathal Seoighe

Cancer is a disease of multicellularity, observed across the tree of life. In principle, animals with larger body sizes and longer lifespans should be at increased risk of developing cancer. However, there is no strong relationship between these traits and cancer across mammals. Previous studies have proposed that increased copy number of cancer-related genes may enhance the robustness of cancer suppression pathways in long-lived mammals, but these studies have not extended beyond known cancer-related genes. In this study, we conducted a phylogenetic generalized least squares analysis to test for associations between copy number of all protein-coding genes and longevity, body size, and cancer prevalence across 94 species of mammals. In addition to investigating the copy number of individual genes, we tested sets of related genes for a relationship between the aggregated gene copy number of the set and these traits. We did not find strong evidence to support the hypothesis that adaptive changes in gene copy number contribute to the lack of correlation between cancer prevalence and body size or lifespan. However, we found several biological processes where aggregate copy number was associated with malignancy rate. The strongest association was for the gene set relating to transforming growth factor beta, a cytokine that plays a role in cancer progression. Overall, this study provides a comprehensive evaluation of the role of gene copy number in adaptation to body size and lifespan and sheds light on the contribution of gene copy number to variation in cancer prevalence across mammals.

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PREPRINT

Levels of telomerase in cancer are contingent on senescence and inflammation at bulk tissue and single-cell spatial resolution

Telomerase activity plays a critical role in tumor growth and is quantified based on its level of expression. However, how these levels are associated with different pathways across various cancer types remains elusive due to the lack of a classification schema. Here, we defined an unsupervised learning metric for the quantitative measurement of telomerase activity and robustly classified the samples into low and high telomerase groups across different cancers. Using this classification system, we analyzed the data for over 9000 bulk tumors, single cells, and spatially organized tissues, and we found that telomerase high groups across the majority of cancers are strongly associated with genomic instability. On the contrary, lower group of telomerase across various cancers are significantly associated with cellular senescence, inflammation, ROS, and MAPK pathway activities. Cellular senescence, a hallmark of cellular aging, was dominant in older adults over the high telomerase levels in the majority of cancers, normal tissues, and human development phases. Our study comprehensively illustrates that lower levels of telomerase are associated with senescence-phenotype in the majority of cancers, which is strongly favorable for better survival outcomes.

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PREPRINT

Telomeric antisense oligonucleotides reduce premature aging phenotypes in telomerase mutant zebrafish

Giulia Allavena, Francesca Rossiello, Aurora Irene Idilli, Marina Mione, Fabrizio d'Adda di Fagagna, Miguel Godinho Ferreira, Bruno Lopes-Bastos

Telomerase activity is restricted in somatic cells, resulting in progressive telomere shortening. Telomere erosion eventually activates the DNA damage response (DDR), inducing cell-cycle arrest and cellular senescence or apoptosis. We previously reported that telomere dysfunction induces the transcription of telomeric non-coding RNAs (tncRNAs) which are critical mediators of DDR activation. Blocking tncRNAs with telomeric antisense oligonucleotides (tASOs) suppresses in vivo DDR signaling and its downstream effects. Here, we show that tASO-mediated inhibition of telomeric DDR in second-generation *tert*−/− zebrafish embryos with critically short telomeres leads to improved developmental outcomes and rescues premature aging phenotypes, including enhanced survival. Notably, a single tASO treatment administered at the one-cell stage of first-generation *tert*−/− embryos leads to enhanced fertility observed in 6-month-old adults. Overall, these findings demonstrate that tASO-based inhibition of telomeric DDR is sufficient to effectively rescue premature aging phenotypes in zebrafish.

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PREPRINT

Ultradeep N-glycoproteome Atlas of Mouse Reveals Spatiotemporal Signatures of Brain Aging and Neurodegenerative Diseases

The current depth of site-specific N-glycoproteomics is insufficient to fully characterize glycosylation events in biological samples. Herein, we achieved an ultradeep and precision analysis of the N-glycoproteome of mouse tissues by integrating multiple workflows. The largest N-glycoproteomic dataset to date was established on mice, which contained 91,972 precursor glycopeptides, 62,216 glycoforms, 8,939 glycosites and 4,563 glycoproteins. The database consisted of 6.8 million glyco-spectra (containing oxonium ions), among which 160,928 were high-quality spectra with confident N-glycopeptide identifications. The large-scale and high-quality dataset enhanced the performance of current artificial intelligence models for glycopeptide tandem spectrum prediction. Using this ultradeep dataset, we observed tissue specific microheterogeneity and functional implications of protein glycosylation in mice. Furthermore, the region-resolved brain N-glycoproteomes for Alzheimer's Diseases, Parkinson Disease and aging mice revealed the spatiotemporal signatures and distinct pathological functions of the N-glycoproteins. A comprehensive database resource of experimental N-glycoproteomic data from this study and previous literatures were further established. This N-glycoproteome atlas serves as a promising tool for revealing the role of protein glycosylation in biological systems.

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Multisystem failure, tipping points, and risk of Alzheimer's disease

Introduction: Medical conditions including obesity, diabetes, hyperlipidemia, and depression significantly increased risk of Alzheimer's disease (AD). However, effect of their duration, influenced by non-modifiable factors like chromosomal sex and apolipoprotein E (APOE) genotype, remains unclear.

Methods: Data from 5644 UKBiobank participants were analyzed using Cox regression model to identify critical tipping points based on age of onset, risk factor (RF) duration and their interaction with sex and APOE genotype.

Results: Hypertension or diabetes before age 62 exerted greater AD risk than APOEε4 alone. Obesity before age 62 increased AD risk by 54%, with the risk nearly tripling between ages 62-72. Hyperlipidemia and depression were associated with age-independent risk increases of 33% and 69%, respectively. After age 72, APOEε4 became the dominant RF.

Discussion: Duration of AD-risk-factors can have a greater impact than APOEε4. Identification of critical age-related tipping points highlights temporal dynamics of AD progression and role of multisystem failure in AD progression.

Highlights: AD risk factors impact AD onset, especially diagnosed between ages 62 and 72. Later diagnoses of hypertension, diabetes, and obesity delayed AD onset. Hyperlipidemia and depression increased AD risk by 33% and 69%, age-independent. APOEε4 carriers regardless of sex exhibited a higher risk increasing with age. Trajectories differed between APOEε4 carriers and non-carriers across sex.

Keywords: AD prevention strategies; AD-risk-factors; APOE genotype; Alzheimer's disease (AD); Cox proportional hazard model (CPHM); UK Biobank; chromosomal sex; depression; hyperlipidemia (HLP); hypertension (HTN); late onset Alzheimer's disease (LOAD); modifiable risk factors; obesity; type 2 diabetes (T2D); unmodifiable risk factors.

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PREPRINT

Spatiotemporal profiling reveals the impact of caloric restriction on mammalian brain aging

Aging induces functional declines in the mammalian brain, increasing its vulnerability to cognitive impairments and neurodegenerative disorders. Among various interventions to slow the aging process, caloric restriction (CR) has consistently demonstrated the ability to extend lifespan and enhance brain function across different species. Yet the precise molecular and cellular mechanisms by which CR benefits the aging brain remain elusive, especially at region-specific and cell type-specific resolution. In this study, we performed spatiotemporal profiling of mouse brains to elucidate the detailed mechanisms driving the anti-aging effects of CR. Utilizing highly scalable single-nucleus genomics and spatial transcriptomics platforms, *EasySci* and *IRISeq*, we profiled over 500,000 cells from 36 mouse brains across three age groups and conducted spatial transcriptomic analysis on twelve brain sections from aged mice under CR and control conditions. This comprehensive approach allowed us to explore the impact of CR on over 300 cellular states and assess region-specific molecular alterations. Our findings reveal that CR effectively modulates key aging-associated changes, notably by delaying the expansion of inflammatory cell populations and preserving cells critical to the neurovascular system and myelination pathways. Moreover, CR significantly reduced the expression of aging-associated genes involved in oxidative stress, unfolded protein stress, and DNA damage stress across various cell types and regions. A notable reduction in senescence-associated genes and restoration of circadian rhythm genes were observed, particularly in ventricles and white matter. Furthermore, CR exhibited region-specific restoration in genes linked to cognitive function and myelin maintenance, underscoring its targeted effects on brain aging. In summary, the integration of single-nucleus and spatial genomics provides a novel framework for understanding the complex effects of anti-aging interventions at the cellular and molecular levels, offering potential therapeutic targets for aging and neurodegenerative diseases.

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NF-κB-mediated developmental delay extends lifespan in *Drosophila*

Ping Kang, Peiduo Liu, Yanhui Hu, +14, and Hua Bai Authors Info & Affiliations

Developmental time (or time to maturity) strongly correlates with an animal's maximum lifespan, with late-maturing individuals often living longer. However, the genetic mechanisms underlying this phenomenon remain largely unknown. This may be because most previously identified longevity genes regulate growth rate rather than developmental time. To address this gap, we genetically manipulated prothoracicotropic hormone (PTTH), the primary regulator of developmental timing in *Drosophila*, to explore the genetic link between developmental time and longevity. Loss of *PTTH* delays developmental timing without altering the growth rate. Intriguingly, *PTTH* mutants exhibit extended lifespan despite their larger body size. This lifespan extension depends on ecdysone signaling, as feeding 20-hydroxyecdysone to *PTTH* mutants reverses the effect. Mechanistically, loss of *PTTH* blunts age-dependent chronic inflammation, specifically in fly hepatocytes (oenocytes). Developmental transcriptomics reveal that NF-κB signaling activates during larva-to-adult transition, with PTTH inducing this signaling via ecdysone. Notably, time-restricted and oenocyte-specific silencing of *Relish* (an NF-κB homolog) at early 3rd instar larval stages significantly prolongs adult lifespan while delaying pupariation. Our study establishes an aging model that uncouples developmental time from growth rate, highlighting NF-κB signaling as a key developmental program in linking developmental time to adult lifespan.

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PREPRINT

Unveiling the Biochemical Mechanisms of Aging and the Implications of Oxidative Stress on Cellular Senescence through Multi-Omics Analysis of Fibroblasts

Rajarshi Mandal, Ning Xie, Gil Alterovitz

This research investigates the complex biochemical mechanisms underlying aging by analyzing primary human fibroblasts using a longitudinal multi-omics dataset. This dataset includes cytology, DNA methylation and epigenetic clocks, bioenergetics, mitochondrial DNA sequencing, RNA sequencing, and cytokine profiling. Key findings indicate that mitochondrial efficiency declines with age, while glycolysis becomes more prevalent to compensate for energy demands. Epigenetic clocks, such as Hannum and PhenoAge, showed strong correlations with biological age ($\rho > 0.650$, $p < 1e\text{-}6$), validating the experimental setup and confirming that the cultured fibroblasts were aging appropriately. Fibroblasts with SURF1 mutations exhibited accelerated aging, marked by bioenergetic deficits, increased cell volume, and reduced proliferative capacity, underscoring the pivotal role of mitochondrial dysfunction in cellular senescence. Novel insights were gained from analyzing cytokines like IL18 and PCSK9, some of which were linked to age-related diseases such as Alzheimer's and cardiovascular disorders.

Experimental treatments revealed distinct effects on cellular aging. Dexamethasone reduced inflammation but also increased DNA methylation, induced metabolic inefficiencies, and shortened cellular lifespan. Oligomycin heightened oxidative stress and RNA degradation, emphasizing how such treatments contribute to cellular stress and metabolic imbalance while shedding light on aging mechanisms. By uncovering connections between mitochondrial dysfunction, epigenetic biomarkers, and immune dysregulation, this study identifies potential therapeutic targets for age-related diseases. Future research could validate the most promising biomarkers across diverse cell types and experimental treatments to build a more comprehensive understanding of aging.

Modifiable Risk Factors and Attributable Burden of Cardiac Arrest: An Exposome-wide and Mendelian Randomization Analysis

Huihuan Luo, PhD · Qingli Zhang, PhD · Lu Zhou, MS · Anni Li, BA · Haidong Kan, PhD · Renjie Chen, PhD

Background

In this study, we aimed to identify nonclinical modifiable risk factors associated with sudden cardiac arrest (SCA) incidence, and to assess attributable burden.

Methods

Data on 125 potentially modifiable risk factors were extracted from the UK Biobank cohort. An exposome-wide association study was conducted using a Cox proportional hazard model, followed by validation of significant associations using Mendelian randomization to identify causal relationships. The attributable burden of SCA was evaluated on the basis of improvements in unfavourable profiles. We also evaluated the attributable burden to be eliminated via improvement of unfavourable profiles.

Results

Of 502,094 individuals, 3147 developed SCA during a median follow-up duration of 13.8 years. SCA was associated with 56 risk factors spanning lifestyles, physical measures, psychosocial factors, socioeconomic status, and the local environment. Mendelian randomization analysis confirmed protective effects associated with 2 factors (ie, higher rates of consumption of champagne and/or white wine and fruit intake) and adverse effects associated with 7 factors (ie, time spent using the computer, fed-up feelings, greater arm fat mass and percentage, body mass index, systolic blood pressure, and lower education level). Between 40% (conservative elimination) and 63% (thorough elimination) of SCA cases could be prevented by improving unfavourable profiles, with lifestyle modifications accounting for the largest proportion of preventable cases, followed by improvements in physical measures, psychosocial factors, socioeconomic status, and the local environment.

Conclusions

This large-scale, prospective cohort study offers compelling evidence on the profile of modifiable risk factors and the attributable burden of SCA.

Multivitamins After Myocardial Infarction in Patients With Diabetes

A Randomized Clinical Trial

Francisco Ujueta, MD, MS[1]; Gervasio A. Lamas, MD[2]; Kevin J. Anstrom, PhD[3]; et al

Interventions Six caplets daily of a 28 component OMVM or matching OMVM placebo, and 40 weekly infusions of an EDTA-based chelation solution or matching placebo, in a 1:1:1:1 allocation ratio.

Main Outcomes and Measures The primary end point was the composite of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina.

Results A total of 1000 participants were randomized (500 in the active OMVM group and 500 in the placebo group). The median (IQR) age was 67 (60-72) years, and 730 (73%) were male. Median (IQR) follow-up was 48 (34-58) months. The primary end point occurred in 175 participants (35%) in the active OMVM group and 175 (35%) in the placebo group (hazard ratio [HR], 0.99 [95% CI, 0.80-1.22]; $P = .92$). The 5-year event rate for the primary end point in the EDTA chelation + active OMVM group was 34.0%; in the EDTA chelation + placebo OMVM group, 35.7%; in the placebo infusion + active OMVM group, 36.0%; and in the placebo infusion + placebo OMVM group, 34.3%. The comparison of the active infusion + active OMVM with the placebo infusion + placebo OMVM was not significant (HR, 0.91 [95% CI, 0.67-1.23]; $P = .54$). Although nonsignificant, there was a numerically higher event rate of MI, stroke, mortality from cardiovascular causes in the active OMVM compared to placebo OMVM group.

Conclusions and Relevance The results of this randomized clinical trial demonstrated that, for participants with chronic coronary disease, diabetes, and a previous MI, high-dose OMVM alone or in conjunction with EDTA-based chelation did not reduce cardiovascular events.

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Blue Zone, a Demographic Concept and Beyond

Michel Poulain [1], Anne Herm [1]

Affiliations + expand

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Abstract

The concept of Blue Zone (BZ) refers to regions with exceptionally high concentrations of centenarians, often in good health. Four BZs have been validated, Okinawa (Japan), Sardinia (Italy), Nicoya (Costa Rica), and Ikaria (Greece), with Martinique recently emerging as the fifth. Despite their popularity, BZs face criticism regarding data reliability, particularly the accuracy of centenarians' ages. This article reviews the process used to identify a BZ through a three-step methodology. First, it outlines the strict age validation procedures used to confirm longevity claims. Second, it reviews key demographic indicators to assess population longevity. Third, it defines BZ criteria, using the Sardinian BZ as a reference and requiring the eligible area to show a longevity level at least 50% higher than the national average. Martinique meets these criteria, while Galicia's validation is still ongoing. The study also highlights core longevity factors-diet, physical activity, social support, and environment-and underscores the importance of adopting the 7 BZ principles to foster longer, healthier lives worldwide. The BZ thus remains a valuable model for understanding the impact of lifestyle on aging and for applying these insights in public health and lifestyle medicine strategies.

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High diversity of dietary flavonoid intake is associated with a lower risk of all-cause mortality and major chronic diseases

Benjamin H. Parmenter, Alysha S. Thompson, Nicola P. Bondonno, Amy Jennings, Kevin Murray, Aurora Perez-Cornago, Jonathan M. Hodgson, Anna Tresserra-Rimbau, Tilman Kühn ✉ & Aedín Cassidy ✉

Higher habitual intakes of dietary flavonoids have been linked with a lower risk of all-cause mortality and major chronic disease. Yet, the contribution of diversity of flavonoid intake to health outcomes remains to be investigated. Here, using a cohort of 124,805 UK Biobank participants, we show that participants who consumed the widest diversity of dietary flavonoids, flavonoid-rich foods and/or specific flavonoid subclasses had a 6–20% significantly lower risk of all-cause mortality and incidence of cardiovascular disease, type 2 diabetes, cancer, respiratory disease and neurodegenerative disease. Furthermore, we report that both quantity and diversity of flavonoids are independent predictors of mortality and several chronic diseases, suggesting that consuming a higher quantity and wider diversity is better for longer-term health than either component alone. These findings suggest that consuming several different daily servings of flavonoid-rich foods or beverages, such as tea, berries, apples, oranges or grapes, may lower risk of all-cause mortality and chronic disease.

Causal impact of genetically-determined fish and fish oil intake on epigenetic age acceleration and related serum markers

Methods

Bidirectional Mendelian randomization was performed in the two-sample setting with publicly available GWAS summary statistics. GWAS data from the UK Biobank for oily fish consumption (n = 460,443) and fish oil supplementation (n = 461,384) were used as the primary exposures. First-generation epigenetic clocks Hannum age and intrinsic epigenetic age acceleration (IEAA), as well as second-generation clocks GrimAge and PhenoAge were collected from an independent dataset of individuals of European ancestry (n = [34,449–34,667]). Finally, data from the Integrative Epidemiology Unit database was used for serum proxies of lipidemia and systemic inflammation (n = [61,308–78,700]). Additional sensitivity analyses, such as reverse causation testing and the Cochran's Q test were performed for exposure-outcome pairs where the inverse variance weighted (IVW) method was significant (p-value < 0.05), and where the MR Egger method indicated an effect in the same direction as the IVW result.

Results

We report that oily fish consumption appears to decrease PhenoAge acceleration ($p < 0.0086$), whereas fish oil supplementation appears to decrease GrimAge ($p = 0.037$). Both omega-3 exposures modify the epigenetic clocks in the expected negative, or age-decelerating, direction. For the serum biomarkers, we find evidence that fish oil consumption leads to a reduction in triglycerides ($p = 0.004$), although HDL and LDL were not significantly modified. Finally, we also detected a suggestive inverse relationship between oily fish consumption and hsCRP ($p = 0.064$).

Conclusions

Our analysis shows that consuming fish oil, whether through whole food or as a supplement, can have a rejuvenating impact as measured by PhenoAge and GrimAge acceleration. We have also provided evidence further linking fish oil intake and lower triglyceride levels. These results, based on robust MR-based analyses, emphasize the effectiveness of dietary choices in modifying emerging measures of healthspan.

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Spicy food consumption and biological aging across multiple organ systems: a longitudinal analysis from the China Multi-Ethnic cohort

Background: Biological aging is a common starting point for many chronic diseases and multimorbidity. Spicy food consumption is showing a growing trend worldwide. However, the association of spicy food consumption with the comprehensive biological age (BA) and organ-specific BAs remains unclear.

Methods: This study included 7874 participants from the China Multi-Ethnic Cohort (CMEC), all participating in baseline and follow-up surveys. The CMEC was located in Southwest China, which has become one of the most prominent and typical regions regarding spicy food consumption in China and the world. We constructed comprehensive BA and organ-specific BAs based on composite indicators using the widely validated Klemera-Doubal method. The frequency of intake of spicy food was obtained by an electronic questionnaire. Follow-up analyses adjusted for baseline data were then employed to assess the longitudinal associations of spicy food consumption at baseline with both the comprehensive BA and the organ-specific BAs at follow-up.

Results: Compared with non-spicy consumers, spicy consumers showed a decrease in comprehensive BA acceleration, with adjusted β = -0.23 (- 0.60 to 0.13) for 1-2 days/week, β = -0.69 (- 1.10 to - 0.29) for 3-5 days/week and - 0.32 (- 0.63 to - 0.01) years for 6-7 days/week, respectively. Higher estimates were observed for metabolic and kidney BA accelerations than for cardiopulmonary and liver BA accelerations. Compared to non-spicy consumers, spicy consumers showed a decrease in metabolic BA acceleration (3-5 days/week: β = -0.76 (- 1.28 to - 0.24) years) and kidney BA acceleration (3-5 days/week: β = -1.89 (- 2.76 to - 1.02) years).

Conclusion: Spicy foods may have potential benefits for biological aging. Our findings highlight that spicy foods may slow comprehensive and organ-specific biological aging, especially metabolic and kidney biological aging.

C. elegans aging research

Hyperactivation of mTORC1 by an endogenous *raga-1* gain-of-function mutation does not reduce lifespan in *C. elegans*

Tatiana M Moreno [1], Michelle E Brown [2], Caroline Kumsta [2]

Inhibition of mTORC1, a conserved nutrient-sensing complex, extends lifespan across model organisms, but the effects of mTORC1 hyperactivation are less understood. RagA, a GTPase essential for mTORC1 activation, can be locked in its active GTP-bound state through gain-of-function mutations, such as Q63L in *C. elegans* RAGA-1. We found that transgenic expression of *raga-1[Q63L]* mutation (*egIs12*) decreases lifespan without hyperactivating mTORC1, suggesting mTORC1-independent effects or transgene toxicity. In contrast, we show that a CRISPR-generated Q63L mutation at the endogenous *raga-1* locus (*viz128)* hyperactivates mTORC1 without affecting lifespan, challenging the paradigm that mTORC1 hyperactivation accelerates aging. Thus, genetic context and potential compensatory mechanisms may contribute to mTORC1-mediated lifespan regulation, at least in metazoans.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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New Journal

Geromedicine is a quarterly, gold open-access journal published by Science Exploration Press, offering a comprehensive platform for research in geroscience. Progress in geroscience - the study of aging - has laid the foundation for geromedicine, which focuses on evidence-based medical interventions to keep individuals and populations healthy and fit. Precision geromedicine will rely on aging biomarkers to assess an individual's biological aging process (gerodiagnosis) and apply targeted interventions to enhance health and longevity... more >

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The vocabulary of geromedicine: gerovocabulary

Guido Kroemer, ... Andrea B. Maier

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Geromedicine: A new journal for the clinical application of geroscience

Guido Kroemer, ... Andrea B. Maier

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Editorial

Rethinking healthcare through aging biology

Marco Demaria[1]

Modern medicine has revolutionized the way we diagnose and treat diseases, achieving remarkable success in extending life expectancy. Yet, despite these advances, the traditional disease-centric healthcare model has significant limitations. This approach typically kicks in only after pathology has manifested—when patients exhibit symptoms, seek treatment, receive a diagnosis, and begin therapy. While reactive care has its merits, it increasingly falls short in addressing the needs of aging populations. As people age, they often develop a constellation of chronic conditions—multimorbidity—that strains the healthcare system and diminishes quality of life. Conditions such as cardiovascular disease, type 2 diabetes, osteoarthritis, neurodegeneration, and cancer frequently coexist, leading to complex and often ineffective treatments. Polypharmacy—the use of multiple medications to treat co-existing diseases—introduces further complications, including drug interactions, side effects, reduced adherence to treatment regimens, and increased hospitalizations.

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Replacement as an aging intervention

Sierra Lore, Jesse R. Poganik, Anthony Atala, George Church, Vadim N. Gladyshev, Morten Scheibye-Knudsen & Eric Verdin

Substantial progress in aging research continues to deepen our understanding of the fundamental mechanisms of aging, yet there is a lack of interventions conclusively shown to attenuate the processes of aging in humans. By contrast, replacement interventions such as joint replacements, pacemaker devices and transplant therapies have a long history of restoring function in injury or disease contexts. Here, we consider biological and synthetic replacement-based strategies as aging interventions. We discuss innovations in tissue engineering, such as the use of scaffolds or bioprinting to generate functional tissues, methods for enhancing donor–recipient compatibility through genetic engineering and recent progress in both cell therapies and xenotransplantation strategies. We explore synthetic approaches including prostheses, external devices and brain–machine interfaces. Additionally, we evaluate the evidence from heterochronic parabiosis experiments in mice and donor–recipient age-mismatched transplants to consider whether systemic benefits could result from personalized replacement approaches. Finally, we outline key challenges and future directions required to advance replacement therapies as viable, scalable and ethical interventions for aging.

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Beyond genes and environment: mapping biological stochasticity in aging

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Affiliations + expand

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Abstract

Aging is characterized by extensive variability in the onset of morbidity and mortality, even in genetically identical populations with carefully controlled environments. This points to the important role stochasticity plays in shaping the divergent aging process between individual organisms. Here, we survey how stochastic factors at the level of molecules, cells, tissues, and organisms manifest in and impact the aging process, with a focus on the nematode Caenorhabditis elegans. Findings of stochasticity in C. elegans give additional insights for aspects of aging in the more complex settings of mammals with parallels drawn between organisms when appropriate. The emerging understanding of the stochastic contributors to longevity will enhance research strategies and medical interventions for personalized medicine.

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Impacts of systemic milieu on cerebrovascular and brain aging: insights from heterochronic parabiosis, blood exchange, and plasma transfer experiments

Aging is a complex biological process that detrimentally affects the brain and cerebrovascular system, contributing to the pathogenesis of age-related diseases like vascular cognitive impairment and dementia (VCID) and Alzheimer's disease (AD). While cell-autonomous mechanisms that occur within cells, independent of external signals from neighboring cells or systemic factors, account for some aspects of aging, they cannot explain the entire aging process. Non-autonomous, paracrine and endocrine, pathways also play a crucial role in orchestrating brain and vascular aging. The systemic milieu modulates aging through pro-geronic and anti-geronic circulating factors that mediate age-related decline or confer rejuvenative effects. This review explores the impact of systemic factors on cerebrovascular and brain aging, with a particular focus on findings from heterochronic parabiosis, blood exchange, and plasma transfer experiments. We discuss how these factors influence fundamental cellular and molecular processes of aging and impact cerebrovascular endothelial function, neurovascular coupling mechanisms, blood–brain barrier integrity, neuroinflammation, capillary density, and amyloid pathologies, with significant consequences for cognitive function. Additionally, we address the translational potential and challenges of modifying the systemic milieu to promote brain health and prevent age-related cognitive impairment.

In-silico evaluation of aging-related interventions using omics data and predictive modeling

Georg Fuellen [1], Daniel Palmer [2], Claudia Fruijtier [3], Roberto A Avelar [2]

A major challenge in aging research is identifying interventions that can improve lifespan and health and minimize toxicity. Clinical studies cannot usually consider decades-long follow-up periods, and therefore, in-silico evaluations using omics-based surrogate biomarkers are emerging as key tools. However, many current approaches train predictive models on observational data, rather than on intervention data, which can lead to biased conclusions. Yet, the first classifiers for lifespan extension by compounds are now available, learned on intervention data. Here, we review evaluation methodologies and we prioritize training on intervention data whenever available, highlight the importance of safety and toxicity assessments, discuss the role of standardized benchmarks, and present a range of feature processing and predictive modeling approaches. We consider linear and non-linear methods, automated machine learning workflows, and use of AI. We conclude by emphasizing the need for explainable and reproducible strategies, the integration of safety metrics, and the careful validation of predictors based on interventional benchmarks.

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Telomeres as hallmarks of iPSC aging: A review on telomere dynamics during stemness and cellular reprogramming

Carlota Tavares-Marcos [1], Magda Correia [1], Bruno Bernardes de Jesus [2]

Telomeres, the protective ends of chromosome, are key to tissue repair and regeneration. Telomere shortening is linked to aging and age-related disorders, while excessive telomerase activity may support tissue regeneration or transformation. Some of the functions of telomeres and telomerase may be mediated by its important role in the process of stemness. Active telomerase, and subsequent telomerase-dependent telomere extension, supports stem-cells self-renewal and pluripotency - essential for tissue healing. During cellular reprogramming, differentiated cells are converted into induced pluripotent stem cells (iPSCs), which resemble embryonic stem cells. During iPSC derivation, telomere length is reset, enhancing iPSCs' regenerative potential. During this process, incomplete telomerase activation and telomere extension can lead to genomic instability and/or haltered cell functionality. Understanding the intricate relation of telomeres, telomerase and stemness may be critical when designing novel cell-based therapies targeting degenerative diseases or to unlock strategies to delay aging. Here, we explore the recent bibliography linking these areas, raising awareness of their important when designing novel breakthroughs in health and longevity.

Meta-epigenetic shifts in T cell aging and aging-related dysfunction

Lorène Rousseau [# 1 2], Karina L Hajdu [# 1 2], Ping-Chih Ho [3 4]

Epigenetic regulation, including DNA methylation and histone modifications, play a pivotal role in shaping T cell functionality throughout life. With aging, these epigenetic changes profoundly affect gene expression, altering T cell plasticity, activation, and differentiation. These modifications contribute significantly to immunosenescence, increasing susceptibility to infections, cancer, and autoimmune diseases. In $CD8^+$ T cells, chromatin closure at key regulatory regions suppresses activation and migration, while chromatin opening in pro-inflammatory gene loci amplifies inflammation. These changes drive terminal differentiation, characterized by increased expression of senescence-associated markers, impaired migration and loss of epigenetic plasticity. $CD4^+$ T cells experience fewer but critical epigenetic alterations, including disrupted pathways, a skewed Th1/Th2 balance, and reduced Treg functionality. These epigenetic changes, compounded by metabolic dysfunctions, such as mitochondrial deficiency and oxidative stress, impair T-cell adaptability and resilience in the aging organism. Therefore, understanding the interplay between epigenetic and metabolic factors in T cell aging offers promising therapeutic opportunities to mitigate immunosenescence and enhance immune function in aging populations. This review explores the interplay between DNA methylation, histone alterations, and metabolic changes underlying T cell aging.

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Towards Precision Geromedicine in Singapore

Since the discovery that ageing is a modifiable process in animal models, significant advancements in geroscience have led to the emergence of the field of Precision Geromedicine, which aims to optimise health and healthspan by targeting ageing-related processes. Ageing-related diseases (ARDs), accounting for 80% of Singapore's disease burden in 2019, are on the rise as the nation approaches the "super-aged" status by 2030. In response, Singapore is reshaping its healthcare system to focus on healthy ageing, as seen in the launch of the Healthier SG initiative in 2023, which empowers citizens to manage their health proactively with support from over 1800 private general practices. Additionally, Singapore is investing in geroscience to build the foundations of Precision Geromedicine, aiming to integrate gerodiagnostics and gerotherapeutics into clinical practice. Leveraging its robust healthcare system, digital infrastructure, and socio-political stability, Singapore is well-positioned to become a model for addressing ARDs amidst global demographic shifts.

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Aging and Lifestyle Modifications for Preventing Aging-Related Diseases

Qiao Li [1 2], Heng Zhang [1 2], Nanyin Xiao [1 2], Guangyu Liang [1 2], Yan Lin [1 2], Xiao Yang [1 2], Jiankun Yang [1 2], Zonghao Qian [1 2], Yangguang Fu [1 2], Cuntai Zhang [2 3], Anding Liu [1 2]

Affiliations + expand

PMID: 40293686 DOI: 10.1096/fj.202402797RR

Abstract

The pathogenesis of various chronic diseases is closely associated with aging. Aging of the cardiovascular system promotes the development of severe cardiovascular diseases with high mortality, including atherosclerosis, coronary heart disease, and myocardial infarction. Similarly, aging of the nervous system promotes the development of neurodegenerative diseases, such as Alzheimer's disease, which seriously impairs cognitive function. Aging of the musculoskeletal system is characterized by decreased function and mobility. The molecular basis of organ aging is cellular senescence, which involves multiple cellular and molecular mechanisms, such as impaired autophagy, metabolic imbalance, oxidative stress, and persistent inflammation. Given the ongoing demographic shift toward an aging society, strategies to delay or reduce the effects of aging have gained significance. Lifestyle modifications, such as exercise and calorie restriction, are now recognized for their anti-aging effects, their capacity to reduce modification, their potential to prolong lifespan, and their capacity to lower the risk of cardiovascular disease. This review elucidates the molecular mechanisms and application significance of various anti-aging approaches at the molecular level, based on research progress in aging. It aims to provide a reference for the prevention and treatment of age-related diseases in progressively aging societies.

Protein-Restricted Diets and Their Impact on Metabolic Health and Aging

Sora Q Kim [1], Redin A Spann [1], Cristal M Hill [2], Claire E Berryman [1], Hans-Rudolf Berthoud [1], David H McDougal [1], Yanlin He [1], Heike Münzberg [1], Sangho Yu [1], Christopher D Morrison [1]

Recent improvements in human longevity have highlighted the challenge of maintaining health throughout extended lifespans. This review examines how organisms regulate nutrient intake and metabolism, focusing on dietary protein's unique role in health and longevity. While caloric restriction enhances longevity, adherence to a low-calorie diet is challenging. Protein restriction represents an alternate nutritional intervention that improves longevity and health in model organisms and may be easier to translate to humans. However, its impacts are complex, and its mechanisms are poorly understood. The beneficial effects of protein restriction on metabolism and longevity may come at a cost to lean mass and physical resilience. Conversely, while public health recommendations often emphasize high protein intake, human epidemiological data and work on model organisms suggest that excessive protein consumption correlates with increased mortality. Understanding this paradox is crucial for developing evidence-based protein intake recommendations that balance longevity with physical performance.

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Dietary and pharmacological energy restriction and exercise for healthspan extension

Maria Lastra Cagigas [1], Isabella De Ciutiis [1], Andrius Masedunskas [1], Luigi Fontana [2]

Affiliations + expand

PMID: 40318928 DOI: 10.1016/j.tem.2025.04.001

Abstract

Extending healthspan - the years lived in optimal health - holds transformative potential to reduce chronic diseases and healthcare costs. Dietary restriction (DR), particularly when combined with nutrient-rich diets and exercise, is among the most effective, evidence-based strategies for enhancing metabolic health and longevity. By targeting fundamental pathways, it mitigates the onset and progression of obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), neurodegeneration, and cancer. This review synthesizes human data on the impact of DR and exercise on metabolic and age-related diseases, while emphasizing key biological mechanisms such as nutrient sensing, insulin sensitivity, inflammation, mitochondrial function, and gut microbiota. We also examine the emerging role of pharmacologically induced DR, focusing on glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) that partially mimic DR and present opportunities for chronic disease prevention.

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Exercise Mimetics in Aging: Suggestions from a Systematic Review

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Affiliations + expand

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Abstract

Background/Objectives: Growth in the aging world population is accompanied by an increase in comorbidities, profoundly impacting the quality of life of older people. This development has motivated a large effort to investigate the mechanisms underlying aging and the search for countermeasures. The most investigated strategies envisage the control of diet and physical exercise, which exploit both common and distinct mechanisms to promote health. Since the application of nutritional and exercise protocols to aged persons introduces several issues due to their disabled state, some strategies have been developed. The nutritional approach exploits a wide range of compounds, including calorie restriction mimetics, supplements, antioxidants, and others. In the context of exercise, in recent years, molecules able to provide similar effects to exercise, the so-called exercise mimetics, have been developed. **Methods:** To have a better perspective on exercise mimetics and their connection with nutrition, we performed a systematic search of the PubMed and Scopus databases using the term "exercise mimetics". **Results:** In total, 97 research articles were selected and discussed. The present review provides evidence of the presence of multiple exercise-mimetic compounds and physical strategies that can target metabolic pathways, oxidative stress defense mechanisms, or myokine modulation. **Conclusions:** Interestingly, this review highlights that an important number of exercise mimetics are represented by products of natural origin and supplements assimilable with diet. This evidence provides a further link between exercise and nutrition and confers a central role on nutrition in the context of exercise mimetics.

SASP Modulation for Cellular Rejuvenation and Tissue Homeostasis: Therapeutic Strategies and Molecular Insights

by Saud Alqahtani [1], Taha Alqahtani [1], Krishnaraju Venkatesan [1,*], Durgaramani Sivadasan [2], Rehab Ahmed [3], Nizar Sirag [4], Hassabelrasoul Elfadil [3], Hanem Abdullah Mohamed [5,6], Haseena T.A. [7], Rasha Elsayed Ahmed [8,9], Pooja Muralidharan [10] and Premalatha Paulsamy [7]

Cellular senescence regulates aging, tissue maintenance, and disease progression through the Senescence-Associated Secretory Phenotype (SASP), a secretory profile of cytokines, chemokines, growth factors, and matrix-remodeling enzymes. While transient SASP aids wound healing, its chronic activation drives inflammation, fibrosis, and tumorigenesis. This review examines SASP's molecular regulation, dual roles in health and pathology, and therapeutic potential. The following two main strategies are explored: senescence clearance, which eliminates SASP-producing cells, and SASP modulation, which refines secretion to suppress inflammation while maintaining regenerative effects. Key pathways, including NF-κB, C/EBPβ, and cGAS-STING, are discussed alongside pharmacological, immunotherapeutic, gene-editing, and epigenetic interventions. SASP heterogeneity necessitates tissue-specific biomarkers for personalized therapies. Challenges include immune interactions, long-term safety, and ethical considerations. SASP modulation emerges as a promising strategy for aging, oncology, and tissue repair, with future advancements relying on multi-omics and AI-driven insights to optimize clinical outcomes.

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The cGAS–STING pathway in atherosclerosis

Si-Yu Wang [1 2], Yu-Shan Chen [1 3], Bo-Yuan Jin [1 2], Ahmad Bilal [1 2]

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Abstract

Atherosclerosis (AS), a chronic inflammatory disease, remains a leading contributor to cardiovascular morbidity and mortality. Recent studies highlight the critical role of the cGAS-STING pathway-a key innate immune signaling cascade-in driving AS progression. This pathway is activated by cytoplasmic DNA from damaged cells, thereby triggering inflammation and accelerating plaque formation. While risk factors such as aging, obesity, smoking, hypertension, and diabetes are known to exacerbate AS, emerging evidence suggests that these factors may also enhance cGAS-STING pathway, which amplifies inflammatory responses. Targeting this pathway offers a promising therapeutic strategy to reduce the burden of cardiovascular diseases (CVD). In this review, we summarize the mechanisms of the cGAS-STING pathway, explore its role in AS, and evaluate potential inhibitors as future therapeutic candidates. By integrating current knowledge, we aim to provide insights for developing novel treatments to mitigate AS and CVD burden.

Recent Advances in Aging and Immunosenescence: Mechanisms and Therapeutic Strategies

by Shuaiqi Wang [1], Tong Huo [1], Mingyang Lu [1], Yueqi Zhao [1], Jianmin Zhang [1,2], Wei He [1,*] and Hui Chen [1,2,*]

Cellular senescence is an irreversible state of cell cycle arrest. Senescent cells (SCs) accumulate in the body with age and secrete harmful substances known as the senescence-associated secretory phenotype (SASP), causing chronic inflammation; at the same time, chronic inflammation leads to a decrease in immune system function, known as immunosenescence, which further accelerates the aging process. Cellular senescence and immunosenescence are closely related to a variety of chronic diseases, including cardiovascular diseases, metabolic disorders, autoimmune diseases, and neurodegenerative diseases. Studying the mechanisms of cellular senescence and immunosenescence and developing targeted interventions are crucial for improving the immune function and quality of life of elderly people. Here, we review a series of recent studies focusing on the molecular mechanisms of cellular senescence and immunosenescence, the regulation of aging by the immune system, and the latest advances in basic and clinical research on senolytics. We summarize the cellular and animal models related to aging research, as well as the mechanisms, strategies, and future directions of aging interventions from an immunological perspective, with the hope of laying the foundation for developing novel and practical anti-aging therapies.

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Mesenchymal stem cells and their derivatives as potential longevity-promoting tools

Mesenchymal stem cells (MSCs) and blood plasma/MSC-derived extracellular vesicles (EVs) offer promising tools to promote longevity and treat age-related diseases. MSCs have low immunogenicity and tumorigenicity, and their efficacy is relatively independent of the donor age in humans (but not in rodents). Systemic administration of MSCs and stem cell/blood-derived EVs modified the omic profiles of various organs of aged rodents towards the young ones. The application of EVs appears to be even more beneficial than MSCs. Remarkably, over 70% of microRNAs, which are over-presented in ESC-derived EVs, were found to target longevity-associated genes. Along with MSCs, other types of stem cells were reported to display health- and lifespan-extending effects. Pluripotent Muse cells, a specific subpopulation of MSCs, which possess a number of unique features, could be particularly relevant for promoting healthspan. The rejuvenation potential of MSCs, EVs, and Muse cells warrants further investigation in both animal models and clinical trials, using aging clocks for biological age determination as one of the endpoints.

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A Critical Appraisal of the Utility of Targeting Therapy-Induced Senescence for Cancer Treatment

Tareq Saleh; Edward F. Greenberg; Anthony C. Faber; Hisashi Harada; David A. Gewirtz

Cancer chemotherapy and radiotherapy are rarely successful in eliminating the entire tumor population, often leaving behind a subpopulation of senescent cells that can contribute to disease recurrence. These senescent tumor cells also secrete various chemokines and cytokines that may be tumor promoting and immunosuppressive. Recognition of the deleterious impact of therapy-induced senescence has led to the preclinical development of senolytic compounds that eliminate senescent cells, representing a potential strategy to enhance the efficacy of conventional and targeted anticancer therapy. However, it remains uncertain whether this strategy can or will be translated to the clinic. This review provides a summary of the recent preclinical literature supporting the use of senolytics as an adjunct for cancer treatment, discusses the limitations associated with their use in the current preclinical models, and provides perspectives on the clinical development of senolytics in cancer treatment regimens. Overall, preclinical studies support the potential of senolytics to enhance efficacy and prolong the antitumor activity of current standard-of-care cancer therapies that promote senescence. However, further work is needed to develop optimal senolytic agents with the appropriate combination of properties for clinical testing, specifically, activity in the context of therapy-induced senescence with acceptable tolerability.

OTHER RESEARCH & REVIEWS

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Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease

Authors: Kiran Musunuru, M.D., Ph.D. , Sarah A. Grandinette, B.S., Xiao Wang, Ph.D., Taylor R. Hudson, M.S., Kevin Briseno, B.S., Anne Marie Berry, M.S., Julia L. Hacker, M.S., +37 , and Rebecca C. Ahrens-Nicklas, M.D., Ph.D. Author Info & Affiliations

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Summary

Base editors can correct disease-causing genetic variants. After a neonate had received a diagnosis of severe carbamoyl-phosphate synthetase 1 deficiency, a disease with an estimated 50% mortality in early infancy, we immediately began to develop a customized lipid nanoparticle–delivered base-editing therapy. After regulatory approval had been obtained for the therapy, the patient received two infusions at approximately 7 and 8 months of age. In the 7 weeks after the initial infusion, the patient was able to receive an increased amount of dietary protein and a reduced dose of a nitrogen-scavenger medication to half the starting dose, without unacceptable adverse events and despite viral illnesses. No serious adverse events occurred. Longer follow-up is warranted to assess safety and efficacy. (Funded by the National Institutes of Health and others.)

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Self-assembling protein nanoparticles for cytosolic delivery of nucleic acids and proteins

Intracellular delivery of biomacromolecules is hampered by low efficiency and cytotoxicity. Here we report the development of elastin-based nanoparticles for therapeutic delivery (ENTER), a recombinant elastin-like polypeptide (ELP)-based delivery system for effective cytosolic delivery of biomacromolecules in vitro and in vivo. Through iterative design, we developed fourth-generation ELPs fused to cationic endosomal escape peptides (EEPs) that self-assemble into pH-responsive micellar nanoparticles and enable cytosolic entry of cargo following endocytic uptake. In silico screening of α-helical peptide libraries led to the discovery of an EEP (EEP13) with 48% improved protein delivery efficiency versus a benchmark peptide. Our lead ELP–EEP13 showed similar or superior performance compared to lipid-based transfection reagents in the delivery of mRNA-encoded, DNA-encoded and protein-form Cre recombinase and CRISPR gene editors as well as short interfering RNAs to multiple cell lines and primary cell types. Intranasal administration of ELP–EEP13 combined with Cre protein achieved efficient editing of lung epithelial cells in reporter mice.