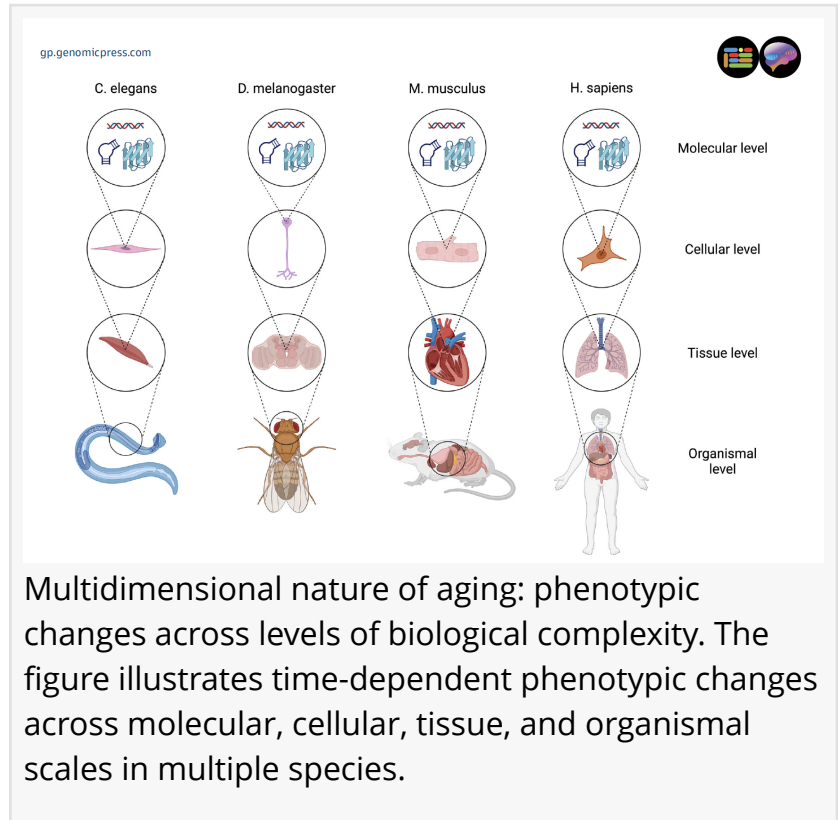


Scientists ask: If we eliminated age-related diseases, what would stop us from living decades longer?

New analysis from German researchers suggests conquering age-related diseases, not "aging" per se, holds the key to radical life extension

BONN, NRW, GERMANY, December 2, 2025 /EINPresswire.com/ -- A landmark review published today in [Genomic Psychiatry](#) challenges researchers to fundamentally reconsider how the field measures and conceptualizes biological aging. Dr. Dan Ehninger, who leads the Translational Biogerontology Laboratory at the German Center for Neurodegenerative Diseases, and Dr. Maryam Keshavarz present a systematic analysis arguing that widely used proxies for aging, including lifespan extension, epigenetic clocks, frailty indices, and even the celebrated hallmarks of aging framework, may conflate genuine modifications of aging trajectories with simpler age-independent effects on physiology.

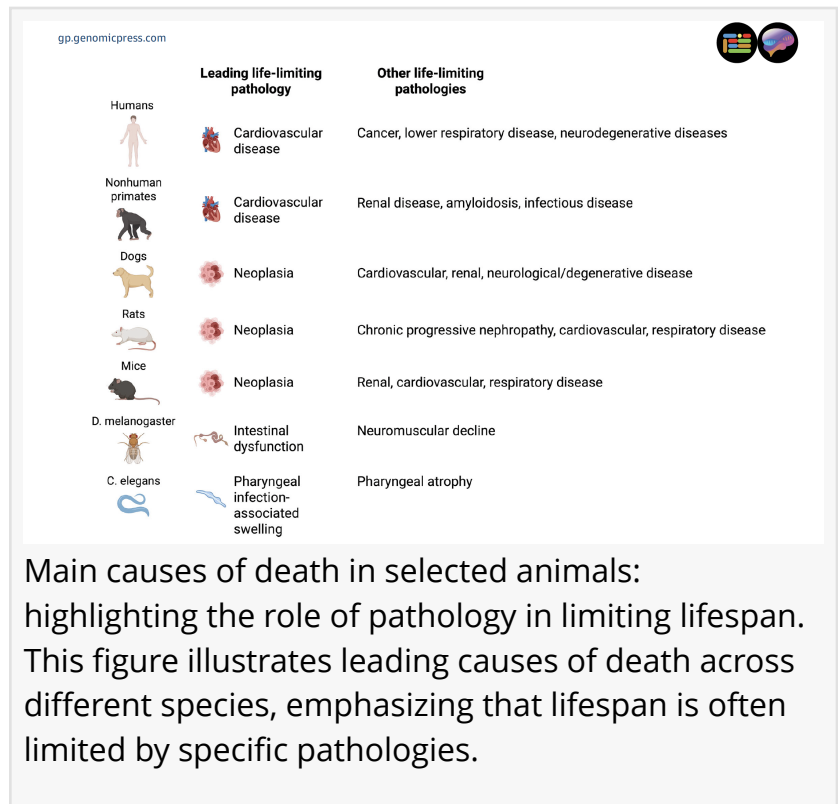


The Lifespan Paradox: When Living Longer Does Not Mean Aging Slower. Perhaps the most counterintuitive finding emerges from the authors' cross-species analysis of what actually kills organisms as they age. In humans, cardiovascular disease consistently accounts for 35 to 70 percent of deaths among older adults, with autopsy studies revealing that even centenarians perceived as healthy before death universally died from identifiable diseases rather than from pure old age. One striking study of individuals aged 97 to 106 years found that vascular conditions remained leading causes of mortality, emphasizing that extreme longevity rarely ends without specific pathological processes.

The pattern shifts dramatically across species. In mice, neoplasia dominates, accounting for 84 to

89 percent of age-related deaths across multiple studies. Dogs show similar patterns, with nearly half of older canine deaths attributed to cancer. Captive nonhuman primates mirror humans, with cardiovascular disease causing over 60 percent of deaths in aged rhesus macaques. Even invertebrates display species-specific bottlenecks: intestinal or neuromuscular failure limit lifespan in *Drosophila*, while pharyngeal infections and deterioration determine mortality in *C. elegans*.

"This pattern illustrates that interventions targeting specific pathologies can extend lifespan by addressing critical bottlenecks to survival, but they do not necessarily slow the overall aging process," the authors write.



Historical Lessons From the Epidemiologic Transition: Why does this distinction matter? Consider the dramatic increase in human lifespan over the past two centuries. Infectious diseases once dominated as primary causes of death, with pandemics like the bubonic plague, smallpox, and tuberculosis claiming millions. Scientific advances including vaccines, antibiotics, and improved public health measures dramatically reduced mortality from these conditions. Yet this epidemiologic transition, the authors argue, represents a shift in dominant causes of death rather than a fundamental slowing of aging itself. Reduced mortality from infections primarily delayed the occurrence of death without altering the underlying biological rate of aging.

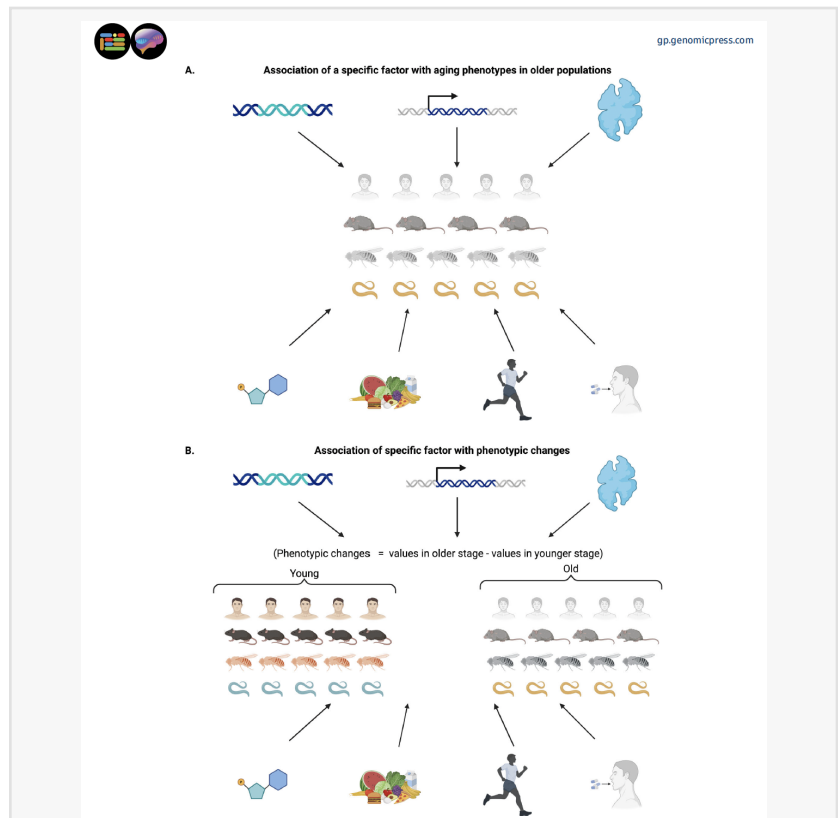
“ This pattern illustrates that interventions targeting specific pathologies can extend lifespan by addressing critical bottlenecks to survival, but they do not necessarily slow the aging process.”
Maryam Keshavarz and Dan Ehninger

What relevance does this historical observation hold for contemporary aging research? If lifespan extension can result from targeting specific life-limiting pathologies without broadly modifying aging, then interpreting pro-longevity effects requires knowing precisely which pathologies limit survival in each experimental context. An intervention extending mouse lifespan by delaying cancer onset differs fundamentally from one that slows systemic physiological decline, even if both produce identical survival curves.

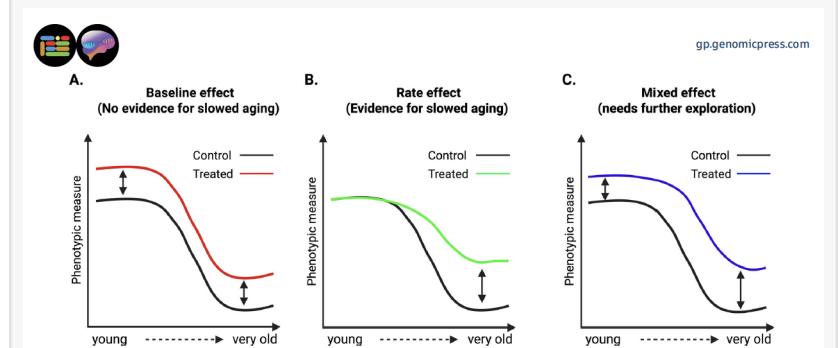
The Clock Conundrum: Correlation Without Causation: Aging clocks, particularly those based on DNA methylation patterns, have become increasingly popular tools for estimating biological age and evaluating interventions. The review acknowledges their value for stratification, risk prediction, and tracking age acceleration across populations. However, Dr. Ehninger and Dr. Keshavarz raise fundamental concerns about what these molecular tools actually measure.

A central issue involves the correlational nature of aging clocks. These models are trained on age-associated changes but may not distinguish whether measured features causally influence aging or merely represent downstream consequences. The authors draw an illuminating analogy: estimating age based on facial images can be highly predictive, yet wrinkles and gray hair offer limited insight into the biological processes driving aging. Supporting this concern, they cite recent epigenome-wide Mendelian randomization studies finding that traditional aging clocks are not significantly enriched for CpG sites with causal roles in aging.

Furthermore, most clocks provide only static snapshots of biological age. When an intervention appears to reduce biological age, how can researchers determine whether this reflects genuine slowing of aging or simply baseline shifts in biomarker values? Even newer approaches like DunedinPACE, designed to estimate rates of aging rather than absolute biological age, often rely on biomarkers correlating with age-related phenotypes without necessarily identifying underlying mechanisms.



How to identify regulators of aging? This panel illustrates a commonly used strategy in aging research, where experimental variables, such as genetic, pharmacological, or lifestyle factors, are tested for their influence on phenotypes measured.



Distinguishing intervention effects on aging: baseline shifts versus changes in aging rate. The effects of PAI on ASPs can be explained by three possible models: (1) the baseline model, (2) the rate model, or (3) a combination of both.

Frailty Indices: Capturing Fragments of a Complex Process. Frailty indices face parallel limitations. Typically constructed from small numbers of semiquantitative traits such as fur condition, kyphosis, or tumor presence scored on simple categorical scales, these measures capture only narrow subsets of age-related phenotypic changes. By summing diverse deficits into single scores, frailty indices implicitly assign equal biological weight to each component. Improvements in isolated features like reduced tumor burden could lower overall scores, potentially creating misleading impressions of broad antiaging effects when changes actually reflect improvements in specific pathologies.

The Hallmarks Reckoning: A Systematic Evaluation. The most provocative section of the review systematically evaluates evidence supporting the hallmarks of aging framework, first introduced in 2013 and expanded to twelve hallmarks in 2023. These hallmarks, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, and cellular senescence among others, have profoundly influenced research priorities, funding allocation, and intervention strategies. But does the evidence actually support claims that targeting these hallmarks modifies aging trajectories?

Dr. Keshavarz and Dr. Ehninger examined primary studies cited in support of each hallmark, focusing on those used to establish causal relationships with aging. Their analysis reveals a striking methodological gap: between 56.86 and 99.96 percent of supporting phenotypes for each hallmark were examined solely in aged animals without parallel assessments in young treated cohorts. This design limitation means most cited studies cannot distinguish between interventions that alter aging rates versus those producing age-independent baseline shifts. Where studies did include young groups, effects frequently appeared in both young and old animals. Across all studies cited in support of the hallmarks framework, the authors identified 602 phenotypes that included assessments in young animals. Of these, 436, corresponding to 72.4 percent, showed intervention effects in young groups, indicating that baseline effects accounted for the majority of cases. "Consequently, the evidence cited for most hallmarks supports the presence of general physiological effects rather than true antiaging mechanisms," the review concludes.

Distinguishing Baseline Effects From Rate Effects: A Methodological Framework. What would rigorous evidence for genuine aging modulation actually look like? The authors propose a conceptual framework distinguishing three categories of intervention effects on age-sensitive

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THOUGHT LEADERS INVITED REVIEW

Beyond the hallmarks of aging: Rethinking what aging is and how we measure it

Maryam Keshavarz¹ , and Dan Ehninger¹ 

Aging is frequently assessed through lifespan extension and proxy biomarkers, yet these approaches may not fully capture the complexity of biological aging. Here, we propose refinements to discovery and evaluation strategies in aging research. Drawing on cross-species data, from humans to invertebrate models, we show mortality is often driven by a narrow set of life-limiting pathologies rather than a uniform systemic decline. This suggests lifespan extension can result from delayed disease onset without broadly slowing aging. Similarly, while tools like DNA methylation clocks and frailty indices offer value for stratification and prediction, their largely correlational nature limits mechanistic insight. Our systematic review exposes a key limitation in the widely cited "hallmarks of aging" framework: many supporting studies conflate baseline physiological shifts with genuine changes in aging rate. We advocate for study designs that enable differentiation of symptomatic effects from alterations to the trajectory of age-related phenotypic change. By integrating these refinements, the field can move toward a more mechanistic, nuanced understanding of aging, one that supports identifying causal regulators and developing interventions that truly modify aging trajectories.

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Keywords: Aging, aging clocks, biomarkers, frailty, hallmarks of aging, interventions, lifespan, pathology, study design



Beyond the hallmarks of aging: Rethinking what aging is and how we measure it

phenotypes. Rate effects occur when treatments reduce the slope of age-dependent change, consistent with targeting processes underlying phenotypic aging. Baseline effects appear when similar changes occur in both young and old animals, indicating age-independent symptomatic action. Mixed effects, where phenotypes change in both age groups but more strongly in older animals, require careful interpretation as they could reflect combined mechanisms or differences in treatment duration.

The review cites recent experimental findings illustrating this distinction. Studies examining well-known pro-longevity interventions including intermittent fasting, rapamycin, and genetic manipulations of mTOR and growth hormone signaling applied deep phenotyping to both young and old treated cohorts. Despite established lifespan-extending effects, these interventions predominantly produced baseline shifts rather than changes in age-dependent progression rates across many age-sensitive phenotypes. The interventions altered phenotype values similarly at young and old ages rather than slowing rates of age-dependent change.

What We Still Do Not Know: Critical Gaps in Understanding. Several fundamental questions emerge from this synthesis. Why do tissues age at different rates, and to what extent is aging systemically coordinated across organs? The review notes that tissue-specific aging trajectories are well documented but their causes remain unclear, likely reflecting developmental patterning and lifelong differences in turnover, metabolic demand, and exposure to stressors. Whether aging is driven chiefly by central non-cell-autonomous pacemakers or by predominantly cell-autonomous processes, stochastic or programmed, remains an open question requiring integrated multitissue studies.

Can cross-species translation succeed when life-limiting pathologies differ so fundamentally? The leading causes of death diverge markedly: cardiovascular disease in humans, neoplasia in mice, infections in fish, intestinal or neuromuscular failure in flies, bacterial infection in worms. This divergence underscores that aging manifests as a mosaic of species and tissue-specific mechanisms shaped by evolutionary history and environmental context rather than as a single universal process.

From Evidence to Impact: Implications for Research and Translation. The implications extend well beyond academic methodology debates. If widely used aging biomarkers and frameworks conflate baseline effects with genuine aging modulation, resources may flow toward interventions offering symptomatic benefits without fundamentally altering aging trajectories. The authors emphasize that geroscience aims to uncover mechanisms influencing age-related phenotypic change, not merely those regulating phenotypes per se, which are already addressed by established fields like endocrinology, neuroscience, and immunology.

A treatment enhancing cognitive performance generally at any age may have valuable applications, but it cannot be said to target cognitive aging unless it demonstrably alters the rate of cognitive decline over time. This distinction carries substantial consequences for drug development, clinical trial design, and ultimately for patients seeking interventions that modify their aging trajectories rather than merely masking symptoms.

The Research Agenda Ahead: Practical Recommendations. The review concludes with concrete methodological recommendations. First, researchers should build and harmonize multitissue age-sensitive phenotype panels spanning molecular, cellular, tissue, and organismal levels across multiple organ systems. Second, study designs must include both young-treated and old-treated groups to distinguish rate effects from baseline shifts, testing for intervention by age interactions. Third, analysis should classify phenotypes into rate, baseline, or mixed effect categories rather than assuming all intervention effects reflect aging modulation.

Fourth, researchers should map age-sensitive phenotype trajectories to select assessment ages that capture widespread changes while minimizing survival bias. Fifth, claims about systemic aging modulation must be grounded in evidence spanning diverse phenotypes; improvements in single outcomes or tissues should not be generalized.

"Refining both discovery pipelines and intervention testing frameworks will support a more mechanistic understanding of aging by enabling researchers to distinguish between interventions that simply extend lifespan or improve isolated age-sensitive phenotypes, and those that fundamentally modify the biological processes driving age-related decline," the authors write.

The Team Behind the Synthesis; Dr. Dan Ehninger leads the Translational Biogerontology Laboratory at the German Center for Neurodegenerative Diseases (DZNE) in Bonn, Germany. His research program focuses on understanding the biological mechanisms of aging and developing strategies to extend healthy lifespan. Dr. Maryam Keshavarz, also at DZNE, conducted the systematic literature analysis underpinning the review's evaluation of hallmark evidence. The work was supported by the ETERNITY project consortium, funded by the European Union through the Horizon Europe Marie Skłodowska-Curie Actions Doctoral Networks under grant agreement number 101072759.

This review article represents a critical synthesis of the current state of knowledge in aging biology, providing researchers, clinicians, and policymakers with a comprehensive framework for understanding how aging is measured and what those measurements actually capture. By systematically analyzing pathology data across multiple species and evaluating the evidence base for the hallmarks of aging framework, the authors offer both a historical perspective on how the field has evolved and a roadmap for future investigations. The synthesis reveals patterns that were invisible in individual studies, specifically the predominance of baseline over rate effects, and reconciles apparent contradictions in the literature regarding intervention efficacy. Such comprehensive reviews are essential for translating the accumulated weight of evidence into actionable insights that can improve research design and therapeutic development. The rigorous methodology employed, including systematic evaluation of young versus old treatment groups across cited studies, ensures the reliability and reproducibility of the synthesis. This work exemplifies how systematic analysis of existing literature can generate new understanding and guide the allocation of research resources toward the most critical

unanswered questions.

The peer-reviewed Thought Leaders Invited Review In Genomic Psychiatry titled "Beyond the hallmarks of aging: Rethinking what aging is and how we measure it," is freely available via Open Access, starting on 2 December 2025 in Genomic Psychiatry at the following hyperlink:

<https://doi.org/10.61373/gp025w.0119>.

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