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Peer Review

Review of: "The Future of Longevity Medicine: Repairing the Parts or Preserving the Whole?Holmes' Carriage as a Metaphor for Two Fundamentally Different Models of Aging"

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This manuscript presents an original conceptual framework that contrasts two paradigms of aging —"fragmented aging" and "coherent aging"—using the metaphor of Holmes' carriage. The authors argue that contemporary longevity medicine has primarily focused on repairing age-related damage at the molecular and organ levels, whereas considerably less attention has been devoted to understanding the mechanisms responsible for maintaining organism-level functional coherence over time.

Although the manuscript is thought-provoking, it remains largely speculative. Many of its central claims are presented without sufficient empirical support, and several conceptual assumptions require clearer definition and stronger integration with the existing literature.

Overall, the manuscript is well written, logically organized, and intellectually engaging. However, several aspects require further clarification and strengthening before publication.

1. The distinction between fragmented and coherent aging is interesting and potentially valuable. Nevertheless, the manuscript remains largely speculative. Many of its central propositions—including the existence of "systemic coherence" as a primary determinant of healthy aging—are presented as plausible hypotheses rather than evidence-based conclusions. The authors should explicitly emphasize that the manuscript is intended as a conceptual perspective and clearly distinguish hypotheses from established biological knowledge.

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2. The concept of "systemic coherence" is central to the manuscript, yet it remains insufficiently defined. Because the entire argument depends on this concept, the manuscript would benefit from a dedicated section defining systemic coherence and explaining how it differs from already established concepts in systems biology. Providing a clearer conceptual framework would substantially strengthen the manuscript.
3. The manuscript argues that traditional or rural populations exhibit coherent aging whereas technologically advanced societies experience fragmented aging. However, these assertions are not sufficiently supported. The manuscript would be strengthened by incorporating evidence from longitudinal cohort studies, frailty research, resilience studies, and systems biology.
4. The Holmes' carriage metaphor is engaging but is revisited repeatedly throughout the manuscript. Some sections could be shortened to improve readability. Several paragraphs contain rhetorical questions that are effective stylistically but may be reduced to maintain a more formal scientific tone. Certain claims would benefit from additional supporting references, particularly those discussing wealthy versus traditional populations and the possible biological superiority of coherent aging.
5. The manuscript presents fragmented aging and coherent aging almost as mutually exclusive models. In reality, aging is likely to involve both processes simultaneously. Repair mechanisms and systemic integration are not necessarily competing paradigms but interconnected aspects of biological aging. A more nuanced discussion acknowledging that both mechanisms probably contribute to healthy longevity would considerably strengthen the manuscript.
6. The conclusion could better distinguish between speculative future directions and evidence-supported conclusions.
7. The manuscript would benefit from a schematic figure.
8. The manuscript is considerably longer than necessary for a conceptual perspective and contains multiple repetitive passages reiterating the same central idea. Several examples (e.g., billionaires investing in anti-aging technologies) appear anecdotal and somewhat speculative. Their scientific value is limited and they could be shortened or removed.

This manuscript presents an original conceptual contribution to the field of longevity medicine. Although its arguments are necessarily speculative, the perspective is scientifically interesting and may stimulate valuable discussion regarding future directions in aging research. Prior to publication, the manuscript would benefit from clearer definition of its central concepts, stronger integration with

existing theoretical frameworks, more balanced discussion of supporting evidence, and a clearer distinction between hypothesis and established biological knowledge.

Declarations

Potential competing interests: No potential competing interests to declare.