Harnessing the power of lifestyle interventions to combat biological aging: Insights from the DO-HEALTH trial

Kun Guo[1] **and Rongcan Luo**[2,*]

[1]Department of Anatomy and Histology & Embryology, Faculty of Basic Medical Science, Kunming Medical University, Kunming 650500, China
[2]Gansu Key Laboratory of Biomonitoring and Bioremediation for Environmental Pollution, and Ministry of Education Key Laboratory of Cell Activities and Stress Adaptations, School of Life Sciences, Lanzhou University, Lanzhou 730000, China
*Correspondence: luorc@lzu.edu.cn

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INTRODUCTION

The aging process is characterized by a progressive decline in physiological functions, increased vulnerability to diseases, and a higher mortality rate.[1] While chronological age is an immutable metric, biological age, which reflects the functional state of an individual's cells and tissues, is influenced by a myriad of genetic, environmental, and lifestyle factors.[1] In recent years, the advent of epigenetic clocks, particularly those based on DNA methylation, has revolutionized our ability to quantify biological aging and assess the impact of interventions.[2,3] The DO-HEALTH trial,[4] a landmark study involving over 700 older adults, has emerged as a pivotal platform for investigating the effects of vitamin D, omega-3 fatty acids, and exercise on various health outcomes, including biological aging. It is worth mentioning that the DNA methylation analysis in the DO-HEALTH trial was conducted as a post hoc exploration. This commentary delves into the nuances of the study's findings and their broader implications for aging research and public health.

The DO-HEALTH trial: A comprehensive intervention study

The DO-HEALTH trial is a multicenter, randomized, placebo-controlled trial designed to evaluate the individual and combined effects of vitamin D, omega-3 fatty acids, and a home-based exercise program on health outcomes in older adults.[4] The study's comprehensive design, rigorous methodology, and large sample size provide a robust foundation for drawing meaningful conclusions. Notably, the trial's participants were aged 70 years and older, a demographic that is particularly vulnerable to age-related diseases and functional decline. By focusing on this cohort, the study offers valuable insights into interventions that could potentially delay the onset of frailty and improve overall healthspan.

Vitamin D, omega-3, and exercise: Individual and additive effects on biological aging

The study's primary findings revolve around the impact of vitamin D, omega-3, and exercise on four next-generation DNA methylation (DNAm) measures of biological aging: PhenoAge, GrimAge, GrimAge2, and Dunedin-PACE. The results indicate that omega-3 supplementation alone had a modest but significant protective effect on several DNAm clocks, slowing down biological aging by up to 3.8 months over a three-year period. This finding is particularly noteworthy given the widespread consumption of omega-3 fatty acids for their purported health benefits, including anti-inflammatory and cardioprotective effects. The study also revealed that the combination of omega-3, vitamin D, and exercise had an additive protective effect on PhenoAge, further underscoring the potential of these interventions to modulate biological aging.

The mechanisms underlying these effects are likely multifaceted and intersect across several biological pathways. Vitamin D, known for its role in calcium homeostasis and bone health, has also been implicated in immune function and inflammation regulation. Specifically, it can modulate the expression of genes involved in the inflammatory response, potentially reducing chronic low-grade inflammation, which is a hallmark of aging. Omega-3 fatty acids, rich in alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert anti-inflammatory effects by competing with pro-inflammatory arachidonic acid for incorporation into cell membranes and influencing the production of anti-inflammatory eicosanoids. Additionally, omega-3 fatty acids may influence cellular metabolism and gene expression through peroxisome proliferator-activated receptors (PPARs), which play a role in lipid metabolism and energy homeostasis.[5] Exercise, particularly resistance training, has been shown to improve muscle strength, reduce inflammation, and enhance mitochondrial function. Physical activity can stimulate the production of mitochondrial biogenesis factors, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), leading to increased mitochondrial density and improved cellular energy metabolism. This enhanced mitochondrial function can reduce the production of reactive oxygen species (ROS) and oxidative stress, which are key contributors to cellular aging. Moreover, exercise-induced increases in circulating cytokines and growth factors can have systemic anti-inflammatory effects and promote tissue repair and regeneration. The synergistic effects observed in the DO-HEALTH trial suggest that these interventions may act through complementary pathways to collectively impact biological aging. For example, the anti-inflammatory effects of vitamin D and omega-3 fatty acids may be enhanced by the reduction in inflammation achieved through exercise, leading to a more pronounced impact on DNAm clocks. Similarly, the improvements in mitochondrial function and energy metabolism driven by exercise may create a more favorable cellular environment for the actions of vitamin D and omega-3 fatty acids, further modulating gene expression and epigenetic regulation. Future research could aim to elucidate the precise molecular mechanisms and interactions between these interventions to better understand their combined effects on biological aging.

While the DO-HEALTH trial provides some evidence for the potential benefits of these interventions, it is important to note that the trial did not find significant associations between vitamin D supplementation and the epigenetic clocks. Additionally, the home-based exercise program (SHEP) also did not show significant effects on the clocks. Therefore, the discussion of potential mechanisms through which vitamin D and exercise might influence biological aging could be considered speculative and based on broader scientific literature rather than direct evidence from the DO-HEALTH trial.

GENERALIZABILITY AND FUTURE RESEARCH

The study's reliance on Swiss participants limits the generalizability of the findings. Factors such as diet, genetics, and healthcare access can significantly influence the efficacy of interventions and the observed outcomes. Future research could prioritize including participants from diverse backgrounds to account for these variations. International replication studies and multi-center trials could help validate the findings and identify population-specific effects.

Safety considerations for Omega-3 supplementation

Although the study highlights the potential of omega-3 supplementation to slow epigenetic aging, it is crucial to address the safety concerns associated with its use, especially in older populations. Omega-3 fatty acids, while generally considered safe, can have potential side effects and interactions. For instance, high doses of omega-3 may increase the risk of bleeding, particularly in individuals taking anticoagulant medications. Additionally, omega-3 supplements can sometimes cause gastrointestinal symptoms such as nausea, diarrhea, and belching. It is important for future research to carefully monitor and report any adverse effects associated with omega-3 supplementation in older adults to ensure its safe and effective use as an anti-aging intervention.

Methodological considerations and future directions

While the DO-HEALTH trial provides compelling evidence for the potential of vitamin D, omega-3, and exercise to slow biological aging, several methodological considerations warrant attention. First, the study's reliance on epigenetic clocks as biomarkers of aging is both a strength and a limitation. Epigenetic clocks, though increasingly validated, are not yet universally accepted as definitive measures of biological age. There are ongoing debates around the validity and limitations of DNAm clocks, with some researchers questioning their accuracy and applicability across different populations and conditions. Future research should aim to corroborate these findings with additional biomarkers, such as telomere length and cellular senescence markers, to provide a more comprehensive assessment of aging. Second, the study's sample consisted exclusively of Swiss participants, which limits the generalizability of the findings to other populations. The authors acknowledge this limitation and plan to extend their analyses to include participants from other European countries. Such efforts are crucial for accounting for genetic and lifestyle diversity, which may influence the efficacy of interventions. For

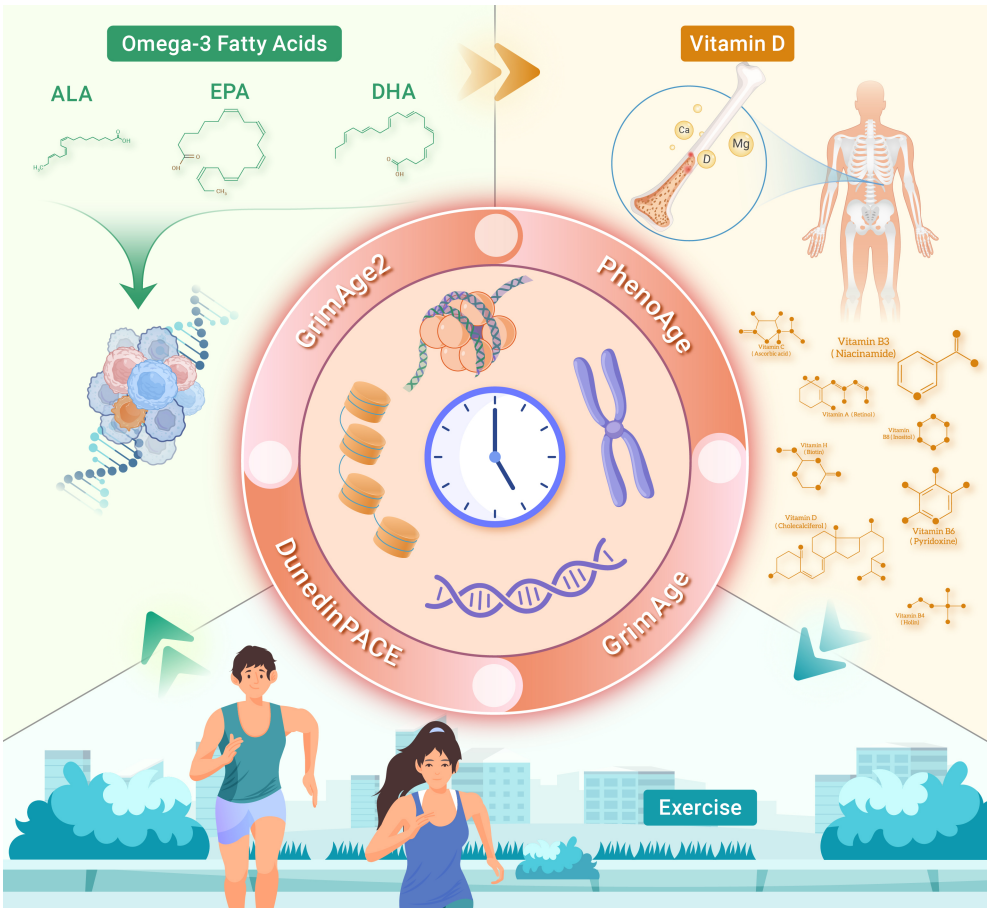

Figure 1. Schematic illustration of the potential mechanisms underlying the effects of vitamin D, omega-3 fatty acids, and exercise on biological aging This figure provides a comprehensive overview of how vitamin D, omega-3 fatty acids, and exercise may collectively impact biological aging through various molecular and physiological pathways. It integrates the key findings from the DO-HEALTH trial with the broader context of aging biology.

example, international replication studies could be conducted in diverse populations to validate the findings across different ethnic and environmental contexts. Moreover, the trial's three-year duration, while substantial, is relatively short in the context of biological aging. Longitudinal studies with extended follow-up periods are needed to fully elucidate the long-term effects of these interventions on healthspan and lifespan. Future studies could consider a follow-up period of 5 to 10 years to better capture the long-term impact of these interventions on aging. Additionally, future research should explore the optimal doses and combinations of vitamin D, omega-3, and exercise for maximizing their anti-aging effects. The study's use of a fixed dose of 2,000 IU/day for vitamin D and 1 g/day for omega-3 (comprising 330 mg EPA and 660 mg DHA) may not be universally applicable, and individualized approaches based on baseline levels and genetic predispositions could enhance the efficacy of these interventions. For instance, trials with biomarker-guided dosing could be designed to tailor the interventions to individual needs, ensuring optimal efficacy. Furthermore, exploring intervention timing, such as mid-life versus later life, could provide insights into the most effective periods for implementing these interventions.

Implications for public health and aging research

The findings from the DO-HEALTH trial have significant implications for public health and aging research. As the global population continues to age, interventions that can delay the onset of age-related diseases and improve functional capacity are of paramount importance. The study's results suggest that simple, accessible interventions such as vitamin D supplementation, omega-3 consumption, and regular exercise could collectively contribute to healthier aging. Public health initiatives aimed at promoting these lifestyle changes could have a profound impact on reducing the burden of chronic diseases and enhancing the quality of life in older adults. However, it is crucial to critically assess the clinical relevance of the observed changes in DNAm clocks. While the study shows that these interventions can slow down biological aging by up to 3.8 months over a three-year period, the direct impact on healthspan and clinical outcomes remains to be fully understood. Future research should aim to link these DNAm changes to tangible health outcomes, such as reduced incidence of age-related diseases, improved cognitive function, and enhanced physical performance. Moreover, the study's emphasis on the additive effects of these interventions highlights the potential of multimodal approaches in addressing the complex biology of aging. However, interpreting these additive effects from a post hoc analysis requires caution. The observed synergistic effects, while promising, need to be validated in prospective studies designed specifically to test these combinations. Future research should continue to explore the synergistic interactions between nutritional and lifestyle factors, as well as their underlying molecular mechanisms. This knowledge could inform the development of personalized interventions tailored to individual needs and genetic profiles. Additionally, the potential use of epigenetic clocks to guide future intervention strategies and health policies should be explored. DNAm clocks could serve as early indicators of biological aging, allowing for timely interventions to prevent or delay age-related diseases. However, their integration into clinical practice and public health policies will require further validation and standardization.

CONCLUSION

The DO-HEALTH trial represents a significant advancement in our understanding of the impact of vitamin D, omega-3, and exercise on biological aging. By leveraging robust epigenetic clocks and a well-designed clinical trial framework, Bischoff-Ferrari et al. provide compelling evidence for the potential of these interventions to slow down the aging process. While acknowledging the study's limitations, we must also recognize its potential to shape future research and public health strategies. As we continue to unravel the complex interplay between lifestyle factors and biological aging, the insights gained from the DO-HEALTH trial will undoubtedly play a crucial role in guiding our efforts to promote healthy longevity (Figure 1).

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AUTHOR CONTRIBUTIONS

All authors conceived the original idea, wrote and reviewed the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.