

# The Role of Micronutrient Deficiency in Delayed Immunosenescence and Healthy Ageing

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## Abstract

Immunosenescence presents a major clinical challenge by increasing susceptibility to infections, reducing vaccine efficacy, and elevating the risk of chronic diseases. This state is characterized by a paradoxical combination of immunodeficiency and chronic low-grade inflammation termed "inflammaging." Key hallmarks include thymic involution, a shrinking T-cell repertoire, accumulation of senescent cells, and dysregulated inflammatory responses. This review explores the compelling evidence that micronutrient deficiencies, which are highly prevalent in the elderly, are not merely a consequence but an active accelerator of this immune decline. The mechanisms linking deficiency to immunosenescence are detailed, including increased oxidative stress and DNA damage, impaired lymphocyte proliferation, and dysregulated cytokine production. Preclinical and clinical studies demonstrate that replenishing deficient levels of key nutrients like vitamin D and zinc can rejuvenate thymic function, improve T-cell responses, and enhance vaccine efficacy in older adults. The review concludes that targeted nutritional interventions, particularly synergistic multi-nutrient approaches, represent a viable strategy to bolster immune resilience in the ageing population, thereby promoting healthier longevity and reducing the burden of age-related immune pathology.

## 1. Introduction

Ageing is an inevitable biological process characterized by a progressive decline in physiological integrity. This decline impairs normal bodily functions and increases susceptibility to a wide range of diseases. While ageing affects every system in the body, the process of deterioration of the immune system was known as the immunosenescence (Ventura et al., 2017). Immunosenescence is not merely a weakening of immune defences; it is a complex reprogramming that leads to a paradoxical state of both immunodeficiency and chronic, low-grade inflammation, often referred to as inflammaging (Salminen, 2021). This dual burden leaves the ageing individual more vulnerable to severe infections, reduces the efficacy of vaccinations, and contributes to the rising incidence of cancer, autoimmune disorders, and other chronic age-related diseases. The hallmarks of immunosenescence are evident across the entire immune landscape. At the cellular

level, we observe a thymic involution, which drastically reduces the output of T-cells, limiting the immune system's ability to respond to new pathogens (Thomas et al., 2020). The immune cell repertoire becomes dominated by memory cells. Simultaneously, innate immune cells, such as neutrophils and macrophages, show impaired phagocytic ability and dysregulated inflammatory responses (Solana et al., 2012). This intricate cascade of cellular and molecular changes creates an immune system that is both overactive in a destructive, inflammatory way and underactive in its specific, protective functions. The clinical implications are severe, as seen in the higher mortality rates from influenza and pneumonia in the elderly and the increased prevalence of cancers driven by failing immune surveillance.

In the search for strategies to counteract immunosenescence, nutritional interventions have emerged as a highly promising and modifiable approach. Among

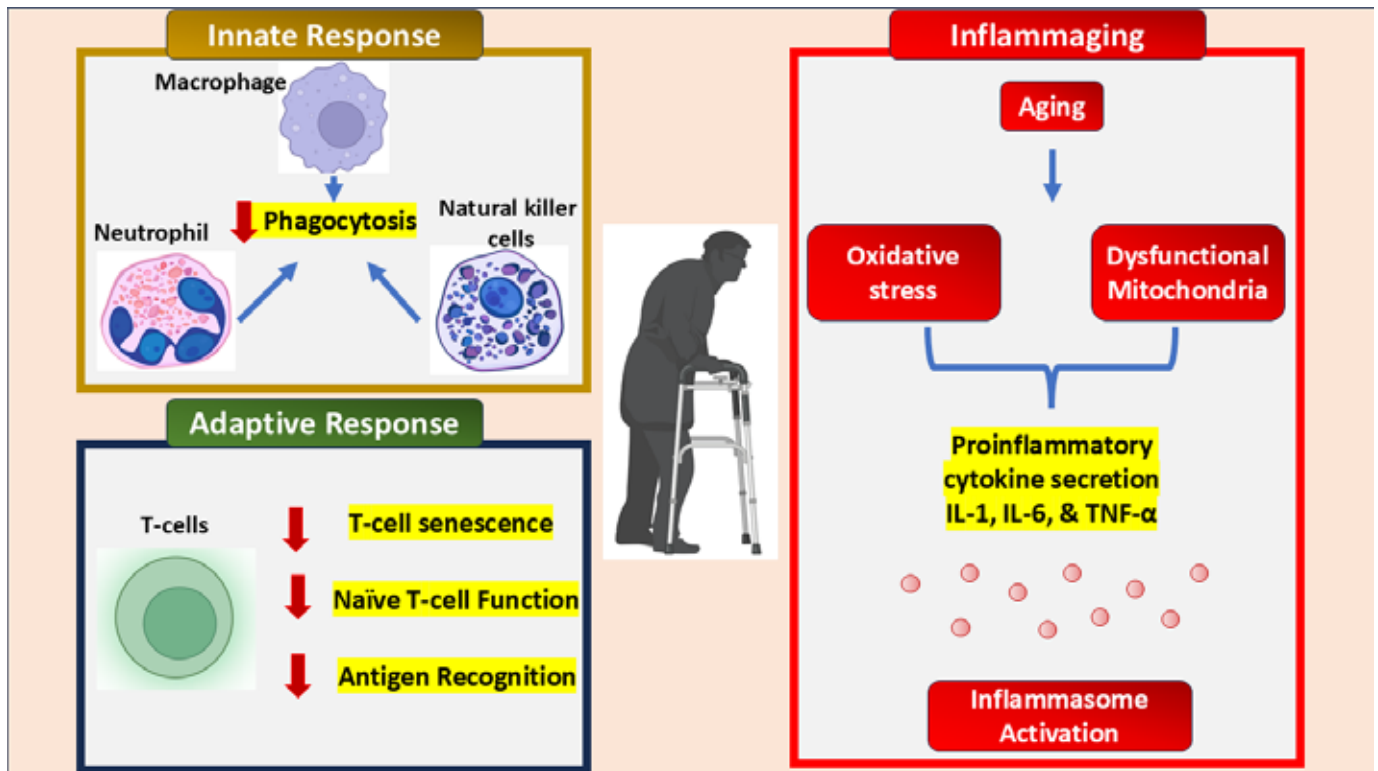
nutritional factors, the vitamins and minerals required in small quantities for essential physiological functions play a fundamental role in supporting immune competence. They are not merely fuel; they act as crucial cofactors and regulators in nearly every aspect of the immune response. For instance, Vitamin D is now recognized as a potent immunomodulator, influencing both innate and adaptive immunity (Ghaseminejad-Raeini et al., 2023). Zinc is used for the development and function of a wide range of immune cells, and its deficiency can lead to profound immunosuppression (Bonaventura et al., 2015). Similarly, Vitamin C acts as a powerful antioxidant, protecting immune cells from oxidative damage, while also supporting cellular functions like chemotaxis and phagocytosis. Selenium, Vitamin E, and B each contribute unique and non-redundant roles, from facilitating antibody production to maintaining the integrity of mucosal barriers. However, a micronutrient deficiencies in the ageing population are remarkably common. This can result from a combination of factors, including reduced dietary intake due to loss of appetite or social isolation, impaired nutrient absorption in the ageing gut, and the increased utilization of micronutrients by a chronically inflamed system. This interplay suggests that suboptimal micronutrient status may not just be a consequence of ageing and illness, but an active contributor to the pace and severity of immunosenescence. The aim of this article is to synthesize and critically evaluate the current evidence linking specific micronutrient deficiencies to the hallmarks of immunosenescence. Our scope will encompass a detailed examination of key micronutrients including Vitamin D, Zinc, Vitamin C, and Selenium and their specific roles in mitigating thymic atrophy, reducing senescent cell burden, curbing chronic inflammation, and enhancing immune cell function.

## 2. Immunosenescence

Immunosenescence can be defined as the gradual deterioration of the immune system that occurs naturally with advancing age. This immune dysregulation is driven by profound cellular and molecular changes affecting both the innate and adaptive arms of our immunity (Pawelec et al., 2020). One of the most significant events is the involution of the thymus. This organ, located behind the breastbone, is the primary factory for producing T-cells, which are essential for recognizing new pathogens (Al-Suhaimi et al., 2021). The integrity of our adaptive immune defense rests heavily on a diverse T-cell population. However, with age, the T-cell compartment experiences a profound shift. The reservoir of T-cells, essential for responding to novel pathogens,

shrinks dramatically. This gap is filled by an expansion of highly differentiated, memory-like T-cells, particularly CD28- T-cells (Barnaba, 2022; Sharma et al., 2022). While abundant, these cells have shortened telomeres and a limited replicative capacity. They are prone to senescence and exhibit a reduced functional diversity, leaving the body poorly equipped to handle new immunological challenges.

This T-cell exhaustion is only one part of a broader dysfunction. The B-cell lineage also faces age-related hurdles. There is a documented decline in the generation of new B-cells from the bone marrow, a process known as B-cell lymphopoiesis. The resulting B-cell pool shows less diversity in the antibodies it can produce (de Mol et al., 2021). Older B-cells often display a preference for producing antibodies of lower affinity and a tendency towards non-specific, auto-reactive responses. This contributes to the dual problem of reduced efficacy against new infections and an increased risk of autoimmunity. Beyond the adaptive system, innate immunity also undergoes significant recalibration. Antigen-presenting cells, such as dendritic cells, show impaired migration and a reduced capacity to activate T-cells (Bandola-Simon and Roche, 2019). This failure in initial immune activation creates a significant bottleneck in mounting an effective coordinated response. Furthermore, the delicate balance between pro-inflammatory and anti-inflammatory signaling becomes disrupted. Key regulatory pathways, including NF- $\kappa$ B and inflammasome activation, become persistently upregulated. This creates a systemic environment of sterile, low-grade inflammation that is not triggered by an active infection but is instead a hallmark of the aged physiological state. This inflammatory milieu itself further accelerates immune cell dysfunction and tissue damage. The clinical manifestations of these intricate cellular and molecular failures are profound. The impaired function of dendritic cells and the lack of naïve T-cells directly explain the suboptimal antibody responses and reduced protection observed after vaccination in the elderly. Furthermore, the compromised immune surveillance, resulting from weakened cytotoxic T-cell and Natural Killer (NK) cell activity, allows pre-malignant cells to evade detection and establish tumors (Ge et al., 2020). The chronic inflammatory state, driven by dysregulated innate signaling and the accumulation of senescent cells, directly damages tissues and is implicated in the pathogenesis of a range of age-related conditions, from atherosclerosis to neurodegeneration. Thus, immunosenescence is not a single defect but a cascade of failures across the entire immune network, creating a predictable pattern of vulnerability in the ageing adult (Figure 1).



**Figure 1:** Key immunological mechanisms contributing to immunosenescence. The innate system is characterized by altered macrophage and neutrophil activity, while the adaptive system suffers from T-cell senescence and a loss of naïve T-cell function. These dysregulated processes fuel inflammaging through mechanisms such as oxidative stress, dysfunctional mitochondria, and the sustained secretion of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF- $\alpha$ ) via inflammasome activation.

### 3. Micronutrients and Immune Health

#### 3.1. Overview of Essential Micronutrients

The term "micronutrients" encompasses a diverse group of vitamins and minerals that the body cannot produce in sufficient quantities, making dietary intake paramount. The fat-soluble vitamins, particularly Vitamin D and Vitamin A, are powerful immunoregulators. Vitamin D, often called the "sunshine vitamin," functions more like a hormone, influencing the expression of hundreds of genes in immune cells (Riccio, 2024). Vitamin A and its metabolites, like retinoic acid, are indispensable for the development and specialization of lymphocytes. Among the water-soluble vitamins, Vitamin C is a cornerstone of cellular antioxidant defense and supports various immune cell functions, while Vitamin B6, B9 (folate), and B12 are vital for the rapid cell division and proliferation required to mount an effective immune response. On the mineral side, Zinc and Selenium are arguably the most crucial. Zinc acts as a cofactor for over 300 enzymes involved in immune signaling and cell division, and Selenium is integral to powerful antioxidant enzymes that protect immune cells from self-inflicted oxidative damage during an inflammatory response (Table 1) (Elmadfa and Meyer, 2019; Ferenčík and Ebringer, 2003; Ross, 2012).

#### 3.2. Role of Micronutrients in Innate Immunity

Our innate immune system relies heavily on micronutrients to function effectively. The physical barriers of our body, such as the skin and the lining of our respiratory and gut tracts, require Vitamin A to maintain their structural integrity, acting as a gatekeeper against invading pathogens. The neutrophils and macrophages have their ability to kill pathogens and the process is known as chemotaxis and phagocytosis (Teng et al., 2017). It is significantly influenced by Vitamins C and D. Furthermore, the "innate intelligence" of these cells, their ability to recognize patterns common to many microbes, depends on proper signaling that involves Zinc and Selenium. For instance, a deficiency in Selenium can impair the production of "selenoproteins," which reduces the excessive inflammation that macrophages can produce, preventing collateral tissue damage (Lee et al., 2022).

#### 3.3. Role of Micronutrients in Adaptive Immunity

The adaptive immune system is the specialized special forces, and its development and precision are intensely micronutrient-dependent. The very genesis of T-cells and B-cells in the bone marrow and thymus is organized by nutrients like Vitamin A, Zinc, and folate. Once generated, these cells must be activated and proliferate massively to combat an infection (Wintergerst et al., 2007). This process of clonal expansion is a highly demanding metabolic event,

requiring Vitamin B6, B12, and folate to synthesize new DNA and proteins. Vitamin D plays a direct role in steering T-cells away from inflammatory pathways and towards more regulatory functions, helping to fine-tune the response (Stein and Ruef, 2019). Perhaps most critically, for the adaptive system to form a long-term memory in the basis of vaccination, immune cells must undergo complex differentiation. Vitamin A-derived retinoic acid is a master conductor in this process, particularly in the gut mucosa, guiding the homing and function of memory cells.

### 3.4. Antioxidant Micronutrients and Inflammation Control

A successful immune response inherently generates a reactive oxygen species (ROS) to destroy pathogens. However, this oxidative stress is a double-edged sword; if left unchecked, it can severely damage our own immune and surrounding cells, prolonging inflammation and contributing to the chronic "inflammaging" state. This is where antioxidant micronutrients form a critical defense network. Vitamin E, a fat-soluble vitamin which protects the lipid-rich cell membranes from oxidative damage, while the water-soluble Vitamin C can regenerate Vitamin E, restoring its antioxidant capacity (Zarkasi et al., 2019). Selenium is the central component of the enzyme glutathione peroxidase, one of the body's most powerful internal antioxidant systems (Battin and Brumaghim, 2009). This enzyme neutralizes hydrogen peroxide and lipid hydroperoxides. By controlling this oxidative stress, these micronutrients help to resolve inflammation efficiently, protecting tissues and preventing the immune system from transitioning into a state of persistent, damaging activation.

## 4. Micronutrient Deficiency and Accelerated Immunosenescence

### 4.1 Vitamin Deficiencies

The absence of adequate vitamins creates distinct vulnerabilities that mirror the hallmarks of an aged immune system. Without sufficient Vitamin D, the differentiation of monocytes into macrophages is impaired, and T-cell activity becomes skewed towards a pro-inflammatory state, directly contributing to inflammaging (Balamurugan

et al., 2024). Vitamin A deficiency leads to a phenomenon known as mucosal thinning, weakening the barriers in the gut and respiratory tract and making them more permeable to pathogens (Cantorna et al., 2019). This forces the internal immune system into a constant state of alert.

The antioxidant vitamins, C and E, act as a protective shield for immune cells. When they are lacking, immune cells like neutrophils and lymphocytes become highly susceptible to oxidative damage, leading to premature cellular senescence and functional failure (Saeed et al., 2016). Finally, the B-complex vitamins especially B6, B9, and B12 are known for their role in cell division (Franco et al., 2022). A deficiency in any of these vitamins stops the progress and severely hampering the rapid proliferation of T-cells and B-cells needed to mount a clonal response to a new infection or vaccine. This results in the ineffective immune responses characteristic of immunosenescence.

### 4.2 Mineral Deficiencies

Mineral deficiencies similarly act at the core of immune competence. Zinc is often described as the gatekeeper of immune function. A zinc deficiency triggers a rapid and dramatic atrophy of the thymus, the very organ responsible for producing new T-cells (Kido et al., 2022). This mimics and accelerates the age-related thymic involution, leading to a precipitous drop in T-cell output. Selenium deficiency damage the activity of glutathione peroxidase, the body's master antioxidant enzyme (El-Demerdash, 2004). This leaves the entire system vulnerable to unchecked oxidative stress, which damages DNA and proteins within immune cells.

Iron is essential for the metabolic activity and proliferation of all rapidly dividing cells, including immune cells. An iron-deficient state leads to impaired generation of reactive oxygen species in macrophages and reduces the capacity for lymphocyte clonal expansion (Cronin et al., 2019). Magnesium is a critical cofactor for the enzymes involved in DNA synthesis and repair. It also is essential for the proper function of immunoglobulins (Ashique et al., 2023). A magnesium deficiency can therefore undermine the fundamental processes of immune cell generation and antibody effectiveness.

**Table 1:** Impact of Micronutrient Deficiencies on Hallmarks of Immunosenescence

	Impact on Innate Immunity	Impact on Adaptive Immunity	Specific Hallmark of Immunosenescence Accelerated
Vitamin D	Impairs differentiation of monocytes into macrophages.	Reduces proportion of pro-inflammatory cells and supports regulatory T-cells when supplemented.	Contributes directly to "inflammaging"; reduces vaccine efficacy
Zinc	-	Triggers rapid atrophy of the thymus	Mimics and accelerates age-related thymic involution; leads to a precipitous drop in naïve T-cell output.

Vitamin C & E	Leaves neutrophils and other immune cells susceptible to oxidative damage.	Leads to premature cellular senescence and functional failure of lymphocytes.	Accumulation of senescent, non-functional T-cells; and increased oxidative stress damage.
Selenium	Impairs the ability of macrophages to control excessive inflammation.	-	Leaves the immune system vulnerable to unchecked oxidative stress, damaging DNA and proteins within immune cells.
B Vitamins (B6, B9, B12)	-	Severely hampers the rapid proliferation of T-cells and B-cells.	Results in inadequate and delayed immune responses to new infections or vaccines, characteristic of immunosenescence.

## 5. Mechanisms Linking Deficiency to Immune Dysfunction

### 5.1 Oxidative Stress and DNA Damage

Micronutrients like Vitamins C, E, and the mineral selenium form the body's primary antioxidant network. When they are deficient, this defense system collapses. The result is a surge in ROS that goes uncontained. This oxidative stress directly damages the DNA within immune cells, leading to genomic instability (J.Kim et al., 2006). For a T-cell, this can mean prematurely triggering senescence, a state where the cell is alive but can no longer divide. The accumulation of these senescent, non-functional T-cells is a core feature of the immunosenescent landscape.

### 5.2 Impaired Lymphocyte Function and Proliferation

The entire lifecycle of lymphocytes is a micronutrient-dependent process. Zinc deficiency directly starves the thymus, halting T-cell production. Inside existing T-cells and B-cells, a lack of Zinc, Magnesium, and B-vitamins disrupts the intricate signaling pathways that are activated when a cell encounters a pathogen (Mitra et al., 2022). The result is a failure to launch an effective response. Furthermore, the incredible burst of cell division required to build an army of clones is hobbled without the raw materials provided by these minerals and vitamins, leading to an inadequate and delayed immune reaction.

### 5.3 Dysregulated Cytokine Production

Cytokines are the messaging system of the immune system, and their balance is crucial. Micronutrients, particularly Vitamin D and Zinc, are critical for maintaining this balance. In their absence, the cytokine network becomes chaotic. There is a measurable shift towards the overproduction of pro-inflammatory cytokines like TNF- $\alpha$  and IL-6, while the production of regulatory cytokines is suppressed (Luo and Zheng, 2016). This creates the exact low-grade, chronic inflammatory environment that defines inflammaging. This constant inflammatory background

not only damages tissues but also further exhausts and dysregulates immune cells, creating a vicious, self-perpetuating cycle of decline

## 6. Micronutrient Supplementation and Delayed Immunosenescence

The strategic use of micronutrient supplementation represents a promising, practical approach to minimize the immunosenescence. The goal here is not to reverse ageing, but to provide the immune system with the essential biochemical tools it needs to function at its optimal capacity for longer. Research is increasingly showing that targeted nutritional support can help recalibrate the immune system, pushing back against the dysregulation that defines the ageing immune phenotype. Much of the foundational evidence for this comes from preclinical studies conducted in animal models. These controlled experiments allow scientists to observe the direct biological effects of supplementation. For instance, studies in aged mice have demonstrated that zinc supplementation can lead to a remarkable rejuvenation of thymic architecture and function, resulting in an increased output of T-cells (Wong et al., 2009). This is a significant finding, as thymic involution was long considered an irreversible feature of ageing. Similarly, supplementing with antioxidants like Vitamin E in animals has been shown to reduce markers of oxidative stress in immune cells, decrease the number of senescent T-cells, and improve the functional capacity of NK cells and macrophages (Beharka et al., 1997).

Translating these findings to human populations is, of course, more complex, but clinical trials are providing encouraging results. For example, clinical research has consistently found that correcting Vitamin D insufficiency in older adults leads to a measurable shift in the T-cell profile, reducing the proportion of pro-inflammatory cells and supporting the function of regulatory T-cells (Fisher et al., 2019). Trials with zinc supplementation have demonstrated improvements in T-cell-mediated immunity and a reduction in the incidence of infections (Barnett et al., 2016). The key

insight from these human studies is that the greatest benefits are often seen in those who are demonstrably deficient at the outset, highlighting the importance of precision in nutritional interventions. One of the most practical and significant measures of immune resilience in the elderly is their response to vaccination. A robust antibody response after a flu or pneumonia shot is a real-world test of the adaptive immune system's vitality. Here, micronutrient supplementation has shown particular promise. Studies have found that older adults with sufficient Vitamin D levels generate significantly higher and more durable antibody titers following influenza vaccination compared to their deficient counterparts (Goncalves-Mendes et al., 2019). Similar enhancements in vaccine efficacy have been observed with zinc and Vitamin E supplementation. This is not a marginal improvement; it can mean the difference between a vaccine that provides adequate protection and one that fails, directly impacting morbidity and mortality. Perhaps the most forward-thinking approach involves moving beyond single-nutrient supplementation. The immune system does not rely on vitamins and minerals in isolation; they work in intricate, synergistic networks. Zinc is required for the proper transport and function of Vitamin A. Vitamin C can regenerate oxidized Vitamin E, restoring its antioxidant capacity. Selenium and Vitamin E work together to protect cell membranes. This has led to the exploration of combination therapies. Emerging evidence suggests that a balanced combination of several key micronutrients such as Vitamin D, zinc, and selenium may have a more powerful and holistic effect on immune function than any single nutrient alone. This synergistic approach more accurately mirrors a healthy, nutrient-dense diet and may be the key to developing effective nutritional strategies to support healthy immune ageing, helping the elderly population maintain its defenses against the dual threats of infection and chronic inflammation.

## 7. Future Perspectives and Limitations

While the evidence linking micronutrient status to immune health in ageing is compelling, this field of research is still developing and faces several important limitations. Many studies have been too short in duration to observe the long-term impact of supplementation on the gradual process of immunosenescence. Furthermore, study populations are often heterogeneous, with varying baseline nutritional status, genetic backgrounds, and overall health, making it difficult to draw universal conclusions. There is also a significant gap in our understanding of how sex-specific differences influence micronutrient requirements and their immunomodulatory effects in older adults. Perhaps the most complex limitation is the interplay of nutrients; most research focuses on single micronutrients, but in reality, these compounds work in intricate metabolic networks.

The effect of correcting one deficiency might be limited by a suboptimal level of another, a phenomenon known as nutrient-nutrient interaction.

The future research must move towards more personalized and sophisticated approaches. We need large-scale and long-term studies that stratify participants based on their precise biochemical deficiencies, genetic profiles, and even the composition of their gut microbiome, which itself influences nutrient absorption. This will help identify which specific individuals stand to benefit most from which interventions. Another exciting frontier is the development of novel biomarkers. Instead of just measuring nutrient levels in the blood, we need validated functional biomarkers that can directly report on the biological impact of a nutrient on immune cells. Finally, research should explore the synergistic potential of multi-nutrient formulations, often called immunonutrition, which are rationally designed based on the biochemical pathways that become dysregulated in immunosenescence.

## 8. Conclusion

The micronutrient deficiency is a key modifiable factor that actively accelerates immune ageing. The evidence strongly suggests that addressing these deficiencies through targeted strategies is not merely about preventing disease, but about proactively strengthen the immune system's resilience. By ensuring adequate intake of essential vitamins and minerals, we hold a viable and powerful key to delaying immunosenescence and promoting a longer, healthier life.

## Declarations

### Ethics approval statement

Not applicable

### Consent to participate

Not applicable

### Consent to publish

Not applicable

### Data Availability Statement

The data are available from the corresponding author upon reasonable request

### Competing Interests

The authors declare that they have no conflict of interest

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**Author contribution**

Conceptualization, Data curation, Investigation, Writing, Formal analysis, and Editing: P.B, A.E.R.S.R, and C.A.A. All authors have read and agreed to the published version of the manuscript.

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