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Review

Plasma Transfusions for Healthy Ageing: Myth or Reality?

Giulia Accardi, Anna Aiello and Calogero Caruso *

Laboratory of Immunopathology and Immunosenescence, Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, 90134 Palermo, Italy
* Correspondence: calogero.caruso@unipa.it

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Abstract: Over the past century, life expectancy has risen markedly in Western societies. While lifespan has increased, prolonged life does not necessarily coincide with prolonged health. Among the strategies under investigation to counteract age-related decline, transfusions of plasma from young donors into older recipients have attracted both scientific and public interest. This article reviews the historical origins, experimental evidence, and translational challenges of heterochronic parabiosis and plasma exchange and plasma transfusion. In particular, the translational aspects of parabiosis will be discussed, as it appears to be highly informative for identifying circulating molecules that either drive or delay aging. We discuss the scientific basis, potential mechanisms, and ethical as well as regulatory implications of these practices. Ultimately, lifestyle factors remain the most powerful determinant of healthy ageing, without relying on purported miracle interventions.

Keywords: ageing; lifestyle; longevity; parabiosis; plasma transfusion

1. Introduction

We are all aware that, at least in the Western world, life expectancy increased dramatically over the course of the twentieth century. Yet, while many individuals today live longer, this does not necessarily mean they live in good health [1,2]. Regardless of their physical condition, however, most people wish to extend their lives for as long as possible [3]. Since antiquity, humankind has been in pursuit of the secret to immortality. The Fountain of Youth is a legendary spring or well believed to possess mystical powers capable of halting or reversing ageing, and in some traditions, even bestowing immortality on those who drink or bathe in its waters. Variations of this myth appear in the folklore of many cultures throughout history, but in Western tradition it is most famously linked to the 16th-century Spanish explorer Juan Ponce de León, who was said to have sought this "miraculous elixir" during his voyages [4].

In modern times, some have turned their hopes toward slowing down the ageing process through transfusions of plasma, the liquid component of blood, donated by young individuals. In the United States, several private facilities offer such treatments, promising to rejuvenate older patients and to alleviate age-associated diseases [5]. But where does this idea originate? According to a dubious and oft-repeated historical account, the dying Pope Innocent VIII (1432–1492) was allegedly given a transfusion of blood drawn from three ten-year-old boys, who are said to have perished the very same evening as a result of phlebotomy. Yet apart from a single note by the chronicler Stefano Infessura (ca. 1435–1500), who attributed this atrocity to the Jewish papal physician Giacomo di San Genesio, likely with antisemitic intent, no evidence of this event exists in contemporary sources. The story, therefore, must be rejected as historically unfounded [6].

2. Parabiosis and Ageing Research

The true roots of these modern treatments can instead be traced back to research on parabiosis, an experimental technique in which two animals are surgically joined so as to share a common circulatory system.

The word parabiosis derives from the Greek para ("beside" or "next to") and bios ("life"). The French physiologist Paul Bert (1833–1886) is generally regarded as a pioneer of this method [7]. Bert initially developed parabiosis as a means to better understand organ transplantation and the interactions between distinct circulatory systems. His work laid the groundwork for later investigations into ageing, tissue regeneration, and the influence of circulating factors on physiological processes.

Parabiosis has renewed interest in blood as a potential therapeutic agent. Since the mid-2000 s, several studies have documented the rejuvenating effects of heterochronic blood parabiosis (HBP), where an old mouse is paired with a young partner. A defining feature of ageing is the progressive decline in tissue regenerative capacity, often linked to dysfunction of stem and progenitor cells as well as the presence of a low-grade systemic inflammation, called inflamm-ageing [8,9]. Parabiosis experiments have compellingly demonstrated that exposure of older animals to a youthful systemic environment can reactivate signalling pathways in hepatic, muscle, and neural stem cells, thereby enhancing tissue repair as well as inflamm-ageing control. Subsequent work has begun to identify circulating factors that contribute to these benefits, such as the chemokine CCL11 (eotaxin-1, an inflammatory chemokine that recruits eosinophils during allergic and inflammatory responses; elevated levels are linked to ageing, reduced neurogenesis, and cognitive decline) and GDF11 (Growth Differentiation Factor 11. involved in tissue development and regeneration. It has been associated with anti-ageing effects, including improved vascular, muscle, and neural function in animal models) [10,11].

In experiments of HBP, old mice appear to benefit from exposure to young blood: their health improves and their lifespan is extended. Conversely, young mice exposed to the blood of older animals display deleterious effects, suggesting that age-related circulating factors may in fact accelerate the ageing process. Two distinct phenomena thus emerge: induced rejuvenation**,** whereby an older organism gains systemic benefits from youthful circulation, and accelerated ageing, in which youthful organisms suffer physiological decline when exposed to older blood [12].

Experimental evidence has shown that virtually all cell types can undergo modifications in response to changes in blood composition. Remarkably, exposure to young blood even appears to reverse certain molecular hallmarks of ageing, influencing epigenetic markers, proteomic and metabolomic profiles. By contrast, older blood exerts the opposite effect on young mice, hastening their physiological decline [13,14].

This model has proven highly informative for identifying circulating molecules that either drive or delay ageing (Table 1). In general, systemic factors exchanged through parabiosis can modulate cellular senescence by promoting it or, conversely, by facilitating the clearance of senescent cells. Evidence also indicates that parabiosis restores mitochondrial performance across multiple tissues and regulates inflammatory pathways, either intensifying inflammation under conditions of accelerated ageing or suppressing it when rejuvenation is induced. In the central nervous system, accelerated ageing through parabiosis results in impaired intercellular signalling, enhanced DNA damage, and subsequent genomic instability. By contrast, rejuvenating conditions improve proteostasis and promote favourable epigenetic remodelling. In tissues such as bone marrow, skeletal muscle, and liver, stem cell attrition is attenuated during rejuvenation. Enhanced mitochondrial activity has been observed in neurons, hematopoietic and immune cells, vascular endothelium, and muscle fibres. Moreover, macroautophagy has emerged as a key contributor to rejuvenation in skeletal muscle and renal tissue. Induced rejuvenation also prevents the accumulation of senescent cells in the brain, pancreas, hematopoietic and immune systems, skeletal muscle, and visceral adipose tissue (VAT). Conversely, accelerated ageing under parabiosis fosters chronic inflammation in multiple organs, including brain, bone, skeletal muscle, liver, vascular endothelium, kidney, eye, and VAT, whereas rejuvenating conditions suppress inflammatory responses in these compartments [11,13,15]. This is not surprising given the previously stated key role of low-grade chronic inflammation in the ageing process [9].

The connection between organisms in heterochronic parabiosis permits the exchange of a wide variety of circulating components, including hormones, enzymes, blood cells, non-coding RNAs, extracellular vesicles, and even mitochondria, that can shape cellular and tissue function. As previously noted, one of the most compelling findings from this line of research is that certain aspects of age-related decline may not only be slowed but potentially reversed. Specific circulating proteins seem to play a pivotal role in this process, yet the underlying mechanisms remain only partially understood. Deciphering these pathways is crucial for the development of effective strategies to delay ageing and to promote healthy longevity. Proteins or other molecules identified as key mediators of ageing may first serve as valuable tools to deepen our understanding of the ageing process, and eventually as therapeutic targets for interventions designed to mitigate age-associated conditions, thereby enhancing quality of life [13,15,16].

Table 1. Circulating factors identified by heterochronic parabiosis that influence ageing.

Organ	Age of Mice	Crosslinking Time	Factor	Effect	Description
Brain	2–3 months (young) 20–22 months (old)	5 weeks	CCL11	Detrimental	Trigger pro-oxidant and inflammatory pathways to promote cellular senescence.
	3 months (young) 23 months (old)	5 days	β2M	Detrimental	Stabilize the interaction of MHC-1 and PIRB to interfere with synaptic refinement.
	3 months (young) 20 months (old)	24 days	PF4	Beneficial	Disrupt NMDA signaling. Bind to CXR3 to mitigate inflammatory factors.
	3–4 months (young) 20–22 months (old)	4–5 weeks	HSF1	Beneficial	Induce transcription of heat shock chaperones.
Bone	3 months (young) 21 months (old)	4 weeks	GDF11	Beneficial	Upregulate the SMAD2/3 pathway to promote COL2A1 secretion
Muscle	3 months (young) 21 months (old)	4 weeks			Promote differentiation by activating the SMAD2/3 pathway. Improve mitochondrial activity by increasing PGC1α levels.
Heart	2–3 months (young) 21–23 months (old)	4 weeks			Reduce senescent cells, inflammation, and reverse cardiac hypertrophy.
Liver	4 months (young) 20 months (old)	5 weeks	MANF	Beneficial	Decrease inflammation.
	3–4.5 months (young) 19 months (old)	5 weeks	miR-29c-3p	Detrimental	Target extracellular and secretory proteins
Eye	3 months (young) 11 months (old)	4 months	TPM1	Beneficial	Regulate inflammatory responses

All the studies used mice of the C57BL/6 strain. Reproduced from [13] under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). Abbreviations: C-C motif chemokine ligand 11 (CCL11), β2-microglobulin (β2M), growth differentiation factor 11 (GDF11), heat shock factor 1 (HSF1), mesencephalic astrocyte-derived neurotrophic factor (MANF), platelet factor 4 (PF4), Tropomyosin α1-chain protein (TPM1). References are in [13].

3. Parabiosis: Translational Challenges

In an extensive study [17], the authors conducted prolonged HPB for three months, followed by a two-month separation period of the paired animals. Strikingly, older mice that underwent detachment displayed improved physiological performance and lived significantly longer than age-matched isochronic controls. Epigenetic analyses demonstrated that HPB markedly reduced the biological age of both blood and liver, as assessed by multiple clock models across two independent platforms, with these rejuvenating effects persisting even after the detachment phase. At the transcriptomic level, parabiosis exhibited a strong positive correlation with other longevity-promoting interventions and an inverse correlation with ageing signatures. Gene set enrichment analyses revealed sustained upregulation of pathways linked to energy metabolism, such as the Krebs cycle, oxidative phosphorylation, mitochondrial biogenesis, and fatty-acid metabolism, while pro-inflammatory programs, and general inflammatory responses, were consistently downregulated in heterochronic animals. Several genes previously associated with longevity showed durable expression changes even after separation. Together, these findings indicate that extended HPB drives stable remodelling of both the epigenome and transcriptome, resulting in prolonged improvements in healthspan and lifespan. Notably, the study highlights that long-term (3-month) parabiosis produces substantially stronger rejuvenation of molecular and physiological profiles compared to short-term (5-week) exposure, with older mice acquiring intermediate features between youthful and old states. Although both reduced representation bisulphite sequencing and RNA-seq consistently captured these effects across attached and detached groups, the limited overlap between the two omics layers suggests that parabiosis simultaneously reshapes multiple regulatory dimensions [17]. Currently, several strategies are known to reverse epigenetic age, including early embryonic rejuvenation, pharmacological interventions, and transient expression of reprogramming factors [18–20]. Future investigations comparing these approaches may uncover shared molecular mechanisms that could be leveraged to reproduce the rejuvenating benefits of parabiosis without resorting to an invasive and technically challenging surgical model [17].

Research groups worldwide are actively exploring the development of pharmacological agents capable of suppressing pro-ageing pathways while simultaneously activating those that favour resilience and repair. Molecules identified through this approach represent indeed critical candidates both for dissecting the biology of ageing and for guiding the development of therapeutic strategies aimed at delaying age-associated pathologies and improving healthspan. Such molecules may serve as targets for inhibitors when they promote ageing or for activators when they confer rejuvenation. Such strategies may ultimately open the way toward innovative therapies aimed at counteracting the progressive decline characteristic of old age [13,17].

An especially intriguing dimension of this research is its parallel to a naturally occurring phenomenon that resembles heterochronic parabiosis: pregnancy [18]. During gestation, mother and foetus share circulating factors, raising the fascinating question of whether the foetus might experience detrimental effects from certain maternal blood components. A recent study has suggested that pregnancy accelerates the biological ageing of the mother. However, childbirth appears to exert a compensatory effect, slowing this process. Even if such findings are not universally confirmed, understanding how they are regulated could yield novel insights into the biology of ageing as well as maternal health.

Returning to experimental parabiosis, the direct transferability of results to humans is, of course, not feasible. It should primarily be taken into account that laboratory mice are simplified models. They are inbred, genetically identical and highly homozygous as a result of repeated brother-sister mating across many generations, and live their entire lives in cages under controlled conditions. Human ageing and age-related diseases are, instead, multifactorial processes influenced by uncontrolled environmental factors, lifestyle diversity, and random events. But most importantly, in the previously cited study reporting highly interesting positive outcomes [17], heterochronic parabiosis was carried out for a duration of three months. Clearly, permanently connecting the vascular systems of an older subject and a younger one is inconceivable, not only for obvious ethical and practical reasons but also for biological ones. Such a procedure would require the use of immunosuppressive drugs to prevent immunological incompatibility, thereby undermining any potential beneficial effects.

However, heterochronic parabiosis is widely used as an experimental model to investigate circulating factors that modulate the ageing process. Exposure of young organisms to the blood of older counterparts accelerates age-associated decline, whereas exposure of older organisms to young blood can exert rejuvenating effects. The biomedical relevance of these studies ultimately depends on the identification and isolation of the active components, whose safety must then be carefully evaluated and adapted to the complexity of human biology. Nonetheless, more comprehensive investigations are clearly required. A major challenge in this field lies in the substantial variability across heterochronic parabiosis experiments. Differences in study design, including the sex and age of the animals, the anatomical site and technique of vascular anastomosis, the duration of cross-linking, surgical procedures, diet, and levels of physical activity, limit reproducibility and comparability. Additional studies in alternative animal models would also be valuable. For these reasons, the establishment of standardized conditions is critical to enhance reliability and facilitate the broader translation of results. Although current findings are promising, the cellular and molecular mechanisms underlying these effects remain incompletely understood, and ongoing research should aim to elucidate, particularly through studies that explicitly account for the role of sex, given its importance in human ageing processes [21,22].

4. A Different Approach: Therapeutic Plasma Exchange

A distinct though related approach is plasmapheresis, which involves withdrawing blood from an individual and immediately separating its liquid component from the cellular fraction using an automated mechanical separator, generally via centrifugation. During this procedure, the plasma is removed while the cellular elements are reinfused through the same venipuncture. Plasmapheresis is used either for plasma donation (productive plasmapheresis) or for therapeutic purposes. The therapeutic variant, known as plasma exchange or therapeutic plasma exchange (TPE**)**, entails the removal of plasma from a patient affected by a systemic disease with organ dysfunction (e.g., autoimmune or metabolic conditions) and its replacement with donor plasma or albumin [23–26]. In the United States, ongoing attempts have focus on repeated transfusions of young plasma into older recipients to delay ageing and cure or prevent age-related diseases. Yet no clinical trial has ever standardized these procedures (for example, how many transfusions correspond to a single day of parabiosis?), demonstrated their efficacy, or, crucially, established their safety.

However, pilot clinical studies and reviews have suggested that TPE, by removing plasma containing potentially harmful systemic age-related factors, could serve as a rapid and effective rejuvenation therapy. This technique should contribute to restoring a “youthful” state of key signalling pathways [27]. Accordingly, findings from a study involving only eight participants [28] seems to support the hypothesis that, as in mice, human ageing

is driven by systemic molecular overload associated with advancing age, and that mitigating this excess can reverse biological age. In this paper, biological age was defined as the deregulation, or "noise," of ten newly identified protein biomarkers. The data indicate that repeated sessions of TPE induce a broad shift toward a younger systemic proteomic profile. This includes the restoration of pro-regenerative, anticancer, and apoptotic regulators to more youthful levels, as well as a rejuvenated distribution of myeloid and lymphoid markers in circulating cells, accompanied by reduced senescence and lower DNA damage. At the mechanistic level, TPE appears to rebalance key signalling pathways, like NF-κB, and Toll-like receptor (TLR) signalling, primarily through normalization of TLR-4 (both NF-κB and TLR-4 are involved in inflamm-ageing [22]), which the authors identify as a central regulator of molecular rejuvenation. Moreover, the procedure counters age-related features of blood, such as inflamm-ageing, elevated DNA damage and senescence in peripheral blood mononuclear cells, and immune dysregulation, all of which increase disease susceptibility. By rapidly diluting age-accumulated inhibitors of canonical pathways that govern tissue repair and maintenance, TPE reconditions the systemic environment to a more youthful state. The immediate outcome is a reduction in inflammatory activity, followed by improved cellular and molecular homeostasis, supported by more precise intercellular communication and decreased biological noise, as described in the study [28]. Nonetheless, it is concerning that one of the authors of these studies already advertises bookings for this treatment on a personal website, not only for ageing, but also for Alzheimer's disease and long COVID-19, despite the extremely limited evidence [5]. As below discussed, in most countries such practices are tightly regulated and confined to transfusion centres. Unfortunately, in the United States, alongside prestigious medical schools and research institutions, there also exist ventures promoting scientifically unvalidated treatments, thereby exposing patients to considerable risks.

On the other hand, a more recent investigation evaluated whether plasmapheresis, performed without replacement by young plasma or albumin, could influence epigenetic age and additional biomarkers in healthy adults. In this trial [29] healthy blood donors were randomized into two groups by stratified allocation. Participants underwent either eight plasmapheresis sessions or four sessions over an 18-week period, with a minimum interval of 14 days between procedures. Collected samples were analysed using biochemical and haematological assays as well as epigenetic clock measurements. No participant withdrew due to serious adverse events or illness directly linked to the procedures. Clinically relevant reductions in total cholesterol, non-HDL cholesterol, and triglycerides were observed, supporting the notion that plasmapheresis may positively influence dyslipidaemia, a major cardiovascular risk factor. Nevertheless, significant decreases in albumin and total protein levels were also detected, and no evidence of epigenetic rejuvenation was obtained. Although plasmapheresis has been proposed to modulate circulating concentrations of pro-inflammatory and other pro-ageing molecules, the applied protocols did not provide conclusive support for general health benefits in the studied population. Importantly, the dataset failed to demonstrate any rejuvenating effects. On the contrary, an increase in specific epigenetic ageing markers suggested that repeated sessions may induce biological changes aligned with accelerated ageing. These findings emphasize the importance of further investigation to determine whether protocol modifications, such as albumin supplementation or longer intervals between donations, could reduce potential adverse effects. While plasma donation every two weeks is considered safe in many countries, robust data addressing its long-term impact on donor health remain limited. The present study indicates that, although reductions in LDL cholesterol and triglycerides were achieved, definitive therapeutic benefits were not established. Moreover, epigenetic analyses not only failed to reveal rejuvenation but in some cases pointed toward accelerated ageing, raising concerns regarding possible long-term risks of frequent plasma extraction [29].

It is puzzling that, on 13 October 2021, the millionaire Johnson announced an anti-ageing attempt called "Project Blueprint". In this project, Johnson underwent a series of six monthly 1-liter plasma transfusions with his son as the donor for one of the transfusions, but he said he will not repeat the transfusions due to lack of benefits. Now, Johnson follows a strict dietary and lifestyle regimen in pursuit of life extension and he self-proclaims himself as the healthiest human on Earth [30].

In conclusion, despite the enthusiasm generated by prior literature suggesting a rejuvenating role for plasmapheresis, the current findings argue against its readiness for clinical application as an anti-ageing intervention. Future research should aim to refine the procedure by extending inter-donation intervals, restoring essential plasma components such as albumin, and directly comparing plasmapheresis with alternative interventions. Ultimately, the promise of this technology may lie in its ability to lower cholesterol and potentially eliminate additional harmful pro-inflammatory or pro-ageing factors, thereby reducing reliance on pharmacological therapies. However, achieving this goal will require careful optimization to ensure a balance between effective clearance of detrimental molecules and preservation of systemic homeostasis, paving the way for a safe, individualized rejuvenation strategy. Again, the future goal is to translate these findings by isolating and using specific rejuvenating factors, rather than whole plasma, to develop effective anti-ageing therapies.

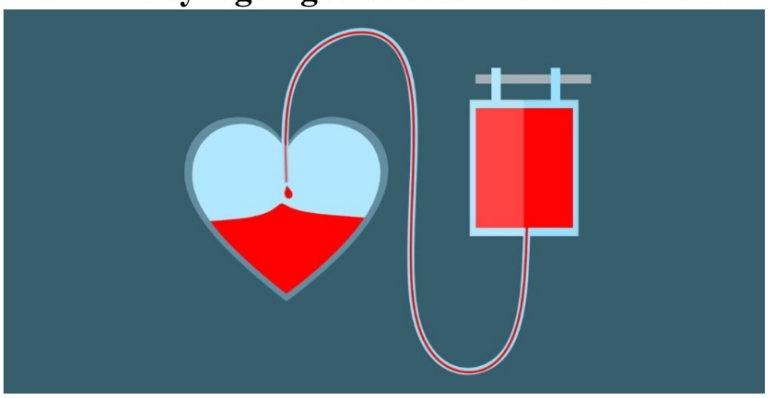
The U.S. Food and Drug Administration [31] as expressed serious public health concerns regarding plasma transfusions marketed as treatments for ageing, memory loss, dementia, Parkinson's disease, multiple sclerosis, Alzheimer's disease, and cardiovascular diseases. No scientific evidence supports their effectiveness, and plasma products carry inherent risks, including allergic reactions, infections, and significant adverse effects from large-volume transfusions.

In most European countries such risks do not exist, as the use of blood components is strictly regulated and restricted to authorized Transfusion Centres. No other public or private entity is permitted to collect or administer blood components. Plasma collection is just sufficient for legitimate transfusion needs and blood derivative production. Unlike in the U.S., European donors cannot sell their blood.

However, as evolutionary medicine teaches us, there is no single model of ageing: everyone is a unique case of ageing because the process is influenced by a diverse mix of genetic, lifestyle, environmental, health, and psychological factors, leading to significant individual variability in physical and cognitive decline, the emergence of diseases, and functional abilities. Moreover, sex and gender have not been into account and it is well known that men and women follow different ageing and longevity trajectories. Factors like diet, exercise, access to healthcare, and even cultural context shape a person ageing experience, making it a complex and highly personalized journey rather than a uniform process. each individual ages and becomes ill uniquely, shaped by their distinct genotype and exposome. The exposome encompasses all non-genetic exposures that can influence human health as well as ageing trajectories, including the physical environment, diet, lifestyle, chemicals, infections, and socioeconomic status [22,32]. Anti-ageing therapies therefore require personalized approaches. It is by no means certain that, once the factors counteracting ageing are identified in "young" blood, their infusion would prove beneficial for all recipients.

The risks and benefits of plasmapheresis are outlined in Figure 1.

Therapeutic Plasma Exchange (Plasmapheresis) and Healthy Ageing: Benefits and Limitations



Potential Benefits	Limitations and Risks
Removal of pro-inflammatory factors (cytokines, inflammatory molecules associated with inflamm-agEing).	Lack of robust clinical evidence: findings are preliminary or derived from animal models.
Possible systemic rejuvenation effects, with improvements in cognition and metabolism suggested in preclinical and early human studies.	Procedural risks: hypotension, electrolyte imbalances, infections, allergic reactions to plasma substitutes, and depletion of immunoglobulins with repeated sessions.
Effect comparable to plasma dilution: benefits may arise from reducing or diluting harmful age-associated plasma proteins.	Scalability and cost: invasive procedure, resource-intensive, not easily applicable to the general population.
Established clinical use in autoimmune diseases, providing a known safety profile when performed in specialized centers.	Ethical and regulatory hurdles: plasmapheresis for anti-ageing is not currently approved and raises significant concerns.
	Unclear durability of benefits: potential effects may be temporary without evidence of long-term health improvements.

Figure 1. The risks and benefits of plasmapheresis.

5. Lifestyle and Healthy Ageing

Ultimately, the pursuit of healthy ageing does not depend on elusive "miracle cures" but on well-established behavioural choices. A substantial body of evidence demonstrates that lifestyle has a profound impact on life expectancy in the general population, particularly up to the eighth and ninth decades of life. Genetic factors appear to play only a marginal role until these ages, becoming decisive primarily for those who achieve extreme longevity beyond the century mark. In contrast, lifestyle factors exert a much stronger influence earlier in life [33].

Notably, life expectancy in the United States remains shorter than in most other high-income countries. Analyses from the Nurses Health Study and the Health Professionals Follow-up Study identified five key low-risk lifestyle components [34]: never smoking, maintaining a body mass index between 18.5 and 24.9 kg/m^2, engaging in at least 30 min per day of moderate-to-vigorous physical activity, consuming alcohol in moderation, and adhering to a high-quality diet (top 40% by score). These studies estimated hazard ratios (HRs) for mortality across lifestyle scores ranging from 0 to 5, using life table methods to project life expectancy. Over up to 34 years of follow-up, 42,167 deaths were recorded. Individuals who adhered to all five factors, compared with none, had markedly lower risks of death: HR 0.26 for all-cause mortality, 0.35 for cancer, and 0.18 for cardiovascular disease (CVD). The proportion of deaths attributable to non-adherence was striking—60.7% for all-cause mortality, 51.7% for cancer, and 71.7% for CVD. Life expectancy at age 50 for those adopting none of the low-risk behaviours was 29.0 years for women and 25.5 years for men. By contrast, adherence to all five behaviours extended life expectancy at age 50 to 43.1 years for women and 37.6 years for men, gains of 14.0 and 12.2 years, respectively. These findings provide compelling evidence that lifestyle modification can markedly reduce premature mortality and prolong survival in U.S. adults [34].

More recently, data from the Veteran Affairs Million Veteran Program (2011–2019), which enrolled 719,147 participants aged 40–99 years, further underscored the cumulative benefits of health behaviours [35]. A subgroup of 276,132 veterans with complete baseline information on eight lifestyle factors was followed for 1.12 million person-years, over which period 34,247 deaths were recorded. The eight behaviours considered were: maintaining a healthy diet, engaging in regular physical activity, ensuring adequate sleep, managing stress effectively, fostering social connections, avoiding smoking, preventing opioid misuse (a particularly pressing issue in the United States), and moderating alcohol intake. Mortality risk declined progressively with each additional behaviour adopted: adjusted HRs ranged from 0.74 with one factor to 0.13 with all eight, compared to veterans with none. At age 40, projected life expectancy varied dramatically: men adopting all eight factors could expect to live 47.0 years longer (to about age 87), whereas those adopting none averaged 23.0 additional years. For women, the corresponding projections were 47.5 years versus 27.0 years, a difference of 20.5 years. These results demonstrate that adopting multiple health-promoting behaviours is associated with substantially extended life expectancy, with a graded benefit depending on the number of factors incorporated [35].

6. Conclusions

Together, these studies as well as those performed in Blue Zones characterized by healthy longevity [36], provide strong empirical support for the principles of lifestyle medicine, highlighting the extent to which individuals can shape their own health trajectories through behavioural choices, without relying on purported miracle interventions. However, even optimal adherence to health-promoting lifestyles does not guarantee survival to 100 years. Achieving exceptional longevity requires not only favourable behaviours but also a contribution from genetic inheritance, which grows increasingly important with advancing age [16].

Author Contributions

The authors contributed equally to the paper. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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