



## The Relationship Between Vitamin B12 and Telomere Length: A Systematic Review

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### ABSTRACT

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Telomeres are natural nucleoprotein structures that cover the ends of chromosomes. The phenomenon of telomere shortening, which plays a crucial role in maintaining the stability of the genome, occurs gradually over time when cells undergo division due to the end replication issue. Multiple studies have demonstrated a correlation between telomere shortening and a range of illnesses, including diabetes, dyslipidemia, cardiovascular disease, cancer, and mortality. Diet and lifestyle can affect telomere length. There exists a beneficial association between telomere length and the Mediterranean diet, particularly with regards to the consumption of dietary fiber derived from whole grains and vegetables. Micronutrients such as vitamins and trace elements also play a role in cell metabolism. Some micronutrients, such as vitamin D, folate, and vitamin B12, are associated with telomere biology and cellular aging. Vitamin B12 is essential for DNA synthesis and epigenetic methylation processes. The present systematic review examines the results from clinical trials conducted in humans evaluating the role of vitamin B12 on telomere length. Cellular senescence is a state characterized by inflammation, altered cellular metabolism, genomic instability, and telomere dysfunction, which can be induced by changes in methylation patterns and oxidative stress. Vitamin B12 maintains antioxidative defense. Through these pathways, sufficient amounts of vitamin B12 may potentially play a role in the restoration of DNA damage. Most of the evidence is based on very few randomized clinical trials. Therefore, more extensive prospective cohort studies and better-designed randomized clinical trials are required to validate the correlations outlined in this review.

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### Introduction

Telomeres are repetitive nucleotide sequences that protect the ends of chromosomes and ensure genomic stability and are considered a biomarker of biological aging (Pusceddu et al., 2015). Telomere shortening is a phenomenon that takes place with every occurrence of cell division, functioning as a reliable marker of the cell's chronological age and its near to senescence (Nomura et al., 2017). The reduction in telomere length has been found to be correlated with an increased susceptibility to various illnesses and mortality (Zarei et al., 2021). Certain micronutrients, namely vitamin D, folate, and vitamin B12, have a role in telomere biology and the process of cellular aging (Pusceddu et al., 2015). Vitamin B12, which has an antioxidant function that reduces oxidative stress, is involved in methylation reactions and increases homocysteine, the deficiency of which can compromise telomere length through increased oxidative stress (Praveen et al., 2020). The presence of sufficient vitamin B12 in the human body has the potential to facilitate the

process of DNA damage repair. Additionally, it is reasonable to anticipate that vitamin B12 might play a role in safeguarding the integrity of telomeric DNA (Nomura et al., 2017).

This review aims to assess the correlation between vitamin B12 and telomere length.

### Methods

#### Search strategy

The studies included in this systematic review were identified by a literature search conducted in both PubMed and Cochrane Library databases. The databases were searched from their inception to November 2023 using the following term: "vitamin b12 and telomere length". The search included cross-sectional studies and Randomized Controlled Trials (RCT) as well as a manual search. All studies included in the current systematic review are summarized in Table 1.

Table 1. Studies related to vitamin B12 and telomere length

Reference	Design	Population	Method	Results
Pusceddu et al., 2019	cross-sectional study	2970 participants of the LURIC study.	qPCR	Vitamin B12 was associated with all-cause mortality, telomere length and high-sensitive CRP in a non-linear fashion.
Praveen et al., 2020	cross-sectional study	428 apparently healthy subjects: 219 men and 209 women aged 21–88 years	qPCR and radioimmunoassay	Elderly people ( $\geq 60$ years) have shorter telomeres and lower mtCN than the younger ones ( $< 60$ years). Vitamin B12 status may delay aging by preventing the reduction in length and mitochondrial DNA copy number
Shin and Baik, 2016	cross-sectional study	798 men and women aged 55-79 years	qPCR	A weak inverse relationship was found between serum homocysteine levels and leukocyte telomere length in those with elevated serum high-sensitive CRP levels. A weak inverse relationship was observed between serum vitamin B12 levels and leukocyte telomere length.
Nomura et al., 2017	cross-sectional study	7458 US adults ( $\geq 20$ years of age) of the 1999–2000 and 2001–2002 cycles of the NHANES	qPCR	Serum vitamin B12 and $\alpha$ -tocopherol were not associated with LTL in all 4 years combined.
Ulak et al., 2023	RCT	600 Nepalese infants (aged 6 -11 month)	qPCR	Providing daily vitamin B12 for 1 year during infancy in a population at risk of vitamin B12 deficiency does not affect LTL.
Tucker, 2019	cross-sectional study	5581 adults of the NHANES study.	qPCR	Serum vitamin B12 and telomere length had a nonsignificant, inverse relationship in women, but no relation in men. Dietary vitamin B12 was linearly related to telomere length in women, after adjusting for age and race, but not in men.
Pusceddu et al., 2017	RCT	65 subjects ( $> 54$ years)	qPCR	After 1 year of supplementation with B and D vitamins, the relative telomere length correlated negatively with methylmalonic acid. Subjects with a change in relative telomere length above the group median also had a greater change in choline when compared to subjects below the median RTL. Changes in relative telomere length correlated positively with 5,10-methenyl-THF.
Dhillon et al., 2017	RCT	56 subclinically vitamin B12 deficient participants (27 males and 29 females)	qPCR	Whey protein isolate improves vitamin B12 and folate status in adults with subclinical vitamin B12 deficiency. The intervention provided suggestive evidence that whey protein isolate may exert significant effects on the maintenance of genome integrity. Whey protein isolate is more beneficial than soy protein isolate in people with subclinical vitamin B12 deficiency.
Pusceddu et al., 2016	RCT	60 elderly subjects	qPCR	tHcy was significantly reduced in the group taking B vitamins supplements. 5-methylTHF has been shown to be significant determinants of LINE-1 methylation in the group taking B vitamins supplements.
Chen et al., 2022	cross-sectional study	1247 pregnant women of the GUSTO study.	qPCR	Lower vitamin B12 levels are associated a higher risk of giving birth to offspring with shorter TL.

Abbreviations: qPCR, quantitative Real-Time Polymerase Chain Reaction; CRP, C-reactive protein; mtCN, mitochondrial DNA copy number; RCT, randomized clinical trial; LTL, leukocyte telomere length; RTL, relative telomere length; THF, tetra hydro folate; GUSTO, Growing Up in Singapore Towards healthy Outcomes

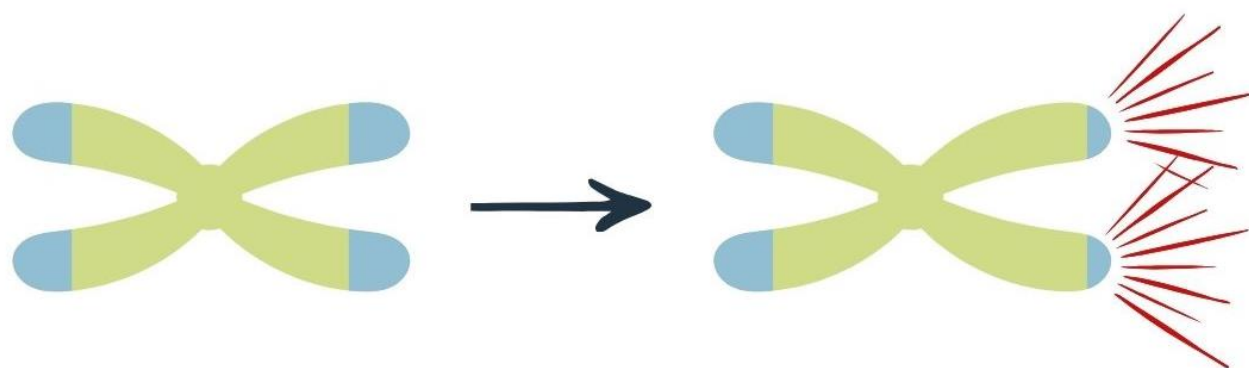


Figure 1. DNA Damage Occurring After Cell Divisions.  
(Shay and Wright, 2019).

### ***Telomere Structure and Properties***

Telomeres in humans are the natural ends of chromosomes. Telomeres are composed of hexameric tandem repeat DNA sequences, namely the highly conserved "TTAGGG" motif, along with related proteins. These ends, which close and protect the eukaryotic chromosome ends, are processed as DNA double-strand breaks (Raftopoulou et al., 2022; Shin and Baik, 2016).

Telomeres are of paramount importance in preserving the integrity of the genome and controlling the process of cellular senescence. Telomere length control is influenced by several factors, including telomere binding proteins, telomere covering proteins, telomerase, and DNA replication enzymes (Zarei et al., 2021). The length of telomeres undergoes a gradual reduction over time due to the end replication issue, and this phenomenon is closely linked to the development of age-related ailments (Taub et al., 2022).

Telomeres are specialized nucleotide sequences situated at the terminal ends of chromosomes, serving as protective structures that safeguard the chromosome against destruction and maintain its structural integrity. Having long telomeres is an advantage. Telomere regions serve to mitigate the destruction of genes located in proximity to the terminal sections of chromosomes by facilitating the inevitable shortening of chromosome ends that transpires during the process of chromosomal replication. Telomere lengths undergo a gradual reduction as a consequence of repeated cellular divisions occurring over the course of an individual's lifespan (Zarei et al., 2021).

The length of telomeres is greater in females than to males (Paul, 2011). A study involved the examination of blood samples obtained from a sample of 43 young individuals (aged 18-32 years) and 47 older adults (aged 65-83 years). The analysis revealed that the telomere length in the younger cohort was observed to be 11.52% greater compared to the older cohort. In the older age group, it has been observed that females exhibit a telomere length that is 12.5% more than that of males (Bull et al., 2009).

Telomeres in humans refer to the repeated DNA sequences located in the terminal regions of linear chromosomes. In the context of normal cellular division, it is seen that telomeres undergo a progressive shortening

process. When some chromosomal termini experience a reduction in length, an uncapped telomere has the potential to induce a signal of DNA damage, leading to the cessation of cellular growth (Figure 1) (Taub et al., 2022).

The regulation of telomere length is governed by epigenetic mechanisms including DNA and histone methylation. Deficiency in the DNA methyltransferases DNMT1 or both DNMT3a and DNMT3b or the histone methyltransferases Suv39 or Suv4-20h results in longer-than-normal telomeres without epigenetic markers. The deficit of methyltransferase does not result in any changes to telomerase expression, either through DNA loss or histone methylation. The regulation of telomere length is influenced by the methylation status of telomeric and subtelomeric regions, which governs the accessibility of telomere extender proteins to these areas (Paul, 2011).

Genomic DNA damage triggers a transient DNA damage response (DDR) that is not sufficient for the occurrence of senescence. The occurrence of irreversible DNA damage at telomeres leads to an extended DDR and the activation of senescence-associated secretory phenotype (SASP)-mediated inflammation, ultimately resulting in cellular senescence. Senescent cells undergo chromatin rearrangement, resulting in the creation of heterochromatin. This process leads to significant alterations in gene expression, an increase in cell size and protein content, as well as modifications in the structure of both the cell and its organelles (Tchkonina et al., 2013). These events in the stem cell context disrupt the properties of the stem cell and alter differentiation. In tissues that undergo rapid cell division, the length of telomeres decreases and elicits a DDR when they reach a dangerously short threshold. Telomere malfunction in non-proliferating, post-mitotic tissues can be attributed to irreversible DNA damage occurring inside the telomeres. Persistent DDR activation maintains a senescent phenotype characterized by aborted proliferation and activation of the SASP (Rossiello et al., 2022). Senescent cells have the potential to induce chronic inflammation throughout the aging process, hence contributing to the development of several age-related illnesses. SASP factors are the main mediators of this effect (Di Micco et al., 2021).

The absence of telomeres during cell divisions results in the loss of chromosomal ends and the vital genetic material they carry. Telomeres serve as protective caps located at the termini of chromosomes, effectively safeguarding their integrity. Over the course of cellular division, telomeres undergo attrition, although they are subsequently restored by the action of the enzyme telomerase. Telomerase deficiency has been shown in association with a range of chronic illnesses and pathological states, including diabetes, dyslipidemia, bacterial infections, cancer, and psychological stress. Risk of early death may increase with telomere shortening (Schellnegger et al., 2022; Zarei et al., 2021).

Aplastic anemia, Alzheimer's disease, chronic kidney disease, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, age-related macular degeneration, ischemia-reperfusion injury, myelodysplastic syndrome, non-alcoholic fatty liver disease, alcoholic liver disease, primary biliary cirrhosis, Parkinson's disease, and Type 2 diabetes are examples of age-related diseases that are linked to cellular aging and telomere dysfunction (Rossiello et al., 2022).

### ***Nutrition and Telomere Length***

The process of biological aging involves the depletion of telomeres and changes in mitochondrial DNA, whereas dietary variables can impact genomic stability (Praveen et al., 2020). Telomere length gradually decreases with each cell division, and emerging research indicates that lifestyle factors may contribute to the process of telomere shortening (Welendorf et al., 2019). The length of telomeres can be influenced by diet and lifestyle factors, since these factors have the potential to impact inflammation, oxidative stress, and psychological stress, all of which contribute to the erosion of telomeres (Paul, 2011).

The consumption of whole grains and other plant-based diets has been found to have a mitigating effect on inflammation. Hence, it may be inferred that the consumption of dietary fiber, particularly derived from whole grains, exhibits a favorable correlation with telomere length (Paul, 2011).

Micronutrients, including vitamins and trace elements, exert a significant influence on cellular metabolism, hence directly affecting telomere biology and the process of cellular aging (Zarei et al., 2021).

The Mediterranean diet is widely acknowledged as a prominent dietary regimen for the purpose of disease prevention and promoting healthy aging. This reputation is mostly attributed to its well-documented anti-inflammatory and antioxidant characteristics, which have been seen to have an impact on the length of telomeres. The findings of a comprehensive examination and statistical analysis of cross-sectional research indicate a positive correlation between increased adherence to the Mediterranean Diet and extended telomere length (Canudas et al., 2020). In a study examining the effects of dietary patterns and inflammation indicators on telomere length, a negative relationship was observed between processed red meat intake and telomere length (Nettleton et al., 2008).

The findings derived from a sample of American adults that accurately represents the nation's population indicate a positive correlation between the oxidative balance score and the length of leukocyte telomeres in women. The utilization of the oxidative balance score serves as a means to assess the impact of one's food and lifestyle on the exposure to oxidative stress. There exists a positive correlation between a higher oxidative balance score, which signifies a greater prevalence of antioxidant exposure relative to prooxidant exposure in one's food and lifestyle, and an extended leukocyte telomere length. The present discovery implies that the adherence to an antioxidant-based diet and lifestyle has a safeguarding influence on the length of telomeres (Zhang et al., 2022).

A probable association exists between the length of telomeres and lifestyle factors, such as levels of physical activity and dietary patterns. The implementation of regular physical activity and a healthy diet have been postulated to potentially mitigate the process of telomere shortening, hence exhibiting potential anti-aging properties (Güneşliol et al., 2023).

### ***Vitamin B12***

Vitamin B12 is found in foods of animal origin and is necessary for genomic stability and cellular metabolism. Vitamin B12 is known to have a significant effect on the development of the nervous system and blood cells, especially in cases where cells change rapidly (Owen et al., 2021).

B vitamins (Folate, vitamin B6, and vitamin B12) in the one-carbon metabolism pathway have been associated with DNA methylation (An et al., 2019). Vitamin B12 plays an important role in DNA methylation metabolism due to its participation in homocysteine metabolism. (Boughanem et al., 2020). Vitamin B12 acts as a cofactor for the methionine synthase enzyme, ensuring the conversion of homocysteine to methionine (Ankar and Kumar, 2022). This enzyme catalyzes the formation of methionine from homocysteine using 5-methyltetrahydrofolate, which is then converted to tetrahydrofolate. Methionine undergoes a conversion process leading to the formation of 5-adenosylmethionine, which serves as a crucial element in several biological methylation events, such as DNA and histone methylation (Boughanem et al., 2020).

In the context of vitamin B12 insufficiency, the conversion of homocysteine to methionine and methyl tetrahydrofolate (THF) to THF is impaired. Consequently, the accumulation of homocysteine levels occurs, leading to the impairment of pyrimidine base formation, so impeding the process of DNA synthesis and resulting in the development of megaloblastic anemia. Anemia subsequently gives rise to symptoms such as weariness and paleness, which are frequently observed in individuals with a shortage in vitamin B12 (Ankar and Kumar, 2022). Furthermore, increased homocysteine levels can cause cognitive decline through oxidative damage (An et al., 2019).

Vitamin B12 serves as a cofactor for the enzyme methylmalonyl-CoA mutase, facilitating the conversion of methylmalonyl-CoA to succinyl-CoA. In individuals suffering from vitamin B12 deficiency, the concentration of methylmalonic acid (MMA) will increase due to the inability of its conversion to succinyl-CoA.

There exists a hypothesis suggesting that the coexistence of elevated levels of MMA and homocysteine contributes to the occurrence of myelin destruction, hence elucidating the underlying mechanisms behind the observed neurological impairments, such as neuropathy and ataxia, in affected individuals (Ankar and Kumar, 2022; Green and Miller, 2022). The presence of a deficiency in Vitamin B12 has been linked to several health conditions, including pernicious anemia, abnormal neurological development, neural tube defects, insulin resistance and, paradoxically, an increased risk of gestational diabetes mellitus. (Owen et al., 2021).

Absorption of vitamin B12 in the distal ileum requires intrinsic factor (Silverstein et al., 2022). The production of intrinsic factor, a glycoprotein, occurs inside the parietal cells located in the stomach. The glycoprotein in question serves a pivotal function in promoting the absorption of vitamin B12, particularly inside the terminal ileum. Once absorbed, vitamin B12 is used as a cofactor for enzymes that participate in the biosynthesis of DNA, fatty acids, and myelin (Ankar and Kumar, 2022).

Due to the higher prevalence of malabsorption in the elderly, vitamin B12 deficiency appears to be more common (Green and Miller, 2022). Those who have had a stomach or small bowel resection, those with inflammatory bowel disease, those who have used metformin for more than four months, those who have used proton pump inhibitors for more than 12 months, those who use histamine H2 blockers, vegans or strict vegetarians, and adults over the age of 75 are at risk for B12 deficiency (Langan and Goodbred, 2017).

#### **The Role of Vitamin B12 in Telomere Length**

The regulation of telomere length and mitochondrial DNA structure involves epigenetic mechanisms, namely methylation and histone modifications. These epigenetic processes can be influenced by dietary micronutrients, including vitamin B12 (Ma et al., 2019).

Vitamin B12 is an essential cofactor required for two enzymatic reactions in the human body. One important aspect is that vitamin B12 serves as a cofactor in the remethylation process of homocysteine to methionine, which is facilitated by the enzyme methionine synthase. On the other hand, vitamin B12 is the cofactor for the

isomerization of methylmalonyl CoA to succinyl CoA by the enzyme methylmalonyl CoA mutase (Pusceddu et al., 2019). Figure 2 shows the reactions related to the recruitment of vitamin B12 as a cofactor.

Homocysteine due to its role in one-carbon metabolism; folate is considered a functional marker of vitamin B6 and B12 availability. The inadequate presence of any of these vitamins might impede the process of homocysteine detoxification, resulting in hyperhomocysteinemia. This condition can lead to an imbalance in oxidative reactions and an elevated production of reactive oxygen species (ROS), including peroxides and free radicals. ROS has the capability to induce detrimental effects on DNA, such as causing damage to DNA bases, breaking DNA strands, and hastening the process of telomere shortening (Herrmann and Herrmann, 2022).

Vitamin B12 plays a crucial role in the maintenance of the body's anti-inflammatory defensive mechanisms (Herrmann ve Herrmann, 2022). Cellular senescence is a state that is brought about by changes in methylation and oxidative stress, resulting in many manifestations such as inflammation, disturbances in cellular metabolism, instability in the genome, and failure of telomeres (Pusceddu et al., 2019; Shin and Baik, 2016). DNA damage and altered DNA methylation are important risk factors for cancer, cardiovascular diseases, developmental and neurological abnormalities (Fenech, 2012).

Vitamin B12 is essential for the biosynthesis of methionine and S-adenosyl methionine (SAM), which serves as a crucial methyl donor involved in the maintenance of DNA methylation patterns that regulate gene expression and chromosomal conformation (Fenech, 2012; Liu et al., 2013). The process of converting homocysteine into methionine, which serves as the precursor for SAM, is catalyzed by a reaction that relies on the presence of vitamin B12 (Paul, 2011). Adequate concentrations of vitamin B12 may contribute to the repair of DNA damage or would be expected to promote the maintenance of telomeric DNA (Nomura et al., 2017). DNA damage is significantly higher in individuals with inadequate folate, vitamin B12, and vitamin B6 intake (Jiang-Hua et al., 2014; Rossiello et al., 2022). Figure 3 shows the relationship between DNA methylation and vitamins.

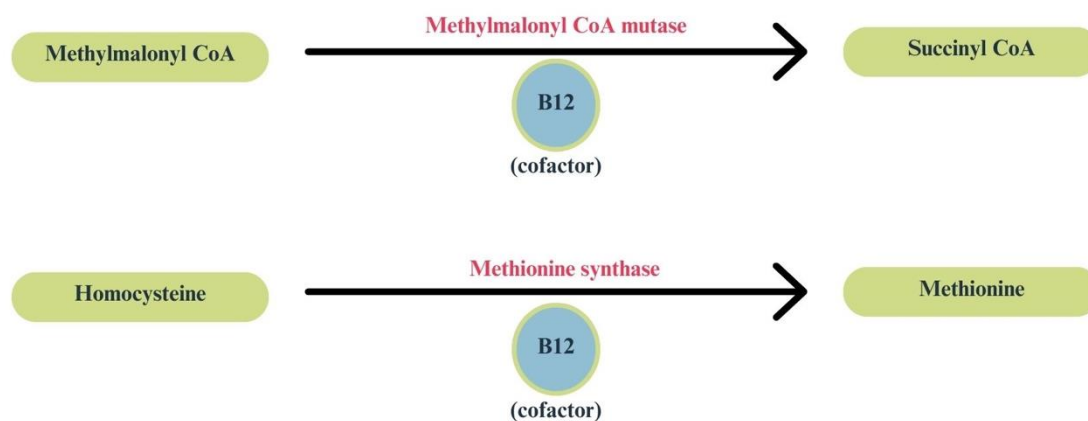


Figure 2. Reactions in which Vitamin B12 Serves as a Cofactor (Boachie et al., 2020).

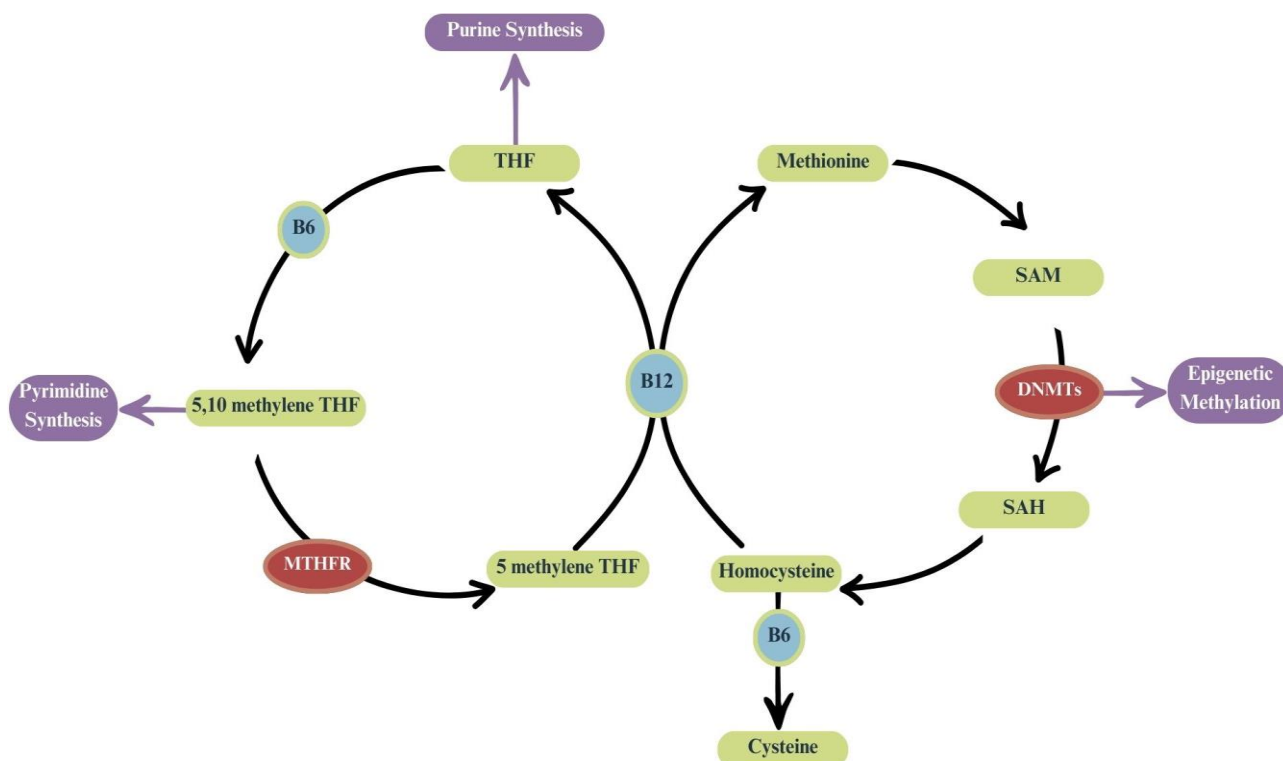


Figure 3. DNA Methylation and Vitamin Relationships (Froese et al., 2019).

Abbreviations: THF, tetra hydro folate; MTHFR, methyl tetra hydro folate reductase; DNMTs, DNA methyltransferases; SAM, S-adenosyl methionine; SAH, S-adenosyl homocysteine.

In a cross-sectional study evaluating the relationships between telomere length and serum folate, vitamin B12 and homocysteine; Serum homocysteine levels due to low-grade systemic inflammation and the presence of adequate folate and vitamin B12 were found to be inversely related to leukocyte telomere length. The research further proposed the maintenance of circulating homocysteine and C-reactive-protein (CRP) levels within the range of normal values as a potential strategy for postponing biological aging in individuals who are in good health (Herrmann and Herrmann, 2022).

It has been shown that plasma folate and vitamin B12 levels in elderly individuals may affect the integrity of the mitochondrial genome, telomere length, and epigenetic regulation of telomere length through DNA methylation (Chou et al., 2007). Plasma folate and vitamin B12 levels may influence aging by stabilizing telomere length and mitochondrial DNA copy number. (Praveen et al., 2020).

According to the findings of Pusceddu et al. (2019), individuals exhibiting either a deficiency or an excess of vitamin B12 display certain features that are linked to increased death rates when compared to those individuals with intermediate levels of vitamin B12. Insufficient vitamin B12 levels and hyperhomocysteinemia appear to be associated with overall DNA methylation and telomere length.

In a different study, telomere length shortened as serum folate and vitamin B12 levels decreased in women. Folate and vitamin B12 have been identified as significant micronutrients in the biological aging process of women (Tucker, 2019).

The length of telomeres in women is positively correlated with the consumption of vitamin B12 supplements. The administration of excessive amounts of

vitamin B12 through supplements has the potential to impede the activity of nitric oxide synthase, leading to a potential decrease in inflammation. The potential mechanism underlying the observed elongation of telomeres in individuals who use high doses of vitamin B12 supplements might be attributed to the mitigated levels of oxidative stress and inflammation resulting from the supplementation (Paul, 2011).

The potential impact of folate, vitamins B6, and B12 on telomere biology has been seen in blood cells. Additionally, insufficient levels of vitamin B and elevated levels of homocysteine in the blood have been linked to changes in DNA methylation and telomere length (Pusceddu et al., 2016). Vitamin B12 (cofactor for methionine synthase) plays a role in the conversion of homocysteine to methionine in one-carbon metabolism and is important for the development of the placenta and fetus in sufficient concentrations during pregnancy (Wilson et al., 2016). Given the crucial impact of maternal nutrition on fetal development, a recent study examined the potential influence of prenatal plasma fatty acids and vitamin levels on the length of telomeres in newborns. The findings of this study revealed a noteworthy positive correlation between the level of vitamin B12 during pregnancy and the length of telomeres in newborns (Chen et al., 2022).

Vitamin B12, which is involved in the production of methyl groups and nucleotides necessary for DNA and histone methylation, is also linked to genome stability. Research has demonstrated a correlation between plasma levels of vitamin B12 and the length and functionality of telomeres (Herrmann and Herrmann, 2022; Praveen et al., 2020; Pusceddu et al., 2019).

All studies included in the current systematic review are summarized in table 1.



## Conclusion

The present review aims to examine the impact of vitamin B12 on telomere length. Telomeres are natural regions that envelop and safeguard the termini of chromosomes. The process of biological aging is influenced by telomere attrition, which may be modulated by variables such as genomic stability, dietary elements, stress, and elevated levels of ROS. Vitamin B12, recognized for its involvement in methylation processes, furthermore exhibits antioxidant properties that mitigate oxidative damage. B12 deficiency increases homocysteine, which can compromise telomere length through increased oxidative stress. The length of telomeres has the potential to be influenced by dietary micronutrients, including vitamin B12. Further research is required to explore the correlation between vitamin B12 and telomere length.

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