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Dietary fat, telomere length and cognitive function: Unravelling the complex relations.

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Abstract

Purpose of review:

The review aims to explore the recent evidence on the associations between different dietary fat intake and cognitive function, and to understand the role of telomere length (TL) in this relationship.

Recent findings:

Clinical and pre-clinical studies included in this review suggest that dietary fat intake is associated with cognitive function and TL. High intake of saturated fats (SF) and trans fats (TF), commonly found in ultra-processed foods, appears to have negative effects on cognitive function and TL, while other dietary fats, such as omega-3 polyunsaturated fatty acids (n-3 PUFAs) and monounsaturated fatty acids (MUFAs) are associated with improved cognitive performance and reduced telomere attrition. Controversial results related to omega-6 PUFA (n-6 PUFA) intake and its impact on cognitive function were found. Dietary fats may affect TL and cognition through oxidative stress, inflammation, and insulin resistance (IR).

Summary:

The current review illustrated the relationship between dietary fat and cognitive function by focusing on the role of TL as a potential mediator. More future studies are required, however, in order to develop targeted interventions aimed at preserving cognitive well-being throughout life.

Keywords:

Dietary fat, Telomere length, Cognition, Cognitive function, PUFAs

1. Introduction

Cognition, encompassing various mental processes such as attention, memory, language, and problem-solving, plays a fundamental role for overall well-being and quality of life (1). However, cognitive decline and cognitive-related disorders are becoming increasingly prevalent, raising concerns about strategies to preserve and enhance cognitive abilities (2). Subtle cognitive decline, mostly affecting thinking speed and attention, is a natural process of aging that can negatively influence health and wellbeing. In abnormal aging, declines in cognition are more severe and affect several cognitive domains, with difficulties in memory recall, attention deficits, language comprehension, problem-solving challenges, or reduced overall cognitive capacity, with an important burden not only in patients, but also their families and friends who usually act as caregivers. Although age is considered the most significant risk factor for cognitive decline, with a prevalence of 10–15% of mild-cognitive impairment (MCI) in the population after the age of 65 years (3), subtle imbalances in cognitive functions can be detected before the age of 50 (4), suggesting that prevention efforts need to begin in midlife.

Recent research has focused on identifying modifiable factors that can influence cognitive function. Diet has been suggested to have an important role in cognitive health and a recent systematic review highlighted the need for adequate nutritional strategies to protect against cognitive impairment (5). Dietary patterns such as the Mediterranean diet (MD), which is rich in fruits, vegetables, whole grains, and healthy fats, have been associated to slower rates of cognitive decline and lower risk of Alzheimer's disease (AD) (6,7). In particular, the total intake of dietary fat and more important the quality of fat has shown varying effects on cognitive health. For example, some systematic reviews and meta-analyses have investigated the relationship between dietary fats and cognitive function, linked saturated fat (SF) intake to a higher risk of cognitive impairment (8,9), while others suggested an inverse relationship

between omega-3 polyunsaturated fatty acids (n-3 PUFAs) intake and MCI and AD risks (10,11). Dietary fats may affect several biological processes such as insulin resistance (IR), oxidative stress, inflammation and vascular function (12,13). However, the biological mechanisms underlying the complex relationship between types of dietary fat and cognition still remain elusive.

Telomeres are nucleoprotein caps found at the end of the linear chromosomes, playing a vital role in chromosome replication (14,15). Telomere attrition is typically associated with aging and mainly occurs due to oxidative stress and chronic inflammation (14,16). Previous studies have demonstrated an inverse relationship between telomere length (TL) and various chronic and aging-related diseases such as AD, type 2 diabetes and cardiovascular disease (14,17). The association between TL and nutritional factors has also been demonstrated in several studies. For example, a systematic review and meta-analysis examining the association between the Mediterranean diet and TL highlighted a direct correlation between adherence to the Mediterranean diet and TL (18). Besides, other systematic reviews discussed the relationship between dietary fats and TL (19,20). However, the significant variation in the types and durations of dietary interventions limits the ability to draw definitive conclusions regarding the relationship between different diets and TL (21). Whether TL and telomerase activity-related genes would mediate the relationships between dietary fat and cognitive health is also unknown.

In this review, we aim to summarise the clinical and pre-clinical evidence on the relation between dietary fat consumption and cognitive function and the potential role of TL in this relationship.

2. Literature search methods

We have considered clinical trials (observational studies and randomized controlled trials (RCT)) and pre-clinical studies conducted *in vitro* or *in vivo*. A comprehensive literature search

was conducted in PubMed (last accessed 1st of July 2023). The specific keywords used were: dietary fat, polyunsaturated fat, monounsaturated fat, saturated fat, trans fat, telomere length, Alzheimer's disease, cognitive function, and dementia.

3. Link between dietary fat, telomere length and cognitive function

To understand the association between dietary fats and cognitive functions and how TL could be an intermediate factor, it is important to review recent evidence in the literature regarding the three-way relationship.

3.1 Dietary fat and cognitive function

In recent years, several observational studies and RCT have examined the impact of different types of dietary fat on cognitive function. Overall, the findings suggest that a high intake of SF and TF, mainly found in ultra-processed foods, may have detrimental effects on cognitive function. These effects include hindering the attention and overall detectability, reducing cerebral perfusion, increasing the risk of AD by altering cerebrospinal fluid (CSF) AD biomarkers and increasing the levels of SF and TF in the brain of AD patients (22–24). Conversely, healthy fats, such as n-3 PUFAs found in fatty fish, nuts, and dietary patterns like MD, ketogenic diet (KD) and MIND diet, have been associated with improved cognitive performance, better quality of life and a reduced risk of cognitive decline (22,23,25–28). Animal models further support these findings. For example, the beneficial effects of MD and KD on cognitive function such as improving spatial working memory, motor coordination and delaying the early stages of neurodegeneration have been demonstrated in male C57BL/6 and female NMRI mice models, respectively (29,30). Another study conducted on mice fed with a high-fat diet (HFD) showed increased working memory and reduced anxiety compared to the group fed with a conventional diet (31). However, some studies have yielded different results, showing that HFD triggered cognitive deficits (29,32,33). The authors explained it by the differences in the feeding period, age and strain of the animals (31). The aforementioned animal

studies with their controversial results emphasize the importance of the type of the dietary fats and suggest that while SF may have negative effects on cognition, diets higher in PUFAs and monounsaturated fats (MUFAs) tend to be associated with better cognitive performance.

3.2 Dietary fat and telomere length

Human studies have discussed the relationship between dietary fat and TL lately. A cohort study of 174 healthy adults in South Australia found a positive association between PUFA intake and TL, while SF intake showed a negative association with TL (34). Similarly, a case-control study with 711 coronary artery diseases (CAD) cases and 638 CAD controls from Singapore revealed a positive association between plasma n-3 PUFAs levels and longer TL, along with a negative association between the plasma n-6:n-3 PUFAs ratio and TL (35). Another cross-sectional study of 2494 US males aged 40-75 years suggested that higher PUFA intake, particularly from canned tuna, had a beneficial effect on TL (36). A recent meta-analysis involving five clinical trials involving 337 mid-age and older adults participants further supported the positive effects of n-3 PUFA consumption on telomere maintenance (37). Recent RCT have also supported these results. For example, the consumption of walnut and pistachio, which are rich in PUFAs and MUFAs, was associated with longer TL (38,39). In animal studies, recent research on telomerase-deficient mice revealed that groups fed with a long-term n-3 PUFA-enriched diet (between 10-24 months) showed lower telomere attrition compared to the control group (40,41). However, a study conducted on female Sprague Dawley rats showed no modification in TL or telomerase reverse transcriptase (TERT) expression in several tissues upon following a HFD rich in SF (42). Overall, while SF intake seem to have deleterious effects on TL, n-3 PUFA consumption has been associated with reduce telomere attrition in both human and animal studies.

3.3 Telomere length and cognitive function

Telomere maintenance is critical for maintaining optimal neural function. Telomere attrition can cause alterations such as apoptosis, blocked cell division, cell aging, and death (43). Telomere shortening in the brain has been linked to aging and aging-related diseases in human studies, including AD, Parkinson's disease, schizophrenia among others (44–52). Notably, individuals with AD had a higher rate of leukocyte telomere shortening per year compared to healthy individuals and those with MCI (53). Data from the UK Biobank, encompassing 435,046 men and women with a mean follow-up of 12.2 years, revealed that longer mid-life leukocyte TL was associated with lower risk of incident AD, better cognitive performance, and less structural lesions (brain imaging data from 43,390 individuals) (54). Thus, TL may serve as a potential biomarker for AD risk, predicting long-term cognitive function before dementia development (55,56). In women and black Americans, longer telomeres were associated with better verbal and phonemic fluency, as well as executive function (57–59). Furthermore, Finnish individuals aged 60-77 years, who followed healthy lifestyles, cognitive training, and monitored metabolic and vascular risk factors, had better TL maintenance and cognitive function (60). In mice hippocampus, telomere attrition in neural stem cells (NSCs) hindered adult neurogenesis and impaired the maintenance of post-mitotic neurons (61). Several animal studies have linked telomerase deficiency to neurodegeneration. Telomerase-deficient mice models (G1, G2, G3, or G4 *Tert*^{-/-} generations with >95% C57BL/6 background, *αSYN*^{Tg/Tg} G3 *Terc*^{-/-}, and Line D mice) exhibited signs of neurodegeneration similar to those observed in physiological aging of mice (62–64). Delivery of telomerase gene therapy to the brain ameliorated this phenotype (62), suggesting potential new strategies for treating neurodegenerative diseases. Overall, existing studies suggest that longer TL would be beneficial for cognition both during the aging process and disease.

4. Mechanistic insights and potential pathways

As previously mentioned, with each chromosome replication, telomeres get shorter until the cells can no longer divide, leading to replicative senescence, and tissue aging. To compensate for telomere shortening, the telomerase enzyme adds repetitive sequences that stabilize TL (65). Telomere attrition and decreased levels of telomerase have been observed in various neuropathological conditions that impact cognition (66–70). The replicative senescence that occurs in proliferating cells as a result of telomere shortening may contribute to some of the mechanisms that cause this deterioration (71). The molecular mechanism by which telomere shortening induces cell senescence is not well known, nevertheless, some studies hypothesize that it involves activating the ATM kinase and subsequent p53 cell senescence pathway which can trigger either cellular senescence or apoptosis (71,72). Additionally, p53 also operates upstream of the telomere-capping protein complex, where it inhibits one of its components, resulting in the activation of ATM. This process forms a positive feedback loop that enhances the cellular responses mediated by p53 (73).

Previous studies have shown that TL and telomerase activity are negatively affected by exposure to pro-inflammatory cytokines and oxidative stress, two processes associated with cognitive decline (74,75). Nutritional interventions with PUFAs have proven to be effective in modulating inflammation and TL (35,37). Generally, n-3 PUFAs such as Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) exert their antioxidant properties by lowering serum pro-inflammatory cytokines (76) and upregulating the transcription factor *NRF2* (77), which is responsible for the expression of cytoprotective proteins and detoxification enzymes (78). Furthermore, it has been demonstrated in mice models that DHA intervention can repair DNA damage and exert anti-inflammatory effects by downregulating PARP1, which involved in DNA repair and apoptosis; and downregulation of NF-kB via the NLRP3/caspase-1 pathway, which helps to restore mitochondrial homeostasis (41). Altogether, DHA hinders all potential telomere attrition-causing mechanisms. Mitochondrial dysfunction serves as another source of

reactive oxygen species (ROS) (79). When cytosolic fatty acids accumulate, they can lead to mitochondrial dysfunction, triggering an upsurge in ROS production. This elevated ROS level can subsequently cause damage to telomeres and telomerase enzyme (80). Therefore, reducing the oxidative burden and inflammation prevents DNA damage at the telomeric levels and telomere attrition (81), and subsequently, it inhibits cell senescence and early cognitive decline.

On the other hand, n-6 PUFAs play a more complex and insufficiently understood role in relation to TL. Lower plasma n-6:n-3 PUFAs ratio is reported to be associated with longer TL (35), although this association is mainly driven by n-3 PUFAs levels, with n-6 PUFAs having little effect on TL (35). Additionally, there are several different types of n-6 PUFAs, and not all of them promote inflammation under the same circumstances (82). For instance, arachidonic acid was associated with enhanced cognitive function (83), while it has been also reported to have both a direct and an inverse correlation with shorter TL (34,84). These contradictory results might be explained by the different metabolic pathways and tissues that n-6 PUFAs take to be metabolized. Arachidonic acid is metabolized into anti-inflammatory derivatives, such as lipoxin A (85,86). Hence, according to the metabolic pathway they take, arachidonic acid and its derivatives might induce pro-inflammatory (leukotrienes and prostaglandins derivatives) or anti-inflammatory (lipoxin A and cytochrome P450 derivatives) actions (85). Therefore, further investigation is essential to understand whether n-6 PUFAs contribute to oxidative stress, telomere attrition and cognitive decline. In contrast, the role of TF and SF is much more defined. Diets high in these fatty acids lead to increased levels of inflammatory biomarkers (87), associated with shorter telomeres. Telomere attrition in microglia may also alter the normal immune functions within the brain and produce neurocognitive deficits (88).

Trans fats exerting their action through ROS (89), may alter cognition by causing mutations in the telomerase enzyme. Given the fact that telomerase restores TL, polymorphisms in the components of telomerase might lead to neurodegeneration, raising the possibility that this

enzyme's mutations may contribute to telomere shortening in diseases like AD (90). It should be noted that telomerase activity might be dependent on the fat concentration, with DHA having different effects at high and low concentrations (91).

Saturated fats are also known to cause peripheral IR by promoting inflammation (92,93). IR and elevated glycaemic levels may explain telomere shortening. As telomeres are rich in guanine residues, they are more susceptible to ROS driven by IR and hyperglycaemia (94). Thus, this creates the perfect environment for telomere shortening, subsequent cellular senescence, and cognitive decline. Nevertheless, the research conducted thus far, are debatable. While short telomeres have been associated with a higher degree of IR, others have found no relation, or even shorter relative leukocyte TL associated with lower IR (95,96). The inconsistencies in the findings could be due to the variation in study populations and methodologies used in these studies. Moreover, it could also be explained by the fact that IR depends on body mass index (BMI) and waist size to explain biological aging, and evidently, there would not be a correlation between IR and TL if all the subjects had the same BMI or waist size (97). Plasma glucagon-like peptide 1 (GLP-1) may provide another explanation. This neurotrophic brain-gut peptide helps maintain glucose homeostasis by enhancing insulin sensitivity with anti-inflammatory and antioxidant-like properties. In a model of young stressed bonnet macaques, higher levels of GLP-1 indicated higher protection for adult TL (98). **Figures 1 and 2** illustrate the mechanisms involved in the complex relationships between dietary fats, TL and cognition.

5. Conclusion

The current review uncovers the complex relationships between dietary fat, TL, and cognitive function. SF and TF appear to have detrimental effects on TL and cognition, whereas diets rich in healthy fats like n-3 PUFAs show promise in reducing telomere attrition and supporting cognitive health. Longer telomeres generally benefit cognitive function. Mechanistically,

oxidative stress, inflammation, and IR play pivotal roles in mediating these relationships. However, further research is needed to establish definitive causality and develop targeted interventions for preserving cognitive well-being throughout life.

Author contribution

H.M., C.P. and M.B. formulated the research questions and designed the review; H.M., L.G.T. and J.M. conducted the literature search, screened the articles, extracted the data, and drafted the manuscript; C.P. and M.B. critically reviewed the manuscript drafting. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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This study describes the association between adult telomere length and adolescent insulin resistance and high pGLP-1. This observation may reflect an adaptive, compensatory response after early-life stress exposure.

Bullet points

- Omega-3 polyunsaturated fatty acids (n-3 PUFAs) and monounsaturated fatty acids (MUFAs) contribute to improved cognitive performance.
- Healthy fats like n-3 PUFAs exhibit potential to preserve telomere length and cognitive well-being.
- High saturated fats (SF) and trans fats (TF) consumption accelerates telomere shortening, impacting cognitive health.
- Inconclusive evidence regarding omega-6 polyunsaturated fatty acids (n-6 PUFA) intake and its cognitive effects.
- Oxidative stress, inflammation, and insulin resistance (IR) are key mechanisms connecting dietary fat, telomere length (TL) and cognition.

Figure titles and legends

Figure 1: The protective role of dietary fats for telomere maintenance and cognitive health.

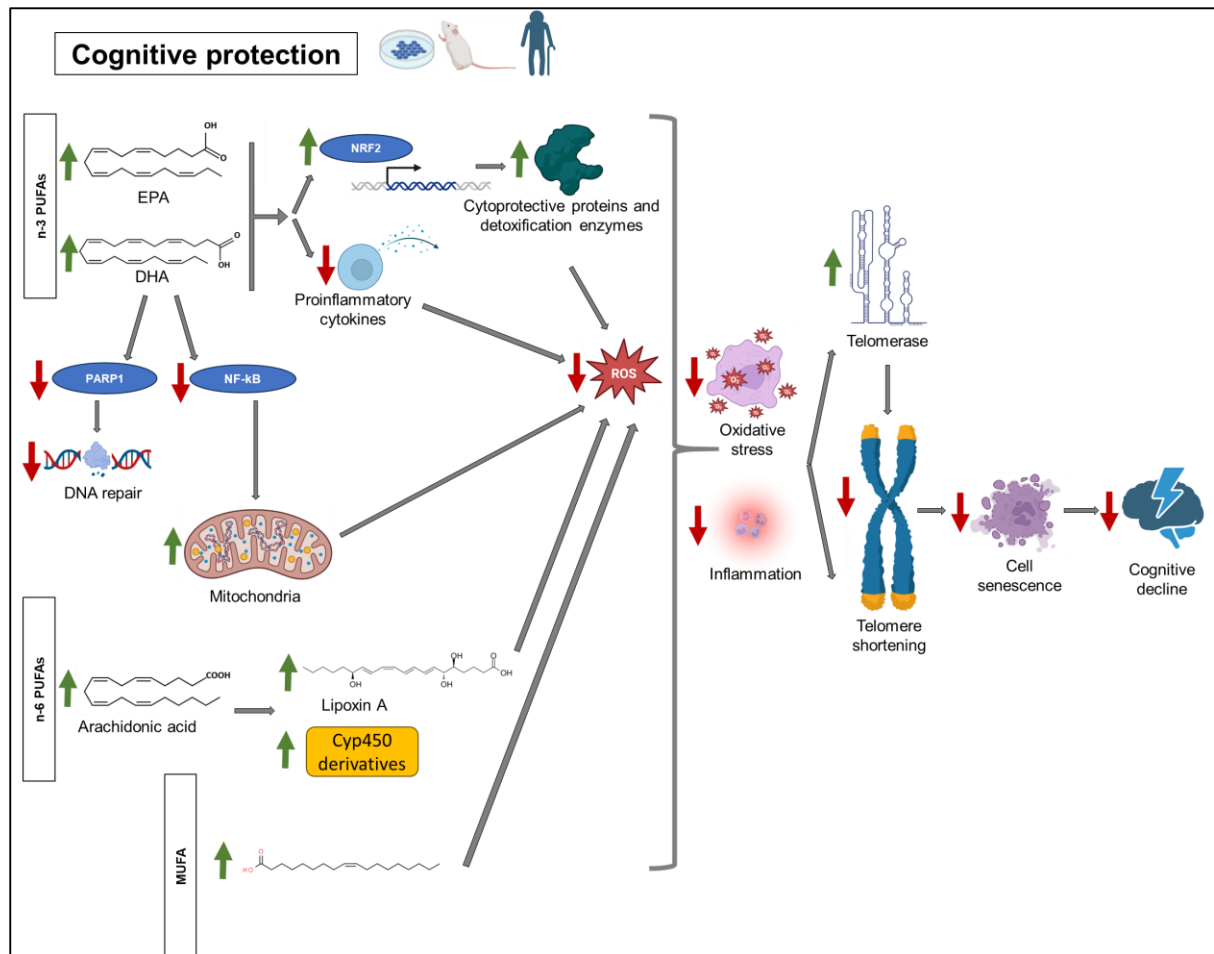
n-3 PUFAs: omega-3 polyunsaturated fatty acids, EPA: eicosapentaenoic Acid, DHA: docosahexaenoic Acid, ROS: reactive oxygen species, n-6 PUFAs: omega-6 polyunsaturated fatty acids.

Figure 2: Mechanisms of cognitive decline by dietary fats and telomere attrition.

n-6 PUFAs: omega-6 polyunsaturated fatty acids, ROS: reactive oxygen species, pGLP-1: Plasma glucagon-like peptide 1.

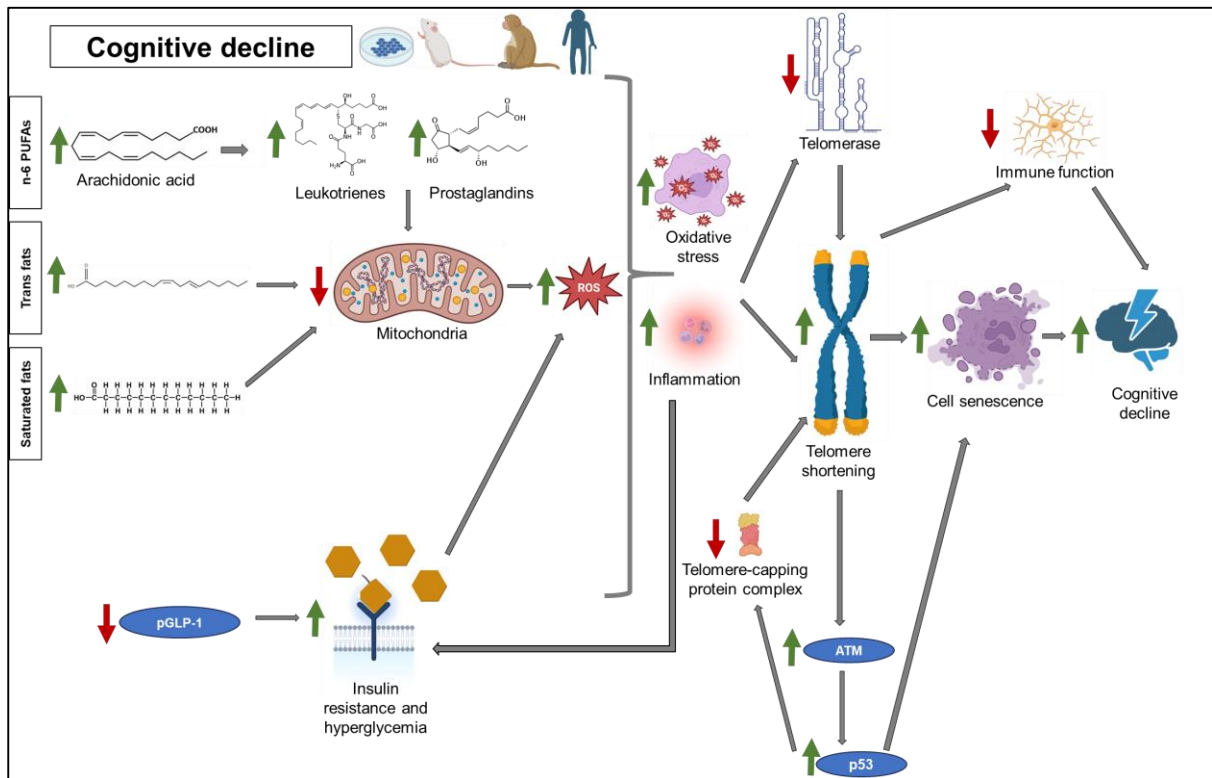
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Figure 1: The protective role of dietary fats for telomere maintenance and cognitive health.



n-3 PUFAs: omega-3 polyunsaturated fatty acids, EPA: eicosapentaenoic Acid, DHA: docosahexaenoic Acid, ROS: reactive oxygen species, n-6 PUFAs: omega-6 polyunsaturated fatty acids.

Figure 2: Mechanisms of cognitive decline by dietary fats and telomere attrition.



n-6 PUFAs: omega-6 polyunsaturated fatty acids, ROS: reactive oxygen species, pGLP-1: Plasma glucagon-like peptide 1.