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Unravelling the nutritional threads with novel associations of cognitive functions and telomerase

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Review Article

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Abstract

Cognitive decline is a hallmark of brain ageing. Leucocyte telomere length (LTL) has emerged as a candidate biomarker related to brain ageing and neurodegeneration; however, reported associations with cognition and brain structure vary across cohorts. Long-chain omega-3 polyunsaturated fatty acids (PUFA), notably docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), exert anti-inflammatory and antioxidant effects that may, in some contexts, relate to slower telomere attrition. Here, we synthesise evidence on *n*-3 PUFA, telomere biology and cognitive outcomes, integrating clinical, epidemiologic and experimental data. We emphasise biological plausibility (oxidative stress/inflammation, membrane remodelling, mitochondrial function and expression of telomerase reverse transcriptase (TERT) through PI3K/Akt/mTOR, NRF2 and epigenetic modifications) while acknowledging heterogeneous human findings and methodological considerations (assay variability, life-course timing, cognitive domains and biomarker stratification). We outline priorities for future studies to clarify causal pathways and inform dietary strategies that support healthy cognitive ageing.

Exploring *n*-3 PUFA, cognitive function and telomerase-activity-dependent telomere length

Neuroscientists have recently been delving into how to prevent or mitigate the effects of ageing (see Glossary), particularly in cognitive decline (see Glossary)[1]. When it comes to cognitive decline and brain senescence, leucocyte telomere length (LTL) (see Glossary) proved to be a significant biomarker[2]. Along with long-chain omega-3 polyunsaturated fatty acids (*n*-3 PUFA (DHA/EPA)) (see Glossary), consumption of vitamin A, vitamin B_{12}, vitamin C, vitamin D, nicotinamide, folate, zinc, magnesium and polyphenols (see Glossary) maintains high telomere length (TL).

This review explores recent evidence examining the associations between *n*-3 PUFA intake and its impact on cognitive function, focusing on LTL as a potential intermediary. Clinical and pre-clinical studies have commenced, unravelling the intricate interactions and correlations between dietary fatty acids and markers of cognitive wellbeing. We aim to contribute to this burgeoning field by exploring nuanced associations and shedding light on the impacts of *n*-3 PUFA on cognitive performance and TL.

Telomeres and their role in ageing and health

Eukaryotic cells use highly complex processes to ensure genome stability and the proper regulation of transcription and translation[3]. Telomeres (see Glossary) are specialised structures at the ends of linear chromosomes in eukaryotic cells. These nucleoprotein complexes ($(TTAGGG)_n$ in mammals, including humans) have several crucial functions, primarily related to the protection and stability of the genome[4,5]. The linear configuration of chromosomes presents two significant challenges: the end-replication problem and the end-protection problem (for example, preventing end-to-end fusions)[5]. During each replication cycle, a small fraction of telomeric DNA at the chromosome ends is lost; if this process remains unabated, chromosomal degradation and cell death are observed. Situated at the ends of the chromosomes, telomeres serve as the main solution against the end replication problem. In addition, telomeres employ mechanisms to tackle the end protection problem[2,6]. To prevent the genome from fusing with other parts of DNA from the hanging endpoints, telomeres behave as caps by attaching telomeric DNA via proteins[7]. Most of the eukaryotes, but not all, engage telomerase (see Glossary) to maintain TL in certain cells[7]. Telomerase includes the telomerase reverse transcriptase (TERT) (see Glossary), which is a unique human telomerase element, not expressed ubiquitously, and a telomerase RNA component (TERC) (see Glossary), enabling the

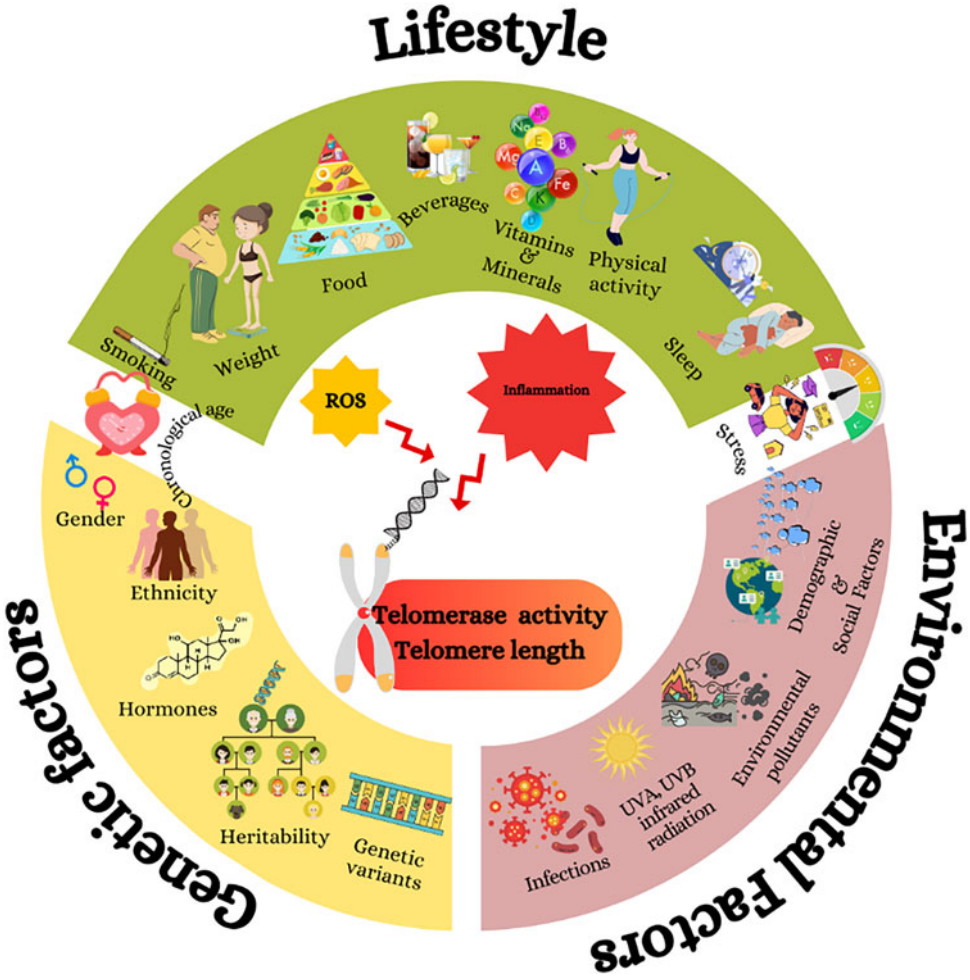

Fig. 1 The effects of genetics, environmental factors and lifespan on telomerase activity and dependent telomere length. Genetic factors such as sex and hormones, environmental factors such as infections; UVA, UVB, infrared radiation; and lifestyle factors such as dietary habits and sleeping trigger reactive oxygen species and inflammation, which cause telomere shortening by decreasing telomerase activity.[16]

template for telomere extension during *de novo* addition of TTAGGG repeats onto chromosome ends[8]. TERT is largely repressed in somatic tissues, with activity in germ cells and subsets of stem/activated immune cells[4]. Cancer cells synthesise telomerase to withstand extreme genomic and oxidative stress (see Glossary) and overcome their replication problem[9].

With each cell division, imperfect copies of the DNA at the ends of each chromosome are generated, leading to the gradual shortening of telomeres. Once telomeres reach a critical length without sufficient telomerase, replication ceases, and cells enter a state known as 'senescence'[10]. However, reintroducing the telomerase enzyme can reverse senescence, highlighting the critical relationship between TL and cell senescence[11].

The link between telomere shortening, inflammation and senescence has recently been suggested as a key factor in neurodegenerative diseases. TERT could regulate oxidative stress and inflammatory responses, thus, slowing down telomere attrition is critical for T-cell senescence and neurodegenerative diseases. Several pieces of evidence point out the modulation of TERT expression is regulated by the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2)[12]. NRF2 promotes the expression of telomere-associated genes, including TERT, and enhances antioxidant defenses, telomere maintenance and protection against disrupted oxidative metabolism. Activation of NRF2 can repair DNA damage as well, thus contributing to telomere integrity.

A body of evidence indicates some determinant signalling pathways for telomerase activity targeting the regulation of TERT. Among them, mTOR, a serine/threonine protein kinase and member of the phosphatidyl inositol-3 kinase (PI3K)-Akt pathway, has been involved in the pathogenesis of cognitive dysfunction and in the onset of disorders and neurodegenerative diseases[13]. It plays a key role in senescence, and the activation of the PI3K/Akt/mTOR pathway led to a decrease in telomerase activity and sped up ageing, whereas inhibition of the PI3K/ Akt/ mTOR pathway increased telomerase activity and delayed aging[14]. The pathway impacts TERT expression through transcriptional regulation, and its downstream effects influence telomere maintenance by influencing the stability and localisation of telomeric proteins such as TRF1[15].

Cellular oxidative stress and low-grade inflammation accelerate telomere attrition by increasing guanine oxidation (for example, 8-oxoG) within telomeric repeats, inhibiting telomerase activity, and perturbing shelterin binding. These processes contribute to DNA damage responses and senescence phenotypes relevant to neurodegeneration. We therefore centralise this mechanism here and, in later sections, reference this subsection rather than restate the same material. Alternative lengthening of telomeres (ALT), a telomerase-independent, recombination-based pathway, is introduced here alongside telomerase to complete the telomere-maintenance landscape; while most prominent in telomerase-negative tumors and immortalised lines, ALT-like

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Table 1 Summary of studies investigating telomere length and cognitive health

Authors	Study type	Model organism and sample size	Method	Results
Sindi *et al.*, 2021[26]	RCT	Human $n = 756$ (377 intervention, 379 control)	Participants aged 60–77 years were assigned to a multidomain lifestyle intervention or control group. Cognitive change was measured using the Neuropsychological Test Battery *z*-score. Relative leucocyte telomere length (LTL) was measured via quantitative real-time polymerase chain reaction (qPCR)	Interaction analyses revealed better LTL maintenance among specific subgroups. LTL maintenance correlated with more pronounced cognitive intervention benefits, suggesting the potential role of telomere length (TL) in cognitive ageing and dementia prevention
Wikgren *et al.*, 2014[27]	OCS	Human $n = 102$ (51 female, 51 male)	Non-demented individuals aged 64–75 years were assessed for leucocyte TL using qPCR. Brain atrophy and white matter hyperintensities (WMHs) were evaluated via magnetic resonance imaging (MRI)	TL was associated with subcortical WMHs than periventricular WMHs, suggesting a link between TL and vascular changes. TL may reflect cumulative exposure to age-related processes affecting white matter integrity
Cao *et al.*, 2023[28]	PCS	Human peripheral blood samples $n = 439\,961$	LTL was measured using qPCR in participants from the UK Biobank. Electronic health records tracked dementia cases, and MRI assessed brain structure in a subset	Shorter LTL was associated with an increased risk of dementia and Alzheimer's disease (AD), as well as smaller total brain volume and reduced volumes of specific brain regions. LTL may serve as a predictive biomarker for assessing brain health
Bernardes de Jesus *et al.*, 2012[30]	Experimental study	Mouse $n = 89$	Mice were injected with adeno-associated vectors expressing different genes. Various assays assessed treatment effects, including telomere Q-FISH analysis, bone density measurements and neuromuscular coordination tests	Telomerase gene therapy extended the health span and lifespan in adult and old mice without increasing cancer risk. Treatment led to rejuvenating effects, including delayed osteoporosis and improved metabolic function. The therapy increased TL and decreased the abundance of short telomeres, indicating potential long-term benefits
Roberts *et al.*, 2014[31]	OChS	Human $n = 437$ (with MCI) $n = 691$ (control)	TL was measured using qPCR. Associations with MCI risk and other factors were assessed using regression models	The shortest and longest TLs were associated with an increased risk of amnestic MCI (aMCI) compared with the middle quintile. TL may be a surrogate marker for aetiologic mechanisms influencing cognition
Scarabino *et al.*, 2019[32]	OCS	Human $n = 176$ ($n = 76$ control; $n = 38$ pre-manifest HD patients; $n = 62$ manifest HD patients)	Leucocyte telomere length (LTL) was measured using real-time PCR. Statistical analyses examined relationships between LTL and Huntington's disease (HD) development	LTL was negatively correlated with age. Differences in TL trends were observed between pre-manifest HD patients and controls. LTL may serve as a measure of time to clinical HD onset
Khan *et al.*, 2015[29]	Experimental study	C57BL/6J mice $n = 12$ ($n = 6$ for TERC KO (G3 KO); $n = 6$ WT)	Using various experimental techniques, telomerase function was manipulated in mice to investigate its effects on microglial cells	Telomerase-deficient mice exhibited reduced microglial numbers and impaired spatial learning abilities compared with wild-type mice

RCT, randomised controlled trial; OCS, observational cross-sectional study; PCS, prospective cohort study; OChS, observational cohort study; MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; HD, Huntington's disease; CAG, the number of trinucleotide repeats of cytosine–adenine–guanine in the HTT gene; TERC KO (G3 KO), TERC knockout mice; WT, wild type.

recombination events have been observed in normal mammalian somatic cells, although convincing *in vivo* evidence that ALT alone sustains telomere elongation enough to bypass replicative limits in normal tissues remains limited[16–20].

Experimental evidence indicates that telomerase contributes to tissue maintenance with potential implications for the ageing brain. In telomerase-deficient aged mice, telomerase reactivation reversed tissue degeneration[21]. Within the CNS, hippocampal telomerase activity has been linked to neurogenesis and mood-relevant behaviours[22], highlighting a mechanistic bridge between telomere maintenance and hippocampal function, a structure central to memory and cognitive ageing.

Finally, TL, telomerase activity and epigenetic modifications are closely inter-related, and this cross-talk accompanies ageing and age-related pathologies. DNA methylation, histone methylation–acetylation and non-coding RNAs can be actors in the regulation of TERT expression in ageing and cancer, which in turn affect telomerase activity[23]. Recent research indicates that cognitive decline in patients with Alzheimer's is concomitant with interaction between TL and DNA methylation for triggering secondary cascades such as mitochondrial dysfunction, disrupted intercellular signalling and chronic inflammation[24].

The impacts of telomere length and telomerase activity on brain functions

The research on cognitive function over the lifespan is an emerging interest as cognitive function changes throughout the lifespan, which is essential for healthy ageing[25]. LTL affects global, regional and subcortical grey matter volumes, as well as cortical thickness in certain regions[2], which serves as markers for neurodegenerative disease (Box 1). TL is associated with several neurodegenerative disorders such as cognitive decline, Alzheimer's disease (AD) (see Glossary), Parkinson's disease (PD) (see Glossary) and Huntington's disease, as presented in Table 1[26–29].

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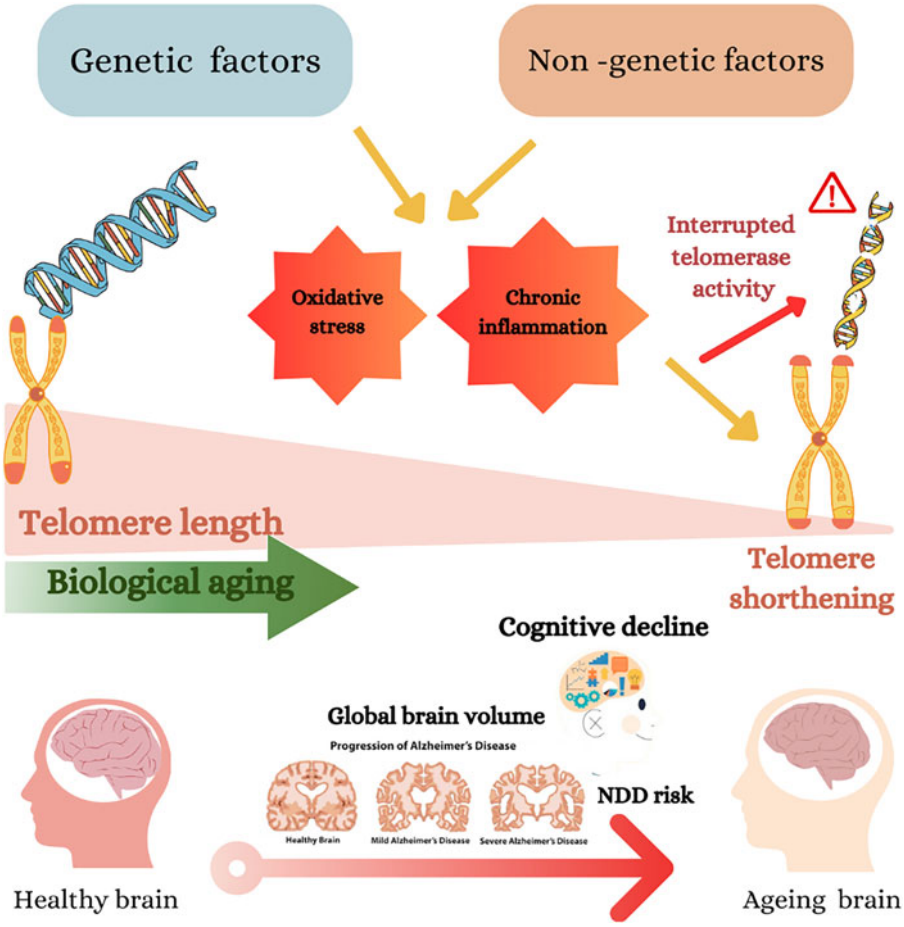

Fig. 2 Genetic and non-genetic factors impact telomere length, biological ageing and cognitive decline. Genetic and non-genetic factors may cause oxidative stress and chronic inflammation, which cause telomere shortening[16]. The shortening of telomeres accelerates biological ageing, shown as a gradient from longer telomeres (healthier) to shorter telomeres (aged)[24]. The diagram further connects telomere shortening to cognitive decline and the risk of neurodegenerative diseases (NDD), including Alzheimer's disease (AD). This is depicted by a progression of brain images from a healthy brain to severe AD, showing a reduction in global brain volume.[28]

Genetic and non-genetic factors contribute to oxidative stress and chronic inflammation (see Glossary).

Across human studies, leucocyte telomere length (LTL) shows heterogeneous associations with cognitive trajectories and brain structure. Several cohorts report that shorter LTL or faster attrition relate to poorer cognitive performance or smaller brain volumes[33–45]. In contrast, other studies observe no association[46–48] or inverse patterns (longer LTL associated with worse outcomes or smaller hippocampal volume)[49–52]. These discrepancies likely reflect differences in age windows (midlife *v.* late-life), study design (cross-sectional *v.* longitudinal), LTL assay methods (monochrome qPCR, Southern blot, flow-FISH), cognitive domains tested, neurodegenerative biomarker status, APOE genotype, sociodemographic composition (race/ethnicity, socioeconomic status [SES]), sample size and statistical adjustment. Reverse causation (preclinical disease accelerating telomere attrition) and regression–dilution bias may also contribute. Overall, evidence supports a biologically plausible link between telomere biology and brain ageing, but effect sizes are modest and context-dependent, underscoring the need for standardised LTL measurement, harmonised cognitive outcomes and biomarker-stratified analyses.

Positive associations (longer LTL/slower attrition resulting in better outcomes):

In non-demented older adults, shorter LTL tracked with poorer cognitive-ageing indices[33]. In the Nurses' Health Study, shorter baseline LTL predicted greater 10-year cognitive decline[35]. Longer LTL is related to larger total and regional brain volumes in a population cohort[38]. Faster telomere attrition associated with medial temporal lobe atrophy and white-matter microstructural decline[42]. Short baseline LTL predicted subsequent memory decline over about 20 years, while within-person LTL change was not informative[44].

Null reports:

Community and family-based samples have also found no association between LTL and global cognition[46–48].

Inverse/context-dependent findings:

In APOE ε3/ε3 carriers, longer LTL correlated with smaller hippocampal volume, suggesting genotype-specific effects[46]. In individuals along the Alzheimer's biomarker cascade, longer baseline LTL is related to faster executive decline (stage-specific effects)[38]. In Mild cognitive impairment (MCI), telomere length was related to connectome features and showed a negative association with executive function after covariate control[49].

Neurodegenerative disorders occur because of cell senescence, canonically triggered by LTL shortening[53]. Cell senescence induces an imbalance in energy metabolism[54]. Alterations in mitochondrial structure or mitochondrial DNA led to mitochondrial respiration dysfunction, which is the process that leads cells to generate energy in the form of ATP. Energy demands in the brain are notably higher than in other organs owing to its high metabolic activity. Impaired mitochondrial respiration can decrease ATP production in neurons and astrocytes, influencing various cellular processes, including neurotransmitter release, synaptic function and overall brain function. Dysfunctional mitochondria and

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shorter LTL, in turn, induce cellular senescence, an irreversible cell-cycle arrest linked to age-dependent physiopathology and phenotypic alterations[55].

Microglia play vital roles in maintaining brain homeostasis by responding to molecular signals, such as ATP, and regulating synaptic activity by releasing immune transmitters such as cytokines and chemokines. Moreover, microglia interact with neural circuits and impact cognitive processes, including learning and memory. Microglia also regulate adult neurogenesis and influence neurogenesis throughout the lifespan[59]. Research showed a positive correlation between microglia number and telomerase-activity-dependent TL. Dysregulation in telomerase-activity-dependent TL causes a reduction in the number of microglia[29]. Reports in injury models link microglial activation/state to telomerase/TL metrics, while the causal direction in humans remains unclear[57].

Neurons are terminally differentiated cells that do not undergo mitosis and are regarded as post-mitotic cells[58]. Owing to their non-replicative nature, the neurons must be maintained and aided. Although at first glance, telomere shortening, a direct result of ageing, should not be an issue for a non-dividing cell, it turns out that despite their terminal differentiation, longer telomeres and healthy maintenance of telomeres are extremely important for the health of brain cells[59].

Although telomerase is mainly known as a telomere-maintaining enzyme (its canonical function), TERT has suggested telomere maintenance-independent functions, named non-canonical functions, such as DNA repair, apoptosis regulation and modulation of signalling pathways[60]. TERT protects neurons against apoptosis by contributing to them becoming more resistant to programmed cell death. TERT affects brain metabolism by regulating cellular redox homeostasis and abating oxidative stress. It plays a crucial role in protecting mitochondria against reactive oxygen species (ROS)-induced (see Glossary) damage and improves mitochondrial function, strengthening mitochondrial membrane potential and decreasing mitochondrial ROS production[61]. Wan *et al.*[23,62] suggested that increased TERT activation improved motor functions such as gait and motor coordination in a transgenic mouse model for PD. TERT also improved the markers of autophagy and degraded toxic alpha-synuclein, which is a protein characterised by PD pathology.

Studies on the relationship between telomere length, *n*-3 PUFA and cognitive performance

PUFA are also known to be indispensable for the wellbeing of the brain by constituting 35% of the brain lipids[63]. Docosahexaenoic acid (DHA) (see Glossary) has been particularly effective in supporting the brain against the onset of dementia and unhealthy brain ageing in completed clinical trials[64–67]. Indeed, supplementation with DHA seems to have protective effects against brain ageing and cognitive decline[68]. In addition, supplementation with *n*-3 docosapentaenoic acid (DPA) has also been associated with slower cognitive decline and AD[69]. Interestingly, the variation in TL, irrespective of chronological age, suggests that it is a modifiable factor that is regulated and affected by other factors such as DNA damage, cell division, ageing, oxidative stress, and inflammation. As such, specific dietary constituents may be potential tools for preserving TL throughout life.

Anti-inflammatory and antioxidant-rich dietary patterns, such as Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND), are associated with lower systemic inflammation and oxidative stress and have been linked to slower cognitive decline and healthier brain structure in multiple cohorts. Because oxidative stress and inflammation accelerate telomere shortening, these diets provide a biologically plausible pathway whereby *n*-3 PUFA and broader dietary patterns may preserve telomere integrity and, in turn, support healthy cognitive ageing. Mechanistically, reduced NF-κB signaling, improved redox balance (for example, via NRF2-regulated responses), and membrane remodelling may converge on slower telomere attrition and improved neurocognitive outcomes.

One of the most relevant observations of brain ageing research pointed out that age-related cognitive decline is not only due to neuronal loss, as previously thought. Oxidative imbalance and chronic inflammation are key issues in this deterioration. Both conditions can contribute to the development of neurodegenerative diseases (see Glossary) or be a result of neuronal degeneration. Moreover, these two pathological hallmarks are linked, and it is known that oxidative stress can affect the inflammatory response. TL is affected by both oxidative stress and inflammation. In fact, oxidative stress highly addresses telomere shortening/dysfunction[70]. Nutritional interventions with fish oils enriched in *n*-3 PUFA have shown ameliorating effects on the triad of inflammation, oxidative stress and immune cell ageing, representing important mechanisms underlying ageing. Therefore, a higher intake of *n*-3 PUFA can play a role in telomere maintenance and influence overall health and longevity[71]. *n*-3 PUFA may protect chromosomal integrity and attenuate DNA oxidative damage by anti-inflammatory and pro-resolving actions, and modulation of redox pathways through the contribution of nuclear factor erythroid 2 (NF-E2)-related factor-2 (NRF2) (see Glossary)[72]. NRF2 plays a critical role in the antioxidant response (see Glossary) and activates the expression of cytoprotective proteins and detoxification enzymes. Anti-inflammatory properties of *n*-3 PUFA are associated with inhibition of proinflammatory transcription factors, leucocyte chemotaxis and oxylipin production[73]. Their enzymatic anti-inflammatory metabolites, such as eicosanoids and docosanoids, can influence low-grade systemic inflammatory conditions associated with endothelial dysfunction, with significant changes in the immune system. A close interaction exists among PUFA and their metabolites, telomere length and the ageing process.

The relationship between TL, *n*-3 PUFA and cognitive performance has garnered significant scientific interest, revealing intricate connections between diet, cellular ageing and mental health. Cassidy *et al.*[74] suggested that body composition and dietary factors affect leucocyte TL in the population of middle- and older-age women. Numerous studies have highlighted how specific dietary components can influence telomere attrition, with particular attention to the benefits of monounsaturated fatty acids (MUFA; see Glossary) and PUFA, especially within dietary patterns such as the Mediterranean diet, known for its high content of these nutrients[75–77]. Such diets have been associated with slower telomere shortening and, consequently, decelerated ageing processes. The results of a prospective cohort study on 608 ambulatory outpatients by Farzareh *et al.*[78] indicated that higher *n*-3 PUFA levels were positively correlated with a smaller decrease in TL over a 5-year period. Even after adjusting for various confounders, the association between higher *n*-3 PUFA may play a role in slowing the ageing process at the cellular level.

A recent study utilising Mendelian-randomisation analysis aimed to investigate how MUFA, PUFA, and saturated fatty acids

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(SFA; see Glossary) affect ageing by comparing proxy indicators of the frailty index (FI), facial ageing (FA), and TL[51]. While MUFA and PUFA were found to be halting the progress of ageing, SFAs were detected to hasten the process. No significant correlations were detected among FI and FA, and MUFA, PUFA, and SFAs. The main indicator and the molecular biomarker for the effect of ageing was TL, and while MUFA and PUFA were correlated with higher TL, SFA had an inverse correlation.

Reduction in TL with increasing age is a common phenomenon in all somatic cells. However, recent studies have suggested that TL can also be enhanced in somatic cells[79,80]. Such a reverse attrition difference in TL was attributed to changes in oxidative stress. Thus, supplementation with *n*-3 PUFA provoked significant changes in TL, which were associated with effects on oxidative stress, inflammation, and immune cell ageing, which were improved with dietary modifications[81]. Healthy lifestyle and anti-inflammatory diets may reduce oxidative stress and thus indirectly support telomere maintenance via canonical pathways; the effects on ALT in normal tissues are unproven[82]. A proposed working mechanism of ALT is a controlled homology-directed repair mechanism created in a controlled manner. Another suggested model explaining ALT is the formation of Holliday junctions at the T-loop structures in mammalian DNA, where the loop is formed by the 3′ overhang fusing to its preceding strand[71].

A meta-analysis study by Ali *et al.*[83] put forward that *n*-3 PUFA supplementation may contribute to telomere maintenance and, by extension, influence ageing and disease prevention despite the limited number of clinical studies. The researchers suggested that the protective effects of *n*-3 PUFA on telomeres may be attributed to their anti-inflammatory and antioxidant properties. These fatty acids modulate inflammatory pathways and enhance antioxidant defenses, potentially through the activation of NRF2 and the regulation of antioxidant properties. The convergence of findings from studies on TL, *n*-3 PUFA and cognitive performance suggests a synergistic relationship (Box 2). The anti-inflammatory and antioxidative effects of *n*-3 PUFA may contribute to the preservation of TL, which in turn could mitigate cognitive decline. A study by O'Callaghan *et al.*[84] revealed that older adults with MCI who received eicosapentaenoic acid (EPA; see Glossary) and DHA supplements had reduced telomere shortening compared with those who took *n*-6 linoleic acids supplements. Wu *et al.*[85] found that DHA supplementation significantly attenuated telomere attrition in blood leucocytes and various tissues, suggesting a protective effect against telomere shortening. The follow-up study with mice supplemented with DHA led to reduced ageing phenotypes, such as lower β-galactosidase activity, indicative of reduced cellular senescence. DHA intervention reduced telomere attrition-induced DNA damage as indicated by lower γ-H2AX levels and enhanced recruitment of poly(ADP-ribose) polymerase 1 (PARP1), a key protein in DNA repair. DHA suppressed the NF-κB/NLRP3/caspase-1 pathways, suggesting anti-inflammatory effects. DHA also improved mitochondrial function, reduced ROS accumulation and decreased markers of oxidative stress by improving mitochondrial homeostasis, and thus reduced mitochondrial damage. All these effects are crucial to maintaining healthy ageing and cognitive functions (see Glossary). Barden *et al.*[86] also stated that the potential impact of *n*-3 acids on the increase of telomere length, adjusted for neutrophil count, may be associated with diminished oxidative stress and enhanced elimination of neutrophils with shorter telomeres from the circulation. All these animal and human studies reveal that there is an association between *n*-3 PUFA, TL and cognitive outcomes.

Discussions of findings and potential mechanisms

TL is a critically important parameter in all cells for optimal functioning, even in terminally differentiated post-mitotic neuronal cells, as demonstrated in a recent study comparing astrocytes and motor neurons generated with different TL[59]. Cells with shorter TL showed elevated inflammation, higher cellular senescence and increased DNA damage. Combined with highly substantial evidence accumulating in the last decade that non-canonical functions of TERT are associated with preserving the genome against sources of DNA damage, including oxidative stress, and the fact that neither the correlation of telomeres nor TERT is properly elucidated, telomeres and TERT emerge as highly promising research for nutrition, ageing and therapeutic medicine.

Another promising research related to non-canonical cellular TERT mechanisms is the capacity for MUFA and PUFA to mitigate telomere attrition. The beneficial effects of different diets on maintaining TL have already been discovered[75]. However, pinpointing the exact sources of nutrients leading to this effect and the exact molecular mechanisms underlying it are not well elucidated.

Interestingly, *n*-3 PUFA supplementation has been associated with pathways affecting TERT expression and telomerase activity. The mTOR pathway is known to be activated by multiple factors, including insulin and nutrients. Both *in vitro* and *in vivo* studies have reported mTOR as an omega-3 target in different pathological conditions[87]. In fact, *n*-3 PUFA inhibit mTOR through different mechanisms, including interference with the PI3K/Akt pathway. The regulatory role of the mTOR signalling pathway has been closely associated to the prevention of major neurological diseases, considering its ability to modulate autophagy, protein synthesis in neurons and the maintenance of synaptic plasticity underlying memory formation. Furthermore, the inhibition of mTOR could exert a protective effect on the brain against inflammation.

n-3 PUFA are suggested to possess the ability to restore NRF2 function, maintain a proper redox balance and preserve telomere length during ageing. In particular, oxidised lipid metabolites as eicosanoids and docosahexanoids coming from the enzymatic action of cyclooxygenases, lipoxygenases and cytochrome P450 over EPA and DHA, are suggested as effective NRF2 inducers[88]. These metabolites are lipid mediator triggers for the NRF2 pathway by quickly reacting with specific cysteine residues of KEAP1, which is the endogenous inhibitor of NRF2.

Among mechanisms to control TERT gene regulation, some dietary compounds, such as *n*-3 PUFA, can alter normal epigenetic states, influencing gene expression, development, metabolism and phenotype. Diet components can also modulate epigenetic modifications, resulting in reverse abnormal gene activation or silencing. Supplementation with *n*-3 PUFA influence gene methylation and modulates the expression of several key pathways associated with the onset of cognitive decline, including those related to inflammation, immune responses, and lipid metabolism[89]. DHA and EPA are suggested as DNA methylation modulators owing to their ability to correct aberrant acetylation and methylation profiles and restore normal patterns. This effect of repair is a key epigenetic mechanism that regulates gene expression in the brain.

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Gaps in literature and areas for future research

The telomeres need to withstand oxidative stress and other possible causes of DNA damage even when the chromosome is not being replicated. Mechanistic pathways are summarised in the 'consolidated mechanisms' subsection[95,96]. Considering the recent findings of how TERT is also somehow related to neuronal health by non-canonical means, the underlying mechanisms need to be fully resolved[60]. A recent similar experiment was designed by creating neurons with different TL from induced pluripotent stem cells (iPSCs), and indeed, a correlation between short TL and neurodegenerative diseases was found[59]. However, the mechanism that can explain this correlation is still not clear.

Among many nutrients, MUFA and PUFA help protect the brain against ageing. A significant amount of the molecular constitution of brain lipids is PUFA; however, the molecular process of how the consumption of PUFA protects against brain ageing is not well explained in relation to the protective effect on TL. While fish oil, especially DHA and EPA, was observed to protect cells against oxidative stress in some studies, long-term consumption of fish oil was observed to increase oxidative stress and even promote ageing[92,93]. This counter relation of PUFA promoting oxidative stress and ageing on their long-term intake illustrates how the exact mechanism of PUFA, ageing, and TL still needs to be well studied, with research focusing on lipid metabolism.

Concluding remarks

Evidence linking *n*-3 PUFA, epigenetic/signalling modulation and broader anti-inflammatory and antioxidant patterns to telomere biology and cognitive ageing is biologically plausible and supported in several cohorts, yet findings are heterogeneous across designs, age windows, assays and populations. Effect sizes appear modest and may depend on neurodegenerative biomarker status, APOE genotype, and sociodemographic context; thus, claims of uniform benefit are not warranted.

To clarify causality and resolve discrepancies, future work should (*i*) standardise LTL measurement and reporting across platforms (qPCR, Southern blot, flow-FISH), (*ii*) harmonise cognitive outcomes and integrate multimodal magnetic resnonace imaging (MRI), (*iii*) adopt longitudinal, life-course designs with pre-specified analyses, (*iv*) stratify by biomarkers (for example, amyloid/tau) and APOE, (*v*) ensure diverse sampling with SES/race adjustments, and (*vi*) complement observational data with median randomization (MR) and rigorously powered dietary or supplementation trials. These steps will determine when, and for whom, dietary strategies may help preserve telomere integrity and support brain health.

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C.Y.: conceptualisation, study design, original draft preparation, review and editing, and visualisation. C.A.: study design, original draft preparation, review, and editing. I.M.: study design, original draft preparation, supervision, review, and editing.

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