Cognitive Function with Nutritional Supplements in Aging

Subjects: Geriatrics & Gerontology

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Cognitive impairment and dementia are burgeoning public health concerns, especially given the increasing longevity of the global population. These conditions not only affect the quality of life of individuals and their families, but also pose significant economic burdens on healthcare systems.

Keywords: dementia ; cognitive function ; dietary supplement intervention

1. Introduction

Cognitive impairment and dementia are among the most significant health challenges of our time, especially as the global population ages [1][2][3][4]. The prevalence of dementia increases exponentially with advancing age [5][6][7], with a prevalence of 0.8% to 6.4% in the population over 65 years of age [8], and 28.5% at age 90 in the European Union [9]. The World Health Organization (WHO) estimates that approximately 50 million people worldwide live with dementia, a number expected to triple by 2050 [10]. Dementia, a syndrome encompassing over 200 conditions [11], is characterized by progressive cognitive impairment [12][13][14] and a decline in functional abilities, often accompanied by behavioral and psychological symptoms [15]. Two of the most prevalent forms of dementia are Vascular Cognitive Impairment (VCI) and Alzheimer's Disease (AD), both contributing significantly to the global dementia burden [16][17][18][19]. These conditions not only impact the individuals suffering from them, but also place a considerable strain on families, caregivers, and healthcare systems. The societal and economic implications are profound, encompassing lost productivity, increased healthcare costs, and substantial emotional and physical burdens on caregivers [15].

The search for effective interventions to prevent, delay, or ameliorate cognitive decline is of paramount importance, especially given the complex mechanisms underlying age-related cognitive decline and dementia [20]. These mechanisms encompass a spectrum of pathologies, ranging from microvascular issues [21], including blood–brain barrier (BBB) disruption [22][23][24][25], impaired cerebral blood flow regulation [26][27][28][29], impaired glymphatic function [30], and small vessel disease [31][32] to macrovascular pathologies such as atherosclerosis [33] and stroke. Additionally, neuroinflammation [34][35], synapse loss, white matter damage [36][37] and changes in connectivity [38][39], neuronal metabolic dysfunction [40][41] and amyloid pathologies [42][43] play significant roles in the progression of cognitive impairment and dementia. These multifaceted and interrelated pathologies highlight the complexity of brain aging and the challenges in mitigating cognitive decline. While pharmacological treatments have shown some benefits, they may not fully address the multifaceted nature of cognitive decline [44][45][46]. This has led to growing interest in alternative approaches [47][48][49][50], particularly dietary interventions and nutritional supplementation [51][52][53][54], as a potential means to support cognitive health. Nutrition plays a crucial role in brain health, and deficiencies in specific nutrients have been linked to cognitive impairments [55][56][57].

Recent studies, including findings from the Chicago Health and Aging Project (CHAP), have highlighted the importance of a healthy lifestyle, comprising a balanced diet, regular physical activity, and cognitive engagement, in extending life expectancy and delaying the onset of dementia [51][58]. Moreover, as the efficiency of nutrient absorption decreases with age and is affected by certain medications, the role of dietary supplementation, such as vitamins B, C, D, antioxidants, and polyunsaturated fatty acids (PUFAs), becomes increasingly significant [59][60][61]. Moreover, elderly individuals typically engage in less physical activity and spend reduced time outdoors, leading to lower levels of sun exposure [62] and, consequently, diminished vitamin D synthesis in their skin. Given these factors, vitamin D supplementation emerges as a crucial intervention for health protection in the elderly [63]. The typical diet often lacks sufficient omega-3 PUFAs, leading to recommendations for consuming fatty fish like tuna or salmon twice a week, or taking fish oil capsules, particularly for those on a vegan diet [52][64][65][66][67][68][69][70][71][72].

2. Vitamin B

B vitamins play a crucial role in maintaining cognitive function during aging, acting as essential cofactors in various neurological processes [73]. As individuals age, the risk of B vitamin deficiencies increases, potentially leading to cognitive decline [74]. Vitamins B6, B9 (folate), and B12 are particularly important, as they contribute to the maintenance of normal brain function by influencing homocysteine metabolism, an amino acid linked to neurodegenerative diseases and cardiovascular and cerebrovascular impairment when present at elevated levels [75][76]. Studies [77][78][79] have demonstrated that a high intake of these B vitamins can significantly slow cognitive decline in older adults, particularly in those with elevated homocysteine levels or mild cognitive impairment [74][80]. For instance, supplementation with B vitamins has been shown to lower homocysteine levels, thereby reducing the rate of brain atrophy and improving cognitive outcomes [81]. Additionally, B vitamins are involved in the synthesis of neurotransmitters and the maintenance of myelin, the protective sheath around nerve fibers, which is crucial for efficient brain signaling [81]. This protective effect of B vitamins against cognitive decline is especially beneficial for older adults who are at an increased risk of dementia, suggesting that adequate intake of these nutrients could play a key role in preserving cognitive health in the aging population [73][74][77][78][80].

3. Vitamin C, Vitamin E and Other Antioxidants

Supplementation with vitamin C, vitamin E, and other antioxidants plays a potential important role in preserving cognitive function during aging, primarily through their ability to combat oxidative stress [82], a key factor in cellular aging [83] and the development of cardiovascular [84] and cerebrovascular impairment [85], neurodegeneration [86] and age-related cognitive decline [87].

Vitamin C is a potent antioxidant that can help protect the brain from oxidative stress, which can impair cognitive functions [88]. In addition, vitamin C plays a pivotal role in the synthesis and functioning of the neurotransmitters dopamine and noradrenaline found in the brain [88]. Several studies have explored the associations between vitamin C and physical and mental well-being; its deficiencies may increase the risk of severe conditions such as cancer, heart disease, and diabetes [89][90][91]. Research has also found links between vitamin C deficiency and attention, concentration, executive function, memory, linguistic and conceptual thinking [92][93][94]. Low levels of vitamin C can negatively affect mood, potentially leading to depression and cognitive impairment [95], in other words, higher levels of vitamin C are correlated with improved mood and reduced depression and confusion [92]. A meta-analysis has described how vitamin C supplementation can enhance the mood in individuals with depression [96]. Consequently, this can improve cognitive performance and reduce the “brain fog” associated with depression [96]. Further research and long-term follow-up studies involving more patients are needed to establish the preventive effect of vitamin C against the development and progression of Alzheimer’s disease [97]. In conclusion, there existing evidence suggests that maintaining healthy levels of vitamin C may be protective against age-related cognitive decline and neurodegenerative diseases, and that cognitive function improves with vitamin C supplementation [97][98].

Vitamin E is a potent fat-soluble antioxidant. It interacts and synergizes with several other antioxidants, such as glutathione, selenium, vitamin C, carotenes, and carotenoids [99]. Vitamin E protects brain cells from oxidative stress-induced damage [100] and is particularly effective in maintaining neuronal integrity and function. It is known for its protective effects against lipid peroxidation in cell membranes, which is vital for preserving cognitive health. Studies have shown that individuals with a higher intake or serum levels of these antioxidants have a lower risk of cognitive decline and dementia, including Alzheimer’s disease [99][100][101]. The existing evidence supports the inclusion of vitamin E supplementation in a dietary protocol aimed at preserving cognitive health in the elderly.

Polyphenols, including resveratrol and curcumin, represent a diverse group of compounds with potent antioxidant and anti-inflammatory properties, playing a significant role in the preservation of cognitive function in aging. Resveratrol, found in grapes and red wine, has gained attention for its potential neuroprotective effects. It is believed to activate pathways that help in protecting cells from damage and improve blood flow to the brain, thereby potentially enhancing cognitive functions and reducing the risk of neurodegenerative diseases [102]. Clinical evidence suggests that resveratrol supplementation can improve memory and cognitive performance in older adults [102][103].

Curcumin, the active component of turmeric, is another widely studied polyphenol known for its strong anti-inflammatory and antioxidant properties. It has been shown to cross the blood–brain barrier and exert neuroprotective effects, potentially helping in the prevention of age-related cognitive decline. Studies indicate that curcumin may improve memory and mood in people with mild, age-related memory loss [104][105].

Other polyphenols, like flavonoids, found in berries, tea, and cocoa, are also crucial for cognitive health [106][107]. Flavonoids have been associated with improved cognitive abilities, reduced risk of dementia, and enhanced memory and learning in older adults [108]. For example, epigallocatechin gallate (EGCG) from green tea has been studied for its role in protecting neurons, reducing the formation of amyloid plaques, and improving cognitive function [109].

Another class of polyphenols, anthocyanins, found in dark-colored fruits like blueberries, have been shown to improve neural signaling and enhance memory [110]. Regular consumption or supplementation with these polyphenols can provide antioxidative and anti-inflammatory benefits, which are particularly beneficial in countering age-related cognitive decline [103]. However, while the biological effects of these compounds are well-documented, more large-scale, long-term clinical trials are needed to conclusively establish their efficacy in preventing or slowing down cognitive impairment in older adults.

4. Vitamin D

Vitamin D, essential for overall health, plays a multifaceted role ranging from maintaining bone health to supporting immune system functions [111][112]. It aids in the absorption of calcium and phosphorus, crucial for optimal bone density, and is involved in normal muscle function and blood sugar metabolism [113][114]. Its significance extends to the development of the brain and nervous system in early childhood and is crucial for cognitive functions such as memory, thinking, and concentration in later life [115]. Vitamin D is also instrumental in producing neurotransmitters like dopamine and serotonin, which regulate mood and emotions [115].

Approximately 40% of the European population is affected by vitamin D deficiency, which can worsen during the late winter months [116]. Consequently, the recommended daily intake for adults has been increased to 2000 IU/day [116][117]. The elderly, along with individuals with chronic diseases, specific dietary preferences, or certain health conditions, are particularly vulnerable to this deficiency [118][119]. Notably, vitamin D deficiency is linked to an increased risk of diseases like type 2 diabetes, cancer, multiple sclerosis, depression, Parkinson's, and Alzheimer's disease [120][121]. A study [122] involving over 1600 elderly individuals revealed that those with mild vitamin D deficiency were over 50% more likely to develop dementia, and the risk was even higher in those with severely low levels. These findings underscore the importance of maintaining adequate vitamin D levels for cognitive health.

Clinical evidence supports the role of vitamin D supplementation in preserving cognitive function, especially in older adults [123][124][125]. Research has shown that adequate levels of vitamin D are associated with improved cognitive performance, and supplementation has been found to benefit those with deficiencies [123][124][125]. This is particularly crucial for cerebrovascular health, as vitamin D supports blood flow to the brain and reduces the risk of cerebrovascular diseases, which can impact cognitive abilities [120][121]. Its role in neuroprotection, neurotransmission, and brain plasticity highlights its potential as a key nutrient in maintaining brain health during aging [126][127]. Therefore, vitamin D supplementation could be a strategic approach in mitigating the risk of age-related cognitive impairment and supporting overall brain health in the elderly population. The exact mechanisms are thought to involve vitamin D's role in neuroprotection, neurotransmission, and brain plasticity, highlighting its potential as a crucial nutrient in maintaining brain health with aging. However, while these associations are promising, further large-scale, long-term studies are needed to establish definitive causal links between vitamin D supplementation and cognitive function preservation in older adults [126][127].

5. Vitamin K

In the human body, vitamin K is an essential component for physiological processes and is also a fat-soluble vitamin [128]. It is naturally expressed in two forms, namely K1 (phylloquinone) and K2 (menaquinone), both of which play pivotal roles in a wide spectrum of physiological processes [128]. Its principal function is to modulate hemostasis through the synthesis of coagulation factors. In addition to these primary roles, vitamin K is also required for various functions in cell growth, proliferation, cell genesis, and apoptosis [128][129][130]. Maintenance of normal vitamin K levels may also contribute to the preservation of memory in the elderly [130]. There are studies suggesting a link between reduced serum concentrations of vitamin K and deterioration of cognitive function in the geriatric population (aged 65 years and above) [130][131][132]. Preclinical studies raise the possibility that vitamin K2 may protect nerve cells against the toxicity of amyloid β [133].

6. Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) [56][111] are increasingly recognized for their critical role in maintaining cognitive function during aging, with ongoing research continuously examining their positive effects on central nervous system functions, including memory, attention, concentration, learning capabilities, and overall well-being [52][65][134][135]

[136][137]. These fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are crucial components of cell membranes in the brain and are involved in various neurophysiological processes [52][64][134][136][138][139][140][141]. DHA, the most abundant omega-3 fatty acid in the brain, is vital for the maintenance and function of neural cells [65][135][136][137]. It is known for its role in enhancing synaptic plasticity and neuronal signaling, which are key factors in cognitive processes like learning and memory [139]. EPA, on the other hand, contributes to cognitive health primarily through its anti-inflammatory properties, which are beneficial in reducing neuroinflammation, a contributing factor to cognitive decline and the development of neurodegenerative diseases [52][64][134][136][138][139][140][141][142][143]. Higher doses of omega-3, typically ranging from 500 to 2000 mg per day, have been suggested to alleviate symptoms of depression and anxiety, further supporting cognitive health [144]. The Western diet, unfortunately, tends to contain more omega-6 fatty acids compared to omega-3, which can be detrimental to health [145]. The optimal ratio of omega-6 to omega-3 is closer to 2:1, and since the body cannot produce these fatty acids, they must be obtained through diet or supplements, with effective doses for various health conditions ranging from 250 to 4000 mg of omega-3 per day [145][146]. Sources of omega-3 include fatty fish like salmon, mackerel, tuna, and plant sources such as flaxseed, chia seeds, nuts, and canola oil [52][64].

Regular consumption of omega-3 supplements is beneficial for cognitive and emotional development, reading skills, and cognitive and concentration abilities [52][65][134][135][136][137]. Furthermore, omega-3 PUFAs have shown potential in reducing the risk of neurodegenerative diseases like Alzheimer’s disease [147], potentially slowing the progression of the disease, delaying its onset, and being associated with improved cognitive abilities. Clinical studies have also demonstrated that regular intake of omega-3 fatty acids can alleviate symptoms of mental health disorders such as depression [134][148][149]. DHA is also essential for the retina, with deficiency leading to vision problems and increased risk of eye diseases [150]. Additionally, omega-3 fatty acids positively affect bones, muscles, and joints, enhancing bone strength and reducing the risk of osteoporosis [151][152]. Therefore, consistent use of omega-3 supplements has been associated with multifaceted health benefits, including improved cognitive ability and reduced susceptibility to cognitive decline [52][64][134][136][138][139][140][141].

7. Mineral Supplementation

Mineral supplementation plays a critical role in supporting brain and cognitive health, particularly in the aging population [153][154]. Minerals, being inorganic substances essential for the body’s physiological functions, cannot be synthesized endogenously and must be obtained through diet or supplementation. Their impact on cognitive abilities is increasingly recognized [153][154].

Magnesium supplementation, for instance, is associated with enhanced cognitive functions and a reduced risk of dementia [155]. Studies [155][156] have demonstrated that individuals with higher magnesium levels have a notably lower risk of dementia. Increased magnesium intake is particularly beneficial for brain health and may help in preserving intellectual function and reducing the risk of dementia, as it protects nerve cells and positively influences blood pressure.

Iron is vital for numerous physiological processes, including cognitive function and cellular metabolism [157][158][159][160][161][162]. Even mild forms of iron deficiency can impair concentration and reduce immunity, and are linked with delayed neurological development and poorer academic performance. Iron supplementation has been shown to positively affect intelligence quotient (IQ) scores and iron-deficiency anemia in the elderly is associated with an increased prevalence of dementia and Alzheimer’s disease [157][158][159][160][161][162].

Selenium is a crucial component of antioxidant enzymes like glutathione peroxidase [163]. These enzymes protect the brain from oxidative stress, which is implicated in aging and neurodegenerative diseases like Alzheimer’s and Parkinson’s [163]. Oxidative stress damages brain cells and impairs cognitive function, so selenium’s role in combating this stress is vital for maintaining cognitive health [87][164][165][166][167][168]. Selenium, contributing to antioxidant defenses, can reduce the risk of diseases by boosting immune function. It has been found that higher levels of selenium in the blood are associated with a reduced risk of cognitive decline and certain types of cancer [169][170]. Selenium is also crucial for the proper functioning of the thyroid gland and plays a vital role in immune health.

Zinc, essential for growth, development, and immune system function [171], is beneficial for the nervous system and may help prevent depression due to its tranquilizing properties. However, zinc deficiency can lead to a decline in cognitive functions and memory [172][173]. Zinc is also vital for the functionality of the antioxidant enzyme superoxide dismutase, which helps eliminate free radicals [174][175][176].

Copper, involved in energy production, connective tissue formation, and the integrity of the cardiovascular and immune systems, requires a balanced intake with zinc [177]. Copper is found in diverse food sources and is also available as a dietary supplement. While copper performs many vital biological functions, the relationship between its intake and the development of diseases like Alzheimer's disease remains complex, with research suggesting that both excess and deficiency may have adverse consequences [178][179].

In summary, minerals such as magnesium, iron, selenium, zinc, and copper are integral to maintaining cognitive health, particularly in the aging population. Their supplementation can support various brain functions, from cognitive performance to reducing the risk of neurodegenerative diseases. This highlights the importance of ensuring adequate mineral intake, either through diet or supplementation, as part of a strategy to preserve cognitive function and overall brain health in older adults.

References

1. Iadecola, C.; Duering, M.; Hachinski, V.; Joutel, A.; Pendlebury, S.T.; Schneider, J.A.; Dichgans, M. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. J. Am. Coll. Cardiol. 2019, 73, 3326–3344.
2. Lane, C.A.; Hardy, J.; Schott, J.M. Alzheimer's disease. Eur. J. Neurol. 2018, 25, 59–70.
3. Li, L.; Hu, L.; Ji, J.; McKendrick, K.; Moreno, J.; Kelley, A.S.; Mazumdar, M.; Aldridge, M. Determinants of Total End-of-Life Health Care Costs of Medicare Beneficiaries: A Quantile Regression Forests Analysis. J. Gerontol. A Biol. Sci. Med. Sci. 2022, 77, 1065–1071.
4. Sebastiani, P.; Andersen, S.L.; Sweigart, B.; Du, M.; Cosentino, S.; Thyagarajan, B.; Christensen, K.; Schupf, N.; Perls, T.T. Patterns of multi-domain cognitive aging in participants of the Long Life Family Study. Geroscience 2020, 42, 1335–1350.
5. Corrada, M.M.; Brookmeyer, R.; Paganini-Hill, A.; Berlau, D.; Kawas, C.H. Dementia incidence continues to increase with age in the oldest old: The 90+ study. Ann. Neurol. 2010, 67, 114–121.
6. Stephan, Y.; Sutin, A.R.; Luchetti, M.; Terracciano, A. Subjective age and risk of incident dementia: Evidence from the National Health and Aging Trends survey. J. Psychiatr. Res. 2018, 100, 1–4.
7. Valsdottir, V.; Magnusdottir, B.B.; Chang, M.; Sigurdsson, S.; Gudnason, V.; Launer, L.J.; Jonsdottir, M.K. Cognition and brain health among older adults in Iceland: The AGES-Reykjavik study. Geroscience 2022, 44, 2785–2800.
8. Rizzi, L.; Rosset, I.; Roriz-Cruz, M. Global epidemiology of dementia: Alzheimer's and vascular types. BioMed Res. Int. 2014, 2014, 908915.
9. Lobo, A.; Launer, L.J.; Fratiglioni, L.; Andersen, K.; Di Carlo, A.; Breteler, M.M.; Copeland, J.R.; Dartigues, J.F.; Jagger, C.; Martinez-Lage, J.; et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000, 54 (Suppl. 5), S4–S9.
10. Shin, J.H. Dementia Epidemiology Fact Sheet 2022. Ann. Rehabil. Med. 2022, 46, 53–59.
11. Scott, K.R.; Barrett, A.M. Dementia syndromes: Evaluation and treatment. Expert Rev. Neurother. 2007, 7, 407–422.
12. Gumus, M.; Multani, N.; Mack, M.L.; Tartaglia, M.C.; Alzheimer's Disease Neuroimaging, I. Progression of neuropsychiatric symptoms in young-onset versus late-onset Alzheimer's disease. Geroscience 2021, 43, 213–223.
13. Van der Willik, K.D.; Licher, S.; Vinke, E.J.; Knol, M.J.; Darweesh, S.K.L.; van der Geest, J.N.; Schagen, S.B.; Ikram, M.K.; Luik, A.I.; Ikram, M.A. Trajectories of Cognitive and Motor Function Between Ages 45 and 90 Years: A Population-Based Study. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, 297–306.
14. Bendayan, R.; Zhu, Y.; Federman, A.D.; Dobson, R.J.B. Multimorbidity Patterns and Memory Trajectories in Older Adults: Evidence From the English Longitudinal Study of Aging. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, 867–875.
15. Duong, S.; Patel, T.; Chang, F. Dementia: What pharmacists need to know. Can. Pharm. J./Rev. Pharm. Du Can. 2017, 150, 118–129.
16. Czakó, C.; Kovács, T.; Ungvari, Z.; Csiszar, A.; Yabluchanskiy, A.; Conley, S.; Csipo, T.; Lipecz, A.; Horváth, H.; Sándor, G.L.; et al. Retinal biomarkers for Alzheimer's disease and vascular cognitive impairment and dementia (VCID): Implication for early diagnosis and prognosis. Geroscience 2020, 42, 1499–1525.
17. D'Arbeloff, T. Cardiovascular fitness and structural brain integrity: An update on current evidence. Geroscience 2020, 42, 1285–1306.
18. Levit, A.; Hachinski, V.; Whitehead, S.N. Neurovascular unit dysregulation, white matter disease, and executive dysfunction: The shared triad of vascular cognitive impairment and Alzheimer disease. Geroscience 2020, 42, 445–

465.

19. Lopez, M.E.; Turrero, A.; Cuesta, P.; Rodriguez-Rojo, I.C.; Barabash, A.; Marcos, A.; Maestu, F.; Fernandez, A. A multivariate model of time to conversion from mild cognitive impairment to Alzheimer's disease. Geroscience 2020, 42, 1715–1732.
20. Fang, X.; Zhang, J.; Roman, R.J.; Fan, F. From 1901 to 2022, how far are we from truly understanding the pathogenesis of age-related dementia? Geroscience 2022, 44, 1879–1883.
21. Istvan, L.; Czako, C.; Elo, A.; Mihaly, Z.; Sotonyi, P.; Varga, A.; Ungvari, Z.; Csiszar, A.; Yabluchanskiy, A.; Conley, S.; et al. Imaging retinal microvascular manifestations of carotid artery disease in older adults: From diagnosis of ocular complications to understanding microvascular contributions to cognitive impairment. Geroscience 2021, 43, 1703–1723.
22. Verheggen, I.C.M.; de Jong, J.J.A.; van Boxtel, M.P.J.; Gronenschild, E.; Palm, W.M.; Postma, A.A.; Jansen, J.F.A.; Verhey, F.R.J.; Backes, W.H. Increase in blood-brain barrier leakage in healthy, older adults. Geroscience 2020, 42, 1183–1193.
23. Verheggen, I.C.M.; de Jong, J.J.A.; van Boxtel, M.P.J.; Postma, A.A.; Jansen, J.F.A.; Verhey, F.R.J.; Backes, W.H. Imaging the role of blood-brain barrier disruption in normal cognitive ageing. Geroscience 2020, 42, 1751–1764.
24. Kerkhofs, D.; Wong, S.M.; Zhang, E.; Uiterwijk, R.; Hoff, E.I.; Jansen, J.F.A.; Staals, J.; Backes, W.H.; van Oostenbrugge, R.J. Blood-brain barrier leakage at baseline and cognitive decline in cerebral small vessel disease: A 2-year follow-up study. Geroscience 2021, 43, 1643–1652.
25. Montagne, A.; Barnes, S.R.; Nation, D.A.; Kisler, K.; Toga, A.W.; Zlokovic, B.V. Imaging subtle leaks in the blood-brain barrier in the aging human brain: Potential pitfalls, challenges, and possible solutions. Geroscience 2022, 44, 1339–1351.
26. Fan, F.; Roman, R.J. Reversal of cerebral hypoperfusion: A novel therapeutic target for the treatment of AD/ADRD? Geroscience 2021, 43, 1065–1067.
27. Wang, S.; Lv, W.; Zhang, H.; Liu, Y.; Li, L.; Jefferson, J.R.; Guo, Y.; Li, M.; Gao, W.; Fang, X.; et al. Aging exacerbates impairments of cerebral blood flow autoregulation and cognition in diabetic rats. Geroscience 2020, 42, 1387–1410.
28. Tarantini, S.; Balasubramanian, P.; Delfavero, J.; Csipo, T.; Yabluchanskiy, A.; Kiss, T.; Nyul-Toth, A.; Mukli, P.; Toth, P.; Ahire, C.; et al. Treatment with the BCL-2/BCL-xL inhibitor senolytic drug ABT263/Navitoclax improves functional hyperemia in aged mice. Geroscience 2021, 43, 2427–2440.
29. Vestergaard, M.B.; Lindberg, U.; Knudsen, M.H.; Urdanibia-Centelles, O.; Bakhtiari, A.; Mortensen, E.L.; Osler, M.; Fagerlund, B.; Benedek, K.; Lauritzen, M.; et al. Subclinical cognitive deficits are associated with reduced cerebrovascular response to visual stimulation in mid-sixties men. Geroscience 2022, 44, 1905–1923.
30. Sabayan, B.; Westendorp, R.G.J. Neurovascular-glymphatic dysfunction and white matter lesions. Geroscience 2021, 43, 1635–1642.
31. Szczesniak, D.; Rymaszewska, J.; Zimny, A.; Sasiadek, M.; Poltyn-Zaradna, K.; Smith, E.E.; Zatonska, K.; Zatonski, T.; Rangarajan, S.; Yusuf, S.; et al. Cerebral small vessel disease and other influential factors of cognitive impairment in the middle-aged: A long-term observational cohort PURE-MIND study in Poland. Geroscience 2021, 43, 279–295.
32. Cai, M.; Jacob, M.A.; Norris, D.G.; de Leeuw, F.E.; Tuladhar, A.M. Longitudinal Relation Between Structural Network Efficiency, Cognition, and Gait in Cerebral Small Vessel Disease. J. Gerontol. A Biol. Sci. Med. Sci. 2022, 77, 554–560.
33. Gardner, A.W.; Montgomery, P.S.; Wang, M.; Shen, B.; Casanegra, A.I.; Silva-Palacios, F.; Ungvari, Z.; Yabluchanskiy, A.; Csiszar, A.; Waldstein, S.R. Cognitive decrement in older adults with symptomatic peripheral artery disease. Geroscience 2021, 43, 2455–2465.
34. Luo, J.; le Cessie, S.; Blauw, G.J.; Franceschi, C.; Noordam, R.; van Heemst, D. Systemic inflammatory markers in relation to cognitive function and measures of brain atrophy: A Mendelian randomization study. Geroscience 2022, 44, 2259–2270.
35. Lazar, G., Jr.; Varga, J.; Lazar, G.; Duda, E.; Takacs, T.; Balogh, A.; Lonovics, J. The effects of glucocorticoids and a glucocorticoid antagonist (RU 38486) on experimental acute pancreatitis in rat. Acta Chir. Hung. 1997, 36, 190–191.
36. Boutzoukas, E.M.; O'Shea, A.; Kraft, J.N.; Hardcastle, C.; Evangelista, N.D.; Hausman, H.K.; Albizu, A.; Van Etten, E.J.; Bharadwaj, P.K.; Smith, S.G.; et al. Higher white matter hyperintensity load adversely affects pre-post proximal cognitive training performance in healthy older adults. Geroscience 2022, 44, 1441–1455.
37. Hausman, H.K.; Hardcastle, C.; Albizu, A.; Kraft, J.N.; Evangelista, N.D.; Boutzoukas, E.M.; Langer, K.; O'Shea, A.; Van Etten, E.J.; Bharadwaj, P.K.; et al. Cingulo-opercular and frontoparietal control network connectivity and executive functioning in older adults. Geroscience 2022, 44, 847–866.

38. Bray, N.W.; Pieruccini-Faria, F.; Witt, S.T.; Rockwood, K.; Bartha, R.; Doherty, T.J.; Nagamatsu, L.S.; Almeida, Q.J.; Liu-Ambrose, T.; Middleton, L.E.; et al. Frailty and functional brain connectivity (FBC) in older adults with mild cognitive impairment (MCI): Baseline results from the SYNERGIC Trial. Geroscience 2023, 45, 1033–1048.
39. Chino, B.; Cuesta, P.; Pacios, J.; de Frutos-Lucas, J.; Torres-Simon, L.; Doval, S.; Marcos, A.; Bruna, R.; Maestu, F. Episodic memory dysfunction and hypersynchrony in brain functional networks in cognitively intact subjects and MCI: A study of 379 individuals. Geroscience 2023, 45, 477–489.
40. Sanchez-Roman, I.; Ferrando, B.; Holst, C.M.; Mengel-From, J.; Rasmussen, S.H.; Thinggaard, M.; Bohr, V.A.; Christensen, K.; Stevnsner, T. Molecular markers of DNA repair and brain metabolism correlate with cognition in centenarians. Geroscience 2022, 44, 103–125.
41. Jiang, J.; Sheng, C.; Chen, G.; Liu, C.; Jin, S.; Li, L.; Jiang, X.; Han, Y.; Alzheimer's Disease Neuroimaging, I. Glucose metabolism patterns: A potential index to characterize brain ageing and predict high conversion risk into cognitive impairment. Geroscience 2022, 44, 2319–2336.
42. Lu, W.H.; Giudici, K.V.; Morley, J.E.; Guyonnet, S.; Parini, A.; Aggarwal, G.; Nguyen, A.D.; Li, Y.; Bateman, R.J.; Vellas, B.; et al. Investigating the combination of plasma amyloid-beta and geroscience biomarkers on the incidence of clinically meaningful cognitive decline in older adults. Geroscience 2022, 44, 1489–1503.
43. Uleman, J.F.; Melis, R.J.F.; Quax, R.; van der Zee, E.A.; Thijssen, D.; Dresler, M.; van de Rest, O.; van der Velpen, I.F.; Adams, H.H.H.; Schmand, B.; et al. Mapping the multicausality of Alzheimer's disease through group model building. Geroscience 2021, 43, 829–843.
44. Casey, D.A. Pharmacotherapy of neuropsychiatric symptoms of dementia. Pharm. Ther. 2015, 40, 284–287.
45. Chaudhari, K.; Reynolds, C.D.; Yang, S.H. Metformin and cognition from the perspectives of sex, age, and disease. Geroscience 2020, 42, 97–116.
46. Balazs, N.; Bereczki, D.; Ajtay, A.; Oberfrank, F.; Kovacs, T. Cholinesterase inhibitors for the treatment of dementia: Real-life data in Hungary. Geroscience 2022, 44, 253–263.
47. Mandolesi, L.; Polverino, A.; Montuori, S.; Foti, F.; Ferraioli, G.; Sorrentino, P.; Sorrentino, G. Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits. Front. Psychol. 2018, 9, 509.
48. Wang, H. Nexus between cognitive reserve and modifiable risk factors of dementia. Int. Psychogeriatr. 2020, 32, 559–562.
49. Dhana, K.; Franco, O.H.; Ritz, E.M.; Ford, C.N.; Desai, P.; Krueger, K.R.; Holland, T.M.; Dhana, A.; Liu, X.; Aggarwal, N.T. Healthy lifestyle and life expectancy with and without Alzheimer's dementia: Population based cohort study. BMJ 2022, 377, e068390.
50. Berg-Weger, M.; Stewart, D.B. Non-pharmacologic interventions for persons with dementia. Mo. Med. 2017, 114, 116.
51. Choi, H. Healthy lifestyles and more life years without dementia. BMJ 2022, 377, o885.
52. Poddar, J.; Pradhan, M.; Ganguly, G.; Chakrabarti, S. Biochemical deficits and cognitive decline in brain aging: Intervention by dietary supplements. J. Chem. Neuroanat. 2019, 95, 70–80.
53. Ungvari, A.; Gulej, R.; Csik, B.; Mukli, P.; Negri, S.; Tarantini, S.; Yabluchanskiy, A.; Benyo, Z.; Csiszar, A.; Ungvari, Z. The Role of Methionine-Rich Diet in Unhealthy Cerebrovascular and Brain Aging: Mechanisms and Implications for Cognitive Impairment. Nutrients 2023, 15, 4662.
54. Ungvari, Z.; Fazekas-Pongor, V.; Csiszar, A.; Kunutsor, S.K. The multifaceted benefits of walking for healthy aging: From Blue Zones to molecular mechanisms. Geroscience 2023, 45, 3211–3239.
55. Azhar, G.; Wei, J.Y.; Schutzler, S.E.; Coker, K.; Gibson, R.V.; Kirby, M.F.; Ferrando, A.A.; Wolfe, R.R. Daily Consumption of a Specially Formulated Essential Amino Acid-Based Dietary Supplement Improves Physical Performance in Older Adults With Low Physical Functioning. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, 1184–1191.
56. Dalle, S.; Van Roie, E.; Hiroux, C.; Vanmunster, M.; Coudyzer, W.; Suhr, F.; Bogaerts, S.; Van Thienen, R.; Koppo, K. Omega-3 Supplementation Improves Isometric Strength But Not Muscle Anabolic and Catabolic Signaling in Response to Resistance Exercise in Healthy Older Adults. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, 406–414.
57. Kim, C.S.; Cha, L.; Sim, M.; Jung, S.; Chun, W.Y.; Baik, H.W.; Shin, D.M. Probiotic Supplementation Improves Cognitive Function and Mood with Changes in Gut Microbiota in Community-Dwelling Older Adults: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, 32–40.
58. Dhana, K.; Evans, D.A.; Rajan, K.B.; Bennett, D.A.; Morris, M.C. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 longitudinal studies. Neurology 2020, 95, e374–e383.
59. Cristina, N.M.; Lucia, D. Nutrition and Healthy Aging: Prevention and Treatment of Gastrointestinal Diseases. Nutrients 2021, 13, 4337.

60. Miller, J.W. Proton pump inhibitors, H2-receptor antagonists, metformin, and vitamin B-12 deficiency: Clinical implications. Adv. Nutr. 2018, 9, 511S–518S.

61. Suliburska, J.; Chmurzynska, A.; Kocylowski, R.; Skrypnik, K.; Radziejewska, A.; Baralkiewicz, D. Effect of iron and folic acid supplementation on the level of essential and toxic elements in young women. Int. J. Environ. Res. Public Health 2021, 18, 1360.

62. Mooldijk, S.S.; Licher, S.; Vernooij, M.W.; Ikram, M.K.; Ikram, M.A. Seasonality of cognitive function in the general population: The Rotterdam Study. Geroscience 2022, 44, 281–291.

63. Fantini, C.; Corinaldesi, C.; Lenzi, A.; Migliaccio, S.; Crescioli, C. Vitamin D as a Shield against Aging. Int. J. Mol. Sci. 2023, 24, 4546.

64. Fekete, M.; Csípő, T.; Fazekas-Pongor, V.; Fehér, Á.; Szarvas, Z.; Kaposvári, C.; Horváth, K.; Lehoczki, A.; Tarantini, S.; Varga, J.T. The Effectiveness of Supplementation with Key Vitamins, Minerals, Antioxidants and Specific Nutritional Supplements in COPD-A Review. Nutrients 2023, 15, 2741.

65. Dighriri, I.M.; Alsubaie, A.M.; Hakami, F.M.; Hamithi, D.M.; Alshekh, M.M.; Khobrani, F.A.; Dalak, F.E.; Hakami, A.A.; Alsueaadi, E.H.; Alsaawi, L.S. Effects of omega-3 polyunsaturated fatty acids on brain functions: A systematic review. Cureus 2022, 14, e30091.

66. De Magalhães, J.P.; Müller, M.; Rainger, G.E.; Steegenga, W. Fish oil supplements, longevity and aging. Aging 2016, 8, 1578.

67. Fekete, M.; Szarvas, Z.; Fazekas-Pongor, V.; Lehoczki, A.; Tarantini, S.; Varga, J.T. Effects of omega-3 supplementation on quality of life, nutritional status, inflammatory parameters, lipid profile, exercise tolerance and inhaled medications in chronic obstructive pulmonary disease. Ann. Palliat. Med. 2022, 11, 2819–2829.

68. Innes, J.K.; Calder, P.C. Omega-6 fatty acids and inflammation. Prostaglandins Leukot. Essent. Fat. Acids 2018, 132, 41–48.

69. Kim, J.S.; Thomashow, M.A.; Yip, N.H.; Burkart, K.M.; Lo Cascio, C.M.; Shimbo, D.; Barr, R.G. Randomization to Omega-3 Fatty Acid Supplementation and Endothelial Function in COPD: The COD-Fish Randomized Controlled Trial. Chronic Obs. Pulm. Dis. 2021, 8, 41–53.

70. Leitão, C.; Mignano, A.; Estrela, M.; Fardilha, M.; Figueiras, A.; Roque, F.; Herdeiro, M.T. The Effect of Nutrition on Aging-A Systematic Review Focusing on Aging-Related Biomarkers. Nutrients 2022, 14, 554.

71. Lane, K.; Derbyshire, E.; Li, W.; Brennan, C. Bioavailability and potential uses of vegetarian sources of omega-3 fatty acids: A review of the literature. Crit. Rev. Food Sci. Nutr. 2014, 54, 572–579.

72. Smith, D.; Refsum, H.; Oulhaj, A.; de Jager, C.A.; Jerneren, F. Beneficial Interactions Between B Vitamins and Omega-3 Fatty Acids in the Prevention of Brain Atrophy and of Cognitive Decline in Early Stage Alzheimer's Disease. FASEB J. 2016, 30, 407.6.

73. Xu, H.; Wang, S.; Gao, F.; Li, C. Vitamin B6, B9, and B12 Intakes and Cognitive Performance in Elders: National Health and Nutrition Examination Survey, 2011–2014. Neuropsychiatr. Dis. Treat. 2022, 18, 537.

74. Smith, A.D.; Refsum, H.; Bottiglieri, T.; Fenech, M.; Hooshmand, B.; McCaddon, A.; Miller, J.W.; Rosenberg, I.H.; Obeid, R. Homocysteine and dementia: An international consensus statement. J. Alzheimer's Dis. 2018, 62, 561–570.

75. Kataria, N.; Yadav, P.; Kumar, R.; Kumar, N.; Singh, M.; Kant, R.; Kalyani, V. Effect of vitamin B6, B9, and B12 supplementation on homocysteine level and cardiovascular outcomes in stroke patients: A meta-analysis of randomized controlled trials. Cureus 2021, 13, e14958.

76. Fekete, M.; Fazekas-Pongor, V.; Szőllősi, G.; Varga, J.T. A krónikus obstruktív tüdőbetegség metabolikus következményei. Orvosi Hetil. 2021, 162, 185–191.

77. Wang, Z.; Zhu, W.; Xing, Y.; Jia, J.; Tang, Y. B vitamins and prevention of cognitive decline and incident dementia: A systematic review and meta-analysis. Nutr. Rev. 2022, 80, 931–949.

78. Gong, X.; Shi, L.; Wu, Y.; Luo, Y.; Kwok, T. B Vitamin Supplementation Slows Cognitive Decline in Mild Cognitive Impairment Patients with Frontal Lobe Atrophy. J. Alzheimer's Dis. 2022, 89, 1453–1461.

79. Smith, A.D.; Smith, S.M.; De Jager, C.A.; Whitbread, P.; Johnston, C.; Agacinski, G.; Oulhaj, A.; Bradley, K.M.; Jacoby, R.; Refsum, H. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. PLoS ONE 2010, 5, e12244.

80. Bottiglieri, T. Folate, vitamin B12, and neuropsychiatric disorders. Nutr. Rev. 1996, 54, 382–390.

81. Calderón-Ospina, C.A.; Nava-Mesa, M.O. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. CNS Neurosci. Ther. 2020, 26, 5–13.

82. Jurcau, A. The role of natural antioxidants in the prevention of dementia—Where do we stand and future perspectives. Nutrients 2021, 13, 282.
83. Mock, J.T.; Chaudhari, K.; Sidhu, A.; Sumien, N. The influence of vitamins E and C and exercise on brain aging. Exp. Gerontol. 2017, 94, 69–72.
84. Moreau, K.L.; Hildreth, K.L.; Klawitter, J.; Blatchford, P.; Kohrt, W.M. Decline in endothelial function across the menopause transition in healthy women is related to decreased estradiol and increased oxidative stress. Geroscience 2020, 42, 1699–1714.
85. Feng, J.; Zheng, Y.; Guo, M.; Ares, I.; Martínez, M.; Lopez-Torres, B.; Martínez-Larrañaga, M.-R.; Wang, X.; Anadón, A.; Martínez, M.-A. Oxidative stress, the blood–brain barrier and neurodegenerative diseases: The critical beneficial role of dietary antioxidants. Acta Pharm. Sin. B 2023, 13, 3988–4024.
86. Sadowska-Bartosz, I.; Bartosz, G. Effect of antioxidants supplementation on aging and longevity. BioMed Res. Int. 2014, 2014, 404680.
87. Shah, H.; Dehghani, F.; Ramezan, M.; Gannaban, R.B.; Haque, Z.F.; Rahimi, F.; Abbasi, S.; Shin, A.C. Revisiting the Role of Vitamins and Minerals in Alzheimer’s Disease. Antioxidants 2023, 12, 415.
88. Figueroa-Méndez, R.; Rivas-Arancibia, S. Vitamin C in health and disease: Its role in the metabolism of cells and redox state in the brain. Front. Physiol. 2015, 6, 397.
89. McCall, S.J.; Clark, A.B.; Luben, R.N.; Wareham, N.J.; Khaw, K.-T.; Myint, P.K. Plasma vitamin C levels: Risk factors for deficiency and association with self-reported functional health in the European Prospective Investigation into Cancer-Norfolk. Nutrients 2019, 11, 1552.
90. Morelli, M.B.; Gambardella, J.; Castellanos, V.; Trimarco, V.; Santulli, G. Vitamin C and cardiovascular disease: An update. Antioxidants 2020, 9, 1227.
91. Conner, T.S.; Fletcher, B.D.; Haszard, J.J.; Pullar, J.M.; Spencer, E.; Mainvil, L.A.; Vissers, M.C. KiwiC for Vitality: Results of a Placebo-Controlled Trial Testing the Effects of Kiwifruit or Vitamin C Tablets on Vitality in Adults with Low Vitamin C Levels. Nutrients 2020, 12, 2898.
92. Sharma, Y.; Popescu, A.; Horwood, C.; Hakendorf, P.; Thompson, C. Relationship between vitamin C deficiency and cognitive impairment in older hospitalised patients: A cross-sectional study. Antioxidants 2022, 11, 463.
93. Pearson, J.F.; Pullar, J.M.; Wilson, R.; Spittlehouse, J.K.; Vissers, M.C.; Skidmore, P.M.; Willis, J.; Cameron, V.A.; Carr, A.C. Vitamin C status correlates with markers of metabolic and cognitive health in 50-year-olds: Findings of the CHALICE cohort study. Nutrients 2017, 9, 831.
94. Travica, N.; Ried, K.; Sali, A.; Hudson, I.; Scholey, A.; Pipingas, A. Plasma vitamin C concentrations and cognitive function: A cross-sectional study. Front. Aging Neurosci. 2019, 11, 72.
95. Plevin, D.; Galletly, C. The neuropsychiatric effects of vitamin C deficiency: A systematic review. BMC Psychiatry 2020, 20, 315.
96. Yosaee, S.; Keshtkaran, Z.; Abdollahi, S.; Shidfar, F.; Sarris, J.; Soltani, S. The effect of vitamin C supplementation on mood status in adults: A systematic review and meta-analysis of randomized controlled clinical trials. Gen. Hosp. Psychiatry 2021, 71, 36–42.
97. Von Arnim, C.A.; Herbolsheimer, F.; Nikolaus, T.; Peter, R.; Biesalski, H.K.; Ludolph, A.C.; Riepe, M.; Nagel, G. Dietary antioxidants and dementia in a population-based case-control study among older people in South Germany. J. Alzheimer’s Dis. 2012, 31, 717–724.
98. Harrison, F.E. A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer’s disease. J. Alzheimer’s Dis. 2012, 29, 711–726.
99. Pincemail, J.; Meziane, S. On the Potential Role of the Antioxidant Couple Vitamin E/Selenium Taken by the Oral Route in Skin and Hair Health. Antioxidants 2022, 11, 2270.
100. Rizvi, S.; Raza, S.T.; Ahmed, F.; Ahmad, A.; Abbas, S.; Mahdi, F. The role of vitamin E in human health and some diseases. Sultan Qaboos Univ. Med. J. 2014, 14, e157.
101. Mangialasche, F.; Solomon, A.; Kåreholt, I.; Hooshmand, B.; Cecchetti, R.; Fratiglioni, L.; Soininen, H.; Laatikainen, T.; Mecocci, P.; Kivipelto, M. Serum levels of vitamin E forms and risk of cognitive impairment in a Finnish cohort of older adults. Exp. Gerontol. 2013, 48, 1428–1435.
102. Rudrapal, M.; Khairnar, S.J.; Khan, J.; Dukhyil, A.B.; Ansari, M.A.; Alomary, M.N.; Alshabrmi, F.M.; Palai, S.; Deb, P.K.; Devi, R. Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism (s) of action. Front. Pharmacol. 2022, 13, 283.

103. Meccariello, R.; D’Angelo, S. Impact of polyphenolic-food on longevity: An elixir of life. An overview. Antioxidants 2021, 10, 507.

104. Sharifi-Rad, J.; Rayess, Y.E.; Rizk, A.A.; Sadaka, C.; Zgheib, R.; Zam, W.; Sestito, S.; Rapposelli, S.; Neffe-Skocińska, K.; Zielińska, D. Turmeric and its major compound curcumin on health: Bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications. Front. Pharmacol. 2020, 11, 1021.

105. El-Saadony, M.T.; Yang, T.; Korma, S.A.; Sitohy, M.; El-Mageed, A.; Taia, A.; Selim, S.; Al Jaouni, S.K.; Salem, H.M.; Mahmmod, Y. Impacts of turmeric and its principal bioactive curcumin on human health: Pharmaceutical, medicinal, and food applications: A comprehensive review. Front. Nutr. 2023, 9, 1040259.

106. Pervin, M.; Unno, K.; Ohishi, T.; Tanabe, H.; Miyoshi, N.; Nakamura, Y. Beneficial effects of green tea catechins on neurodegenerative diseases. Molecules 2018, 23, 1297.

107. Tolun, A.; Altintas, Z. Medicinal properties and functional components of beverages. In Functional and Medicinal Beverages; Elsevier: Amsterdam, The Netherlands, 2019; pp. 235–284.

108. Minocha, T.; Birla, H.; Obaid, A.A.; Rai, V.; Sushma, P.; Shivamallu, C.; Moustafa, M.; Al-Shehri, M.; Al-Emam, A.; Tikhonova, M.A. Flavonoids as promising neuroprotectants and their therapeutic potential against Alzheimer’s disease. Oxidative Med. Cell. Longev. 2022, 2022, 6038996.

109. Fernandes, L.; Cardim-Pires, T.R.; Foguel, D.; Palhano, F.L. Green tea polyphenol epigallocatechin-gallate in amyloid aggregation and neurodegenerative diseases. Front. Neurosci. 2021, 15, 718188.

110. Zheng, T.; Bielinski, D.F.; Fisher, D.R.; Zhang, J.; Shukitt-Hale, B. Protective effects of a polyphenol-rich blueberry extract on adult human neural progenitor cells. Molecules 2022, 27, 6152.

111. Lu, W.H.; de Souto Barreto, P.; Rolland, Y.; Bouyahia, A.; Fischer, C.; Mangin, J.F.; Giudici, K.V.; Vellas, B.; Group, M.D. Biological and Neuroimaging Markers as Predictors of 5-Year Incident Frailty in Older Adults: A Secondary Analysis of the MAPT Study. J. Gerontol. A Biol. Sci. Med. Sci. 2021, 76, e361–e369.

112. Guralnik, J.M.; Sternberg, A.L.; Mitchell, C.M.; Blackford, A.L.; Schrack, J.; Wanigatunga, A.A.; Michos, E.; Juraschek, S.P.; Szanton, S.; Kalyani, R.; et al. Effects of Vitamin D on Physical Function: Results From the STURDY Trial. J. Gerontol. A Biol. Sci. Med. Sci. 2022, 77, 1585–1592.

113. Wacker, M.; Holick, M.F. Vitamin D—Effects on skeletal and extraskeletal health and the need for supplementation. Nutrients 2013, 5, 111–148.

114. Fekete, M.; Szarvas, Z.; Fazekas-Pongor, V.; Feher, A.; Csipo, T.; Forrai, J.; Dosa, N.; Peterfi, A.; Lehoczki, A.; Tarantini, S. Nutrition strategies promoting healthy aging: From improvement of cardiovascular and brain health to prevention of age-associated diseases. Nutrients 2022, 15, 47.

115. Anjum, I.; Jaffery, S.S.; Fayyaz, M.; Samoo, Z.; Anjum, S. The role of vitamin D in brain health: A mini literature review. Cureus 2018, 10, e2960.

116. Takács, I.; Dank, M.; Majnik, J.; Nagy, G.; Szabó, A.; Szabó, B.; Szekanecz, Z.; Sziller, I.; Toldy, E.; Tislér, A. Magyarországi konszenzusajánlás a D-vitamin szerepéről a betegségek megelőzésében és kezelésében. Orvosi Hetil. 2022, 163, 575–584.

117. Dědečková, E.; Viták, R.; Jirásko, M.; Králová, M.; Topolčan, O.; Pecen, L.; Fürst, T.; Brož, P.; Kučera, R. Vitamin D3 Supplementation: Comparison of 1000 IU and 2000 IU Dose in Healthy Individuals. Life 2023, 13, 808.

118. Kennel, K.A.; Drake, M.T.; Hurley, D.L. Vitamin D deficiency in adults: When to test and how to treat. Mayo Clin. Proc. 2010, 85, 752–758.

119. Dominguez, L.J.; Farruggia, M.; Veronese, N.; Barbagallo, M. Vitamin D sources, metabolism, and deficiency: Available compounds and guidelines for its treatment. Metabolites 2021, 11, 255.

120. Wang, W.; Li, Y.; Meng, X. Vitamin D and neurodegenerative diseases. Heliyon 2023, 9, e12877.

121. Berridge, M.J. Vitamin D cell signalling in health and disease. Biochem. Biophys. Res. Commun. 2015, 460, 53–71.

122. Littlejohns, T.J.; Henley, W.E.; Lang, I.A.; Annweiler, C.; Beauchet, O.; Chaves, P.H.; Fried, L.; Kestenbaum, B.R.; Kuller, L.H.; Langa, K.M. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014, 83, 920–928.

123. Mayne, P.E.; Burne, T.H. Vitamin D in synaptic plasticity, cognitive function, and neuropsychiatric illness. Trends Neurosci. 2019, 42, 293–306.

124. Roy, N.M.; Al-Harthi, L.; Sampat, N.; Al-Mujaini, R.; Mahadevan, S.; Al Adawi, S.; Essa, M.M.; Al Subhi, L.; Al-Balushi, B.; Qoronfleh, M.W. Impact of vitamin D on neurocognitive function in dementia, depression, schizophrenia and ADHD. Front. Biosci.-Landmark 2020, 26, 566–611.

125. Shea, M.K.; Barger, K.; Dawson-Hughes, B.; Leurgans, S.E.; Fu, X.; James, B.D.; Holland, T.M.; Agarwal, P.; Wang, J.; Matuszek, G. Brain vitamin D forms, cognitive decline, and neuropathology in community-dwelling older adults.

Alzheimer’s Dement. 2023, 19, 2389–2396.

126. Maharjan, R.; Diaz Bustamante, L.; Ghattas, K.N.; Ilyas, S.; Al-Refai, R.; Khan, S. Role of Lifestyle in Neuroplasticity and Neurogenesis in an Aging Brain. Cureus 2020, 12, e10639.

127. DeLuca, G.; Kimball, S.; Kolasinski, J.; Ramagopalan, S.; Ebers, G. The role of vitamin D in nervous system health and disease. Neuropathol. Appl. Neurobiol. 2013, 39, 458–484.

128. National Institutes of Heath Office of Dietary Supplements. Vitamin K Fact Sheet for Health Professionals. 2018. Available online: https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/ (accessed on 14 November 2023).

129. Mladěnka, P.; Macáková, K.; Kujovská Krčmová, L.; Javorská, L.; Mrštná, K.; Carazo, A.; Protti, M.; Remião, F.; Nováková, L.; Researchers, O.; et al. Vitamin K–sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. Nutr. Rev. 2022, 80, 677–698.

130. Huang, S.-H.; Fang, S.-T.; Chen, Y.-C. Molecular mechanism of vitamin K2 protection against amyloid-β-induced cytotoxicity. Biomolecules 2021, 11, 423.

131. Presse, N.; Belleville, S.; Gaudreau, P.; Greenwood, C.E.; Kergoat, M.J.; Morais, J.A.; Payette, H.; Shatenstein, B.; Ferland, G. Vitamin K status and cognitive function in healthy older adults. Neurobiol. Aging 2013, 34, 2777–2783.

132. Chouet, J.; Ferland, G.; Féart, C.; Rolland, Y.; Presse, N.; Boucher, K.; Barberger-Gateau, P.; Beauchet, O.; Annweiler, C. Dietary Vitamin K Intake Is Associated with Cognition and Behaviour among Geriatric Patients: The CLIP Study. Nutrients 2015, 7, 6739–6750.

133. Popescu, A.; German, M. Vitamin K2 Holds Promise for Alzheimer’s Prevention and Treatment. Nutrients 2021, 13, 2206.

134. DiNicolantonio, J.J.; O’Keefe, J.H. The Importance of Marine Omega-3s for Brain Development and the Prevention and Treatment of Behavior, Mood, and Other Brain Disorders. Nutrients 2020, 12, 2333.

135. Glück, T.; Alter, P. Marine omega-3 highly unsaturated fatty acids: From mechanisms to clinical implications in heart failure and arrhythmias. Vasc. Pharmacol. 2016, 82, 11–19.

136. Djuricic, I.; Calder, P.C. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. Nutrients 2021, 13, 2421.

137. Román, G.C.; Jackson, R.E.; Gadhia, R.; Román, A.N.; Reis, J. Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Rev. Neurol. 2019, 175, 724–741.

138. Derbyshire, E. Brain Health across the Lifespan: A Systematic Review on the Role of Omega-3 Fatty Acid Supplements. Nutrients 2018, 10, 1094.

139. Fekete, M.; Szőllősi, G.; Németh, A.N.; Varga, J.T. Clinical value of omega-3 polyunsaturated fatty acid supplementation in chronic obstructive pulmonary disease. Orvosi Hetil. 2021, 162, 23–30.

140. Witte, A.V.; Kerti, L.; Hermannstädter, H.M.; Fiebach, J.B.; Schreiber, S.J.; Schuchardt, J.P.; Hahn, A.; Flöel, A. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb. Cortex 2014, 24, 3059–3068.

141. Fekete, M.; Csípő, T.; Fazekas-Pongor, V.; Bálint, M.; Csizmadia, Z.; Tarantini, S.; Varga, J.T. The Possible Role of Food and Diet in the Quality of Life in Patients with COPD-A State-of-the-Art Review. Nutrients 2023, 15, 3902.

142. Marton, J.; Farkas, G.; Takacs, T.; Nagy, Z.; Szasz, Z.; Varga, J.; Jarmay, K.; Balogh, A.; Lonovics, J. Beneficial effects of pentoxifylline treatment of experimental acute pancreatitis in rats. Res. Exp. Med. 1997, 197, 293–299.

143. Márton, J.; Farkas, G.; Nagy, Z.; Takacs, T.; Varga, J.; Szasz, Z.; Balogh, A.; Lonovics, J. Plasma levels of TNF and IL-6 following induction of acute pancreatitis and pentoxifylline treatment in rats. Acta Chir. Hung. 1997, 36, 223–225.

144. Su, K.P.; Tseng, P.T.; Lin, P.Y.; Okubo, R.; Chen, T.Y.; Chen, Y.W.; Matsuoka, Y.J. Association of Use of Omega-3 Polyunsaturated Fatty Acids With Changes in Severity of Anxiety Symptoms: A Systematic Review and Meta-analysis. JAMA Netw. Open 2018, 1, e182327.

145. Simopoulos, A.P. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: Nutritional implications for chronic diseases. Biomed. Pharmacother. 2006, 60, 502–507.

146. Simopoulos, A.P. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed. Pharmacother. 2002, 56, 365–379.

147. Avallone, R.; Vitale, G.; Bertolotti, M. Omega-3 Fatty Acids and Neurodegenerative Diseases: New Evidence in Clinical Trials. Int. J. Mol. Sci. 2019, 20, 4256.

148. Grosso, G.; Galvano, F.; Marventano, S.; Malaguarnera, M.; Bucolo, C.; Drago, F.; Caraci, F. Omega-3 fatty acids and depression: Scientific evidence and biological mechanisms. Oxidative Med. Cell. Longev. 2014, 2014, 313570.

149. Ross, B.M.; Seguin, J.; Sieswerda, L.E. Omega-3 fatty acids as treatments for mental illness: Which disorder and which fatty acid? Lipids Health Dis. 2007, 6, 21.

150. Hodge, W.; Barnes, D.; Schachter, H.M.; Pan, Y.; Lowcock, E.C.; Zhang, L.; Sampson, M.; Morrison, A.; Tran, K.; Miguelez, M.; et al. Effects of omega-3 fatty acids on eye health. Evid. Rep. Technol. Assess. (Summ.) 2005, 1–6, PMCID:PMC4780934.

151. Orchard, T.S.; Pan, X.; Cheek, F.; Ing, S.W.; Jackson, R.D. A systematic review of omega-3 fatty acids and osteoporosis. Br. J. Nutr. 2012, 107, S253–S260.

152. Sharma, T.; Mandal, C.C. Omega-3 fatty acids in pathological calcification and bone health. J. Food Biochem. 2020, 44, e13333.

153. Hathcock, J. Vitamins and minerals: Efficacy and safety. Am. J. Clin. Nutr. 1997, 66, 427–437.

154. Klimova, B.; Dziuba, S.; Cierniak-Emerych, A. The effect of healthy diet on cognitive performance among healthy seniors—A mini review. Front. Hum. Neurosci. 2020, 14, 325.

155. Alateeq, K.; Walsh, E.I.; Cherbuin, N. Dietary magnesium intake is related to larger brain volumes and lower white matter lesions with notable sex differences. Eur. J. Nutr. 2023, 62, 2039–2051.

156. Ozawa, M.; Ninomiya, T.; Ohara, T.; Hirakawa, Y.; Doi, Y.; Hata, J.; Uchida, K.; Shirota, T.; Kitazono, T.; Kiyohara, Y. Self-Reported Dietary Intake of Potassium, Calcium, and Magnesium and Risk of Dementia in the J apanese: The H isayama Study. J. Am. Geriatr. Soc. 2012, 60, 1515–1520.

157. Abbaspour, N.; Hurrell, R.; Kelishadi, R. Review on iron and its importance for human health. J. Res. Med. Sci. Off. J. Isfahan Univ. Med. Sci. 2014, 19, 164.

158. East, P.; Doom, J.R.; Blanco, E.; Burrows, R.; Lozoff, B.; Gahagan, S. Iron deficiency in infancy and neurocognitive and educational outcomes in young adulthood. Dev. Psychol. 2021, 57, 962.

159. Chen, Z.; Yang, H.; Wang, D.; Sudfeld, C.R.; Zhao, A.; Xin, Y.; Chen, J.C.; Fawzi, W.W.; Xing, Y.; Li, Z. Effect of Oral Iron Supplementation on Cognitive Function among Children and Adolescents in Low-and Middle-Income Countries: A Systematic Review and Meta-Analysis. Nutrients 2022, 14, 5332.

160. Schieffer, K.M.; Chuang, C.H.; Connor, J.; Pawelczyk, J.A.; Sekhar, D.L. Iron deficiency anemia is associated with hearing loss in the adult population. JAMA Otolaryngol. Head. Neck Surg. 2017, 143, 350.

161. Wolters, F.J.; Zonneveld, H.I.; Licher, S.; Cremers, L.G.; Ikram, M.K.; Koudstaal, P.J.; Vernooij, M.W.; Ikram, M.A.; Group, H.B.C.C.R. Hemoglobin and anemia in relation to dementia risk and accompanying changes on brain MRI. Neurology 2019, 93, e917–e926.

162. Hong, C.H.; Falvey, C.; Harris, T.B.; Simonsick, E.M.; Satterfield, S.; Ferrucci, L.; Metti, A.L.; Patel, K.V.; Yaffe, K. Anemia and risk of dementia in older adults: Findings from the Health ABC study. Neurology 2013, 81, 528–533.

163. Huang, Z.; Rose, A.H.; Hoffmann, P.R. The role of selenium in inflammation and immunity: From molecular mechanisms to therapeutic opportunities. Antioxid. Redox Signal. 2012, 16, 705–743.

164. Olufunmilayo, E.O.; Gerke-Duncan, M.B.; Holsinger, R.D. Oxidative Stress and Antioxidants in Neurodegenerative disorders. Antioxidants 2023, 12, 517.

165. Cardoso, B.R.; Ong, T.P.; Jacob-Filho, W.; Jaluul, O.; Freitas, M.I.d.Á.; Cozzolino, S.M.F. Nutritional status of selenium in Alzheimer's disease patients. Br. J. Nutr. 2010, 103, 803–806.

166. Zhou, J.; Zhang, W.; Cao, Z.; Lian, S.; Li, J.; Nie, J.; Huang, Y.; Zhao, K.; He, J.; Liu, C. Association of Selenium Levels with Neurodegenerative Disease: A Systemic Review and Meta-Analysis. Nutrients 2023, 15, 3706.

167. Feng, Y.; Wang, X. Antioxidant therapies for Alzheimer's disease. Oxidative Med. Cell. Longev. 2012, 2012, 472932.

168. Zuo, Y.; Li, Y.; Gu, X.; Lei, Z. The correlation between selenium levels and autoimmune thyroid disease: A systematic review and meta-analysis. Ann. Palliat. Med. 2021, 10, 4398–4408.

169. Cai, X.; Wang, C.; Yu, W.; Fan, W.; Wang, S.; Shen, N.; Wu, P.; Li, X.; Wang, F. Selenium exposure and cancer risk: An updated meta-analysis and meta-regression. Sci. Rep. 2016, 6, 19213.

170. Peters, U.; Takata, Y. Selenium and the prevention of prostate and colorectal cancer. Mol. Nutr. Food Res. 2008, 52, 1261–1272.

171. Vega-Cabello, V.; Caballero, F.F.; Lana, A.; Arias-Fernandez, L.; Banegas, J.R.; Rodriguez-Artalejo, F.; Lopez-Garcia, E.; Struijk, E.A. Association of Zinc Intake With Risk of Impaired Physical Function and Frailty Among Older Adults. J. Gerontol. A Biol. Sci. Med. Sci. 2022, 77, 2015–2022.

172. Ranjbar, E.; Shams, J.; Sabetkasaei, M.; M-Shirazi, M.; Rashidkhani, B.; Mostafavi, A.; Bornak, E.; Nasrollahzadeh, J. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived

neurotrophic factor in patients with major depression. Nutr. Neurosci. 2014, 17, 65–71.
173. Szewczyk, B. Zinc homeostasis and neurodegenerative disorders. Front. Aging Neurosci. 2013, 5, 33.
174. Mondola, P.; Damiano, S.; Sasso, A.; Santillo, M. The Cu, Zn superoxide dismutase: Not only a dismutase enzyme. Front. Physiol. 2016, 7, 594.
175. Pal, A.; Cerchiaro, G.; Rani, I.; Ventriglia, M.; Rongioletti, M.; Longobardi, A.; Squitti, R. Iron in Alzheimer’s Disease: From Physiology to Disease Disabilities. Biomolecules 2022, 12, 1248.
176. Wang, L.; Yin, Y.-L.; Liu, X.-Z.; Shen, P.; Zheng, Y.-G.; Lan, X.-R.; Lu, C.-B.; Wang, J.-Z. Current understanding of metal ions in the pathogenesis of Alzheimer’s disease. Transl. Neurodegener. 2020, 9, 1–13.
177. Kitala, K.; Tanski, D.; Godlewski, J.; Krajewska-Włodarczyk, M.; Gromadziński, L.; Majewski, M. Copper and Zinc Particles as Regulators of Cardiovascular System Function—A Review. Nutrients 2023, 15, 3040.
178. Gunturu, S.; Dharmarajan, T. Copper and zinc. Geriatr. Gastroenterol. 2020, 1–17.
179. Bagheri, S.; Squitti, R.; Haertlé, T.; Siotto, M.; Saboury, A.A. Role of copper in the onset of Alzheimer’s disease compared to other metals. Front. Aging Neurosci. 2018, 9, 446.