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PII: S2772-4085(26)00152-3

DOI: https://doi.org/10.1016/j.nsa.2026.107033

Reference: NSA 107033

To appear in: *Neuroscience Applied*

Received Date: 22 December 2025

Revised Date: 11 June 2026

Accepted Date: 3 November 2026

Please cite this article as: Cvejić, J.H., Matusheski, N., Bowman, G.L., Cirulli, F., Contreras Rodriguez, O., Chrousos, G., Dye, L., Dickson, S.L, Godos, J., Hepsomali, P., Korosi, A., Manach, C., McEvoy, C., Minihane, A.-M., Musillo, C., Santos, C.N., Panza, F., Proitsi, P., Rudka, T., Teeling, J., Tonti, M., Vanden Berghe, W., Vanhatalo, A., Vauzour, D., Vermeiren, Y., Verstraeten, L., Wojdała, A.L., Thuret, S., Nutrition for the Ageing Brain: Towards Integration of Dietary and Lifestyle Strategies, *Neuroscience Applied*, https://doi.org/10.1016/j.nsa.2026.107033.

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Nutrition for the Ageing Brain: Towards Integration of Dietary and Lifestyle Strategies

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Abstract

The global rise in life expectancy has brought cognitive ageing and brain health to the forefront of public health priorities. Advances in neuroscience and systems biology have redefined the brain as a dynamic, multisystem organ, deeply interconnected with peripheral physiology, immune function, and metabolism. This integrative perspective highlights the substantial influence of lifestyle factors including nutrition, physical activity, sleep, and psychosocial stress on neural plasticity, cognitive performance, and emotional resilience in ageing.

The 2025 ILSI Symposium on the Ageing Brain convened international experts to explore the interplay between diet, lifestyle, and cognitive health. Key themes included the role of diet quality and composition in modulating neuroinflammatory pathways, neurogenesis, and metabolic regulation. Evidence supports Mediterranean-style dietary patterns, certain bioactive compounds, and nutraceuticals as promising strategies to enhance neuroprotection and resilience against age-related cognitive decline and neurodegeneration. Multi-omics and biomarker research are further elucidating the molecular mechanisms linking nutrition to brain ageing, while fluid biomarkers are enabling earlier detection and precision prevention trials.

The proceedings highlight the importance of early-life nutrition, the influence of psychosocial and socioeconomic factors, and the intersection of sex differences, menopause, and undernutrition in shaping cognitive trajectories. Emerging evidence on oral health and the oral microbiome as contributors to neuroinflammation and cognitive decline expands the scope of modifiable risk factors.

Despite considerable progress, translating mechanistic insights into effective, population-level interventions remains a challenge. The symposium emphasizes the need for multidisciplinary collaboration, large-scale longitudinal studies, and the integration of advanced biomarkers to make evidence-based recommendations. Ultimately, promoting brain health across the lifespan will require bridging scientific discovery with practical application, ensuring that longer lives are accompanied by preserved cognitive function, emotional well-being and quality of life.

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Abbreviations: AD, Alzheimer's disease; aHEI, Alternative Healthy Eating Index; AHN, Adult Hippocampal Neurogenesis; *APOE4*, Apolipoprotein E4; BBB, Blood-Brain Barrier; CSF, Cerebrospinal Fluid; dACC, Dorsal Anterior Cingulate Cortex; DASH, Dietary Approaches to Stop Hypertension; DHA, Docosahexaenoic Acid; DNRA, Dissimilatory Nitrate Reduction to Ammonia; ELS, early life stress; EPA, Eicosapentaenoic Acid; GFAP, Glial Fibrillary Acidic Protein; HPA, Hypothalamic-Pituitary-Adrenal (axis); HRT, Hormone Replacement Therapy; KYN, Kynurenine LBN, Limited Bedding and Nesting; LLD, Late-Life Depression; MCI, Mild Cognitive Impairment; MEDAS, Mediterranean Diet Adherence Screener, MedDiet, Mediterranean Diet; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; MRI, Magnetic Resonance Imaging; MDD, Major Depressive Disorder; NFL, Neurofilament Light; NO, Nitric Oxide; p-tau, Phosphorylated Tau; PUFA, Polyunsaturated Fatty Acid; PYRAMID, Continuous Mediterranean Diet Pyramid; RA, Rosmarinic Acid, RCT, Randomised Controlled Trial; RET, Resistance Exercise Training; TRP, Tryptophan; UPF, Ultra-Processed Food; WMH, White Matter Hyperintensity; WBC, White Blood Cell.

Keywords: nutrition, cognitive ageing, neuroinflammation, lifestyle, oral health, microbiome

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Introduction

Neurological and neuropsychiatric conditions now account for the largest share of years lived with disability worldwide, affecting more than one in three individuals (GBD 2019 Dementia Forecasting Collaborators, 2022). Among these, neurodegenerative diseases impose a rapidly escalating burden in ageing populations. Dementia alone currently affects over 55 million people globally, with projections rising to approximately 78 million by 2030 (Gauthier et al., 2021). This growing prevalence elevates brain health to a critical public health priority, demanding not only a deeper understanding of the underlying mechanisms but also effective translation of scientific insights into meaningful, population-level impact.

Over recent decades, advances in neuroscience, systems biology and metabolic research have transformed the prevailing view of the brain from an isolated neural structure to a dynamic, multisystem organ. Once considered primarily through the lens of neuroanatomy and cognition, the brain is now recognised as a central regulatory hub intricately linked to peripheral physiology, immune surveillance, metabolic homeostasis and behavioural regulation. This paradigm shift toward a network-based model underscores the reciprocal interactions among neural, endocrine and immune systems and highlights how these connections are shaped by environmental and lifestyle factors such as diet, physical activity, sleep and psychosocial stress (Agorastos and Chrousos, 2022; Dhabhar, 2014; Hötting and Röder, 2013; Kim et al., 2024; Sanaeifar et al., 2024).

As research in neuroscience and brain health advances, the complex interdependence between the brain and other physiological systems becomes increasingly evident, underscoring the remarkable integrative nature of neural function. These dynamic interactions form a highly interconnected network that governs both cognitive and physical well-being (Gonçalves and De Felice, 2021; Yin et al., 2024), shaping neural plasticity, cognitive performance, and emotional balance throughout the lifespan. Each system exerts reciprocal influences on neural activity and structure, reinforcing the need for multidisciplinary approaches that integrate neuroscience, nutrition, physiology and the social sciences (Table 1).

[Table 1.]

Understanding brain health through this integrative lens has profound implications for elucidating the mechanisms of ageing and for identifying modifiable determinants of mental and cognitive resilience (Jiang et al., 2025). In this context, the World Health Organization defines brain health as “a state of brain functioning across cognitive, sensory, social-emotional,

behavioural, and motor domains, enabling individuals to realize their full potential throughout life" (World Health Organization, 2022). Achieving this vision requires coordinated action across scientific disciplines, healthcare systems, and communities with nutrition, lifestyle, and psychosocial factors offering powerful opportunities for prevention and health promotion throughout the lifespan.

Reflecting this holistic perspective, the ILSI Symposium on the Ageing Brain, held in Crete in 2025, convened international experts from academia, research, and industry to explore how nutrition and lifestyle contribute to cognitive health and ageing. The Nutrition Network of the European College of Neuropsychopharmacology (ECNP) participated in the Symposium enlarging the perspective and bringing insight on the fundamental but critical role of nutrition for brain health. Emerging evidence highlights the central role of diet quality and composition in shaping brain structure, neuroinflammatory pathways and emotional regulation. Nutritional strategies such as Mediterranean-style and hybrid dietary patterns, along with bioactive compounds and nutraceuticals, are increasingly recognised for their potential to enhance neuroprotection and resilience against age-related cognitive decline. In parallel, insights into processes such as metabolic regulation and adult hippocampal neurogenesis (AHN) are expanding our understanding of how lifestyle and nutrition sustain cognitive vitality. Despite these advances, translating mechanistic discoveries into effective public health strategies remains a pressing challenge. This requires integration across basic science, clinical research, and public communication to support brain health across the human lifespan. Building strong collaborations among scientists, healthcare professionals, industry and policymakers is essential to ensure new findings and therapeutic strategies reach both public and relevant stakeholders, ultimately advancing the importance of nutrition science in promoting brain health (Adan et al., 2022, 2019; Higgs et al., 2025).

This overview summarises the principal themes discussed during the event, highlighting how mechanistic insights, ranging from neuroinflammation and neurogenesis to microbiome modulation, can be translated into actionable evidence-based strategies for maintaining brain health across populations (Figure 1). To establish an integrative framework, the following section begins by considering how systemic immune system activity and neuroinflammatory processes connect diet, metabolism and cognitive health.

[Figure 1.]

1. Immune function, diet and cognitive decline

The interaction of the body and the brain plays a fundamental role in physiology, enabling adaptive responses to stress, improved regulation of sleep and emotions. Among these interactions, the link between the brain and the immune system is particularly crucial in maintaining homeostasis.

Systemic inflammation and brain function

Immune cells, cytokines, and other mediators influence brain function, while the brain, in turn, can modulate immune responses (Leunig et al., 2025; Schirrmacher, 2025). This bidirectional communication is vital for homeostasis, particularly during stress, infection or injury. At least three immune-brain communication pathways are known: 1) signalling through regions lacking a blood-brain barrier (BBB), such as the circumventricular, organs and the choroid plexus, 2) direct transport or activation of vascular endothelial cells, and 3) the gut-brain axis, including vagal nerve activation (Quan, 2007).

Peripheral immune mediators can interact with endothelial cells and microglia in the brain, triggering cytokine release. In the healthy young brain, these adaptive responses maintain homeostasis, causing fever and transient behavioural changes. However, chronic systemic inflammation or ageing-related neurodegeneration can render these signals maladaptive, amplifying neuroinflammation and damage. This maladaptive response is mediated by microglia 'primed' by neuropathology, such as amyloid deposition and loss of synaptic integrity (Bivona et al., 2023; Ebrahimi et al., 2025). The BBB and the gut barrier also influence how systemic inflammation affects the brain. They serve as selective barriers that regulate the entry of immune cells and molecules into the central nervous system and prevent leakage of metabolites and microbial-derived virulence factors into the circulation via the gut. Under pathological conditions, such as infection, inflammation or dysbiosis of the gut microbiome, the integrity of these barriers can be compromised, allowing increased influx of immune mediators and immune cell infiltration into the brain, ultimately driving neuroinflammation (Beltran-Velasco and Clemente-Suárez, 2025; Mohammad et al., 2025). Understanding these interactions is key to clarifying mechanisms underpinning neurological and psychiatric disorders.

The onset and progression of clinical symptoms are often exacerbated when patients with mild cognitive impairment (MCI) or Alzheimer's disease experience systemic inflammatory insults, particularly microbial infections (Holmes et al., 2009). Experimental models of ageing and

neurodegeneration have provided insight into the biological mechanism by which systemic inflammation drives brain dysfunction. Exposure to live bacterial infections increases neuroinflammation, evidenced by phenotype changes in microglia and astrocytes and increased production of pro-inflammatory cytokines, increased amyloid load, stronger phosphorylation of tau and faster spreading of tau pathology. These observations align with human studies showing significant associations between clinical outcomes and biomarkers of dementia (phosphorylated tau, neurodegeneration) and markers of inflammation (Michopoulou et al., 2022). These immune-barrier interactions are not limited to the gut-brain axis. As discussed later in this review, oral health and the oral microbiome may also contribute to systemic inflammatory burden and neuroinflammatory signalling through microbial, vascular, and immune-mediated pathways (Dibello et al, 2021).

Taken together, evidence indicates that systemic inflammation can induce neuroinflammation and microglial phenotype switching, making it a risk factor for disease progression. However, questions remain on the source of systemic inflammation with recent studies highlighting the composition of the gut microbiome as a promising candidate. Neuroinflammation plays a central role in the onset and progression of dementia and other neurodegenerative diseases (Pasqualetti et al., 2015). It involves chronic activation of immune cells in the brain - especially microglia and astrocytes - which, under pathological conditions, shift from protective roles to promoting neuronal damage (Bivona et al., 2023). Importantly, neuroinflammation is not merely a consequence but a driving force in dementia, often preceding clinical symptoms by years. This makes it a compelling target for early intervention, including dietary strategies, and therapeutic development.

Diet: A Powerful Defence Against Neuroinflammation and Cognitive Decline

Diets such as the Mediterranean, ketogenic and calorie-restriction, have shown potential to modulate key biological pathways involved in brain health (Robbins and Solito, 2022). Diets rich in (poly)phenols, n-3 polyunsaturated fatty acids (PUFAs) and fibre can reduce systemic and neuroinflammation by modulating immune responses and oxidative stress (Wood et al., 2022; Jalouli et al., 2025). However, the exact molecular pathways linking diet to reduced neuroinflammation and improved cognition remain incompletely understood. Preclinical models of neuroinflammation are being used to understand how a (poly)phenol enriched diet (by berry supplementation) counteract chronic inflammation and its effects on behaviour and brain mechanisms associated with neuroinflammation (Tavan et al., 2024).

Dietary phenolic compounds such as flavonoids, phenolic acids, stilbenes, and coumarins exhibit promising neuroprotective effects in the context of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases. These compounds help combat key pathological processes including oxidative stress, inflammation, mitochondrial dysfunction and neuronal apoptosis (Shannon et al., 2021; Tavan et al., 2024). Their ability to cross the BBB and modulate signalling pathways makes them particularly effective in supporting neuronal health and cognitive function (Carecho et al., 2024). Additionally, (poly)phenols are generally well-tolerated and lack serious side effects, making them attractive candidates for long-term dietary interventions.

Research indicates that dietary (poly)phenols undergo extensive metabolism into low-molecular-weight compounds which are the most abundant forms that reach the systemic circulation (Carregosa et al., 2022). These metabolites are primarily produced through gut microbial metabolism and phase II liver metabolism (e.g., sulfation, glucuronidation) and are highly abundant in the bloodstream, though their plasma concentrations and half-lives vary depending on the parent compound and individual metabolism. Typically, they appear in plasma within 1–2 hours post-ingestion and may persist for several hours, with some showing peak concentrations in the low micromolar range. Importantly, some of these metabolites have demonstrated the ability to cross the BBB in both in vitro and in vivo models and have been detected in human cerebrospinal fluid (CSF) (Carecho et al., 2024; Le Sayec et al., 2023). Moreover, certain compounds can protect BBB integrity against insults (Marques et al., 2024).

Because cardiometabolic health risk is closely tied to neuroinflammation, stratification approaches integrating inflammatory and metabolic markers can help clarify how dietary patterns influence cognitive ageing.

Metabolic and inflammatory risk scores

The *Lancet Commission on Dementia Prevention, Intervention and Car*e 2024 (Livingston et al., 2024) reported that targeting modifiable risk factors, such as hypertension, diabetes, obesity, smoking, and dyslipidaemia, through medication and lifestyle changes could prevent or delay up to 40–45% of dementia cases worldwide. Diet was not explicitly included in the report, reflecting the complexity of its relationship with dementia and the challenges of research on nutrition and individual dietary components. Nevertheless, diet-related factors such as cholesterol levels and obesity are recognized as modifiable risk factors, and growing

evidence supports a protective association between certain nutrients or food groups, particularly adherence to the Mediterranean diet (MedDiet), and cognitive outcomes and dementia (Scarmeas et al., 2018). Specifically, adherence to various types of MedDiet, such as Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), Alternative Healthy Eating Index (aHEI), and Dietary Approaches to Stop Hypertension (DASH), has been linked to preserved cognitive function (Tessier et al., 2025) and lower dementia risk (Shannon et al., 2023), although, the molecular pathways remain poorly understood.

Multi-omics approaches, which integrate diverse biological data such as metabolites and proteins, offer powerful tools to capture the biological processes underlying risk profiles (Green et al., 2023; Lord et al., 2022). Understanding these mechanisms can help identify actionable targets for dementia prevention or intervention.

A UK Biobank analysis investigated whether circulating metabolites and inflammatory proteins help explain how diet influences dementia risk and brain health (Shannon et al., 2023). Leveraging large-scale metabolomics and proteomics data with up to 15 years of follow-up, composite signatures of metabolites and inflammatory proteins were identified that improved prediction of all-cause dementia, Alzheimer's disease, and vascular dementia beyond traditional risk factors. Adherence to healthy dietary patterns, including Mediterranean Diet Adherence Screener (MEDAS), Continuous Mediterranean Diet Pyramid (PYRAMID), MIND, aHEI, and DASH, was associated with a lower risk of all-cause dementia. These diet–dementia associations were not modified by Apolipoprotein E4 (*APOE4*) or Alzheimer's disease polygenic risk score. Diet adherence also correlated with beneficial metabolite and protein profiles, particularly for MIND and MEDAS diets. However, mediation analyses indicated that only a small subset of metabolites and proteins partially explained the diet–dementia association, and some molecules appeared to suppress rather than mediate these associations, highlighting the complexity of underlying pathways.

The findings support three conclusions. First, composite metabolite and protein signatures capture dementia-relevant biology and enhance risk prediction beyond traditional factors. Second, cardio-metabolically healthy diets associate with lower dementia risk and more favourable imaging profiles, largely independent of genetic risk. Third, systemic metabolic and inflammatory processes contribute modestly and sometimes bidirectionally, suggesting that diet acts through multiple overlapping pathways. These insights advocate for biomarker-guided prevention using molecular signatures to enrich clinical trials and monitor intervention

responses, while motivating deeper investigations into mechanisms linking diet and brain ageing.

2. Recent advances further highlight the immune system as both a driver and a biomarker of neurodegenerative risk. These findings reinforce a systems-biology approach that links molecular nutrition to brain health across the lifespan. Building on these immune and metabolic pathways, the next section explores how circulating nutrient and metabolic biomarker signatures, reflecting diet–inflammation interactions, serve as quantifiable markers for brain ageing and support earlier detection of cognitive ageing. **Biomarkers of Cognitive Ageing and Nutrition**

A key question is how circulating nutrients, body-fluid indicators of Alzheimer's disease, and diet-related exposures can be quantified and tracked to illuminate mechanisms of cognitive ageing and to guide prevention trials. Integrated, rigorously standardized biomarker strategies are essential to sharpen risk stratification, enable earlier detection of diet-responsive biology and accelerate nutrition-focused prevention trials in cognitive ageing.

Nutrient biomarker patterns and brain ageing

Analyses of plasma nutrient biomarkers in older adults have identified reproducible multi-nutrient patterns that relate to cognitive and neuroimaging measures of brain ageing (Bowman et al., 2012). These include patterns enriched in B-vitamins and antioxidant nutrients, those enriched in marine long-chain n-3 PUFAs, and those characterized by higher circulating trans fatty acids. In community-based cross-sectional studies, both the B-vitamin/antioxidant and marine n-3 PUFA patterns were associated with better global cognitive performance, lower white matter hyperintensity (WMH) burden and larger brain volumes, whereas the trans-fat dominant pattern correlated with poorer cognitive and MRI outcomes. Across cohorts, these patterns explained roughly 17–37 % of the variance in brain health measures, underscoring the value of a nutrient-pattern approach over single-nutrient analyses for understanding late-life brain health. Longitudinal data from the Nutrition and Brain Aging Study showed moderate-

to-high intra-individual stability for most nutrient biomarkers over two to four years, supporting their utility in precision nutrition research for ageing populations (Bowman et al., 2025). Independent systematic reviews have similarly reported that dietary or nutrient patterns rich in unsaturated fats and antioxidants are associated with favourable neuroimaging markers in adults without dementia (Drouka et al., 2022; Townsend et al., 2022).

Building on these observations, a marine n-3 PUFA–rich dietary pattern has been specifically linked to lower WMH burden and better cognitive outcomes (Bowman et al., 2012), informing a randomised, placebo-controlled trial in adults ≥75 years with low n-3 PUFA status and substantial WMH burden (Shinto et al., 2024). Participants received daily triacylglyceride-form fish oil (Eicosapentaenoic acid, EPA and Docosahexaenoic acid, DHA) or soybean-oil placebo for three years, with annual MRI assessments of WMH volume, medial temporal lobe volume and white matter integrity. In modified intention-to-treat analysis, no overall group differences emerged for WMH progression or neuronal integrity decline; however, *APOE4* carriers in the treatment arm showed significantly less neuronal integrity loss. Per-protocol and post hoc analyses revealed that participants attaining a predefined plasma EPA + DHA threshold (11 mg/dL) experienced ~50 % less annual WMH progression than those below this level, underscoring the importance of biochemical target attainment for clinical efficacy. Mechanistic studies support these findings: long-chain n-3 PUFAs generate pro-resolving lipid mediators, modulate vascular function, and reprogram microglia to a less inflammatory state - processes relevant to cerebral small-vessel disease and structural brain ageing (Bhatt et al., 2019; Virtanen et al., 2008).

Ultra-processed foods and drinks, mental and brain health

At the opposite end of the nutrient health spectrum are ultra-processed foods (UPFs). According to the NOVA classification (Monteiro et al., 2016), UPFs are industrial formulations with low nutrient density and high energy density, typically rich in saturated/trans fats and added sugars, often containing additives (e.g., artificial sweeteners) and potential chemical contaminants (e.g., bisphenols). UPF intake has risen sharply, now contributing >50% of energy in the US/UK versus ~10% in Italy (Marino et al., 2021). High UPF consumption has been associated with a range of adverse health effects such as overeating, the promotion of inflammatory and oxidative stress processes, gut dysbiosis, and metabolic dysfunction including problems in glucose regulation (Lane et al., 2024).

In a sample of 152 adults (mean age 50.2 years; 73.6% female; 58.6% with obesity and a mean Body Mass Index of 42.9; all free of metabolic disease), higher UPF consumption was associated with lower grey matter volumes (Contreras-Rodriguez et al., 2023) yet higher cerebral perfusion in the amygdala, ventral striatum, and dorsal anterior cingulate cortex (dACC) – key areas for salience/reward processing and executive control (Unpublished results). Some effects depended on obesity status, suggesting an interaction between UPF exposure and adiposity. Consistent with prior literature (Lane et al., 2024), higher UPF intake was also linked to depressive symptoms in the overall sample and among participants with obesity. This association largely attenuated after adjustment for specific macronutrients, except fibre. UPF consumption also showed an association with white blood cell (WBC) count, but not with other inflammatory parameters (i.e., high-sensitivity C-reactive protein, serum lipopolysaccharide-binding protein) and WBC / lymphocytes mediated links between UPF, depressive symptoms, and perfusion, implicating neuroinflammation. Complementing human data, a 6-week UPF diet (Álvarez-Monell et al., 2025) in Long-Evans rats (from prenatal or from weaning to adolescence) increased functional connectivity in dACC, mirroring human observations and suggesting UPF-related perturbations of executive circuits during vulnerable developmental windows (Unpublished results).

Alzheimer's disease fluid biomarkers

Alzheimer's disease (AD) is the most common form of dementia. Its pathology is characterized by progressive amyloid-β and tau pathology that begins decades before clinical symptoms emerge (Jack et al., 2024). This long preclinical phase offers a critical window for therapeutic and lifestyle interventions, underscoring the importance of early risk identification. Recent approvals of first disease-modifying therapies (e.g., lecanemab, donanemab) and promising lifestyle studies further highlight the urgency of early risk detection. Fluid biomarkers - objective indicators of underlying biology - are central to these efforts. CSF remains the reference matrix, but technological advances now enable precise measurement in blood, with plasma phosphorylated tau (p-tau) emerging as a robust marker alongside additional proteins showing potential (Jack et al., 2024). Blood-based biomarkers allow repeated, minimally invasive sampling and support accessible, affordable diagnostics and staging.

Fluid biomarkers are also pivotal for randomised controlled trials (RCTs), including those focused on nutritional and lifestyle studies (Yassine et al., 2022). They facilitate participant screening, help adjustment for baseline confounders, and reveal biological effects earlier than cognitive or imaging endpoints (Cummings et al., 2025b; Jack et al., 2024). While CSF

biomarkers might be feasible in smaller studies, large-scale trials particularly benefit from non-invasive blood-based measures (Yassine et al., 2022). Several ongoing large-scale RCTs already incorporate fluid biomarkers mainly as exploratory endpoints (Oosthoek et al., 2024). For example, the IN-TeMPO and FINGER-NL protocols, designed to evaluate multicomponent interventions including nutrition, integrate baseline and follow-up (12 and 24 months, respectively) analyses of blood-based biomarker panels. These panels include markers of amyloid burden (p-tau217; FINGER-NL only: Aβ40/42), neuroaxonal damage (neurofilament light chain, NFL), and reactive astrogliosis (glial fibrillary acidic protein, GFAP; (Deckers et al., 2024; Sala et al., 2025). Similarly, two phase 3 trials of semaglutide (a GLP-1 receptor agonist) in early symptomatic AD track p-tau181, GFAP, and NFL longitudinally (Cummings et al., 2025a). A CSF sub-study adds markers of neuroinflammation, synaptic and vascular integrity, oxidative stress, and BBB function. Notably, CSF-confirmed AD pathology minimally affects nutritional biomarker levels in blood, whereas fasting versus postprandial sampling can alter AD biomarker levels (de Leeuw et al., 2020; Huber et al., 2023). These findings underscore the need for rigorous adherence to standardized biospecimen protocols to ensure comparability and interpretation.

In conclusion, the design of nutrition-oriented clinical trials targeting AD pathology can leverage fluid biomarkers, maximizing study insights within the framework of a precision medicine approach. These biomarker approaches may also strengthen the interpretation of dietary, nutraceutical, and multidomain lifestyle interventions discussed in later sections by enabling biological response monitoring before measurable cognitive changes emerge.

As biomarkers elucidate early diet–brain mechanisms, interventions become central. The next section explores how targeted dietary factors and nutraceuticals modulate hippocampal neurogenesis and cognitive resilience, spanning early development through senescence (Du Preez et al., 2022a; Stangl and Thuret, 2009). This transition reflects the translation from biomarker discovery to actionable nutritional strategies.

3. Nutritional considerations for brain plasticity and cognition in ageing

It is increasingly recognized that diet and lifestyle play a pivotal role in maintaining brain plasticity and cognition in ageing. Emerging research demonstrates that early life stress, dietary interventions and nutraceuticals can modulate hippocampal neurogenesis, cognitive function and resilience against age-related decline.

Dietary modulation of adult hippocampal neurogenesis

Adult hippocampal neurogenesis (AHN) refers to the generation of new neurons in the dentate gyrus of the hippocampus postnatally and throughout adulthood (Denoth-Lippuner and Jessberger, 2021). It is integral to learning, memory, and mood regulation and is altered in conditions such as AD and major depressive disorder (MDD). While AHN decreases with age, it remains modifiable throughout life and is influenced by environmental factors including physical activity (Farmand et al., 2025), stress and diet (Stangl and Thuret, 2009). Emerging evidence suggests that dietary factors can modulate AHN early on, thereby impacting the trajectory of cognitive decline associated with ageing and the risk and progression of neuropsychiatric and neurodegenerative disorders such as MDD and AD.

The serum metabolome may mediate the concert of diet, exercise, and neurogenesis, influencing dementia risk. In a recent study, the impact of lifestyle factors was assessed for their impact on *in-vitro* neurogenesis measures using serum samples from a well-characterized prospective cohort. Diet- and physical activity-driven alterations in the serum metabolome affected hippocampal progenitor cell integrity and apoptosis, observable up to 12 years before cognitive decline, suggesting potential for early biomarkers (Du Preez et al., 2022b).

Diet-related factors may also modulate hippocampal neurogenesis in ageing. In an *in-vitro* model of neuronal plasticity in ageing, human hippocampal progenitor cells were exposed to serum from participants in a longitudinal ageing cohort and changes in neurogenesis markers were observed. Reduced cell death and increased neuronal differentiation were associated with later-life depressive symptomatology, and specific diet-related metabolites (butyryl carnitine and certain glycerophospholipids) were positively or negatively linked to these neurogenic changes (Du Preez et al., 2022a). This suggests that diet-induced alterations in the serum metabolome can modulate AHN, influencing the trajectory of depressive symptoms in older adults.

Dietary and nutritional factors may also interact with neurogenesis-centred biological susceptibility to cognitive decline, dementia and depression in older adults. In a recent longitudinal cohort study of older adults, increased plasma lycopene concentrations and higher red meat consumption were associated with increased risk for AD in individuals with a susceptibility centred on impaired neurogenesis susceptibility. Furthermore, higher vitamin D intake and plasma γ-tocopherol concentrations were linked to modestly increased risks of vascular dementia and depressive symptoms, respectively, but only in susceptible individuals

(Du Preez et al., 2024). This study suggests a nuanced role of diet in modulating disease risk, particularly in those with underlying vulnerabilities in neurogenesis.

Collectively, these studies highlight the critical role of diet and nutrition in modulating AHN and influencing the risk and progression of cognitive decline, dementia and depression, particularly in individuals with a neurogenesis-centred susceptibility. The sensitivity of AHN to diet and metabolic signals also provides a mechanistic bridge to early-life stress, which can durably alter hippocampal structure, microglial function, and later-life cognitive vulnerability.

Implications of early life stress for cognitive function in ageing

Early life represents a sensitive period during which adverse exposures (maternal depression, abuse, neglect, malnutrition) shape brain development trajectories into adulthood (Lucassen et al., 2013; Reemst et al., 2022b). Clinical and preclinical data link prenatal/early postnatal early life stress (ELS) to altered ageing trajectories and increased risk of later mental and metabolic disease (Franke et al., 2018; Juncker et al., 2021).

In humans, ELS is associated with adverse neurodevelopmental outcomes and higher adult rates of cognitive decline, anxiety, and depression (Juncker et al., 2021). It has also been linked to reduced grey matter, smaller hippocampal volumes, and altered cortical-limbic circuitry (prefrontal cortex, amygdala), as well as accelerated MRI-based brain age (Franke et al., 2018). Preclinical models corroborate these findings (Lucassen et al., 2013). For example, the limited nesting/bedding (LBN) paradigm (postnatal days 2-9) reliably induces later-life cognitive and plasticity deficits in mice (Rice et al., 2008; Walker et al., 2017). LBN-exposed mice show reduced hippocampal volume and long-term changes in microglia, astrocytes, and adult neurogenesis that likely contribute to cognitive decline (Abbink et al., 2019; Hoeijmakers et al., 2016).

Mental and metabolic diseases frequently co-occur, including depression with obesity and diabetes, alongside cognitive decline and AD, suggesting converging biological pathways (Milaneschi et al., 2019). Early life stress may underlie this comorbidity: beyond mental health risk, it elevates metabolic and cardiovascular risk (including obesity) and alters adipose tissue and the leptin system (Yam et al., 2017b). ELS-exposed mice are lighter with reduced white fat and browning postnatally, yet accumulate more fat on a Western-style diet, indicating heightened vulnerability to obesogenic environments (Yam et al., 2017a). The hypothalamus, which develops early and integrates ghrelin, insulin, and leptin signals, likely mediates this vulnerability; ELS perturbs these hormones and feeding-related hypothalamic circuitry in sex-

and age-specific ways (Yam et al., 2017b). Given the interplay between stress and nutrition and their shared early origins, systemic approaches, especially nutritional strategies, are promising for mitigating ELS effects (Marx et al., 2021). Early-life nutrition is critical for the rapidly developing, energy-demanding brain, and even minor deficiencies can have lasting structural and functional impacts.

Early nutritional interventions can preserve cognition after ELS (Geertsema et al., 2025). Postnatal supplementation with choline, folic acid, methionine, zinc, and vitamins B6/B12 (P2–P9) restored brain/plasma methionine after LBN exposure and rescued hippocampus-dependent memory (Naninck et al., 2017). Similarly, an early diet enriched in n-3 long-chain PUFAs (low LA n-6 / ALA n-3 ratio; P2–P42) prevented adult cognitive deficits, normalized hippocampal cell survival, and reduced phagocytic microglia (Yam et al., 2019), and reshaped brain molecular, lipid, and oxylipin profiles (Reemst et al., 2024, 2022a).

Together, these findings support early nutritional strategies to protect against ELS-related altered ageing trajectories and cognitive decline. An improved mechanistic understanding of the interplay between early life stress, nutrition, mental and metabolic health creates opportunities for future research toward nutrition-based clinical applications.

Nutraceutical interventions for cognitive resilience in ageing

Regular intake of nutraceuticals (natural bioactive compounds) shows promise for promoting healthy ageing. These compounds activate adaptive cellular pathways, such as antioxidant and anti-inflammatory responses, which are increasingly recognized as a potential tool to promote healthy ageing (García-García et al., 2024; Carlberg et al., 2025). Their mechanism of action aligns with the “hormesis hypothesis”, suggesting that cells may detect nutraceuticals as mild threats and respond by triggering stress-response pathways (Mattson and Cheng, 2006; Maglioni et al., 2014; Ristow and Schmeisser, 2014). Despite their potential to impact health and the growing interest in this class of compounds, rigorous clinical trials addressing their effects are limited and challenges remain in elucidating their mechanisms of action (Adan et al., 2022; Marx et al., 2017).

A recent systematic review and meta-analysis of preclinical studies confirmed the effectiveness of various nutraceuticals on healthspan, through attenuating oxidative stress and enhancing cognitive function (Musillo et al., 2021). Recent *in vivo* studies further demonstrated that rosmarinic acid (RA), a polyphenol found in *Lamiaceae* species, significantly improves health-span in a mouse model. RA enhanced learning and memory performance, improved glucose

homeostasis and exerted protective effects against chronic Western diet consumption in a sex-dependent manner (Musillo et al., 2023). Specifically, RA prevented insulin resistance in males and ameliorated diet-induced memory impairments in both sexes (Giona et al., 2024). Hippocampal RNA sequencing analyses revealed sex-specific effects: RA attenuated oxidative stress-related signalling in the hippocampus in males and modulated immune and sex hormone-related pathways in females. Moreover, RA treatment was associated with enrichment in transcription factors such as NF-κB, GR, and STAT3. These findings position nutraceuticals, and RA in particular, as promising candidates to counter age-related cognitive decline. Translation of these findings will require well-designed clinical trials to establish efficacy, safety and mechanisms in humans. Incorporating nutraceuticals into evidence-based strategies may represent a viable approach to extending healthspan and improving quality of life in the ageing population.

Collectively, these recent findings demonstrate new epidemiologic and mechanistic links between diet/lifestyle factors and brain plasticity, cognitive function and ageing. They provide new insights into cognitive health in ageing and highlight opportunities for interventions that promote lifelong brain resilience through dietary modification and nutraceutical interventions.

The neurogenic and metabolic effects of nutrition parallel those observed in muscle physiology and frailty. Section 4 explores how brain and body ageing intersect through sarcopenia, showing shared metabolic and inflammatory pathways, and how lifestyle patterns such as the MIND and Mediterranean diets support both muscle and brain integrity (Morris et al., 2015a; Robinson et al., 2023).

4. Frailty, Sarcopenia, and Cognitive Function

Loss of muscle mass and strength increases vulnerability to falls and disability, while changes in brain structure and metabolism heighten the risk of cognitive impairment and dementia. Nutrition and physical activity are key modifiable determinants of these processes, with mounting evidence that targeted dietary patterns, and structured exercise can help maintain both muscle and brain health.

Nutrition and exercise interventions for sarcopenia

Progressive muscle loss begins by the third decade of life and accelerates with inactivity, poor nutrition, and disease, potentially leading to sarcopenia – the age-related loss of muscle mass and strength. Despite its clinical relevance, sarcopenia is often overlooked in practice. It is

linked to falls, fractures, hospital readmission, functional decline, and higher mortality. International groups such as the European Working Group on Sarcopenia in Older People (EWGSOP) have proposed diagnostic criteria, and sarcopenia was formally recognized as a disease (ICD-10 M62.84) in 2016. Yet lack of consensus hinders implementation, yielding variable prevalence estimates (10–15% in community-dwelling older adults, 25–40% in hospital settings). In 2021, the Global Leadership Initiative on Sarcopenia - GLIS was launched to harmonize definitions; its Delphi process endorsed muscle mass and strength as diagnostic criteria and physical performance as an outcome (Kirk et al., 2024).

Awareness remains low: only 9% of community-dwelling and 3% of geriatric rehabilitation patients know the term (Verstraeten et al., 2024a). Healthcare professionals report limited confidence; in a Dutch survey, 20% screened for sarcopenia but only 3% correctly measured both muscle mass and strength (Verstraeten et al., 2024b). Barriers include limited knowledge, time, equipment, and standardized protocols.

Prevention and treatment combine nutrition and exercise. Better diet quality, including Mediterranean patterns, is linked to lower risk, though interventional data remain sparse (Robinson et al., 2023). Protein requirements rise with age and disease, and malnutrition, sharing mechanisms such as chronic low-grade inflammation, quadruples sarcopenia risk (Beaudart et al., 2019). Protein supplementation combined with resistance exercise training (RET) improves muscle mass and strength in sarcopenic older adults, whereas protein alone shows limited benefit (Gielen et al., 2021). Vitamin D deficiency is associated with sarcopenia, but supplementation alone is largely ineffective (Robinson et al., 2023). Other promising approaches include n-3 PUFAs, which may act via anti-inflammatory and anabolic pathways, and microbiota-targeted therapies that may support the gut–muscle axis (Robinson et al., 2023).

Resistance exercise training remains the best-supported exercise intervention, with guidelines recommending 2–3 weekly sessions at 60–80 % of one-repetition maximum. Feasibility is challenging, particularly in hospitalized elders who prioritize regaining mobility and independence and may undervalue RET (Verstraeten et al., 2024b).

The MIND diet and cognitive ageing

Dietary patterns such as the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diet are associated with slower cognitive decline (Morris et al., 2015a). Developed in 2015, the MIND diet emphasizes ten brain-healthy food groups while limiting five considered harmful, aiming to enhance neuroprotection (Morris et al., 2015b). Emerging research suggests

that these benefits may partly involve modulation of tryptophan (TRP) metabolism. TRP is an essential amino acid and precursor of serotonin and kynurenine (KYN); chronic inflammation and ageing can shift its metabolism toward the KYN pathway, generating metabolites implicated in neuroinflammation, oxidative stress, and neuronal damage. Altered TRP–KYN balance has been linked to both cognitive decline and muscle catabolism, highlighting a shared metabolic axis that may underlie frailty across organ systems.

Using plasma samples and data from the HELI study - a 6-month multidomain lifestyle trial in 85 older adults at risk of cognitive decline that examined brain function in relation to immunometabolic markers and gut health (van Loenen et al., 2025) - the analysis explored whether greater adherence to the MIND diet affected TRP metabolic pathways. The study focused primarily on the metabolic kynurenine-, biosynthetic serotonin- and microbiota-related indole pathways by applying UHPLC-ESI-MS/MS (Anesi et al., 2019) and assessed whether a changes in MIND-NL diet adherence (Beers et al., 2024) were associated with a change in systemic TRP metabolite concentrations and related ratios. Increased MIND scores significantly increased systemic TRP levels, and reduced neuroinflammatory KYN pathway activation, as reflected by lower KYN/TRP and KYN/large neutral amino acid ratios. Additionally, improved dietary adherence favourably increased kynurenic acid/quinolinic acid (KA/QA) ratios and higher MIND scores reduced indoxyl sulphate and indole-3-acriloylglycine levels, suggestive of decreased oxidative stress and (neuro)toxicity (Beers et al., 2025).

By making use of available data and samples of 100 Dutch healthy older adults from the NU-AGE study (Berendsen et al., 2018) it was also possible to explore the relationship between one-year Mediterranean diet (MedDiet) adherence, fibre intake, TRP metabolism (plasma/faecal) and cognitive performance. Higher MedDiet adherence (NU-AGE index), and, fibre intake (intervention arm only), were associated with significantly increased plasma indole/TRP ratios, indicative of enhanced microbial TRP metabolism. While no longitudinal cognitive changes were observed, specific faecal indole derivatives, such as indole-3-propionic acid and indole-3-lactic acid, were identified as predictors of episodic memory, executive functioning and visuospatial ability. Plasma and faecal data showed congruent trends, supporting the role of the MedDiet on the gut-brain axis in cognitive health with ageing.

Initial evidence indicates that brain-healthy, Mediterranean-style dietary patterns, such as MIND, modulate TRP metabolism to promote neuroprotection. These metabolic shifts may contribute to reduced neuroinflammation and preserved cognitive function in ageing

populations. However, ongoing analyses need to further integrate cognitive scores, BOLD fMRI data, and plasma Alzheimer biomarkers to more comprehensively characterize diet-induced changes in TRP metabolism across different biomatrices and study populations.

In parallel with gut-derived pathways, emerging evidence also suggests that the oral microbiome may mirror systemic frailty processes and modulate neuroinflammation. The following section therefore focuses on oral health, highlighting how diet, oral microbial composition, and nitric oxide metabolism converge to affect cognitive ageing (Baker et al., 2024; Vanhatalo et al., 2021).

5. Importance of oral health for the ageing brain

Oral health is a neglected but important area in ageing research, with growing recognition of its contribution to cognitive health (Dibello et al., 2021). Recent research has revealed an increasing number of direct and indirect mechanistic links between oral health indicators and the maintenance of cognitive function in ageing, and the importance of diet and lifestyle interventions for optimal brain health.

Association of oral frailty and cognitive impairment in late life

Frailty is a biophysiological disorder that affects daily living in older age, characterized by diminishing physiological reserves and resistance to stress (Dent et al., 2019). Oral frailty includes age-related gradual loss of oral function with a decline in cognitive and physical functions (Dibello et al., 2021). Previous systematic reviews and meta-analyses examined the association of some oral frailty indicators with late-life cognitive and late-life depression indicators, but with a limited number of indicators and outcomes. A recent systematic review examined sixty-three studies with eleven oral frailty indicators in four categories: 1) oral health status deterioration, 2) decline in oral motor skills, 3) chewing, swallowing, and saliva disorders, and 4) oral pain. Four indicators of oral frailty (number of remaining teeth, periodontal disease, difficulties in chewing, and difficulties in swallowing) were consistently associated with late-life cognitive impairment/decline, MCI, dementia, and late life depression (Dibello et al. 2025a). These findings underline the importance of integrating oral health assessments into broader health evaluations for older adults, suggesting that managing periodontal disease is a key component in preserving cognitive and mental health, and quality of life in older age. In fact, through biological, functional and psychosocial pathways including inflammation, malnutrition and social isolation, oral health and disease may contribute to systemic ageing and frailty. Building on the concept of oral frailty, validated oral health

indicators, widely captured in ageing surveys, should be integrated into multidimensional frailty frameworks to improve prediction, early intervention and holistic care for older adults (Dibello et al., 2025a).

Role of the oral microbiome in brain health

The human oral microbiome comprises hundreds of bacterial, fungal and other species, residing in distinct ecological niches of the oral cavity (Baker et al., 2024). This ecosystem is not only essential for maintaining oral health but also systemic physiology via the immune system, vascular system, and the central nervous system (Thaiss et al., 2016). Increased inflammation caused by pathogenic bacteria such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Prevotella intermedia*, which also proliferate in periodontal diseases, have been linked to brain function (Liccardo et al., 2020). Individuals with AD exhibit significant alterations in oral microbial composition compared to cognitively healthy controls (Bello-Corral et al., 2023), including increased chronic inflammation-associated taxa (Könönen et al., 2022), which predicted risk of cognitive decline years before dementia diagnosis (Sparks Stein et al., 2012). Worse overall oral hygiene in AD patients has also been linked to microbial dysbiosis and inflammation (Lauritano et al., 2019).

Emerging evidence suggests that periodontal pathogens and their inflammatory products can enter the systemic circulation and reach distant organs, including the brain (Ranjan et al., 2018). Notably, elevated serum antibody titers against periodontal pathogens have been detected in AD patients, supporting the notion of systemic microbial exposure and immune activation (Hamza et al., 2021). Once in the bloodstream, microbial components (e.g., lipopolysaccharides, gingipains) may traverse the BBB (Narengaowa et al., 2021). Inflammatory cytokines and bacterial endotoxins released from periodontal sites can also increase BBB permeability by disrupting endothelial tight junctions and activating endothelial and glial cells (Li et al., 2024). In addition to direct bloodstream access, oral microbes may also reach the brain via neural pathways such as the trigeminal nerve (Pisani et al., 2022) via pathways associated with glial vesicular trafficking (Catumbela et al., 2023; Tessarin et al., 2024).

Oral health and neuroinflammation

As discussed earlier, the gut barrier plays an essential role in regulating the entry of virulence factors into the central nervous system. Similarly, the entry of oral pathogens and their inflammatory byproducts into the central nervous system is thought to initiate or exacerbate

neuroinflammation, a process central to the pathogenesis of AD (Popescu et al., 2024). While neuroinflammation may initially serve a protective function, chronic activation of glial cells contributes to synaptic loss, neuronal dysfunction, and the accumulation of neuropathological hallmarks of AD, including β-amyloid (Aβ) plaques and hyperphosphorylated tau tangles (Kwon and Koh, 2020). Recent studies have revealed that oral pathogens, such as *P. gingivalis*, may directly influence amyloidogenesis (Nie et al., 2019; Zeng et al., 2021). Moreover, *P. gingivalis* and its gingipains have been detected in postmortem brain tissue of AD patients and have been shown to promote Aβ aggregation and tau pathology in murine models (Beydoun et al., 2020; Dominy et al., 2019; Matsushita et al., 2020; Wu et al., 2021). In parallel, the Aβ peptide itself, long implicated in AD pathophysiology, has been proposed to function as an antimicrobial peptide within the innate immune system, suggesting that its overproduction in AD may be an immune response to chronic microbial insult (Moir et al., 2018).

Influence of the oral nitric oxide pathway on cognition

An additional mechanism by which the oral microbiome may modulate cognitive health is via the signalling molecule nitric oxide (NO), which, among many other functions, regulates vascular tone and neurotransmission. The capacity for endogenous NO production via the endogenous NO synthase pathway declines in older age, contributing to development of arterial hypertension, reduced physical and cognitive functional capacity, and increased morbidity (Bryan et al., 2017). Therefore, the oral bacteria capable of reducing dietary nitrate into NO precursor nitrite become increasingly important for the maintenance of NO homeostasis as we age. The composition of the oral microbiota may be particularly important to enable older people to benefit from nitrate-rich diets, such as the Mediterranean diet, which has been associated with reduced risk of developing dementia in older age (Shannon et al., 2023).

Dietary nitrate supplementation has been shown to alter the oral microbiome by reducing modules of bacteria dominated by *Prevotella* and by increasing *Neisseria* bacteria (Vanhatalo et al., 2021, 2018). Nitrate-rich diets may benefit cognitive health by promoting a *Neisseria*-dominated oral microbiome, which supports NO bioavailability (Morou-Bermúdez et al., 2022; Takeshita et al., 2016). The increase in *Neisseria* and co-occurring bacteria has been associated with beneficial effects on cognition after only two weeks of nitrate supplementation in older men and women (Vanhatalo et al., 2021).

A recent study of 60 healthy and 60 MCI volunteers found that *Neisseria* and *Haemophilus* correlated with several cognitive tests in the MCI group, and *P. gingivalis* was identified as a

potential MCI biomarker. The balance between two metabolic pathways for oral nitrate reduction, denitrification and dissimilatory nitrate reduction to ammonia (DNRA), was skewed toward DNRA in MCI volunteers, and *P. intermedia* was more abundant in *APOE4* carriers (L'Heureux et al., 2025). These results suggest dietary nitrate may help delay age-related cognitive decline, and provides another mechanistic link between diet, vascular function, cardiometabolic risk and cognitive aging.

The mediating role of diet on oral health and cognition

Diet plays a pivotal role in shaping the composition, structure, and function of the oral microbiota (Santonocito et al., 2022). Growing interest in the therapeutic modulation of the oral microbiota has led to the exploration of probiotics, prebiotics, and phytochemicals as potential strategies to prevent oral diseases and influence neurodegenerative disorders (Homayouni Rad et al., 2023; Maitre et al., 2021).

Probiotics have shown promise in oral health applications (Lundtorp-Olsen et al., 2024). Mechanistically, they act through competitive exclusion of pathogens, modulation of immune responses, and enhancement of epithelial barrier function. Probiotic supplementation (including *L. acidophilus, B. bifidum,* and *B. longum*) may have a positive effect on cognitive function, reducing markers of oxidative stress and inflammation (Beattie, 2024; Sureda et al., 2020). However, limited intervention studies are available to provide causal evidence of their efficacy for cognition (Xiao et al., 2025).

Prebiotics, which are nondigestible food components that selectively stimulate the growth or activity of beneficial bacteria, have been proposed as adjuncts to probiotics in managing oral and systemic health (Luo et al., 2024). While traditional prebiotics may not be suitable for the oral cavity due to their fermentability and potential to contribute to acid production, compounds like xylitol, xylose, and arabinose may inhibit the growth of *S. mutans* while supporting beneficial *Lactobacilli* strains (Yangheng Zhang et al., 2018).

Dietary (poly)phenol intake has also been associated with a reduced risk of cognitive decline (Godos et al., 2024). Diets high in (poly)phenol-rich foods, may exert antimicrobial effects that could counteract pathogenic microbial activity and suppress virulence factors (Arzani et al., 2025; Guo et al., 2023). By reducing oral inflammation and pathogen load, these compounds may decrease the risk of bacteraemia and systemic immune activation, both of which have been implicated in the pathogenesis of AD (Caruso et al., 2022; Santonocito et al., 2022).

Taken together, oral health is essential for the maintenance of optimal cognitive function in ageing, as evidenced by the emerging links between oral frailty, the oral microbiome, neuroinflammation and cognitive function. Diet exerts profound effects on oral health and the oral microbiome, both directly - through nutrient availability, selective pressure and nitrate metabolism, and indirectly - via systemic immune modulation and metabolic changes. While certain dietary components can exacerbate dysbiosis and oral disease, others may contribute to prevention and potentially offer therapeutic potential to restore microbial balance and possibly mitigate cognitive decline. Further observational and intervention studies are needed to clarify the role of diet in modulating the oral microbiome-brain axis.

Beyond biology, psychosocial and cultural stressors shape nutrition, lifestyle, and cognitive trajectories. Section 6 integrates these dimensions, sex differences, menopause, undernutrition, and socioeconomic inequalities, showing that cognitive ageing is inseparable from broader societal and technological contexts (Livingston et al., 2024; Mosconi et al., 2021).

6. Intersection of psychosocial, sex and nutrition inequalities with cognition in ageing

Psychosocial factors, sex, nutrition, and socioeconomic inequalities intersect to shape cognitive ageing. These factors interact in complex ways, influencing brain health and resilience over time. An understanding of these aspects allows for the design of equitable diet and lifestyle interventions that support cognitive function and reduce disparities in ageing populations.

Psychosocial, cultural, and techno-ecologic stressors on the ageing brain

Chronic stress is a deeply rooted biological and cultural phenomenon. Drawing from ancient Greek philosophical traditions and modern biomedical science, a comprehensive picture of stress as a disruption of homeostasis has arisen (Figure 2.). This concept traces back to Pythagoras's harmony, Alcmaeon's isonomia, Hippocrates' eucrasia, and Epicurus' eustatheia (Kontopoulou and Marketos, 2002; Lempesis et al., 2024; Yapijakis and Chrousos, 2022). Modernized by Walter Cannon and Hans Selye and integrated into complex systems theory, homeostasis has become a centrepiece of understanding human adaptation and disease (Breitenbach et al., 2021).

[Figure 2.]

Chronic stress is a known risk factor for adverse brain outcomes, including cognitive decline. While acutely these responses are protective, chronic activation can lead to serious health consequences (Kim and Kim, 2023). Stress engages the hypothalamic-pituitary-adrenal (HPA)

axis and locus coeruleus-norepinephrine systems, increasing glucocorticoids and catecholamines. With persistent exposure, this can produce allostatic overload and structural/functional changes in stress-sensitive regions such as the hippocampus and prefrontal cortex (McEwen and Gianaros, 2010). Higher cumulative stress burden and lower socioeconomic status are associated with accelerated cognitive ageing and greater dementia risk across populations (Lupien et al., 2009).

Digital technologies introduce additional, context-dependent stressors. In youth, higher screen and social media use are associated with sleep disruption, decreased attention, and lower psychological well-being (Twenge and Campbell, 2018). In older adults, digital engagement can offer cognitive stimulation but may also heighten stress when linked to information overload or dependence (Wen et al., 2024). The concept of digital exclusion has also emerged as a societal stressor associated with depression (Wang et al., 2025). Mitigation should prioritize modifiable determinants: stress-reduction and sleep-hygiene strategies; physical activity; enhancement of social support; and policies that reduce socioeconomic disparities. At a systems level, population-wide risk-reduction (e.g., education access, hearing loss and hypertension control, air-quality improvements) is supported by dementia prevention frameworks (Livingston et al., 2024).

The human brain is a product of human evolutionary history and present-day environmental interactions. It is uniquely sensitive to psychosocial stress, cultural dynamics, and technological influences. Evidence-based public health strategies and greater societal awareness can foster cognitive development and support healthy and happy ageing for future generations.

APOE4 genotype, menopause and cognition in ageing

In most countries there is a higher prevalence of dementia in women compared to men. Alzheimer Europe estimates that women account for 68% of people living with dementia ("Prevalence of dementia in Europe," 2025). The higher prevalence in women cannot be explained by 4-5 years higher life expectancy, with higher age-standardised rates in women over 65 years (GBD 2019 Dementia Forecasting Collaborators, 2022).

A higher incidence of common risk factors such as poverty, low education attainment, and depression and anxiety may contribute to the higher prevalence in females (Castro-Aldrete et al., 2025). Differences in brain structure and metabolism may also contribute. More AD tauopathy has been reported in females with equivalent β-amyloid load (Coughlan et al., 2025).

Differences in the brain proteome between sexes have been observed (Mei et al., 2025) along with higher neuroinflammation and glia cell activation (Acosta-Martínez et al., 2025) and greater penetrance of the *APOE4* genotype (Neu et al., 2017) in females. Menopause may also be important. Oestrogen supports brain function via its role in synaptic integrity, neurotransmitter metabolism, glucose utilisation, blood brain barrier and cerebrovascular function and inflammation (Brinton et al., 2015), with the menopause transition associated with neuro-vulnerability and identified as an endocrine tipping point contributing to life-long dementia risk (Mosconi et al., 2021). Collectively these factors underpin accelerated neuropathological progression, with a higher annual MCI to AD progression of 2-3 absolute % in females compared to males (Levine et al., 2021; Tifratene et al., 2015).

Up to half of dementia risk is modifiable (Tifratene et al., 2015), with *APOE4* females around mid-life (40-60y) being a priority for intervention. Early observational studies found oestrogen therapy was associated with reduced dementia (Yaffe et al., 1998), whereas more recent evidence and RCTs have mixed findings (Espeland et al., 2013; Nerattini et al., 2023). In the European Prevention of Alzheimer's Dementia - EPAD cohort, beneficial associations were mainly evident in *APOE4* carriers and when Hormone Replacement Therapy (HRT) was introduced early (Saleh et al., 2023). Further research is needed to identify particularly responsive subgroups.

The brain is enriched in the n-3 PUFAs, especially DHA compared to other tissues (Arterburn et al., 2006). Both DHA and EPA have defined structural and functional roles in brain tissue (Bazinet et al., 2020; Pontifex et al., 2018). In rodent models, ageing and menopause in female *APOE4* carriers has been associated with depleted brain DHA (Martinsen et al., 2019; Pontifex et al., 2021). DHA intake and status have been associated with greater brain volumes, better cognition and reduced dementia risk, with some evidence of more benefits in females (Pottala et al., 2014; Y. Zhang et al., 2018). Interventional evidence is mixed and improved trial designs (Yassine et al., 2022) are needed to establish efficacy of increasing EPA and DHA status with females with a low habitual intake likely to be a responsive subgroup. These sex- and genotype-specific considerations align with the earlier discussion about n-3 PUFA biomarker patterns, in which attainment of adequate n-3 PUFA levels and *APOE4* status have been linked to brain ageing outcomes.

The gut microbiome is emerging as an important determinant of oestrogen metabolism, recycling and status (Liaquat et al., 2025). Menopause and *APOE4* (Tran et al., 2019) modulate the microbiome, and nutrition interventions that target microbiome speciation and metabolism

such as fibre (Schneider et al., 2024) and flavonoids (Taherkhani et al., 2024) deserve further investigation in order to establish their role in mitigating age-related cognitive decline, in a sex specific manner.

Interventions for undernutrition and cognitive decline

Undernutrition, a prevalent yet under-recognised condition in older adults, is marked by loss of muscle, weight, and functional capacity (Cruz-Jentoft and Volkert, 2025). Global prevalence among community-dwelling adults is ~18.6%, with increasing prevalence with increasing age, although it is likely underestimated due to under-detection (Salari et al., 2025). These figures likely underestimate the true burden, as undernutrition often remains undetected and untreated in individuals living independently.

Undernutrition in later life is linked to frailty, functional decline, higher healthcare use, and lower quality of life (Cruz-Jentoft and Volkert, 2025; Wei et al., 2018). Evidence also implicates it as a modifiable risk for cognitive decline (Gutierrez et al., 2021). A recent pooled cohort study found that undernutrition increased dementia risk by 57% over 8.6 years (Noale et al., 2024). These findings are supported by a large meta-analysis of prospective studies showing that mid- to late-life weight loss is associated with a higher risk of all-cause dementia (Wang et al., 2021).

Although mechanistic pathways linking undernutrition to neurocognitive deterioration are not understood, early neuropathological changes may impair appetite and sensory function, reducing nutritional intake before cognitive symptoms appear (Murphy, 2019). As cognitive decline progresses, further deterioration in nutritional status is common due to physical impairments, reduced executive function, feeding difficulties, and behavioural disturbances, which can exacerbate both cognitive and functional trajectories (Tang et al., 2025; Volkert et al., 2024).

Undernutrition often precedes cognitive impairment by over a decade, offering a window for preventive intervention. Personalised dietary counselling and nutrient-enriched interventions have shown promise for supporting cognitive health in undernourished but cognitively unimpaired individuals (Gutierrez et al., 2021; Teggart et al., 2022). These findings support the concept of undernutrition as a viable target for early, multidomain prevention strategies for promoting cognitive health.

To address this evidence gap, the PROMED-EX trial in Northern Ireland tested whether a protein-enriched Mediterranean diet plus exercise improves nutrition and cognition in at-risk

adults ≥60 years (Ward et al., 2024, 2023). In this six-month RCT (n=105), participants were randomised to one of three arms: 1) a personalised protein-enriched Mediterranean-style diet plus a structured, moderate-intensity exercise programme (PROMED-EX), 2) the dietary intervention alone (PROMED), or 3) standard care. The primary outcome will be nutritional status with secondary outcomes of cognition, diet, body composition, physical performance, and quality of life. Results are expected in 2025.

These observations collectively support the conclusion that cognitive health in later life is shaped by an intersection of psychosocial and techno-ecologic stressors, biological vulnerabilities and nutritional challenges including undernutrition. The multifactorial nature of cognitive ageing underscores the need for holistic, sex-sensitive, and culturally-informed interventions for the ageing brain. Integrated, actionable intervention strategies can be created from the diverse set of modifiable factors discussed here, based on their influence on the cognitive trajectory in ageing (Table 2).

[Table 2.]

Advancing brain health in ageing will require coordinated efforts in research, public health, and policy, anchored in approaches focused on equity, prevention, and resilience-building that reflect the diverse realities of ageing populations.

Conclusion

Findings shared during the symposium, and reflected in the growing body of literature, reaffirm that brain health cannot be considered in isolation. It is a dynamic outcome of interconnected biological, psychological, and environmental systems. Nutritional factors in particular stand at the crossroads of these systems, influencing immune balance, metabolic homeostasis, and gut and oral microbiota composition (Godos et al., 2024; Vanhatalo et al., 2021; Yassine et al., 2022). Across these domains, several recurrent mechanistic links emerge, including immune activation, metabolic dysregulation, vascular dysfunction, microbiome-mediated signalling, impaired neuroplasticity and the impact of nutritional vulnerability.

While some aspects of ageing and genetic predisposition are beyond control, mounting evidence highlights the modifiable power of lifestyle. Multidomain interventions, combining nutrient-rich diets, physical activity, and psychosocial engagement, are now recognized as viable strategies to delay or even prevent cognitive decline (Livingston et al., 2024).

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Recent findings reinforce the importance of dietary quality and lifestyle factors as accessible means of promoting brain health and cognitive longevity. Yet, despite promising advances, further efforts are needed to bridge the gap between experimental research and real-world implementation. Future directions should prioritise large-scale, longitudinal studies, the integration of advanced biomarkers, and the development of clear, evidence-based recommendations for both clinical practice and public health communication.

[BOX 1: Future Directions]

Ultimately, advancing brain health requires bridging scientific discovery with practical application. Combining mechanistic understanding, technological innovation, and public health implementation can extend not only *lifespan* but *healthspan*, ensuring that longer lives are accompanied by preserved cognitive function, emotional balance, and quality of life.

Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

This review was prepared taken into account the presentations at the symposium mentioned in the abstract. The opinions expressed herein, and the conclusions of this article do not necessarily represent either the views of ILSI Europe or those of its member companies. All authors read and approved the final manuscript.

Funding: The symposium '*Nutrition for the Ageing Brain*" was organised with funds from ILSI Europe. The authors thank 3 companies (Haleon, Danone Nutricia and Kyowa Hakko Bio Co. Ltd) for their additional financial support to the symposium, and ECNP for supporting participation of members of the Nutrition Network (FC, LD, SLD, AK, CM, ST). For further information about ILSI Europe, please access the following website www.ilsi.eu or email info@ilsieurope.be. For further information about ECNP, please access www.ecnp.eu. The symposium programme was defined by a scientific organizing committee with majority of academic experts. Members of the committee are listed on the website https://ilsi.eu/event/5th-symposium-on-nutrition-for-the-ageing-brain/ . The authors of this manuscript did not receive any specific grant to carrying out this research nor write this manuscript from funding agencies in the public, commercial, or not-for-profit sectors.

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2 **Statement**: During the preparation of this work the author(s) used ChatGPT in order to improve
3 readability and language of the manuscript. After using this tool, the author(s) reviewed and
4 edited the content as needed and take full responsibility for the content of the publication.

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Figures

Figure 1. Evidence-based strategies for maintaining brain health in ageing.

Figure 2. Conceptual framework of psychosomatic resilience, defined as the conjunction of ataraxia (emotional equanimity) and aponia (absence of somatic distress). Perturbations induce catabasis from a healthy baseline into distress/eustress, followed by anabasis that may return to the constitutional mood (eustasis), or stabilize in alternative steady states such as hyperstasis (elevated mood) or cacostasis (suppressed mood). Bidirectional arrows emphasize dynamic equilibrium and recovery speed as characteristics. Adapted from Chrousos 2024.

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1 **Tables**

2 **Table 1. Core Biological Pathways & Markers of Cognitive Ageing**

Pathway/System	Mechanism & Impact on Trajectory	Modulation & Intervention Targets
A. Immune-Brain Axis & Neuroinflammation	Chronic neuroinflammation (microglia/astrocyte activation) is a *driving force in dementia*, precedes symptoms. Systemic inflammation exacerbates symptoms. BBB and gut barrier integrity regulates immune mediator influx.	Dietary Interventions (rich in (poly)phenols, n-3 fatty acids, fibre) reduce systemic and neuro-inflammation. (Poly)phenols and their metabolites exhibit neuroprotective effects and can cross the BBB.
B. Metabolic/ Vascular Health	Modifiable risk factors (hypertension, obesity, diabetes, dyslipidemia, smoking) could prevent/delay 40–45% of dementia cases. WMH burden is a marker of vascular ageing.	Adherence to Cardio-metabolically healthy diets (MedDiet, MIND) links to lower dementia risk and favourable imaging, often independent of *APOE4*. n-3 PUFA patterns link to better cognition and lower WMH. Achieving plasma EPA+DHA of 11 mg/dL reduces annual WMH progression by ~50%.
C. Neuroplasticity	AHN - integral to memory, declines with age, altered in AD/MDD. Serum metabolome changes linked to diet and exercise influence progenitor cell integrity up to 12 years prior to cognitive decline.	AHN - modifiable by diet, physical activity, stress. Nutraceuticals (e.g., Rosmarinic Acid) promote healthspan by activating adaptive cellular pathways, aligning with the "hormesis hypothesis".
D. Microbiome Axes (Gut & Oral)	Gut-Brain Axis: Chronic inflammation shifts TRP metabolism towards the neuroinflammatory KYN pathway. Oral Frailty -associated with late-life cognitive impairment. Oral Pathogens (*P. gingivalis*) and inflammatory products reach the brain, promoting neuroinflammation and amyloid beta/tau pathology.	MIND Diet adherence reduces KYN pathway activation (lower KYN/TRP ratios). MedDiet adherence enhances microbial TRP metabolism. Dietary Nitrate metabolism by oral bacteria (*Neisseria*-dominated microbiome) supports NO bioavailability, crucial for vascular health and neurotransmission. Probiotics/phytochemicals modulate the oral microbiome.

3

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Table 2. Integrated Modifiable Determinants & Vulnerabilities

Factor	Influence on Cognitive Trajectory	Actionable Strategies
1. Psychosocial & Socioeconomic Stressors	Chronic Stress (HPA axis activation) leads to allostatic overload and hippocampal structural/functional changes. Higher cumulative stress and lower socioeconomic status accelerate cognitive ageing. Digital Exclusion - societal stressor linked to depression.	Stress-reduction, sleep hygiene, physical activity, and enhancing social support. Population-wide risk-reduction efforts are supported by dementia prevention frameworks.
2. Early Life Stress (ELS) & Nutrition	ELS leads to altered ageing trajectories and increased risk for later mental and metabolic diseases. ELS - linked to reduced hippocampal volumes and altered adult neurogenesis.	Early Nutritional Interventions (e.g., supplementation with choline or PUFAs) can prevent ELS-induced adult cognitive impairments and normalize hippocampal cell survival.
3. Ultra-Processed Food (UPF) Intake	UPFs - associated with adverse outcomes - (promotion of inflammatory/oxidative stress processes, gut dysbiosis, metabolic dysfunction. High intake - linked to lower grey matter volumes, higher cerebral perfusion, depressive symptoms (partially mediated by neuroinflammation).	Limiting consumption of UPFs is a key nutritional strategy.
4. Frailty & Undernutrition	Physical decline (Sarcopenia/Frailty) shares metabolic and inflammatory pathways with cognitive decline. Undernutrition is a modifiable risk factor; it increased dementia risk by 57% in one study and often precedes cognitive impairment by over a decade.	RET combined with protein supplementation addresses sarcopenia. Personalised dietary counselling and nutrient-enriched interventions target undernutrition in the preclinical phase.
5. Sex Differences and Hormonal Factors	Women have a higher prevalence of dementia. Menopause is an "endocrine tipping point" leading to neuro-vulnerability due to decreased oestrogen support for synaptic and cerebrovascular function. *APOE4* female carriers show greater penetrance.	HRT is associated with improved cognition and brain volumes (early introduction in *APOE4* carriers). Targeted nutrition (e.g., increasing EPA and DHA status) may benefit responsive subgroups like females with low habitual intake.

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1

BOX 1: Future Directions

1. Goal: Achieve a longer healthspan (life free from chronic disease and functional decline), ensuring preserved cognitive function, emotional balance, and quality of life.

2. Multidomain Strategy: Promoting brain health requires multidomain interventions that integrate nutrient-rich diets, physical activity, and psychosocial engagement.

3. Research Imperatives: Address challenges in translation by prioritizing large-scale, longitudinal studies, integrating advanced biomarkers (e.g., plasma p-tau, NFL, GFAP) for earlier detection and monitoring, and bridging scientific discovery with practical application.

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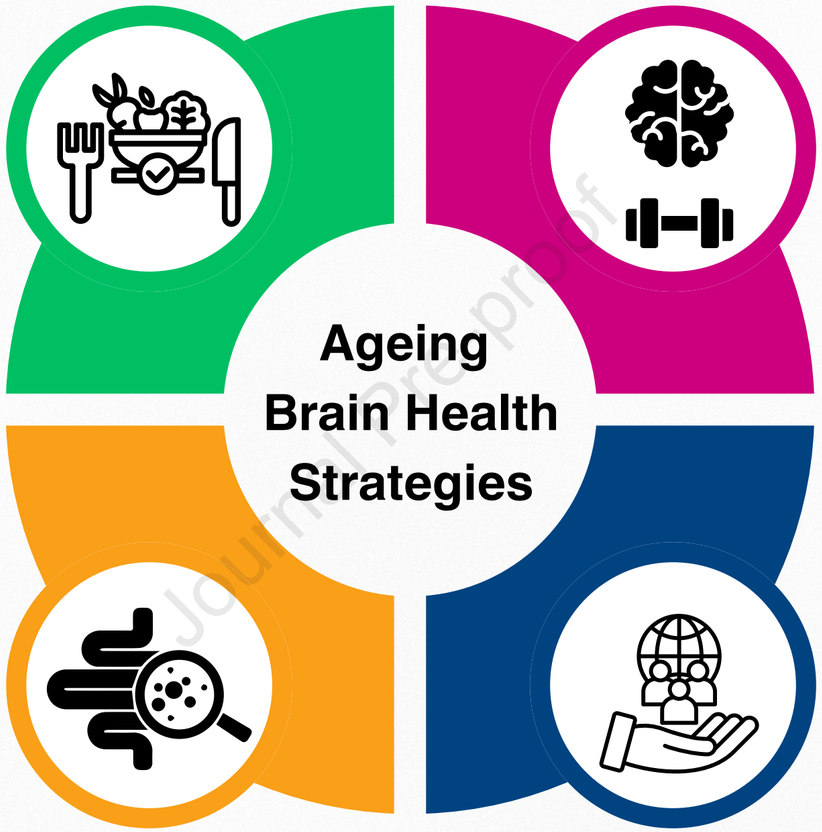
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Dietary focus and metabolic health

- Adopting anti-inflammatory diets
- Managing metabolic risks
- Optimising key nutrients
- Limit Ultra-Processed Foods

Microbiome and systemic links

- Assessing oral-brain axis and frailty indicators
- Targeting link between pathogenic microbiome and neuroinflammation



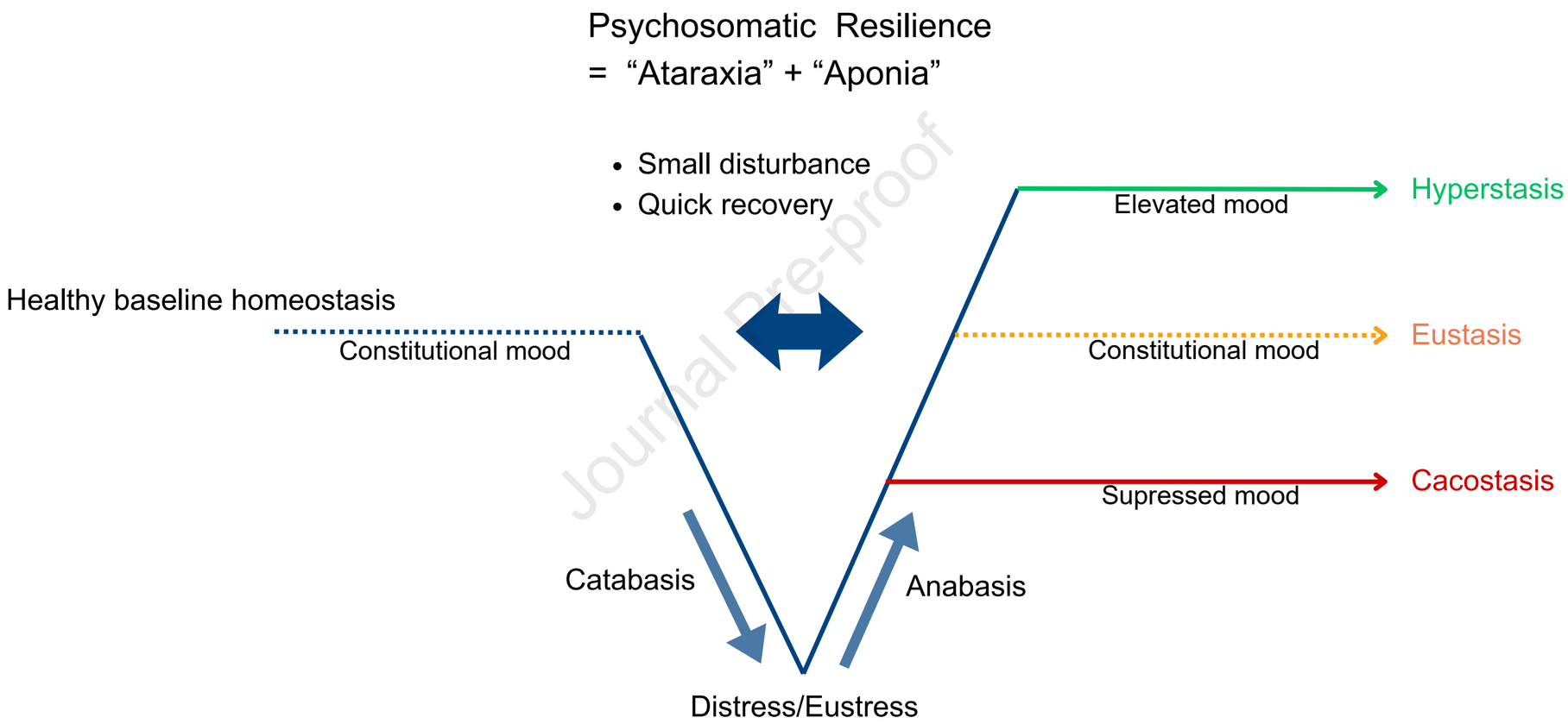
Cognitive and physical interventions

- Promoting cognitive plasticity and neurogenesis
- Combating sarcopenia and functional decline
- Integrating combined interventions (nutrition and exercise)
- Leveraging targeted nutraceuticals

Psychosocial context and policy

- Mitigating impact of chronic stressors and socioeconomic factors
- Managing demographic and genetic risks

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Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

This review was prepared taken into account the presentations at the symposium mentioned in the abstract. The opinions expressed herein, and the conclusions of this article do not necessarily represent either the views of ILSI Europe or those of its member companies. All authors read and approved the final manuscript.

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