



Maintaining brain health across the lifespan

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ABSTRACT

Across the lifespan, the human body and brain endure the impact of a plethora of exogenous and endogenous factors that determine the health outcome in old age. The overwhelming inter-individual variance spans between progressive frailty with loss of autonomy to largely preserved physical, cognitive, and social functions. Understanding the mechanisms underlying the diverse aging trajectories can inform future strategies to maintain a healthy body and brain. Here we provide a comprehensive overview of the current literature on lifetime factors governing brain health. We present the growing body of evidence that unhealthy alimentary regime, sedentary behaviour, sleep pathologies, cardio-vascular risk factors, and chronic inflammation exert their harmful effects in a cumulative and gradual manner, and that timely and efficient intervention could promote healthy and successful aging. We discuss the main effects and interactions between these risk factors and the resulting brain health outcomes to follow with a description of current strategies aiming to eliminate, treat, or counteract the risk factors. We conclude that the detailed insights about modifiable risk factors could inform personalized multi-domain strategies for brain health maintenance on the background of increased longevity.

1. Introduction

Demographers call it the “longevity revolution”. During the last century, the economically developed countries register an increase in life expectancy of more than 30 years (Butler, 2000). Forecast analyses predicted that by 2065 European countries will see an increment in longevity by 10 years (Janssen et al., 2021). This trend was reversed by the COVID-19 pandemic with losses of more than 1 year of life expectancy at birth across a wide range of countries in different continents (Aburto et al., 2022; Yadav et al., 2021). Despite this recent drop in longevity, the trend for a reshaped age pyramid continues with steady increases in the proportion of the population aged 65 years or older representing 20% in Europe (“Population Structure and Ageing” 2022) and 17 % in the US (Reuters, 2021).

In this context, there is much controversy about the relationship between longevity and life quality in old age, which brings the focus on the humans’ health span - the average number of years spent in good health. Aging-associated brain disorders such as neurodegeneration, cerebro-vascular diseases and late-life depression are among the main causes of disability in people above the age of 65 years (Feigin et al., 2019). On the other hand, some individuals can reach old age while maintaining sufficient physical and cognitive performance, the so-called *super-agers* (Zhang et al., 2022). This poses the question about the detailed characterisation of the underlying mechanisms, which could allow for an accurate prediction of behavioural and cognitive outcome in old age (Zhang et al., 2023).

Here, we present a comprehensive overview of the extant literature on brain aging centered on the impact of what we refer to as LiMEE

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(Lifelong, Modifiable, Exo- and Endogenous) factors – cardio-vascular risk, sleep pathologies, suboptimal alimentary regime, and sedentary behaviour. Acting individually and jointly, these factors contribute to the time of onset and progression of aging-associated brain disorders. In the following, we review the definition of brain health whilst looking for differential brain anatomy trajectories related to aging and the concomitant LiMEE factors governing the individuals' cognitive and behavioural outcome. We conclude by presenting the current LiMEE-based prevention strategies holding the promise to maintain cognitive performance on the background of individually specific endogenous and exogenous risk factors.

The LiMEE-based concept proposes a set of falsifiable assumptions and interconnected causal links that might be useful to researchers aiming to discern across different trajectories of brain aging. This concept can also be applied as a theoretical background to design personalized strategies aiming to maintain and improve brain health – as exemplified by the proposal of Brain Health Services (Frisoni et al., 2023).

We searched PubMed for articles published in English or translated to English from January 2000 to July 2023. The search terms included the following keywords connected with Boolean “and” and “or”: “brain”; “MRI”; “magnetic resonance imaging”; “grey matter”; “white matter”; “cognition”; “aging”; “older adults”; “nutrition”; “diet”; “sleep”; “physical (in)activity”; “sedentary”. We excluded articles that did not concern human health, did not focus on brain health as a main outcome measure or were published in non-peer reviewed journals. We also identified additional articles guided by the reference list of the initially obtained articles. We considered longitudinal design studies or large-scale cohorts (n > 5000) to be of particular relevance.

2. What do we mean by brain health in old age

The American Heart Association and the American Stroke Association define brain health as an “...*optimal capacity to function adaptively in the environment. This could be assessed in terms of competencies across the domains of thinking, moving, and feeling*” ((Gorelick et al., 2017) pp. e287). The general assumption of brain health is that it encompasses all stages of human development, maturation, and degeneration. However, only in the context of aging we are confronted with a vast terminology - brain aging gap, brain reserve, brain maintenance, “successful” or “super-normal” aging, that accounts for several related and unrelated processes under the umbrella definition of brain health (Table 1).

From a descriptive point of view, brain age gap refers to the systemic processes associated with a biologically vaguely defined characteristics of “older” appearing brain than one “typical” for a given chronological age (Franke et al., 2010; Stern et al., 2020; Cabeza et al., 2018). Under the assumption of common underlying mechanisms, the chronological age is linked to structural decline of the brain, but also at the same time – to its functional maintenance and growth (Park and Reuter-Lorenz, 2009; Baltes, 1987). Maintenance and growth in the context of aging are key elements of healthy, hence “successful” aging - an optimal aging trajectory characterized by the absence of overt clinical signs of disease, the maintenance of physical and mental health, along with the continued social activity (Rowe and Kahn, 1998). Taken to the concept of brain health, a successful aging trajectory might be thought as the result of brain maintenance, which refers to the preservation of brain structure and function across the lifespan (Stern et al., 2020). As such, the absence of pathology and the presence of mechanisms facilitating growth and maintenance are key factors for healthy aging.

While successful aging and brain maintenance refer to the capacity to resist or to avoid aging-related pathology, there is also the concept of resilience defined as capacity to cope with pathology (Arenaza-Urquijo and Vemuri, 2018). It is common knowledge that individuals without any subjective complaints or objective clinical signs can show molecular, neuroimaging or histopathological signs associated with neurodegeneration (Jansen et al., 2015). A recent example is a case report

Table 1

Glossary of terms that account for interrelated phenomena associated with brain health in the context of aging.

Brain aging	Process that causes the brain to become older, comprising systemic, gradual, and continuous lifelong changes that shape brain structure and that explain mechanisms associated with functional decline, but also with growth and maintenance (Stern et al., 2020; Cabeza et al., 2018; Park and Reuter-Lorenz, 2009; Baltes, 1987)
Brain health	State in which the different brain functions (i.e., sensorimotor, cognitive, behavioural, and emotional) can be performed in such a way that is optimal and adaptive to the environment (Gorelick et al., 2017; Chen et al., 2021)
Brain maintenance	It refers to the minimization or delay of aging-related brain changes and pathology because of a combination of beneficial genetic and lifestyle factors. In other words, it describes the possibility of keeping the brain in a condition that is closely similar to its youthful state (Stern et al., 2020; Nyberg et al., 2012).
Brain reserve	It reflects the idea that there is an extra capacity within the brain to cope with aging processes or with pathology before cognitive dysfunction becomes evident. It follows a threshold model, meaning that when the pathology reaches a certain level, cognitive impairment becomes noticeable (Stern et al., 2020).
Cognitive reserve	Individual differences in the capacity of cognitive processes to function adaptively in the context of aging and brain pathologies. It involves the ability to compensate for damage by recruiting other resources (Stern, 2009).
Successful aging	Trajectory of aging characterized by “the avoidance of disease and disability, the maintenance of high physical and cognitive function, and sustained engagement in social and productive activities” (Rowe and Kahn, 1998)

describing an individual who underwent neuropsychological evaluations every 6 months for the last 6 years of his life. Despite showing brain anatomical signs of three different neurodegenerative conditions, he was able to maintain an intact cognitive function until the end of his life, at 96 years (Melikyan et al., 2022). In this context, brain reserve is a theoretical construct that integrates the mechanisms facilitating the adaptation to the harmful impact of various pathological agents (Stern et al., 2020). Cognitive reserve refers more specifically to the capacity of cognitive processes to maintain stable performance in the context of aging and brain pathology (Stern, 2009). In our opinion, the comprehensive study of brain health in aging needs a detailed insight into both resistance- and resilience- related processes (Arenaza-Urquijo and Vemuri, 2018).

Once brain health is defined, how can we operationalize it to objectively measure the constituting processes and related outcomes? The American Heart Association and the American Stroke Association suggest three broad categories of outcomes associated with brain health: i. present clinical diagnoses; ii. competences across the domains of “feeling-moving-thinking”; iii. neuroimaging biomarkers – e.g., brain volume or cortical thickness derived from magnetic resonance imaging (MRI) (Gorelick et al., 2017). The most frequent and feared conditions determining brain health in advanced age are functional impairment and cognitive decline – Alzheimer’s disease and cerebro-vascular events as leading aetiologies. Given the progressive course of neurodegeneration, the loss of autonomy in one or more domains of daily living defines the transition between minor cognitive impairment and overt dementia. Increasing the complexity of ageing-associated comorbid conditions, late-life depression is observed in both neurodegenerative and cerebro-vascular disorders (Deardorff and Grossberg, 2019). In this context, one of the drawbacks of brain health inferences based on clinical diagnoses is their bimodal distribution by design – present or absent, thus neither including gradients of symptom severity nor the modulatory effects of coexisting conditions (Cuthbert, 2014). Assessing competences across the domains of “feeling-moving-thinking” can provide a fine-grained description of brain function. The characterisation of cognitive performance requires assessing functions that

show aging-related decline - e.g., episodic memory, working memory, and attention/speed of processing, contrasted with functions that remain with stable performance - e.g., vocabulary and world knowledge, denomination, to name but a few. The assessment of emotional adjustment can also be of value, particularly when the evaluation includes symptoms of depression, anxiety, apathy, and impulsive-compulsive behavioural traits. Emotional wellbeing and its different components such as life satisfaction or positive affect should also be evaluated.

Neuroimaging provides a plethora of objective brain anatomy characteristics that is used as determinant of brain health. Well-established local and global metrics of grey and white matter volume, cerebrospinal fluid (CSF) or ventricle volume, cortical thickness, and surface area offer robust and reliable translation to brain health. Advances in MR physics ensured the sensitivity of imaging protocols to the correlates of small vessel disease, microbleeds, or enlarged perivascular spaces. The currently widely used machine-learning based estimation of brain age is another MRI-derived measurement considered to reflect brain health. In short, neuroimaging data are trained to determine the normative trends of brain aging, followed by individual's brain age prediction from unseen data (Franke et al., 2010). The difference between predicted brain age and chronological age is determining the potential brain age gap, which is interpreted as indicative for pathology in the context of a given brain disorder. Besides methodological issues (de Lange et al., 2022), the question that remains unanswered is about causality in the obtained brain age – underlying pathology relationship.

In the following section, we outline how these brain health indicators change with increasing age.

3. Multiple mechanisms of brain aging

Across lifetime, the brain undergoes substantial changes at various levels of observation spanning between molecular, cellular, network and systems levels. At the molecular and cellular level, the underlying processes are summarised under the umbrella term “hallmarks of aging”, which are also present in other organs (López-Otín et al., 2013, 2023). These include mitochondrial dysfunction, insufficient waste elimination and DNA repair, altered neuronal activity, stem cell pool exhaustion, inflammation, impaired oxidative stress response, and dysregulation of the neuronal calcium homeostasis (López-Otín et al., 2023). In the context of brain health these processes have been referred to as the “hallmarks of brain aging” (Mattson and Arumugam, 2018). The aggregation of pathological proteins – amyloid- β (A β), phosphorylated tau or α -synuclein, to name but a few, is a hallmark of neurodegenerative diseases like Alzheimer's or Parkinson's disease (Wilson et al., 2023), tend to accumulate in the temporal lobe and in the hippocampus (Petersen, 2012) and impair hippocampus-dependent memory processes (Mander et al., 2015; Sepulcre et al., 2013). However, individuals without any overt signs of cognitive impairment also show A β accumulation that can be associated with brain atrophy (Mattsson et al., 2014), and Alzheimer's disease (Jansen et al., 2015; Sperling et al., 2011). At various stages of disease, the mechanisms governing the hallmarks of brain aging facilitate the accumulation of abnormal proteins (Mattson and Arumugam, 2018). In turn, the intra- and extracellular protein accumulation aggravates the senescent-related mitochondrial dysfunction and synapse degeneration finally leading to neuronal death (Mattson and Arumugam, 2018).

The normal functioning of brains' small vessels also supports the protein clearance mechanisms through maintaining the perivascular flow and sleep-associated efficacy of the glymphatic system (Wardlaw et al., 2019; Nedergaard and Goldman, 2020). The glymphatic system consists of perivascular spaces formed by astroglia around the cerebral small vessels that supports the exchange of CSF and interstitial fluid to eliminate waste compounds (Jessen et al., 2015). Active only during sleep, it creates a directional flow from the subarachnoid space along the arterial perivascular spaces through the brain tissue to reach the venous perivascular spaces. There is a growing body of evidence that a

dysfunction of the glymphatic system, seen as a point of convergence of cardio- and cerebro-vascular pathology, abnormal sleep and suboptimal clearance of protein waste may underlie the transition of a healthy brain aging trajectory towards neurodegeneration (Nedergaard and Goldman, 2020).

In a mutual interaction, oxidative stress and neuroinflammation, which are associated with brain aging, are also related to mitochondrial dysfunction and finally, to cardio- and cerebro-vascular health (Chistiakov et al., 2018). Given the strong positive correlation between age and cardio-vascular risk, the aging-associated effects are observed across all levels of vessels' anatomy and function – from arteriosclerosis of large arteries to small vessel disease and amyloid angiopathy (De Silva and Faraci, 2020; Wardlaw et al., 2019). The effects of the resulting compromised cerebral blood flow and dysfunctional blood brain barrier are visible on MR brain images as white matter hyperintensities, lacunar lesions, cortical and subcortical microbleeds, and enlarged perivascular spaces (Wardlaw et al., 2013). From the functional point of view, these micro- and macroangiopathic changes are causally linked to late-life depression, apathy, delirium, and fatigue (Fang et al., 2020; Clancy et al., 2021), to executive dysfunction (van der Flier et al., 2018), and represent a risk factor for stroke and cognitive impairment (Wardlaw et al., 2019; Dadar et al., 2020; Kamal et al., 2023).

Brain aging is characterised by global or regional volume loss with corresponding tissue microstructure changes. There is much controversy about the reported trajectories of brain's anatomy maturation and aging that is mainly because most of the obtained results are based on T1-weighted MRI that may produce “spurious” morphometric findings (Lorio et al., 2016). The studies converge on early peaks in brain maturation associated volume and cortical thickness increases between age 2 and 11 years followed by slow, but progressive volume and cortical thickness loss (Bethlehem et al., 2022; Fjell et al., 2015). After age 55–60, the superior temporal gyrus, entorhinal cortex and hippocampus are the brain areas with steepest decline (Storsve et al., 2014; Vinke et al., 2018). Brain's white matter is characterised by an inverted U shape with a peak around the age of 50 years (Sexton et al., 2014; Bethlehem et al., 2022), although the notion of a lifelong continuous remyelination recently finds a lot of support (Hill et al., 2018; Franklin et al., 2021). Cerebro-vascular pathology and neurodegeneration affect the white matter in a spatially differential pattern with predominance of parietal white matter hyperintensities in Alzheimer's disease and frontal areas – in cerebro-vascular cases. Given the pathological substrate of neurodegeneration with loss of axons – i.e. Wallerian degeneration, and demyelination, white matter atrophy after 50 years is more accentuated in individuals who subsequently are diagnosed mild cognitive impairment or dementia (Shafer et al., 2022; Piguet et al., 2009). Finally, and taking over the space that used to belong to grey and white matter, the volume of the cerebrospinal fluid (CSF) shows slow progressive enlargements from years 2–30 (Bethlehem et al., 2022), and its volume increases accelerate after age 50 (Bethlehem et al., 2022; Vinke et al., 2018).

The interdependencies between the aging-associated brain's grey and white matter atrophy are complex and highly dependent on the underlying pathological substrate. Progressive small vessel disease can be characterised by focal oedema, small lesions that over time cause secondary grey matter loss (Wardlaw et al., 2019). Here, the perilesional zone surrounding white matter hyperintensities is vulnerable to ischemic events, causing further damage to both white and grey matter (Wardlaw et al., 2019). Cognitive function is also highly dependent on grey and white matter health. Longitudinal studies have shown that decreases in cortical surface and/or grey matter volume are associated with decline in cognitive function (Simon R. Cox et al., 2018; Cox et al., 2021; Fletcher et al., 2018). Similarly, white matter loss over time has been related to decline in episodic memory, visuospatial function, and processing speed (Shafer et al., 2022). As early as in the beginning of early adulthood, executive functions (namely, working memory and inhibition), long-term memory, and attention/speed of processing show

gradual declines that span until the end of the life (Park and Reuter-Lorenz, 2009; Salthouse, 2019; Singh-Manoux et al., 2012). These cognitive functions have been associated with fluid intelligence (Cattell, 1963).

Not all cognitive domains follow a linear trajectory of aging-associated functional loss. Cognitive functions that require the integration of accumulated knowledge over time – also referred to as crystallized intelligence (Cattell, 1963), are characterised by relative resilience. Vocabulary knowledge is an exemplary case with stable trajectory even in old age (Park and Reuter-Lorenz, 2009; Salthouse, 2019). Denomination and general knowledge are also characterised by a consistent trajectory, present only modest decline even in the case of present biomarkers of neurodegeneration (Vonk et al., 2020). Emotional flexibility is another brain function that requires a special mention with regards to aging-related behavioural changes. Initial evidence suggested the existence of U-shaped relationships between several wellbeing parameters and aging. Depressive mood showed an inverse U-shaped relationship with age, since rates of depression were highest during mid-adulthood and from then on, they showed gradual decrease (Blanchflower and Oswald, 2008). Conversely, studies have questioned the generalisability of these assumptions (Jebb et al., 2020; Steptoe et al., 2015). Using data from the Gallup World Poll, Steptoe et al. showed that the U-shaped relationship between wellbeing and age stands true only for anglophone and high-income countries. In socio-economically less developed countries subjective wellbeing decreases with age (Steptoe et al., 2015). Using the same database spanning over more than 160 countries, another study reported that scores in life satisfaction and in negative affect are subjected to insignificant decrease over time, while positive affect showed globally significant reductions, particularly after the age of 60 years (Jebb et al., 2020).

In summary, there are multiple interrelated mechanisms spanning over different levels of observation – from molecular up to systemic levels that characterize brain aging. The plethora of brain aging trajectories differentiate in a gradual way healthy from pathological brain aging. Despite major progress in quantifying aging-associated brain and behavioural changes, there are still uncertainties about the definition of healthy aging on the background of overwhelming interindividual differences in brain structure-function relationships.

4. The LiMEE framework

There is a combination of risk and protective factors modulating brain health with increasing age. Here, we propose a theoretical framework that can be used to test personalized strategies promoting brain health and preventing cognitive decline in old age. First, we identify the lifetime, modifiable, endogenous, and exogenous (LiMEE) risk factors. Because of their potential to be treated or modified, these factors are the centrepiece of our concept. We formalize a set of assumptions associated with the effect of LiMEE factors on brain health. Next, we focus on the biological mechanisms underlying the relations between these factors and brain health in aging.

Our concept is based on the following assumptions:

- The presence of LiMEE risk factors is associated with compromised brain health.
- Their harmful effects manifest cumulatively during a lifetime exposure.
- The impact could be gradual or dose dependent rather than idiosyncratic. Higher exposure to particular risk factors is associated with increased risk than a lower exposure.
- Strategies to prevent or counteract a LiMEE risk factor will promote the maintenance of brain health and successful aging.
- We do not preclude a certain causal relationship between dietary risks, sedentary behaviour, sleep problems, cardio-vascular factors, and chronic inflammation.

Fig. 1 represents the interrelations between the different LiMEE risk factors that we elaborate in the following.

4.1. Nutrition

Since the description of the Wernicke-Korsakoff syndrome, caused by thiamine (vitamin B1) deficiency and, in most cases, chronic alcohol consumption (Isenberg-Grzeda et al., 2012), it is widely accepted that dietary choices can impact brain health. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has estimated that 12% of strokes can be attributed to diet high in sodium, while other dietary risks such as high red meat consumption, low fruits intake, and alcohol consumption would each account for 6–7% of strokes (Feigin et al., 2019). This dietary regime is also associated with lower cognitive performance and/or risk of dementia in middle-aged and older adults (Mohan et al., 2020; Zhang et al., 2021; Sun et al., 2021; Ylilauri et al., 2022). Conversely, specific nutrients seem to be protective against cognitive decline and might counteract the negative effects of dietary risks. Fish, and especially oily fish, is one of them. Studies have shown that fish intake is associated with better verbal memory scores (Ylilauri et al., 2022), reduced risk of dementia (Nozaki et al., 2021), and lower burden of small vessel disease (Thomas et al., 2021).

B-vitamins and folic acid are micronutrients that may exert neuroprotective effects by lowering homocysteine, which in high concentrations signals the presence of vascular inflammation and endothelial dysfunction (Li et al., 2021). The currently empirical evidence shows rather mixed results. A longitudinal cohort study in 80 years old participants reported that greater intake of foods rich in folic acid at baseline was associated with lower cognitive decline after 4.5 years (Morris et al., 2018). At the same time, randomized placebo-controlled trials in participants at similar age have not demonstrated any significant effects of B12 supplements on cognitive performance (Kwok et al., 2020; Hvas et al., 2004; Dangour et al., 2015). Two Cochrane reviews have concluded that there is a lack of strong evidence proving that specific vitamin or mineral supplementations can help to prevent or delay cognitive decline in mild cognitive impairment patients (McCleery et al., 2018) or to maintain cognitive health in healthy individuals (Rutjes et al., 2018).

Dietary patterns, possibly exerting their effects via interactions between micro- and macronutrients, have potentially relevant effects on brain health. The observation that certain foods, such as processed meat, red meat, and foods with a high content of sugar, show associations with an increase in low-grade inflammatory markers when consumed regularly, has led to the formulation of the so-called “anti-inflammatory” diet (Cavicchia et al., 2009). Despite the discrepancies with reference to its components, the “anti-inflammatory” regimen is rich in fruits and vegetables, sources of omega-3 fatty acids (e.g., nuts and fish), whole grains, plant-based proteins, and a variety of spices, such as ginger and curcumin. It is also characterized by the avoidance of refined and processed foods, alcohol, saturated and trans fats, red meat, and processed meat (Marcason, 2010). One of the best-known anti-inflammatory dietary patterns is the Mediterranean diet, characterized by a high consumption of whole grains, fruits, vegetables, legumes, fish, and olive oil and by a low consumption of red meat. Cohort studies have shown that the Mediterranean diet is associated with better cognitive performance (McEvoy et al., 2017) and with lower risk of Alzheimer’s disease (García-Casares et al., 2021) in a dose-dependent relationship. Additionally, a randomized-controlled trial has shown the potentially neuroprotective effects of a Mediterranean diet enriched with polyphenols (i.e., in this case, the addition of green tea) on age-related brain atrophy (Kaplan et al., 2022).

Part of the effects of nutrition on brain health are related to cardiovascular and immune health. Studies in rodents show that Western diet, a disadvantageous dietary pattern rich in ultra-processed foods, salt, saturated fatty acids, and cholesterol, can compromise the function of the BBB and induce a proinflammatory and neuroinflammatory state

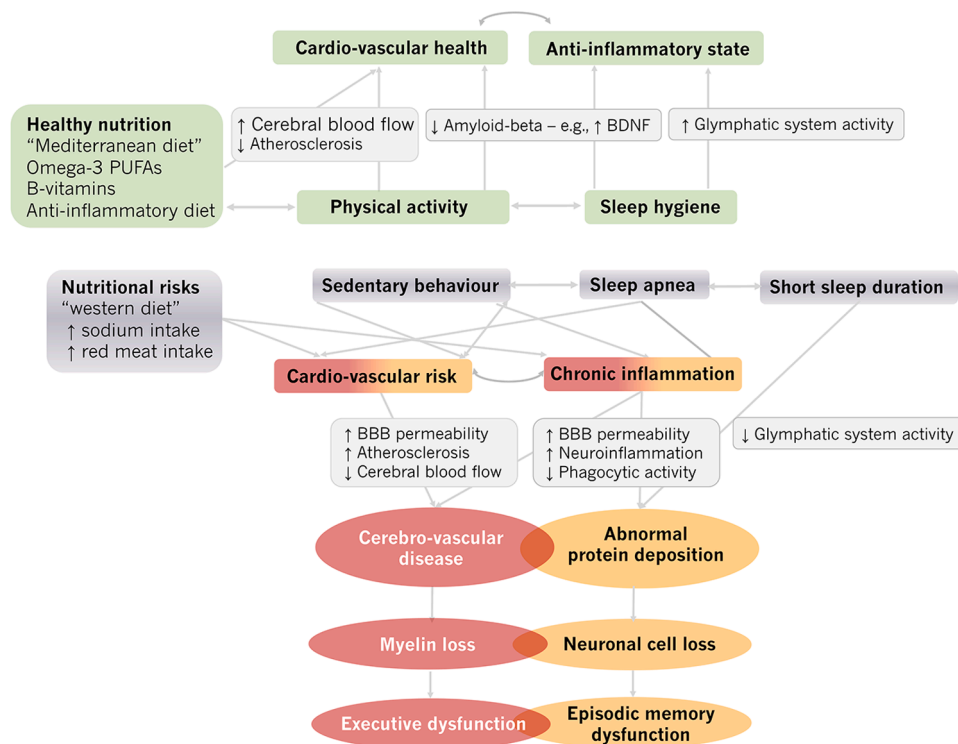


Fig. 1. Schematic representation of associations and causal relationships between LiMEE risk factors

(Więckowska-Gacek et al., 2021), which can in turn lead to hippocampal atrophy and memory impairment (Ivanova et al., 2020; Guillemot-Legris and Muccioli, 2017). It is also possible that some nutrients have direct effects on the cellular and molecular mechanisms of brain aging. Studies have demonstrated that higher sodium is associated with A β increases (Cheng et al., 2015), while antioxidant vitamins (i.e., vitamin C and E), polyphenols, and Omega-3 poly-unsaturated fatty acids can inhibit oxidative stress and neuroinflammation (McGrattan et al., 2019; Miquel et al., 2018).

4.2. Physical activity

Sedentary behaviour and physical inactivity are lifestyle risk factors for brain health. According to the GBD (GBD, Stroke Collaborators, 2019, 2021), the lack of physical activity accounts for 2% of stroke cases on the background of mutual associations between sedentary behaviour and cardio-vascular risk (Lavie et al., 2019). Physical inactivity describes the insufficient amount of moderate-to-vigorous exercise, while sedentary behaviour is defined as reduced amount of energy expenditure while in sitting or reclined position. Here, we use these terms interchangeably, while respecting the adopted nomenclature in the literature.

At the molecular and cellular level, sedentary behaviour is associated with inflammatory processes, oxidative stress, and endothelial dysfunction (Lavie et al., 2019). “Couch potato” behaviour has also been associated with decreased cognitive function over time (Falck et al., 2017). A meta-analysis estimated that physical inactivity increases the risk of dementia by 30 % (Yan et al., 2020)). However, study designs with short follow up periods might inflate the link between physical inactivity and risk of dementia. Along these lines, the socioeconomic status and related educational level should be considered as additional confounding factors for the interaction between physical activity and cognitive performance at old age (Gubelmann et al., 2017). A meta-analysis of longitudinal studies showed that when baseline physical activity measures were taken almost a decade before the diagnosis, physical inactivity was associated with higher risk of dementia

(Kivimäki et al., 2019). Conversely, other longitudinal studies failed to show a causal relationship between physical inactivity and dementia (Kivimäki et al., 2019). The interpretation here was that physical inactivity in late life might be a consequence of subclinical neurodegeneration, rather than a risk factor of dementia (Kivimäki et al., 2019).

At the system level, there is strong empirical evidence about the positive impact of physical activity on brain health (Raichlen and Alexander, 2017). In a longitudinal cohort of women spanning over four decades, physical activity during midlife was associated with lower risk of mixed dementia, but not with Alzheimer’s disease (Najar et al., 2019). A large-scale analysis of UK Biobank data demonstrated that 10,000 steps a day are associated with a 50 % reduction in the risk of all-cause dementia (Del Pozo et al., 2022). Similarly, neuroimaging studies in older populations have shown that moderate-to-vigorous physical activity is associated with higher hippocampal and dorsolateral prefrontal cortex volume, additionally to lower white matter hyperintensity load (Raichlen et al., 2020; Northey et al., 2020).

Part of the beneficial physical activity effects might be mediated by reducing the cardio-vascular risk and by improving the cardio-respiratory fitness defined as the ability of circulation and respiration to provide oxygen to muscles during maintained physical activity. Cardio-respiratory fitness has been related to higher global grey matter volume and lower white matter hyperintensity burden (Raichlen et al., 2020), as well as with higher performance in visuo-spatial reasoning (España-Irla et al., 2021). Sleep is another possible mediator of the physical activity benefits given that regular exercise modulates sleep latency and subjective sleep quality (Kredlow et al., 2015). Studies in rodents showed that physical activity reduces the accumulation of A β proteins in the brain, by increasing the perivascular flow and the capacity of the glymphatic system to clear molecular waste (Brown et al., 2019). Physical activity may reduce the build-up of A β plaques by increasing brain-derived neurotrophic factor and sirtuin-1, which in turn regulate enzymes that cleave the amyloid precursor protein (Brown et al., 2019).

There is ample evidence about the beneficial effects of physical

exercise on brain health in late adulthood. A meta-analysis demonstrated that different physical exercise interventions in participants older than 50 years old improve cognitive performance. Examined separately, all types of exercise - i.e., aerobic exercise, resistance training, multicomponent training, and Tai Chi were significant, except for yoga probably due to the low number of published randomized-controlled trials. These positive effects were present across different cognitive domains: attention, working memory and other executive functions, and memory (Joseph Michael Northey et al., 2018).

4.3. Sleep

Sleep is fundamental to sustain brain functions and undergoes a series of changes during aging (Lewis, 2021). Old age is associated with longer sleep latency, shorter duration of sleep, more fragile sleep (i.e., increased awakenings, and more transitions to phases of non-REM light sleep), and reduced time spent in slow-wave stages of non-REM sleep (Mander et al., 2017). The prevalence of sleep apnea increases with aging, which may be partially confounded by the aging-associated accumulation of cardio-vascular risk (Punjabi, 2008). Common sleep pathologies, such as insufficient sleep and sleep apnea, have negative consequences for brain health. The analysis of the Whitehall II cohort data, looking for dementia incidence 25 years after initial assessment, showed that at age 50 and 60, duration of sleep shorter than 6 h, predicted a higher risk of dementia (Sabia et al., 2021). Similarly, poorer subjective sleep and higher number of self-reported sleep disturbances (e.g., awakenings, temperature discomfort) were associated with progressive cortical thickness loss in the right lateral temporal cortex without evidence for a clear-cut link to cognitive performance (Fjell et al., 2021).

One of the probably most important physiological functions of sleep is the sleep-related activity of the glymphatic system to remove metabolic waste (Lewis, 2021; Hablitz and Nedergaard, 2021). A study reported that 24 h of sleep deprivation were sufficient to impair the waste clearance, and this impairment could still be detected 48 h after sleep deprivation (Eide et al., 2021). Sleep deprivation leads also to increases in A β burden in the thalamus and hippocampus (Shokri-Kojori et al., 2018). Studies in the animal model have shown increments of brain's interstitial fluid by 60% during sleep. This increase facilitates the removal of A β twice as fast as it happens during wakefulness (Xie et al., 2013). The dysfunction of the glymphatic system representing the bidirectional link between sleep pathology and neurodegeneration led researchers to propose it as the end point of convergence of various lifetime risk factors (Nedergaard and Goldman, 2020).

Sleep apnea negatively impacts brain and behaviour because of the continuous deficient oxygen supply. The mutual reinforcement of sleep apnea and cardio-vascular risk factors (Drager et al., 2010; Wolk et al., 2003) naturally leads to a higher risk for stroke and small vessel disease (Culebras and Anwar, 2018). Obesity is one of main risk factors of sleep apnea, and it is estimated that sleep apnea is present in around 40% of obese individuals (Wolk et al., 2003). Given the evidence for higher white matter hyperintensities load (Lee et al., 2023) alongside reduced cortical and subcortical grey matter volume (Tahmasian et al., 2016; Marchi et al., 2020), the lower performance in episodic memory, executive functions, attention, and processing speed becomes evident (Stranks and Crowe, 2016; Leng et al., 2017). Recent findings also stipulate an association between sleep apnea and the glymphatic system that affect the normal "filtering" function through pressure gradient changes (Ju et al., 2016).

Good sleep promotes cognitive health (Scullin and Bliwise, 2015). The empirical evidence comes mainly from randomized controlled trials using continuous positive airway pressure, the treatment of choice for patients with sleep apnea. The use of CPAP has been associated with improvements in quality of life, and symptoms of anxiety, and depression (Campos-Rodriguez et al., 2016), with better performance in attention and processing speed in participants with severe forms of this

disorder (Wang et al., 2020), and with cognitive improvement in Alzheimer's disease patients with comorbid sleep apnea (Bubu et al., 2020).

4.4. Cardio-vascular risk

Cardio-vascular and metabolic health are highly interdependent. Cardio-vascular health entails the absence of pathology the heart and the blood vessels (Payne, 2012). Metabolic factors relate to how the body processes energy and nutrients from food to the regulation of the concentration of blood glucose, and to the balancing of gastrointestinal factors, such as insulin, ghrelin, and leptin (Stefan and Schulze, 2023). Some metabolic dysfunctions, such as type 2 diabetes mellitus, and obesity, increase the risk of cardio-vascular pathology, constituting cardiometabolic or cardio-vascular risk factors (Alberti et al., 2009). Either individually or in combination, cardio-vascular risk factors are associated with poor brain health (García-García et al., 2022). The presence of a metabolic syndrome carries a higher risk of both ischemic and haemorrhagic stroke, along with an increased likelihood of post-stroke disability (GBD, Stroke Collaborators, 2019, 2021). Cardio-vascular risk factors such as abdominal obesity, hypertension, and type 2 diabetes are also associated with a higher risk of Alzheimer's disease (Livingston et al., 2020; Yu et al., 2020) and small vessel disease progressing into vascular dementia (van der Flier et al., 2018).

Cardio-vascular risk factors also increase the "brain age" gap – the difference between individual's chronological age and age estimated from brain MRI data with the help of machine learning techniques (Chen et al., 2022). A higher waist-to-hip ratio, marker of abdominal obesity, makes the white matter of the brain look older (Subramaniapillai et al., 2022). Studies on brain tissue properties provide insight on the effects of cardio-vascular risk on brain's myelin and iron content (Trofimova et al., 2021). Among the different cardio-vascular risk factors, arterial hypertension and abdominal obesity seem to be particularly harmful with substantial myelin loss in the frontal white matter (Trofimova et al., 2023; Cox et al., 2019). The effects of cardio-vascular risk on brain health are gradual (Abdullah et al., 2011). The presence of abdominal obesity during mid-adulthood is associated with higher risk for dementia, however this relationship becomes less significant in late adulthood (Livingston et al., 2020; Yu et al., 2020). An alternative interpretation suggests that preclinical neurodegeneration can be accompanied by weight loss representing a consequence rather than a cause (Jimenez et al., 2017).

The consequence of cardio-vascular pathologies is a global and local reduction of cerebral blood flow (García-García et al., 2022) mediated via the neuro-vascular units and resulting in blood-brain barrier leakage due to endothelial dysfunction (Iadecola and Gottesman, 2019). Cardio-vascular risk factors can also exert their negative effects by promoting neuroinflammatory processes. The link between neuroinflammation and cardio-vascular burden is bidirectional, since in turn, inflammation can also worsen metabolic dysfunctions, such as insulin resistance (de la Monte, 2017). There is empirical evidence for the beneficial effects of cardio-vascular risk reduction on brain health. Bariatric surgery, and subsequent weight loss improve memory performance, attention, and executive functions in morbidly obese patients (Handley et al., 2016). One year after bariatric surgery, the estimates of brain age showed a reduction of 3 years on average (Zeighami et al., 2022). Antihypertensive medication reduces the risk of stroke (Parsons et al., 2016; Zonneveld et al., 2018), and the progression of white matter hyperintensities (van Middelaar et al., 2018). At the same time, anti-hypertensive medication does not have any effects on grey matter volume (van Middelaar et al., 2018), cognitive decline, or dementia risk (Parsons et al., 2016).

4.5. Neuroinflammation

Aging is associated with persistent low-grade inflammation, a phenomenon known as *inflammaging* (Franceschi et al., 2018). The effects

arise because of the accumulated damage along cellular and molecular pathways related to aging, such as mitochondrial dysfunction, disabled macroautophagy, loss of proteostasis, or cellular senescence (López-Otín et al., 2023). Inflammaging also contributes to brain aging. Increases in blood circulating inflammatory markers, such as tumour necrosis factor alpha (TNF α), increase the permeability of the blood-brain barrier and the expression of endothelial cell adhesion proteins, which further increases the concentration of proinflammatory cytokines in the brain. Inflammatory cytokines, such as interleukine-6 (IL16), TNF α , and interleukine-1beta (IL-1 β) can worsen the atherosclerotic plaque, increasing the risk of stroke (Liu et al., 2022). At the same time, TNF α and IL-1 β can activate the pro-inflammatory signalling pathway NF- κ B (Walker et al., 2022). Gene expression controlled by NF- κ B, in turn, produces a further release of proinflammatory cytokines and it can activate the microglia, the CNS innate immune cells (Walker et al., 2022). Microglial dysfunction can lead to further damage to the BBB and to the accumulation of misfolded proteins in the synaptic space, contributing to the pathophysiology of neurodegenerative disorders (Wilson et al., 2023). The increases in markers of vascular inflammation, such as homocysteine, are associated with the white matter hyperintensity load (Low et al., 2019). Increases in inflammatory cytokines also mediate the link between metabolic dysfunction and cerebro-vascular disease: specifically, a study suggested that obesity contributes to white matter hyperintensities via increases in IL6 (Lampe et al., 2019). The effects of neuroinflammation on cortical and subcortical grey matter structures are not unequivocally established (Low et al., 2019). The epigenetic marker of C-reactive protein has been associated with global volume loss and decreased cognitive performance, which showed much stronger relationship with brain health outcomes than the ones with phasic serum CRP (Conole et al., 2021). Maintaining moderately high and increasing blood CRP levels spanning over nearly two decades, resulted in compromised white matter microstructure (O'Donovan et al., 2021).

Epidemiological studies on neurodegenerative disorders provide insights into the crosstalk between immune health and brain health. A large prospective study showed that adults older than 65 years with at least one influenza vaccine were 40 % less likely to develop Alzheimer's disease during a 4-year follow-up compared to unvaccinated people (Bukhbinder et al., 2022). Similar results have been reported with other vaccines, such as herpes zoster vaccination (Scherrer et al., 2021) and support the possibility that immune responses have long-term effects on brain health and impact neurodegenerative mechanisms.

4.6. The interrelations between LiMEE and other risk factors on brain health

Endogenous and non-modifiable risk factors, such as demographic variables and genes have unique and combined effects on brain health. Likewise, exogenous factors, namely, psychosocial stressors, social isolation, pollution, poverty, and lack of education opportunities might also directly affect cognitive performance and psychological adjustment. While acknowledging this, in our model we highlight that some part of their negative effects on brain health might be mediated by their influence on LiMEE components.

Age is a determinant factor of brain health, and part of the aging effects in the brain might be driven by increased cardio-vascular burden. Less obviously, socio-economical, or environmental risk factors might partly exert their effects on brain health via the aggravation of LiMEE threats. Psychosocial stressors are associated with increases in weight gain (Cuevas et al., 2021), especially among obese people (Block et al., 2009) along with a higher risk of developing hypertension (Liu et al., 2017) and sleep problems (Nielsen et al., 2020). As such, several indirect mechanisms might relate psychosocial stress with brain health. Intricate relationships also exist between stress, social isolation, changes in dietary habits, weight gain, and sleep problems, as we might have experienced because of the COVID-19 pandemic and the lockdown measures

to restrain it (Martínez-de-Quel et al., 2021; Mattioli et al., 2020).

There is an association between poverty and general health. Between age 40 and 85, socioeconomic disadvantage has been associated with two years decrease in life expectancy (Stringhini et al., 2017). Low socioeconomic status seems to predict worse longitudinal outcomes in vascular factors, such as hypertension, abdominal obesity, and dyslipidemia, and in lifestyle behaviours, such as smoking, physical inactivity, and alcohol consumption (Schrempft et al., 2021). Having poorer access to healthcare services is probably a related factor that is partly influencing the relationship between low socioeconomic status and general health (Amiri et al., 2020). Studies have described neurocognitive associations with regards to socioeconomic status. For instance, high lifetime socioeconomic status has been linked with increased grey matter volume in the postcentral gyrus, cuneus, and cerebellum (Loued-Khenissi et al., 2022).

Pollution can be present in the air, water, and soil. Air pollution is an important contributor to cardio-metabolic burden. Even at low concentrations, it can increase the risk of myocardial infarction, stroke, and acute heart failure (Bourdrel et al., 2017) along with T2DM (GBD, Diabetes and Air Pollution Collaborators, 2019, 2022). Regarding brain health, for each increase in 10 $\mu\text{g}/\text{m}^3$ of PM_{2.5} levels in the air there is a 14% increase in stroke mortality (Hayes et al., 2020). Breathing polluted air has been associated with markers of neuroanatomical senescence, such as lower cerebral grey matter volumes and higher load of white matter hyperintensities (Furlong et al., 2021). Exposure to air pollutants might also lead to lower cognitive performance. This is especially so regarding linguistic tasks (Nußbaum et al., 2020; Zhang et al., 2018) and, to a lesser extent, immediate and long-term memory (Nußbaum et al., 2020). Of note, the harmful effects of air pollutants might be more significant during the uterine phase (Russ et al., 2021), suggesting that polluted air impacts the brain starting from prenatal stages. There is also a link between air pollution and mental health. Higher concentrations of PM_{2.5} and PM₁₀ are associated with increased incidence of depression (Borroni et al., 2022) along with a higher use of mental health services among psychiatric populations, which indirectly suggests the possibility of a link between air pollution and severity of psychiatric symptoms (Newbury et al., 2021). Multiple pathways might link air pollution with poorer brain health. Here, an often-mentioned mechanism is that nanometer-sized air pollutants might be able to cause neuro-inflammatory responses, activating the microglia, and increasing progressive neuronal damage and the risk of neurodegenerative conditions, such as vascular dementia, Alzheimer's disease, or Parkinson's disease (Jayaraj et al., 2017).

Many open questions remain with regards to the role of air pollution on brain health. For instance, we do not know yet if the effects of pollution are reversible: what happens when a person moves to another place with cleaner air? We also do not know whether there are periods during the lifespan that are especially sensitive to the effects of pollutants, beyond initial data on uterine exposure. With the growing availability of longitudinal studies on air pollution, it is hoped that soon we will be able to provide a better characterization of the effects of air pollution in brain aging.

5. Methodological considerations

This review is based on studies that use a variety of methods to assess and track lifestyle factors, such as sleep, physical activity, and dietary patterns. Regarding sleep, all the studies cited here have used subjective sleep assessments. However, the correlations between subjective sleep measures evaluated with the PSQI and accelerometer-derived measures are around 0.25 at its best (Landry et al., 2015), thus highlighting limits in accuracy and reliability of subjective measurements. In the case of physical activity, accelerometer-derived measurements show better correlations with cardiorespiratory fitness than self-reported measures of physical activity (Arvidsson et al., 2019). At the same time, data derived from accelerometer recordings may also vary depending on the

location of the device (e.g., arm, wrist, or hip), the different epoch length used, the number of days recorded, and other decisions that relate to the quality control treatment of the data (Arvidsson et al., 2019).

Despite these considerations, continuous monitoring devices hold exciting potential for research because of their ability to provide a better characterization of lifestyle factors such as physical activity or sleep. They are also non-invasive, user-friendly, and they increase phenotyping resolution (Gard et al., 2021). By measuring over extended periods of time, continuous monitoring devices allow the identification of patterns and dynamic changes, and enable a higher resolution in the measures of lifestyle factors. They also avoid the limitations of a one-time self-reported measurement and leading to an improved precision. Their use has thus the potential to advance research on brain health, providing a deeper understanding on aging progression and on the effectiveness of lifestyle interventions.

6. Clinical implications: Long-term multimodal interventions

Brain health is impacted across lifetime by a mixture of endogenous and exogenous variables. These variables, in turn, influence each other and exert their effects independently and jointly. For instance, a study on the UK Biobank cohort corroborated the beneficial effects of both high levels of physical activity and regular consumption of high-quality diet. Participants that reported adherence to both positive lifestyle habits had a reduced risk of mortality. Interestingly, none of these two factors separately were able to counteract the other one (Ding et al., 2022), which highlights the importance of taking holistic approaches to protect brain health. It is for this reason that multimodal interventions that simultaneously address different actionable mechanisms of brain health might be specially well suited to prevent cognitive impairment and brain disability (Solomon et al., 2021; Frisoni, 2023; Kivipelto et al., 2018).

Three large multimodal trials aimed at preventing cognitive impairment in population without dementia have been conducted so far: the FINGER trial, which combines nutrition intervention, cognitive stimulation, and cardio-vascular risk monitoring (Ngandu et al., 2015), the PreDIVA study, a multi-domain cardio-vascular intervention (Moll van Charante et al., 2016), and the MAPT trial, which integrates cognitive stimulation, physical activity, and nutrition intervention (Andrieu et al., 2017). All these studies found effects of the interventions on cognitive performance, highlighting that multimodal approaches have a great potential to protect brain health. A note of caution from these studies is that, with the notable exception of the FINGER trial, the significant results were observed in post-hoc analysis or secondary endpoints and were not present in the primary endpoints of the study (Kivipelto et al., 2018).

We advocate that holistic interventions targeting brain health should include the five LiMEE factors, that is, nutrition, physical activity, sleep, cardio-vascular health, and immune health. While the optimal weighting of these factors remains uncertain, here we try to make an approximation into which LiMEE factors are more relevant for brain health. In this regard, we regard cardio-vascular risk factors and inflammation as the two factors that are more directly connected with brain health and, as such, the two factors that should be more closely monitored and controlled in brain health interventions.

7. Conclusions

We have presented a holistic model that provides directly testable hypotheses on the causal links between endogenous and exogenous risk factors and brain health outcomes. In the core of our model, we have five threats: dietary risks, sedentary behaviours, sleep problems, cardio-vascular risk factors, and chronic inflammation. We suggest that these threats exert their negative effects in a cumulative and gradual manner. Ideally, the removal, treatment, or compensation of the threat would improve brain health and promote brain maintenance. Our model can

guide person-based multi-modal clinical strategies aimed at preventing cognitive impairment and other neurological disabilities and at promoting health in the aging brain.

Declaration of Competing Interest

IGG, OD, and AH are employed at Clinique la Prairie. AAC, SGN, SN, CP, ER, GT, SF, and BD are members of scientific committee at Clinique la Prairie. SGN and SN are co-founders of a company active in the field of longevity and health prevention, and they are co-inventors of a pending patent on biological age by means of epigenetic biomarkers. CP has received consulting fees from the Foundation Nutrition 2000plus, Abbott, Baxter, B. Braun, Cosmed, Fresenius-KABI, Huawei, Nestle Medical Nutrition, Novartis, Nutricia-Numico, Pfizer, Shire, and Solvay.

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