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A lifetime perspective on risk factors for cognitive decline with a special focus on early events

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ABSTRACT

Both Alzheimer's disease and vascular dementia are the result of disease processes that typically develop over several decades. Population studies have estimated that more than half of the risk for dementia is preventable or at least modifiable through behavioral adaptations. The association between these lifestyle factors and the risk of dementia is most evident for exposure in midlife. However, habits formed in middle age often reflect a lifetime of behavior patterns and living conditions. Therefore, individuals who, for example, are able to maintain healthy diets and regular exercise during their middle years are likely to benefit from these cognition-protective habits they have practiced throughout their lives. For numerous adult diseases, significant risks can often be traced back to early childhood. Suboptimal conditions during the perinatal period, childhood and adolescence can increase the risk of adult diseases, including stroke, heart disease, insulin resistance, hypertension and dementia. This review aims at summarizing some of the evidence for dementia risks from a life-time perspective with the goal of raising awareness for early dementia prevention and successful aging.

Introduction

Dementia symptoms gradually manifest over many years, and longitudinal studies indicate that even 10–15 years prior to reaching the dementia stage, subtle cognitive decline can be detectable, which may coincide with a subjective perception of cognitive deterioration [1,2]. Dementia, as a neurodegenerative disorder, does not simply manifest at late stages of life, its roots trace back to the individual's genetic disposition, lifestyle, habits, and environmental exposures across the entire lifespan. Understanding dementia from a lifetime perspective offers the opportunity to explore modifiable risk factors in dementia prevention and their role in shaping concepts of resilience and reserve.

Alzheimer's disease and vascular dementia are the two most common forms of dementia, each with its own distinct causes, risk factors, and characteristics. Alzheimer's disease is primarily characterized by the accumulation of abnormal protein deposits in the brain, namely beta-amyloid plaques and tau tangles, which disrupt the normal functioning of brain cells and eventually lead to their death [3]. Vascular dementia is caused by conditions that block or damage the blood vessels in the brain, leading to brain cell death due to lack of oxygen and nutrients. Therefore, the risk factors for vascular dementia largely overlap with those for cardiovascular diseases [4].

From a lifetime perspective, Alzheimer's disease and vascular dementia require to some extent a different focus on their respective risk factors; however, these two types of dementia often coexist. Many older individuals with dementia have brain abnormalities associated with more than one type of dementia [5–7], which underscores the importance of a comprehensive approach to risk factor management. Primary modifiable risk factors for dementia include physical inactivity, smoking, unhealthy diet, midlife hypertension, midlife obesity, diabetes, and depression. Additionally, lower educational attainment and social isolation are associated with increased risk [8]. Prevention strategies primarily focus on adopting a healthy lifestyle, including regular physical exercise, a balanced diet, and engaging in cognitively stimulating activities.

In this review, we place a specific emphasis on early life events from infancy to young adulthood, since midlife risk factors have extensively been dealt with in other reviews (for example see [9–14]. However, due to the long timespan from childhood until dementia diagnosis of at least 5–6 decades, few studies have been able to longitudinally track specific childhood traits and link them directly to a dementia diagnosis. One should be aware that instead, proxy measurements have most often been

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employed. Frequently, childhood proxy measurements have been associated with midlife proxy measurements, which make the link to dementia even less stringent. Proxies belong into three categories: (i) alterations in neuroanatomical and physiological measurements (for example brain volume, brain activation measurements, blood biomarkers), (ii) behavioral and cognitive performance measurements or (iii) the occurrence or accumulation of known risk factors for dementia. Although these measurements have reduced explanatory value, they can still provide a valid approach to form hypothesis and search for underlying mechanisms and preventive measures.

Genetic predisposition

It is a well-known fact that variants of individual genes can increase the likelihood of developing a disease. However, pinpointing the physiological processes and time point of influence can be difficult. Depending on the individual mechanism of action, genetic variants may represent dormant risks that become prevalent later in life by contributing more directly to the prodromal stages of a disease such as dementia. But the influence of genetic variants may also begin in early life, contributing to other, possibly modifiable risk factors that make an individual more susceptible to cognitive impairment later in life [15].

The presence of mutations in genes such as APP, PSEN1, or PSEN2 is associated with early-onset familial Alzheimer's disease and individuals carrying mutations in these genes often develop Alzheimer's at a relatively young age. In comparison, besides the APOE ε4 allele [16], there are few well-known individual genetic risk factors for non-familial late-onset AD [17]. It is assumed that the genetic contribution for a large portion of sporadic AD is rather associated with polygenic or cumulative risk of inheriting multiple genetic variants, each contributing a small amount, which collectively can influence the susceptibility to dementia [18]. The low number of identified individual gene variants with high probability for association with late-onset dementia also led to the abductive conclusion that other mechanisms, such as epigenetic modification, transcriptional regulations and/or gene-environment interactions could play a substantial role in pathogenesis [19–21]. For vascular dementia there is also a growing list of mutations that represent monogenic causes of cerebral small vessel disease, e.g. in genes such as NOTCH3, α-GAL A gene (GLA), TREX1, COL4A1 [22,23]. But similar to AD, sporadic vascular dementia is less well defined by individual genetic risk factors, except for APOE [24].

APOE is one of the best examples that highlights how a well-established genetic risk factor exerts its influence throughout the entire lifespan [25]. APOE is the primary transporter of lipids and cholesterol in the brain and part of complex gene-environment interactions that orchestrate brain cholesterol metabolism. Widespread genotype screening for APOE variants has revealed altered risk for neurodevelopmental alterations in children and young adults, including changes in functional brain activation and connectivity [26–28], receptor trafficking and synapse formation [29,30], cortical thickness and hippocampus volume [31,32], cerebrovascular reactivity [24], as well as cognitive performance [33,34]. Adding to the complexity, APOE variants not only influence brain physiology but also peripheral mechanisms which lead to altered risks for cardiovascular diseases, diabetes, and peripheral chronic low-grade inflammation, all known risk factors for developing dementia later in life [35–37]. This example highlights that a single genetic burden for dementia can manifest at multiple stages of life by increasing the life-course vulnerabilities for later cognitive impairment. While genetic factors are not modifiable *per se*, focusing on the related modifiable risk factors mentioned above gives the opportunity to lower the probability for dementia in high-risk individuals through early interventions [38]. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) found evidence for APOE ε4 carriers benefitting more from a multimodal lifestyle intervention compared to controls [39].

Perinatal neurodevelopmental challenges

The risk for cognitive impairment and dementia may manifest as early as during the prenatal developmental stage. Prenatal malnutrition and reduced birth weight exert enduring adverse effects on cognitive functioning by directly influencing cognitive development [40,41]. Furthermore, indirect effects through increased susceptibility to other chronic diseases linked to dementia, in particular vascular diseases and their known risk factors (such as hypertension, high cholesterol and serum lipid levels, atherosclerosis, hyperinsulinemia and diabetes) have consistently been observed to be increased due to fetal undernutrition or low birth weight [42,43].

When a harmful event to developing brain occurs, it can impact synaptic mechanisms, disrupt normal brain activity and interfere with typical growth and neuroplasticity [44]. Such changes in brain structure and function during the developmental phase can have long-lasting impact by halting maturation or misshaping brain architecture. Moreover, at the behavioral level it may limit the range of experiences and beneficial exposures a child can have during their development [45]. The timing of an insult, particularly with respect to the different critical developmental periods can influence the impact on plasticity and function [46–49], since many forms of neuroplasticity are at their peak during early developmental stages, and some are exclusive to the developing brain [50].

Besides neuronal maturation, the overall blood vessel architecture, and the local cellular integrity of blood vessels can also be affected by developmental disorders or conditions. For example, premature birth is linked to diminished cardiac capacity, lowered vascularity, heightened vascular rigidity, and elevated pressure in both pulmonary and systemic blood vessels [51]. Such vascular vulnerabilities can make organs including the brain more susceptible to damage from reduced blood flow or vascular events later in life [52].

Early life events can also trigger inflammation [53], which negatively impacts neuronal health and contribute to cognitive dysfunction and psychopathological responses at later stages [54]. The process involves complex interactions among neurons and microglia. For instance, microglia play a critical role in pruning neural connections, but under stress or adversity they can switch to an activated form and increase the release of inflammatory factors. This shift in microglial activity and the resulting inflammation can lead to changes in brain networks and are linked to developmental disorders [55].

In addition, due to their functional impairments, individuals with developmental disorders or conditions may be more prone to unhealthy lifestyle behaviors that increase cardiovascular risk [56]. For example, they may have difficulties with physical activity, experience weight gain, or have dietary habits that further aggravate conditions like obesity or diabetes and these risk factors can thus further increase the likelihood of dementia later in life.

Adverse childhood experiences

Childhood is a crucial period in human neural development, characterized by rapid growth and maturation of the sensory and motor systems. During this time, the brain is highly receptive to environmental stimuli and experiences, which play a significant role in shaping the neural pathways associated with sensory perception and motor skills. Sensitive periods in childhood refer to specific windows of time when the brain is particularly receptive to certain types of input [57]. For instance, there are sensitive periods for language acquisition, where children are most receptive to learning and developing language skills [58,59]. However, these periods of brain plasticity and growth also come with a vulnerability to adverse external influences.

Children are uniquely vulnerable to traumatic brain injury (TBI), since they are at increased risk for delayed developmental milestones and mental health problems after such brain insults [60,61]. Abusive head trauma can lead to very severe outcomes, depending on the

frequency and intensity as well as the age at which the abuse occurred [62]. Even mild forms of TBI can have long-lasting effects in children similar to brain pathologies in chronic traumatic encephalopathy observed after repetitive mild brain trauma in contact sports [63].

Severe childhood stress can also have long-lasting impact on the brain, especially since stress experienced early in life can alter the ongoing development of the nervous system and make individuals more susceptible to mood disorders and behavioral maladaptation [64–66]. Severe stress responses occur when a child undergoes intense, frequent, or prolonged adversities, such as physical or emotional abuse, sustained neglect, caregiver substance dependency or psychiatric disorders, exposure to violence, and the cumulative hardships of familial economic distress, all without sufficient adult assistance. Pathological stress from extended or severe early-life adversities leads to an adaptive malfunction of the stress response system [67]. This protracted activation of stress response systems can disrupt the proper maturation of neural structures and other bodily systems [68,69].

Studies investigating children exposed to violence have consistently observed certain neural changes, including a reduction in amygdala volume, heightened amygdala responsiveness to threat signals, and increased activation in the anterior insula [70]. Additionally, reductions in hippocampal volume were most frequently observed in children exposed to adversity related to threats. If physical child abuse is directed to the head, traumatic brain injuries are likely to occur. When it comes to studies of children exposed to deprivation, a different set of findings has emerged. These studies consistently reveal reductions in the volume and thickness of the dorsolateral prefrontal cortex and the superior parietal cortex [70]. These structural findings align with numerous other studies that have documented difficulties in cognitive control among children exposed to deprivation [71,72].

Early life adversities also have a strong impact on immune function characterized by increased inflammation, impaired cellular immunity, and accelerated immunosenescence [73]. The developing immune system is shaped by the continuous exposure to a variety of environmental factors, such as microorganisms forming the microbiota or causing infections, immunomodulatory factors (e.g. hormones and cytokines via breast milk), nutrition, as well as psychosocial factors via stress response mechanisms [74]. It is speculated that such environmental factors in early life can influence transcription profiles in human immune cells via epigenetic mechanisms which in turn may increase the risk for chronic diseases, in particular chronic inflammatory disorders [75].

While studies have clearly demonstrated the effect of adverse childhood experiences on adolescent and adult brain structures and cognitive performance as an intermediate step, few studies have directly linked adverse childhood experiences to dementia. There is some heterogeneity in results due to uncontrolled confounding over the lifespan, however the risk appears to be increased [76–79].

Psychosocial setting

From the evidence presented above it is no surprise that the psychosocial circumstances, in particular parental education and socioeconomic status (SES) can have a strong influence on child development and therefore brain function and cognition later in life [80–82]. There is evidence that lower SES and parental education increase the dementia risk later in life [83–85] and modifiable health factors and lifestyle factors were partially able to explain the SES effects [86].

Regarding more specific brain-related effects, a linear relationship with cortical surface area has been described for parental education [87]. Widespread brain area differences in sensorimotor areas have also been observed in children from low versus high SES families [88], and localized differences, for example in the size of the hippocampus, have been found as well [89,90]. More recent data indicate that both childhood and adult SES separately correlated with gray matter volume and myelin differences. Most importantly, childhood SES was associated with robust neural differences in adults even when controlling for their own adult SES [91]. Higher life-course SES was associated with increased volume in sensorimotor regions, lateralized differences in volumes of temporal lobe structures and higher myelin content in sensorimotor network but lower myelin content in the temporal lobe [91]. SES, a measure frequently used to control for confounding in epidemiological and clinical studies, may thus be an upstream determinant of adversities, since socioeconomic constraints put children at higher risk for experiencing adversities and health disadvantages [92].

Nutrition and adiposity

As mentioned above, evidence suggests that low birth weight, a marker of inadequate nutrition in uterus, may be associated with lower cognitive level in both childhood and adulthood [93]. But the relationship between childhood nutrition and the risk of dementia later in life has also been a topic of growing interest. Studies indicate that nutritional factors during early life can have long-term impacts on cognitive health. A notably higher prevalence of dementia has been detected in older individuals who experienced food insufficiency during childhood compared to those who had sufficient food [69,94]. Moreover, a study found long-lasting DNA methylation changes in humans exposed to malnutrition in early infancy and that these were associated with attentional and cognitive deficits in adulthood [95], highlighting the importance of adequate nutrition in early life for maintaining cognitive function in later years.

Body mass index as an indicator for obesity has been used to establish a link between obesity in adulthood and increased risk for cognitive decline [96]. This connection is thought to be mediated, at least in part, by low-level inflammation [97]. Obesity in adulthood has been correlated with reduced brain volume in various regions, including the hippocampus [96,98,99]. Similar results have been reported for obesity and metabolic syndrome in adolescence, with lower cognitive performance and reductions in brain structural integrity [100]. Additionally, preclinical studies in rodents have shown that high-fat diet impairs hippocampal long-term potentiation, which is essential for learning and memory, providing further insight into the potential mechanisms underpinning obesity-related cognitive impairment [101,102].

Physical activity

Physical activity has a positive impact on brain health in general and the development of dementia in particular across the entire span of a person's life [103]. Traditionally, it was believed that physical activity indirectly influenced these outcomes by lowering the risk of conditions that can harm brain health, such as obesity, diabetes and cardiovascular disease [104]. However, an increasing body of evidence from both human and animal studies is revealing that physical activity also plays a more direct role in promoting brain health by affecting both CNS structure and function [105]. For example, a number of investigations have shown notable associations between increased physical activity and reductions in symptoms of attention-deficit hyperactivity disorder (ADHD) [106]. More specific, physical activity has been linked to improved cognitive functioning in children with ADHD [107].

Several potential mechanisms have been suggested to explain how physical activity can impact brain health, including improvements in cardiovascular health, the release of neurotrophic factors, increased insulin sensitivity, stress reduction, and reduced inflammation [108]. Moreover, physical activity is thought to stimulate neuroplasticity and neurogenesis [109].

Evidence suggests that regular physical activity during childhood can impact the integrity of both gray and white matter in the brain, with potential implications for cognitive development [110]. Using cardiovascular fitness as a proxy measure for physical activity, a cross-sectional imaging study demonstrated that children that were more physically fit exhibited an increased volume of the dorsal striatum, a brain region crucial for regulating attention [111]. Similarly, in

physically fitter 9/10-year-old children, hippocampal volumes were notably larger, and this increase was linked to better performance in tasks involving relational memory [112].

While specific brain regions may modulate particular cognitive functions, the structural integrity and connectivity of white matter tracts that link these regions are essential for cognitive functioning. The microstructural properties of white matter are influenced by an individual's experiences and are sensitive to the level of cardiorespiratory fitness in children [113]. For instance, fitter children have been observed to exhibit increased structural integrity in white matter bundles compared to their less fit counterparts [114]. Greater cardiorespiratory fitness may thus be linked to enhanced white matter integrity and myelination.

Risk factors during adolescence

Adolescence is a distinct phase of development marked by significant changes in social, emotional, and cognitive domains. While the physical growth spurt of childhood may have slowed down, the brain continues to undergo remarkable changes during adolescence. One of the key brain regions involved in this transformation is the prefrontal cortex, which is responsible for higher-order cognitive functions such as working memory, planning, concept formation, and inhibitory control. These functions continue to mature throughout adolescence.

While childhood includes the sensitive periods for the development of the sensory and motor systems, adolescence includes sensitive periods for social, emotional and cognitive development in that the networks subserving these domains are undergoing plasticity based on the experiences of the individual [115–117]. Adolescence is characterized by a continued maturation of functions mediated by the prefrontal cortex including working memory, planning, concept formation, inhibitory control and others, a thinning of the cortex within the prefrontal cortex (and many other brain regions) and an increase in white matter density and volume [118]. With the maturation of these complex behaviors comes a vulnerability to exogenous influence and the increased possibility that functional and structural maturation can become abnormal and psychopathology can ensue. There is ample evidence that the adolescent brain responds differently to many stimuli compared to the adult, but empirical evidence that experience modifies specific connections, which in turn modify specific behaviors, is limited [119]. However, identical twin studies have demonstrated that the experience of each twin leads to alterations in the epigenetic profile of each twin which is suggestive of the importance of experience in modifying the genetic expression and therefore behavior [120].

As children grow into adolescence, previously mentioned risk factors, such as nutrition, physical activity and cognitive stimulation remain to be important and, with larger independence in decision making for the individual, may even increase their impact. The list of risk factors is further extended by additional unhealthy lifestyle choices including nicotine use and abuse of alcohol and illicit drugs drastically increases in adolescence [121]. Exposure to exogenous substances, such as alcohol, nicotine, and cannabis can interfere with normal brain development during adolescence and produce structural and behavioral disruption [122–130]. Alcohol- and drug intoxication in male adolescents have indeed been shown to increase the risk for young-onset dementia [131]. During adolescence, there is also an increasing influence of the social environment, especially since the activities of peers become increasingly important and drug exposure during adolescence can markedly alter later social interactions [132]. Moreover, poor sleep habits during adolescence, including insufficient sleep or sleep disorders, can further impact brain structure and cognitive function [133–135].

Adolescents who experience head injuries, particularly from sports or accidents, may be at greater risk of developing dementia later in life. Such injuries, especially if they occur multiple times, can lead to chronic traumatic encephalopathy (CTE), which is a neurodegenerative disease found in individuals with a history of repetitive brain trauma, including concussions and subconcussive hits to the head that do not cause immediate symptoms [136]. The disease is characterized by a buildup of abnormal tau protein in the brain, leading to symptoms such as memory loss, confusion, impaired judgment, aggression, depression, anxiety, impulse control issues, and sometimes suicidal behavior [137].

Limited cognitive stimulation during adolescence may also increase the risk of dementia. A lower cognitive performance on IQ-tests in adolescent males has been associated with an increased risk for young-onset dementia and mild cognitive impairment [138]. Staying mentally active through education, engaging in challenging cognitive activities, and pursuing lifelong learning can help increase cognitive abilities that may delay the onset of dementia symptoms.

Mental health issues during adolescence, such as depression, anxiety, and chronic stress, may contribute to an increased risk of dementia in later years. Chronic stress, for example, can lead to inflammation and other physiological changes in the brain. In this respect, the advantages of physical activity throughout childhood and adolescence extend beyond the known effects on cognitive performance and academic achievement. A low cardiorespiratory fitness during adolescence have been shown to increase the risk for young-onset dementia [138]. The available evidence also indicates several psychological benefits of physical activity, which encompass a decrease in symptoms of depression [139–142] and anxiety [139,143–145], as well as enhancements in self-esteem [143,146].

Manifestation of childhood and adolescent experiences

For early life conditions and experiences to influence brain functions many decades in the future and to become risk factors for dementia, some form of long-term consolidation is required. As we have seen in the previous studies, this can take the form of persistent behavioral shaping or habit formation, lifestyle adaptations, chronification of metabolic diseases and inflammation or the endurance of affective disorders. But ultimately these conditions will have to *"imprint"* on the structure and physiology of the adult and aging brain in order to contribute to the induction of dementias. At the cellular level this translates to, e.g. changes in the number of neurons and glial cells, changes in the relative composition of neuronal subtypes, synapses and dendrites, altered activation states of glial cells as well as myelination and connectivity changes. For example, exposure to stress or trauma can change regions such as the prefrontal cortex, amygdala or hippocampus in terms of altered synaptic spine density and atrophy of the basal dendritic tree [147–151]. Different types of neurons (e.g., excitatory, inhibitory) show differential susceptibility to stressful conditions [152], potentially altering the balance and functionality of neural circuits.

Dysfunction in glial cells has been linked to neurodegenerative processes related to dementia [153–156]. The intricate interplay between neurons and glial cells ensures the brain's homeostasis, and any disturbance in this balance can contribute to the progression of neurodegeneration. It comes to no surprise that glial cells can be affected by early life experiences, such as exposure to stress or nurturing environments. Astrocytes are involved in regulating the chemical composition of the brain's extracellular space, providing metabolic support to neurons, and participating in the formation and maintenance of synapses. Early life experiences can influence the development and function of astrocytes, potentially impacting the neural circuits they interact with [157,158]. As the resident immune cells of the brain, microglia play a crucial role in immune surveillance and response to injury or infection. Early experiences can influence the activation state and reactivity of microglia, which, in turn, may affect the brain's immune response and contribute to neuroinflammation [159–161]. Oligodendrocytes are responsible for myelinating axons and crucial components for efficient signal transmission in the nervous system. Early experiences can impact the development of oligodendrocytes and myelination processes, influencing the speed and efficiency of neural communication. Disruptions in

myelination have been implicated in a variety of neurological disorders, including those with neurodegenerative components.

Epigenetic modifications

An important aspect of childhood and adolescent experiences, be it positive or negative, is their influence on gene expression through epigenetic modifications, such as DNA methylation, histone modification and non-coding RNAs. These changes can persist throughout a person's life and affect the functioning of genes related to stress regulation, neural plasticity, and cognitive function [162]. They are considered key elements in the permanent adoption of physiological (or pathophysiological) states that show resistance to change later in life [163]. Chromatin remodeling could thus provide one of main mechanisms of *"imprinting"* stable cellular responses early in life which may ultimately lead to pathological changes involved in dementia.

DNA methylation is one of the most studied epigenetic modifications associated with childhood adversities [164]. DNA methylation involves the addition of methyl groups to specific cytosine residues in the DNA. When methyl groups are added to the promoter region of a gene, it often results in gene silencing. Childhood adversities, such as chronic stress, trauma, or neglect, have been linked to altered DNA methylation patterns [165]. This can permanently affect the expression of genes involved in stress regulation, neural development, and cognitive function [166]. For example, in individuals who experienced early-life adversity increased DNA methylation of genes involved in the regulation of the stress hormone cortisol has been observed, such as corticotrophin-releasing hormone (CRH) and glucocorticoid receptor (GR) [167–169]. This may lead to dysregulated stress responses that contribute to mental health problems and cognitive impairment in adulthood and aging.

Histone modifications can affect the accessibility of DNA to the cellular machinery responsible for gene expression. Childhood adversities can lead to changes in histone modifications that impact expression of immediate early genes [170] or genes associated with immune signaling in the amygdala [171]. Epigenetic changes can also involve non-coding RNAs, which play essential roles in regulating gene expression.

MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are examples of non-coding RNAs that can be influenced by childhood adversities. For example, dysregulation of certain miRNA species, that were associated with Alzheimer's disease, were elevated in plasma of adults with a history of childhood traumatization [172]. However, it is important to note that not all individuals who experience early adversities will exhibit the same epigenetic changes. There is significant variability in how individuals respond to stressors and how their epigenetic marks are modified [173,174].

Resilience, maintenance and reserve

The effects of early life and juvenile conditions and experiences on the brain are multifaceted, impacting its structure, cellular composition, connectivity and functional responses. These changes can either increase resilience or susceptibility to neurodegenerative diseases later in life. In dementia research, building up resilience to dementia signs and symptoms should be viewed as a process that is developed over the lifespan. The concept of *resilience* and its associated concepts of *brain maintenance, cognitive reserve* and *brain reserve* have been intensely debated in recent years, questioning in particular the attempted operationalization of these concepts [175–180]. Within the frame of this review, we define these concepts in rather simple terms useful for our discussion on life-time risk factors.

Not all individuals that are exposed to risk factors, including age, genetic disposition or the numerous factors mentioned above, will develop dementia. *Brain resilience* refers to the brain's ability to adapt to or recover from stress, trauma or neurological damage associated with dementia. *Brain maintenance* on the other hand refers to the ongoing upkeep and preservation of brain structure and function. It involves actively engaging in behaviors and practices that support brain health, such as maintaining a healthy lifestyle, engaging in regular physical and mental exercise, and ensuring proper nutrition. *Brain reserve* relates to the brain's physical characteristics and is understood, depending on the level of examination, in terms of brain size or the number of neurons, synapses and other necessary cellular elements. The idea is that a larger, more neuron-dense and synaptically connected brain has a greater capacity to withstand damage without showing signs of slowing or impairment. Brain reserve can be thought of as a structural pool of neural elements that can be employed in the face of pathology before cognitive symptoms emerge. Cognitive reserve instead refers to an individual's overall cognitive resources at a given time point, including general intelligence, learning ability and quality and quantity of problem-solving strategies, which can be attained through education and other activities. With higher cognitive reserve it is hypothesized that, given a set level of brain reserve, an individual can manage the symptoms of aging, cognitive decline or dementia more effectively, since the individual is more adaptable and can thereby compensate for structural loss or increased pathology.

Higher resilience to dementia pathologies later in life is likely the product of all three: (i) a greater brain reserve as a neurobiological resource to start with, (ii) the continuous maintenance of brain structure and function, and (iii) greater adaptability of cognitive strategies to perform a task. Resilience reflects the individual differences in brain structure and function that can be built over the lifespan. Resilience factors may include regular physical activity, a balanced diet, maintaining a healthy weight, treating chronic inflammatory states, avoiding smoking and excessive alcohol consumption, managing stress and treating conditions like depression and anxiety and staying socially active and connected with others. Understanding the impact of each mechanism is key to developing interventions that could prevent or delay the onset of dementia by targeting early and life-long influences. Management of risk factors throughout the lifespan requires timely detection, monitoring, and treatment in order to minimize dementia incidences in future generations.

Summary Table

Genetic predisposition	Few individual genetic risk factors are known, but for these, the genetic burden for dementia may manifest itself at multiple stages of life by increasing vulnerability to later cognitive impairment over the life-course.For example, APOE variants directly increases the risk of dementia in later life, but also indirectly by increasing the risk for cardiovascular diseases.
Perinatal neurodevelopmental challenges	Premature birth, developmental disorders and injury to the developing brain can impact synaptic mechanisms, disrupt normal brain activity, and interfere with typical growth and neuroplasticity. The risk for cognitive decline may be further increased by these perinatal factors through indirect effects on the vascular system or behavioral mechanisms.
Adverse childhood experiences	While studies have clearly demonstrated the effect of adverse childhood experience, such as physical or emotional abuse, prolonged stress, or neglect, on adult brain structures and cognitive performance as an intermediate step, few studies have directly linked adverse childhood experiences to dementia. Although heterogenous data exist, there appears to be an increased risk for dementia.
Psychosocial setting	Parental education and socioeconomic status (SES) are predictors for dementia. SES directly correlates with size differences in several brain area and may also mediate the effects of childhood adversities on cognitive health.
Nutrition and adiposity	Adequate nutritional intake during early life is important for maintaining long-term cognitive

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	function. Adult and adolescent obesity affects the structural integrity of the brain and increases the risk for low-grade inflammation, which has been linked to cognitive impairment.
Physical activity	Physical activity is positively correlated with cognitive function and is associated to both gray and white matter integrity. Potential mechanisms include neuroplasticity, cardiovascular health, stress reduction and reduced inflammation.
Risk factors during adolescence	During adolescence, the prefrontal cortex, which is responsible for higher-order cognitive functions, undergoes many changes, that can be influenced by several factors including nutrition, physical activity, cognitive stimulation, drugs and alcohol use, sleep, head injury and mental health, which in turn can affect cognitive function and hence the risk for dementia.
Manifestation of childhood and adolescent experience	Early life conditions can influence brain functions for many decades through behavioral mechanisms including habit formation and lifestyle adjustments, but also by "imprinting" on the structure and physiology of the adult brain through cellular mechanisms that can lead to neurodegeneration later in life.
Epigenetic modifications	Childhood adversity, such as chronic stress, can affect gene expression through epigenetic modifications. These modifications can influence the expression and functioning of genes involved in stress regulation, neural plasticity, and cognitive function later in life.
Resilience, Maintenance and Reserve	Greater resilience to dementia pathologies later in life is likely the product of: (i) a greater brain reserve as a neurobiological resource to start with, (ii) the continuous maintenance of brain structure and function, and (iii) greater adaptability of cognitive strategies to perform tasks. Resilience factors may include regular physical activity, a balanced diet, maintaining a healthy weight, managing chronic inflammatory conditions, avoiding smoking and excessive alcohol consumption, managing stress and conditions such as depression and anxiety, and staying socially active and connected with others.

CRediT authorship contribution statement

H. Georg Kuhn: Writing – review & editing, Writing – original draft, Conceptualization. **Simon Skau:** Writing – review & editing, Conceptualization. **Jenny Nyberg:** Writing – review & editing, Conceptualization.

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.

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