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Review Article

Alzheimer's Disease Across the Lifespan: A Comparative Review of Early-Life Determinants and Adult Neurodegeneration

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ABSTRACT

Alzheimer's disease (AD) is an age-related neurodegenerative disease, but there are increasing recognition the role of early-life factors in its development. This comparative review examines the interplay between developmental factors, such as nutrition, education, psychosocial stress, and the environment, and adult neuropathology in determining risk of AD. Through integration of epidemiological, clinical and experimental research, the review highlights the risk trajectory that spans early life to late age. Early exposures to adverse events such as suboptimal cognitive stimulation and metabolic imbalance may set the stage for anatomical and physiological brain changes that develop into dementia. On the other hand, factors such as cognitive stimulation and nutrition seem to reduce risk. Neurodegenerative disease in adulthood is considered in the context of these early determinants, with a focus on how biological and environmental factors interact to accelerate or slow down the disease process. Such a view of AD expands the traditional consideration of the disease as an ageing process and prioritises holistic approaches to prevention across the life course. Finally, the review calls for the coordination of public health strategies across the life course to minimizing impact of Alzheimer's disease.

INTRODUCTION

About 60–70% of dementia cases globally are caused by Alzheimer's disease (AD), making it the most common cause of dementia. It is a progressive illness of memory loss, intellectual decline and behavioral changes that result in a loss of independent functioning. AD is one of the largest public health problems linked to the population ageing, as currently more than 55 million people have this disease worldwide and this number is expected to nearly triple by 2050.^[1-3]

The formation of amyloid- β plaques, tau neurofibrillary tangles, synaptic dysfunction, and neuronal death are thought to be the causes of AD, a neurodegenerative disease.^[4,5] Research has therefore been concentrated on late life risk factors (hypertension, diabetes, obesity and lifestyle habits).^[6,7] Recent findings, however, indicate that developmental exposures have the potential to affect

susceptibility many decades before the onset of clinical signs of AD.^[8-10]

However, growing epidemiologic and experimental data suggest that nutritional, educational, psychosocial and environmental factors in early life have long-term effects on brain development, cognitive reserve and neurodegenerative risk.^[11-15] These developmental factors are thought to influence the progression of Alzheimer's disease throughout life, in addition to the metabolic and vascular risk factors seen in adults, which helps support a life-course perspective of Alzheimer's disease.^[6,16]

While a number of recent reviews have investigated the concept of Alzheimer's disease as a life course disorder, these generally have concentrated on individual areas, including genetic susceptibility, modifiable risk factors, neuropathology, or preventive intervention.^[4,6,10,16]

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In contrast, the present review provides an integrated comparative framework that connects early-life determinants including nutrition, education, psychosocial adversity, and environmental exposures with adult neuropathological changes, cumulative risk factors, and public health strategies. This review integrates evidence drawn from developmental, clinical, and epidemiological research, outlining the lifelong nature of the interplay between childhood and adult determinants of the Alzheimer's disease and the importance of the prevention opportunities throughout the life course.

Therefore, this review integrates the most recent findings regarding early-life determinants and the adult mechanisms involved in neurodegenerative disease to provide a briefly picture of Alzheimer's disease from birth through adulthood. The review highlights developmental risk factors and compares them to risks in adulthood to emphasize the importance of opportunities for prevention that begin early in life and continue throughout life.

Childhood risk factors of Alzheimer's disease

Nutrition and metabolic health

The nutrition of early childhood is crucial for proper brain development and functioning. Iron, folate, and vitamin D deficiencies at critical developmental windows interfere with neuronal maturation by affecting neurogenesis, synaptogenesis, and myelination, hence enhancing the risk of Alzheimer's disease (AD) later in life.^[17,21] In addition to reducing energy metabolism, iron deficiency also interferes with synthesis of neurotransmitters, while malnutrition and stunted growth decrease cognitive reserve, which diminishes the brain's capacity to compensate for age-related neuropathological changes.^[18,21] Conversely, a proper amount of the omega-3 fatty acids, antioxidants and dietary proteins maintain the integrity of the neuronal membrane, improve synaptic plasticity, decrease oxidative stress, and fertilize long-term cognitive resilience.^[19,22] The growing global pandemic of childhood obesity has been associated to chronic low-grade inflammation, insulin resistance, dyslipidemia, oxidative stress, impaired insulin signaling in the brain, and microglial activation.^[20,23] These metabolic disturbances could contribute to an early build-up of amyloid- β , hyperphosphorylation of tau, and neuroinflammation, all of which may lead to Alzheimer's disease in later life.^[23,24] Overall, these results underscore the importance of providing optimal nutrition in early life to promote normal neurodevelopment and promote cognitive resilience, and potentially lower risk for Alzheimer's disease later in life.

Education and cognitive reserve

The cognitive reserve theory offers a framework to understand the protective role of enriched learning environments and educating in the prevention of Alzheimer's disease (AD). Children who are educated in a way that enriches their lives create efficient

neuronal networks by improving synaptic connectivity, neuroplasticity, and the capacity of the brain for cognitive reserve, thus better protecting themselves from age-related neurodegeneration.^[25] The importance of education, as a health risk for dementia, has been consistently noted, especially in low to the middle income countries.^[26] The brain's capacity to recruit alternative neural networks and use other networks more efficiently has been proposed as a mechanism of compensation for those with higher levels of education, which results in a later age of onset of AD even when similar levels of neuropathological changes are seen.^[27,28] On the other hand, cognitive deficits are also clinically expressed at an earlier age with similar neuropathological burden in the presence of less education.^[25,28] Therefore, early education investment is not only socially advantageous but also biologically advantageous because it fortifies the cognitive resilience and the onset of Alzheimer's disease may be delayed.

Psychosocial stressors

Early-life stressors such as adverse childhood experiences (ACEs) like trauma, neglect and poverty have lifelong impacts on brain development and raise the like of progressing Alzheimer's disease (AD) later in the life. The effects of ACEs on hypothalamic-pituitary-adrenal (HPA) axis led to the chronic state of activation of the stress response and continued glucocorticoid (cortisol) exposure.^[29] Increased cortisol disrupts hippocampal neurogenesis, decreases dendritic complexity, decreases BDNF signaling, and increases neuroinflammation, resulting in structural and functional changes in prefrontal cortex, amygdala, hippocampus, and other brain regions which mediate learning, memory and emotional regulation.^[29-32] Persistent HPA-axis dysregulation could also further promote amyloid precursor protein processing, amyloid- β buildup, and tau hyperphosphorylation, leading to greater susceptibility to Alzheimer's decades later.^[33,34] Social disadvantage and poverty further exacerbate vulnerability by impacting on cognitive reserve, including nutrition (including poor dietary quality), health services, and education opportunities at an early age, thereby increasing the like of cognitive impairment and dementia later in the life.^[30,31] Childhood psychosocial adversity is also shown to induce long-term alterations of the hippocampal and prefrontal cortical structure and function, thereby driving increased vulnerability to age-related neurodegeneration.^[32] The findings suggest that decreasing childhood psychosocial stressors and enhancing social support may increase cognitive resilience and help to decrease lifetime risk for Alzheimer's disease.

Environmental exposures

Long-term cognitive decline has been associated with exposure to environmental toxins during early life. Lead, pesticide and air pollutant exposure disrupts



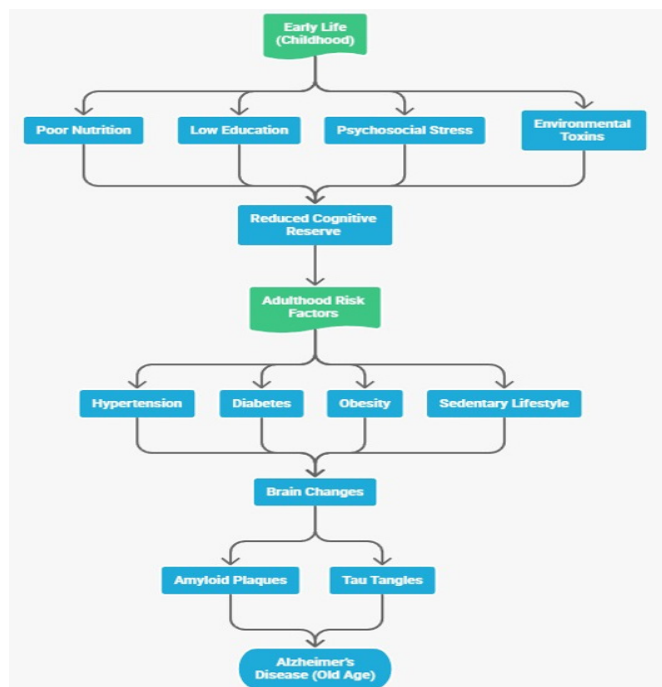


Fig. 1: Early life and adult risk factor in Alzheimer's disease^[6]

neurodevelopment, making individuals more susceptible to neurodegenerative diseases later in life ^[35]. On a molecular level, these environmental toxins cause oxidative stress, mitochondrial dysfunction and microglial activation, leading to chronic neuroinflammation and neuronal injury.^[39,40] Fetal exposure to stress and maternal infection also leads to further changes in fetal brain development as a result of immune dysregulation and inflammatory signaling, which further increases the risk for adult cognitive impairment and dementia.^[36] One of the most widely studied air pollutants, fine particulate matter (PM_{2.5}), can disrupt the blood-brain barrier, raise the formation of the reactive oxygen species, and stimulate sustained neuro-inflammatory responses, which will eventually lead to increased amyloid- β deposition and tau hyper-phosphorylation, the two major neuropathological markers of Alzheimer's disease.^[37,39] Exposure during childhood has been shown to lower cognitive functioning and structural changes in the brain that could impact cognitive reserve and thereby raise the risk of dementia later in life.^[38,41] Together, these results underscore the role of minimizing environmental hazards and exposures to neurotoxic compounds in early life as public health measures to support healthy brain aging preventing alzheimer's prevention.

Genetic Susceptibility and Gene-Environment Interactions in Alzheimer's Disease

In addition to environmental and developmental factors, genetic susceptibility is also a significant factor in the pathogenesis of Alzheimer's disease (AD), but genes account for only a small proportion of the lifetime risk.

The most important identified genetic risk factors are the apolipoprotein E (APOE) $\epsilon 4$ allele and its dose-dependent effects are a genetic risk factor for sporadic late-onset AD, and increase susceptibility to the disease.^[42-44] The $\epsilon 4$ allele of the APOE gene causes a decrease in the efficiency of lipid transport, neuronal repair, and amyloid- β (A β) clearance, resulting in increased A β deposition, increased tau hyperphosphorylation, increased oxidative stress, increased neuroinflammation, and increased blood-brain barrier dysfunction.^[42-44] Apart from APOE $\epsilon 4$, rare mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes that interfere with the processing of APP and increase the levels of pathogenic amyloid beta (A β) peptide are the other genes that have been identified, which cause autosomal dominant early-onset AD.^[45,46] In addition, a number of susceptibility loci for immune regulation, lipid metabolism and endosomal trafficking have been identified by genome-wide association studies (GWAS) that have led to progression of the polygenic risk scores (PRSs) to measure overall genetic susceptibility to AD.^[47,48] Importantly, genetic susceptibility and environmental exposures are not independent exposures, but rather are to be thought of as interacting throughout the life course. APOE $\epsilon 4$ does not automatically mean AD; environmental factors in early life and throughout life greatly modulate the effects of APOE $\epsilon 4$. Cognitive reserve and brain resilience are shaped by early life determinants, such as maternal nutrition, childhood education, cognitive stimulation,

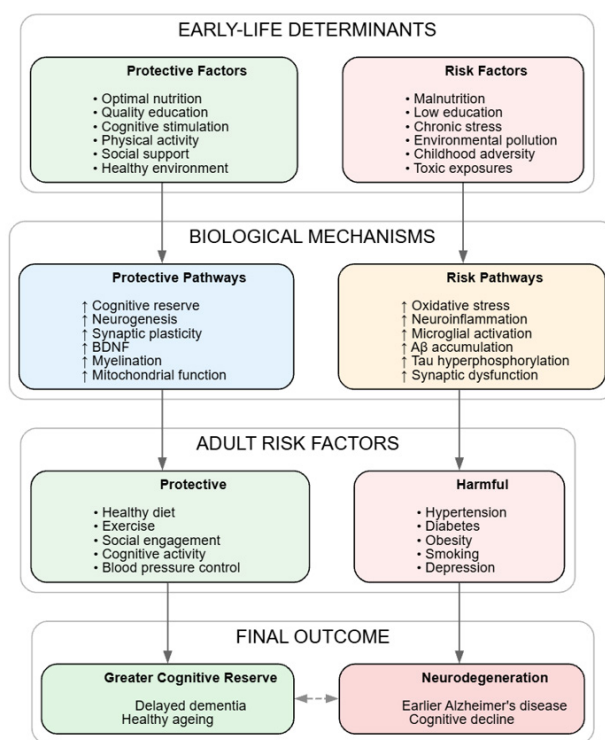


Fig. 2: Mechanistic Model Illustrating the Balance Between Protective and Risk Pathways Across the Lifespan in Alzheimer's Disease^[6]

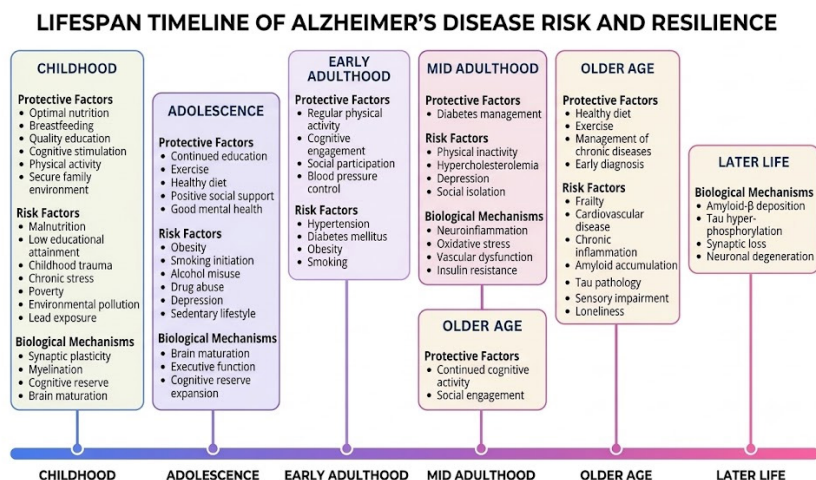


Fig. 3: Life-course timeline illustrating protective and risk factors influencing Alzheimer's disease from prenatal life to old age^[6]

psychosocial support, and environmental exposures, which influence the clinical expression of genetic risk.^[49-52] They might have an accelerated progression of the disease if exposed to unfavorable factors like malnutrition, air pollution, chronic psychosocial stress factors and cardiovascular risk factors, which can lead to increased neuroinflammation and reduced neuronal resilience.^[49,50] However, a combination of good developmental factors, as well as lifelong healthy lifestyle habits (such as improved cognitive reserve, decreased neuroinflammation, and healthy vascular health) can partially mitigate genetic risk and reduce the likelihood of clinical symptoms appearing in adulthood.^[51,52] Thus, Alzheimer's disease should be viewed as being the result of a dynamic interplay of inherited genetic susceptibility to the disease and cumulative exposures to the environment throughout life, and thus personalized prevention strategies that combine genetic risk with life course determinants should be employed.

Lifespan Integration

Early life determinants are related to risk factors that emerge in adulthood, and these risks compound each other. Childhood poor nutrition, low education, psychosocial stress, and environmental exposures combine with adult factors of hypertension, diabetes, and sedentary lifestyle to hasten the process of neurodegeneration.^[53] In contrast, healthy factors throughout childhood, such as a healthy diet, a stimulating environment, a positive family environment, and lower exposure to toxins, increase resilience and postpone the development of disease.^[54] A developmental perspective of AD as a continuum throughout the life-course redefines the concept of prevention to focus on interventions that start in childhood and continue into adulthood.^[55] This holistic view emphasizes the need for integrated public health

policies that bridge pediatric and geriatric healthcare to promote brain health across the life-course.^[56]

Neurodegenerative Changes in Adulthood

Neuropathological Hallmarks

The pathological changes in Alzheimer's disease (AD) alter brain function. A hallmark pathological feature of Alzheimer's disease is the accumulation of extracellular amyloid- β plaques, which disrupt synaptic transmission and trigger neuroinflammatory responses.^[57] The intracellular accumulation of neurofibrillary tangles comprising hyperphosphorylated tau protein also results in disruption of microtubules, leading to synaptic dysfunction and neuronal death.^[58] Synapse loss, mostly in the hippocampus and cortex, is tightly linked with cognitive impairment and memory deficit.^[59] Activated microglia and astrocytes contribute to neuroinflammation, exacerbating neuronal insults and progression of the disease.^[60] These features cooperate to form a pathogenic network that underpins AD clinical symptoms.

Cumulative Risk Factors

Systemic vascular risk factors significantly contribute to Alzheimer's disease progression. Hypertension and cardiovascular disease compromise cerebrovascular integrity, thereby promoting amyloid- β deposition and white matter lesions.^[61] Metabolic imbalances such as diabetes and insulin resistance cause glucose dysregulation in the brain, which can lead to oxidative stress and hyperphosphorylation of the tau protein.^[62] Cigarette smoking, physical inactivity, and poor diet also increase the risk, with a synergistic effect on neurodegenerative disease.^[63] Middle-age obesity and metabolic syndrome are associated with dementia.^[64] These promote the importance of systemic factors in AD.



Table 1: Summary of Cumulative Risk Factors and Their Mechanisms in Alzheimer's Disease [61-64]

<i>Risk Factor</i>	<i>Mechanism</i>	<i>Impact on AD Progression</i>
Hypertension	Vascular dysfunction, reduced cerebral perfusion, white matter damage	Promotes amyloid deposition and accelerates cognitive decline.
Diabetes & Insulin Resistance	Impaired glucose metabolism, oxidative stress, tau hyperphosphorylation	Increases neuronal vulnerability and accelerates neurodegeneration.
Obesity & Metabolic Syndrome	Chronic inflammation, altered lipid metabolism, vascular stress	Strongly associated with higher dementia incidence in late life.
Smoking	Oxidative stress, vascular damage, reduced oxygen supply	Amplifies neuronal injury and accelerates pathology.
Physical Inactivity	Reduced cerebral blood flow, impaired neurogenesis	Weakens resilience and increases risk of dementia.
Poor Diet	Deficiency in antioxidants, high saturated fat intake	Enhances oxidative stress and amyloid accumulation.

Interaction with early-life exposures

Emerging evidence indicates that early-life determinants interact with adult risk factors across the life-course to influence Alzheimer's disease risk. Adequate childhood nutrition and higher educational attainment promote cognitive reserve, enhancing resilience against neuropathological changes and delaying cognitive decline.^[65] Early life stress (trauma, poverty) alters the stress response and development of the hippocampus, leading to more rapid decline with exposure to adult risk.^[66] Early-life toxins and pollutants may lead to increased neuroinflammation, which, with vascular and metabolic dysfunction in later life, may accelerate AD.^[67] This stresses the need for a life-course approach, in which adult neurodegenerative disease is the culmination of life events.

Protective factors

However, protective factors reduce the incidence of disease. Education and cognitive training foster cognitive reserve, increasing the brain's capacity to compensate for neuropathological alterations and maintain cognitive function.^[68] Increased blood flow, inflammation reduction,

and neurogenesis slow down cognitive decline.^[69] Supportive social relationships and sustained social engagement promote cognitive resilience, attenuate stress-related neurobiological responses, and are linked with a lower risk of dementia.^[70] The Mediterranean diet has consistently associated with improved cognitive health owing to its more content of the antioxidants, polyphenols, and unsaturated fatty acids, which collectively exert neuroprotective and anti-inflammatory effects.^[71] All these protective factors lead to a reduction in the incidence of AD when the multidomain interventions are carried out, such as education, lifestyle, and social interaction.

Lifespan integration

Adult neurodegenerative processes in AD are not in isolation and are shaped by the interplay between the neuropathology, systemic risk factors, and early life factors.^[72] Life-course protective factors, such as education and physical and social activity, confer resilience, and cumulative adversities accelerate disease onset. This integrated approach provides a new framework for AD as a life-course disease, with new prevention and treatment

Table 2: Comparison of Early-Life Determinants and Adult Risk Factors in Alzheimer's Disease

<i>Feature</i>	<i>Early-Life Determinants</i>	<i>Adult Risk Factors</i>
Stage of action	Prenatal, infancy, childhood, and adolescence ^[9,12]	Midlife and older adulthood ^[6,7]
Examples	Nutrition, education, psychosocial stress, environmental pollution, genetic susceptibility ^[12,14]	Hypertension, diabetes mellitus, obesity, smoking, depression, physical inactivity ^[6,7]
Primary mechanism	Brain development, neurogenesis, synaptogenesis, cognitive reserve ^[12]	Neuroinflammation, vascular dysfunction, amyloid- β accumulation, tau hyperphosphorylation ^[5,6]
Major biological effects	Synaptic plasticity, myelination, neuronal maturation, enhanced cognitive resilience ^[12]	Oxidative stress, insulin resistance, microglial activation, cerebrovascular injury ^[5,6]
Reversibility	Limited once critical developmental periods are completed ^[12]	Many factors are modifiable through lifestyle and medical interventions ^[6,16]
Prevention strategy	Maternal health, early-life nutrition, education, psychosocial support, pollution control ^[9,12]	Lifestyle modification, cardiovascular risk management, physical activity, healthy diet, smoking cessation ^[6,16]
Overall contribution	Establishes lifelong susceptibility and cognitive reserve ^[12]	Accelerates disease progression and clinical manifestation ^[5,6]

Table 3: Major biomarkers used in Alzheimer's disease diagnosis and monitoring

<i>Biomarker</i>	<i>Sample/Technique</i>	<i>Indicates</i>	<i>Clinical Significance</i>
CSF A β 42/A β 40	Cerebrospinal fluid	Amyloid pathology	Early diagnosis of AD ^[101]
Amyloid PET	PET imaging	Cerebral amyloid deposition	Detection of preclinical AD ^[101]
Plasma p-tau181	Blood	Tau pathology	Early diagnosis and monitoring ^[103]
Plasma p-tau217	Blood	Tau pathology	High diagnostic accuracy ^[104]
Tau PET	PET imaging	Neurofibrillary tangles	Disease staging ^[102]
Neurofilament light chain (NfL)	Blood/CSF	Neurodegeneration	Disease progression ^[104]
GFAP	Blood	Astrocyte activation	Early neuroinflammation ^[104]
MRI	Brain imaging	Hippocampal atrophy	Structural neurodegeneration ^[101]
FDG-PET	PET imaging	Reduced cerebral glucose metabolism	Functional brain changes ^[102]

strategies in development and adulthood. This approach enables researchers and policymakers to implement measures to reduce the global burden of AD.^[73]

Comparative Lifespan Perspective

Interactions between developmental and adult determinants

Alzheimer's disease (AD) is increasingly being recognised as the result of life-course exposures. Adverse developmental exposures, including nutrition, education, psychosocial stress and toxins, and adult health risk points such as hypertension, diabetes and lifestyle factors, interact to confer risk.^[74] This moves the view of AD from an age-specific to a life-course process. Deficits in early life reduce the cognitive reserve, and pathology in adulthood accelerates the decline, and a trajectory of risk is established over decades.^[75]

Neurocognitive Trajectory

The term "neurocognitive trajectory" describes the trajectory of brain function across the life-course, affected by genetic, environmental and social factors.^[76] Positive exposures, such as good nutrition in childhood, enriched educational opportunities and positive environments, lead to reserve and resilience. On the other hand, adverse exposures lead to vulnerabilities and dementia.^[77] Cohort studies have shown that individuals with greater cognitive reserve remain cognitively functional despite significant neuropathology, highlighting its role in delaying the clinical manifestation of Alzheimer's disease.^[78]

Evidence from Longitudinal and Cohort Studies

Longitudinal studies are consistent with the lifespan model. The Framingham Heart Study has demonstrated middle-aged vascular risk factors are associated with dementia.^[79] Similarly, the Whitehall II study found low education and childhood adversity are predictive of dementia.^[80] Recent birth cohorts from developing countries show that malnutrition and stunting are linked to low cognitive reserve and dementia prevalence.^[81]

These studies suggest early and sustained prevention of AD.^[82]

Regional and Cultural Variation of Risk and Resilience

Risk and resilience are diverse. In developed countries, health care and education are protective, whereas lifestyle factors such as obesity and low physical activity are risks.^[83] In lower- and middle-income countries, malnutrition, poverty and low education levels still play a role.^[84] Healthy cultural practices, particularly adherence to the Mediterranean diet, contribute to cognitive resilience, whereas environmental pollution associated with rapid urbanisation may increase susceptibility to Alzheimer's disease.^[85] These differences are important when considering population-specific interventions.^[86]

Public Health and Prevention

Importance of Early Interventions

Nutritional, education and psychosocial interventions in early life are essential in minimising risks of dementia in later life. Early-life interventions to prevent malnutrition and micronutrient deficiencies in childhood enhance neurodevelopment.^[87] Universal education maximises cognitive reserve and psychosocial interventions minimise the effects of trauma and poverty.^[88] Therefore, comprehensive dementia prevention strategies should integrate policies that promote child health and early-life development with interventions targeting adult risk factors across the lifespan.^[89]

Health & Well-being for Cognitive Resilience

Adult health promotion also enhances resilience. Exercise increases blood flow and decreases inflammation.^[90] Healthy diets, such as the Mediterranean and plant-based, prevent oxidative stress and amyloid burden.^[91] Social and cognitive stimulation maintain cognitive reserve delaying symptom onset.^[92] Multidomain approaches incorporating diet, exercise, cognitive training and stroke prevention have been effective.^[93]



Policy Implications: Integrating Child and Elderly Health

Policies need to align child health programmes and geriatrics. Early education, nutrition and environment investments have long-term gains via decreased dementia.^[94] The inclusion of dementia within non-communicable disease response provides a lifelong approach.^[95] Health services need to take an integrated approach, connecting child and aged care services to reduce cumulative risk factors.^[96]

Increasing Global Efforts to Reduce AD

With a tripling of dementia expected by 2050, there is a need for global approaches.^[97] Global public health initiatives, including the World Health Organisation Global Dementia Observatory, emphasise a lifespan approach to dementia prevention through continuous risk reduction and health promotion across the lifespan.^[98] Regional differences should be considered, focusing on malnutrition in low-income countries and lifestyle-related risks in high-income countries.^[99] Education and policy reforms aimed at reducing the burden of AD are also important.^[100]

Comparative Perspective: Early-Life Determinants versus Adult Risk Factors

There is biological, environmental and lifestyle factors at play over the life span that contributing to the progression of Alzheimer's disease. Early-life determinants and adult risk factors are discussed separately, but they are linked to each other as different points in a disease process. While early-life risk factors have a primary effect on brain development, cognitive reserve and resilience throughout life, adult risk factors have a primary effect on established neuropathological processes such as accumulation of the biochemical factors like amyloid- β , hyperphosphorylation of tau, neuroinflammation, and vascular dysfunction.^[64–66] Structural and functional development of the brain is influenced during critical periods of life by early-life determinants including nutrition, education, psychosocial adversity, environmental exposures and genetic susceptibility. These factors shape the baseline cognitive reserve and their effect on vulnerability to neurodegeneration decades later.^[62,64,67] Adult risk factors, such as hypertension, diabetes mellitus, obesity, smoking, physical inactivity, depression, and cardiovascular disease, on the other hand, mostly contribute to existing pathological processes by way of increased oxidative stress, chronic inflammation, metabolic dysfunctions, and reduced cerebral blood flow.^[60,65,68]

Importantly, these factors should not be taken as being independent. Inadequate childhood nutrition can lead to obesity and metabolic syndrome in adulthood and lower education levels can lower health literacy and be associated with increased exposure to modifiable vascular risk factors.^[60,62,69] The same is true of adverse childhood experiences, which can lead to chronic stress,

depression and neuroinflammation later in life through persistent hypothalamic-pituitary-adrenal (HPA) axis dysregulation.^[28,69] Therefore, the biological basis for the cumulative effects of the adult risk factors is set in place by the early-life determinants.

Together, this view on the lifespan implies that prevention of Alzheimer's disease should involve early-life interventions to optimise brain development along with adult strategies to decrease vascular, metabolic and lifestyle-related risk factors. This holistic approach will probably be more effective than means of intervention that begin only in the older age (60 and 62).

Alzheimer's Disease Biomarkers

Implications for Early Diagnosis and Lifespan Prevention Alzheimer's disease (AD) biomarkers have been revolutionized the diagnosis and treatment of Alzheimer's disease, allowing detection of pathological changes years prior to clinical symptoms. There was a significant amount of neurodegeneration before being diagnosed, with cognitive evaluation being the main method. Conversely, modern biomarkers can be used to detect the presence of amyloid- β (A β) deposition, tau pathology, and neurodegeneration in preclinical and prodromal phases of the AD, which can aid in early diagnosis, patient classification, and personalizing treatments strategies^[101,102].

The National Institute on Aging-Alzheimer's Association (NIA-AA) research framework categorizes AD biomarkers by the AT(N) system, in which A refers to amyloid pathology, T refers to tau pathology and (N) indicates neurodegeneration.^[101] Amyloid biomarkers involve the presence of amyloid in the cerebrospinal fluid (CSF) with decreased CSF A β 42 concentration, reduced CSF A β 42/A β 40 ratio, and positive amyloid positron emission tomography (PET) imaging. The CSF phosphorylated tau (p-tau) and tau PET imaging are used to assess tau pathology; the structural magnetic resonance imaging (MRI) and fluorodeoxyglucose PET (FDG PET) are used to assess neurodegeneration, and CSF is also used to measure total tau and neurofilament light chain (NfL).^[101,103]

In recent years, new studies in blood-based markers have greatly enhanced the potential of large-scale screening for AD. Philpou, a phosphorylated tau isoform, shows a high diagnostic value for AD and a strong correlation with both amyloid and tau pathology, especially in the case of p-tau181 and p-tau217. Similarly, plasma neurofilament light chain (NfL) is a marker of neuronal injury, while glial fibrillary acidic protein (GFAP) is a marker of early stages of disease progression involving astrocytic activation.^[103,104]

These are the minimally invasive biomarkers that are now being used in clinical research and precision medicine strategies and may serve as useful substitutes for CSF analysis and PET imaging in the future.

The clinical expression of AD is affected by the cognitive reserve and cumulative environmental exposures experienced throughout the lifespan, so it is important to

consider biomarkers within the broader context of a life course. Those who have favorable early life determinants (good nutrition, more education, cognitive stimulation, and supportive psychosocial factors) may be able to have a positive biomarker result and still be cognitively normal due to greater cognitive reserve. On the other hand, people who have faced harmful developmental conditions can have symptoms earlier, even if their biomarkers are the same.^[12,101] Combining biomarker measurement with genetic predisposition, early life exposures and modifiable lifestyle factors might help to enhance the prediction of risk, enable personalized prevention strategies, and maximize the timing of disease-modifying interventions.

Early-Life Determinants and Their Implications for Modern Alzheimer's Disease Management

Early-Life Determinants and Response to Anti-Amyloid Monoclonal Antibodies

The development of drugs that selectively target aggregated amyloid- β (A β) and promote clearance from the brain has been a major development in recent years in the field of Alzheimer's disease (AD) therapeutics, such as lecanemab and donanemab. These treatments have been shown to slow cognitive deterioration in patients with early symptomatic AD, such as in the mild cognitive impairment and mild dementia phases, and to lower the amount of cerebral amyloid.^[105,106] But each person's individual response to treatment will depend on their cognitive reserve developed over the lifespan. Enrichment in early life, such as having optimal nutrition, quality education, enriched cognitive environments and psychosocial support, increases cognitive reserve, which allows for greater neuropathological burden before clinical symptoms arise. Thus, factors related to cognitive reserve could be related to the onset of cognitive impairment when given the same amyloid pathology, which could have an impact on the timing of treatment and the magnitude of response. Incorporating life-course determinants into clinical decision-making could then enhance the selection of patients for clinical trials and maximize effectiveness of disease-modifying treatments.

Immunologic and Inflammatory Markers for Diagnosis and Management of Early-life Non-communicable Diseases

Application of fluid and imaging biomarkers has revolutionized the early diagnosis of AD. Pathological changes can be detected years in advance of clinical symptoms by plasma phosphorylated tau (p-tau181 and p-tau217) and CSF A β 42/A β 40 ratio, as well as by neurofilament light chain (NfL) and amyloid positron emission tomography (PET) imaging.^[107,108] However, cognitive impairment is not always predicted by biomarker positivity. Having a higher cognitive reserve (due to better

early life experiences) could allow people to have marked abnormalities in their biomarkers but not impact their cognitive functioning. Thus, a life-course perspective on education, nutritional status, socioeconomic status, and environmental factors should be used along with interpretation of biomarker results to better stratify and prognosticate.

Early-Life Determinants and Precision Medicine

The goal of precision medicine is to tailor the prevention and treatment of AD to the individual by combining all of the above (genetic, environmental, lifestyle and biological) information. While genetic factors, such as ApoE ϵ 4, are known risk factors for AD, other potentially modifiable risk factors throughout life, termed life-course determinants, also play a strong role in disease development.^[109] Early-life nutrition, education, socioeconomic factors, environmental exposures, and cognitive stimulation, in conjunction with biomarker signatures and genes, could help to predict and plan individualized risk and therapeutic interventions. This strategy would allow for the detection of high-risk patients at an earlier stage and for targeted interventions before irreversible neurodegeneration has taken place.

Early-Life Determinants and Preventive Interventions

Evidence to date suggests that dementia prevention should start early in life, not once the signs of cognitive decline start to occur. The brain develops and builds cognitive reserve that decreases vulnerability to long-term AD through maternal health care, providing optimal nutrition to children, universal education, psychosocial support, cognitive stimulation, and healthy environmental conditions.^[6,110] In adulthood, regular exercise, eating a healthy diet (including the Mediterranean diet), quitting smoking, maintaining a healthy blood pressure, managing diabetes and engaging in activities with others helps reduce dementia risk further. The results highlight the need for a comprehensive view of the life-course, beginning at early childhood and continuing to older adulthood, with preventive interventions in place throughout.

Evidence from Multidomain Prevention Trials

A number of recent multidomain intervention trials have shown that more than one lifestyle intervention is needed to offer more protection against cognitive decline than a single intervention. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) findings indicated that a combination of dietary counselling, physical exercise, cognitive training, social engagement and vascular risk management had a significant effect on cognitive performance among older adults with a high risk of dementia.^[16] Other data from the Multidomain Alzheimer Preventive Trial (MAPT) and the Prevention of Dementia by Intensive Vascular



Care (PreDIVA) study reinforce the idea of multidomain preventive strategies, with effects depending on risk factors and patient characteristics.^[111-113] It is important to consider early-life determinants in combination with multidomain lifestyle interventions to enhance cognitive reserve, the onset of disease and healthy ageing of the brain throughout the lifespan for future prevention programs. Limitations of the Review

Although this review offers a thorough review of the existing literature on the influence of early life factors and later life risk factors on Alzheimer's disease (AD), there are several limitations to this review. First, most of the evidence available comes from observational studies, longitudinal cohort studies and epidemiological investigations, which show association, but not necessarily causation between early-life exposures and later development of AD.^[6,12] Moreover, there is high variability across studies in terms of population characteristics, assessment of exposure, outcome variables, and follow-up period, and direct comparisons may be difficult and this may account for some of the differences in the reported results.^[6,12] In addition, many early-life factors such as nutrition, education, psychosocial stress, or environmental exposures are difficult to assess precisely during the life course and are likely to be residual confounders, and recall bias.^[12,114]

A second constraint is that, while the recent progress in genetic susceptibility, biomarkers, anti-amyloid monoclonal antibodies, precision medicine and multidomain preventive interventions are discussed, there is limited evidence of how these novel approaches might interact with early-life determinants.^[101-106] Specifically, the impact of life-course exposures on biomarker trajectories, treatment response, and disease progression remains poorly understood. Furthermore, there is a lack of generalizability of results from the majority of available studies, as they have been conducted in high-income countries, and so cannot be applied to populations with a wide range of genetic makeup, socioeconomic status and environmental exposures.^[6,98] To better understand these complex interactions, and to inform the development of personalized strategies for the prevention and management of Alzheimer's disease.^[6,16,101-104,115], future large-scale prospective longitudinal studies combining life-course exposures, genetic susceptibility in particular APOE ϵ 4, biomarkers and multidomain interventions are needed.

CONCLUSION

Understanding Alzheimer's disease (AD) as a lifelong disorder requires an understanding that early life determinants and adult risk factors play a synergistic rather than additive role in disease susceptibility and progression. Neurodevelopmental exposure (such as

nutrition, education, psychosocial stress, environmental pollutants, and socio-economic factors) influences brain development and cognitive reserve, which can predispose a person to be more vulnerable or resilient to subsequent neurodegeneration. In adulthood, modifiable risk factors like hypertension, diabetes, obesity, smoking, physical inactivity, depression and social isolation, can speed up pathological changes such as amyloid- β deposition, tau hyperphosphorylation, synaptic dysfunction, and neuronal loss. All of this constitutes a life course of brain development and functioning that can either be protected by good experiences over the years or that can become a vulnerability due to repeated negative experiences over time. Longitudinal and cohort studies suggest that it's possible for people to maintain their mental abilities despite having substantial neuropathological changes if they had a rich early-life environment and continued to engage in intellectual, physical and social activities throughout their lives, but people who experienced malnutrition, limited education, trauma, or exposure to environmental toxins are at significantly higher risk for developing AD later in life. Thus, prevention strategies should be life-course based, combining early-life prevention approaches (including nutrition, universal education, and psychosocial support) with lifelong promotion of cardiovascular health, healthy dietary patterns, regular physical activity, cognitive stimulation and social participation. Dementia prevention strategies need to be integrated with other NCD prevention programs, with the understanding that the chance to prevent dementia is greatest when a risk reduction strategy is followed throughout one's lifespan, and will have the greatest potential impact on reducing the onset of the disease, maintaining cognitive function and quality of life. This comparative review suggests that while early-life factors contribute to the biological and cognitive substrates of resilience or susceptibility, adult risk factors have the effect of influencing progression of diseases, so that a comprehensive and life-course perspective on prevention is key. This requires a collaborative effort between healthcare providers, policymakers, and communities to ensure that the resources are put into the right places and public awareness campaigns are carried out effectively. Creating a supportive environment that encourage physical and mental well-being can improve overall health and wellbeing and help to set up a supportive environment for people of all ages.

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