Cognitive resilience in ageing: determinants and interventions

Alice Powell, Karina Chan, Claire E Shepherd, Henry Brodaty

Lancet Neurol 2026; 25: 492–505

Centre for Healthy Brain Ageing, Discipline of Psychiatry and Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia (A Powell MBBS, K Chan MClinNeuro, Prof H Brodaty DSc); **Neuroscience Research Australia** (C E Shepherd PhD), **School of Biomedical Sciences** (C E Shepherd), **University of New South Wales, Sydney, NSW, Australia**

Correspondence to: Prof Henry Brodaty, Centre for Healthy Brain Ageing, Discipline of Psychiatry and Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, NSW 2052, Australia
h.brodaty@unsw.edu.au

Understanding the factors that contribute to the preservation of cognitive abilities into advanced age despite brain injury or disease is a key goal of ageing research. Up until the last two decades, the extent of brain pathology could only be fully appreciated at autopsy. Advances in laboratory and imaging biomarkers now mean that cognitive function can be understood in the context of markers of brain injury and specific pathologies (eg, Alzheimer's disease, Lewy body disease, and cerebrovascular disease). Knowledge on the characteristics of individuals displaying cognitive resilience and its social determinants across the lifespan can inform strategies to enhance resilience at individual and population levels. There is some evidence of the effectiveness of interventions to improve cognitive functioning from high-income countries, supported by biomarker data. Looking ahead, translation of cognitive resilience research to low-income and middle-income countries—the regions with the fastest growth in dementia burden—will require addressing key challenges and seizing opportunities.

Introduction

Multiple community-based autopsy studies have shown that common neuropathologies, including Alzheimer's disease neuropathology, Lewy body disease, TDP-43 protein inclusions, and cerebrovascular disease are strongly but not deterministically associated with dementia.[1–10] Indeed, some individuals can resist the neurodegenerative potential of multiple proteinopathies with less cognitive decline, thereby demonstrating cognitive resilience.[11–13]

Cognitive resilience has previously only been identifiable by comparing cognitive performance against posthumously identified brain pathology. Advances in neuroimaging, EEG, and CSF and serum biomarkers now allow cognitive resilience to be measured in vivo and to be tracked longitudinally.[14,15] In this Review, we discuss the concept of cognitive resilience, outlining the current state of knowledge on psychosocial and clinical factors associated with cognitive resilience and their potential biological mechanisms. The genetic underpinnings of cognitive resilience have recently been reviewed[16] and are not included in this paper. We also highlight differences in cognitive resilience for people in low-income and middle-income countries (LMICs), and discuss advances in measures of resilience incorporating cognitive testing and markers of brain pathology including imaging, CSF, and blood biomarkers. Finally, we summarise the current evidence for strategies to enhance cognitive resilience.

Panel 1: **Glossary of terms**

Cognitive resilience
Cognitive performance that is better than expected for the degree of life-course related brain changes and brain injury or disease.[14]

Cognitive reserve
An individual's total or overall cognitive resources;[17] it is the basis for cognitive resilience.[14,17]

Brain maintenance
The relative absence of deterioration over time in brain structure or function.[14,17]

Brain reserve
The neurobiological status of the brain (eg, numbers of neurons and synapses) at any point in time.[14] It refers to total neural resources or neurobiological capital.[17] It does not involve active adaptation of cognitive processes in the presence of injury or disease.[14]

Definition of cognitive resilience

There is no universal definition of cognitive resilience and its related constructs, although several theoretical frameworks have been proposed. The Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging established in 2019, involving investigators from the USA and Europe, developed consensus definitions over a period of 3 years. The investigators defined resilience as an overarching term encompassing concepts of cognitive reserve, brain maintenance, and brain reserve.[14] These constructs all underly the capacity of the brain to maintain cognition and function with ageing and disease.[14] Cognitive reserve and cognitive resilience have been used interchangeably throughout the literature but we adhere to Kremen and colleagues'[17] conceptualisation of cognitive reserve reflecting an individual's total cognitive resources at a given timepoint, with high cognitive reserve allowing for greater cognitive resilience. We have avoided conflating these terms (panel 1). Figure 1 depicts the pathological characteristics of an individual showing cognitive resilience to Alzheimer's disease.

Determinants

Several reviews published in the last 5 years have summarised the proposed mechanisms underlying cognitive resilience. These mechanisms include, but are not limited to: increased brain volume, connectivity, and synaptic structure and function; increased neurogenesis

and mitochondrial function; and improved regulation of neuroinflammatory processes.[11–13,18] Importantly, many of the biological mechanisms that have been proposed converge on common pathways, including neuronal density, synaptic connectivity, and energy metabolism, which contribute to brain volume and functional capacity. Emerging evidence suggests that synaptic dysfunction reflects loss of cognitive function, positioning it as a reliable correlate of cognitive decline.[18] Maintaining synaptic structure and function has therefore been proposed as a key mechanism of cognitive resilience, with resilient individuals displaying reductions in synaptic protein oligomers, such as amyloid β, tau and alpha-synuclein, resilience to glial-mediated engulfment, increased levels of synapse-protective factors, such as neurotrophic factors, and improved synaptic integrity.[18] Figure 2 summarises the proposed inter-relationship between psychosocial factors and biological mechanisms contributing to cognitive resilience. Unfortunately, empirical research examining their combined effects remains scarce. Rather than revisiting the proposed underlying biological processes in detail, in this Review, we have discussed the potential biological mechanisms behind psychosocial determinants of cognitive resilience and identifying gaps in knowledge.

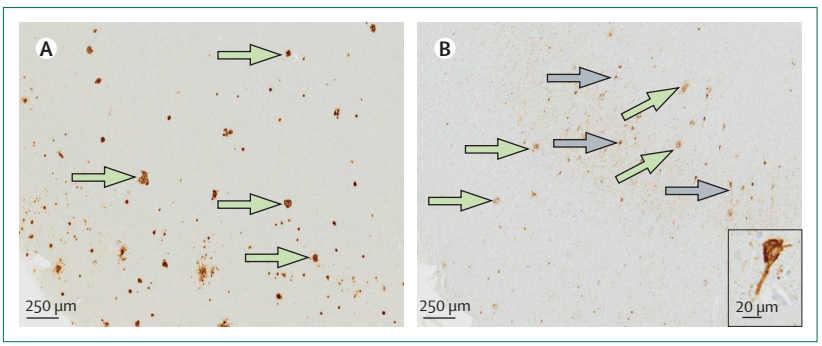

Figure 1: **Amyloid β and tau immunohistochemistry in the temporal cortex of a man aged 99 years with no cognitive impairment**
Numerous amyloid β (A) and tau-immunopositive plaques and tau-immunopositive neurons and neurofibrillary tangles (B) were present throughout the brain. Green arrows show representative amyloid β (A) or tau (B) staining of plaques. Blue arrows (B) show tau staining of neurons. Inset in B shows a tau-immunopositive neuron. Immunohistochemistry was done with antibodies against PHF-tau at 1:1500 dilution (clone AT8, Thermo Fisher Scientific, MN1020) and amyloid β at 1:2000 dilution (clone 6F/3D, Agilent, M087201–2) on a BenchMark GX stainer with a proprietary OptiView detection kit and hematoxylin II counterstain (Roche Diagnostics, Switzerland). Sections for amyloid β staining were deparaffinised and incubated in 98% formic acid for 3 min before staining. This donor was recruited through the Sydney Brain Bank.

Social and environmental factors

The social and environmental conditions that we live in are known to affect several health outcomes, which likely translate to cognitive resilience. Within high-income countries (HICs), living in with low socioeconomic status has been cross-sectionally associated with decreased cognitive resilience. This association has been indicated by poorer performance on cognitive screening (Mini Mental State Examination), when controlling for disease severity of ten dementia associated proteinopathies, including Alzheimer's disease, Lewy body disease, and limbic age-related TDP-43 encephalopathy.[19] The reasons for this association are not known. Possibilities include better access to health services in non-disadvantaged neighbourhoods and such areas offering more cognitively stimulating environments through greater availability of green spaces and pedestrian and physical activity infrastructure. This effect might be greater in LMICs, where lower socioeconomic status might confer even greater disadvantage, although this factor has not been studied.

In LMICs, where dementia rates are rising, a higher percentage of cases might be attributed to modifiable risk factors including lower education, more smoking. and higher rates and less treatment for of hypertension and diabetes.[20] Poverty and systemic disadvantage might impede progress in tackling these factors. Following a healthy diet, for example, can be difficult on a low income. Also, the consumption of ultra-processed foods, which are associated with cognitive decline, is increasing in LMICs.[20] Nevertheless, it seems likely that several of the determinants of cognitive resilience examined in HICs would be applicable to LMICs. Indeed, a higher composite score of cognitive resilience, which integrated factors such as education, occupational complexity, mental activity, and social support, was associated with better cognitive functioning when controlling for Alzheimer's disease-related plasma biomarkers in a sample of rural Chinese villagers.[21]

Years of education and occupational complexity are forms of mental enrichment, which build cognitive reserve, thereby promoting greater cognitive resilience. For example, greater lifetime years of education are associated with better-than-expected cognitive performance for grey matter volume,[22] amyloid β deposition,[23] and Alzheimer's disease-signature cerebral hypometabolism.[23] In some studies, higher lifetime occupational complexity has been associated with weaker links between both CSF amyloid ratios and hippocampal volume with memory, and between *APOEε4* and cognitive decline.[24] Although intelligence is also associated with cognitive resilience, it has been mostly measured with the use of a reading test.[23,25] However, reading is the learned component of intelligence that is highly influenced by education and broader socioeconomic factors. Whether fluid intelligence—the component less driven by explicitly learned knowledge—is similarly associated with cognitive resilience requires further investigation. Given that synaptic plasticity is the major cellular mechanism underlying learning and memory, it could represent one plausible biological explanation whereby mental enrichment promotes cognitive resilience. Education, in particular, has been associated with reductions in cerebrovascular disease, suggesting that comorbid pathologies or improved neurovascular function might play an important role in cognitive resilience to

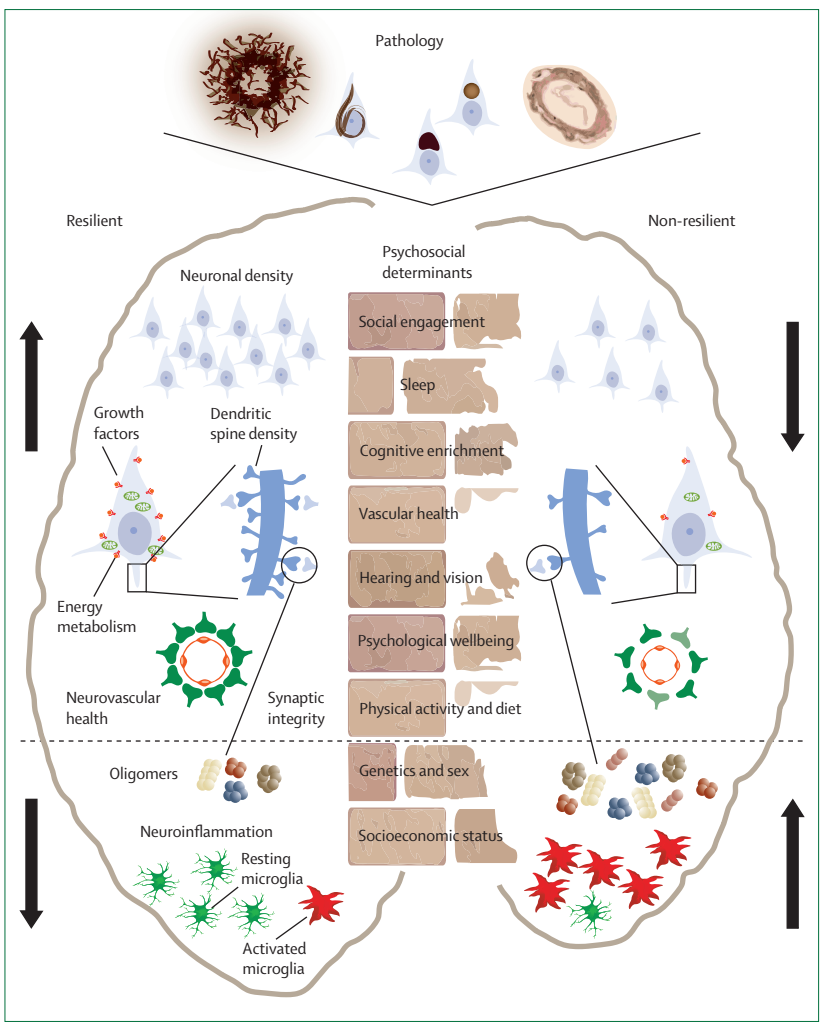

Figure 2: **A schematic representation illustrating the proposed association between psychosocial factors and biological mechanisms contributing to cognitive resilience independently of common neuropathologies**
The central wall represents psychosocial, genetic, and sexual factors proposed to support cognitive resilience. When these factors are negatively affected (depicted by the wall falling), the biological mechanisms associated with resilience are affected. Many of these biological mechanisms converge on shared pathways, including neuronal density, synaptic integrity, dendritic spine density, glial-mediated synaptic engulfment, and energy metabolism, and underlie greater brain volume and functional capacity (depicted by the larger brain on the resilient side). Unfortunately, empirical research examining their combined effects remains scarce but should be integrated into future studies. The dashed line separates factors on either side of the wall that are increased or decreased, as indicated by the black arrows.

Alzheimer's disease.[11] Additionally, the biological link between mental enrichment and cognitive resilience might reflect laying down more complex or denser neural networks,[26] and preservation of grey matter volume.[27,28]

Lifestyle and behavioural factors

Other cognitive activities beyond education and occupation are associated with cognitive resilience and might share similar mechanisms. Self-reported engagement in past activities (eg, visiting a library or reading a newspaper) across the early-to-mid life span (ie, ages 6–40 years) has been associated with greater cognitive resilience in older adults.[29] Similarly, lifelong cognitive activities (eg, going to concerts or writing letters) have been shown to moderate the cognitive effects of glucose hypometabolism in brain regions typically affected by Alzheimer's disease.[30] Cognitive reserve is thought to be dynamic and could be enhanced in later life.[17] Indeed, in a large longitudinal cohort study of 9294 participants in France,[31] cognitively stimulating engagement in leisure activities in later life was associated with greater cognitive resilience to genetic susceptibility to dementia based on *APOEε4* status and Alzheimer's disease-specific genetic risk scores. Learning a second language weakens the association between age and CSF Alzheimer's disease-biomarkers,[32] and is thought to contribute to cognitive resilience through fostering the brain regions that support executive control, which overlap with regions important for language control.[33] This observation supports the theory that cognitive resilience displays locoregional specificity. Although most studies do not examine cognitive domains, there is evidence to suggest that non-amnestic cognitive domains show greater resilience.[34] A prospective cohort study of 351 middle-aged and older individuals in South Korea[23] found that education, occupation, premorbid intelligence quotient, and lifetime cognitive activities have different moderating effects on the association between global cognition and in vivo markers of Alzhemier's disease pathology. This is one of the few studies to have examined multiple social determinants, and highlights the need for more studies that evaluate the relative contribution of each determinant.

Healthy lifestyle factors associated with improved cardiovascular health, including diet, exercise, avoidance of smoking and alcohol consumption, are associated with improved cognitive resilience.[30] A large clinical-pathological study on 754 participants in the USA[35] found that a healthy lifestyle, as defined by adherence to the Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay diet, more frequent late life cognitive and physical activity, and non-current smoking, was associated with better cognitive functioning proximate to death independent of common dementia-related brain pathologies. Physical activity increases blood flow and has been shown to enhance brain function through improved synaptic plasticity, dendritic remodelling, and mitochondrial function and the release of a plethora of bioactive molecules that regulate systemic metabolism and health.[36] Other reviews[37,38] have covered beneficial effects of physical exercise that might be mediated through improved vascular function, enhanced neuroplasticity, inhibition of inflammatory markers, and regulation of neurotransmitters associated with wellbeing. A recent post-mortem study (Rush Memory and Aging Project, USA)[39] showed that physical activity was associated with increased expression of several presynaptic protein markers independent of nine neuropathologies, suggesting that exercise might boost cognitive resilience

through improvements in synaptic integrity. This effect might be mediated by microglial activation.[40]

Psychological and personality factors

The well established association between psychological wellbeing and maintenance of cognitive abilities might at least partly be due to cognitive resilience. Social adversity measures, such as loneliness and reduced social interaction, have been linked to cognitive outcomes via biological pathways, such as inflammation and stress dysregulation.[41] A cohort study[42] of older adults found that psychological wellbeing and lower levels of depressive symptoms were independently associated with greater cognitive resilience, examined by better global cognition than expected for postmortem neuropathological burden. Similarly, a longitudinal study of 99 cognitively unimpaired older adults in the USA[43] found that greater use of adaptive coping styles is associated with better global cognitive trajectories independent of Alzheimer's disease pathology. Larger social network size, high network diversity, and stronger ties between members were associated with greater cognitive resilience, indicated by better-than-expected cognitive performance for brain structural changes including grey and white matter volumes and white-matter hyperintensities on MRI.[44] Social participation has been shown to be particularly important in reducing the risk of cognitive decline in several of LMICs.[45] However, the possibility of reverse causality and the strong association between psychological wellbeing and social engagement must be acknowledged. A systematic review[46] of the neural correlates of wellbeing has highlighted associations with brain regions involved in the salience and default mode networks, which have also been implicated in cognitive resilience.

Personality traits have also been examined, albeit in a mostly limited fashion (with most research examining openness, conscientiousness, extraversion, agreeableness, and neuroticism) and with heterogeneous findings. Based on the results from two cohort studies[47] of adults aged 70 years and older at baseline, only neuroticism was associated with lower cognitive resilience cross-sectionally and longitudinally. Greater openness has also been associated with better global cognition when controlling for CSF biomarkers.[48] Some personality traits might predispose to engagement in cognitive reserve building leisure activities, although more research is required in this area.

Sex differences

A review[49] on sex differences in cognitive resilience suggested that women have greater resilience to Alzheimer's pathology than men at earlier stages of the disease, while men are more resilient at later stages. Sex differences in cognitive resilience have also been observed in autosomal dominant frontotemporal dementia, with women showing greater executive functioning and social cognition at similar cortical thickness on MRI.[50] Several factors might be relevant, including sex hormones and chromosomes,[51] survival bias, and gender social norms. However, it is not apparent how such factors explain the differences in trajectories of Alzheimer's disease or frontotemporal dementia between men and women, and there might be a complex interplay between the possible contributors. This issue warrants further investigation and highlights the importance of sex stratified analyses when examining other determinants of cognitive resilience.

Clinical factors and comorbidities

Many different comorbidities as well as multiple comorbidities within the same individual are associated with reduced cognitive resilience.[52] Clinical predictors of higher cognitive resilience, expressed as a continuous measure comparing cognitive test scores and neuropathological lesion burden at autopsy, include better cardiovascular health, absence of depression, preserved hearing, and the need to take fewer medications.[53] A higher percentage of dementia cases are attributable to modifiable risk factors in LMICs than in HICs.[20] Depression,[54] hearing loss,[20] and visual impairments[55] might be particularly important.

Vascular risk factors and vascular disease are linked with cognitive decline in older adults both independently and synergistically with Alzheimer's disease and other neuropathologies.[56,57] Vascular dementia accounts for twice as many dementia cases in LMICs than in HICs.[20] However, cardiovascular medications have been shown to moderate the associations between Framingham Coronary Risk Profile score, total cholesterol, and LDL cholesterol on amyloid β and tau burdens as measured by PET and CSF.[58] Cognitive resilience defined as the absence of cognitive impairment in the presence of severe Alzheimer's disease pathology has also been reported in patients taking anticoagulant or antiplatelet medications.[59] Caution is required in interpreting single observations but this finding might suggest that treating vascular risk factors supports cognitive resilience.

Importantly, resilient individuals often have fewer cerebrovascular lesions, and healthy lifestyle factors associated with improved cardiovascular health, including diet, exercise, reduced smoking and alcohol use, are associated with improved cognitive outcomes independently of pathological burden.[35] An intervention study[60] showed a beneficial effect of physical activity on cognition and cerebrovascular regulation in older adults, suggesting that improved regulation of the neurovascular unit, which is key for brain function, might be a common mechanism underlying these observations.[61] Further research is required to advance our understanding of vascular pathologies in the context of cognitive decline. A recent harmonisation study[10] of six large community-based autopsy studies has

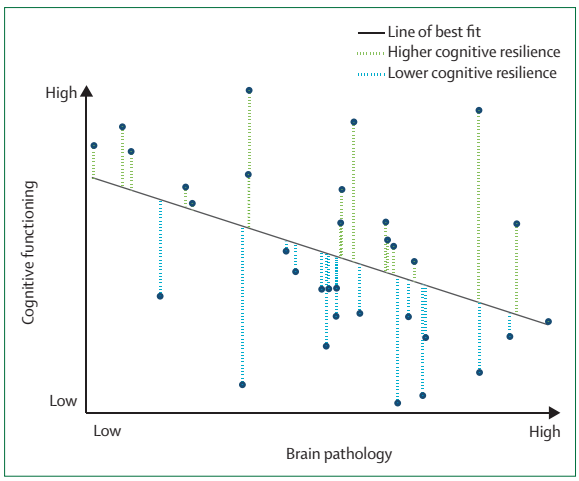

Figure 3: **Theoretical graph using simulated data to show the use of residual analysis for measuring cognitive resilience**
The graph highlights the variability in the relationship between cognitive functioning and brain pathology. Datapoints represent individuals. Dotted lines represent residual error, reflecting the difference between observed and predicted cognitive functioning based on the line of best fit. Datapoints above the line of best fit (as indicated by the dotted green line) represent individuals demonstrating higher cognitive resilience. Datapoints below the line (as indicated by the dotted red line) represent the inverse. Measures of cognitive functioning might involve cognitive screens or neuropsychological tests. Measures of brain pathology might involve neuroimaging, EEG, magnetoencephalography, or fluid biomarkers.

identified limitations in how vascular pathologies are assessed and the authors called for new diagnostic neuropathology frameworks for characterising cerebrovascular disease.

White-matter hyperintensities have been identified as a potential marker of ischaemic change and might be representative of reduced blood–brain barrier integrity and inflammation,[62] with a recent systematic review and meta-analysis[63] supporting a role for this vascular phenomenon in dementia risk. White-matter hyperintensities are common in the general population and can be easily detected radiologically.[64] These changes appear to be dynamic in nature, which complicates the identification of reliable radiological–pathological correlates.[65] However, targeting individuals with white-matter hyperintensities might offer a key therapeutic window to preserve cognitive resilience. Future studies evaluating functional changes in the neurovascular unit[66] and blood–brain barrier integrity[67] could aid progress in this field and facilitate longitudinal assessment of cerebrovascular pathologies. Such approaches might also facilitate research in LMIC settings, which is urgently needed due to higher vascular cognitive imapairment and higher dementia rates in these populations compared with HICs.[20] Analysis of cerebrovascular changes in the context of atrophy will also be important given that atrophy appears to have an additive effect on cognitive decline.[68]

Sleep disordered breathing is associated with cognitive decline at younger age. The evidence base for an effect of treatment with continuous positive airway pressure on cognition is mixed, but overall supports its role in reducing the risk of all cause cognitive impairment and dementia, delaying decline or slightly improving cognitive scores.[69] Deep non-rapid eye movement slow wave sleep is known to enhance cognition and has been shown to moderate the effect of amyloid β status on memory function.[70] A range of systemic inflammatory diseases are associated with cognitive decline and dementia with more research required to support the benefits of early disease control to offset this risk.[71]

Measurement of cognitive resilience

There is no consensus for measuring cognitive resilience, although two systematic reviews[72,73] have examined existing and emerging methods. Cognitive resilience requires quantification of both brain status and cognition, so that the degree to which cognition is preserved at any given level of cerebral pathology can be assessed. Many of the assessment approaches discussed in this paper are not available in LMICs or might not be culturally appropriate (eg, Western biased neuropsychological tests might not appropriately measure the cognitive abilities of individuals from different cultural, ethnic, linguistic, or educational backgrounds).

A common approach of combining measures of brain pathology and cognition to measure cognitive resilience is the regression-based method. With the use of this approach, a brain marker is regressed onto a measure of cognition, with the residuals of the analysis being an indicator of cognitive resilience (figure 3). Various factors (eg, genes and social determinants) can be correlated with these residuals to assess their association with cognitive resilience. A systematic review and meta-analysis evaluating this approach found that it was an appropriate method of measuring resilience, capturing clinically meaningful information about cognition in ageing. However, the study noted heterogeneous applications of the method across the literature and risk of publication bias, meaning the meta-analysis did not capture negative or weaker associations between the residual-based approach of measuring cognitive resilience and ageing variables.[73] Although post-hoc sensitivity analyses excluding studies at moderate risk of bias yielded similar overall effects, the risk of publication bias observed highlights the need for caution when interpreting results. The systematic review also cautioned against the use of the residual-based regression approach in some instances, highlighting that residuals are often highly collinear with cognitive performance, making this method statistically inappropriate in some circumstances.[73] Other statistical and machine learning approaches have assessed whether some factors moderate or mediate the relationship between brain measures and cognitive functioning, but await further development.[74–76]

Cognitive testing

Approaches to measuring the cognitive component of cognitive resilience vary. Some studies use cognitive screening tools, such as the Mini Mental State Examination or Montreal Cognitive Assessment, which are advantageous for their brevity, but are vulnerable to ceiling effects, have low sensitivity to cognitive change, and do not allow detailed examination of specific cognitive domains.[19,44] More extensive standardised neuropsychological assessment batteries provide measures of different cognitive domains, and can also be combined into a single composite score. Such batteries often examine various domains, including attention, processing speed, semantic memory, episodic memory, and executive functioning. Differences in these approaches might explain disparate findings. For example, years of education is generally associated with greater cognitive resilience when global scores of cognition are used, although some studies indicate that the association is domain specific.[25] Future studies

	Observation	Putative mechanism
Structural MRI		
105 mutation carriers (*C9orf72, MAPT, GRN*) mean age 51 years, 47% female, and 69 non-carriers, mean age 49 years, and 44% women[81]	More active lifestyle in autosomal dominant gene carriers for FTLD associated with better cognitive performance than their less active peers but with comparable rates of frontotemporal atrophy	Benefits of cognitive and physical activity on cognition in the presence of neurodegenerative pathology
160 participants who were amyloid positive (mean age 75 years, 51% women)[82]	Thicker cortex in eight regions associated with less decline in executive function and memory	Quantification of brain reserve supporting cognitive resilience in Alzheimer's disease
Resting state functional MRI		
590 participants (212 men, 378 women), aged 15–85 years[83]	Functional network redundancy might accumulate over the lifespan, declining at older ages	Moderation of the effect of ageing on executive function
519 participants: 184 cognitively normal amyloid negative (mean age 72 years, 61% women), 89 cognitively normal amyloid positive (mean age 76 years, 63% women), 59 mild cognitive impairment amyloid positive (mean age 76 years, 42% women), eight with Alzheimer's disease (mean age 74 years, 38% women), 108 dominantly inherited Alzheimer's disease gene carriers (mean age 38 years, 63% women), and 71 non-carriers (mean age 38 years, 62% women)[84]	Higher levels of functional network segregation seen in individuals with autosomal dominant Alzheimer's disease and later onset of cognitive decline. Separately, less global cognitive and episodic memory decline seen in individuals with sporadic Alzheimer's disease per unit increase in temporal lobe tau	Compensatory mechanism underlying cognitive resilience to Alzheimer's disease pathology
271 participants (mean age 67 years, 22% women)[85]	Greater network integration seen in patients with high cognitive scores despite moderate to severe vascular disease	Compensatory mechanism in the presence of CVD
318 participants: 112 healthy controls (mean age 69 years, 46% women), 206 on the Alzheimer's disease neuropathological continuum defined as amyloid pathology with or without cognitive symptoms (mean age 72 years, 49% women)[86]	Intrinsic network connectivity in the DMN in a functional MRI study in people with better-than-expected cognition (residual model) in in participants with Alzheimer's disease pathology measured with the use of CSF biomarkers	Mechanism underlying cognitive resilience to Alzheimer's disease pathology
230 participants (mean age 65 years, 50% women)[87]	Increased connectivity in the frontoparietal network and between the salience network and medial frontal cortex in people with better-than expected cognition for the degree of vascular damage	Mechanism underlying cognitive resilience to CVD
1021 participants, mean age 71 years, 61% female, 42% *APOEε4* carriers, 52% amyloid positive[88]	Stronger connectivity in the left frontoparietal control network associated with slower cognitive decline in individuals with cortical amyloid	Compensatory changes in network connectivity underlying cognitive resilience to CVD
125 participants, mean age 74 years, 58% women[89]	Attenuation in episodic memory impairment associated with entorhinal tau pathology (tau PET) seen in individuals with higher global left frontal cortex connectivity	Mechanism underlying cognitive resilience to Alzheimer's disease pathology
153 participants, mean age 69 years, 63% women[90]	Higher engagement with cognitive activities associated with connectivity between the dorsal attention network; higher physical activity with connectivity between the default mode, limbic, and frontoparietal control networks; and higher cognitive and physical activity levels associated with higher network modularity. All associations were independent of *APOE4* genotype and amyloid burden[90]	Cognitive and physical activity might strengthen connectivity between some brain regions in the presence of Alzheimer's disease pathology
DTI and resting state functional MRI		
511 participants: 184 resilient (mean age 69 years, 16·3% women), 133 non-resilient (mean age 73 years, 15·8% women)[91]	Preserved white matter integrity and differences in functional connectivity in individuals showing cognitive resilience as defined by high cognitive performance despite hippocampal atrophy	Either compensation for pathology or lifelong differences between resilient and non-resilient groups

(Table 1 continues on next page)

	Observation	Putative mechanism
(Continued from previous page)		
FDG-PET		
475 participants in full sample (mean age 84 years, 42% women), 192 cognitively stable (mean age 83 years, 47% women)[92]	Increased FDG-PET uptake in the bilateral anterior cingulate cortex and anterior temporal lobe in people older than 80 years maintaining normal cognition for an average of 5 years	Preserved function despite pathology in some brain areas
181 participants: 48 healthy controls (mean age 69 years, 52% women), 94 with MCI suspected secondary to Alzheimer's disease (mean age 75 years, 55% women), 39 with MCI and amyloid positive (mean age 74 years, 46% women)[93]	Relatively preserved metabolism in the right middle temporal gyrus and left orbitofrontal cortex in amyloid positive people with MCI and later conversion to dementia	Preserved function despite pathology in some brain areas
604 participants: 240 cognitively normal (mean age 73 years, 48% women), 252 MCI (mean age 73 years, 41% women), 112 Alzheimer's disease (mean age 74 years, 44% women)[94]	Higher locus coeruleus metabolism in people with Alzheimer's disease pathology and attenuated memory decline	Preserved function despite pathology in some brain areas
848 participants (mean age 73 years, 48% women): 268 cognitively normal, 454 MCI, and 126 with dementia[95]	Relative preservation of brain glucose metabolism or metabolic resilience in individuals showing cognitive resilience	Metabolic resilience signature
Amyloid and tau PET		
120 participants: untreated (mean age 63 years, 75% women) and treated with antihypertensive and lipid lowering drugsmean age 64 years, 73% women)[58]	Reduced amyloid and tau burden in patients with higher vascular risk profile with the use of antihypertensive and lipid lowering drugs	Medication use or other control of vascular risk factors might moderate Alzheimer's disease pathogenesis
260 participants (mean age 69 years, 56% women)[15]	Higher level of education and greater cortical thickness associated with cognitive resilience in participants who were amyloid positive (PET or CSF analysis) with MCI or dementia	Demonstration of the effect of determinants of cognitive reserve on resilience to Alzheimer's disease
428 participants (mean age 72 years, 51% women)[96]	Biomarkers of synaptic dysfunction, neuroaxonal injury, inflammation and vascular pathology might be associated with cognitive decline in the presence of amyloid (CSF) and tau (PET) pathology	Co-existing pathologies, especially vascular disease and axonal degeneration, negatively affect cognitive resilience

CVD=cerebrovascular disease. DMN=default mode network. DTI=diffusion tensor imaging. FDG PET=fluorodeoxyglucose positron emission tomography. FTLD=frontotemporal lobar degeneration. MCI=mild cognitive impairment.

Table 1: **Neuroimaging studies of cognitive resilience**

examining cognitive performance on the domain-level are therefore warranted.

Imaging

Neuroimaging has numerous potential applications in the assessment of cognitive resilience. Structural and functional brain imaging have been used to quantify white matter disease and atrophy, and estimate brain age.[77] Structural imaging can be used for assessing markers of brain reserve and brain maintenance; functional imaging for network connectivity; diffusion MRI measures for white matter integrity;[78] and arterial spin labelling and cerebrovascular reactivity techniques for cerebrovascular function.[78] Synaptic density can be quantified with PET and longitudinal synapse loss is associated with cognitive decline.[79] Specific neuropathologies can also be assessed, including amyloid β and tau PET[15] for Alzheimer's disease and emerging alpha-synuclein PET imaging techniques for Lewy body disease and multiple system atrophy.[80] Specific imaging markers of cognitive resilience have also been explored, particularly functional imaging including FDG-PET. Combinations of imaging techniques enable the assessment of cognitive resilience to individual and multiple pathologies. Selected studies with a focus on larger samples and novel findings, are summarised in table 1. We have not included the numerous imaging studies of cognitive reserve investigating proxies of educational attainment or occupational complexity if the studies did not include neuropathology measures from individuals with cognitive resilience.

EEG and magnetoencephalography

EEG has been used to evaluate brain networks in individuals displaying better-than-expected cognitive performance and can be used to study potential mechanisms of regional resilience. EEG can be used to assess synaptic dysfunction in early neurodegenerative disease with the use of both standard and quantitative approaches.[97,98] EEG is believed to directly reflect brain activity at the synaptic level, although whether these data can reliably be used as a surrogate measure of cognitive resilience warrants further research. Activity in the dorsal attention network and ventral attention network has been found to moderate the association between hippocampal volume and word list memory performance.[99] Cognitively unimpaired individuals with markers of Alzheimer's pathology in CSF showed reduced functional connectivity from the temporal regions but greater functional connectivity in the frontal

	N; age (years); population; risk	Intervention	Outcome
FINGER, 2015[111]	1260; 60–77 years; MCI and CAIDE risk score ≥6, and MMSE ≤26 or low list learning test	Multidomain, for 2 years; physical activity, nutrition, cardiovascular health, and social activity	Composite cognitive score effect size 0·04
PreDIVA 2016[112]	3526; 70–78 years; primary care; and age as risk factor	Primary care nurse-led multidomain cardiovascular intervention, for 6·7 years	No difference in dementia incidence or disability score
MAPT 2017[113]	1680; ≥70 years; community; and SCC or IADL limitation or slow gait	Multidomain cognitive training plus physical activity, nutrition, and preventative consultations, plus omega-3 fatty acids or placebo; or placebo alone; 3 years	Composite cognitive score, no significant difference
HATICE 2019[114]	2724; ≥65 years; and increased risk of cardiovascular disease	Interactive internet intervention stimulating coach-supported self-management or control; 18 months	Significantly reduced composite cardiovascular score: sBP, LDL cholesterol, and BMI; no significant differences on cognition
Mindfulness & Exercise 2022[115]	585; 65–84 years; and subjective cognitive complaints	18 months duration, primary endpoint at 6 months, secondary at 18 months	Composite episodic memory and executive function; no significant difference at 6 months or 18 months
AgeWell.de 2024[116]	1030; 60–77 years; and CAIDE risk score ≥9	General practitioner administered multidomain (nutrition, physical, social, cognitive activity, medication review, and general health advice); 24 months	Global composite cognitive: no significant difference
SMARRT 2024[117]	172; 70–89 years; and ≥2 of 8 risk factors for dementia	Multidomain personalised risk reduction, 2 years	Composite cognitive score effect size 0·14 (95% CI 0·03–0·25)
J-MINT 2024[118]	532; 65–85 years; and evidence of cognitive decline	Management of vascular risk factors, exercise, nutrition, cognitive training, for 18 months	No significant difference on a composite cognitive score
SUPERBRAIN[119]	300; 60–85 years; and MCI	Management of metabolic and vascular risk factors, cognitive training, physical exercise, nutrition, and motivational enhancement, for 24 weeks	Repeatable battery for the assessment of neuropsychological status (RBANS scores 8·43 *vs* 4·26, difference=4·17 [95% CI 1·92–6·43] effect size=0·43, p<0·001)
MYB 2025[120]	6104; 55–77 years; community; and ≥2 of 4 risk factors for dementia	Multidomain personalised risk reduction (ie, physical activity, nutrition, brain training, and depression or anxiety treatment *vs* information), online, for 3 years	Composite cognitive score: intervention effect size=0·28, control effect size=0·10; difference effect size=0·18; and p<0·001
US POINTER 2025[121]	2011; 60–79 years; and at higher risk of cognitive decline	Structured or self-guided interventions encouraging physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring, for 2 years	Composite global cognitive score effect sizes per annum for structured=0·243 and self-guided=0·213; and difference=0·029 (p<0·008)

CAIDE=cardiovascular risk factors ageing and incidence of dementia. IADL=instrumental activities of daily living. MMSE=mini mental state examination. sBP=systolic blood pressure. SCC=subjective cognitive complaints. We reviewed multidomain interventions published since 2015 that had cognition as the primary outcome. We did not include trials targeting a specific disease group, such as those with participants with diabetes or post-stroke.

Table 2: **Randomised controlled trials to enhance cognition in people at risk of dementia**

and occipital regions compared with cognitively healthy individuals without CSF pathology, which might reflect compensatory processes to pathology in the temporal lobes.[100] EEG slowing in people with early neurodegenerative disease or dementia tends to be widespread, reflecting alterations in global brain functional connectivity.[97,98]

Fluid biomarkers

Serum and CSF biomarkers are increasingly used in the diagnosis of neurodegenerative diseases, and to assess progression and response to treatment. Classical pathologies (eg, Alzheimer's disease, Lewy body disease, and cerebrovascular disease) can now be detected by the use of specific biomarkers, including CSF and blood amyloid β and phosphorylated tau (particularly p-tau217) for Alzheimer's disease,[101] and alpha-synuclein seed amplification assays in dementia with Lewy bodies and Parkinson's disease.[102] Several emerging biomarkers of neurovascular unit dysfunction have been identified and might aid quantification of cerebrovascular disease.[66] Neurofilament light chain protein, a marker of neuroaxonal injury, and GFAP, a marker of inflammation through astrocytic activation or cell death, are elevated in people with traumatic brain injury,[103] stroke,[104] neuroinflammatory diseases,[105] and a range of neurodegenerative conditions.[106] The interactions between different pathologies and cognitive resilience can also be assessed when, for example, tau-PET and fluid biomarkers of vascular and inflammatory pathology are all measured.[96] Although neurofilament light chain and GFAP are relatively non-specific, concentrations of these markers often correlate with longitudinal cognitive decline and progression of several underlying pathologies.[105,106] Lower serum GFAP concentrations have also been observed in older adults with higher levels of physical activity.[107] Serum BDNF has been used to assess the beneficial effect of a lifestyle

intervention for older people at risk of dementia.[108] Multiple synaptic proteins can be measured in blood and CSF and might be used to track synaptic dysfunction. Abnormalities are seen across several neurodegenerative diseases, but associations with vulnerability and resilience to pathology have been best studied in the context of Alzheimer's disaese.[18,109,110] Measurement of most of these synaptic proteins is not available outside of research settings. When suites of fluid-based biomarkers are accessible in clinical practice, they will likely enhance individualised discussions of dementia risk and strategies to optimise cognitive health. These markers require ongoing validation through post-mortem studies.

We propose that any future measurement of cognitive resilience should incorporate a combined imaging and fluid biomarker assessment of brain pathology. Repeated cognitive measures should include individual cognitive domains and global assessment of cognition to indicate longitudinal resilience. Synaptic markers can be used to measure underlying biological mechanisms of cognitive resilience.

Enhancement of cognitive resilience

Interventions to improve cognitive functioning usually aim to enhance cognitive reserve rather than resilience. We considered enhancement strategies as those that support cognitive function in the presence of in vivo pathology as assessed through neuroimaging or fluid-based biomarkers, or by assuming expected neuropathological burden in people with subjective cognitive decline, mild cognitive impairment, or age 70 years and older (table 2).

Six multi-component randomised controlled trials of psychosocial interventions conducted in HICs have shown statistically significant benefits on cognition in older populations at increased risk for dementia (table 2). The pioneering Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability showed that people with average or lower cognition and increased risk of dementia as determined by the Cardiovascular Risk Factors, Ageing and Dementia score, had a small but significant improvement on a neuropsychological test battery, effect size of 0.22 per year (95% CI 0·002–0·042, p=0·030) over 2 years.[111] For reference, an effect size of 0·2 (eg, antibiotics for acute bronchitis)[122] is considered small, 0·5 is moderate, and 0·8 is strong. In the US Systematic Multi-Domain Alzheimer Risk Reduction Trial,[117] 172 adults aged 70–89 years at increased risk of dementia who received personalised risk-reduction goals delivered by health coaching and nurse visits showed improvements on composite cognitive and risk factor scores compared with controls receiving health education. In the Australian Maintain Your Brain trial,[123] half of the 6104 individuals aged 55–77 years who had at least two risk factors for dementia received intensive personalised active coaching in 10-week blocks of computerised brain training, moderate-to-intensive physical activity, Mediterranean diet-based nutrition, and depression or anxiety treatment in one session with monthly boosters until the end of year 3. The other half received static online information for each of their eligible risk factors with quarterly boosters until the end of year 3. Both groups improved but the active intervention group improved significantly more than controls on a global cognitive composite score.[120] In the South Korean SUPERBRAIN-MEET study, 300 participants with mild cognitive impairment aged 60–85 year were randomly assigned to a multi-domain intervention, combining management of metabolic and vascular risk factors, cognitive training, physical exercise sessions, nutritional education, and motivational enhancement, or a control condition of standard care plus a medical consultation, medication as indicated, an education booklet and possibility of a delayed multidomain intervention. At 24 weeks, the intervention group had significantly better performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS scores 8·43 *vs* 4·26, p<0·001).[119] In the US Pointer study, 2111 participants aged 60–79 years at high risk of cognitive decline were randomised to structured or self-guided interventions encouraging physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring. Both groups improved, with effect sizes of 0·243 and 0·213.[121]

Most trials combined neuropsychological z scores to derive a global cognitive composite score. Although FINGER, MYB, and POINTER measured domains of memory, executive function, and speed of information processing, the tests and their administration, in-person or online, differed. SMARRT calculated a global score with measures of memory, attention, and language administered in-person and then by telephone. Effect sizes were small, but if translated into reduced dementia incidence, could have substantial effects at a population level. For example, a mindfulness intervention for school students had an effect size of 0·20 in reducing depression, which translated into 3–5% fewer students with depression.[124] In a population of a million students, that would be 30 000–50 000 fewer students with depression.

Caveats apply. First, other multicomponent approaches have targeted populations at increased risk of dementia but did not show benefit on primary cognitive outcomes (table 2).[112,113] Second, although many trials have shown reduction in dementia risk scores,[111–113,117,120] none has yet shown a reduction in dementia incidence.[125] Third, there is sample bias in many studies, as participants are usually highly educated and motivated. It is possible, but untested, that benefits might be greater in people with less education. Fourth, there is no clear signal as to interactive effects of *APOE* on outcomes. Finally, all studies have been conducted in HICs; no similar studies have been completed in LMICs. We note that these trials

Panel 2: Key future research areas

- Reliable and uniform measures of cognitive resilience during life, including cognitive test selection, measurements of cerebrovascular disease, and all recognised neuropathologies
- Integration of functional assessments, cognitive performance, neuroimaging, electrophysiology, and fluid-based biomarkers to define both neuropathology and injury and resilience
- Cognitive resilience research in low-income and middle-income countries
- Assessment of the relative contributions of different social determinants and activity types to resilience
- Cognitive domain specific resilience
- Further exploration of known modifiable risk factors for dementia in relation to cognitive resilience, including biological mechanisms
- Multi-component trials of strategies to promote cognitive resilience at individual and at the community levels

Search strategy and selection criteria

Our search strategy involved three academic databases: PubMed (including MEDLINE), Scopus, and the Cochrane Database of Systematic Reviews (appendix). We selected keywords related to cognitive resilience ('cognitive reserve', 'cognitive resilience', 'brain reserve', 'brain maintenance'), determinants ('gene*', 'comorbidities', 'demographics', 'psychosocial'), measurement ('instrument', 'questionnaire', 'tool', 'index', 'neuropsychological assessment', 'cognitive assessment', 'neuroimaging', 'MRI', 'functional MRI', 'DTI', 'MTI', 'PET', 'EEG', 'MEG', 'biomarkers', 'CSF', 'amyloid', 'tau', 'neurofilament light', 'neuropathology') and enhancement ('super-agers', 'centenarians', 'promotion', 'treatment', 'intervention'). Apart from a few landmark papers, our search start and end dates were March 1, 2015 and Nov 30, 2025. We only included studies that made reference to resilience, either through imaging or fluid-based biomarker identification of pathology, neuropathological assessment at autopsy or in relation to advanced age. We could not reference every study that we reviewed and sought to include either review articles synthesising numerous studies, single novel studies or large studies broadly representative of findings from other primary studies.

See Online for appendix

are resource intensive and require access to technology. However, when optimal components of such trials are identified, it will be possible to translate protocols to a range of settings. MYB, for example, is planned to be studied in lower education and socioeconomic settings.

Several studies have assessed the effect of individual interventions on cognitive resilience. Physical activity is known to improve cognitive performance or mitigate age related decline.[126] The type, intensity, and frequency of exercise interventions vary widely across trials.[36] Cognitive training and cognitive stimulation might slow down neurodegeneration in individuals with mild cognitive impairment, and multidomain interventions combining physical activity with cognitive training might affect Alzheimer's pathology in older adults.[127] A Cochrane Systematic Review[128] of cognitive stimulation therapy in people with dementia revealed overall small short-term cognitive benefits, with a small number of studies finding benefits in communication, mood, quality of life, and behaviour. An RCT involving 52 residents of aged care facilities, mean age of 82 years, with mild cognitive impairment and reported significant improvement in cognition on the Mini Mental State Examination or Montreal Cognitive Assessment, with music imaging therapy compared with health education at 1-month and 3-months' follow-up.[129] The variety and evenness of participation in different activities were associated with higher overall cognitive functioning and executive functioning over time in older adulthood.[130] One review[131] suggested that social participation, as well as being associated with lower dementia risk, might reduce or mitigate the effect of neuropathology.

Research on resilience enhancing compounds is scarce. The monoclonal antibodies aducanumab, lecanemab, and donanemab are effective at removing brain amyloid β and moderately effective at slowing rates of cognitive decline[101]—they reduce pathology rather than enhance resilience. A Cochrane Review[132] concluded that Fortasyn Connect (a multi-nutrient combination of B vitamins, vitamin C, vitamin E, long-chain omega-3 fatty acids, choline, uridine, and selenium), which is purported to enhance phospholipid synthesis, had a small effect in slowing the rate of cognitive decline in people with prodromal Alzheimer's disease but showed no significant benefit in individuals with dementia. Lithium orotate, which might correct lower lithium concentrations in the prefrontal cortex, is under investigation.[133] Several novel approaches are effectively increasing synaptic resilience against Alzheimer's disease in animal experiments. Targets include boosting actin network proteins such as filamentous actin, neurotrophic factors, such as BDNF, and scaffolding proteins, such as PSD-95, and inhibition of phosphatases.[134] These approaches are yet to be tested in humans. Ergothioneine and citicoline are thought to be protective for neurons in animal experiments but have not been tested clinically.

Conclusions and future directions

Understanding why some individuals maintain cognitive function while having substantial neuropathological burden is a focus of ongoing research with the potential to identify avenues to ameliorate cognitive decline (panel 2, appendix). However, consistent definitions and measurement of cognitive resilience are required. The use

of biomarker proxies for neuropathologies and vascular disease, and markers of both synaptic dysfunction and resilience will aid in assessing the effects of pathology as well as of multicomponent and targeted interventions. Large longitudinal cohort studies have provided insights into factors underlying cognitive resilience, with increasing recognition of the social determinants of health and their effects on cognition across the lifespan. Optimising vascular health might have cognitive benefits over and above a reduction in clinical cerebrovascular disease, which could be particularly powerful in LMICs, where vascular disease is a greater contributor to cognitive decline. There is growing evidence for multicomponent interventions in enhancing cognitive resilience, although they are yet to be studied in LMICs.

Contributors

HB, AP, CS, and KC conceptualised the outline of the paper. AP searched the literature on clinical factors and measurement regarding imaging, electrophysiology, and fluid-based biomarkers, wrote these sections, and compiled the first draft of this Review. KC searched the literature and wrote the sections on sociodemographic and psychosocial aspects as well as cognitive measures of cognitive resilience. CS searched the literature and wrote the main content relating to neuropathology and biological mechanisms. HB searched the literature and wrote the enhancement of cognitive resilience section. AP designed and drafted panel 1 and table 1. HB designed and drafted table 2. CS co-designed and drafted figures 1 and 2 with Heidi Cartwright and Heather McCann. KC designed and drafted figure 3. All authors edited drafts of the manuscript and reviewed the final version of the manuscript.

Declaration of interests

HB has been an advisory board member or consultant to Eisai, Eli Lilly, Medicines Australia, NovoNordisk, Roche, and Skin2Neuron. All other authors declare no competing interests.

References

1 Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: the 90+ study. *Curr Alzheimer Res* 2012; **9:** 709–17.

2 Azarpazhooh MR, Avan A, Cipriano LE, et al. A third of community-dwelling elderly with intermediate and high level of Alzheimer's neuropathologic changes are not demented: a meta-analysis. *Ageing Res Rev* 2020; **58:** 101002.

3 Brayne C, Richardson K, Matthews FE, et al. Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge city over-75s cohort (CC75C) study. *J Alzheimers Dis* 2009; **18:** 645–58.

4 Tanskanen M, Mäkelä M, Notkola I-L, et al. Population-based analysis of pathological correlates of dementia in the oldest old. *Ann Clin Transl Neurol* 2017; **4:** 154–65.

5 Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Med* 2009; **6:** e1000180.

6 Cholerton B, Larson EB, Baker LD, et al. Neuropathologic correlates of cognition in a population-based sample. *J Alzheimers Dis* 2013; **36:** 699–709.

7 White LR, Edland SD, Hemmy LS, et al. Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies. *Neurology* 2016; **86:** 1000–08.

8 Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis* 2009; **18:** 691–701.

9 Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. *Neurobiol Aging* 2005; **26:** 341–47.

10 Nichols E, Merrick R, Hay SI, et al. The prevalence, correlation, and co-occurrence of neuropathology in old age: harmonisation of 12 measures across six community-based autopsy studies of dementia. *Lancet Healthy Longev* 2023; **4:** e115–25.

11 de Vries LE, Huitinga I, Kessels HW, Swaab DF, Verhaagen J. The concept of resilience to Alzheimer's Disease: current definitions and cellular and molecular mechanisms. *Mol Neurodegener* 2024; **19:** 33.

12 Gómez-Isla T, Frosch MP. Lesions without symptoms: understanding resilience to Alzheimer disease neuropathological changes. *Nat Rev Neurol* 2022; **18:** 323–32.

13 Jia B, Xu Y, Zhu X. Cognitive resilience in Alzheimer's disease: mechanism and potential clinical intervention. *Ageing Res Rev* 2025; **106:** 102711.

14 Stern Y, Albert M, Barnes CA, Cabeza R, Pascual-Leone A, Rapp PR. A framework for concepts of reserve and resilience in aging. *Neurobiol Aging* 2023; **124:** 100–03.

15 Ossenkoppele R, Lyoo CH, Jester-Broms J, et al. Assessment of demographic, genetic, and imaging variables associated with brain resilience and cognitive resilience to pathological tau in patients with Alzheimer disease. *JAMA Neurol* 2020; **77:** 632–42.

16 Marino C, Malotaux V, Giudicessi A, et al. Protective genetic variants against Alzheimer's disease. *Lancet Neurol* 2025; **24:** 524–34.

17 Kremen WS, Elman JA, Panizzon MS, et al. Cognitive reserve and related constructs: a unified framework across cognitive and brain dimensions of aging. *Front Aging Neurosci* 2022; **14:** 834765.

18 Taddei RN, Duff KE. Synapse vulnerability and resilience across the clinical spectrum of dementias. *Nat Rev Neurol* 2025; **21:** 353–69.

19 Kim B, Yannatos I, Blam K, et al. Neighborhood disadvantage reduces cognitive reserve independent of neuropathologic change. *Alzheimers Dement* 2024; **20:** 2707–18.

20 Kalaria R, Maestre G, Mahinrad S, et al. The 2022 symposium on dementia and brain aging in low- and middle-income countries: highlights on research, diagnosis, care, and impact. *Alzheimers Dement* 2024; **20:** 4290–314.

21 Han X, Li Y, Wang J, et al. Associations between lifelong cognitive reserve, Alzheimer's disease-related plasma biomarkers, and cognitive function in dementia-free older adults: a population-based study. *J Alzheimers Dis* 2025; **103:** 821–32.

22 van Loenhoud AC, Wink AM, Groot C, et al. A neuroimaging approach to capture cognitive reserve: application to Alzheimer's disease. *Hum Brain Mapp* 2017; **38:** 4703–15.

23 Ko K, Yi D, Byun MS, et al. Cognitive reserve proxies, Alzheimer pathologies, and cognition. *Neurobiol Aging* 2022; **110:** 88–95.

24 Kleineidam L, Wolfsgruber S, Weyrauch A-S, et al. Midlife occupational cognitive requirements protect cognitive function in old age by increasing cognitive reserve. *Front Psychol* 2022; **13:** 957308.

25 Gazes Y, Lee S, Fang Z, et al. Effects of brain maintenance and cognitive reserve on age-related decline in three cognitive abilities. *J Gerontol B Psychol Sci Soc Sci* 2023; **78:** 1284–93.

26 Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 2012; **11:** 1006–12.

27 Cai Y, Fang L, Li A, et al. Educational attainment, Aβ, tau, and structural brain reserve in Alzheimer's disease. *Alzheimers Dement* 2025; **21:** e14400.

28 Bocancea DI, Svenningsson AL, van Loenhoud AC, et al. Determinants of cognitive and brain resilience to tau pathology: a longitudinal analysis. *Brain* 2023; **146:** 3719–34.

29 Boyle R, Townsend DL, Klinger HM, et al. Identifying longitudinal cognitive resilience from cross-sectional amyloid, tau, and neurodegeneration. *Alzheimers Res Ther* 2024; **16:** 148.

30 Ourry V, Binette AP, St-Onge F, et al. How do modifiable risk factors affect Alzheimer's disease pathology or mitigate its effect on clinical symptom expression? *Biol Psychiatry* 2024; **95:** 1006–19.

31 Wagner M, Neuffer J, Le Grand Q, et al. Associations of the LIBRA index with cognitive resilience to genetic susceptibility to dementia. *Am J Epidemiol* 2025; **194:** 2457–66.

32 Estanga A, Ecay-Torres M, Ibañez A, et al. Beneficial effect of bilingualism on Alzheimer's disease CSF biomarkers and cognition. *Neurobiol Aging* 2017; **50:** 144–51.

33 Mendez MF. Can speaking more than one language help prevent Alzheimer's disease? *J Alzheimers Dis* 2023; **95:** 363–77.

34 Carbone C, Maramotti R, Balboni E, et al. Cognitive reserve in young-onset cognitive impairment. *Brain Cogn* 2025; **186:** 106297.

35 Dhana K, Agarwal P, James BD, et al. Healthy lifestyle and cognition in older adults with common neuropathologies of dementia. *JAMA Neurol* 2024; **81:** 233–39.

36 Tari AR, Walker TL, Huuha AM, Sando SB, Wisloff U. Neuroprotective mechanisms of exercise and the importance of fitness for healthy brain ageing. *Lancet* 2025; **405:** 1093–118.

37 Mandolesi L, Polverino A, Montuori S, et al. Effects of physical exercise on cognitive functioning and wellbeing: biological and psychological benefits. *Front Psychol* 2018; **9:** 509.

38 Quigley A, MacKay-Lyons M, Eskes G. Effects of exercise on cognitive performance in older adults: a narrative review of the evidence, possible biological mechanisms, and recommendations for exercise prescription. *J Aging Res* 2020; **2020:** 1407896.

39 Casaletto K, Ramos-Miguel A, VandeBunte A, et al. Late-life physical activity relates to brain tissue synaptic integrity markers in older adults. *Alzheimers Dement* 2022; **18:** 2023–35.

40 Casaletto KB, Lindbergh CA, VandeBunte A, et al. Microglial correlates of late life physical activity: relationship with synaptic and cognitive aging in older adults. *J Neurosci* 2022; **42:** 288–98.

41 Guarnera J, Yuen E, Macpherson H. The impact of loneliness and social isolation on cognitive aging: a narrative review. *J Alzheimers Dis Rep* 2023; **7:** 699–714.

42 Willroth EC, James BD, Graham EK, et al. Well-being and cognitive resilience to dementia-related neuropathology. *Psychol Sci* 2023; **34:** 283–97.

43 Palpatzis E, Locascio JJ, Palmer P, et al. Adaptive stress coping is associated with cognitive resilience in at-risk cognitively unimpaired older adults. *Alzheimers Dement* 2025; **21:** e70713.

44 Peng S, Roth AR, Apostolova LG, Saykin AJ, Perry BL. Cognitively stimulating environments and cognitive reserve: the case of personal social networks. *Neurobiol Aging* 2022; **112:** 197–203.

45 Smith L, Shin JI, López Sánchez GF, et al. Social participation and mild cognitive impairment in low- and middle-income countries. *Prev Med* 2022; **164:** 107230.

46 King ML. The neural correlates of well-being: a systematic review of the human neuroimaging and neuropsychological literature. *Cogn Affect Behav Neurosci* 2019; **19:** 779–96.

47 Graham EK, James BD, Jackson KL, et al. Associations between personality traits and cognitive resilience in older adults. *J Gerontol B Psychol Sci Soc Sci* 2021; **76:** 6–19.

48 Tautvydaitė D, Kukreja D, Antonietti J-P, et al. Interaction between personality traits and cerebrospinal fluid biomarkers of Alzheimer's disease pathology modulates cognitive performance. *Alzheimers Res Ther* 2017; **9:** 6.

49 Arenaza-Urquijo EM, Boyle R, Casaletto K, et al. Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimers Dement* 2024; **20:** 5695–719.

50 Garcia Castro J, Rubio-Guerra S, Casaletto KB, et al. Sex differences in the executive and behavioral reserve of autosomal dominant frontotemporal dementia. *Alzheimers Dement* 2025; **21:** e70070.

51 Eissman JM, Dumitrescu L, Mahoney ER, et al. Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. *Brain* 2022; **145:** 2541–54.

52 Gaspar PM, Campos-Magdaleno M, Pereiro AX, Facal D, Juncos-Rabadán O. Cognitive reserve and mental health in cognitive frailty phenotypes: Insights from a study with a Portuguese sample. *Front Psychol* 2022; **13:** 968343.

53 Phongpreecha T, Godrich D, Berson E, et al. Quantitative estimate of cognitive resilience and its medical and genetic associations. *Alzheimers Res Ther* 2023; **15:** 192.

54 Thibaut P, Mwamuka R, Nyamayaro P, et al. Cognitive performance in depression in low- and middle-income countries: a systematic review with meta-analytic components. *J Affect Disord* 2023; **342:** 16–32.

55 Gbessemehlan A, Guerchet M, Helmer C, et al. Association between visual impairment and cognitive disorders in low-and-middle income countries: a systematic review. *Aging Ment Health* 2021; **25:** 1786–95.

56 Rabin JS, Schultz AP, Hedden T, et al. Interactive associations of vascular risk and β-amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard Aging Brain Study. *JAMA Neurol* 2018; **75:** 1124–31.

57 Rundek T, Tolea M, Ariko T, Fagerli EA, Camargo CJ. Vascular cognitive impairment (VCI). *Neurotherapeutics* 2022; **19:** 68–88.

58 Köbe T, Gonneaud J, Pichet Binette A, et al. Association of vascular risk factors with β-amyloid peptide and tau burdens in cognitively unimpaired individuals and its interaction with vascular medication use. *JAMA Netw Open* 2020; **3:** e1920780.

59 Ahangari N, Fischer CE, Schweizer TA, Munoz DG. Cognitive resilience and severe Alzheimer's disease neuropathology. *Aging Brain* 2023; **3:** 100065.

60 Guadagni V, Drogos LL, Tyndall AV, et al. Aerobic exercise improves cognition and cerebrovascular regulation in older adults. *Neurology* 2020; **94:** e2245–57.

61 He Z, Sun J. The role of the neurovascular unit in vascular cognitive impairment: current evidence and future perspectives. *Neurobiol Dis* 2025; **204:** 106772.

62 Wardlaw JM, Makin SJ, Valdés Hernández MC, et al. Blood–brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort study. *Alzheimers Dement* 2017; **13:** 634–43.

63 Hu H-Y, Ou Y-N, Shen X-N, et al. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. *Neurosci Biobehav Rev* 2021; **120:** 16–27.

64 d'Arbeloff T, Elliott ML, Knodt AR, et al. White matter hyperintensities are common in midlife and already associated with cognitive decline. *Brain Commun* 2019; **1:** fcz041.

65 Humphreys CA, Smith C, Wardlaw JM. Correlations in post-mortem imaging-histopathology studies of sporadic human cerebral small vessel disease: a systematic review. *Neuropathol Appl Neurobiol* 2021; **47:** 910–30.

66 Hansra GK, Jayasena T, Hosoki S, et al. Fluid biomarkers of the neurovascular unit in cerebrovascular disease and vascular cognitive disorders: a systematic review and meta-analysis. *Cereb Circ Cogn Behav* 2024; **6:** 100216.

67 Kadry H, Noorani B, Cucullo L. A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS* 2020; **17:** 69.

68 Xu X, Phua A, Collinson SL, et al. Additive effect of cerebral atrophy on cognition in dementia-free elderly with cerebrovascular disease. *Stroke Vasc Neurol* 2019; **4:** 135–40.

69 Tian Q, Sun J, Li X, et al. Association between sleep apnoea and risk of cognitive impairment and Alzheimer's disease: a meta-analysis of cohort-based studies. *Sleep Breath* 2024; **28:** 585–95.

70 Zavecz Z, Shah VD, Murillo OG, et al. NREM sleep as a novel protective cognitive reserve factor in the face of Alzheimer's disease pathology. *BMC Med* 2023; **21:** 156.

71 Jaramillo Ramos JJ, Galindo Pupo NM, Mena D, et al. Cognitive decline in chronic inflammatory conditions: exploring links between systemic inflammation and neurodegeneration. *Cureus* 2025; **17:** e88397.

72 Pappalettera C, Carrarini C, Miraglia F, Vecchio F, Rossini PM. Cognitive resilience/reserve: myth or reality? A review of definitions and measurement methods. *Alzheimers Dement* 2024; **20:** 3567–86.

73 Bocancea DI, van Loenhoud AC, Groot C, et al. Measuring resilience and resistance in aging and Alzheimer disease using residual methods: a systematic review and meta-analysis. *Neurology* 2021; **97:** 474–88.

74 Boyle R, Connaughton M, McGlinchey E, et al. Connectome-based predictive modelling of cognitive reserve using task-based functional connectivity. *Eur J Neurosci* 2023; **57:** 490–510.

75 Song S, Stern Y, Gu Y. Modifiable lifestyle factors and cognitive reserve: a systematic review of current evidence. *Ageing Res Rev* 2022; **74:** 101551.

76 Carrigan M, Bocancea DI, Vogel J, et al. A novel approach to resilience and its links with education and Alzheimer's disease genetics. *Alzheimers Dement* 2025; **21:** e70379.

77 Cole JH, Marioni RE, Harris SE, Deary IJ. Brain age and other bodily 'ages': implications for neuropsychiatry. *Mol Psychiatry* 2019; **24:** 266–81.

78 Vemuri P, Decarli C, Duering M. Imaging markers of vascular brain health: quantification, clinical implications, and future directions. *Stroke* 2022; **53:** 416–26.

79 Wang J, Huang Q, Chen X, et al. Prediction of longitudinal synaptic loss in Alzheimer's disease using tau PET and plasma biomarkers. *Alzheimers Dement* 2025; **21:** e70333.

80 Endo H, Ono M, Takado Y, et al. Imaging α-synuclein pathologies in animal models and patients with Parkinson's and related diseases. *Neuron* 2024; **112:** 2540–2557.e8.

81 Casaletto KB, Staffaroni AM, Wolf A, et al. Active lifestyles moderate clinical outcomes in autosomal dominant frontotemporal degeneration. *Alzheimers Dement* 2020; **16:** 91–105.

82 Williams ME, Fennema-Notestine C, Bell TR, et al. Neuroimaging predictors of cognitive resilience against Alzheimer's disease pathology. *Ann Neurol* 2025; 97: 1038–50.

83 Sadiq MU, Langella S, Giovanello KS, Mucha PJ, Dayan E. Accrual of functional redundancy along the lifespan and its effects on cognition. *Neuroimage* 2021; **229:** 117737.

84 Ewers M, Luan Y, Frontzkowski L, et al. Segregation of functional networks is associated with cognitive resilience in Alzheimer's disease. *Brain* 2021; **144:** 2176–85.

85 Hu W, Wang Y, Xie Z, et al. Functional segregation-integration preference configures the cognitive decline against cerebral small vessel disease: an MRI study. *CNS Neurosci Ther* 2024; **30:** e70162.

86 Ersoezlue E, Perneczky R, Tato M, et al. A residual marker of cognitive reserve is associated with resting-state intrinsic functional connectivity along the Alzheimer's disease continuum. *J Alzheimers Dis* 2023; **92:** 925–40.

87 Benson G, Hildebrandt A, Lange C, et al. Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. *Alzheimers Res Ther* 2018; **10:** 109.

88 Boyle R, Klinger HM, Shirzadi Z, et al. Left frontoparietal control network connectivity moderates the effect of amyloid on cognitive decline in preclinical Alzheimer's disease: the A4 study. *J Prev Alzheimers Dis* 2024; **11:** 881–88.

89 Neitzel J, Franzmeier N, Rubinski A, Ewers M. Left frontal connectivity attenuates the adverse effect of entorhinal tau pathology on memory. *Neurology* 2019; **93:** e347–57.

90 Soldan A, Pettigrew C, Zhu Y, et al. Association of lifestyle activities with functional brain connectivity and relationship to cognitive decline among older adults. *Cereb Cortex* 2021; **31:** 5637–51.

91 Topiwala A, Suri S, Allan C, et al. Predicting cognitive resilience from midlife lifestyle and multi-modal MRI: A 30-year prospective cohort study. *PLoS One* 2019; **14:** e0211273.

92 Arenaza-Urquijo EM, Przybelski SA, Lesnick TL, et al. The metabolic brain signature of cognitive resilience in the 80+: beyond Alzheimer pathologies. *Brain* 2019; **142:** 1134–47.

93 Bauckneht M, Chincarini A, Piva R, et al. Metabolic correlates of reserve and resilience in MCI due to Alzheimer's Disease (AD). *Alzheimers Res Ther* 2018; **10:** 35.

94 Koops EA, Dutta J, Hanseeuw BJ, et al. Elevated locus coeruleus metabolism provides resilience against cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* 2025; **21:** e14385.

95 Lee H, Kim B-H, Lee EH, et al. Brain metabolic resilience in Alzheimer's disease: a predictor of cognitive decline and conversion to dementia. *Am J Geriatr Psychiatry* 2024; **33:** 678–88.

96 Svenningsson AL, Bocancea DI, Stomrud E, et al. Biological mechanisms of resilience to tau pathology in Alzheimer's disease. *Alzheimers Res Ther* 2024; **16:** 221.

97 Smailovic U, Koenig T, Kåreholt I, et al. Quantitative EEG power and synchronization correlate with Alzheimer's disease CSF biomarkers. *Neurobiol Aging* 2018; **63:** 88–95.

98 Brown CW, Chen H-Y, Panegyres PK. Electroencephalography in young onset dementia. *BMC Neurol* 2023; **23:** 202.

99 Katayama O, Stern Y, Habeck C, et al. Detection of neurophysiological markers of cognitive reserve: an EEG study. *Front Aging Neurosci* 2024; **16:** 1401818.

100 Al-Ezzi A, Arechavala RJ, Butler R, et al. Disrupted brain functional connectivity as early signature in cognitively healthy individuals with pathological CSF amyloid/tau. *Commun Biol* 2024; **7:** 1037.

101 Jack CRJ, Andrews SJ, Beach TG, et al. Revised criteria for the diagnosis and staging of Alzheimer's disease. *Nat Med* 2024; **30:** 2121–24.

102 Simuni T, Chahine LM, Poston K, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. *Lancet Neurol* 2024; **23:** 178–90.

103 Shahim P, Pham DL, van der Merwe AJ, et al. Serum NfL and GFAP as biomarkers of progressive neurodegeneration in TBI. *Alzheimers Dement* 2024; **20**: 4663–76.

104 Vollmuth C, Fiessler C, Montellano FA, et al. Incremental value of serum neurofilament light chain and glial fibrillary acidic protein as blood-based biomarkers for predicting functional outcome in severe acute ischemic stroke. *Eur Stroke J* 2024; **9:** 751–62.

105 Cross AH, Gelfand JM, Thebault S, et al. Emerging cerebrospinal fluid biomarkers of disease activity and progression in multiple sclerosis. *JAMA Neurol* 2024; **81:** 373–83.

106 Chouliaras L, Thomas A, Malpetti M, et al. Differential levels of plasma biomarkers of neurodegeneration in Lewy body dementia, Alzheimer's disease, frontotemporal dementia and progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 2022; **93:** 651–58.

107 Roccati E, Collins JM, Callisaya ML, et al. Physical activity and blood-based biomarkers of neurodegeneration in community dwelling Australians from ISLAND (Island Study Linking Ageing and Neurodegenerative Disease). *Alzheimers Dement* 2025; **17:** e70166.

108 Lee SM, Kim S, Jeong JH, et al. Impact of a multidomain lifestyle intervention on white matter integrity: the SUPERBRAIN exploratory sub-study. *Front Aging Neurosci* 2023; **15:** 1242295.

109 Lista S, Santos-Lozano A, Emanuele E, et al. Monitoring synaptic pathology in Alzheimer's disease through fluid and PET imaging biomarkers: a comprehensive review and future perspectives. *Mol Psychiatry* 2024; **29:** 847–57.

110 Guo Y, Chen S-D, You J, et al. Multiplex cerebrospinal fluid proteomics identifies biomarkers for diagnosis and prediction of Alzheimer's disease. *Nat Hum Behav* 2024; **8:** 2047–66.

111 Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015; **385:** 2255–63.

112 Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016; **388:** 797–805.

113 Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol* 2017; **16:** 377–89.

114 Richard E, Moll van Charante EP, Hoevenaar-Blom MP, et al. Healthy ageing through internet counselling in the elderly (HATICE): a multinational, randomised controlled trial. *Lancet Digit Health* 2019; **1:** e424–34.

115 Lenze EJ, Voegtle M, Miller JP, et al. Effects of mindfulness training and exercise on cognitive function in older adults: a randomized clinical trial. *JAMA* 2022; **328:** 2218–29.

116 Zülke AE, Pabst A, Luppa M, et al. A multidomain intervention against cognitive decline in an at-risk-population in Germany: results from the cluster-randomized AgeWell.de trial. *Alzheimers Dement* 2024; **20:** 615–28.

117 Yaffe K, Vittinghoff E, Dublin S, et al. Effect of personalized risk-reduction strategies on cognition and dementia risk profile among older adults: the SMARRT randomized clinical trial. *JAMA Intern Med* 2024; **184:** 54–62.

118 Sakurai T, Sugimoto T, Akatsu H, et al. Japan-multimodal intervention trial for the prevention of dementia: a randomized controlled trial. *Alzheimers Dement* 2024; **20:** 3918–30.

119 Moon SY, Park YK, Jeong JH, et al. South Korean study to prevent cognitive impairment and protect brain health through multidomain interventions via face-to-face and video communication platforms in mild cognitive impairment (SUPERBRAIN-MEET): a randomized controlled trial. *Alzheimers Dement* 2025; **21:** e14517.

120 Brodaty H, Chau T, Heffernan M, et al. An online multidomain lifestyle intervention to prevent cognitive decline in at-risk older adults: a randomized controlled trial. *Nat Med* 2025; **31:** 565–73.

121 Baker LD, Espeland MA, Whitmer RA, et al. Structured *vs* self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. *JAMA* 2025; **334:** 681–91.

122 Killeen BM, Wolfson AB. Antibiotics for acute bronchitis. *Am Fam Physician* 2020; published online Nov 1. https://www.aafp.org/pubs/afp/issues/2020/1101/od2.pdf.

123 Heffernan M, Andrews G, Fiatarone Singh MA, et al. Maintain your brain: protocol of a 3-year randomized controlled trial of a personalized multi-modal digital health intervention to prevent cognitive decline among community dwelling 55 to 77 year olds. *J Alzheimers Dis* 2019; **70:** S221–37.

124 Kuyken W, Weare K, Ukoumunne OC, et al. Effectiveness of the Mindfulness in Schools Programme: non-randomised controlled feasibility study. *Br J Psychiatry* 2013; **203:** 126–31.

125 Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. *Cochrane Database Syst Rev* 2021; **11:** CD013572.

126 Erickson KI, Donofry SD, Sewell KR, Brown BM, Stillman CM. Cognitive aging and the promise of physical activity. *Annu Rev Clin Psychol* 2022; **18:** 417–42.

127 Bellelli F. Cognitive interventions: symptomatic or disease-modifying treatments in the brain? *JAR Life* 2024; **13:** 60–64.

128 Woods B, Rai HK, Elliott E, et al. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst Rev* 2023; **1:** CD005562.

129 Zhou M, Wang X, Wang Z, et al. Effects of music imaging on older adults with mild cognitive impairment: a randomized controlled trial. *J Am Med Dir Assoc* 2025; **26:** 105821.

130 Lee S, Charles ST, Almeida DM. Change is good for the brain: activity diversity and cognitive functioning across adulthood. *J Gerontol B Psychol Sci Soc Sci* 2021; **76:** 1036–48.

131 Sommerlad A, Kivimäki M, Larson EB, et al. Social participation and risk of developing dementia. *Nat Aging* 2023; **3:** 532–45.

132 Burckhardt M, Watzke S, Wienke A, Langer G, Fink A. Souvenaid for Alzheimer's disease. *Cochrane Database Syst Rev* 2020; **12:** CD011679.

133 Aron L, Ngian ZK, Qiu C, et al. Lithium deficiency and the onset of Alzheimer's disease. *Nature* 2025; **645:** 712–21.

134 Pham AQ, Dore K. Novel approaches to increase synaptic resilience as potential treatments for Alzheimer's disease. *Semin Cell Dev Biol* 2023; **139:** 84–92.