Ageing without dementia: can stimulating psychosocial and lifestyle experiences make a difference?

Laura Fratiglioni, Anna Marseglia, Serhiy Dekhtyar

In a world with an ageing population, dementia has become an urgent threat to global health and wellbeing. Psychosocial and lifestyle factors, such as higher socioeconomic positions, longer times spent in education, greater occupational complexity, reduced stress at work, and engagement in mental, physical, and social activities, have been hypothesised to supply resilience against dementia. Although questions remain surrounding the role of these factors in the development of dementia, scientific advancements have considerably expanded our understanding of modifiable psychosocial and lifestyle factors and their neuroprotective and compensatory influences over a life course. Evidence from observational studies is robust enough to suggest that stimulating psychosocial and lifestyle factors are protective against dementia. And, although the corresponding evidence from intervention studies is still scarce, public health campaigns promoting psychosocial and lifestyle factors might improve the health and wellbeing of people aged 60 years and older.

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See In Context page 490

Aging Research Center, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm, Sweden (L Fratiglioni PhD, Prof A Marseglia PhD, S Dekhtyar PhD); **and Stockholm Gerontology Research Center, Stockholm, Sweden** (L Fratiglioni)

Correspondence to: Dr Serhiy Dekhtyar, Aging Research Center, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm 171 65, Sweden **serhiy.dekhtyar@ki.se**

Introduction

Ageing and dementia are closely related and overlapping processes. Ageing is the accumulation of biological deficits resulting from genetically and environmentally induced alterations that undermine the homoeostatic balance of the organism, progressively leading to physical and cognitive impairment.[1] Emerging perspectives on the ageing process also recognise the existence of homoeostatic repair mechanisms, which restrict the spread of damage across structural and functional levels. Thus, ageing can be considered an equilibrium between multifactorial stressors and resilience mechanisms.[2]

The onset of dementia begins gradually after years of progressive neurocognitive deficits due to multiple genetic and environmental factors.[3] Decline processes that will result in dementia are initially indistinguishable from normal cognitive ageing because of a lengthy preclinical stage[4] and the existence of an intermediate state known as mild cognitive impairment.[5] Yet, although dementia is an age-dependent condition, it is neither a normal part of ageing, nor an exacerbation of ageing.[6] Research into people who are 100 years old or older indicates that, even in this age group, a sizeable proportion is free from dementia.[7] Some studies have found that the age-specific incidence of dementia might have declined over the last 20–30 years,[8] potentially reflecting improved education and reduced cardiovascular burden. Thus, in dementia, much the same way as in ageing, there might be mechanisms able to delay or even prevent the onset of clinical disease. Identification of these resilience-enhancing factors represents one of the areas for intervention, especially considering the paucity of effective pharmacological treatment.

Aspects of individual lives, such as higher socioeconomic positions and mental stimulation at school and work, have been suggested to reduce dementia risk. These aspects, termed psychosocial factors because they relate psychological phenomena to the social environment,[9] have been hypothesised to facilitate access to resources[10] or limit the disuse and deterioration of cognitive function.[11] Equally, another set of contributors to ageing without dementia, termed lifestyle factors, has emerged, which emphasise deep social connection and engagement in mentally, socially, and physically stimulating activities.[12] We view resilience against dementia supplied by psychosocial and lifestyle factors as a broad construct involving mechanisms of both neuroprotection and compensation.[13] Neuroprotection entails resistance to brain damage and is reflected by the lower accumulation of neuropathological lesions. Compensation entails coping with pathology in the face of damage through the enhanced flexibility of functional networks, although initial differences with respect to vascular health and brain integrity might be relevant too.[14]

In our 2004 Review,[12] we tentatively suggested the resilience-building role of psychosocial and lifestyle factors in dementia. Yet, substantial gaps in scientific knowledge were identified, precluding conclusions about the role of these factors in ageing without dementia. Given the emergence of multiple new reports since then, a reassessment of the knowledge linking psychosocial and lifestyle factors with dementia is both necessary and timely. In this narrative Review, we provide an account of the most important findings linking the enrichment of psychosocial environments and lifestyles with resilience against dementia. We consider resilience as enabled not just by the absence of risk factors, but through engagement in activities promoting neuroprotection and compensation. Thus, although risk factors such as smoking, alcohol misuse, and traumatic brain injury are undoubtedly relevant for overall dementia risk, they are beyond the scope of this Review. Additionally, we focus primarily on dementia as a whole. Although Alzheimer's disease is the most common type of dementia, other subtypes of dementia, including vascular dementia, dementia with Lewy bodies, and frontotemporal dementia, are also relevant. The complexity of dementia is further underscored by the evidence indicating that neuropathological hallmarks of Alzheimer's disease often coexist with vascular lesions and other neurodegenerative alterations. Therefore, mixed

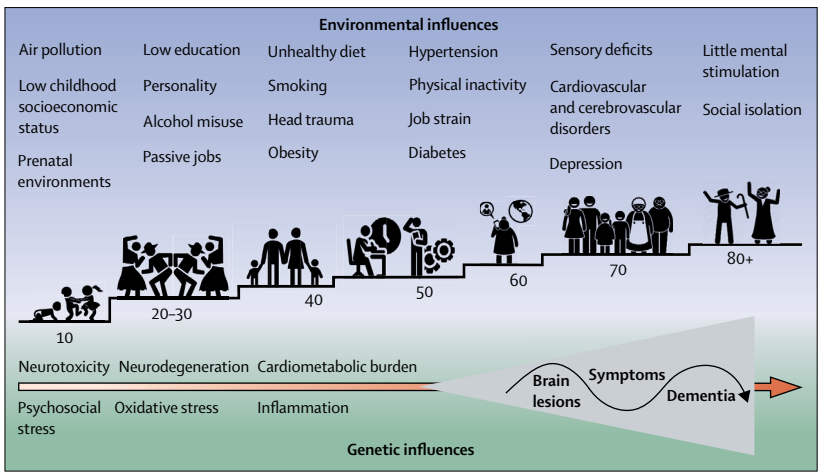

Figure 1: **A life course model of dementia development**
Starting from childhood and continuing into older age, genetic and environmental factors synergistically interact, triggering a cascade of pathological changes that eventually lead to symptom development and dementia onset. Environmental factors (placed against the purple background) and pathological processes (placed along the orange arrow) are not ordered according to the timing of occurrence or importance for dementia. A gradual saturation of the orange arrow throughout the lifecourse highlights the growing intensity of pathological processes (eg, neurotoxicity and oxidative stress), brought about by environmental and genetic factors. These pathological processes ultimately lead to lesions, symptoms, and dementia, although there are non-linearities and interindividual variabilities in the pathological, functional, and clinical changes during the transition to dementia, as represented by the curved arrow in the grey triangle. The life stages represented by the different icons along the lifecourse ladder are approximate and refer to typical life transitions in high-income countries. The timing of the different life stages is likely to be different in other contexts.

pathologies are a common underlying feature of dementia.[15] Finally, as dementia is being increasingly viewed as a lifelong disorder, we approach resilience-enhancing psychosocial and lifestyle factors in dementia by way of a life course model.

Life course model of dementia prevention

A life course model of dementia emphasises the stages during which exposure to co-occurring and interacting genetic, environmental, vascular, psychosocial, and lifestyle factors are likely to be the most clinically relevant (figure 1).[16] The risk of dementia might begin at conception,[17] given that many risk factors, including hypertension, obesity, and diabetes, can be traced to the fetal stage.[18] Similarly, neonatal nutrition has been associated with intelligence quotient and brain development throughout childhood and adolescence.[19] In turn, individuals with larger brains might be able to withstand greater underlying dementia pathology.[20] Differences in dementia occurrence according to adolescent personality have also been described, adding to the evidence on early-life influences in dementia.[21]

Modifiable factors might together account for as much as a third of all dementia cases.[22,23] The influences of modifiable factors have been incorporated into three interconnected strategies for dementia prevention: encouraging healthy lifestyles and behaviours; decreasing brain damage due to vascular, neurotoxic, inflammatory, or oxidative insults; and promoting mental and social enrichment (figure 2).[3] Psychosocial and lifestyle factors are relevant for all three strategies. The influences of these factors possibly unfold in accordance with the biopsychosocial model of frailty, which combines psychosocial adversity with biological deficits at a crucial stage of the ageing process,[24] culminating in a cascade of vascular and neurodegenerative changes. Compensatory mechanisms are probably involved too, with several conceptual hypotheses having been proposed, including cognitive reserve,[25] brain maintenance,[26] resistance,[14] and compensation[27] (figure 2).

Still, many questions surrounding the role of psychosocial and lifestyle factors in ageing without dementia remain, especially in the context of the life course perspective. First, is the importance of stimulating mental environments, such as prolonged education or complex occupational roles, simply a reflection of the underlying differences in premorbid intelligence in individuals with dementia? Second, what are the consequences of prolonged exposure to stimulation, as opposed to the consequences of specific life stages at which these experiences were acquired? Finally, what is the interrelationship between modifiable psychosocial and lifestyle contributors to resilience and the non-modifiable risk factors for dementia, such as genetic predisposition?

Answers to these questions will elucidate the life stage at which intervening in psychosocial and lifestyle factors is likely to be the most efficacious for the prevention of dementia, and whether this strategy is likely to be effective in all risk subpopulations. The literature that has emerged in the past 5 years has provided some answers to these pressing questions. Unfortunately, most of these findings have originated in high-income populations, which has a bearing on both the interpretation of the findings and the design of interventions in the global context. We begin by summarising the evidence concerning stimulating psychosocial and lifestyle experiences from three life periods (early life [0–25 years], midlife [26–59 years], and late life [≥60 years]). We then consider the entire life course and the interactions between these experiences and well known risk factors for dementia, both genetic and non-genetic.

Early life: childhood circumstances and education

Childhood circumstances have been proposed to affect cognitive health in late-life (≥60 years of age), although the evidence linking these circumstances with dementia is scarce and inconclusive.[29] Some longitudinal studies[30,31] from Sweden, which used both clinical and register-based diagnoses of dementia, have reported an association of childhood academic and cognitive performance with dementia risk. This association could be explained by the cognitive reserve hypothesis, the preserved differentiation model (that emphasises the stability of cognition throughout life),[32] or the pathways model, whereby better childhood cognitive abilities lead to improved midlife education, health, and behaviours that are ultimately responsible for the reduction in dementia risk.

By examining childhood socioeconomic situation, one longitudinal study[33] of 7916 men found an association between the mother's education with memory impairment and dementia in US men of all ethnicities. In another longitudinal study of 20 244 individuals, an index comprising housing quality, overcrowding, and the presence of books in the home at age 10 years was associated with the level (but not the change) of cognitive function in older (median 71 years) European individuals, according to data from the Survey of Health, Ageing and Retirement in Europe (SHARE).[34] Level-only effects of childhood socioeconomic situation on cognition were also reported in a longitudinal study of 859 Swedish twins and were likely due to genetic influences.[35] Adding parental occupation to a childhood socioeconomic situation index, another study of 24 066 people that used SHARE found an accelerated rate of cognitive decline in older adults aged 50–96 years with advantageous, affluent childhood socioeconomic situation.[36] This fast decline could be explained by the cognitive reserve model, which suggests that, once decline has begun, it will be faster in those with greater cognitive reserve, since these individuals had accumulated more brain damage.

Childhood adversity and negative life events have been suggested to increase the likelihood of dementia,[37,38] although not all studies have supported this finding.[39] The association could be attributable to multifactorial influences, including allostatic load leading to depression,[40] stress-induced dysregulation of the hypothalamic–pituitary–adrenal axis,[41] or the adoption of unhealthy behaviours. The role of childhood factors in dementia risk remains tentative. Childhood experiences might also influence downstream risk and protective factors, such as educational attainment, which, in turn, might contribute to dementia. To better understand the role of childhood circumstances in dementia risk, an approach that integrates these circumstances with other factors over the life course is required, and we will evaluate a few such attempts in this Review.[42,43]

A low educational level has been consistently linked with an increased risk of dementia.[44] More recently, attempts have been made to clarify the issues of the influence of the quantity and quality of education. One review of prospective studies has suggested that there is about a 7% decline in dementia risk per each additional year of schooling.[45] Interpreting education as a linear variable might be misleading because a change in 1 year of schooling is likely to have non-uniform effects depending on the structure of the educational hierarchy. The changes over time in both the access and quality of education[46] have probably changed the meaning of additional schooling across generations, leading some authors to suggest that the association between education and dementia could reflect differences in cognitive status across birth cohorts.[47] Discussion has centred around reconciling the role of education in dementia as opposed to the role of education in ageing-associated declines. Some have argued that the effect of education on cognitive ageing is negligible and that the threshold model of dementia can account for the observable relationship between education and dementia risk.[48] The threshold model suggests that dementia will not occur until a threshold level of brain damage is reached, although those individuals with a similar number of lesions might cross the threshold at different times, depending on their underlying reserve (in part supplied by education).[49,50] A study of clinicopathological data combined with cognitive testing from 1239 older adults (aged 75–79 years) found that education was neither related to the timing of accelerated cognitive decline, nor to the presence of neuropathological markers.[51] Also, education did not attenuate the association of higher neuropathological burden with more rapid cognitive decline, but instead only influenced baseline levels of cognition, a conclusion replicated in another longitudinal Swedish study.[52] By contrast, a different longitudinal study[53] found that the effect of education on cognitive decline was dependent on the extent of brain atrophy, with higher schooling being associated with slower cognitive decline in individuals with lesser atrophy, but with faster cognitive decline in those with greater atrophy. This finding was observed in a population characterised by high educational heterogeneity, adding to the evidence supporting the context-specific effects of schooling on dementia, which are especially relevant for international comparisons.

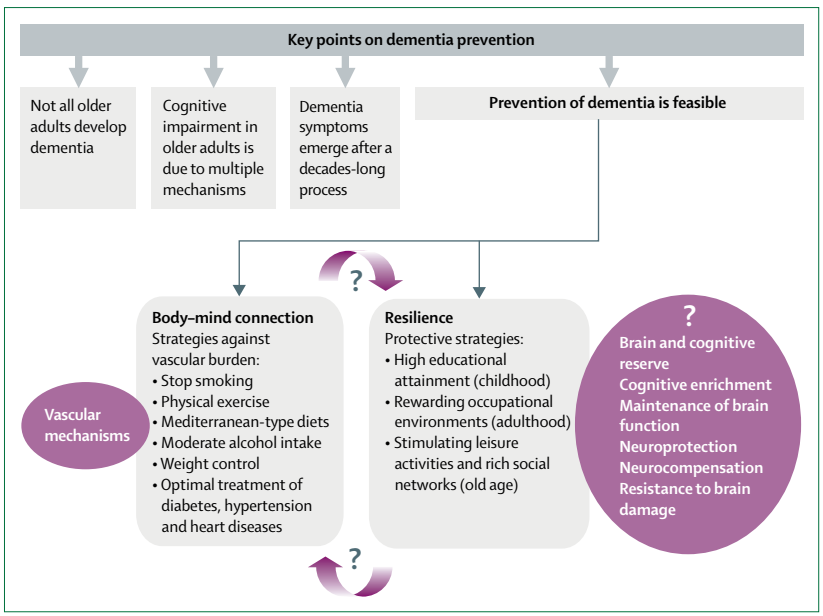

Figure 2: **Preventive strategies in dementia**
The question marks in grey refer to a hypothetical inter-relationship between the two dementia prevention strategies: one emphasising the control of cardiovascular risk factors (the body—mind connection) and the other stressing resilience-enhancing enrichment. These interactions, although plausible, have not yet been described and remain tentative. The question mark in white refers to yet unidentified brain mechanisms that underpin the potential resilience-type influences of psychosocial and lifestyle factors in dementia. The figure also highlights the absence of definitional clarity, with several conceptual models for resilience having been proposed. The key points on prevention were derived from Winblad et al.[28]

Even if the contribution of education to cognitive ageing is confined to influencing individual differences in cognitive skills that then persist into older age, education can nonetheless contribute to the delay of dementia onset. Furthermore, the role of education in dementia development ought to be evaluated within the context of a dynamic model whereby education affects (and is affected by) a multitude of interconnected factors across the life course.[54]

Midlife: psychosocial occupational environments and physical activity

Occupational environments are characterised by several psychosocial domains, including characteristics of job tasks (complexity) and the balance between workload and decision making autonomy (job strain). Several of these work attributes have been linked with dementia risk, although many of the studies on psychosocial working conditions in relation to dementia have originated in northern Europe, which limits the generalisability of the findings.[55]

The mental complexity of job tasks is typically measured by use of the job-exposure matrix that differentiates between the domains of data, people, and things.[56] Occupations characterised by high data complexity (the extent to which occupational tasks imply manipulating data) and high people complexity (the extent to which occupational tasks imply taking directions from, or instructing, people) have emerged as being protective against dementia.[57,58] This finding remained in twins discordant for dementia,[59] suggesting little genetic and shared familial confounding. Explanations for this result have involved the role of mental stimulation in promoting cortical plasticity and reduced atrophy of cortical areas, which would be deactivated in the face of low mental demands.[60] More recently, one cross-sectional study[61] of 323 participants has related occupational complexity with the neuropathological processes in dementia, reporting that, despite unchanged cognitive performance, individuals with jobs characterised by high complexity had decreased hippocampal volumes and increased whole brain atrophy. This finding suggests that these individuals have preserved cognitive function despite increased brain damage, as per the cognitive reserve model.

Job strain is often measured by use of the dimensions of job demands (the amount of workload and time limitations) and job control (the autonomy of decision making in doing work tasks).[62] These factors are generally combined to capture occupational strain at work, differentiating between active (high demand and high control), passive (low demand and low control), low strain (low demand and high control), and high strain (high demand and low control) occupations.[63] An increased risk of dementia has been reported in relation to greater job demands during midlife in Finland (although the association was attenuated over extended follow-up),[64] high-strain jobs and passive occupations in Sweden (relative to active occupations),[65] and high-strain occupations in the Swedish Twin Registry (although the effect of high strain was stronger for vascular dementia than Alzheimer's disease or all-type dementia and especially in combination with poor social support at work).[66] In this regard, one longitudinal study[67] from Sweden has suggested that social support at work could buffer the negative consequences of job strain on cognitive functioning after 60 years of age. Similarly, accelerated cognitive decline in individuals with low complexity, preretirement occupations has been found to be attenuated by late-life engagement in cognitive or physical leisure activities.[68] These findings highlight the need to consider that psychosocial and lifestyle factors are deeply interconnected throughout the entire life course.

Nowadays, much effort is being directed towards the promotion of physical exercise[69] because of the well-established benefits of exercise for vascular and cardiometabolic health. The effects of physical activity have been explored in relation to dementia too, although studies examining midlife physical exercise are still scarce. In the Finnish CAIDE study,[70] moderate and low levels of midlife physical activity during leisure time were associated with an elevated risk of dementia in comparison with the most active category of physical activity. In the subsequent CAIDE study,[71] maintaining high levels of physical activity over extended periods and increasing leisure-time physical activity after midlife emerged as especially protective against dementia. The relevance of leisure time in particular was emphasised in a systematic review that reported reductions in the risk of dementia if physical activity was done for leisure, but not if physical activity was related to work.[72] On the one hand, the little protection attained from work-related physical activity could be due to the clustering of greater physical demands in manual occupations and lower socioeconomic environments. On the other hand, engagement in physical activities in leisure time often coincides with other social and cognitive activities that could promote neuroprotection and compensation, providing additional protection against dementia.

The protective effects of physical exercise on dementia have been suggested in various observational studies.[73] Concerns have been raised about recall bias (whereby midlife physical engagement is misreported because of the individual's current health problems) and reverse causality (whereby physical activity is affected by changes associated with impending dementia). In accordance with these concerns, a study from the Whitehall II cohort, whose physical activity was recorded at 35–55 years of age and who were subsequently followed up for an average of 27 years for incident dementia (thus eliminating reverse causality and recall bias), did not report an association between physical activity and dementia risk.[74] Potential reverse causality has been suggested by a meta-analysis that reported an increased dementia risk in the physically inactive group when activity was measured less than

10 years before a diagnosis of dementia and no differences in dementia risk between groups when activity was measured 10 years or more before diagnosis.[75] However, regardless of the real effect of exercise on dementia or cognition, promotion of physical activity ought to continue. Practical to implement, physical exercise has been unequivocally shown to be beneficial for vascular and metabolic health, physical function, and psychological wellbeing, all of which have non-trivial relevance for cognitive health in older age.[76]

Late life: social network and stimulating leisure pursuits

Evidence linking deep social connection with reduced dementia risk emerged over 20 years ago.[77] Since then, several systematic reviews and meta-analyses[78,79] have confirmed the beneficial effect of large and supportive social networks on dementia. A review of the published literature that used 65 studies with at least 1 year of follow-up has found that the protective role of social connection in cognitive ageing and dementia remained regardless of duration of follow-up, sex, or cognitive domain (ie, global cognition, memory, and executive function).[80] Explanations for this protection have involved improved access to economic resources and informal care and support, reduced stress, promotion of healthy lifestyles and behaviours, and enhanced mental stimulation.[12,81]

Despite numerous consistent findings, the association between social connection and dementia risk is far from being fully understood. One of the caveats of this research relates to the heterogeneity of measurements of social connection. These measurements tend to conflate structural (eg, marital status and number of close contacts) and functional (eg, social support) aspects, but also involve subjective appraisals of social situations (eg, feelings of loneliness).[80] Uncertainties regarding the most relevant features of social life for dementia risk, and their underlying mechanisms, complicate the design of interventions. Furthermore, the validity of these instruments of measurement might be questionable, as illustrated by the frequent use of marital status or living situation as a proxy for social isolation, which might not accurately identify isolated people.[80] Much critique has centred around the issue of reverse causality, whereby incipient dementia leads to social withdrawal years before the diagnosis.[82] Although some studies have attempted to overcome this problem by excluding cases of incident dementia early in the follow-up period,[42,43] careful longitudinal investigations are still warranted.[78]

If the promising role of social connection in protecting against dementia is confirmed in robustly designed observational studies, interventions aimed at enhancing social connections need to follow. This path might encounter challenges too. Evidence from meta-analyses suggests that the effect size of social connection is small,[80] especially compared with programmes targeting physical function or cognitive activity. Enhancing social connections will probably need to be placed within the context of multidomain interventions,[83] which simultaneously target multiple risk-reducing psychosocial and lifestyle factors. Social connection, isolation, and loneliness all vary widely internationally.[84,85] Because of these differences and the growing burden of dementia in low-income countries, much work is required to contextualise socially based interventions for low-income and middle-income regions.

Many of the conclusions made for late-life social connections also apply to late-life leisure activities. Several systematic reviews[80,86] have shown the risk-attenuating effects of non-productive leisure activities on dementia. Leisure activities are typically measured according to composite categories that differentiate between mental, physical, and social domains of leisure, although studies vary in the underlying activities contributing to these domains. Thus, overall conclusions are tentative considering the heterogeneity of the approaches to measure leisure. The differences in measuring the intensity of leisure participation add to this heterogeneity.[86] The scale of participation frequency (eg, daily, weekly, and monthly) varies widely across studies, while the intensity of engagement is often categorised as low-medium-high by use of non-standardised procedures. To begin with, the division of leisure domains might be questionable, given that activities typically stimulate multiple modalities.[80] This issue might be exacerbated when estimating the contribution of activity participation independent of social connection. Some researchers have attempted to circumvent these challenges by using structural equation modelling to focus on the shared variance across several mentally, socially, and physically stimulating activities.[42,43] Others have involved older people (≥75 years) themselves in the designation of leisure domains to achieve greater instrument validity.[87] Another development in the field is the use of objective measures such as accelerometer data for physical leisure activities. A clinicopathological cohort study of 454 brain autopsies from the Rush Memory and Aging Project has shown that, in older adults, 7 day accelerometer measurements of physical activity were associated with better cognition, which appeared independent of Alzheimer's disease and other pathology measures, suggesting that physical leisure in late-life promotes the maintenance of brain function, despite the presence of brain damage.[88] Unfortunately, the study was cross-sectional and thus susceptible to reverse causality. Future longitudinal studies building on these new approaches are therefore needed.

Emerging perspectives that use a life course approach

In the previous section, we described several psychosocial and lifestyle factors that could supply resilience against dementia. These factors were largely discussed independently, although emerging life course perspectives on dementia highlight the interconnected nature of risk and protective factors.

Accounting for premorbid intelligence

It has long been unclear whether the beneficial role of extra schooling, or complex work environments, was merely a consequence of differences in previous cognitive abilities, known as preserved differentiation.[32] A series of observational and longitudinal studies were able to account for the potentially confounding influences of early cognition. In the Lothian birth cohort of 1936, high scores of occupational complexity with people and occupational complexity with things at midlife were associated with improved cognitive performance at a mean age of 70 years, even after accounting for intelligence quotient at age 11 years.[89] Similarly, a longitudinal Swedish cohort study[30] has found that higher education and occupational complexity with data (although not with people) remained protective against dementia after adjusting for school grades at age 10 years. This finding was replicated in another Swedish cohort of 440 individuals,[31] albeit with slight differences with respect to the effects of education, attributed by the authors to cohort differences across study populations. Another longitudinal study, also based on the Lothian birth cohort, has shown that, even after accounting for both intelligence at age 11 years and early adulthood (20–35 years) education, engagement in leisure activities in midlife was associated with higher levels of cognitive ability around the age of 79 years; greater physical activity in late adulthood was linked with less cognitive decline between the ages of 79 years and 87 years.[90] Thus, the influence of resilience-enhancing factors on cognition in older people and dementia is probably not confounded by initial differences in cognitive abilities, although other factors beyond intelligence can still be correlated with both psychosocial plus lifestyle factors and dementia risk.

The role of crucial periods and accumulated experiences

A life course approach enables the investigation of time windows and duration intervals over which a factor conveys protection against cognitive decline or dementia. A longitudinal study from the US Health and Retirement Survey examined socioeconomic status from three life stages (childhood [captured by parental educational attainment, father's occupation, and financial capital], early adulthood [captured by the completion of 12 or 16 years of schooling], and late-life [captured by income]) in relation to late-life memory. The study concluded that both early adulthood socioeconomic status and late-life socioeconomic status were relevant for memory function.[91] Early adulthood socioeconomic status predicted higher levels of memory function and late-life socioeconomic status predicted less decline in memory function.[91] Importantly, high socioeconomic status at all three life stages (compared with persistently low socioeconomic status over the life course) was linked with the highest baseline levels of cognitive function and the slowest decline.[91] This conclusion was further supported in another study[92] that used the same data but examined global cognition and not memory function, and thus showed the relevance of lifelong socioeconomic status in the function of other cognitive domains. The importance of cumulative engagement in stimulating, resilience-enhancing activities throughout life was further shown in a longitudinal Swedish cohort study, which reported the largest risk reduction for dementia in individuals with high scores on mental and social experiences from early life, midlife, and late life.[42] On the basis of these few life course-informed studies, two conclusions can be drawn. First, it is never too late to initiate interventions aimed at psychosocial and lifestyle factors that enhance resilience to dementia. Second, fostering engagement in stimulating activities and good habits is required at every stage of life,[93] given the interconnected nature of protective factors and the large benefits associated with cumulative engagement in stimulating activities.

Interactions between modifiable and non-modifiable contributors to resilience

The effects of modifiable resilience-enhancing psychosocial and lifestyle factors on dementia might vary in accordance with individual profiles of non-modifiable risk factors. Specifically, much interest has focused on the inter-relationship of these modifiable factors with genetic susceptibility, particularly the presence of the *APOE* ε4 allele, a recognised genetic risk factor for Alzheimer's disease and dementia.[94] A population-based study[95] of 6352 individuals from Rotterdam (Netherlands) examined dementia incidence over 15 years in relation to an index of modifiable factors (eg, regular physical activity, adherence to a healthy diet, no social isolation, no smoking, no diabetes, and no depression) and a genetic risk score comprising *APOE* ε4 and 27 other genetic variants. Lifestyle factors produced risk-reducing effects in those with low and intermediate, but not high, genetic risk. By contrast, a retrospective cohort study from the UK biobank that used a similar index of modifiable lifestyle factors, but included a more extensive, polygenic risk measure, concluded that a favourable lifestyle was associated with reduced dementia risk in individuals with both low and high genetic risk.[96] The SNAC-K longitudinal cohort study[43] of adults aged 60 years or older also showed that engagement in mentally and socially stimulating activities was protective independent of *APOE* ε4 status. Interactions between the *APOE* ε4 allele and psychosocial factors were explored in two longitudinal studies from the H70 cohort in Gothenburg, Sweden, which reported a moderation of genetic effects by job control (the amount of autonomy an individual has in their job),[97] but equivalent associations of *APOE* ε4 status with dementia across the levels of social network.[98] The few studies that investigated whether the genetic risk of dementia can be modified by enriching psychosocial factors and lifestyles differ in measuring genetic risk, dementia ascertainment, and sample sizes. Overall, understanding dementia in those most at risk is increasingly important and the focus should not only be

on people with genetic predispositions, but also on those with frailty and multimorbidity.[99]

Diabetes and stroke are the two age-related conditions known to affect the risk of dementia,[100,101] and their interactions with psychosocial and lifestyle factors have been explored, albeit in a small number of studies. Findings from the SNAC-K study have indicated that high levels of engagement in mentally, socially, and physically stimulating activities mitigate the risk of dementia associated with diabetes, with nearly a 70% reduction in diabetes-associated dementia risk attributable to the possession of a rich social network (large and frequent social contact deemed as satisfactory).[102] This finding was mirrored in a retrospective cohort study[103] of 1013 patients admitted to an acute stroke unit in Hong Kong that reported a reduced incidence of dementia after stroke in those who participated regularly in intellectual activities. These preliminary results, although in need of further confirmation, tentatively suggest that psychosocial and lifestyle factors that enhance resilience might represent a viable intervention target, especially in subpopulations at a high risk of dementia.

Conclusions and future directions

Evidence linking psychosocial and lifestyle factors with dementia has grown considerably in the past 5 years (table). A more widespread use of life course approaches has enabled researchers to start tackling issues of recall bias, reverse causality, and confounding by premorbid intelligence. Although methodological issues are far from fully resolved, observational evidence is robust enough to conclude that stimulating psychosocial and lifestyle factors are protective against dementia. Comprehensive engagement in stimulating activities from as early as childhood and throughout the entire life course is likely to be beneficial. Because the pathophysiology of dementia involves multiple processes, improvements in psychosocial and lifestyle factors can be of clinical significance as a result of the ability of these factors to interfere with several pathological pathways, especially in populations with genetic or cardiometabolic risk.

At least two key issues remain to be clarified in the future. First, more research is required to identify the biological mechanisms underlying the influences of psychosocial and lifestyle experiences on dementia. Do these mechanisms primarily involve vascular pathways, given the role of psychosocial and lifestyle factors in the expression of cerebrovascular disease? Do psychosocial and lifestyle factors have neuroprotective effects, restricting the development of primary neurodegenerative pathologies, as has been explored, but not universally confirmed?[105–110] Or can the effects of these factors on dementia primarily be explained by compensatory pathways that emphasise the preservation of cognitive function despite brain damage? How are these potential mechanistic influences expressed across the diverse spectrum of dementia?[111] In addition to better models of resilience, there is an urgent need for improved quantitative and qualitative precision in defining psychosocial and lifestyle factors, which would help to address problems of low specificity, multidirectionality, and collinearity that exist when assessing the influence of these factors. Addressing these questions will be of importance for designing effective, personalised preventive strategies and for devising global recommendations for populations with diverse risk profiles.

Although robust biological explanations need to be formulated, observational findings regarding the

	Evidence strength	Future directions
Psychosocial and lifestyle factors		
Early life (0–25 years)		
Childhood factors	Weak	Assessment of the link between childhood factors and later life risk factors and protective factors; disentanglement of the psychosocial and socioeconomic influences of childhood experiences; and understanding of mechanisms
Education	Strong	Assessment of the context-specific influences of education; disentanglement of the quality and quantity aspects of schooling; reconcilement of the conflicting findings for dementia risk versus those for cognitive ageing; and understanding of mechanisms
Midlife (26–59 years)		
Work complexity	Moderate	Exploration of the changes in mental demands throughout working careers; and understanding of mechanisms
Job strain	Moderate	Replication of the findings found in northern European contexts in other populations; investigation of the interplay between workplace characteristics and lifestyle and social factors; and understanding of mechanisms
Physical activity	Strong	Methodological improvements to reduce recall bias and reverse causality; assessment of the effects of changes in physical activity; use of novel instruments for measuring physical activity (eg, accelerometers); and understanding of mechanisms
Late life (≥60 years)		
Social network	Moderate	Improvements in the consistency of assessments of social network; to address reverse causality; and understanding of mechanisms
Leisure activities (mental, physical, and social)	Moderate	Reductions in the heterogeneity of leisure assessments; to address reverse causality; and understanding of mechanisms
Lifelong accumulated factors	Strong	Accounting for the influences of premorbid intelligence; assessment of the life stages at which protective influences are most pronounced; exploration of the interactions between accumulated factors and neuropathological lesions related to dementia; and understanding of mechanisms
Modifying the effect of other factors		
Genetic factors	Moderate	Confirmation of initial findings in other study populations; consideration of the interactions between genetic and psychosocial and lifestyle influences in cognitive impairment before dementia onset; and understanding of mechanisms
Other conditions (eg, diabetes and stroke)	Weak	Doing more relevant studies exploring this topic; consideration of the modifying role of psychosocial and lifestyle factors for the association between health conditions and cognitive change during the preclinical and prodromal dementia stages; and understanding of mechanisms

Evidence is ranked in accordance with the number of studies reporting an association between the given factor and dementia, and the methodology of the relevant studies. High evidence is characterised by many community-based studies, done in samples exceeding 1000 people, with clinical examination of dementia, reliable, objective measurement of exposures, collected from individuals before the probable onset of cognitive impairment, and with adjustment for known confounders. Criteria are derived from a previous evaluation of evidence for the influence of brain reserve in dementia.[104]

Table: **Summary of recent advancements and future directions**

Search strategy and selection criteria

We identified references for this Review by searches of PubMed for articles published between Jan 1, 1980, and Sept 1, 2019, with a focus on the period 2014–19. We also used references from the relevant articles identified via these searches. We used the search items "dementia", "prevention", "psychosocial", "lifestyle", "education", "childhood conditions", "work complexity", "job strain", "physical activity", "social network", "leisure activities", "life course", "APOE ε4", "stroke", and "diabetes". We restricted the search to articles published in English. We generated the final reference list on the basis of relevance to the topics covered in this Review.

resilience-enhancing effects of psychosocial and lifestyle factors need to be supported by interventional evidence. Unfortunately, interventional evidence has been much less conclusive.[3] Several possibilities could explain the differences between observational and interventional findings: administration of interventions at a time when a factor no longer confers risk-modifying effects, short treatment durations, or insufficient consideration of the influences of multiple interacting factors.[112] Although multidomain interventions[83] have attempted to mitigate some of these limitations, these interventions are still far from being implemented as large-scale public health campaigns, given that several questions remain about the efficacy, cost, and intensity required to change behaviours.[3] To start, clinicians could address particularly adverse situations, such as social isolation and loneliness. Although initial indications for alleviating loneliness in older adults are encouraging, especially when integrated interventions combining multiple therapeutic and treatment approaches are used,[113] conclusive evaluation of efficacy has not yet been done. Whether psychosocial and lifestyle factors could produce the same reduction in dementia risk is also unclear in low-income countries characterised by distinctly different educational opportunities, working conditions, and social bonds. These issues should be addressed in the future to make the prevention of dementia possible. In summary, dementia is the endpoint of multifactorial pathological processes that last for decades and these processes should be addressed by interventions to prevent or postpone the disease. Considering these factors, healthcare professionals can only, in part, rely on randomised control trials, which are often too short and too late, and include few people who are either too healthy or too diffuse in their risk profiles for the trial to show any benefit of psychosocial or lifestyle interventions.

Ultimately, although the paucity of unequivocal evidence from randomised control trials is a concern, it is clear that targeting psychosocial and lifestyle factors is straightforward, safe, and can also achieve other health benefits, including improved cardiovascular fitness and general wellbeing. If these strategies also result in an enhanced resilience against dementia, an even greater effect on public health will be achieved. Improvements in childhood circumstances, promotion of access to education, balance between demands and control at work, support for individuals to be physically, mentally, and socially active throughout life, and reductions in loneliness in older age will increase our chances to live longer, healthier, and, potentially, even happier lives.

Contributors

All authors contributed to the literature search and the writing and revision of this Review.

Declaration of interests

We declare no competing interests.

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