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Review

The impact of psychological stress and trauma on later-life cognitive function and dementia

D. Nilaweera[1], R. Freak-Poli[1 2], J. Ryan[1 3]

[1] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; [2] Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands; [3] INSERM, U1061, Neuropsychiatrie, Recherche Clinique et Epidémiologique, Univ. Montpellier, Montpellier, France

Dementia is an increasing global issue, currently affecting an estimated 50 million people worldwide. This number is predicted to increase to 82 million by the year 2030, due to the ageing global population. Theoretically, preventing late-onset dementia may seem extremely difficult as the greatest risk factor, age, is unmodifiable. However, it is estimated that a third of dementia cases could potentially be prevented or delayed by removing or reducing modifiable risk factors. Increasing evidence suggests that chronic stress, which may arise from experiencing a traumatic event or daily stress, may be a potential risk factor for dementia. Whilst it may not play a vital role in causing the syndrome, stress may contribute to the progression of cognitive decline, which is the main symptom of dementia. The primary stress hormone, cortisol, may have detrimental effects on cognitive brain regions when its levels are elevated for long durations. Preliminary evidence suggests that stress may have different effects on brain structure and function, depending on the individual's age when exposed to the stress. Stress during early and later life may lead to more permanent brain changes, which may contribute to cognitive decline in later life. Limited evidence links chronic stress or major trauma at specific stages of the lifespan, with cognitive decline and incidence of dementia. Whether or not an accumulation of stress across the lifespan influences later life cognition and risk of dementia, still remains to be determined. Understanding to what extent stressful events are risk factors for later-life cognitive decline and dementia will be crucial to the implementation of targeted psychosocial interventions efforts.

Key words: Stress, Trauma, Post-traumatic Stress Disorder, Cortisol, Dementia, Alzheimer's Disease

MENTAL STRESS AND TRAUMA

Mental stress refers to a state of strain and pressure on cognitive processes [1]. In response, the body alters its physiology in order to deal with the stressor. This innate mechanism, termed 'eustress', is advantageous and allows perceived threats to be dealt with immediately [2]. However, the long-term exposure to these hormones can cause 'distress' to the individual, and can increase their risk of various physical and mental diseases. Mental stress is common and has huge social and economic impacts. A commonly experienced daily stressor in adults includes workplace stress [3]. In 2002, the European Union estimated the annual economic burden of workplace stress within EU-15 countries (including the UK) to be €20 billion. In the US alone, workplace stress costs $300 billion annually, when taking into account factors such as the loss of productivity and healthcare costs [4].

Traumatic events from witnessing or being part of often life-threatening situations can also lead to chronic and severe stress which, in a small proportion of people, can clinically manifest in the form of Post-Traumatic Stress Disorder (PTSD) [5]. PTSD is a chronic and highly debilitating psychiatric disorder which can manifest in different ways including flashbacks, avoidance

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Correspondence: Joanne Ryan, School of Public Health and Preventive Medicine, Monash University, 99 Commercial Road, Melbourne, 3004 Victoria, Australia. E-mail: joanne.ryan@monash.edu

behaviour and negative alterations in cognition. Common traumatic events in children under 18 years include sexual victimisation and witnessing violence [6]. On a global level, the most common adult traumatic events include the unexpected death of a loved one and vehicle-related accidents [7]. An estimated 28-90% of adults in the developed world will encounter at least one traumatic event throughout their lifetime. A recent analysis of 26 World Health Organisation World Mental Health Surveys, across 24 countries, estimated the global prevalence of PTSD to be 3.9% [8].

Both stress and traumatic events can have immediate and long-lasting negative effects on the brain and can alter the structure of regions involved in cognition [9]. Indeed, there is some evidence to suggest that stress and trauma can negatively affect cognitive function, in particular when these occur at sensitive periods of the life (i.e. critical periods of brain development in childhood, and brain decline in old age) or when there is an accumulation of stress over the lifetime [10]. The effects of stress and trauma on cognitive function in later life and the risk of dementia, will be the focus of this review.

Mechanisms of the stress response

Mental stress elicits a threat to the body's natural homeostatic processes [2]. In response, the body aims to restore equilibrium by neutralising this threat with a combination of physiological and behavioural responses. Collectively this is known as the "adaptive stress response". The adaptive stress response is mainly mediated by two biological mechanisms - the Hypothalamic Pituitary Adrenal (HPA) axis and the sympathetic nervous system. Specifically, the HPA axis mediates the slow-onset stress response, whilst the sympathetic nervous system mediates the acute stress response to an immediate danger, otherwise known as the 'fight or flight' response [11]. The mechanisms of both systems are outlined in Figure 1, and results in the release of stress mediators via the adrenal gland. The HPA axis is characterised by the release of corticotropin-releasing

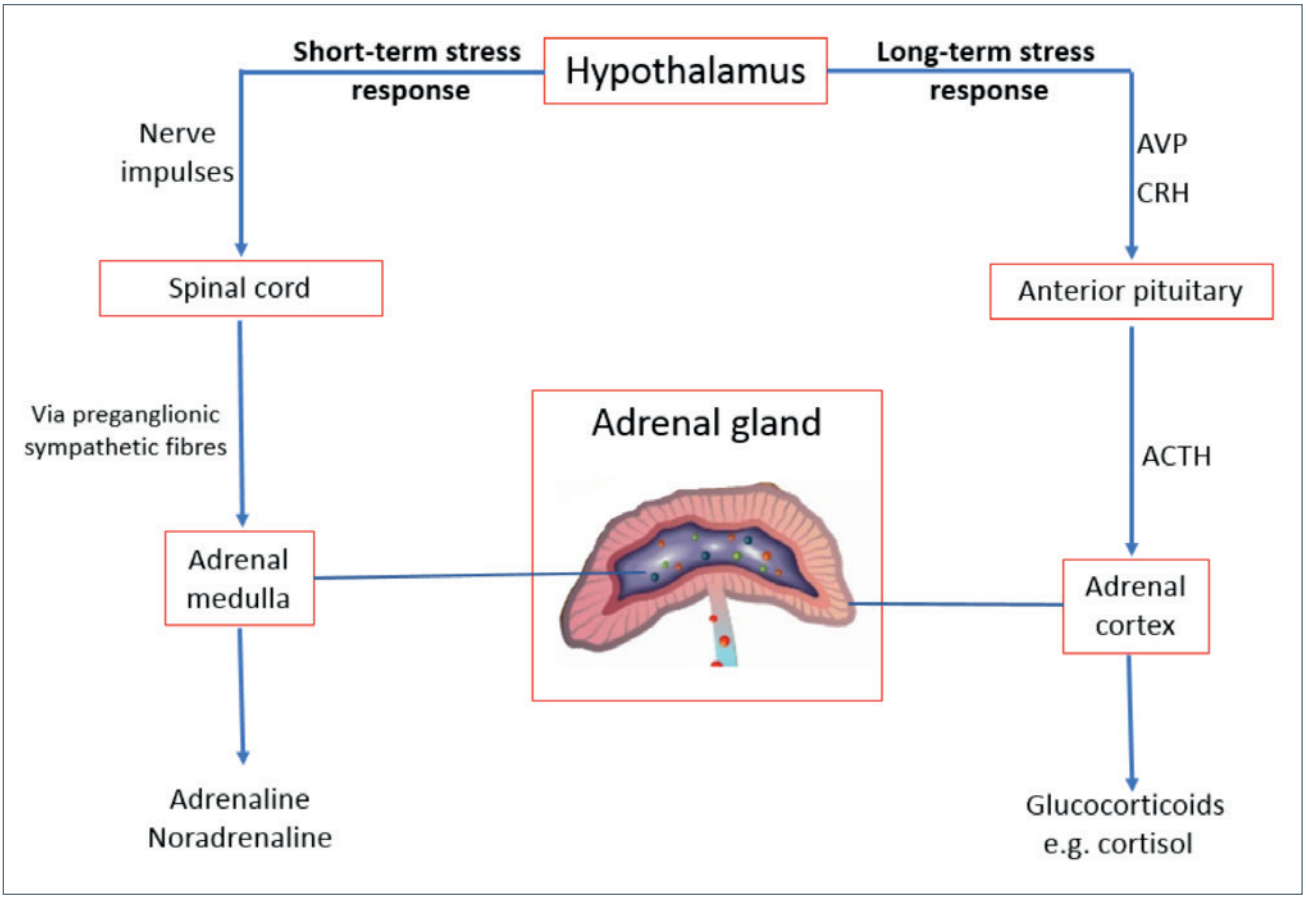

Figure 1. Short-term and long-term stress response. Shows the mechanisms of the short-term stress response mediated by the sympathetic nervous system, and the long-term stress response mediated by the HPA axis. Both responses are regulated by the hypothalamus, and result in the release of stress mediators by the adrenal gland. The adrenal cortex releases glucocorticoids in the HPA axis pathway, whilst the adrenal medulla releases adrenaline and noradrenaline via the sympathetic nervous system.

hormone (CRH) and vasopressin (AVP) by the paraventricular nucleus in the hypothalamus. Both hormones promote the secretion of adrenocorticotropic (ACTH) from the anterior pituitary to the systemic circulation, where it triggers the synthesis and release of the primary class of stress hormones, glucocorticoids, from the adrenal cortex. Glucocorticoids act to redistribute energy to enable the body to respond to the actual/perceived threat [12]. These responses include increasing cardiovascular, respiratory, metabolic, and behavioural responses in the body. Similarly, these responses are regulated by the short-term stress response – the sympathetic nervous system. Nerve impulses from the hypothalamus are relayed to the spinal cord, and travel through pre-ganglionic fibres to the adrenal medulla [13]. This results in the release of adrenaline and noradrenaline noradrenergic neurons in the adrenal medulla [13]. The HPA axis and sympathetic nervous system also interact with each other to trigger the adaptive stress response. This joint action is mediated by the corticotropin-releasing hormone. This is a hormone responsible for relaying signals to neurons, which causes the release of pro-opiomelanocortin (POMC) in the arcuate nucleus of the hypothalamus [14]. In turn, this inhibits the sympathetic nervous system. Similarly, noradrenergic neurons in the sympathetic nervous system can relay signals to the arcuate nucleus to regulate neurons which produce corticotropin-releasing hormone.

Complications of chronic stress

The adaptive stress response can be beneficial when improving personal performance to overcome short-term stressful events [2]. Contrarily, distress is related to chronic stress and results when stress overuses and diminishes the integrity of the HPA axis and the sympathetic nervous system. As stress redistributes energy to certain tissues, chronic stress may deprive other tissues, leading to detrimental physiological effects. This phenomenon is known as allostatic load, or 'wear and tear,' and can lead to complications such as inflammation, and may also play a role in cognitive decline [15]. For example, cortisol, the primary glucocorticoid of the human stress response, influences memory in a dose-dependent fashion [16]. Intermediate levels of cortisol has been shown to consolidate memory in order to respond to the perceived threat. However in high levels, cortisol can have a negative effect on cognition [17].

Chronic stress and cognitive brain regions

There is some evidence that increased levels of cortisol, resulting from acute and chronic exposure to stress, are negatively associated with cognitive processes including learning and memory [16]. For example, hyperactivity of the HPA system has been observed in those with self-reported memory loss [18]. It has been suggested that increased cortisol may affect cognitive processes due to the abundance of glucocorticoid receptors in brain regions associated with these cognitive processes, including the hippocampus, amygdala and prefrontal cortex [19]. These are also the main brain regions affected in AD and dementia.

The hippocampus has been well characterised in the stress response as it contains the greatest concentration of cortisol receptors within the brain, possibly due to its role in regulating the negative feedback mechanism of the HPA axis. Its primary role includes the formation of long-term memory through processes such as long-term potentiation [20]. Studies have shown a correlation with dysregulated long-term potentiation and elevated cortisol, which may result in hippocampal atrophy and decreased cognition [21 22]. Elevated cortisol and hippocampal atrophy have both also been noted in AD and dementia [23 24]. Imaging studies of patients with AD show decreased levels of hippocampal grey matter (which is comprised of neuronal cell bodies) [25]. The greater the severity of the disease, the more pronounced the atrophy.

These detrimental effects on the hippocampus may be explained by the Glucocorticoid Vulnerability Hypothesis [26]. This hypothesis suggests that the death of hippocampal neurons occurs due to a stress-induced dendritic retraction when exposed to elevated glucocorticoid levels. Elevated glucocorticoid levels binds and downregulates to glucocorticoid receptors to activate a negative feedback system which leads to a greater release of glucocorticoids [27]. An increase in glucocorticoids in turn increases extracellular glutamate levels, which can have a neurotoxic effect. Thus dendritic retraction may occur in hippocampal neurons to prevent further exposure to glutamate [26].

However, this seemingly protective mechanism has a downside as retracted dendrites may make the cell vulnerable during metabolic events (e.g. ischemia and hyperglycaemia) which can occur in the hippocampus, leading to cell death [28]. Hippocampal damage is greater when such metabolic events are introduced after periods of chronic stress (when glucocorticoid levels are elevated for an extended time), than periods of acute stress [29]. Conrad et al. demonstrated that rats with a history of chronic stress induced over 21 days suffered from greater hippocampal damage than rats injected once with the rodent form of cortisol-corticosterone [29]. Chronic stress is of particular interest to this study as it can be assumed to result from a lifetime accumulation of stress and trauma [15]. These findings suggest that older people are more likely to suffer from hippocampal damage in the face of metabolic events. In the case of no such metabolic event, cell death is avoided and

the dendritic retraction is reversible once glucocorticoid levels reduce [29].

Likewise, elevated glucocorticoids also causes reversible dendritic retraction in the prefrontal cortex [30]. The prefrontal cortex is involved in a wide range of processes (e.g. working memory and attention) which are required to execute goal-directed behaviour [31]. Chronic stress is associated with decreased prefrontal cortex grey matter, which impairs these functions and its ability to interact with the hippocampus to regulate working memory [32]. Similarly with the hippocampus, atrophy in the prefrontal cortex has also been noted in AD and dementia [33].

In addition, chronic stress decreases prefrontal cortex regulation of the amygdala, which has a role in the formation of emotional memory (when interacting with the hippocampus) [34]. Unlike in the hippocampus and prefrontal cortex, elevated glucocorticoids increases activity in the basolateral amygdala and promotes dendritic growth in an irreversible manner [35]. Thus this basolateral hypertrophy is likely to enhance emotional memory through an increase in synaptic connections, and contribute to the affective symptoms associated with stress (e.g. anxiety and depression) [36].

Critical periods of brain development susceptible to stress

The effect of stress on brain regions involved in cognition is suspected to vary throughout the lifespan [37]. It has been hypothesised that the most critical periods where the brain is most susceptible to damage by stress, is in early and later-life [10]. Brain regions involved in learning/memory are extremely vulnerable to cortisol during these life periods, as it is when the brain undergoes many changes during early-life and in the ageing process [38 39].

Changes to the ageing brain mainly include the reduction of total brain volume, which decreases at a rate of 5% per decade after 40 years of age [40]. This may result from neuronal cell death briefly described in “Section 3.3”. A reduction in dendritic growth and synapses has also been described during the ageing process. Several molecular mechanisms have been proposed to explain neurodegeneration in ageing. One mechanism includes a decline in levels of neurotransmitters such as dopamine [41]. In addition, decreased gene expression of various components involved in the release of neurotransmitters have also been reported [42]. Other mechanisms also include mitochondrial dysregulation and reactive oxygen species [43]. Despite the mechanism involved for neurodegeneration, these changes could make the ageing brain particularly susceptible to damage by cortisol.

In terms of early-life, the human brain is not fully developed at birth. For example, the hippocampus undergoes rapid growth until two years of age, and more delayed growth until age 14 [44]. The hippocampus also undergoes the most continuous change after birth, compared to other regions [44 45]. These changes include synaptic pruning and dendritic growth [46]. The amygdala and prefrontal cortex also undergo similar changes during childhood. The amygdala undergoes most changes during adolescence or sexual maturation [47 48]. The prefrontal cortex undergoes changes throughout early-life and fully matures at age 25 [47].

The effect of stress on these brain regions may induce lasting changes in adulthood [10]. Early-life stress has been shown to be associated with hippocampal atrophy in later life [49]. This has been noted in studies involving PTSD, although has not been investigated for milder forms of stress. A reduction in hippocampal size is observed in adults with PTSD related to childhood maltreatment, but not observed in children with PTSD related to mistreatment [50]. This suggests that trauma does not cause hippocampal damage immediately, but impairs its development over time. However, the age in which the trauma occurred can make a difference in the type of brain impairments which are accumulated in later life. For example, whilst childhood trauma showed an association with hippocampal atrophy in adulthood, trauma during adolescence showed an association with prefrontal cortex atrophy [51]. Thus the effect of stress differs depending on the stage of brain development the individual is experiencing. In contrary to the prefrontal cortex and hippocampus, early-life stress is associated with increased amygdala activity [52]. For example, adults raised in a negative family environment displayed greater amygdala activity and decreased cortical activity in comparison to adults raised by more nurturing families [53].

A number of animal studies also suggests that early-life stress may induce cognitive deficits in adulthood [38]. Maternal deprivation is commonly used to show this link as disruptions to standard maternal care is the main source of early-life stress [54]. For example, one study showed that maternally deprived rats in early life performed worse in cognitive tasks associated with the hippocampus in mid-adulthood rather than young adulthood [55]. Stress induced hippocampal damage occurred over-time, with its functional effects seen in later-life. However, there are opportunities to reverse the effects of early-life stress in the rat model [56]. In these models, hippocampal volume can be restored and cognitive deficits can be reversed, when introducing pharmacological intervention or social housing to maternally deprived pups [57]. The possibility to reverse the effects of early-life stress has also been observed in humans, as supported by observational studies in institutionalised children [58]. Children raised in nurturing

households after being institutionalised performed better on cognitive tasks compared to those still being institutionalised [59].

ASSOCIATIONS BETWEEN CHRONIC STRESS, COGNITION AND DEMENTIA

As discussed above, elevated cortisol from chronic stress may be associated with the atrophy of brain regions such as the hippocampus and prefrontal cortex. This may lead to declined cognition and symptoms associated with dementia, as atrophy in these brain regions are also observed in AD [60]. In addition, elevated cortisol levels have been shown to promote an increase in AD neuropathology and is also observed in the natural ageing process [61]. The strongest evidence is observed in animal studies. In mouse models of AD and in vitro studies, elevated levels of glucocorticoids are associated with an increased expression of amyloid precursor protein and β-secretase, thus shifting the amyloid precursor protein processing towards the pathogenic, amyloidogenic pathway [62]. This glucocorticoid-induced increase in the amyloidogenic pathway and hence amyloid plaques, is suggested to influence downstream tau pathology and the formation of neurofibrillary tangles [63]. Further animal studies also show evidence to suggest that elevated amyloid precursor protein, amyloid plaques, and abnormal tau are linked with cognitive impairment through the process of neuronal death and synaptic dysfunction in brain areas involved in learning and memory [64]. Cortisol may interact with amyloid plaques and further exacerbate cognitive impairment in learning than amyloid deposits alone, regardless of other factors [65].

These animal studies are consistent with the limited findings of studies in humans which suggest that chronic stress and elevated cortisol is associated with negative effects on both cognitive outcomes and risk of AD. This is best illustrated by two large-scaled and prospective longitudinal studies, which are most ideal to determine this association. The first study by Johansson et al. analysed a Swedish female population (n = 1415) over 35 years [66]. Participants were asked to self-report frequent stress in the last 5 years at 3 time points. Diagnosis of dementia subtype by neuropsychiatric examination was also performed at each of these time points. Various potential risk factors for dementia (e.g. smoking and socioeconomic status) were adjusted for in their analyses. They found an association between self-reported frequent stress during mid-life, and an increased likelihood of both early and late onset dementia. In particular, the incidence of dementia increased according to the amount of times the participants reported stress at the three different time points. Participants who reported frequent stress at all 3 time points had a greater likelihood of developing dementia (particularly AD) than participants who reported stress at only 2 or 1 time points (HR = 2.7, 1.7, 1.1 respectively). This supports the notion that chronic stress across the lifespan may be a risk factor for dementia. However, there are some limitations to consider. Firstly, the study cannot be generalisable to the male population, despite dementia being more prevalent in the female population [67]. In addition, the study focused solely on the frequency of common everyday stress and did not take into account more severe stress (e.g. arising from traumatic events). To date, there are no longitudinal studies which combine both common and severe stressors, to investigate the association between stress and incidence of dementia.

The second longitudinal study investigated morning plasma cortisol levels across a period of 6 years as a marker for chronic stress [68]. This prospective cohort study (n = 416) observed cognitively normal adults over the age of 60 with preclinical AD, as identified by the presence of high levels of amyloid plaques via neuroimaging techniques. Likewise to the previous study, various potential risk factors for AD were accounted for in their analyses. Their results found that adults with preclinical AD and high plasma cortisol levels, had lower cognitive scores than adults with preclinical AD and low plasma cortisol levels, across the 6 year period. This supports the notion that chronic stress, which is related to elevated cortisol over a significant duration (6 years), is only associated with cognitive decline in the presence of AD neuropathology. This also supports animal findings that cortisol accelerates cognitive decline associated with AD [65]. However, unlike the previous study, this study cannot be generalised to other types of dementia. A second limitation to this study, is that cortisol levels were only collected in the morning across the 6 year period. Cortisol levels naturally fluctuate throughout the day in order to regulate the wake-sleep cycle, with its level highest in the early morning [69]. Diurnal collection of cortisol may have produced more accurate results.

The role of cortisol in AD has also been observed in post-mortem studies, which is the only method, to date, that can provide an accurate diagnosis of AD [70]. One study observed significant increases in cortisol collected from cerebrospinal fluid after death, in early-onset AD patients, compared to age matched controls [71]. Interestingly, this association was not observed in late-onset AD patients compared to their age matched controls. This may be due to the natural increase of cortisol, with age, even in the absence of dementia, and may explain the normal decline in cognition in the elderly [72].

The HPA axis naturally increases in activity with age [73]. Several studies indicate that diurnal cortisol levels are significantly higher in older adults [17]. Cortisol may facilitate cognitive decline in the normal ageing process, as neuroimaging studies indicate similar changes to the brain in AD and ageing [74]. In ageing, there is grey matter reduction in the hippocampus and prefrontal cortex, with the majority comprising of prefrontal cortex atrophy [74]. In addition, a reduction in synaptic density has been noted in structures associated with cognition. These changes to brain structures are present in both the normal ageing process, and in early-onset AD which is independent of old age [75]. Thus, these findings suggest that cortisol facilitates cognitive decline in both situations.

Further human evidence linking stress with dementia and cognitive decline, include studies of PTSD populations. As mentioned earlier, PTSD is a disease characterised by chronic stress. In a large-scaled retrospective cohort study of 181,093 US veterans over 55 years, veterans diagnosed with PTSD were found to be more than twice as likely to develop dementia, than veterans without PTSD [76]. However it is important to note that PTSD is a unique, clinically significant condition that is diagnosed according to a set criteria [77]. These findings may not be directly applicable to either chronic or acute stress in the absence of a clinical PTSD diagnosis. However, due to the similar physiological responses in PTSD and chronic stress, they may be more applicable to chronic than acute stress [78]. In addition, both PTSD and dementia observe similar structural changes to the brain such as hippocampal and prefrontal cortex atrophy [79]. It is not yet determined if structural changes in both diseases are due to common risk factors. This study adjusted for some known risk factors e.g. low education levels. However, as there are further risk factors yet to be identified in both PTSD and dementia, an unconfounded causal link cannot be accurately established.

Similar associations between trauma and dementia have been observed in the Aboriginal Australian population, which have reported both higher exposure to stressful events (especially childhood trauma), and higher rates of dementia [80]. A cross-sectional study by Radford et al. surveyed 336 Aboriginal and Torres Strait Islander participants aged 60-92 years regarding the frequency of their childhood trauma, using a validated childhood trauma questionnaire. All-cause dementia and AD were both diagnosed clinically, in adherence with the National Institute on Aging-Alzheimer's Association criteria [81]. Higher frequencies of childhood trauma were associated with an increased risk of all-cause dementia (OR = 1.70, 95% CI 1.14-2.54) and AD (OR = 1.77, 1.08-2.91) [80]. These findings suggest that early-life trauma may contribute to dementia in later-life. This may be due to the vulnerability of the developing brain to cortisol, which may lead to lasting changes (as discussed in Section 3.4). However, the strongest evidence would ideally be derived from larger-scaled and prospective longitudinal studies following participants from childhood to adulthood. Due to time and financial constraints, such studies may not be feasible. Current longitudinal prospective cohort studies recruiting in mid-adulthood are likely to have too few participants with the development of dementia at present. Furthermore, longitudinal prospective cohort studies tend to focus on chronic diseases which are of high burden at the initiation of the cohort and as dementia is a relatively new burden. Finally, the effects of stress on health is a relatively new concept, and therefore longitudinal prospective cohort studies that undertook recruitment 15 years ago are unlikely to have a measure at baseline. These factors contribute to the lack of evidence regarding stress as a risk factor for dementia. No studies to date have investigated if not only early-life trauma, but the accumulation of stress and trauma across the lifespan, is associated with later-life dementia and cognitive decline.

CONCLUSIONS

There is an accumulation of evidence which links chronic stress or major trauma at specific stages of the lifespan with impairments in cognitive function. However whether or not an accumulation of stress over the lifetime influences later life cognition and the dementia risk (as well as the age of onset), remains to be determined.

Understanding to what extent stressful events are risk factors for later-life cognitive decline and dementia, as well as potentially modifiable factors which can help reduce this risk, will be crucial to the implementation of psychosocial interventions targeted on an individual basis (given a person's place of residence, social support and family networks). Delaying the onset and/or progression of dementia or helping an individual to maintain independence as long as possible, will be beneficial to the individual, their family, carers and the wider community.

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Conflict of interest

The Authors declare to have no conflicts of interest.

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