# Modifiable midlife risk factors for late-life dementia

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Dementia is currently defined as a disorder characterized by acquired cognitive impairment of sufficient severity to interfere with social and occupational functioning [1]. Alzheimer's disease (AD) is the most common type of dementia, followed by mixed vascular/AD and vascular dementia. The worldwide prevalence of dementia is estimated to be 35.6 million, with future projections as high as over 100 million by 2050 [2]. The impact of dementia is far reaching. It affects not only the health and well-being of the patient, but is also associated with a heavy caregiver burden, increased health service utilization and long-term care needs, as well as a drain on personal and societal and resources. Delaying the onset of dementia by one year through prevention efforts may reduce the overall prevalence by 9.2 million in 2050 [3].

The pathology of dementia develops over years before symptoms and deficits are experienced [4]. Therefore, epidemiologic studies of dementia need to be conducted at earlier points in the life course in order to assess modifiable risk factors that are operating in early and midlife [5]. Identifying these factors will likely show the greatest potential in effectively reducing the burden of dementia in subsequent decades through primary and secondary prevention efforts.

The risk for dementia is associated with both genetic and environmental factors. While there is potentially strong genetic risk [6], genetic factors are, of course, not modifiable at this time. Environmental factors may modify risk for dementia by affecting the timing of clinical expression of symptoms, even if they do not influence the overall presence or absence of pathology, by contributing to 'brain reserve' or 'cognitive reserve' [7,8]. Among the non-genetic, modifiable factors in midlife, vascular conditions, diet and exercise, and mental engagement are most consistently linked to the risk of dementia and will be reviewed here. A previous review [9] has addressed other non-genetic factors that are either less easily modified or have very limited data available. These factors include occupation, head injury, exposure to anesthesia, depression, personality, alcohol and tobacco use, hormone therapy, non-steroidal anti-inflammatory drugs, and *Ginkgo biloba*.

Evidence for the associations between vascular conditions, except diabetes mellitus and related conditions, and dementia suggests a nonlinear (U- or J-shaped) association, with high levels in midlife and low levels in late life being associated with elevated probability of subsequent dementia [9,10]. Potential mechanisms explaining the link between high midlife blood pressure and increased risk of dementia include atherosclerosis, white matter lesions (indicative of ischemia), as well as increased neuritic plaques and tangles in the neocortex and hippocampus, and hippocampal and amygdalar atrophy. The role of cholesterol in the pathology of dementia seems intuitively linked with the APOE ε4 allele that is associated with poorer transport and clearance of serum cholesterol resulting in elevated serum cholesterol at mid and late life. High total cholesterol may then lead to atherosclerosis, which impairs blood flow to the brain, and acceleration of AD neurodegeneration by affecting the metabolism of β-amyloid (Aβ) protein, which is seen in excess in AD brains and is the primary component of plaques. Type II diabetes mellitus, impaired insulin secretion, glucose intolerance, and insulin resistance in midlife have been shown to be associated with an increased risk for dementia. Three inter-related processes associated with diabetes that likely contribute to dementia symptoms include:

– Damage to the cerebrovasculature that may contribute to brain ischemia.

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– Altered metabolism of Aβ and tau leading to the formation of neuritic plaques and tangles.
– Elevated inflammatory factors and reactive oxygen species.

Additional prospective studies and clinical trials beginning in midlife are needed to determine if medications to control hypertension, hypercholesterolemia, and to improve glycemic control can reduce the prevalence of cognitive impairment and dementia. The most obvious mechanism linking overweight and obesity to higher dementia risk is through vascular-related conditions. However, adjustment for these conditions has not been shown to attenuate the association; suggesting that other factors (e.g., increased secretion of proinflammatory cytokines, hormones, and growth factors that cross blood-brain barrier from adipose tissue) may also independently contribute to the risk of dementia [9,10].

Diet is an important part of a healthy lifestyle and influences the risk of several diseases and the aging process in general. Few studies have examined the associations between midlife micro- (e.g., vitamins $B_6$, $B_{12}$, folic acid, and antioxidants) and macro-nutrients (e.g., fats and caffeine) and dementia risk [9]. No prospective studies of midlife $B_6$, $B_{12}$ and folic acid and the risk of incident dementia have been conducted, and the findings from late-life prospective studies and randomized trials of B vitamins on dementia have been inconsistent [11]. Midlife dietary intake of antioxidants through food sources have been examined in two studies. One study reported no protection against dementia with higher intake [12] and the other reported a lower risk of dementia [13]. Intake of antioxidants may reduce the risk of dementia by reducing cerebrovascular disease and/or decreasing oxidative stress and inflammation that contributes to changes in the brain with aging and pathological processes associated with dementia [14].

Moderate consumption of polyunsaturated fats at midlife has also been associated with a lower risk of dementia among ApoE ε4 carriers, while saturated fat increased the risk [15]. One randomized controlled trial of the effect of fish oil, which is a source of polyunsaturated fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), observed no overall effect of fish oil supplementation on cognitive performance in older adults. An exception was a small effect for APOE ε4 carriers and males for the specific cognitive domain of attention [16]. The primary mechanism may be through blood cholesterol levels; although studies in rodents suggest that dietary fat also may be involved in amyloid deposition [17].

Greater consumption of caffeine has been found to be associated with reduced risk of AD in a retrospective study that measured caffeine consumption over a 20 year period prior to AD assessment [18]. The beneficial effects of caffeine may be through mechanisms that reduce Aβ production [19], or by increasing the level of brain proteins important for learning and memory such as brain derived neurotrophic factor [20].

Finally, interactions of nutrients, or patterns of diet are being examined such as the Mediterranean diet. This diet is high intake of fruits, vegetables, whole-grain products, and fish with higher adherence in late-life associated with a reduced risk for AD [21]. Studies are needed to assess dietary patterns in midlife in relation to dementia risk.

The importance of physical activity in physical health is well known, but the role of physical activity in brain and cognitive health has only recently received attention. Two of three studies suggest that higher midlife engagement in physical activity is associated with a reduced risk of dementia and AD [22,23]. The third midlife study did not report such a relationship [24]; however, the discrepancy may be due to the measure of physical activity being based on both leisure-time and occupational physical activity. Only one randomized trial has been conducted to confirm the observational findings of the effect physical activity has on cognitive function in older adults. A modest reduction in cognitive decline was observed in those who were assigned to the 6-month physical activity intervention compared to usual care over an 18-month follow-up period [25]. Physical activity may benefit cognitive health through benefits seen in the cardiovascular system that extend to the cerebrovascular system or through increased neurogenesis, enhancement of brain cytoarchitecture (blood vessels, dendrites, microglia) and electrophysiological properties, increased brain growth factors, and a reduction in the formation of amyloid plaques in AD [26]. Specific recommendations with regard to the type, intensity, frequency, and duration of midlife physical activity that may most effectively reduce the risk of dementia await more research.

There is interest in whether mentally stimulating activity benefits brain and cognitive health, analogous to the well established benefits of physical activity on physical health. Only two studies to date have prospectively examined the role of midlife cognitive activities on the risk of dementia in AD. Both studies included a twin analysis to control for genetics and unmeasured early-life environment. The results of each of these studies suggest that higher

engagement in cognitively stimulating activities is associated with a reduced risk for dementia [27,28] and for AD in women [27]. This conclusion is generally supported in prospective studies of late-life cognitive activity [29], but evidence from randomized controlled trials involving cognitive training is mixed [30-32]. Engaging in mentally stimulating activities may be considered the most direct strategy to increase brain reserve by inducing neurogenesis and synaptogenesis, increasing hippocampal synaptic reactivity, enhancing cerebrovasculature, reducing brain Aβ deposition, reorganizing neurocognitive networks, attenuating the adverse effects of stress hormones on the brain, and modifying the association between white matter lesion density, reflective of small vessel disease, and cognitive performance [33]. While current evidence is promising, there is inadequate data to make any specific recommendations about which particular cognitive activities, their timing, their dosage, and their duration may offer protection against dementia.

Maintaining cognitive health in late life is a public health priority as the older adult population grows at an unprecedented rate. This review focuses on evidence for modifiable behaviors in midlife that may lower the risk of dementia in later life by contributing to brain/cognitive reserve and delaying the clinical expression of dementia symptoms. In summary, there is little definitive evidence that the risk for dementia can be modified through behavioral changes in midlife, however, managing cardiovascular conditions, eating a healthy diet, and staying physically and mentally active offer the most hope. Additional well-designed observational studies using the life course approach, and/or randomized controlled trials when feasible, will be needed before specific recommendations can be made to middle-aged adults regarding behavioral changes that may lower their future risk of dementia.

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