

Dementia: Risk Factors and Updated Review

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Abstract

With the tremendous rise in the aging population around the world, the prevalence of Major Neurocognitive Disorders is skyrocketing. In the same manner, the burden of the morbidity and mortality associated with the such disorders has been a global health problem. Most of the time, the cause of Major Neurocognitive Disorder is unknown. Our review article is an attempt to summarize the likely modifiable risk factors associated with the disorder. In this manner there could be insight into further confirmatory and exploratory evidence based studies of these factors for early intervention to prevent and delay the progression of full blown disease. Among the modifiable risk factors, the ones that have been discussed here are smoking, activity both physical and cognitive, cardiovascular risk factors, depression, traumatic brain injury and sleep.

Keywords: Major Neurocognitive Disorder, Modifiable Risk Factors

INTRODUCTION

While there are many causes of Major Neurocognitive Disorder including sudden, monophasic brain injury ("static encephalopathies"), this article deals with those disorders in which there is a progressive neurocognitive course caused by a combination of genetic and environmental risk factors leading to insidious and functional decline until death (1). Many risk factors for the occurrence and progression of dementia have been identified; early intervention may prevent and delay the progression of full blown dementia.

PREVALENCE

There has been a demographic shift in the trajectory of human aging, mainly due to people living longer and the aging of the "baby boomer" generation with relatively fewer newborns (2). A Delphi consensus study revealed that the prevalence of dementia rapidly increases from approximately 2-3% among those

aged 70-75 years to 20-25% among those aged 85 years or more (3). At present the global prevalence of dementia is estimated at 5-7% of the population aged above 60 years (4). There is variation in the prevalence and distribution of dementia around world probably due to cultural and socioeconomic differences among nations (5). Dementia was considered a less significant problem in the past. But today, with an aging populace, dementia represents a significantly greater societal and economic burden (6). In particular, it is a more widely recognized problem in low- and middle- income countries as this is the first time that their population is achieving a longer life expectancy (7). In many of these countries the incidence of dementia is expected to double by 2050 (5).

MODIFIABLE RISK FACTORS

The presence of modifiable risk factors helps to understand the mechanisms of mild cognitive decline and dementia (8). It also helps to identify

those individuals who are at greatest risk for developing the dementia. Thus, early intervention could be provided for initiating treatment and prevention for those high risk groups. Different studies reveal similar modifiable risk factors which include diabetes, mid-life obesity, mid-life hypertension, smoking, history of depression, sleep disturbance, hyperlipidemia, and traumatic brain injury (8-11).

SMOKING AND DEMENTIA

Smoking is a modifiable risk factor for several chronic illnesses; however, its long-term relationship with dementia is still controversial (12). Numerous past studies exploring the effect of smoking on cognitive outcomes were inconclusive as the majority of them showed weak or null associations (13-17). However, a number of other cohort studies revealed positive association between smoking and risk of developing dementia (18-21).

CARDIOVASCULAR RISK FACTORS

Several lines of evidence suggests strong correlation at mid-life of cardiovascular disease with dementia (9, 22, 23). Cardiovascular risk must be elevated over an extended time to impact the risk of dementia (23). The factors associated with increased cardiovascular risk during mid-life include obesity, diabetes, hypertension, dyslipidemia (24). While it was thought at one time that such factors raised only the risk of vascular dementias, it is now established that these same factors mitigate toward developing Alzheimer type dementia through enhanced accumulation of associated toxic proteins through cardiovascular risk factors at the microvascular level (8). A recent clinical study revealed that dementia is closely associated with cardiovascular disease, especially hypertension and atrial fibrillation (25). Hyperinsulinemia and elevated systolic blood pressure independently predicted white matter hyperintensities with associated cognitive decline in the middle-aged offspring of the patients with dementia (24). The additive effects of all the components of the metabolic syndrome is found higher than the individual component for the development of dementia in late life. Having more criteria for the metabolic

syndrome raises dementia risk greater than having fewer criteria.

Vlad and co-workers found a positive correlation between long-term nonsteroidal anti-inflammatory (NSAID) use and a lower incidence of Alzheimer's type dementia in a study of 50,000 veterans (26).

PHYSICAL AND MENTAL ACTIVITY AS PREVENTIVE FACTORS

The evidence linking physical inactivity with dementia risk has been largely based on educated assumptions. The common saying, "use it or lose it" makes common sense to many, but what established evidence exists for recommending physical activity as a protective factor. There are different mechanisms of protective effect of physical activity on cognition which include proper cerebral blood flow (27), elevation of aerobic capacity, adequate cerebral nutrient supply and brain-derived neurotropic factor that increases neuronal survival, enhances learning, and is a protective factor for cognitive decline (28,29).

Animal models of neuropsychiatric disorders have lended some objective support to the value of physical activity on prevention (30). For example, a murine model of hippocampal found increased cell numbers in animals which exercised (running paradigm) than controls (31). In an associated human study, number of footsteps was positively correlated with less decline on the Mini-Mental State Exam (32). Other studies have suggested that exercise be recommended not only as primary prevention but also as secondary prevention due to already demonstrated benefits on cardiovascular risk factors (33).

There is much interest in the potential value of cognitive stimulation strategies as a protective factor in dementia (34). Cognitive reserve appears to have a protective effect as demonstrated in Snowden's famous Nun Study (48). Cognitive reserve could act as a buffer to prevent destruction by amyloid, tau, and other toxic proteins (35). An important question, however, is can cognitive reserve be successfully enhanced by various mental activities (e.g., videogaming) to the point that it has demonstrable preventative effects on dementia

risk (36)? Recent meta-analyses indicate that computerized cognitive training is efficacious in global cognition, in select cognitive domains, and in psychosocial functioning in mild cognitive disorder (37), however evidence for a protective role in dementia remains limited.

SLEEP AND COGNITIVE FUNCTION

Hallmark symptoms of Alzheimer's include impaired hippocampus-dependent episodic memory, disrupted sleep, and altered circadian rhythms. Sleep and circadian disruption can impair hippocampus-dependent learning and memory (38). Brain interstitial fluid A-beta amyloid (the toxic form of amyloid associated with Alzheimer's type dementia) has been found to correlate with the degree of wakefulness in a murine model of sleep effects (39). Interstitial fluid A-beta levels are higher in acute sleep deprivation. Other studies indicated women in the lowest quartile of average sleep efficiency (<74%) had a 1.5-fold higher odds of developing cognitive decline (41). Longer average sleep latency and greater variability in both sleep efficiency and total sleep time were also associated with greater marked cognitive decline (40). Past studies have demonstrated that sleep disordered breathing is associated with increased risk of cognitive decline (41).

DEPRESSION AND COGNITION

Depression is the most common reason to seek psychiatric attention in elderly. Depression has been directly linked to decreased cognition. Dinez and co-workers studied late-life depression and risk of vascular dementia and Alzheimer's disease. In the 23 cohort studies included, their systematic review and meta-analysis of community-based cohort studies demonstrated that late-life depression was associated with a significant risk of all-cause dementia (42). This raises the question of whether depression treatment or prevention can reduce dementia risk. In a retrospective study using a mouse model, administration of a selective serotonin reuptake inhibitor led to reduction of interstitial fluid A-beta levels (43). This avenue of dementia prevention is ripe for further study.

TRAUMATIC BRAIN INJURY AND DEMENTIA

Age at injury is associated with the long-term cognitive outcome of traumatic brain injuries (44). Traumatic brain injury commonly results in diffuse axonal injury, accumulation of Amyloid and Tau, reduction in synaptic efficacy, breakdown of the blood brain barrier, inflammatory microglial activation, and cell death as well. Moderate to severe brain injury, including repetitive concussive injuries has been demonstrably associated with early cognitive decline (45). This study finding was implied in a 9 year Veteran study in which greater risk of cognitive degeneration is associated with a comorbid neuropsychiatric conditions including depression, post-traumatic stress disorder, and cerebrovascular disease (46).

FUTURE DIRECTION

There are numerous risk factors for dementia; however, the potentially important modifiable risk factors having consistent evidence of an association with dementia are diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment. If prevalence of the risk factors were reduced by 10% or 20% per decade over these 40 years, a substantial proportion of Alzheimer's disease cases could, theoretically be prevented (44). Thus by 2050, it has been estimated that a 10% reduction in these risk factors would decrease the incidence of Alzheimer's cases in the United States 8.7%, and globally by 8.3% (8.8 million) (44).

CONCLUSION

There is a high potential impact for implementing strategies focused on the modifiable risk factors for cognitive decline leading to mild cognitive impairment and dementia. Thus, addressing these risk factors at an appropriate time is highly recommended. Further confirmatory and exploratory evidence based studies are needed given the massive burden facing the global health burden.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work, and is solely responsible for the content

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