J Young Pharm, 2019;11(3):230-237
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Review Article

Preventing Dementia: Shifting Focus Towards Potential Modifiable Risk Factors

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ABSTRACT

Around the world, 50 million people live with dementia, an incurable disease. The number is expected to surpass 150 million in three decades. The burden on the economy keeps escalating every year. However, encouraging evidence from studies in Europe reveal a decline in rates of incidence dementia. Although the prevalence still remains high, new cases have become fewer. Therefore, research has shifted focus to the role of potential modifiable factors in curbing incidence dementia. Better management of vascular risk factors over the last couple of decades has seen the risk of dementia decrease dramatically. Studies on adherence to Mediterranean diet, moderate alcohol consumption and incorporation of physical activity into daily activities suggest the risk of dementia might be modified in vulnerable population. Smokers should be encouraged and supported to give up the habit. Identification of these potential modifiable risk factors doesn't mean that dementia can eventually be stopped, but this is a start toward decreasing the risk and improving lives of people with dementia. For this review paper, we searched for original articles and review papers in EMBASE and PubMed. Keywords were used individually or in combination in the searches. The keywords used include: dementia, diabetes mellitus, hypertension, Vitamin B_{12}, Vitamin D, hypercholesterolemia, cognitive reserve, physical activity, physical exercise, smoking, alcohol consumption, Mediterranean diet and hyperhomocysteinemia. We, therefore, review epidemiological longitudinal studies, with a focus on their associations with risk of dementia.

Key words: Cognitive impairment, Dementia, Diabetes mellitus, Mediterranean diet, Physical activity, Risk factors.

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DOI: 10.5530/jyp.2019.11.48

INTRODUCTION

The World Health Organization (WHO) estimates dementia affects 50 million people and this number will triple by the year 2050.[1] Better standards of living and higher life expectancy mean more people will grow older; however, these elderly individuals are at increased risk of dementia.[2] This is a reason for concern because dementia still remains incurable. In 2015, the WHO estimated the cost of treatment to be US$818 billion[1] and is expected to increase with the increase in incidence of dementia. Epidemiological studies on secular trends of incidence of dementia, therefore, have huge implication for policy makers in the health sectors.

A two-decade study in Central Sweden reported that prevalence of dementia remained stable between 1897 to 2004, after controlling for age, sex and education. The participants from the Sweden National study on Aging and Care in Kungsholmen (SNAC-K) survived longer than those from Kungsholmen Project (KP) (hazard ratio 0.77, 95% confidence interval 0.62-0.96).[3] Interestingly, the Rotterdam study revealed a declining trend in the age-adjusted incidence of dementia rates. The rates were 25% lower in the subcohort from 2000 when compared to the one from 1990, however, this difference was nonsignificant (incidence ratio 0.75, 95% confidence interval 056-1.02).[4] A similar observation was reported by the Zaragoza Study where the prevalence of dementia declined between 1988-89 to 1994-96 (prevalence ratio, 0.75, 95% confidence interval 0.56-1.02).[5] Notably, in later subcohorts from both studies, improved control of potential risk factors such as diabetes,[6] midlife hypertension,[7] physical inactivity[8] and smoking[9] might have influenced the rates of dementia. Moreover, longer survival of dementia patients could mask the declining incidence of dementia.

For instance, Norton *et al.* estimates that a third of incident Alzheimer's Disease (AD) cases are preventable through potentially modifiable risk factors. For example, low educational attainment posed the highest population attributable risk for AD worldwide.[10] Compression of cognitive morbidity through building cognitive reserve and maintaining cognitive stimulation might reduce the burden of dementia on the population at large.[11] The above studies provide evidence that the course of dementia is malleable. In this review, we focus on identifying those risk factors of dementia that might be modified based on previous population studies.

MATERIALS AND METHODS

We searched for original articles and review papers in EMBASE and PubMed. Keywords were used individually or in combination in the searches. The keywords used include: Dementia, diabetes mellitus, hypertension, Vitamin B_{12}, Vitamin D, hypercholesterolemia, cognitive reserve, physical activity, physical exercise, smoking, alcohol consumption, Mediterranean diet, hyperhomocysteinemia,

Classic Vascular Risk Factors

Diabetes mellitus

In 2017, the International Diabetes Federation (IDF) estimated that 451 million people were diabetic and will exceed 690 million by 2045.[12]

Epidemiological studies have associated diabetes mellitus with increased risk of dementia.[13-16] A cohort of 71,433 diabetes mellitus patients followed for 11 years supports this association.[17] Diabetes mellitus can accelerate the conversion of Mild Cognitive Impairment (MCI) to dementia. For example, in Kungsholmen Project, MCI patients with diabetes converted to dementia by 4 years earlier than MCI patients without diabetes.[18] Poor glycemic control may induce vascular dysfunctions leading to cognitive decline. The adjusted hazard ratio of risk of dementia in patients with a longer duration of diabetes is 1.66, 95% CI (1.07-2.26).[18] However, even newly diagnosed type 2 diabetes mellitus patients are also at an increased risk of dementia (hazard ratio, 1.63; 95% CI, 1.33-1.99).[19] Higher HbA1c level predicts cognitive decline and brain damage.[15] Further, hypoglycemia can cause subclinical brain damage. A recent meta-analysis suggests that recurrent episodes of severe hypoglycemia impairs memory and processing speed.[20]

A meta-analysis revealed an association between diabetes and risk of dementia in patients with diabetes.[21] However, not all studies support this association. For instance, the Framingham study failed to find an association between diabetes mellitus and increased risk of incident dementia.[22] The Tehran Lipid and Glucose Study (TLGS) found an association between diabetes and increased Cardiovascular Events (CVD).[23] Both cardiovascular events and stroke in type 2 diabetes mellitus accounts for increased risk of conversion of MCI to dementia.[16] Increase in prevalence of diabetes mellitus can upsurge incidence of dementia, which will be an economic burden especially for low-and middle-income countries. These associations between diabetes and dementia suggest that better glycemic control might reduce the incidence of dementia. Therefore, interventional longitudinal studies with better glycemic control and a longer follow-up period are required to understand the progression of diabetes associated-dementia. Table 1 provides a summary of major longitudinal studies done on diabetes patients whose major outcome was dementia.

Hypertension

Elevated midlife systolic blood pressure is associated with dementia.[30] Studies propose various mechanisms of cognitive impairment such as damage of blood-brain barrier via hypoperfusion,[31] arteriosclerosis and cerebral infarction.[32] Antihypertensive treatment might reduce the risk of dementia. For example, the randomized controlled trial of Perindopril or Indapamide (ACE inhibitors) reduced the risk of dementia compared to the placebo.[33] Potassium-sparing diuretics reduced the incidence of dementia in people aged 65 years and older.[7] In contrast, other studies failed to show a protective action of antihypertensive drugs on cognitive impairment.[34,35] The results are discordant because of methodological differences including age of onset of hypertension,[30] age of participants,[30] duration of follow-up,[36] different antihypertensive drugs,[37,38] outcome measures and definitions of cognitive impairment.[30,33] Though epidemiological studies employ various methodologies, the evidence supports that management of hypertension might modify the risk of dementia.

Hypercholesterolemia

The relationship between hypercholesterolemia and risk of dementia remains unclear, with some studies revealing an association,[39-41] lack of association[42] and a bidirectional relationship.[43] Interestingly, decreasing cholesterol levels in midlife predict risk of dementia in late-life.[42,43] However, elevated cholesterol in late-life protects against the risk of dementia.[44] The age on onset of dyslipidemia might determine the course of dementia. Longitudinal cohort studies of dyslipidemia with different age groups are required to address this controversy.

Modifiable Lifestyle Factors

Smoking

Cigarette smoking increases risk of dementia.[45-48] Tobacco smoke contains Reactive Oxygen Species (ROS) such as hydrogen peroxide and peroxynitrite. ROS causes oxidative stress in the brain,[49] and inflammation in rats.[50] Apart from causing cardiovascular mitochondrial injury and hypertension in mice, ROS is an independent risk factor for dementia.[51]

Dementia risk is greater in smokers without apo E e4 allele than smokers with the apo E e4 allele (relative risk 4.6 [95% CI 1.5-14.2]).[46] Smokers age faster than non-smokers and are vulnerable to vascular events and stroke. Smoking is associated with greater brain atrophy[52] and cancer.[53-55] Quitting smoking reduces brain atrophy and may prevent cognitive decline.[9,56]

Meta-analyses have confirmed the association between smoking and all-cause dementia for current smokers (RR 1.3 95%CI 1.18-1.45),[56] with greater risk for elderly smokers. Passive smoking also increases risk of dementia, though the association is weak[57,58] and it impairs prospective memory and executive function.[59] The risk of dementia increases 3-fold among passive smokers with carotid artery stenosis.[57] However, Anhui Study failed to find a positive association between passive smoking and

Table 1: Summary of epidemiological studies of diabetes mellitus and dementia.

Authors	Study Name (site)	Age at baseline (years)	Follow-up (years)	Total population (with diabetes)	Cognitive test	Outcome measured	RR of dementia 95% CI
Cheng *et al.* 2011[24]	Columbia Aging Project (USA)	≥65	9	1,488 (253)	DSM-IV	Dementia	1.7 (1.4-2.9)
Ahtiluoto *et al.* 2010[25]	Vantaa 85+ Study (Finland)	≥85	9	553 (NR)	DSM-III-R	Dementia	NR
Akomolafe *et al.* 2006[22]	Framingham Study (USA)	70 (mean)	12.7	2,210 (202)	DSM-IV	Dementia	2.98 (1.0-8.3)
Peila *et al.* 2002[26]	The Honolulu-Asia Aging Study (USA)	≥65	2.9	2,574 (900)	DSM-III-R	Dementia	1.5 (1.0-2.2)
Honig *et al.* 2003[27]	Washington Heights-Inwood Columbia Aging Project (USA)	≥65	7	1,766 (NR)	DSM-IV	Dementia	1.6 (1.0-2.4)
Xu *et al.* 2004[28]	Kungsholmen Project (Sweden)	≥75	6	1,301	DSM-III-R	Dementia	1.5 (1.0-2.1)
MacKnight *et al.* 2002[29]	Canadian Study of Health and Aging (Canada)	≥65	5	5,574	DSM-III-R	Dementia	NA
Ott *et al.* 1999[6]	The Rotterdam Study (The Netherlands)	≥55	2.1	6,370 (692)	DSM-III-R	Dementia	1.9 (1.2-2.8)

DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised for Dementia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition for dementia; NA, no association; NR, Not reported.

moderate dementia syndromes.[60] Most studies reiterate that active or passive smoking is detrimental to cognition. Smoking cessation programme should be promoted within communities to address the risk of dementia.

Alcohol consumption

The association between alcohol and dementia is debatable. In the CONOR study involving 25,635 participants, elderly abstainers were at high risk of dementia related deaths.[61] In addition to total abstinence, excessive alcohol consumption also increases the risk of dementia.[62,63] The Whitehall II cohort study that followed 9087 participants over 23 years found consuming more than 14 units of alcohol per week increased the risk of dementia by 17%.[64] In contrast, a review of 143 studies proposed moderate or light consumption of alcohol reduces the risk of dementia in older people.[65] Nevertheless, low or risky consumption failed to find association with dementia.[66]

Light to moderate alcohol consumption may lower cardiovascular risk, increase brain blood flow, modulate vasodilation of blood vessels and reduce inflammation.[67] Late-life alcohol consumption preserves hippocampal volume. Late-life abstainers have comparatively lesser brain volume than their peers who are moderate drinkers.[68] However, in Whitehall II cohort study in community-dwelling adults, moderate alcohol consumption had increased risk of hippocampal atrophy.[69] Longitudinal studies propose a u-shaped association between alcohol consumption and cognitive outcomes.[70]

The effects of alcohol on dementia may depend on amount of alcohol, type of alcohol and the age of consumption. Though suggested moderate alcohol consumption is beneficial, its overall effect on health has to be weighed. Nevertheless, alcohol consumption as a means to prevent dementia should be carefully considered. Table 2 summarizes epidemiological studies linking alcohol consumption and dementia.

Hyperhomocysteinemia

Homocysteine in serum is determined by Vitamin B_{12} levels and age of the individual.[73] Few studies associated elevated homocysteine levels and cognitive impairment.[74,75] Seshadri *et al.* found that hyperhomocysteinemia was an independent predictor of dementia.[76] Alzheimer's patients have hyperhomocysteinemia.[77] A meta-analysis by Wald and colleagues including eight prospective cohort studies with 8669 participants and a mean follow-up period of 5 years established serum homocysteine was associated with incidence dementia. However, the cause-effect could not be established from the meta-analysis.[78] Therefore, it seems Vitamin B_{12} supplementation to AD patients might lower homocysteine levels consequently preventing further cognitive decline. However, the relationship between them is complicated with longitudinal studies yielding discordant results.[79]

Table 2: Summary of epidemiological studies of alcohol consumption and dementia.

Authors	No. of participants	Age (years)	Classification	Follow-up (years)	Method of ascertainment	Findings
Anttila *et al.* 2004[70]	1464	65-79	Never drinkers Infrequent drinkers Frequent drinkers	23	Dementia	Midlife consumption of alcohol increases the risk of dementia in carriers of Apo E e4. Abstinence and frequent drinking increased the risk of dementia
Langballe *et al.* 2015[71]	40,435	≥ 20	Never drinkers Infrequent drinkers Frequent drinkers	27	Dementia	Frequent drinking increased the risk of dementia. Abstinence was not associated with dementia, adjusted for confounding factors.
Sabia *et al.* 2018[64]	9,087	35-55	Abstinence 1-14 units/week >14 units/week	23	Dementia	Consumption of 14 units/week of alcohol increased the risk of dementia.
Downer *et al.* 2014[72]	2045	>65	Abstainer Light-Moderate Heavy	NR	Impaired learning and memory	Light to moderate drinking in late life among apoE e4 non-carriers protects against cognitive decline, but not in apoE e4 carriers.
Heffernan *et al.* 2016[66]	821	70-79	Previous drinking > 1 year (abstainers) Low consumption Risky consumption	NR	Dementia	Low or risky consumption of alcohol was not associated with incident dementia. However, ApoE e4carriers were at risk of dementia.
Topiwala *et al.* 2017[69]	550	43, mean	Abstinent Light Moderate Unsafe drinking	30	Hippocampal atrophy	Alcohol consumption failed to show any benefits in preventing adverse brain outcomes.
Ormstad *et al.* 2014[61]	25,635	60-80	Several times/week Once/week 2-3 times/month Once/month Abstainer	17	Dementia-related death	Elderly abstainers were likely to die of dementia-related causes.

Vitamin B_{12} deficiency

Cyanocobalamin is essential for brain development and functioning.[80] It is mainly sourced from animal foods. Therefore, vegetarians[81] and elderly people[82] are at risk of Vitamin B_{12} deficiency. Vitamin B_{12} deficient individuals are at risk of cognitive impairment.[83] It elevates brain homocysteine levels, an independent risk factor for cognitive impairment.[84,85] However, randomized controlled trials failed to find benefits of Vitamin B_{12} supplementation on cognition.[86,87] A systematic review in 2012 also observed a similar outcome.[88] It suggests Vitamin B_{12} associated dementia can be addressed by consuming animal sourced foods. But the quantity and type of animal-based diet for preventing cognitive impairment requires further research.

Vitamin D deficiency

Vitamin D is of two types: Vitamin D_2 and D_3; found in diet and synthesized in the human skin, respectively. 1, 25-dihydroxy Vitamin D_3 receptor and 1 α-hydroxylase essential for synthesis of the active form of Vitamin D, are expressed in the hippocampus and dentate gyrus.[89] Neural cells require the active form of Vitamin D (1,25-dihydroxy-Vitamin D_3) for their development and functioning. The active form of Vitamin D modulates neurotrophin expression and reduces cytotoxicity and death of neurons. Levels of 25-hydroxyvitamin D below 50nmol/L increase the risk of development of all-cause dementia up to 6 folds when compared to sufficient levels.[90,91] On the contrary, a study involving 4809 participants failed to find an association between Vitamin D deficiency and cognitive impairment.[92] Little Johns *et al.* suggest a threshold of 50nmol/L during Vitamin D supplementation, to show benefits against cognitive decline.

Table 3: Summary of epidemiological studies of physical activity and dementia.

Study	Sample size	Age (years)	Follow-up (years)	Type of study	Inclusion criteria	Intervention	Outcome
Zhou *et al.* 2017[111]	7,501	>65	9	Prospective cohort study	Dementia-free	PE	Regular PE decreased the risk of dementia
Sink *et al.* 2015[112]	1,635	70-89	2	Randomized controlled trial	Dementia-free sedentary elderly adults	PE vs HE	Moderate PA was not associated with decreased risk of dementia
Lautenschlager *et al.* 2008[113]	170	>50	1.5	Randomized controlled trial	dementia-free with subjective memory complaints	PA	Modest improvement in cognitive function
Scarmeas *et al.* 2011[102]	357	>65	5.2	Prospective cohort study	Dementia-free at baseline	PA	PA decreases the risk of dementia and dementia-related mortality in AD patients
Gross *et al.* 2017[114]	646	38-63	30	Prospective cohort study	Dementia-free	PA or PE	Physical activity is not associated with decreased risk of dementia
Tan *et al.* 2017[115]	5,701	>60	10	Prospective cohort study	Dementia-free	PA	Low PA increased the risk of dementia
Sabia *et al.* 2017[116]	10,308	35-55	27 mean	Prospective cohort study	Dementia-free	PA	PA is not associated with risk of cognitive decline or dementia
Andel *et al.* 2008[104]	3,134	48.1 mean at baseline 79.5 at follow-up	31	Prospective cohort study	Dementia-free	PE	Midlife PE may reduce the risk of dementia in late-life
De Bruijn *et al.* 2013[117]	4,406	61-97	14	Prospective cohort study	Dementia-free	PA	PA is associated with decreased risk of dementia, limited to a follow-up period of 4 years
Chang *et al.* 2010[103]	4,945	51 mean	26	Prospective cohort study	Dementia-free	PA	PA in midlife is associated with a reduced risk of dementia in late-life.
Kishimoto *et al.* 2016[118]	803	>65	17	Prospective cohort study	Dementia-free	PA	PA in midlife may reduce the risk of cognitive decline in late-life.
Buchman *et al.* 2012[119]	716	81.6 mean	4	Prospective cohort study	Dementia-free	PA	Higher level PA may reduce the risk of dementia

PA, physical activity; PE, physical exercise; HE, health education.

Protective Factors

Cognitively training/exercise

Cognitive training improves specific cognitive domains or functions.[93] A systematic review of 35 studies on cognitive training improves general cognitive functions.[94] Cognitive training alters cortical thickness.[95] In an interventional study combining physical activity and cognitive training in dosages ranging from 24 to 110 sessions, global cognitive functions improves in a dose-dependent manner However, these benefits are not seen in elderly people with Neurocognitive Disorders (NCDs).[96] In healthy elderly Italian population study, low-intensity multi-domain cognitive exercises enhances executive functions and short-term memory.[97] Multiple-domain cognitive training ameliorates general cognition, visuospatial abilities and delayed memory, while single-domain enhances attention and executive functions.[98]

Most studies reveal improvement in specific cognitive domains with cognitive training. However, these studies vary in; duration of intervention, number of participants and type of cognitive exercises, hence, interpretation of the findings should be done with caution.[99,100] Further, future research should look into long-term benefits of cognitive training, suitable age for commencing training and impact technology-driven training in cognition.

Physical exercise/activities

Physical exercises and activities increase energy expenditure in the body.[101] Physical exercise improves cerebral flow, production of brain-derived neurotrophic factor and neurogenesis. Studies reveal an association between physical activity and dementia.[102] Midlife physical activity prevents late-life dementia.[103,104] Notably, leisure-time physical activity in midlife decreases the risk of late-life dementia.[105] The intensity and timing of physical activity influences strength of this association.[106,107] Aerobic exercises prevent hippocampal atrophy in older adults.[108] However, meta-analyses contradict positive impact of exercise on dementia. For example, meta-analysis of five RCTs failed to find an association between long-term exercise and dementia.[109] A Cochrane systematic review also found aerobic exercises failed to improve cognitive function in elderly individuals.[110] Methodologic variations such as duration, intensity and type of exercise and outcome measures of dementia might be the reason for these contradictions. Physical activity should be encouraged considering its impact in general well-being. Table 3 gives a summary of epidemiological studies of physical activities and their influence on dementia.

Mediterranean diet

The mediterranean diet includes plenty of vegetables, fruits, nuts, whole-grain cereals, fish and less quantity of meat and dairy products along with moderate alcohol intake and unsaturated fats.[120] Growing evidence suggests that Mediterranean diet prevents dementia,[121,122] but, this association is inconclusive.[123,124] Hellenic Longitudinal Investigation of Ageing and Diet (HELIAD) participants on Mediterranean diet performed better in cognitive tests and had lower dementia rates.[125] It might be due to cumulative effect of the food, as opposed to individual food components.[126] Recently, increased interest on how diet affects cognition has come to the fore. Some studies have focused solely on the individual components of Mediterranean diet such as fish,[127–130] leafy vegetables[131,132] and fruits.[133–135] High fish intake prevents brain atrophy.[136] Mediterranean diet is associated with a decrease in cardiovascular diseases - an independent risk factor for dementia.[137] However, Mediterranean diet failed to prevent cognitive decline in women with cardiovascular disease.[138] Effects of Mediterranean diet in different ethnicities should be explored further. Long-term follow-up of the same can pave ways for prevention therapies using diet.

CONCLUSION

Identification of potentially modifiable factors will not cure dementia. These factors serve the purpose to decrease incidence of dementia. The complex relationship between multiple risk factors and dementia render findings from most studies inconclusive. Results from the studies above support the concept that risk of dementia can be modified by incorporating changes in lifestyle as well as better management of classic vascular risk factors. The recent longitudinal studies from Europe as well as the USA reveal a drop in the number of incident dementia cases. Better management of hypertension, diabetes and stroke, may have had an impact on the prevalence of dementia, because of longer survival times. Available data on moderate drinking of alcohol does not entirely support the idea of abstainers taking up to drinking. Additionally, quitting smoking has other benefits, besides preventing cognitive decline, for example, decreased the risk of cancer in ex-smokers or non-smokers. Leisure activities and physical exercises are also beneficial in decreasing the risk of dementia and cardiovascular events. Socially active individuals tend to have a decreased risk of dementia. With the lack of drugs to stop dementia, physicians may have to rely on modifiable risk factors to alter the course of the disease and curb incident cases.

ACKNOWLEDGEMENT

We are grateful to Dr. Yasam Venkata Ramesh for his comments on a previous draft.

CONFLICT OF INTEREST

The authors declare no competing interests.

ABBREVIATIONS

ACE inhibitors: Acetylcholinesterase inhibitors; **AD:** Alzheimer's disease; **ADDTC:** Alzheimer Disease Diagnostic and Treatment Center for Vascular Dementia; **CONOR study:** Cohort of Norway Study; **DSM-III-R:** Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised for Dementia; **DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders, 4th edition for dementia; **FHS study:** Framingham Heart Study; **GMS:** Geriatric Mental Scale; **HELIAD study:** the Hellenic Longitudinal Investigation of Ageing and Diet Study; **IDF:** International Diabetes Federation; **MAS study:** The Sydney Memory and Ageing Study; **MCI:** Mild cognitive impairment; **MMSE:** Mini-mental state Examination; **MoCA:** Montreal Cognitive Assessment Scale; **NCDs:** Neurocognitive disorders (NCDs); **NINCDS-ADRDA:** National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association for Alzheimer's disease; **RCT:** Randomized controlled trial; **TLGS:** Tehran Lipid and Glucose Study; **WHO:** World Health Organization.

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Article History: Submission Date : 02-05-2019; Revised Date : 28-05-2019; Acceptance Date : 29-06-2019.
Cite this article: Ming'ate MD, Nair NK, Kumar PRAV. Preventing Dementia: Shifting Focus towards Potential Modifiable Risk Factors. J Young Pharm. 2019;11(3):230-7.