



## Alzheimer's Disease and Cardiovascular Risk Factors, Review of Literature and Prospects of Future Research

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Received: Sep 22, 2016; Accepted: Sep 29, 2016; Published: Oct 01, 2016

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Competing interests: The authors have declared that no competing interests exist.

*Cite as: Shoukry EE. Alzheimer's disease and cardiovascular risk factors, review of literature and prospects of future research. J Ageing Disabil Chronic Dis. 2016; 1: 1-3.*

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### SUMMARY

Most of the patients with Alzheimer's disease (AD) are found to have evidence of atherosclerotic cerebrovascular disease on autopsy. Cardiovascular risk factors including hypertension, diabetes mellitus and dyslipidemia are known risk factors for Alzheimer's disease as well.

Higher Systolic Blood pressure (SBP) in midlife has been linked to an increased risk of developing AD in late life [1]. Conversely, increased diastolic Blood pressure (DBP) especially in the elderly was associated with decreased development of AD [2] and low DBP is related to increased incidence [3]. It is conceivable that a higher SBP in midlife will contribute to a rapid progression of atherosclerotic changes and that a decline in DBP, reflecting decreased vascular elasticity, will impair the cerebral perfusion later in life. Whether hypertension plays a role in the development or the progression of AD is unclear. Observational studies suggested that antihypertensive medications may protect against

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development of AD among individuals with hypertension [4]. An interaction between Hypertension and ApoE seems to exist and hypertensive patients with ApoE epsilon 4 have higher incidence of dementia compared to ApoE negative individuals [5].

Diabetes mellitus doubles the risk of Alzheimer's disease. Prediabetes increases the risk of developing dementia by about 70% in people aged above 75 years, even for negative for ApoE epsilon 4 allele [6]. Effective blood glucose control may lower risk of dementia. Diabetics treated with the insulin sensitizers Thiazolidinedions have 20% lower risk of AD compared with people taking insulin. Similar results were obtained when comparing users of this class of oral hypoglycemics and Metformin users [7]. AD may actually represent a brain specific form of diabetes mellitus and has been called Diabetes mellitus type 3. Pronounced insulin/IGF (Insulin-like growth factor) deficiency and resistance develop early in the course of AD [8]. Intranasal insulin may contribute in cognitive improvement or stabilization of cognitive impairment in patients with early AD [9]. Nonetheless, Type 2 diabetes mellitus is not sufficient to cause AD but can possibly serve as cofactor in its pathogenesis or progression. Neuroglycopenia has serious adverse effects on cognitive functioning especially if repetitive.

High total cholesterol in midlife has been reported to increase the risk of AD by about 3 folds. AD patients with high total or LDL cholesterol can experience faster cognitive decline. High HDL also contributes to faster decline but Triglycerides didn't appear to impact that rate. Studies finding a negative correlation between cholesterol level and dementia risk were conducted later in the patients' lives. Moreover, cholesterol may increase the activity of the pro-amyloidogenic Beta and Gamma secretase while repressing the anti-amyloidogenic alpha secretase. Lastly, cholesterol may decrease internalization and degradation of the Amyloid Beta. Many studies have investigated the effect of statins as AD modulating agents. The results of these studies have been inconsistent [10].

In the era of CSF biomarkers of AD, there is a golden opportunity to study the effect of these factors on the pathogenesis and progression of AD. As outlined above, it is crucial to intervene early... in midlife rather than late life and in the preclinical/MCI stage rather than in moderate stages of the disease. An ideal group to study the relative impact of these factors on the incidence and rate of cognitive decline would be individuals in their late 40's-early 50's with strong family history of AD, with positive ApoE epsilon 4 who happened to have detectable levels of Amyloid Beta 1-42 in their CSF.

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