

Coronary Heart Disease, Heart Failure, and Risk of Alzheimer's Disease: How Strong is the Association?

Alzheimer's disease (AD) is the most common cause of dementia worldwide.^[1] AD is multifactorial, as both genetic and epigenetic factors have vital roles. Targeting the epigenetic and environmental factors may inhibit disease progression or even prevent it at earlier stages. The association of cardiovascular disease (CVD) with cognitive impairment is investigated in many previous studies, including community-based studies.^[2] CVD, especially coronary artery heart disease (CAHD) and heart failure, has been associated with vascular cognitive impairment and AD.^[2] CVD and AD are increasingly being studied for their association. Hence, multiple mechanisms are being proposed for the same.

One potential mechanism is the common risk factors involved in CVD and AD. These include age, smoking, hyperlipidemia, hypertension, diabetes mellitus, and atherosclerosis.^[3-5] Another possible mechanism is the pathogenesis initiation in AD occurs due to chronic cerebral hypoperfusion caused by the vascular risk factors mentioned earlier. This mechanism leads to an initiation of amyloid cascade and the formation of neurofibrillary tangles in AD.^[6-8] The brain parenchyma and the blood-brain barrier (BBB) may also be chronically damaged due to these processes, which decrease glucose, oxygen, and nitric oxide.^[8-10] Moreover, the APOE4 allele is considered a risk factor for AD that predisposes to atherosclerosis and CVD.^[11]

Multiple studies have been conducted earlier, including meta-analyses to link CVD and AD.^[3] In this journal issue, Weifeng Sun *et al.*,^[12] have conducted a meta-analysis on the association between coronary artery disease (CAD), heart failure, and the risk of AD. The authors considered 12 studies (1701718 participants and 36913 individuals with AD) to study the association between CHD and AD. All the studies chosen were cohort studies except one case-control study. Of these, seven studies explored myocardial infarction (MI) and AD association, while six explored the risk between heart failure and AD. The authors found CHD associated with an increased risk of AD. In a subgroup analysis, the increased risk was mainly found in the Caucasian population. The authors have noted that CHD and AD are associated due to chronic cerebral hypoperfusion as well as release of proinflammatory cytokines in the brain.^[6-9] CHD and AD are also associated with APOE as a potential variable, according to the authors. The authors also found a similar association between heart failure and AD which they have attributed to common vascular risk factors. No association was found between MI and AD. Notably, although, the association was significant in studies including CHD vs. AD and heart failure vs. AD respectively, the confidence intervals in both cases exceeded 1. In both cases, the I² score was over 95%,

indicating high heterogeneity. However, using meta-regression analysis, it was found that the heterogeneity was independent of the publication year, age, gender, and follow-up time in all the study groups.

The authors have rightly pointed out the association between CVD and AD in their study, and similar results have been found in previous studies.^[13,14] However, the study's results also contradict the similar meta-analyses done recently, which have shown no association between AD and CHF and CHD, respectively.^[2,15] There are certain limitations that the authors have correctly mentioned, like the high heterogeneity between studies and publication bias in the case of MI. Notably, only a few studies in the literature have explored the relationship between MI and AD. The median time to follow up in the different studies ranges from as low as 1.5 years to as high as 31 years. The study's sample size and weight are also highly variable across the studies.

Moreover, certain important points need to be considered. Most studies could link CVD with AD, but vascular cognitive impairment coexisting with AD pathology is also linked with CVD.^[16,17] Medin, which is an aging-associated amyloidogenic protein, has been found to be a potential risk factor for both vascular cognitive impairment and AD.^[18] Second, looking at the confidence interval of more than 1 and the high heterogeneity, it must be considered if the data could have been gathered and analyzed differently. Third, more longitudinal studies are required to prove temporal causation between the two. Such studies need to be population-based and multicentric, involving large and ethnically heterogeneous populations. Fourth, studies could also focus on subclinical CVD associated with AD. This can lead to appropriate interventions targeting the risk factors at the earliest, which can help mitigate the onset of cognitive impairment. Finally, the impact of such results on clinical practice, disease management, and policymaking also needs to be considered.

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