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Dementia prevention and cardiovascular risk factors: a mini-review

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Abstract:

Background and Aim: *Although dementia prevalence is increasing worldwide, currently, there are no effective ways for prevention nor optimal treatment for disease control. In this mini-review, we discuss the results of observational studies and randomized clinical trials (RCTs) about the association between cardiovascular risk factors (CVRFs) and dementia and future perspectives of studies in this topic.*

Methods: *We briefly described the role of cardiovascular risk factors (CVRFs) on dementia risk and the limitations presented by previous studies. Results: CVRFs have been associated with higher risk of dementia in several longitudinal studies and the control of these factors has been considered a promising way to prevent this dreadful disease. However, the available RCT that investigated the effect of CVRF control on dementia incidence have not confirmed this hypothesis. These RCTs have important limitations (e.g. short follow-up time, initiation of treatment at advanced aged) that do not allow definitive conclusions at this time.*

Conclusion: *Currently, there is lack of evidence that the treatment of CVRF will prevent dementia. Future studies should consider the interdependence of risk factors using new analytical methods.*

Key-Words*: Dementia, cardiovascular disease, risk factors*

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INTRODUCTION

Dementia is a general term for a decline in mental abilities, which is severe enough to interfere with activities of daily living. The most common cause of dementia is Alzheimer's disease that accounts for 60 to 80% of dementia cases.[1] Dementia is a highly prevalent disease, with large economic and social burden. Dementia incidence is expected to increase exponentially since that are no effective approaches for its prevention and standard therapy to control the disease progression. In 2010, 35.6 million people had dementia worldwide and this number is expected to reach 115.4 million in 2050.[2] In 2013, the health care costs in the US related to dementia were estimated to be $203 billion.[3] Despite its high prevalence and costs, dementia is the only disease among the top ten causes of death in the US that has no treatment or prevention. Therefore, clear evidence about risk factors for dementia is urgently needed. Cardiovascular risk factors (CVRFs), mainly when the exposure happens during midlife, were associated with increased risk of dementia and AD in observational studies.[4,5] Associations between CVRFs measured during late life and dementia are less clear with the estimates being attenuated or even null.[6-8] It was estimated that around a third of Alzheimer's disease (AD) cases worldwide might be attributable to the joint effect of five midlife CVRFs (diabetes, hypertension, obesity, physical inactivity, and smoking), depression, and low educational attainment.[9] The associations between CVRFs and dementia have been investigated in several meta-analyses of observational studies.[10,11] The association between smoking and dementia is not clear,[12] with some studies showing no effect of smoking on dementia risk at advanced ages.[13,14] Survival bias may be a possible explanation for these findings.[15] Mild to moderate regular alcohol consumption has been shown to reduce dementia risk.[16] Midlife overweight and obesity has been associated with increased the risk of dementia, whereas late-life

overweight-obesity was not.[6,17-19] Diabetic patients seem to have higher risk of dementia,[18,20,21] but the association between hypertension and dyslipidemia with dementia are less clear, with several meta-analyses of observation studies showing mixed results.[9,22-25]

The design of these observational studies mostly use a baseline measure of the CVRF and then investigated their association with late-life dementia.[4,5,26-28] Even when the risk factor was measured multiple times during the life course in observational studies, it was not conditioned on the joint effect of other CVRFs and the effect of previous cognition.[29- 31] This is a particular problem for the analysis of chronic degenerative diseases that develops during many years and has a long asymptomatic phase, like dementia.[32]Recently it was shown that neuropathological lesions may be present even 20 years before clinical cognitive symptoms.[33] Certain CVRFs (e.g. higher BMI) predicts future risk of other CVRFs (e.g. higher risk of diabetes), that may also predict future CVRF risk (e.g. decline in BMI since participants may lose weight as their diet changes because of diabetes diagnosis). Besides interdependence among factors during the life course, particularly to the field of dementia, cognition function may predict future CVRF and also loss to follow-up. Impaired cognition (even many years before the development of clinical dementia symptoms) predicts future CVRFs. For example, participants may experience a decline in BMI due to early appetite changes in pre-clinical dementia,[34] and consequent decline in the arterial blood pressure and glycemic levels. Moreover, a direct of effect of neuropathological lesions of AD in strategic brain areas associated with blood pressure control may cause a decline in blood pressure levels during pre-clinical dementia.[35] Besides the interaction between dementia and CVRFs, impaired cognition during early dementia and preclinical phases may influence the number of dropouts in the study, leading to attrition bias.[36]

Evidence from RCTs also showed mixed results for the effect of antihypertensive treatment[37-40], and a null effect for the treatment of diabetes and cholesterol on reducing dementia risk.[41,42] Meta-analyses of these RCTs on treatment of diabetes, hypertension, and hyperlipidemia showed no benefit for dementia prevention.[41-43] However, most RCTs had important limitations. They were of short duration (mean follow-up≤ 4.5 years), had many participants in the placebo group who received active treatment during the follow-up, treatment was initiated at advanced ages (≥ 50 years-old), and the RCTs were not designed to evaluate multiple interventions simultaneously.

Future perspectives

Besides the absence of definitive evidence from current studies, we should consider that a key factor when planning primary prevention strategies and investigating new treatments is to know the best time to start an intervention. In fact, many recent disease-modifying treatments for dementia might have failed because they were started too late, when the neuropathological lesions were already established.[44-46] Since neurodegenerative diseases like dementia develop over many years and have a long asymptomatic phase,[32] the protective or null associations between late-life exposures and dementia estimated in previous observational studies may be due to preclinical dementia at the time the exposure was measured.[47] Preclinical or early dementia may have a direct effect on CVRFs, leading to a decline in risk factors (i.e. BMI, blood pressure, plasma glucose levels, smoking, alcohol use) or may indirectly affect CVRFs (e.g. through apathy and decreased appetite).[47-49] Therefore, a protective or null association between late-life exposures and dementia may be due to reverse causation.

Therefore, in order to guide better public health strategies for dementia prevention, it is necessary to estimate the effects of interventions on CVRFs (as RCTs do) over long periods and in relatively healthy populations (as observational studies do). However, current standard analytical methods cannot accurately estimate these effects because they cannot handle multiple time-varying exposures that are affected by previous confounders. Future studies designed to evaluate the effect of CVRFs on dementia prevention should use new analytical techniques that appropriately handle time-varying interventions and the interdependence among risk factors.[50,51]

Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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