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Editorial

Association of nonalcoholic fatty liver disease with incident dementia later in life among elderly adults

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In the recent issue of *Clinical and Molecular Hepatology*, Jeong et al.[1] provided evidence that non-alcoholic fatty liver disease (NAFLD) is associated with the risk of developing dementia in the elderly, especially in the form of Alzheimer's disease (AD). Currently, it is not clear whether 1) hepatic pathophysiology related to NAFLD per se is important for the risk of dementia or 2) NAFLD only reflects the underlying metabolic syndrome that is further related to an increased risk of dementia. Previous studies have shown that metabolic syndrome is closely related to NAFLD.[2-6] Also, the authors defined the presence of NAFLD based on the fatty liver index (FLI) that is calculated using the serum triglyceride, body mass index (BMI), and waist circumference, all of which have a close relationship with the definition of metabolic syndrome. Therefore, with the idea that screening for NAFLD could be a good way to find underlying metabolic syndrome, future studies are warranted to assess the potential benefit of treatment for NAFLD in the population-level risk of dementia occurrence.

AD is a slowly progressive disorder with a long prodromal period. Although it is well proven that FLI accurately reflects the severity of NAFLD in a general population level,[7] the relationship between FLI and NAFLD has not been clearly elucidated in patients with dementia or at-risk population, such as mild cognitive impairment (MCI) showing 10–15% annual rate of progression to AD dementia.[8] Moreover, several risk factors for dementia, such as higher BMI or lower education, during normal aging could be paradoxically associated with slower clinical deterioration in MCI patients[9] or AD dementia patients.[10] The underlying progression of dementia pathology could induce weight loss for at-risk population, which could explain the paradoxical relationship between BMI and dementia. On the other hand, more efficient brain network obtained by higher education could delay the onset of dementia symptoms, given the same burden of AD pathology. However, once dementia symptom does begin, the rate of clinical decline in patients with higher education tend to be faster with higher burden of AD pathology. Further studies are warranted to confirm whether FLI or NAFLD is differently associated with cognitive dysfunction or dementia risk according to the level of cognitive status at study inclusion.

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It is also noteworthy that sex had interaction effect with FLI on dementia risk (Supplementary Tables 6 and 7 in Jeong et al.[1]). Specifically, lower FLI was associated with lower risk of dementia in men, but not in women. In contrast, higher FLI was associated with dementia risk in women, but not in men. There could be several explanations for this interaction. First, lower FLI could be an important protective factor for men with low-to-intermediate BMI, while higher FLI could be an important risk factor for women with intermediate-to-high BMI. Second, although men and women have different mean BMI and waist circumference,[11,12] the calculation formula for FLI is not sex-specific. Different effect of FLI on dementia risk according to sex could be originated from the lack of consideration for factors that are different by sex in the FLI calculation formula. Further elucidation considering the sex-specific cut-offs for FLI and BMI may be needed to identify a true association between NAFLD and dementia risk.

Lewy body disease (LBD), including Parkinson's disease (PD) and dementia with Lewy bodies, is the second most common degenerative cause of dementia; however, it is clinically underdiagnosed in dementia patients.[13] In this study, LBD was not considered as a cause of dementia. A recent study showed that NAFLD is differently associated with the risk of PD by sex in that NAFLD is associated with lower risk of PD in men, while it is associated with higher risk in women.[14] As patients with mixed dementia from AD/LBD are common but usually diagnosed as AD dementia, future studies are needed to confirm whether NAFLD is differently associated with underlying causes of dementia.

Conflicts of Interest

The author has no conflicts to disclose.

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Abbreviations:

AD, Alzheimer's disease; BMI, body mass index; FLI, fatty liver index; LBD, Lewy body disease; MCI, mild cognitive impairment; NAFLD, non-alcoholic fatty liver disease; PD, Parkinson's disease