Non-alcoholic fatty liver disease and risk of dementia: A meta-analysis of cohort studies

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Competing Interests:

The authors declare no competing interests in relation to this study.

Author Contributions:

CHH conceived and designed the research; MYW and LYL contributed to the data acquisition;

CHH and YSK analyzed the data and interpreted the results; LYL and CHH drafted, edited,
and revised the manuscript; All authors reviewed the manuscript.

Running Head: NAFLD and risk of dementia
Dear Editor,

We read with great interest the recent large-scale cohort study by Jeong et al [1] suggesting that non-alcoholic fatty liver disease (NAFLD) is associated with a higher risk of incident dementia (aHR, 1.05; 95% CI=1.02–1.08, P=0.001) and there was other research that indicated a similar tendency [2]. Nevertheless, we found there were other studies that demonstrate the opposite result[3-5]. To make sure whether NAFLD was related to dementia, we performed a meta-analysis of cohort studies to investigate the association between NAFLD and the risk of dementia. Because the prevalence of NAFLD increased in recent years [6], we thought it would be a critical issue to detect the potential complication of NAFLD.

Two authors independently carry out records selection from PubMed and Embase from inception to August 2022. We applied the search strategy that included the terms for [“Non-alcoholic Fatty Liver Disease” and “Dementia”] were used for MeSH terms and free-text searches. No limitation on language. We included cohort studies indicating an association between NAFLD and dementia incidence and providing related data as hazard ratio with 95% CI. We used the Newcastle-Ottawa scale for cohort studies to assess the
quality of the included studies. Two authors independently performed data extraction and study quality assessment. Any divisions will be solved by discussion by consulting a third author. In 1136 potentially relevant published studies, 1130 were excluded, due to duplication (n=176) or article types (non-original article) (n=643) or since the title and abstract did not correspond to the including criteria (n=311). Eventually, six cohort studies including the study by Jeong et al met all inclusion [1, 3-5, 7, 8]. A total of 2,345,929 patients were included in this Meta-analysis. The mean age of the included study ranged from 48.2 to 73.4.

In the process of statistical analysis, we used RevMan 5.4 software to perform meta-analysis and use I² test to check heterogeneity. Random effect model was used in the analysis. Pooled Hazard ratio(HR) from six cohorts was 1.04 (95% CI=1.00-1.08, P = 0.04, I² = 63%;) with statistical significance (Figure 1). Heterogeneity was high with an I² of 63% and the weights of the statistical analysis are derived from specific studies. Thus, sensitivity analyses were conducted to confirm the robustness of the meta-analysis. We excluded each study in sequence for sensitivity analysis. The analysis showed some large studies will affect the significance of the result [1, 7]. However, the general direction still indicates a relationship between NAFLD and dementia. A further subgroup analysis will be conducted to explore the causes of heterogeneity.
To the best of our knowledge, this is the first meta-analysis of the association between NAFLD and risk of dementia. Our meta-analysis suggested that NAFLD was a risk factor for dementia. However, due to the heterogeneity of the statistical analysis, interpretation of the result must be very conservative. More prospective research are needed to establish the potential relationship between NAFLD and dementia. We considered that the influence of other factors such as age, gender, ethnicity, and diagnosis would need to be investigated in the future.

Reference:


4. Labenz, C., K. Kostev, L. Kaps, P.R. Galle, and J.M. Schattenberg, Incident Dementia in Elderly Patients with Nonalcoholic Fatty Liver Disease in Germany. Dig. Dis. Sci.,


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ind HR</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labenz 2020</td>
<td>-0.0221</td>
<td>0.031</td>
<td>19.3%</td>
<td>0.98 [0.92, 1.04]</td>
<td>2020</td>
</tr>
<tr>
<td>Shang 2021</td>
<td>-0.2717</td>
<td>0.299</td>
<td>6.6%</td>
<td>0.76 [0.48, 1.12]</td>
<td>2021</td>
</tr>
<tr>
<td>Jeong 2022</td>
<td>0.0484</td>
<td>0.014</td>
<td>34.1%</td>
<td>1.05 [1.02, 1.08]</td>
<td>2022</td>
</tr>
<tr>
<td>Kim 2022</td>
<td>0.0497</td>
<td>0.0049</td>
<td>41.9%</td>
<td>1.05 [1.04, 1.08]</td>
<td>2022</td>
</tr>
<tr>
<td>Shang 2022</td>
<td>0.3188</td>
<td>0.114</td>
<td>2.5%</td>
<td>1.38 [1.10, 1.72]</td>
<td>2022</td>
</tr>
<tr>
<td>Xiao 2022</td>
<td>-0.0861</td>
<td>0.1454</td>
<td>1.6%</td>
<td>0.92 [0.89, 1.22]</td>
<td>2022</td>
</tr>
</tbody>
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Total (95% CI): 100.0% 1.04 [1.00, 1.08]

Heterogeneity: Tau² = 0.00; Chi² = 13.35, df = 5 (p = 0.02); I² = 63%
Test for overall effect: Z = 2.03 (p = 0.04)

Figure 1.