Hippocampal Volume

<table>
<thead>
<tr>
<th>HDL level 5 years before MRI</th>
<th>Regression Coefficient (95% CI)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 503)</td>
<td>0.07 (−0.31 to 0.17)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age 75–85 yr (n = 165)</td>
<td>0.06 (−0.45 to 0.33)</td>
<td>0.76</td>
</tr>
<tr>
<td>HDL level at time of MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 503)</td>
<td>−0.09 (−0.31 to 0.13)</td>
<td>0.43</td>
</tr>
<tr>
<td>Age 75–85 yr (n = 165)</td>
<td>−0.20 (−0.58 to 0.18)</td>
<td>0.30</td>
</tr>
</tbody>
</table>


**Table. The Association between Serum HDL Levels and Hippocampal Volume on MRI in the Rotterdam Scan Study**

**References**


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**References**

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We appreciate the additional information provided by Dr Den Heijer and colleagues and their comments concerning our study.1 Using a well-described large population-based sample of elderly subjects, they did not find a significant association between hippocampal volume (HcV) and serum high-density lipoprotein cholesterol (HDL-C). This may look like a failure to replicate our findings. However, although both studies share a similar design (including the limitation of using only a single hippocampal measurement), we wonder whether they are directly comparable. Our sample was selected to represent cases along the cognitive continuum from normal cognition to mild dementia in Alzheimer's disease (AD) and thus naturally included a considerable proportion of preclinical AD cases. Den Heijer’s sample likely included a larger proportion of cognitively healthy elderly subjects.

We were intrigued by the idea that subgroup effects could have caused the divergent results in the two samples. In their comments, Den Heijer and colleagues also mentioned the possibility that subgroup effects (with preclinical AD cases tending to have smaller HcV and lower HDL-C) could have led to inhomogeneity correlations in our sample. Clinical follow-up information of up to 3 years duration (mean, 2.6; standard deviation [SD], 0.5) was available for 57 of the 61 nondemented subjects in our baseline sample. Fourteen patients with very mild to mild AD diagnosed were also followed up, and the diagnosis was clinically confirmed. In the 57 nondemented subjects, the presence of significant decline was established based on normative change rates more than 1 SD of the normative range, the presence of “possible AD” at baseline was inferred and the subject was redefined as belonging to the possible/probable AD group. The Figure shows the distribution of HcV and HDL-C at baseline in the newly defined “possible/probable AD” group. In fact, there is a tendency toward smaller HcV and lower HDL-C in this subgroup (see Fig). However, the positive correlation between HcV and HDL-C remained and became even stronger in the 24 possible/probable AD cases (r = 0.44, p = 0.03). No significant correlation was present in the remaining cognitively stable subjects (r = 0.12, p = 0.4). The correlations in both subgroups did not differ statistically and yielded an aggregated correlation coefficient of 0.25 (p = 0.03). Controlling for statin use and the presence of coronary artery disease in partial correlation analyses did not alter these results. Hence, we can show that our findings were not caused by statistical artifact. The association between HcV and HDL-C appeared to be weaker or absent in elderly subjects with stable cognitive functions, although not significantly so. This may be caused by a lack of variability in HcV within this subgroup, and it could explain the divergent findings between the two studies.

These modified analyses confirm the previously reported weak association between HcV and serum HDL-C in our sample. Furthermore, they suggest a role of serum HDL-C in AD progression which is in accordance with a previous study.3 Longitudinal studies with several measurements of serum lipids and hippocampal volumes in populations at risk for AD are needed to draw conclusions about the causality of the observed relationship.

We are confident that this discussion will help trigger further research, and we look forward to a fruitful scientific dispute.

This work was supported by the Interdisziplinäres Zentrum für Klinische Forschung (IZKF), and Leipzig at the Faculty of Medicine of the Universität Leipzig (Project 8).

References

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Reply
Henrike Wolf, MD, PhD,1 Miia Kivipelto, MD, PhD,2 Anke Hensel, PhD,1 Bengt Winblad, MD, PhD,2 Steffi G. Riedel-Heller, MD, PhD,1 and Hermann-Josef Gertz, MD, PhD1

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References

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Fig. Black dots indicate cases with mild possible/probable AD, n = 24 (67% female), white dots indicate the remaining subjects n = 46 (67% female). Subjects with missing follow-up information were deleted from the data set. Spearman correlation coefficients were 0.44 (p = 0.03) in the possible/probable AD group and 0.12 (p = 0.4) in the remaining subjects. ICV = intracranial volume; NCI = no cognitive impairment; sMCI = stable mild cognitive impairment; pMCI = progressive mild cognitive impairment; AD = Alzheimer’s disease.