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BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

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## HUMAN NEUROPATHOLOGY

# Plasma high-density lipoprotein levels is associated with preserved hippocampal volume in Alzheimer's disease individuals without vascular co-pathology

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## Abstract

**Background:** Dysregulation of cholesterol metabolism contributes to the increase of cerebral vascular diseases, favoring the development of dementia. In this sense, high levels of high-density lipoprotein (HDL) are considered protective against the outcomes associated with cardiovascular diseases. However, little is known about the effect of plasma HDL levels to alterations of cerebral volume in non-vascular AD and vascular AD individuals. Here we evaluated the association of plasma HDL levels with alterations in brain volume and with plasma neurofilament light chain (NfL) levels.

**Method:** We analyzed 135 AD individuals from the Biobank Innovations for Chronic Cerebrovascular Disease with Alzheimer's Disease Study [BICWALZS] cohort. Based on Fazekas scale for brain white matter lesions, we stratified AD individuals into two groups: non-vascular AD [Fazekas score = 1 and amyloid-$\beta$ (A$\beta$) positive/n = 76], and vascular AD [Fazekas score = 2, 3 and A$\beta$ positive/n = 59] (**Figure 1A**). Linear regression models accounting for vascular co-pathology APOE$\varepsilon$4 carriership, age and sex were used to test associations of plasma HDL with the variables of interest.

**Result:** We observed a significant interaction between plasma HDL levels and presence of vascular pathology on total brain white matter (b = 0.375, p = 0.019, **Fig. 1B**; **Table 2**). Analyzing the hippocampal atrophy through the global Schelten's scale, we observed that high plasma HDL levels was negatively associated with hippocampal

atrophy only in non-vascular AD individuals (b = -0.405, p < 0.001, **Fig. 1C**). However, no effect of plasma HDL levels on total gray matter and hippocampal volume was observed (**Table 1**). Non-vascular AD individuals with high hippocampal atrophy scores showed reduced plasma HDL levels compared to non-vascular AD individuals with low hippocampal atrophy scores (p < 0.01, **Fig. 1D**). Furthermore, no associations of plasma HDL with NfL levels were detected, regardless of the brain vascular status (**Fig. 1E**).

**Conclusion:** We showed that high plasma HDL levels is associated with less white matter pathology and reduced hippocampal atrophy scores, without changing plasma NfL levels. Together our findings indicate that high HDL levels seem to be associated with preserved brain volume only in AD individuals with no vascular co-pathology.

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Table 1: LME coefficients

| | β (95% CI) | *Z*-Score | *P*-value |
|---|---|---|---|
| **Model A: Gray Matter Volume ~ Plasma HDL + Vascular status [A] + Apoe4 carriership [B] + covariates [C]** | | | |
| Non-vascular AD | 0.103 (-0.146 to 0.352) | 0.825 | 0.412 |
| Vascular AD | 0.092 (-0.216 to 0.401) | 0.600 | 0.550 |
| **Model B: White Matter Volume ~ Plasma HDL + Vascular status + Apoe4 carriership + covariates** | | | |
| Non-vascular AD | -0.160 (-0.341 to 0.020) | -1.771 | 0.081 |
| Vascular AD | 0.131 (-0.108 to 0.372) | 1.104 | 0.275 |
| **Model C: Hippocampus Volume ~ Plasma HDL + Vascular status + Apoe4 carriership + covariates** | | | |
| Non-vascular AD | -0.027 (-0.296 to 0.242) | -0.201 | 0.841 |
| Vascular AD | 0.142 (-0.147 to 0.432) | 0.991 | 0.326 |
| | β (SD) | T-value | P-value |
| **Model D: Gray Matter Volume ~ Plasma HDL * Vascular status + Apoe4 carriership + covariates** | | | |
| HDL * Vascular status | 0.069 (0.209) | 0.332 | 0.740 |
| **Model E: White Matter Volume ~ Plasma HDL * Vascular status + Apoe4 carriership + covariates** | | | |
| HDL * Vascular status | 0.375 (0.157) | 2.379 | **0.019** |
| **Model F: Hippocampus Volume ~ Plasma HDL * Vascular status + Apoe4 carriership + covariates** | | | |
| HDL * Vascular status | 0.217 (0.191) | 1.135 | 0.258 |

[A] Vascular status was defined as the presence of high Fazekas scores (2 and 3).
[B] ApoE e2/e4, e3/e4 and e4/e4 individuals were considered positive for Apolipoprotein 4 carriership.
[C] Potential confounder included in the models as covariates are the following: age and sex.

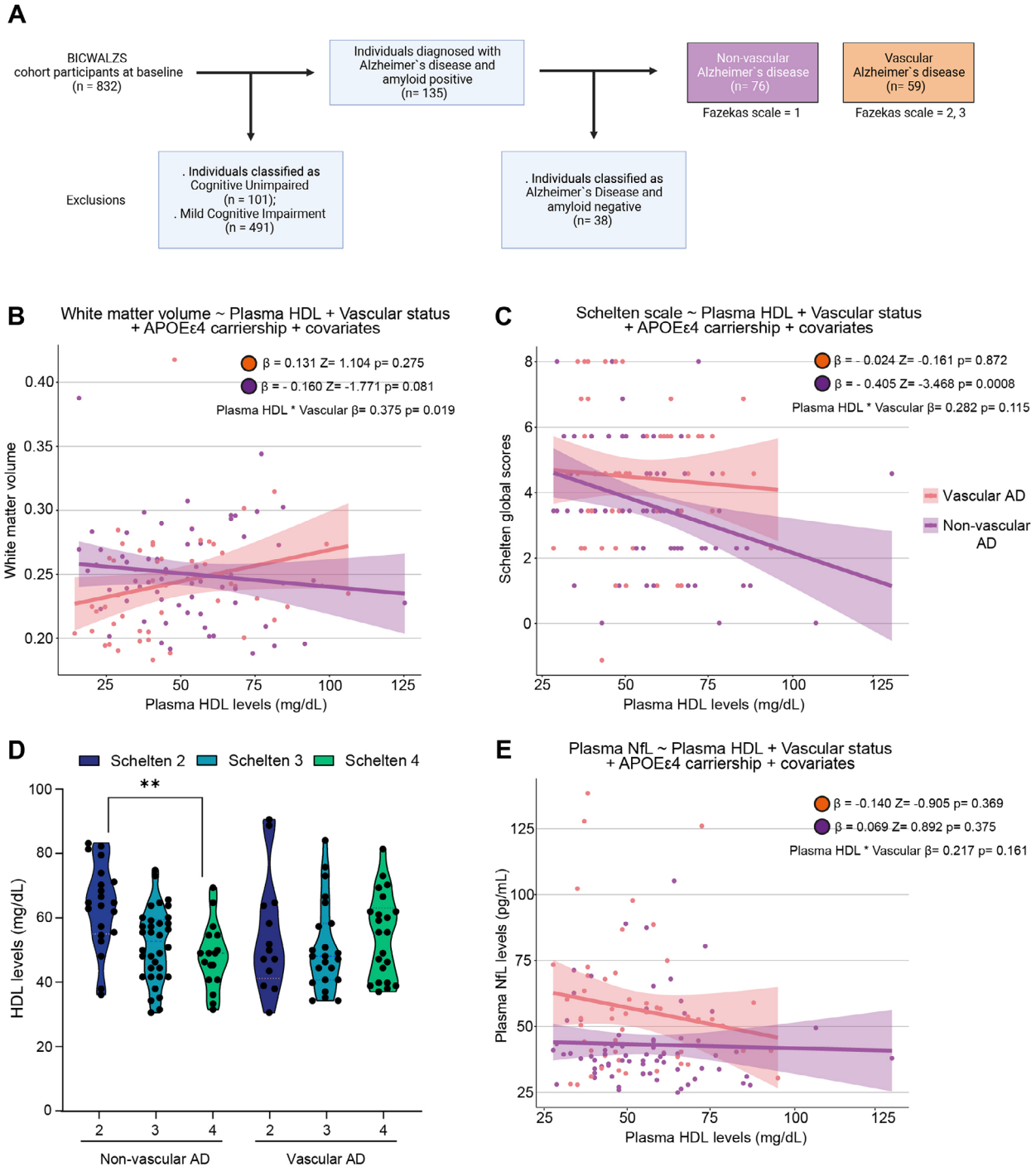


*Figure 1: Plasma high-density lipoprotein (HDL) levels alter brain white matter volume and decreases hippocampal atrophy scores in non-vascular Alzheimer`s Disease (AD) patients.* (A) Flowchart of included patients. (B) Association of brain white matter volume with plasma HDL levels. (C) Association of Schelten scale scores with plasma HDL levels. (D) Association of plasma neurofilament light polypeptide (NfL) levels with plasma HDL levels. All the linear regression models were carried out accounting for brain vascular burden, APOE ε4 carriership, age and sex (E) Plasma HDL levels according to Schelten category in non-vascular and vascular AD.