Assessing the correlation between plasma and cerebrospinal fluid antioxidants in healthy individuals and Alzheimer's patients

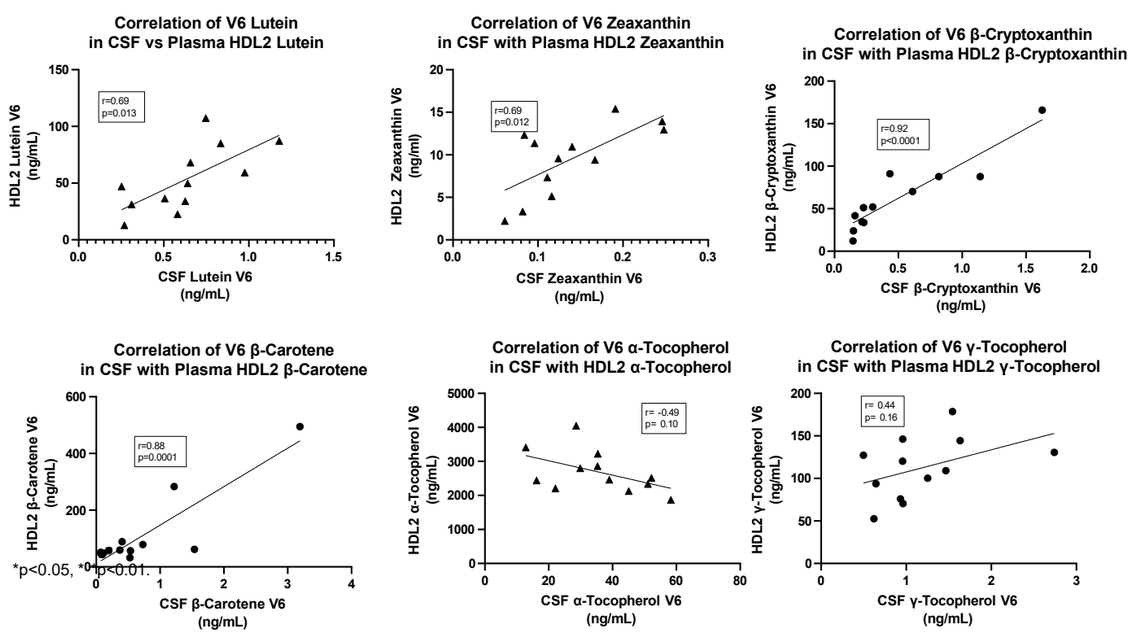
Mathijs A.C. de Kleer[1], Serge Rezzi[2], Pablo Hänggi[2], Andrew Hodgson[2], Larry Lo[1], Marc Ditmarsch[1], John J.P. Kastelein[1], Eric J. Niesor[3]

[1] NewAmsterdam Pharma, Naarden, Netherlands, [2] Hartis Pharma, Nyon, Switzerland, [3] Swiss Nutrition and Health Foundation, Epalinges, Switzerland

Background

- Alzheimer's disease (AD) is linked to neuroinflammation driven by elevated oxidative stress. This oxidative stress may, in turn, be associated with reduced levels of antioxidants—e.g. carotenoids and tocopherols —in the CSF of patients with AD. (1-3).
- Evidence exists that higher plasma levels of antioxidants reduces the rate of neurodegeneration and cognitive impairment in AD (2-4).
- HDL particles serve as a crucial transport system for antioxidants, carrying them from the intestines through the circulation to diverse tissues, including the brain. (5-7).
- Obicetrapib, a phase 3 CETP inhibitor, lowers LDL-C (40%) and substantially raises HDL-C (140%) (8,9).
- In a proof-of-concept, single-arm study in apoE4 AD patients, obicetrapib increased lutein, zeaxanthin, and α-tocopherol levels in both plasma and CSF, with a significant correlation between these compartments (Figure 1) (10).
- A pre-specified analysis assessing the effect of obicetrapib on AD biomarkers, including pTau-217, in a phase 3 study in patients with ASCVD, showed a reduction of biomarkers, particularly in apoE4 carriers (8,11).
- To better characterize antioxidant levels in plasma and CSF across the apoE spectrum, and its correlation between these compartments, antioxidant levels were assessed in untreated AD patients and healthy individuals.

Figure 1. Plasma–CSF Correlation of HDL-associated Carotenoids and Tocopherols after 24 weeks (V6) of obicetrapib 10mg/d in a proof-of-concept study in subjects with AD (n=12); highly positive to moderate correlations were observed for respectively carotenoids, and tocopherols.



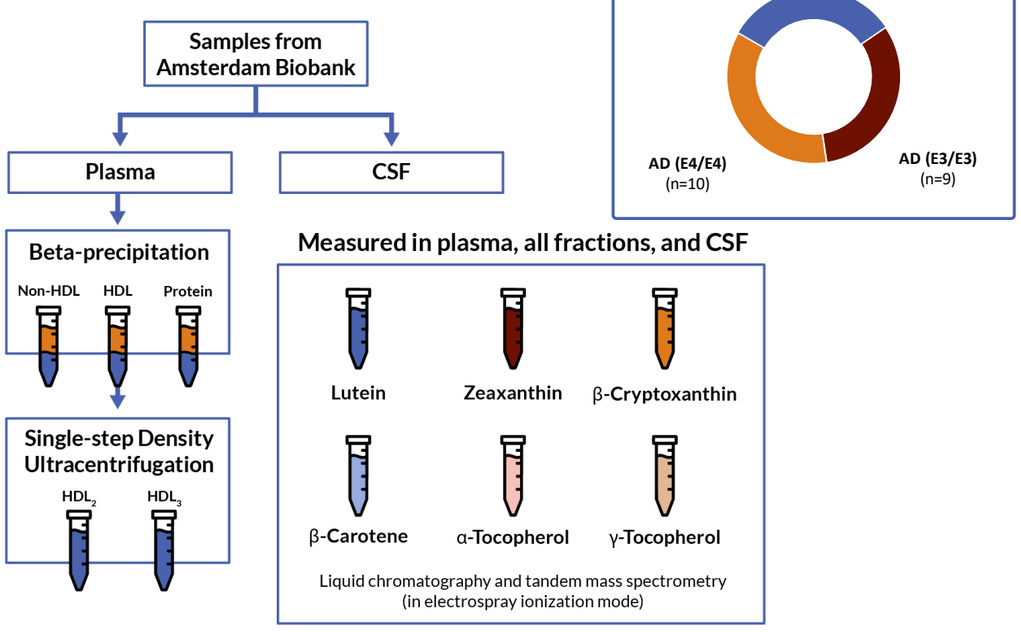
*p<0.05, *0 p<0.01.

Objectives

This study aimed to assess correlations of antioxidant concentrations between (1) whole plasma and CSF and between (2) the plasma derived HDL3 fraction and CSF, across APOE genotypes in healthy individuals and untreated AD patients.

Methods

Figure 2. Study design.



Results

- Overall, highly significant correlations emerged between plasma and CSF antioxidant levels for: lutein, zeaxanthin, β-cryptoxanthin, β- carotene, and α-tocopherol, except for γ-tocopherol (see Figure 3 and Table 1).
- In particular, antioxidant levels correlated significantly between the HDL3 plasma fraction and CSF, except for α- and γ- tocopherol (see Figure 4 and Table 1)
- When assessing the healthy individuals, AD patients with an E3/E3 and AD patients with an E4/E4 genotype separately, similar trends were observed for these correlations.

Figure 3. Correlations between plasma and CSF antioxidant concentration in a cohort of healthy individuals (n=9) and AD patients with E3/E3 (n=9) and E4/E4 (n=10).

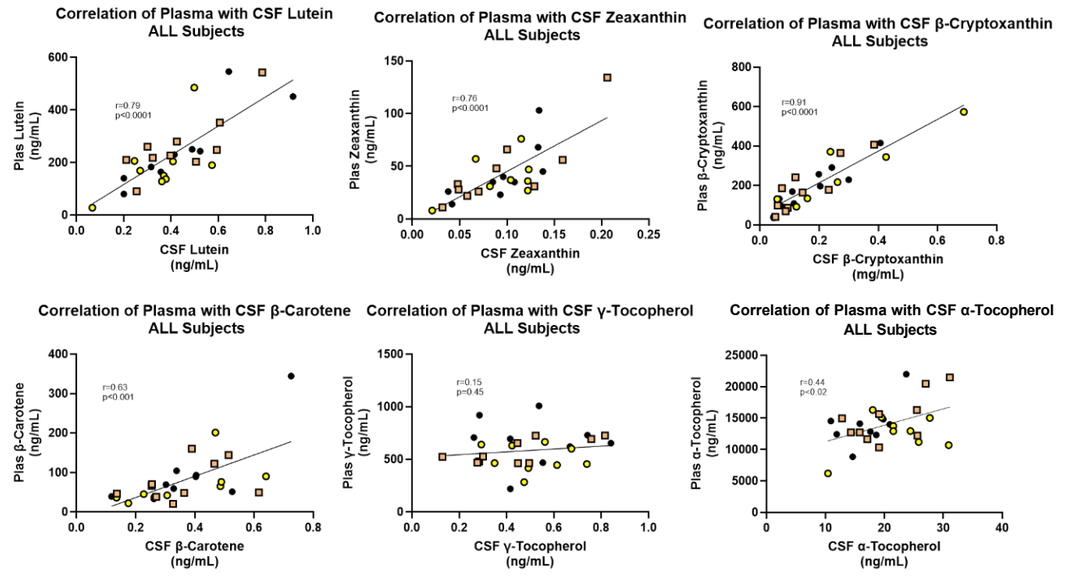


Figure 4. Correlations between HDL3 and CSF antioxidant concentration in a cohort of healthy individuals (n=9) and AD patients with E3/E3 (n=9) and E4/E4 (n=10).

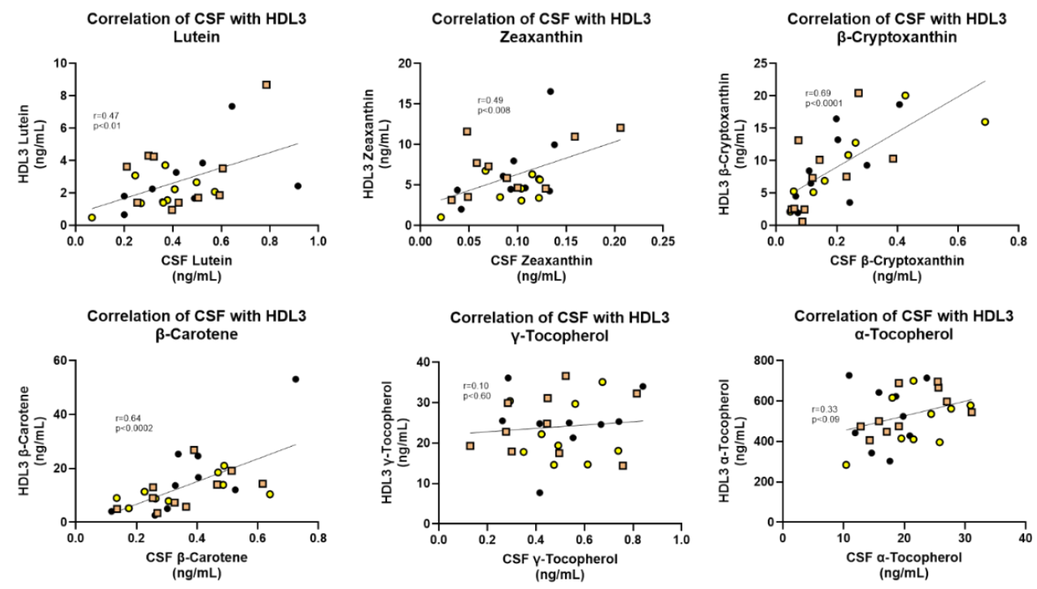


Table 1. Pearson R and Spearman R^2 correlations between whole plasma and CSF and between the plasma-derived HDL3 fraction and CSF in a cohort of healthy individuals (n=9) and AD patients with E3/E3 (n=9) and E4/E4 (n=10).

		Lutein	Zeaxanthin	β-Cryptoxanthin	β-Carotene	γ-Tocopherol	α-Tocopherol
Plasma	**R**	**0.79 (p<0.0001)**	**0.76 (p<0.0001)**	**0.91 (p<0.0001)**	**0.63 (p<0.001)**	0.15 (p=0.45)	**0.44 (p<0.02)**
	R^2	**0.53 (p<0.0001)**	**0.51 (p<0.0001)**	**0.74 (p<0.0001)**	**0.43 (p=0.0002)**	0.02 (p=0.5232)	0.10 (p=0.1062)
HDL3	**R**	**0.47 (p<0.01)**	**0.49 (p<0.008)**	**0.69 (p<0.0001)**	**0.64 (p<0.0002)**	0.10 (p<0.60)	0.33 (p<0.09)
	R^2	**0.15 (p=0.0385)**	**0.18 (p=0.0264)**	**0.56 (p<0.0001)**	**0.45 (p<0.0001)**	<0.01 (p=0.7640)	0.09 (p=0.1176)

Conclusions

- In an untreated cohort of E3/E3 and E4/E4 AD patients as well as healthy individuals, concentrations of antioxidants showed significant correlations between whole plasma and CSF as well as between the plasma derived HDL3 fraction and CSF.
- These correlations support the hypothesis that antioxidants in CSF are derived from the circulation and most likely transported from plasma to CSF by HDL particles.
- These data open up new avenues to treat disorders characterized by low levels of antioxidants, such as AD, and age-related macular degeneration.

References

1. Ionescu-Tucker A, et al. Emerging roles of oxidative stress in brain aging and Alzheimer's disease. *Neurobiol Aging.* 2021;107:86-95.
2. Dorey CK, et al. Low xanthophylls, retinol, lycopene, and tocopherols in grey and white matter in brains with Alzheimer's disease. *J Alzheimers Dis.* 2023;94:1-17.
3. Flieger J, et al. Carotenoid supplementation for alleviating the symptoms of Alzheimer's disease. *Int J Mol Sci.* 2024;25:8982.
4. Liu X, et al. APOE-epsilon4-dependent associations between carotenoids and cognitive decline: findings from the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) randomized controlled trial. *Am J Clin Nutr.* 2025;122:1289-97.
5. Wang W, et al. Effect of dietary lutein and zeaxanthin on plasma carotenoids and their transport in lipoproteins in age-related macular degeneration. *Am J Clin Nutr.* 2007;85:762-9.
6. Zhu P, et al. Mechanisms of high-density lipoprotein in regulating blood-brain barrier function: insights and implications. *Fluids Barriers CNS.* 2025;22:113.
7. Davidson MH, et al. The emerging role of CETP inhibition in the prevention of Alzheimer's disease. *Am J Prev Cardiol.* 2026;in press:101442.
8. Nicholls SJ, et al. Safety and efficacy of obicetrapib in patients at high cardiovascular risk. *N Engl J Med.* 2025;393:51-61.
9. Nicholls SJ, et al. Obicetrapib in patients with heterozygous familial hypercholesterolemia: the BROOKLYN randomized clinical trial. *Nat Med.* 2026;32:1052-60.
10. NewAmsterdam Pharma. Data on file. Proof-of-concept, open-label study in patients with early Alzheimer's disease. ClinicalTrials.gov Identifier NCT05161715.
11. Davidson MH, et al. Effect of obicetrapib, a potent cholesteryl ester transfer protein inhibitor, on p-tau2017 levels in patients with cardiovascular disease. *J Prev Alzheimers Dis.* 2026;13:100394.

Abbreviations

AD, Alzheimer's disease; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CETP, cholesteryl ester transfer protein; CSF, cerebrospinal fluid; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; ns, not significant; Plas, plasma.

Author Disclosures

MACdK, MD, LO JJPK Employees and Shareholders of NewAmsterdam Pharma, SR, Ph, AH, Employees of Hartis Pharma, EJN, Principal and Employee, Swiss Nutrition and Health Foundation,

Support

This study was funded by NewAmsterdam Pharma, Naarden, The Netherlands.

NewAmsterdam Pharma