Distinct biological profile in *oldest-old* Alzheimer's Disease: the role of LDL-C on Blood-Brain Barrier function and disease burden

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Objectives

With **increasing life expectancy**, more patients are diagnosed with **Alzheimer's disease (AD) after the age of 78.** However, if this oldest-old population exhibits distinct biological features remains poorly understood.

- The primary objective of this study was to **characterize this subgroup** by comparing them to age-matched non-AD controls and to patients with typical-onset AD (aged 65–77).
- A secondary objective was **to investigate the relationship between vascular risk factors**—particularly low-density lipoprotein cholesterol (LDL-C)—blood-brain barrier (BBB) permeability (assessed via QAlb), **and CSF AD biomarkers** (Aβ42, t-tau, p-tau181) within each group.

Materials

The study included **157 subjects** with AD diagnosis confirmed by CSF biomarkers: 67 AD patients aged 65–77 (AD-young), 90 AD patients aged ≥80 (AD-old), and 38 age-matched controls (CTRL-old). Collected data included LDL-C, total cholesterol, QAlb, core AD biomarkers and APOE genotype.

Methods

Group comparisons were conducted using ANOVA and X2 test. Pearson's correlation coefficient (r) assessed linear relationships between LDL-C and AD biomarkers in each group. Multivariate linear regression analyses were performed to control for potential confounders (sex and APOE ε4 status). Post hoc analyses were performed following significant ANOVA results. Statistical analyses were conducted using JASP© (Version 0.19.3, JASP Team, 2025).

Results

The table below summarizes the demographic characteristics, CSF biomarkers data, and lipid profile values considered in the study, stratified according to the different patient's groups for comparative analysis. **[tab. 1]**

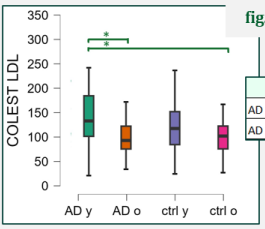
When comparing AD-old and AD-young groups, no significant differences were observed in CSF AD biomarkers and Qalb. However, **LDL-C levels were significantly higher in AD-young** (LDL-C mean = 137.4 ± 50.7 mg/dL) than in AD-old (LDL-C mean = 98.6± 33.4 mg/dL). P value for LDL-C was p < 0.01. **[fig. 1]**

No significant differences were observed in Qalb or cholesterol levels between the AD-old and CTRL-old groups.

tab. 1

		AD young	AD old	CTRL young	CTRL old	p value (ANOVA)
age	mean± SD	70.6± 3.9	80.5± 2.5	70.3± 4.2	79.9± 2.3	<0.001
sex	F%	46%	56%	46%	68%	0.111
ApoE	E4%	47%	28%	14%	10%	< 0.001
CSF Aß 42	mean± SD	376.1± 107.1	358.1± 106.5	930.7± 371.1	854.5± 260.8	< 0.001
CSF t tau	mean± SD	471.4± 303.9	465.9± 423.8	215.5± 73.4	210.8± 79.5	< 0.001
CSF p tau	mean± SD	65.1± 33.8	63.3± 41.6	41.9± 9.4	39.5± 11.4	< 0.001
Qalb	mean± SD	7.6± 3.6	7.8± 6.8	7.1± 3.8	7.7± 5.0	0.918
C tot	mean± SD	187.6± 43.8	173.6± 40.0	179.3± 42.1	182.3± 49.3	0.246
HDL-C	mean± SD	55.7± 15.2	51.4± 15.4	51.0± 14.1	50.9± 13.5	0.217
TGL	mean± SD	114.3± 50.2	118.2± 61.5	137.4± 65.6	126.6± 47.2	0.225
LDL-C	mean± SD	137.4± 50.7	98.6± 33.4	118.4± 48.2	106.0± 45.5	<0.001

fig. 1



p tukey (post hoc)	
AD young-AD old	p < 0.001
AD young- ctrl young	p 0.003

Considering AD patients and stratifying for age, we explored the relationship between LDL-C and several variables such as Qalb, CSF t-tau, CSF p-tau181/Aβ42:

- Among AD-young, LDL-C negatively correlated with QAlb (r = -0.308, p = 0.011). **[fig. 2]**
- Among AD-old, LDL-C positively correlated with CSF t-tau (r=0.239, p=0.023) and with CSF p-tau181/Aβ42 (r=0.237, p=0.024). **[fig. 3]**

fig.2

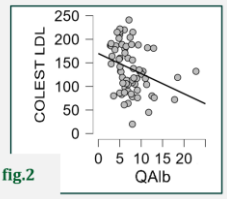
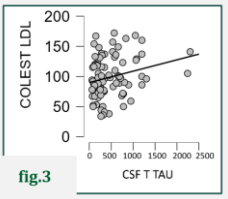


fig.3



The association between LDL-C and Qalb in AD young was confirmed in multivariate regression after correcting for APOE genotype.
The association between LDL-C, CSF t-tau and CSF p-tau181/Aβ42 in AD old were confirmed in multivariate regression after correcting for sex and APOE genotype.

Discussion

Despite a comparable pathological burden and similar BBB permeability between the AD-old and AD-young groups, our findings revealed an association between LDL-C and AD biomarkers in the oldest-old. In contrast, in younger AD patients, LDL-C was associated with BBB integrity but not with CSF biomarkers of AD, despite the higher mean LDL-C levels observed in the younger group. These results suggest that LDL-C may play different roles in disease mechanisms depending on age.

Conclusion

We highlight the need to consider **the oldest-old** as a possible **distinct clinical and biological subgroup** of AD, to tailor therapeutic approaches accordingly.

[1]Bonomi CG et al (2024), Age of onset moderates the effects of Vascular Risk Factors on Neurodegeneration, Blood-Brain-Barrier permeability, and cognitive decline in Alzheimer's Disease. Alzheimers Res Ther. 16;16(1):248. doi: 10.1186/s13195-024-01617-2.

[2]Kawas CH et al (2006), Alzheimer's and dementia in the oldest-old: a century of challenges. Curr Alzheimer Res. 3(5):411-9. doi: 10.2174/156720506779025233.

[3]Ricci F et al (2024), Effect of Vascular Risk Factors on Blood-Brain Barrier and Cerebrospinal Fluid Biomarkers Along the Alzheimer's Disease Continuum: A Retrospective Observational Study. J Alzheimers Dis. 97(2):599-607. doi: 10.3233/JAD-230792.