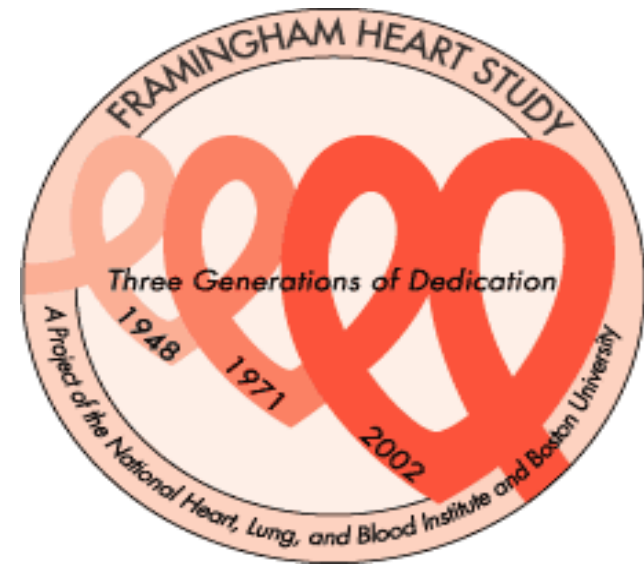


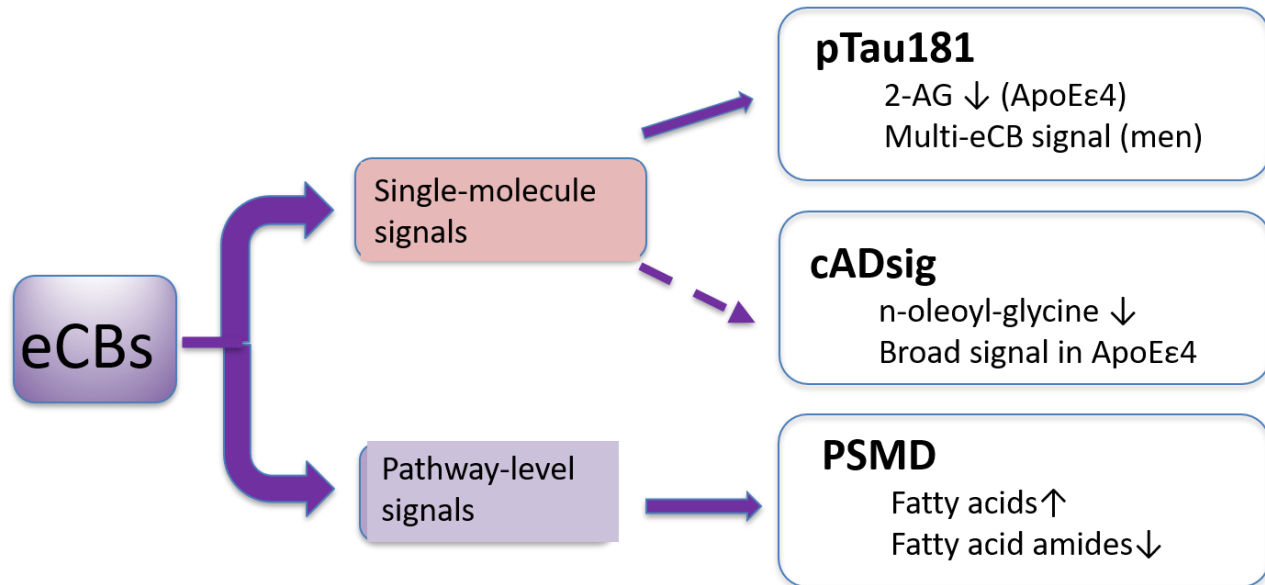
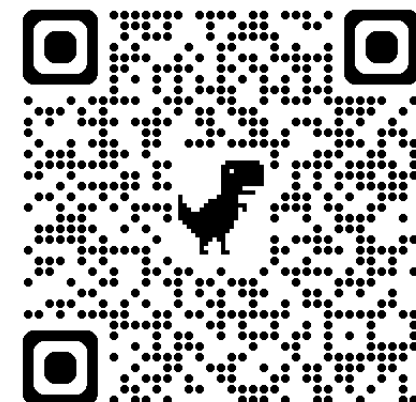
Circulating endocannabinoids, plasma p-tau and neuroimaging markers in cognitively healthy older adults



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eCB associations with neurodegeneration differ by outcome, with molecule-specific effects (pTau181, cADsig) and pathway-level signals (PSMD), particularly in ApoEε4 carriers and men.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																														
- The endocannabinoid (eCB) system regulates neuroinflammation and synaptic function, key processes in Alzheimer’s disease (AD) pathophysiology. - Experimental studies suggest that eCBs influence tau phosphorylation and white matter integrity, but population-based evidence in cognitively healthy older adults is limited. - In prior work, we showed that circulating eCB levels are associated with cognitive function¹ and brain MRI measures ², with significant interactions by sex. - We aimed to explore the associations between circulating eCB levels and key neurodegeneration biomarkers: - Plasma phosphorylated tau181 (pTau181) - Peak width of skeletonized mean diffusivity (PSMD) - Cortical Alzheimer’s disease signature (cADsig)	Serum levels of 44 eCBs and eCB-like compounds were analyzed in 235 cognitively healthy participants aged ≥65 years from the Framingham Heart Study (FHS) Offspring cohort (2011-2014). Associations between eCB levels and neurodegeneration markers (pTau181, PSMD, cADsig) were assessed using: - Linear regression, with false discovery rate (FDR) correction for multiple testing - Least Absolute Shrinkage and Selection Operator (LASSO) regression to evaluate all eCBs simultaneously and perform variable selection. Optimal penalty (λ min) selected via 10-fold cross-validation. All analyses were implemented using the glmnet package in R. - Exploratory factor analysis (FA) to reduce multicollinearity and derive latent eCB profiles. Factors were applied to log-transformed eCB concentrations and exatracted using the regression method (psych pakage, R). Factor scores were used as predictors in linear and LASSO regression. - All models adjusted for age, sex, ApoEε4 genotype and time between blood draw and MRI. - Stratification by sex and ApoEε4 were conducted in all models.	Participants’ mean age was 73.3±6.2 years; 40% were men. Factor analysis suggested retaining 9 factors, which together showed clear biological structure, with each factor grouping molecules sharing fatty acid backbone or head-group chemistry. <table><tr><th>Signal type</th><th>Pattern</th><th>Key drivers</th></tr><tr><td colspan="3">pTau181</td></tr><tr><td>Molecule level</td><td>Single molecule</td><td>2-AG ↓ (ApoEε4+) (β = -0.42, p-FDR = 0.048)</td></tr><tr><td>System level</td><td>34/44 eCBs, suggesting broad system-level reorganization</td><td>Broad LASSO patterns</td></tr><tr><td>System level</td><td>Multiple eCBs (n = 13) indicating a robust signal in men but not women.</td><td></td></tr><tr><td>System level</td><td>In ApoEε4 carriers, signals involved DHA-related glycerols and fatty acid pathways</td><td>Fatty acid pathway</td></tr><tr><td colspan="3">cADsig</td></tr><tr><td>Molecule level</td><td>n-oleoyl-glycine consistent signal in linear regression (p = 0.005) and LASSO</td><td>n-oleoyl-glycine</td></tr><tr><td colspan="3">PSMD</td></tr><tr><td>System level</td><td>Fatty acids were associated with higher PSMD and Fatty acid amides with lower PSMD.</td><td>Pathway-related associations only</td></tr></table> 	Signal type	Pattern	Key drivers	pTau181			Molecule level	Single molecule	2-AG ↓ (ApoEε4+) (β = -0.42, p-FDR = 0.048)	System level	34/44 eCBs, suggesting broad system-level reorganization	Broad LASSO patterns	System level	Multiple eCBs (n = 13) indicating a robust signal in men but not women.		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Pathway-related associations only	- eCB–neurodegeneration associations are outcome-specific: - pTau181 → molecule + system-level effects - cADsig → consistent molecule-specific signal - PSMD → pathway-level (latent) effects - pTau181 showed the strongest signal, driven by: 2-AG ↓ pTau181 in ApoEε4 carriers (only FDR-significant result) - Broad eCB involvement (LASSO) with sex-specific patterns (men) and ApoEε4-related lipid pathways - cADsig was characterized by a single robust metabolite: - n-oleoyl-glycine ↓ cADsig, replicated across methods and subgroups - PSMD reflected pathway-level biology rather than single metabolites: - Fatty acids ↑ PSMD; fatty acid amides ↓ PSMD - Supporting latent eCB profiles (FA) as key drivers of white matter integrity. The endocannabinoid system represents a multi-level biomarker and potential therapeutic target, with precision-medicine relevance depending on outcome and subgroup context.	¹Vered S, Beiser AS, Sulimani L, Sznitman S, Ghosh S, Lewitus GM, Meiri D, Seshadri S, Weinstein G. Circulating Endocannabinoids and Cognitive Function in Older Adults. Aging Dis. 2024 Dec 20;17(1):518-529. ²Vered S, Beiser AS, Sulimani L, Sznitman S, Gonzales MM, Aparicio HJ, DeCarli C, Scott MR, Ghosh S, Lewitus GM, Meiri D, Seshadri S, Weinstein G. The association of circulating endocannabinoids with neuroimaging and blood biomarkers of neuro-injury. Alzheimers Res Ther. 2023 Sep 12;15(1):154.
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