Supplementary Online Content

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Sensitivity Analysis for Alzheimer Disease Diagnosis (CN vs AD) Group Differences in Liver Function Biomarkers

Liver function marker	excluding outliers			keeping outliers		
	Odds Ratio	95% CI	Corrected *P* Value	Odds Ratio	95% CI	Corrected *P* Value
Albumin	5.789	0.040,843.993	4.90×10^{-1}	5.789	0.040,843.993	4.90×10^{-1}
Alkaline Phosphatase	3.620	0.844,15.529	1.25×10^{-1}	3.620	0.844,15.529	1.25×10^{-1}
ALT	0.133	0.042,0.422	3.63×10^{-3}	0.120	0.039,0.374	2.55×10^{-3}
AST	0.229	0.045,1.175	1.25×10^{-1}	0.203	0.041,1.021	1.06×10^{-1}
AST:ALT	7.932	1.673,37.617	2.73×10^{-2}	9.815	2.156,44.670	9.41×10^{-3}
Total Bilirubin	1.405	0.585,3.377	4.90×10^{-1}	1.405	0.585,3.377	4.90×10^{-1}

Abbreviations: AST: Aspartate aminotransferase; ALT: alanine aminotransferase. Age, sex, body mass index, and *APOE* ε4 status included as covariates

eTable 2. Demographic Information of ADNI Participants

Variable	CN (N=407)	SMC (N=20)	EMCI (N=298)	LMCI (N=544)	AD (N=312)	*P* Value
Age (years)	74.5 (5.7)	71.6 (5.1)	70.9 (7.4)	73.5 (7.6)	74.6 (7.7)	1.94×10^{-11}
Sex: (Male/Female)	206/201	10/10	166/132	331/213	171/141	3.35×10^{-2}
Education (years)	16.3 (2.7)	16.8 (2.2)	16.0 (2.6)	15.9 (3.0)	15.1 (3.0)	1.59×10^{-6}
BMI (Kg/M^2)	27.4 (4.5)	29.3 (4.6)	28.4 (5.3)	26.9 (4.3)	26.1 (4.4)	6.94×10^{-9}
APOE ε4 status (0/1)	294/113	15/5	169/129	249/295	98/214	$<2.20 \times 10^{-16}$
Albumin (g/dL)	4.09 (0.31)	3.94 (0.25)	4.10 (0.29)	4.14 (0.32)	4.11 (0.32)	1.29×10^{-2}
Alkaline phosphatase (U/L)	75.3 (20.7)	74.4 (14.1)	71.1 (17.9)	74.9 (22.4)	76.2 (19.2)	2.09×10^{-2}
ALT (U/L)	21.5 (8.4)	24.2 (6.6)	22.2 (9.3)	20.7 (8.0)	19.5 (7.0)	5.44×10^{-5}
AST (U/L)	24.3 (6.2)	25.2 (8.0)	24.7 (7.4)	24.1 (6.1)	23.7 (6.3)	4.66×10^{-1}
AST:ALT	1.22 (0.32)	1.06 (0.22)	1.18 (0.31)	1.25 (0.31)	1.29 (0.35)	1.22×10^{-5}
Total bilirubin (mg/dL)	0.52 (0.26)	0.44 (0.14)	0.54 (0.28)	0.53 (0.24)	0.56 (0.30)	3.02×10^{-1}
Memory composite score	0.94 (0.53)	0.99 (0.57)	0.53 (0.49)	-0.04 (0.57)	-0.77 (0.54)	$<2.20 \times 10^{-16}$
Executive function composite score	0.75 (0.71)	0.82 (0.64)	0.47 (0.76)	0.01 (0.80)	-0.88 (0.82)	$<2.20 \times <10^{-16}$

Abbreviations: AD: Alzheimer's Disease; ALT: alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body Mass Index; CN: Cognitively Normal; EMCI: early mild cognitive impairment; LMCI: late MCI; SMC: subjective memory concerns

eTable 3. Diagnostic Group Differences in Liver Function Biomarkers

Liver function marker	CN vs EMCI		CN vs LMCI		CN vs AD	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Albumin (g/dL)	0.811	0.006,117.8	19.623	0.333,1156.4	5.789	0.040,844.0
Alkaline Phosphatase (U/L)	0.144	0.035,0.588	0.883	0.290,2.694	3.620	0.844,15.53
ALT (U/L)	0.561	0.196,1.604	0.291	0.112,0.755	0.133	0.042,0.422
AST (U/L)	0.742	0.170,3.230	0.393	0.102,1.506	0.229	0.045,1.175
AST:ALT	1.240	0.278,5.540	3.783	0.995,14.38	7.932	1.673,37.62
Total Bilirubin (mg/dL)	1.319	0.556,3.133	0.887	0.417,1.886	1.405	0.585,3.377

Abbreviations: AD: Alzheimer's Disease; ALT: alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body Mass Index; CN: Cognitively Normal; EMCI: early mild cognitive impairment; LMCI: late MCI. Age, sex, body mass index, and APOE ε4 status were included as covariates.

eTable 4. Diagnostic Group Differences of Liver Function Biomarkers With Alzheimer Disease Diagnosis (CV vs AD) Adjusted for Gamma-Glutamyltransferase (GGT) and Statin Use

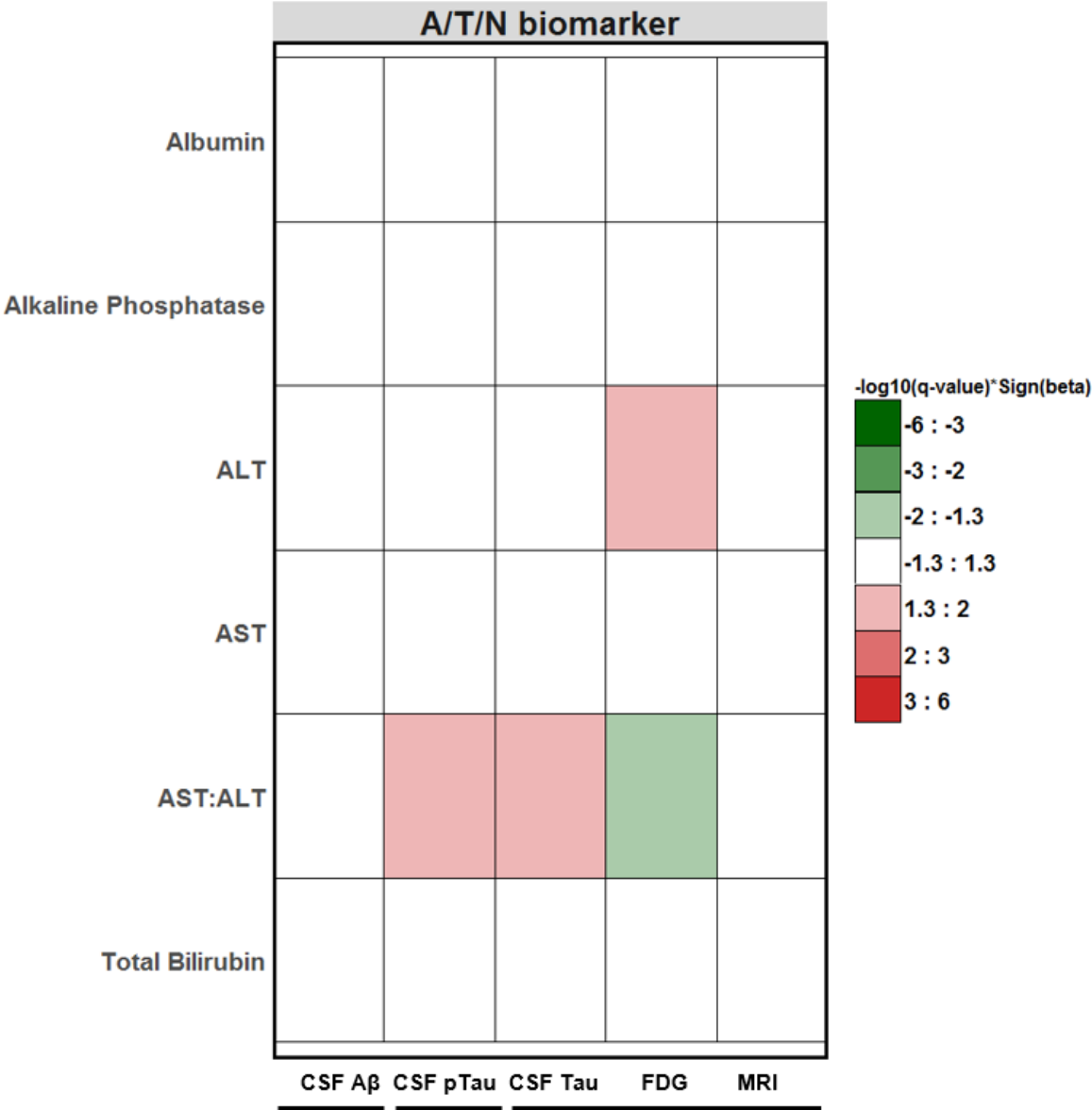| Liver function marker	Odds Ratio	95% CI	Corrected *P* Value
Albumin (g/dL)	5.595	0.037, 840.4	5.01×10^{-1}
Alkaline Phosphatase (U/L)	4.296	0.982, 18.79	1.06×10^{-1}
ALT (U/L)	0.112	0.032, 0.386	3.16×10^{-3}
AST (U/L)	0.246	0.045, 1.348	1.59×10^{-1}
AST:ALT	8.580	1.713, 42.98	2.68×10^{-2}
Total Bilirubin (mg/dL)	1.461	0.603, 3.539	4.82×10^{-1}

Abbreviations: AST: Aspartate aminotransferase; ALT: alanine aminotransferase

eTable 5. Association of Liver Function Biomarkers With Cognition Adjusted for Gamma-Glutamyltransferase (GGT) and Statin Use

Liver function markers	Memory			Executive function		
	β	SE	Corrected *P* Value	β	SE	Corrected *P* Value
Albumin (g/dL)	-0.843	0.578	1.93×10^{-1}	-0.238	0.691	7.31×10^{-1}
Alkaline Phosphatase (U/L)	-0.427	0.163	1.51×10^{-2}	-0.607	0.194	5.52×10^{-3}
ALT (U/L)	0.476	0.139	3.62×10^{-3}	0.733	0.165	1.18×10^{-4}
AST (U/L)	0.366	0.187	7.62×10^{-2}	0.631	0.224	1.16×10^{-2}
AST:ALT	-0.511	0.188	1.33×10^{-2}	-0.709	0.224	5.52×10^{-3}
Total Bilirubin (mg/dL)	-0.066	0.103	6.22×10^{-1}	-0.070	0.123	6.22×10^{-1}

Abbreviations: AST: Aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase. Covariates included age, sex, education, body mass index, *APOE* ε4 status, statins use, and gamma-glutamyl transferase.

Supplementary Figure 1: Liver function biomarkers and their association with ATN biomarkers for Alzheimer's disease adjusted for statin use and gamma-glutamyltransferase. Heat map of q-values of association between liver function biomarkers and the "A/T/N" biomarkers for Alzheimer's disease. P-values estimated from linear regression analyses were corrected for multiple testing using FDR (q-value). Color code: white indicates q-value>0.05, red indicates significant positive associations, and green indicates significant negative associations.