Supplementary Materials

Lower hepatic *CBS* and *PEMT* expression in advanced NAFLD: inferencing strategies to lower homocysteine with a mathematical model

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Supplementary Table 1. Exploratory analyses of the associations between the histologic severity of NAFLD and hepatic expression of genes involved in homocysteine metabolism in subgroups divided by age 50 years and sex: Women aged ≤50 (1a), Women aged >50 (1b), Men aged ≤50 (1c), and Men aged >50 (1d).

1a) Women aged ≤50 (N=20)

Genes	Steatosis grade					NASH					Fibrosis stage				
	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p
BHMT	0.82	3.30	0.20	0.7691	0.7691	1.18	1.98	0.71	0.4995	0.9299	0.97	1.52	0.62	0.8848	0.9548
BHMT2	1.78	4.69	0.67	0.2255	0.6481	1.16	1.69	0.79	0.4280	0.9299	0.96	1.33	0.69	0.7779	0.9548
CBS	1.62	3.54	0.74	0.2064	0.6481	1.08	1.54	0.75	0.6673	0.9299	1.38	1.78	1.08	**0.0148**	0.0741
MARS	1.12	2.53	0.50	0.7675	0.7691	1.00	1.36	0.74	0.9913	0.9913	0.87	1.11	0.68	0.2404	0.4006
MTHFR	1.44	2.81	0.74	0.2592	0.6481	1.04	1.36	0.80	0.7485	0.9299	1.01	1.25	0.81	0.9548	0.9548
PEMT	0.51	3.27	0.08	0.4491	0.7486	0.81	1.62	0.41	0.5312	0.9299	1.63	2.84	0.93	0.0817	0.2722
PON1	1.90	4.66	0.78	0.1459	0.6481	1.27	1.84	0.87	0.1940	0.9299	1.60	2.00	1.29	**0.0004**	**0.0036**
PON2	0.81	2.75	0.24	0.7183	0.7691	1.15	1.79	0.73	0.5277	0.9299	1.19	1.73	0.81	0.3491	0.4987
PON3	0.55	2.49	0.12	0.4130	0.7486	1.06	2.01	0.56	0.8369	0.9299	1.38	2.35	0.81	0.2132	0.4006
HERPUD1	1.15	2.27	0.59	0.6559	0.7691	1.05	1.35	0.81	0.7093	0.9299	1.14	1.39	0.94	0.1685	0.4006

1b) Women aged >50 (N=35)

Genes	Steatosis grade					NASH					Fibrosis stage				
	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p
BHMT	2.66	5.32	1.33	**0.0071**	0.0709	1.18	1.98	0.71	0.4995	0.9299	0.85	1.14	0.64	0.2731	0.4641
BHMT2	1.51	2.57	0.88	0.1258	0.6290	1.16	1.69	0.79	0.4280	0.9299	0.81	0.99	0.67	**0.0369**	0.1229
CBS	1.05	1.80	0.61	0.8487	0.8641	1.08	1.54	0.75	0.6673	0.9299	1.19	1.45	0.98	0.0746	0.1864
MARS	1.04	1.59	0.68	0.8641	0.8641	1.00	1.36	0.74	0.9913	0.9913	0.83	0.97	0.71	**0.0177**	0.0885
MTHFR	0.90	1.19	0.68	0.4445	0.7986	1.04	1.36	0.80	0.7485	0.9299	1.00	1.12	0.89	0.9534	0.9534
PEMT	0.70	1.68	0.30	0.4157	0.7986	0.81	1.62	0.41	0.5312	0.9299	1.64	2.18	1.23	**0.0014**	**0.0143**
PON1	1.21	1.85	0.79	0.3789	0.7986	1.27	1.84	0.87	0.1940	0.9299	0.94	1.11	0.79	0.4304	0.6149
PON2	0.77	1.62	0.37	0.4791	0.7986	1.15	1.79	0.73	0.5277	0.9299	1.01	1.36	0.76	0.9245	0.9534
PON3	1.16	2.34	0.57	0.6774	0.8641	1.06	2.01	0.56	0.8369	0.9299	1.16	1.52	0.88	0.2785	0.4641
HERPUD1	1.07	1.67	0.69	0.7549	0.8641	1.05	1.35	0.81	0.7093	0.9299	1.02	1.21	0.86	0.7922	0.9534

1c) Men aged ≤50 (N=17)

Genes	Steatosis grade					NASH					Fibrosis stage				
	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p
BHMT	1.88	2.92	1.21	**0.0080**	**0.0100**	0.98	1.37	0.69	0.8840	0.9567	1.03	1.58	0.67	0.9022	0.9124
BHMT2	1.34	2.11	0.85	0.1994	0.1994	0.94	1.42	0.62	0.7531	0.9567	1.03	1.74	0.62	0.8943	0.9124
CBS	2.11	2.99	1.49	**0.0003**	**0.0007**	1.19	1.51	0.94	0.1276	0.3189	0.87	1.20	0.63	0.3829	0.9124
MARS	2.10	3.15	1.40	**0.0012**	**0.0020**	0.78	1.01	0.61	0.0622	0.3109	1.02	1.48	0.70	0.9124	0.9124
MTHFR	2.53	3.55	1.80	**0.0000**	**0.0001**	0.97	1.21	0.77	0.7597	0.9567	1.03	1.40	0.77	0.8126	0.9124
PEMT	1.78	3.05	1.04	**0.0382**	**0.0424**	0.65	1.11	0.38	0.1080	0.3189	2.05	3.75	1.12	**0.0230**	0.2301
PON1	2.37	3.59	1.56	**0.0004**	**0.0008**	0.99	1.35	0.73	0.9567	0.9567	1.15	1.70	0.78	0.4457	0.9124
PON2	2.60	3.76	1.79	**0.0000**	**0.0001**	0.97	1.30	0.73	0.8476	0.9567	1.13	1.63	0.79	0.4809	0.9124
PON3	2.64	4.54	1.53	**0.0015**	**0.0022**	1.48	2.21	0.99	0.0565	0.3109	0.80	1.40	0.46	0.4147	0.9124
HERPUD1	2.99	4.39	2.04	**0.0000**	**0.0001**	0.98	1.29	0.75	0.8901	0.9567	0.91	1.30	0.64	0.5885	0.9124

1d) Men aged >50 (N=10)

Genes	Steatosis grade					NASH					Fibrosis stage				
	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p	OR	LLC	ULC	Raw_P	FDR_p
BHMT	0.62	9.03	0.04	0.6498	0.8123	1.18	3.83	0.37	0.7357	0.8327	0.70	3.26	0.15	0.5756	0.8223
BHMT2	0.66	2.97	0.14	0.4877	0.6967	1.32	2.75	0.63	0.3948	0.6929	0.76	1.98	0.29	0.4973	0.8223
CBS	2.58	13.23	0.50	0.1874	0.5084	0.57	1.19	0.27	0.1118	0.4580	2.09	5.12	0.85	0.0897	0.4487
MARS	0.67	1.99	0.23	0.3752	0.6967	1.21	2.28	0.64	0.4850	0.6929	0.95	2.14	0.42	0.8822	0.9101
MTHFR	1.43	4.64	0.44	0.4560	0.6967	0.81	1.56	0.43	0.4674	0.6929	1.39	2.95	0.65	0.3168	0.8175
PEMT	4.85	52.02	0.45	0.1408	0.5084	0.39	0.99	0.15	**0.0477**	0.4580	3.60	10.42	1.24	**0.0268**	0.2680
PON1	1.03	5.10	0.21	0.9628	0.9628	1.07	2.33	0.49	0.8466	0.8466	0.71	1.77	0.28	0.3774	0.8175
PON2	3.10	18.85	0.51	0.1602	0.5084	0.55	1.29	0.24	0.1374	0.4580	1.07	4.22	0.27	0.9101	0.9101
PON3	1.32	14.58	0.12	0.7688	0.8543	0.87	2.49	0.30	0.7494	0.8327	0.63	2.36	0.17	0.4087	0.8175
HERPUD1	1.84	5.57	0.61	0.2034	0.5084	0.74	1.41	0.39	0.2981	0.6929	1.08	2.61	0.45	0.8316	0.9101

OR: odds ratio. LLC: lower limit of 95% confidence interval. ULC: upper limit of 95% confidence interval. Raw_p: raw p-values.

The table presents adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) after controlling for age, BMI, diabetes, alcohol use, smoking, and assay categories [testing vs. validation cohort]. Statistically significant findings based on raw p-values are highlighted in bold. Given the small sample size, these analyses are likely underpowered. Additionally, due to the risk of overfitting in a small cohort, these results are not confirmatory and should be interpreted with caution.