SUPPLEMENTARY MATERIAL

A genetic risk score and diabetes predict development of alcohol-related cirrhosis in drinkers

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Supplementary Figure 1. Comparison of the 3-SNP and 3-SNP-M scores, for patients in the GenomALC-2 cohort calculated as in Table 1. The diagonal line shows x = y.



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Supplementary Figure 2. Effect of varying the 3-SNP score cut-off for classification into the high-risk group on the proportion of cases

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stratified as high-risk and the Odds Ratios comparing the high-and low-risk groups. Data shown are for GenomALC-1.

The left-hand panel shows the distribution of scores in Cases and Controls, as in Figure 1; those with scores below 0 (continuous horizontal line) are always considered as the low-risk group while those above the interrupted horizontal lines (at 0.7, 0.8, 0.9 or 1.0) are in the high-risk group. The Table shows results (OR) at each of the evaluated high-risk thresholds.

Cut-off for high-	Proportion of cases	Odds Ratio, High versus
risk group	above cut-off	Low group (95% CI)
1.0	25%	7.35 (5.01 to 10.78)
0.9	28%	5.86 (4.13 to 8.33)
0.8	37%	4.95 (3.60 to 6.81)
0.7	49%	4.96 (3.67 to 6.71)

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Supplemental Figure 3. Comparison of means for 3-SNP scores between diagnostic groups from three independent studies. Points and bars show means and standard errors. *Other:* no excessive drinking; *Excessive drinker:* high-risk drinking by the 50/80 grams/day criterion; *Alcohol dependence:* alcohol dependence [ICD-10 F10.2]; *Categories of alcohol-related liver disease are:* alcoholic fatty liver, ALD unspecified, alcoholic hepatitis, alcoholic hepatic failure and alcoholic cirrhosis (overall, and sub-divided by HCC status).



Supplementary Figure 4. Means of the 3-SNP score by country (AU Australia, BE Belgium, FR France, DE Germany, CH Switzerland, UK United Kingdom, US United States). Error bars show standard errors for the means.



Supplementary Table 1. Numbers of participants, and diagnostic categories, by country of recruitment. Restricted to participants with relevant genotyping and clinical risk factor data.

GenomALC-1 samples

		Alcohol-	
		related	
	Control	cirrhosis	Total
Australia	175	129	304
France	103	373	476
Germany	142	75	217
Switzerland	33	28	61
UK	77	257	334
USA	58	240	298
Total	588	1102	1690

GenomALC-2 samples

			Alcohol-	
		Alcoholic	related	
	Control	hepatitis	cirrhosis	Total
Australia	68	0	36	104
Belgium	258	223	663	1144
France	58	0	85	143
Germany	31	0	15	46
Switzerland	3	0	0	3
UK	184	771	356	1311
USA	2	277	7	286
Total	604	1271	1162	3037

UK Biobank samples

No relevant diagnosis	494,910	
Excessive drinker, no liver diagnosis	6304	
Alcoholic fatty liver	95	
Alcoholic liver disease, unspecified	428	
Alcoholic fibrosis and sclerosis	17	
Alcoholic hepatitis	130	
Alcoholic hepatic failure	88	
Alcoholic cirrhosis	594	
Alcoholic cirrhosis without HCC		542
Alcoholic cirrhosis with HCC		52
Total	502,566	

Note for UK Biobank cohort: Total number excludes people who withdrew consent and those with unknown sex or alcohol intake. Numbers in italics are for alcohol-related liver diseases other than cirrhosis.

		GenomALC-1 (N = 1390)			GenomALC-2 (N = 1766) ⁽¹⁾				UK Biobank (N= 6898) ⁽²⁾				
		Cases (N =917)	Controls	(N = 473)	Cases (N	= 1162)	Controls	(N = 604)	Cases (N = 594)		Controls (N = 6304)
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
		Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)
Demogr aphics	Age (Mean \pm SD, in years)	53.0 ± 8.5 (674)	51.0 ± 8.9 (243)	50.0 ± 9.5 (331)	50.6 ± 9.7 (142)	55.2 ± 10.4 (702)	54.5 ± 10.1 (288)	47.4 ± 10.9 (394)	50.4 ± 10.1 (186)	57.8 ± 6.9 (477)	57.2 ± 7.7 (117)	56.5 ± 7.6 (4836)	54.8 ± 7.7 (1468)
	Years of Education	12.0 ± 3.5 (665)	11.5 ± 303 (240)	12.0 ± 3.9 (326)	12.8 ± 3.9 (141)					11.3 ± 2.2 (357)	11.2 ± 2.2 (83)	11.4 ± 2.1 (3785)	11.7 ± 2.0 (927)
	BMI, kg/m ²	28.0 ± 5.6 (673)	26.1 ± 6.2 (242)	25.8 ± 4.7 (330)	25.4 ± 5.8 (142)					29.1 ± 5.4 (466)	27.4 ± 5.0 (117)	28.4 ± 4.5 (4836)	26.9 ± 4.8 (1460)
	European ethnicity/race (by self- report)	99.6%	99.6%	99.7%	98.6%	100%	100%	99.7%	99.5%	96.2%	94.8%	98.5%	97.4%
Alcohol use	Alcohol intake, g/day	262 ± 431 (674)	189 ± 349 (243)	251 ± 298 (331)	186 ± 100 (142)					49.0 ± 55.0 (477)	22.4 ± 26.8 (117)	104.1 ± 27.7 (4836)	66.3 ± 19.5 (1468)
	Age started XS drinking	26.9 ± 9.8 (674)	31.3 ± 10.6 (242)	25.5 ± 9.0 (329)	29.7 ± 10.8 (141)								
	Years of high-risk drinking	25.0 ± 11.2 (674)	19.1 ± 9.1 (243)	21.6 ± 9.3 (331)	18.4 ± 7.4 (142)								
	Audit Score	10.5 ± 10.6 (673)	11.6 ± 11.5 (241)	26.8 ± 9.4 (330)	26.8 ± 10.1 (140)								
	Lifetime alcohol intake, kg	2310 ± 4034 (674)	1316 ± 2548 (243)	2073 ± 3327 (331)	1244 ± 892 (142)								
Lab results	Haemoglobin (g/L)	117 ± 26 (653)	113 ± 21 (239)	147 ± 14 (315)	135 ± 14 (136)								
	INR (ratio)	$1.40 \pm 0.43 (609)$	$1.54 \pm 0.58 (223)$	$0.99 \pm 0.17 (272)$	$0.97 \pm 0.11 (111)$	$1.44 \pm 0.52 (51)$	1.44 ± 0.48 (134)	1.11 ± 0.41 (51)	1.04 ± 0.11 (16)				
	Albumin (g/L)	34.5 ± 6.8 (623)	34.8 ± 7.5 (227)	43.2 ± 5.1 (314)	43.2 ± 5.7 (132)	35.0 ± 7.3 (336)	33.5 ± 7.1 (128)	$40.9 \pm 10.7 (100)$	40.8 ± 9.7 (45)	42.5 ± 4.7 (407)	43.1 ± 4.4 (101)	45.5 ± 2.7 (4175)	45.5 ± 2.7 (1250)
	Bilirubin (µmol/L)	60.6 ± 100.5 (661)	81±121 (243)	9.1 ± 5.8 (320)	8.2 ± 5.6 (140)	()		12.8 ± 5.3 (59)	10.2 ± 4.5 (32)	15.3 ± 12.3 (443)	12.1 ± 7.9 (109)	9.9 ± 4.1 (4505)	8.3 ± 3.3 (1357)
	Creatinine (µmol/L)	94 ± 67 (661)	105 ± 486 (242)	75 ± 17 (324)	62 ± 15 (141)					77 ± 34 (445)	59 ± 15 (110)	77 ± 14 (4536)	62 ± 12 (1365)
	ALT (unit/L)	36.8 ± 40.2 (661)	34.3 ±33.2 (242)	43.3 ± 46.3 (326)	38 ± 38 (141)	54.6 ± 219.2 (342)	34.2 ± 25.7 (132)	45.6 ± 45.2 (240)	34.3 ± 43.9 (122)	45.0 ± 38.7 (444)	38.0 ± 26.3 (110)	31.1 ± 19.1 (4529)	(1366) (1366)
	AST (unit/L)	60.2 ± 51.0 (654)	64.5 ± 51.3 (238)	43.6 ± 41.0 (320)	41 ± 38 (140)	90.1 ± 307.7	64.9 ± 51.5 (132)	52.2 ± 56.5 (242)	36.2 ± 22.6 (124)	61.3 ± 46.1 (442)	62.4 ± 51.0 (109)	33.1 ± 19.2 (4504)	26.7 ± 12.6 (1357)
	GGT (unit/L)	225 ± 371 (623)	173 ± 264 (222)	124 ± 255 (315)	122 ± 216 (139)	(0.10)				233 ± 245 (434)	$\begin{array}{c} 216\pm239\\(108)\end{array}$	86.5 ± 87.8 (4528)	$\begin{array}{c} 46.8\pm56.6\\(1366)\end{array}$

Supplementary Table 2. Demographic, clinical and substance use characteristics of participants included.

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Liver	MELD score	11.2 ± 7.4	11.1 ± 9.1	1.9 ± 3.3	-0.7 ± 3.1								
disease		(604)	(222)	(266)	(110)								
	Number with ascites (ever)	520/674	189/243,	0	0	294/572	131/241	None	None				
		(77%)	(78%)			(51%)	(54%)	recorded	recorded				
	Number with oesophageal	358/669	120/239	0	0	49/177	23/87	None	None				
	varices (ever)	(53%)	(49%)			(28%)	(26%)	recorded	recorded				
	Number with encephalopathy	209/651	91/240	0	0	72/531	24/226	None	None				
	(ever)	(31%)	(37%)			(14%)	(11%)	recorded	recorded				
	Number with HCC (ever)	105/674	10/243	0	0	9/157	None	None	None	49/477	3/117	0/4721	0/1458
		(16%)	(4%)			(6%)	recorded	recorded	recorded	(10.3%)	(2.6%)	(0%)	(0%)
	Number abstinent for ≥ 60 days	234/674	154/243	8/332	3/142	Not	Not	3/394	1/186				
	-	(35%)	(63%)	(2%)	(2%)	recorded	recorded	(0.8%)	(0.5%)				
	Number (%) with known	159/674	39/243	26/332	5/142					109/468	16/117	271/4813	34/1466
	diabetes	(24%)	(16%)	(8%)	(4%)					(23.3%)	(13.7%)	(5.6%)	(2.3%)
Cannabi	Regular use, 5+ years, during	67/673	8/142	90/329	24/142								
s use	period of high alcohol use	(10%)	(3%)	(27%)	(17%)								
	Years of regular use (if ever	$17.5 \pm$	$15.9 \pm$	$15.5 \pm$	$14.6 \pm$								
	regular user)	14.2 (66)	11.0(7)	10.1 (89)	10.4 (24)								
	Days per week marijuana	4.6 ± 2.3	5.1 ± 2.2	5.3 ± 2.4	5.7 ± 1.9								
		(67)	(8)	(89)	(24)								
	Occasions total	$4424 \pm$	$4520 \pm$	4374 ±	4279 ±								
		4742 (66)	4119 (7)	3795 (89)	3063 (24)								
Smokin	Regular smoker (ever)	513/674	156/243	279/331	111/142					342/473	78/116	3589/4825	1093/1464
g	-	(76%)	(64%)	(84%)	(78%)					(72.5%)	(67.2%)	(74.4%)	(74.7%)
history													
	Pack years (if ever smoker)	35.4 ±	24.1 ±	$35.3 \pm$	33.8 ±								
	•	32.3 (370)	18.4 (96)	27.8 (174)	21.3 962)								
	Regular use, 5+ years, during	398/674	113/243	240/331	88/142								
	period of high alcohol use	(59%)	(47%)	(73%)	(62%)								
Coffee	Years coffee (if regular user)	32.2 ±	$28.9 \pm$	$25.3 \pm$	$24.2 \pm$								
intake		12.9 (347)	13.3 (100)	11.8 (225)	11.3 (81)								
	Cups caffeinated coffee per day	3.7 ± 3.5	3.7 ± 3.9	4.1 ± 3.6	3.4 ± 2.3					$1.87 \pm$	$1.80 \pm$	2.23 ± 2.36	2.10 ± 2.05
	(if regular user)	(347)	(100)	(224)	(81)					2.23 (430)	2.35 (110)	(4438)	(1378)

Supplementary Table 3. Comparison of score performance measures in men and women.

ROC Curve	Logistic 1	regression	Q1-Q5 Odds Ratio
AUC	Beta	p-value	(95% CIs)

3-SNP score	GenomALC-1	Men	0.671 ± 0.016	1.132 ± 0.116	1.41 x 10 ⁻²²	6.18 (4.05 to 9.41)
		Women	0.650 ± 0.027	0.974 ± 0.192	3.79 x 10 ⁻⁷	5.40 (2.67 to 10.92)
	GenomALC-2	Men	0.592 ± 0.017	0.575 ± 0.107	6.76 x 10 ⁻⁸	2.47 (1.68 to 3.62
		Women	0.635 ± 0.025	0.897 ± 0.172	1.94 x 10 ⁻⁷	3.81 (2.05 to 7.07)
	UK Biobank	Men	0.635 ± 0.016	0.800 ± 0.088	1.14 x 10 ⁻¹⁹	3.44 (2.48 to 4.77)
		Women	0.554 ± 0.036	0.375 ± 0.196	0.056	2.08 (1.11 to 3.89)
3 SNP score + BMI, coffee	UK Biobank	Men	0.645 ± 0.017	0.795 ± 0.082	4.55 x 10 ⁻²²	3.50 (2.34 to 5.24)
		Women	0.594 ± 0.034	0.535 ± 0.164	0.0011	2.79 (1.37 to 5.71)
3-SNP-M score ⁱ	GenomALC-2	Men	0.626 ± 0.017	0.873 ± 0.124	1.94 x 10 ⁻¹²	3.79 (2.50 to 5.75)
		Women	0.638 ± 0.025	0.978 ± 0.186	142 x 10 ⁻⁷	3.27 (1.77 to 6.06)
5-SNP-M score ⁱ	GenomALC-2	Men	0.622 ± 0.017	0.791 ±0.116	7.87 x 10 ⁻¹²	3.47 (2.31 to 5.23)
		Women	0.632 ± 0.025	0.848 ± 0.174	1.09 x 10 ⁻⁶	3.92 (2.18 to 7.03)
8-SNP-M score	GenomALC-2	Men	0.631 ± 0.017	0.789 ± 0.110	6.37 x 10 ⁻¹³	3.34 (2.24 to 4.98)
		Women	0.635 ± 0.025	0.836 ± 0.162	2.55 x 10 ⁻⁷	3.33 (1.90 to 5.85)

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Supplementary Table 4. Significance (p-values, not adjusted for multiple comparisons) for contrasts between groups of excessive drinkers with and without alcohol-related liver disease diagnoses in UK Biobank and GenomALC-2 cohorts. The dependent variable is the 3-SNP score. Boxes in the UK Biobank table emphasise the significant differences between the control groups and the more severe forms of liver disease, and the lack of significant differences among the more severe categories.

UK Biobank	Ν	Excessive drinker, no liver diagnosis	Alcoholic fatty liver	ALD unspecified	Alcoholic fibrosis sclerosis	Alcoholic hepatitis	Alcoholic hepatic failure	Alcoholic cirrhosis
Excessive drinker	5618	-						
Fatty liver	71	0.128	-					
ALD unspecified	327	0.0074	0.824	-				
Alcoholic Fibrosis/sclerosis	910	0.222	0.545	0.466	-			
Alcoholic hepatitis	796	7.75 x 10 ⁻⁴	0.293	0.095	0.904	-		
Alcoholic hepatic failure	52	0.0023	0.191	0.073	0.922	0.667	-	
Alcoholic Cirrhosis	448	2.51 x 10 ⁻²⁰	0.0332	3.30 x 10 ⁻⁵	0.8831	0.335	0.814	-

GenomALC-2	N	Control	Alcoholic hepatitis	Alcoholic cirrhosis
Control	604	-		
Alcoholic hepatitis	1271	7.95 x 10 ⁻⁹	-	
Alcoholic cirrhosis	1162	1.20 x 10 ⁻¹⁴	0.011	-

Supplementary Table 5. Effects of 3-SNP score on risk of alcohol-related liver diseases, graded by severity of liver disease, in GenomALC-1 sample and UK Biobank. In each cohort Controls were people who reported daily alcohol intake of \geq 80 grams (men)/ \geq 50 grams (women), for \geq 10 years. UK Biobank participants with 'mild' alcoholic liver disease had ICD-10 diagnoses of K70.0 (alcoholic fatty liver) or K70.9 (alcoholic liver disease, unspecified); there was no comparable group in the GenomALC participants. 'Severe' alcoholic liver disease comprised ICD-10 diagnoses of K70.1 (alcoholic hepatitis), K70.3 (alcoholic cirrhosis) or K70.4 (alcoholic hepatic failure) for UK Biobank, and alcoholic cirrhosis for GenomALC. HCC, hepatocellular carcinoma (ICD-10 C22.0). Coefficients (B) and Odds Ratios (OR) are expressed per unit change in the 3-SNP score.

			GenomAL			UK Biobank			
	В	SE	p-value	OR	95% CI	В	SE	p-value	C
drinkers) versus			N/A			0.271	0.089	0.0023	1
drinkers) versus no HCC	1.020	0.101	3.49 x 10 ⁻²⁴	2.773	2.277 to 3.377	0.652	0.074	8.77 x 10 ⁻¹⁹	1
drinkers) versus HCC	1.327	0.174	2.05 x 10 ⁻¹⁴	3.769	2.683 to 5.296	1.264	0.229	3.38 x 10 ⁻⁸	3.
s 'Severe'			N/A			0.378	0.111	6.50 x 10 ⁻⁴	1
no HCC versus HCC	0.401	0.155	0.010	1.493	1.102 to 2.022	0.631	0.242	0.0091	1