Supplemental Table 1. Sensitivity Analysis: Characteristics of the population at enrollment comparing patients reporting not drinking vs. drinking monthly or less vs. 2-4 times per month or more

Characteristic	Drinking status			P (Monthly or less vs. 2-4 times per month or more)
	Non-drinker (N=117)	Monthly or less (N=131)	2-4 times per month or more (N=37)	
Demographics				
Age at biopsy, years – mean ± SD	48.5 ± 10.7	45.6 ± 11.0	47.1 ± 11.7	0.45
Female sex – N (%)	89 (76.1)	91 (69.5)	19 (51.4)	0.05
Hispanic – N (%)	11 (9.4)	13 (9.9)	4 (10.8)	1.00
Race, White – N (%)	89 (76.1)	110 (84.0)	34 (91.9)	0.72
Ever smoked – N (%)	36 (30.8)	52 (39.7)	15 (40.5)	0.93
Current smoker – N (%)	9 (7.7)	12 (9.2)	0 (0.0)	0.07
Liver tests – Median (IQR)				
AST, U/L	42 (31-59)	43 (30-69)	49 (33-61)	0.82
ALT, U/L	57 (39-78)	62 (43-99)	65 (55-82)	0.90
Alkaline phosphatase, U/L	86 (70-106)	79 (66-94)	64 (55-82)	0.005
GGT, U/L	40 (29-79)	48 (28-84)	43 (26-64)	0.56
Histology – N (%)				
Steatosis grade				
1 - <33%	54 (46.2)	43 (32.8)	13 (35.1)	0.93
2 – 34-66%	34 (29.1)	47 (35.9)	12 (32.4)	
3 - >66%	29 (24.8)	41 (31.3)	12 (32.4)	
Lobular inflammation				
0 – none	1 (0.9)	-	-	0.06
1 - <2	58 (49.6)	58 (44.3)	21 (56.8)	
2 - 2-4	42 (35.9)	56 (42.8)	8 (21.6)	
3 - >4	16 (13.7)	17 (13.0)	8 (21.6)	
Chronic portal inflammation				
0 – none	16 (13.7)	19 (14.5)	9 (24.3)	0.33
1 – mild	72 (61.5)	85 (64.9)	20 (54.1)	
2 – more than mild	29 (24.8)	27 (20.6)	8 (21.6)	
Ballooning				
0 – none	26 (22.2)	41 (31.3)	13 (35.1)	0.91
1 – few	34 (29.1)	37 (28.2)	10 (27.0)	
2 – many	57 (48.7)	53 (40.5)	14 (37.8)	
Fibrosis stage				
0 – none	25 (21.4)	32 (24.8)	8 (21.6)	0.60
1a/1b/1c	35 (29.9)	41 (31.8)	14 (37.8)	
2	28 (23.9)	23 (17.8)	9 (24.3)	
3 – bridging	24 (20.5)	29 (22.5)	6 (16.2)	
4 – cirrhosis	5 (4.3)	4 (3.1)	0 (0.0)	
Iron grade				
0 – absent	86 (81.1)	95 (79.8)	22 (68.8)	0.49

| Characteristic | Drinking status | | | P (Monthly or less vs. 2-4 times per month or more) |
	Non-drinker (N=117)	Monthly or less (N=131)	2-4 times per month or more (N=37)	
1 – barely discernible, 20x	17 (16.0)	14 (11.8)	5 (15.6)	
2 – discrete granules resolved, 10x	3 (2.8)	9 (7.6)	4 (12.5)	
3 – discrete granules resolved, 4x	0 (0.0)	1 (0.8)	1 (3.1)	
NAFLD activity score				
<4	30 (25.6)	30 (22.9)	11 (29.7)	0.39
≥4	87 (74.4)	101 (77.1)	26 (70.3)	
NAS – mean, SD	4.7 ± 1.5	4.8 ± 1.6	4.6 ± 1.8	0.68
Diagnosis				
0 – NAFLD, not NASH	19 (16.2)	25 (19.1)	10 (27.0)	0.15
1a/1b – Borderline	12 (10.3)	33 (25.2)	4 (10.8)	
2 – Definite NASH	86 (73.5)	73 (55.7)	23 (62.2)	
Biopsy length, mm – mean, SD	19.9 ± 10.5	18.3 ± 8.7	17.0 ± 8.4	0.37
Range, mm	3-66	2-47	4-40	
Lipid panel – Median (IQR)				
Total cholesterol, mg/dL	192 (170-231)	196 (170-220)	184 (164-230)	0.91
HDL cholesterol, mg/dL	44 (37-50)	41 (35-50)	48 (40-53)	0.05
LDL cholesterol, mg/dL	117 (94-150)	122 (99-141)	122 (90-143)	0.67
Triglycerides, mg/dL	146 (113-208)	154 (109-206)	136 (97-188)	0.42
Metabolic factors				
Weight, kg – mean, SD	96.0 ± 22.2	99.1 ± 20.4	91.3 ± 14.8	0.09
BMI, kg/m^2	35.2 ± 7.4	35.3 ± 6.6	31.5 ± 4.7	0.003
Fasting glucose, mg/dL	96 (87-117)	99 (88-116)	100 (91-108)	0.83
Insulin, µU/mL	17 (13-27)	18 (13-29)	17 (12-31)	0.91
HOMA-IR	4.5 (2.8-7.2)	4.5 (3.2-7.6)	4.5 (2.9-7.6)	0.97
Comorbidities				
Diabetes – N (%)	44 (37.6)	44 (33.6)	10 (27.0)	0.55
Hypertension – N (%)	67 (57.3)	58 (44.3)	20 (54.1)	0.35
Hyperlipidemia – N (%)	70 (59.8)	66 (50.4)	17 (46.0)	0.71
Metabolic syndrome – N (%)	81 (70.4)	93 (71.5)	21 (56.8)	0.11
Genotype (N=155) – N (%)				
PNPLA3 rs738409				1.00
CC	16 (22.9%)	22 (33.3%)	6 (31.6%)	
GC	30 (42.9%)	24 (36.4%)	7 (36.8%)	
GG	24 (34.3%)	20 (30.3%)	6 (31.6%)	

Supplemental Table 2. Logistic regression analysis of modest drinking vs. non-drinking among patients with NAFLD (N=264)

	Independent discriminators for modest drinking vs. non-drinking: Full model			Independent discriminators for modest drinking vs. non-drinking: Reduced model*		
	Odds ratio[†]	95% CI	P	Odds ratio[†]	95% CI	P
Demographics			0.007			
Age at biopsy (years)	0.96	0.93 - 0.99	0.02	0.97	0.95 - 1.00	0.03
Female vs. male	0.80	0.37 - 1.76	0.58			
Hispanic vs. non-Hispanic	1.22	0.38 - 3.93	0.74			
White vs. non-white	3.32	1.49 - 7.37	0.003	2.50	1.22 - 5.12	0.01
Ever smoked vs. never smoked	2.14	1.16 - 3.98	0.02	1.97	1.11 - 3.49	0.02
Liver enzymes			0.008			
AST (per 10 U/L)	0.98	0.87 - 1.10	0.77			
ALT (per 10 U/L)	1.06	0.95 - 1.19	0.31	1.05	0.99 - 1.12	0.12
Alkaline phosphatase (per 10 U/L)	0.80	0.71 - 0.91	<0.001	0.82	0.74 - 0.91	<0.001
GGT (per 10 U/L)	1.05	0.98 - 1.12	0.17	1.06	0.99 - 1.12	0.09
Histology			0.01			
Steatosis grade			0.03			0.03
1 - <33% (ref)	1.00			1.00		
2 - 34-66%	2.44	1.22 - 4.87		2.06	1.09 - 3.90	
3 - >66%	1.96	0.94 - 4.10		2.00	1.00 - 3.99	
Lobular inflammation			0.75			
1 - <2 (ref)	1.00					
2 - 2-4	0.89	0.45 - 1.78				
3 - >4	1.29	0.47 - 3.54				
Ballooning			0.57			
0 - None (ref)	1.00					
1 - Few	1.96	0.54 - 7.08				
2 - Many	1.81	0.38 - 8.70				
Portal inflammation			0.93			
0 - None (ref)	1.00					
1- Mild	0.90	0.37 - 2.17				

	Independent discriminators for modest drinking vs. non-drinking: Full model			Independent discriminators for modest drinking vs. non-drinking: Reduced model*		
	Odds ratio[†]	95% CI	P	Odds ratio[†]	95% CI	P
2 - More than mild	0.81	0.27 - 2.43				
Fibrosis stage			0.54			
0 - None (ref)	1.00					
1a/1b/1c	2.25	0.88 - 5.79				
2	1.92	0.66 - 5.60				
3 - bridging	2.33	0.71 - 7.61				
4 - cirrhosis	2.77	0.44 - 17.48				
Diagnosis						
Definite NASH	0.19	0.05 - 0.71	0.01	0.41	0.23 - 0.76	0.004
Lipids			0.31			
HDL cholesterol (per 10 mg/dL)	1.22	0.86 - 1.73	0.27			
LDL cholesterol (per 10 mg/dL)	0.99	0.90 - 1.09	0.82			
Triglycerides (per 50 mg/dL)	0.86	0.69 - 1.06	0.15			
Metabolic factors			0.26			
BMI	0.97	0.92 - 1.02	0.23			
Insulin (per 10 μU/mL)	1.09	0.96 - 1.24	0.19			
Glucose (per 10 mg/dL)	1.11	0.97 - 1.26	0.14			
Metabolic syndrome	1.41	0.61 - 3.28	0.43			
Comorbidities			0.43			
Diabetes	1.24	0.58 - 2.63	0.58			
Hypertension	0.78	0.41 - 1.51	0.46			
Hyperlipidemia	0.72	0.38 - 1.34	0.30			

*Reduced model selected by AIC with forward selection from a logistic regression model that included all candidate variables listed in the table. Minimum AIC=331.8. N=264 due to missing values.
[†] Higher odds ratios favor modest drinkers.

Supplemental Table 3. Sensitivity Analysis: Change in histologic features from enrollment to follow-up comparing patients reporting drinking monthly or less vs. 2-4 times per month or more

	Drinks monthly or less (N=248)	Drinks 2-4 times per month or more (N=37)	Differences in adjusted mean changes from baseline or odds ratio (95% CI) Monthly or less drinker vs. 2-4 times/month or more	P
Steatosis				
Change in score	-0.40 (-0.50, -0.31)	-0.20 (-0.45, 0.05)	0.20 (-0.07, 0.47)	0.14
Patients improved	112 (45%)	13 (35%)	0.66 (0.32, 1.35)	0.25
Lobular inflammation				
Change in score	-0.27 (-0.36, -0.19)	-0.14 (-0.35, 0.07)	0.13 (-0.10, 0.36)	0.25
Patients improved	91 (37%)	11 (30%)	0.73 (0.34, 1.55)	0.41
Ballooning				
Change in score	-0.19 (-0.29, -0.09)	-0.22 (-0.47, 0.04)	-0.03 (-0.30, 0.25)	0.84
Patients improved	80 (32%)	11 (30%)	0.89 (0.42, 1.89)	0.76
Portal inflammation				
Change in score	0.17 (0.10, 0.25)	-0.07 (-0.26, 0.12)	-0.24 (-0.45, -0.03)	0.02
Patients improved	37 (15%)	8 (22%)	1.57 (0.66, 3.69)	0.31
Fibrosis				
Change in score	0.08 (-0.05, 0.21)	0.04 (-0.30, 0.37)	-0.04 (-0.40, 0.32)	0.83
Patients improved	67 (27%)	9 (24%)	0.85 (0.38, 1.90)	0.70
NAFLD Activity Score (NAS)				
Change in score	-0.87 (-1.08, -0.65)	-0.55 (-1.09, 0.001)	0.32 (-0.27, 0.91)	0.29
Patients improved	144 (58%)	16 (43%)	0.55 (0.27, 1.11)	0.09
Resolution of NASH	27 (17%)	3 (13%)	0.73 (0.20, 2.64)	0.64

Changes in scores are presented as adjusted means (95% confidence intervals); P-values and mean changes from baseline were calculated using ANCOVA, regressing change from baseline to time of last biopsy on baseline drinking status and baseline value of the outcome; odds ratios and p-values were calculated using logistic regression models.
Improvement defined as a 1 point or more decrease in the histological grade or score.

Supplemental Table 4. Longitudinal change in histologic and clinical features from enrollment to follow-up biopsy in patients with the GG and GC allele (rs738409)

	Non-drinker (N=54)	Modest-drinker (N=57)	Differences in mean changes from baseline or odds ratio (95% CI) Modest-drinker vs. non-drinker	P
Histologic Features				
Steatosis				
Change in score	-0.39 (-0.57, -0.20)	-0.52 (-0.71, -0.34)	-0.13 (-0.40, 0.13)	0.32
No change (ref.)	26 (48%)	20 (35%)	1.00	
Improved	22 (41%)	33 (58%)	1.95 (0.88, 4.31)	0.10
Worsened	6 (11%)	4 (7%)	0.87 (0.22, 3.49)	0.84
Lobular inflammation				
Change in score	-0.05 (-0.22, 0.11)	-0.49 (-0.65, -0.34)	-0.44 (-0.66, -0.21)	<0.001
No change (ref.)	26 (48%)	26 (46%)	1.00	
Improved	16 (30%)	26 (46%)	1.63 (0.71, 3.71)	0.25
Worsened	12 (22%)	5 (9%)	0.42 (0.13, 1.35)	0.15
Ballooning				
Change in score	-0.13 (-0.35, 0.10)	-0.20 (-0.42, 0.02)	-0.07 (-0.39, 0.25)	0.68
No change (ref.)	22 (41%)	29 (51%)	1.00	
Improved	19 (35%)	14 (25%)	0.56 (0.23, 1.35)	0.67
Worsened	13 (24%)	14 (25%)	0.82 (0.32, 2.08)	0.20
Portal inflammation				
Change in score	0.28 (0.14, 0.43)	0.03 (-0.11, 0.17)	-0.25 (-0.46, -0.05)	0.02
No change (ref.)	30 (56%)	28 (49%)	1.00	
Improved	5 (9%)	13 (23%)	2.79 (0.88, 8.82)	0.08
Worsened	19 (35%)	16 (28%)	0.90 (0.39, 2.09)	0.81
Fibrosis				
Change in score	0.28 (-0.01, 0.58)	0.10 (-0.19, 0.40)	-0.18 (-0.61, 0.24)	0.40
No change (ref.)	15 (28%)	23 (42%)	1.00	
Improved	16 (30%)	13 (24%)	0.53 (0.20, 1.41)	0.20
Worsened	23 (43%)	19 (35%)	0.54 (0.22, 1.31)	0.17
NAFLD Activity Score (NAS)				
Change in score	-0.68 (-1.12, -0.24)	-1.11 (-1.54, -0.68)	-0.43 (-1.04, 0.18)	0.17
No change (ref.)	4 (7%)	18 (32%)	1.00	
Improved	32 (59%)	32 (56%)	0.22 (0.07, 0.73)	0.01
Worsened	18 (33%)	7 (12%)	0.09 (0.02, 0.35)	0.001
Resolution of NASH	11 (26%)	4 (14%)	0.47 (0.13, 1.66)	0.24

Draft 1/2/17

Clinical Features

AST, U/L	-6.27 (-14.79, 2.26)	-0.68 (-8.90, 7.54)	5.59 (-6.25, 17.43)	0.35
ALT, U/L	-21.10 (-29.11, -13.08)	-16.81 (-24.53, -9.08)	4.29 (-6.84, 15.42)	0.45
Alkaline phosphatase, U/L	-22.68 (-31.31, -14.06)	-19.12 (-27.43, -10.80)	3.57 (-8.50, 15.63)	0.56
GGT, U/L	-0.88 (-10.14, 8.38)	-6.75 (-15.51, 2.00)	-5.87 (-18.67, 6.93)	0.37
Homa-IR	0.79 (-1.58, 3.17)	0.33 (-1.97, 2.64)	-0.46 (-3.78, 2.86)	0.78
Total cholesterol, mg/dL	-19.1 (-29.11, -9.09)	-14.03 (-23.77, -4.29)	5.07 (-8.93, 19.07)	0.47
HDL, mg/dL	0.69 (-1.58, 2.96)	-1.93 (-4.14, 0.28)	-2.62 (-5.79, 0.55)	0.10
LDL, mg/dL	-15.00 (-24.16, -5.84)	-10.71 (-19.70, -1.72)	4.29 (-8.56, 17.14)	0.51
Triglycerides, mg/dL	-27.75 (-61.78, 6.28)	-1.59 (-34.71, 31.54)	26.17 (-21.33, 73.66)	0.28
BMI, kg/m^2	-0.11 (-0.93, 0.71)	0.61 (-0.21, 1.42)	0.71 (-0.44, 1.87)	0.22

Changes in scores are presented as adjusted means (adjusted for the baseline value) and 95% confidence intervals; P-values and mean changes from baseline were calculated using ANCOVA, regressing change from baseline to time of last biopsy on baseline drinking status and baseline value of the outcome; odds ratios and p-values were calculated using logistic regression models. Improvement defined as a 1 point or more decrease in the histological grade or score.