Supplementary data

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Supplemental Table 1: Characteristics of homozygous (A/A) or heterozygous rs2642438 carriers (G/A) compared with non-carriers (G/G) that underwent liver MRI, related to Table 1.

	Non carriers (G/G) *n=2 492*	**Heterozygotes (G/A)** *n=2 088*	**Homozygotes (A/A)** *n=455*	**p-Value G/G vs G/A**	**p-Value G/G vs A/A**
Baseline Characteristics				*Univ.*	*Univ.*
Age (years)	55.7±7.5	55.5±7.6	55.6±7.5	.32	.63
Women (%)	53	53	50	.92	.19
BMI (kg/m^2)	26.6±4.1	26.8±4.0	26.5±4.1	.30	.53
Diabetes mellitus (%)	3	2	2	**.019**	.051
MRI of the liver				*Multiv.*	*Multiv.*
Proton density fat fraction (%)	4.1±4.8	3.8±4.4	3.6±4.0	**.013**	.049
Liver Iron (msec)	1.34±0.31	1.35±0.38	1.35±0.43	.95	.70
Liver inflammation factor (units)	0.9±0.3	0.9±0.3	0.9±0.4	.55	.38

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI and principal components of ancestry 1-4. A FDR adjusted significance level of p <= 0.03 was used.

Supplemental Table 2: Characteristics of African American participants in PMBB, comparing homozygous or heterozygous carriers of rs2642438 with non-carriers, related to Table 3.

	Non carriers (G/G) *n=6433*	**Heterozygotes (G/A)** *n=1 252*	**Homozygotes (A/A)** *n=70*	**p-Value G/G vs G/A**	**p-Value G/G vs A/A**
Characteristics				*Univ.*	*Univ.*
Age (years)	55.6±17.3	55.5±13.9	56.9±15.4	.90	.50
Women (%)	65	64	59	.80	.32
BMI (kg/m^2)	32.5±8.2	32.5±6.1	31.4±7.9	.90	.24
Diabetes mellitus (%)	27	29	31	.35	.47
Ethnicity (% African American)	100	100	100		
Liver status				*Multiv.*	*Multiv.*
ALT (U/l)	22.0±30.1	21.0±17.2	21.5±12.8	.26	.82
ALT ≥ULN	6	6	3	.38	.43
AST (U/l)	24±47	22.0±15.7	22±10	.22	.80
AST ≥ULN	6	4	3	.25	.46
GGT (U/l)	130±200	103±166	109±210	.25	.22
GGT (%ULN)	52	42	40	.051	.59
Lipid metabolism					
Triglycerides (mg/dl)	107±52	112±69	109±50	**.029**	.71
HDL cholesterol (mg/dl)	51±15	50±14	49±16	.17	.15
LDL cholesterol (mg/dl)	103±33	100±32	92±34	.041	**.009**
Cholesterol (mg/dl)	176±39	173±39	160±38	**.022**	**.001**
ICD10 coded diagnoses					
Toxic liver disease (K71)	0.6	0.1	0.0	.38	.99
Hepatic failure (K72)	1.0	0.7	1.0	.34	.36
Chronic Hepatitis (K73)	0.2	0.1	0.0	.91	.99
Fibrosis and cirrhosis (K74)	0.4	0.1	0.2	.099	.15
Inflammatory liver diseases (K75)	2.2	1.1	1.4	**.011**[a]	.64
NASH (K75.8)	2.2	1.6	1.8	.10	**.027**[b]
Other liver diseases (K76)	4.4	3.4	2.9	.082	.052
NAFLD (K76.0)	3.3	2.2	2.6	**.027**[c]	.16
HCC (C22.0)	3.2	2.7	0.0	.28	.99
Frequency of well-known NAFLD influencing genes*					
HSD17B13 *rs72621367:TA*	0.14±0.36	0.20±0.44	0.20±0.44	.064	.15
PNPLA3 *rs738409:G*	0.28±0.60	0.41±0.58	0.41±0.58	.044	.049

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI and principal components of ancestry 1-4. A FDR adjusted significance level of p <= 0.03 was used. [a]aOR=0.57[0.38-0.79], [b]aOR=0.70[0.50-0.98], [c]aOR=0.75[0.59-0.96]. *0=non carrier, 1=heterozygous, 2=homozygous.

Supplemental Table 3: Characteristics of Black British participants in UKB, comparing homozygous or heterozygous carriers of rs2642438 with non-carriers, related to Table 1.

	Non carriers (G/G) *n=6 665*	**Heterozygotes (G/A)** *n=857*	**Homozygotes (A/A)** *n=37*	**p-Value G/G vs G/A**	**p-Value G/G vs A/A**
Characteristics				*Univ.*	*Univ.*
Age (years)	51.8±8	52±7.9	53.2±8.8	.90	.50
Women (%)	57	63	60	.80	.32
BMI (kg/m^2)	29.5±5.3	29.4±5.5	28.8±4.9	.90	.24
Diabetes mellitus (%)	11	11	13	.35	.47
Ethnicity (% Black)	100	100	100		
Liver status				*Multiv.*	*Multiv.*
ALT (U/l)	22.2±13.7	21.1±10.4	22.2±19.0	.079	.67
ALT ≥ULN	5	4	3	.67	.095
AST (U/l)	27.2±13.6	26.0±8.2	26.8±16.5	.17	.91
AST ≥ULN	5	4	6	.27	.53
GGT (U/l)	41.9±39.7	39.9±34.4	35.5±22.2	.65	.39
GGT (%ULN)	23	23	16	.93	.17
Lipid metabolism					
Triglycerides (mg/dl)	1.20±0.7	1.29±0.8	1.32±0.88	.11	.18
HDL cholesterol (mg/dl)	1.43±0.3	1.43±0.3	1.40±0.49	.81	.090
LDL cholesterol (mg/dl)	3.26±0.8	3.20±0.8	3.22±0.95	**.005**	.78
Cholesterol (mg/dl)	5.23±1	5.18±1	5.20±1.3	**.013**	.13
ICD10 coded diagnoses					
Toxic liver disease (K71)	0.06	0.0	0.0	.99	.99
Hepatic failure (K72)	0.11	0.10	0.0	.64	.99
Chronic Hepatitis (K73)	0.12	0.0	0.0	.99	.99
Fibrosis and cirrhosis (K74)	0.14	0.08	0.2	.13	.99
Inflammatory liver diseases (K75)	0.19	0.05	0.0	.11	.99
NASH (K75.8)	0.13	0.02	0.0	.32	.99
Other liver diseases (K76)	1.02	0.70	0.0	.51	.99
NAFLD (K76.0)	0.85	0.42	0.0	.31	.99
HCC (C22.0)	0.02	0.00	0.0	.99	.99
Frequency of well-known NAFLD influencing genes*					
HSD17B13 *rs72621367:TA*	0.12±0.36	0.12±0.44	0.18±0.44	.80	.58
PNPLA3 *rs738409:G*	0.24±0.60	0.26±0.58	0.26±0.58	.92	.35

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI and principal components of ancestry 1-4. *0=non carrier, 1=heterozygous, 2=homozygous. A FDR adjusted significance level of p <= 0.03 was used.

Supplemental Table 4: Characteristics of homozygous (A/A) or heterozygous rs2642438 carriers (G/A) compared with non-carriers (G/G) that underwent cardiac MRI, related to Table 1.

	Non carriers *n=2 234*	**Heterozygotes** *n=1 867*	**Homozygotes** *n=401*	**p-Value G/G vs G/A**	**p-Value G/G vs A/A**
Baseline Characteristics				*Univ.*	*Univ.*
Age (years)	55.6±7.5	55.3±7.6	55.3±7.5	.24	.50
Women (%)	54	55	51	.93	.18
BMI (kg/m^2)	26.3±4.1	26.5±4.0	26.2±4.1	.064	.58
Diabetes mellitus (%)	3	2	1	.10	.035
				Multiv.	*Multiv.*
Cardiac ultrasound					
LV ejection fraction (%)	55.8±6.8	55.9±7.2	55.7±7.3	.99	.67
Cardiac output (l/min)	4.7±1.1	4.8±1.2	4.9±1.8	**.016**	.033

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI and principal components of ancestry 1-4. A FDR adjusted significance level of p <= 0.03 was used.

Supplemental Table 5: Characteristics of homozygous (A/A) or heterozygous rs2642438 carriers (G/A) compared with non-carriers (G/G) that underwent carotid ultrasound, related to Table 1.

	Non carriers *n=12 189*	**Heterozygotes** *n=10 081*	**Homozygotes** *n=2 092*	**p-Value G/G vs G/A**	**p-Value G/G vs A/A**
Baseline Characteristics				*Univ.*	*Univ.*
Age (years)	55.0±7.5	55.1±7.5	55.3±7.4	.50	.42
Women (%)	52	52	51	.64	.36
BMI (kg/m^2)	26.6±4.2	26.6±4.2	26.5±4.2	.29	.59
Diabetes mellitus (%)	3	3	2	.74	.52
				Multiv.	*Multiv.*
Mean Intima-Media Thickness (µm)					
120°	676±143	678±144	678±144	.39	.73
150°	669±141	673±140	671±141	.18	.77
210°	686±153	689±153	686±156	.27	.79
240°	686±143	689±144	688±158	.27	.78

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI and principal components of ancestry 1-4. A FDR adjusted significance level of p <= 0.03 was used.

Supplemental Table 6: Total death and selected causes of death in PMBB until June 2020, related to Table 3.

Cause of death (ICD 10)	**PMBB**
Malignancies (C)	1392
Cardiovascular (I)	1529
Respiratory (J)	436
liver related (K7 and C22)	69
Total death	*4170*

Supplemental Table 7: Cox regression models for liver death and cardiovascular death per *MTARC1* rs2642438 allele, related to Figure 3.

	Risk of liver death		**Risk of cardiovascular death**	
	Hazard ratio (HR) [95% CI]	***P* value**	**Hazard ratio (HR) [95% CI]**	***P* value**
Unadjusted	0.82 [0.74-0.92]	<.0001	1.04 [0.97-1.08]	.10
Adjusted for age, sex and PC1-4	0.82 [0.73-0.91]	<.0001	1.03 [0.98-1.08]	.12
Adjusted for age, sex, BMI and PC1-4	0.82 [0.73-0.91]	<.0001	1.04 [0.98-1.08]	.11
Adjusted for DM, smoking, age, sex and PC1-4	0.82 [0.73-0.91]	<.0001	1.04 [0.97-1.08]	.12
Adjusted for BMI, age, sex, alcohol consumption, waist circumference, DM, LDL levels and PC1-4	0.79 [0.70-0.88]	<.0001	1.03 [0.98-1.08]	.15
Adjusted for all above	0.79 [0.71-0.88]	.0001	1.04 [0.98-1.08]	.12

Supplemental Table 8: Characteristics of heterozygous *MTARC1* p.Arg200Ter carriers compared with rs2642438 non-carriers in PMBB, related to Table 3.

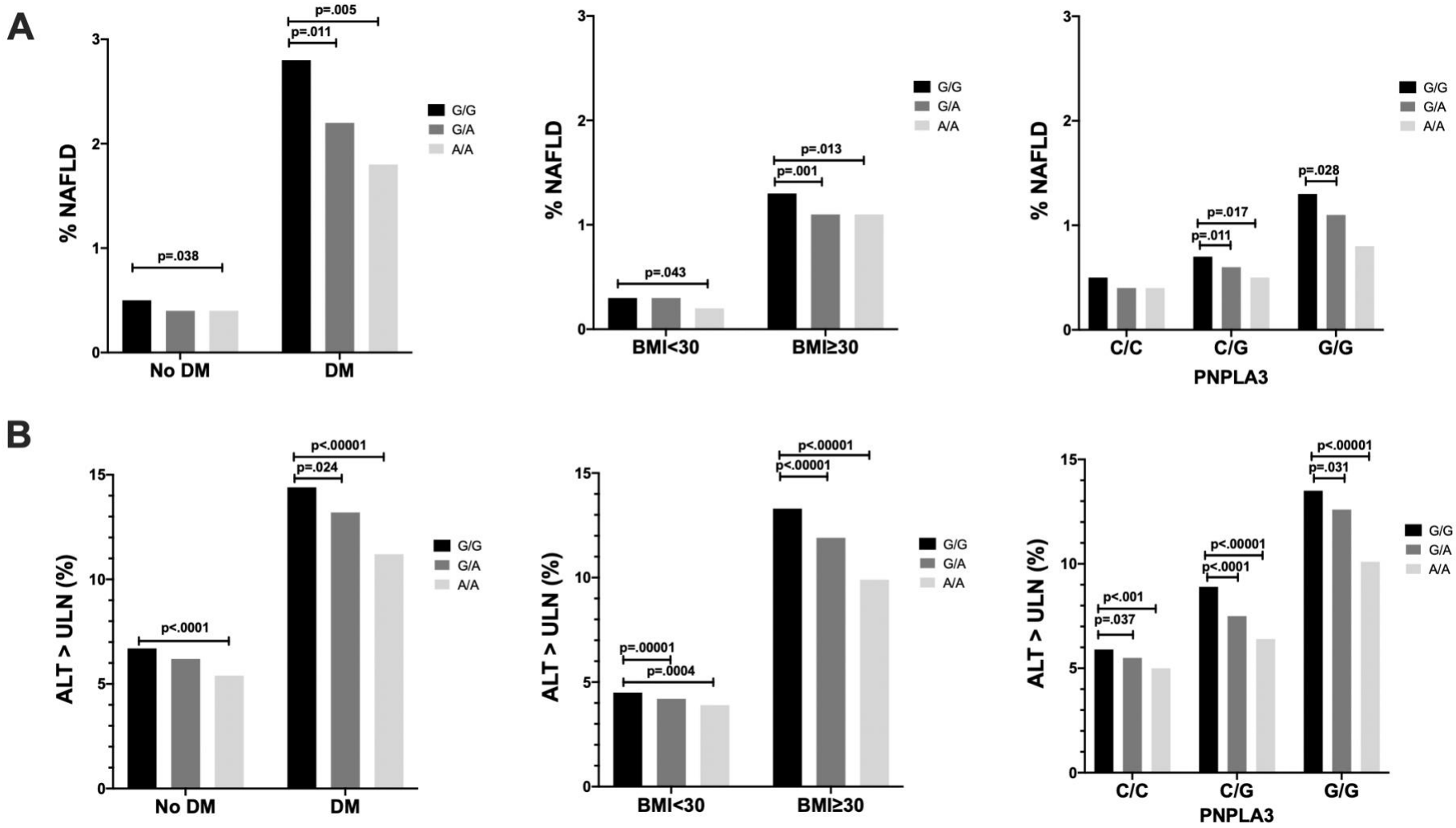
	Non carriers (G/G) *n=9 548*	**Heterozygotes of pLOF variants** *n=10*	**p-Value (uni-variate)**	**p-Value (multi-variate)**
Characteristics				
Age (years)	60.6±17.3	63.7±16.2	.23	
Women (%)	57	50	.25	
BMI (kg/m^2)	29.0±5.9	30.4±7.3	.40	
Diabetes mellitus (%)	26	20	.19	
Ethnicity (% Whites)	33	50	**.001**	
Liver status				
ALT (U/l)	24.4±36.1	23.1±17.6	.091	.19
ALT ≥ULN (%)	7	0	**.027**	.99
AST (U/l)	25.3±44.8	22.0±15.1	.072	**.007**
AST ≥ULN (%)	6	0	.055	.99
GGT (U/l)	130±202	103.5±126.6	.097	.77
GGT ≥ULN (%)	53	50	.51	.96
Lipid metabolism				
Triglycerides (mg/dl)	112±78	158±80	**.001**	**.004**
HDL cholesterol (mg/dl)	50±15	46±12	.15	.29
LDL cholesterol (mg/dl)	100±33	84±23	.037	.13
Cholesterol (mg/dl)	174±39	165±31	.035	.40
ICD10 coded diagnoses				
Toxic liver disease (K71)	0.7	0.0	.59	.99
Hepatic failure (K72)	1.0	0.0	.51	.99
Chronic Hepatitis (K73)	0.7	0.0	.59	.99
Fibrosis and cirrhosis (K74)	0.4	0.0	.85	.99
Inflammatory liver diseases (K75)	2.2	0.0	.24	.99
NASH (K75.8)	2.2	0.0	.24	.99
Other liver diseases (K76)	4.0	0.0	.081	.99
NAFLD (K76.0)	3.0	0.0	.12	.99
HCC (C22.0)	2.4	0.0	.28	.99
Frequency of well-known NAFLD influencing genes*				
HSD17B13 *rs72621367:TA*	0.55±0.63	0.50±0.63	.51	.97
PNPLA3 *rs738409:G*	0.35±0.58	0.40±0.58	.47	.55

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI, and PC1-4. *(0=non carrier, 1=heterozygous, 2=homozygous). A FDR adjusted significance level of p <= 0.03 was used.

Supplemental Table 9: Characteristics of heterozygous *MTARC1* p.Arg200Ter carriers compared with rs2642438 non-carriers in UKB, related to Table 1.

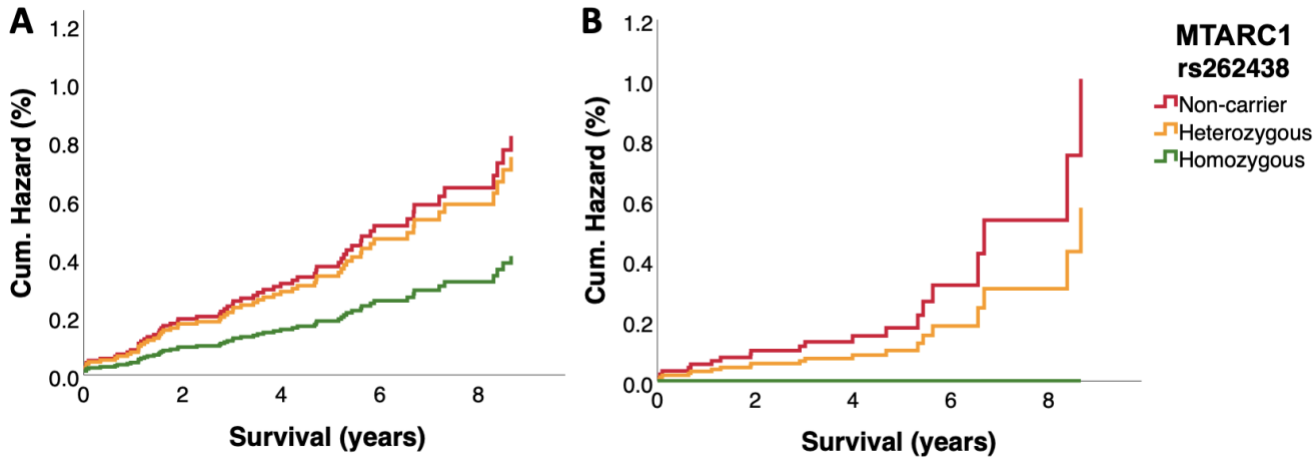
	Non carriers (G/G) *n=227 602*	**Heterozygotes of *MTARC1* p.R200Ter** *n=83*	**p-Value (uni-variate)**	**p-Value (multi-variate)**
Characteristics				
Age (years)	56.6±8.1	57.0±7.3	.71	
Women (%)	55	56	.78	
BMI (kg/m^2)	27.4±4.8	27.3±4.3	.89	
Alcohol (g/d)	8.9±10.1	8.4±11.9	.10	
Diabetes mellitus (%)	5	11	.59	
Ethnicity (% white)	100	100		
Frequency of well-known NAFLD influencing genes*				
HSD17B13 *rs72621367:TA*	0.55±0.63	0.55±0.63	.53	.58
PNPLA3 *rs738409:G*	0.43±0.58	0.43±0.58	.74	.76
Survival				
All-cause mortality (%)	6	2	.20	.18
Liver related death (%)	0.21	0	.73	.99
Cardiovascular death (%)	1.2	1.2	.32	.35
Liver status				
ALT (U/l)	23.7±14.5	21.7±13.5	.19	.25
ALT ≥ULN (%)	7.2	3.8	.15	.28
AST (U/l)	26.2±10.8	25.4±7.9	.39	.54
AST ≥ULN (%)	4.8	4.6	.89	.92
GGT (U/l)	37.1±41.9	27.8±16.9	**.017**	.054
GGT ≥ULN (%)	17.1	11.4	.12	.20
Lipid metabolism				
Triglycerides (mg/dl)	154±89	156±91	.93	.81
HDL cholesterol (mg/dl)	57±15	53±12	.13	**.022**
LDL cholesterol (mg/dl)	138±34	133±35	.18	.22
Cholesterol (mg/dl)	221±44	215±44	.31	.15
Apolipoprotein A1 (g/l)	1.54±0.27	1.50±0.27	.18	.057
Apolipoprotein B (g/l)	1.04±0.24	1.01±0.24	.51	.21
Lipoprotein A (nmol/l)	44.05±48.9	42.00±49.4	.99	.90
ICD10 coded diagnoses				
Overall liver disease (K70-K76)	1.59	0.00	.27	.99
Alcoholic liver disease (K70)	0.23	0.00	.67	.99
Toxic liver disease (K71)	0.02	0.00	.90	.99
Hepatic failure (K72)	0.11	0.00	.76	.99
Chronic Hepatitis (K73)	0.03	0.00	.87	.99
Fibrosis and cirrhosis (K74)	0.25	0.00	.65	.99
Inflammatory liver diseases (K75)	0.25	0.00	.85	.99
NASH (K75.8)	0.07	0.00	.80	.99
Other liver diseases (K76)	1.16	0.00	.33	.99
NAFLD (K76.0)	0.59	0.00	.49	.99

Quantitative measures are expressed as means and standard deviations or as relative frequencies (%). All multivariable analyses were adjusted for age, sex, BMI, and PC1-4. *(0=non carrier, 1=heterozygous, 2=homozygous). A FDR adjusted significance level of $p <= 0.03$ was used.



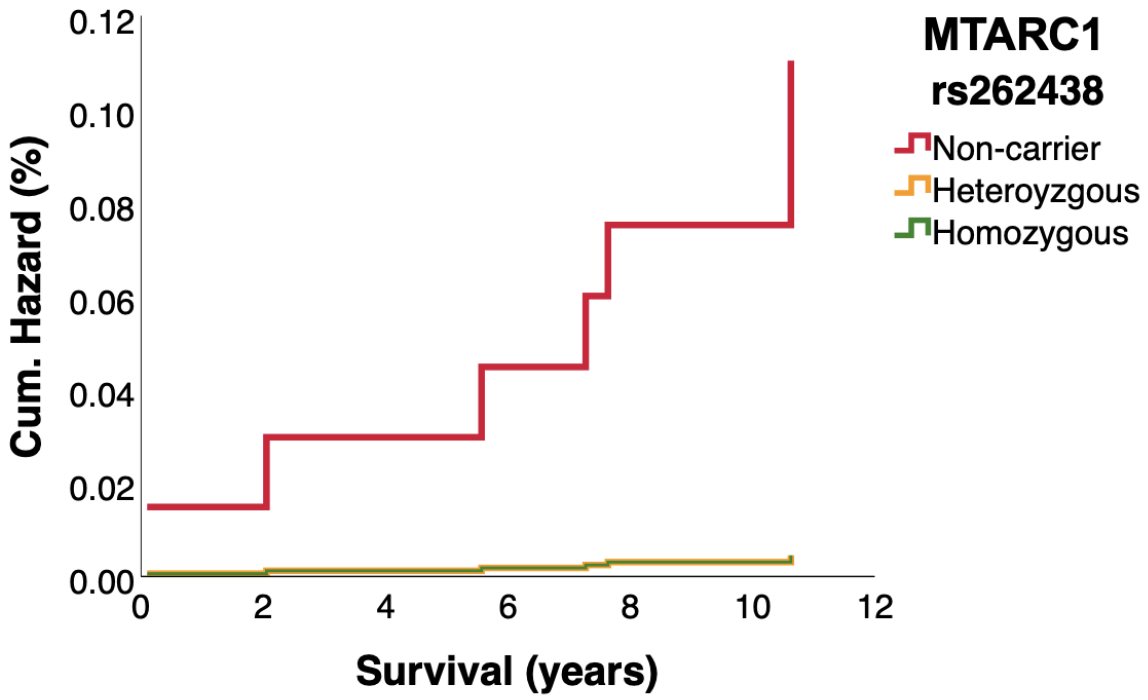
Supplemental Figure 1: Barograph comparing A) the NAFLD percentage and B) elevated ALT serum levels in participants *MTARC1* rs2642438 homozygotes(A/A), heterozygotes(G/A) and non-carriers (G/G) with and without several important risk factors in the UKB, related to Figure 2.

All multivariable analyses were adjusted for age, sex, BMI, and PC1-4.



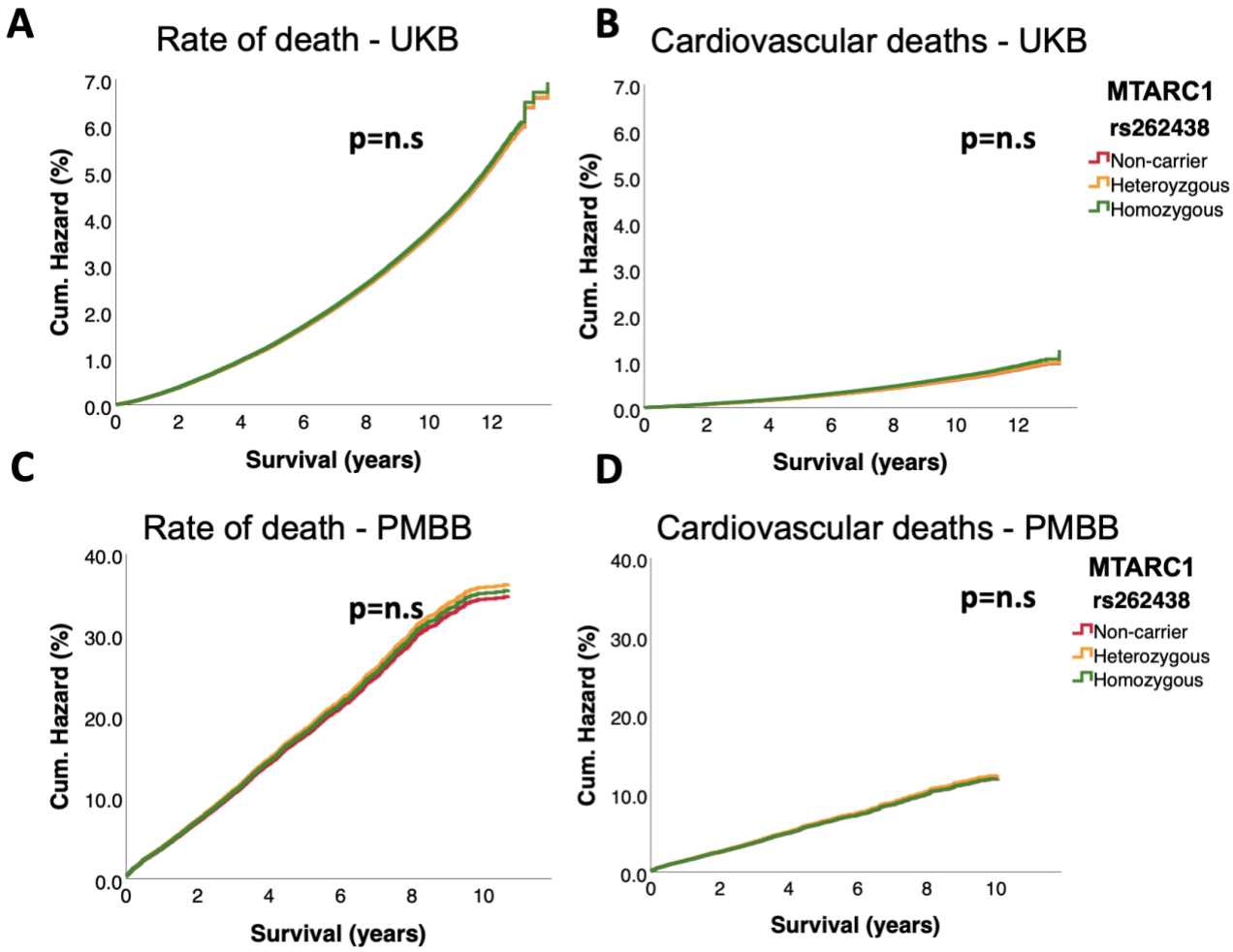
Supplemental Figure 2: Prospective liver-related mortality as a function of *MTARC1* rs2642438 genotype in PMBB, related to Figure 3.

(A) Liver-related mortality in the overall PMBB population as a function of *MTARC1* genotype, B) liver-related mortality as a function of MTARC1 rs2642438 genotype in African-American participants in PMBB. Liver-related mortality comprised death due to liver diseases or hepatocellular carcinoma. Participants were followed prospectively from the time of study entry until death or end of follow-up. Hazard ratios were calculated by Cox regression, adjusted for age, sex, BMI and principal components of ancestry 1-4.



Supplemental Figure 3: Prospective liver-related mortality as a function of *MTARC1* rs2642438 genotype in Black British participants in the UKB, related to Figure 3.

Liver-related mortality comprises death due to liver diseases or hepatocellular carcinoma. (A) Liver-related mortality as a function of *MTARC1* rs264238 genotype. Participants were followed prospectively from the time of study entry until death or end of follow-up. Hazard ratios were calculated by Cox regression, adjusted for age, sex, BMI and principal components of ancestry 1-4.



Supplemental Figure 4: Overall and cardiovascular mortality in participants stratified by *MTARC1* rs264238 genotype in UKB (A,B) and PMBB (C,D), related to Figure 3.

All analyses were adjusted for age, sex, BMI and principal components of ancestry 1-4. Parts of the survival curves overlap each other, so that only one line is visible.