Supplemental materials

Impact of Y loss in blood on male atherosclerosis and cardiovascular risk

Authors

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Table 1. Multivariable adjusted logistic regression analysis for the prevalence of any coronary atherosclerosis in the SCAPIS cohort

Multivariable adjusted logistic regression analysis testing differences in the prevalence of any coronary atherosclerosis between men with low or substantial LOY and men with no detectable LOY. The model is adjusted for age, smoking, BMI, diabetes, diastolic blood pressure, systolic blood pressure, and total cholesterol. OR = odds ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y.

	OR	95% CI	p value
Age	1.11	1.10-1.12	<0.0001
Smoking			
Non-smoker *(reference)*			
Previous smoker	1.20	1.11-1.31	<0.0001
Current smoker	1.53	1.36-1.73	<0.0001
BMI			
Normal *(reference)*			
Underweight	0.28	0.07-0.87	0.0371
Overweight	1.15	1.05-1.25	0.0027
Obese	1.54	1.37-1.73	<0.0001
Diabetes			
Normoglycemic *(reference)*			
Pre-diabetes	1.12	1.01-1.24	0.0375
Diabetes mellitus	1.83	1.56-2.15	<0.0001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	1.04	0.93-1.15	0.4852
Hypertension Stage 2	1.01	0.85-1.18	0.9406
Hypertensive crisis	0.22	0.03-1.12	0.0859
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.22	1.09-1.37	0.0005
Hypertension Stage 2	1.29	1.12-1.48	0.0005
Hypertensive crisis	1.60	0.86-3.13	0.1497
Total cholesterol	1.19	1.15-1.24	<0.0001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.02	0.86-1.20	0.8351
Substantial LOY	1.48	1.08-2.07	0.0180

Table 2. Multivariable adjusted logistic regression analysis for the prevalence of stenosis >50% in any coronary segment in the SCAPIS cohort

Multivariable adjusted logistic regression analysis testing the difference in prevalence of coronary stenosis >50% in men with LOY and men without. The model is adjusted for age, smoking, BMI, diabetes, diastolic blood pressure, systolic blood pressure, and total cholesterol. OR = odds ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y

	OR	95% CI	p value
Age	1.1	1.08-1.11	<0.0001
Smoking			
Non-smoker *(reference)*			
Previous smoker	1.21	1.04-1.4	0.0127
Current smoker	1.63	1.34-1.98	<0.0001
BMI			
Normal *(reference)*			
Underweight	0.76	0.04-4.09	0.799
Overweight	1.26	1.06-1.5	0.0105
Obese	1.5	1.22-1.84	0.0001
Diabetes			
Normoglycemic *(reference)*			
Pre-diabetes	1.28	1.08-1.52	0.005
Diabetes mellitus	2.06	1.66-2.54	<0.0001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	1.01	0.84-1.21	0.9278
Hypertension Stage 2	0.88	0.68-1.15	0.3524
Hypertensive crisis	-	-	-
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.15	0.95-1.4	0.1533
Hypertension Stage 2	1.59	1.26-1.99	0.0001
Hypertensive crisis	2.03	0.84-4.36	0.0895
Total cholesterol	1.26	1.18-1.34	<0.0001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	0.97	0.74-1.26	0.8392
Substantial LOY	1.57	1.06-2.28	0.0202

Table 3. Multivariable adjusted ordinal logistic regression analysis for segment involvement score in the SCAPIS cohort

Multivariable adjusted ordinal logistic regression analysis for the segment involvement score in men with LOY and men without. The model is adjusted for age, smoking, BMI, diabetes, diastolic blood pressure, systolic blood pressure, and total cholesterol. CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y

	beta	95% CI	p value
Age	0.11	0.10-0.11	<0.0001
Smoking			
Non-smoker *(reference)*			
Previous smoker	0.23	0.16-0.31	<0.0001
Current smoker	0.50	0.40-0.60	<0.0001
BMI			
Normal *(reference)*			
Underweight	-1.27	-2.57--0.17	0.0343
Overweight	0.15	0.07-0.23	0.0003
Obese	0.46	0.35-0.56	<0.0001
Diabetes			
Normoglycemic *(reference)*			
Pre-diabetes	0.16	0.07-0.25	0.0006
Diabetes mellitus	0.70	0.57-0.83	<0.0001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	-0.02	-0.12-0.07	0.6112
Hypertension Stage 2	-0.10	-0.24-0.04	0.1790
Hypertensive crisis	-1.58	-3.57-0.00	0.0688
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	0.25	0.16-0.35	<0.0001
Hypertension Stage 2	0.38	0.26-0.50	<0.0001
Hypertensive crisis	0.51	-0.01-1.03	0.0528
Total cholesterol	0.17	0.13-0.20	<0.0001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	0.09	-0.06-0.23	0.2315
Substantial LOY	0.29	0.04-0.54	0.0207

Table 4. Multivariable adjusted logistic regression analysis for coronary artery calcium score in the SCAPIS cohort

Multivariable adjusted logistic regression analysis for coronary artery calcium score in men with LOY and men without. The model is adjusted for age, smoking, BMI, diabetes, diastolic blood pressure, systolic blood pressure, and total cholesterol. CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y

	beta	95% CI	p value
Age	0.13	0.12-0.14	<0.0001
Smoking			
Non-smoker *(reference)*			
Previous smoker	0.26	0.15-0.37	<0.0001
Current smoker	0.58	0.43-0.75	<0.0001
BMI			
Normal *(reference)*			
Underweight	0.57	-0.62-2.49	0.4464
Overweight	0.24	0.12-0.36	0.0001
Obese	0.49	0.34-0.65	<0.0001
Diabetes			
Normoglycemic *(reference)*			
Pre-diabetes	0.21	0.07-0.35	0.0027
Diabetes mellitus	0.87	0.67-1.07	<0.0001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.06	-0.07-0.19	0.4137
Hypertension Stage 2	-0.06	-0.27-0.16	0.6135
Hypertensive crisis	-2.78	-4.62-0.38	0.012
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	0.28	0.14-0.42	0.0002
Hypertension Stage 2	0.43	0.25-0.62	<0.0001
Hypertensive crisis	0.78	0.05-1.71	0.0527
Total cholesterol	0.12	0.07-0.17	<0.0001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	0.03	-0.18-0.26	0.7734
Substantial LOY	0.45	0.08-0.86	0.0247

Table 5. Baseline characteristics for UK Biobank men with carotid IMT data.
Comparison of baseline parameters from the initial assessment visit among men with carotid intima-media thickness measures, stratified by LOY measurements. Variables are presented as median (IQR) or number (%). Abbreviations: LOY = mosaic loss of chromosome Y, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, S1 = stage 1, S2 = stage 2, CVD = cardiovascular disease, PRS = polygenic risk score.

	No LOY	Low LOY	Substantial LOY
N	33,527 (84%)	4,828 (12%)	1,642 (4%)
Age in years	54 (48, 60)	60 (56, 64)	63 (60, 66)
Smoking status			
Never	19,567 (58%)	2,514 (52%)	707 (43%)
Previous	11,559 (34%)	1,881 (39%)	703 (43%)
Current	2,401 (7.2%)	433 (9.0%)	232 (14%)
Diabetes	1,080 (3.2%)	132 (2.7%)	61 (3.7%)
Total cholesterol	5.59 (4.91, 6.31)	5.56 (4.87, 6.24)	5.54 (4.81, 6.25)
BMI			
Normal	10,036 (30%)	1,480 (31%)	513 (31%)
Underweight	51 (0.2%)	3 (<0.1%)	1 (<0.1%)
Overweight	17,162 (51%)	2,552 (53%)	870 (53%)
Obese	6,278 (19%)	793 (16%)	258 (16%)
SBP			
Normal	10,948 (33%)	1,262 (26%)	382 (23%)
Hypertension S1	8,611 (26%)	1,201 (25%)	363 (22%)
Hypertension S2	13,508 (40%)	2,254 (47%)	860 (52%)
Hypertensive crisis	460 (1.4%)	111 (2.3%)	37 (2.3%)
DBP			
Normal	11,939 (36%)	1,724 (36%)	623 (38%)
Hypertension S1	13,144 (39%)	1,909 (40%)	630 (38%)
Hypertension S2	8,415 (25%)	1,191 (25%)	388 (24%)
Hypertensive crisis	29 (<0.1%)	4 (<0.1%)	1 (<0.1%)
CVD PRS	-0.16 (-0.81,0.49)	-0.19 (-0.84,0.47)	-0.24 (-0.88,0.41)

Table 6. ANOVA and post-hoc test for right carotid artery intima-media thickness in the UK Biobank cohort

The differences in intima-media thickness (μm) for the right carotid artery were compared between men with no LOY, men with low LOY, and men with substantial LOY. **A)** Displays the type II ANOVA results, **B)** the computed estimated marginal means, and **C)** the Tukey's post-hoc test. The tests are adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, and systolic blood pressure. BMI = body mass index, LOY = mosaic loss of chromosome Y, Df = degrees of freedom, EMMs = estimated marginal means, SE = Standard error, CI = confidence interval.

A) ANOVA type II

	LR Chisq	Df	p value
Age	3176.14	1	<0.001
Smoking status	86.92	2	<0.001
Diabetes	3.86	1	0.049
Cholesterol	103.95	1	<0.001
BMI	137.96	3	<0.001
Diastolic blood pressure	169.45	3	<0.001
Systolic blood pressure	338.07	3	<0.001
LOY groups	10.20	2	0.006

B) Estimated marginal means

	EMMs	SE	Df	Lower CI	Upper CI
No LOY	695.90	7.78	39980	680.66	711.14
Low LOY	693.24	8.01	39980	677.54	708.95
Substantial LOY	705.79	8.48	39980	689.17	722.42

B) Tukey's post-hoc test

Contrast	Estimate	SE	Df	t ratio	p value
No LOY - Low LOY	2.65	2.18	39980	1.22	0.443
No LOY - Substantial LOY	-9.90	3.58	39980	-2.77	0.016
Low LOY - Substantial LOY	-12.55	3.94	39980	-3.19	0.004

Table 7. ANOVA and post-hoc test for left carotid artery intima-media thickness in the UK Biobank cohort

The differences in intima-media thickness (μm) for the left carotid artery were compared between men with no LOY, men with low LOY, and men with substantial LOY. **A)** Displays the type II ANOVA results, **B)** the computed estimated marginal means, and **C)** the Tukey's post-hoc test. The tests are adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, and systolic blood pressure. BMI = body mass index, LOY = mosaic loss of chromosome Y, Df = degrees of freedom, EMMs = estimated marginal means, SE = Standard error, CI = confidence interval.

A) ANOVA type II

	LR Chisq	Df	p value
Age	2235.23	1	<0.001
Smoking status	98.37	2	<0.001
Diabetes	19.56	1	<0.001
Cholesterol	194.50	1	<0.001
BMI	270.13	3	<0.001
Diastolic blood pressure	183.61	3	<0.001
Systolic blood pressure	420.03	3	<0.001
LOY groups	10.02	2	0.007

B) Estimated marginal means

	EMMs	SE	Df	Lower CI	Upper CI
No LOY	724.20	8.62	39980	707.32	741.09
Low LOY	720.21	8.88	39980	702.81	737.60
Substantial LOY	733.94	9.40	39980	715.52	752.37

C) Tukey's post-hoc test

Contrast	Estimate	SE	Df	t ratio	p value
No LOY - Low LOY	4.00	2.42	39980	1.65	0.223
No LOY - Substantial LOY	-9.74	3.96	39980	-2.46	0.037
Low LOY - Substantial LOY	-13.74	4.36	39980	-3.15	0.005

Table 8. Multivariable adjusted logistic regression analysis for the prevalence of carotid plaques in the SCAPIS cohort

Multivariable adjusted logistic regression analysis testing the difference in prevalence of carotid plaques in men with LOY and men without. The model is adjusted for age, smoking, BMI, diabetes, diastolic blood pressure, systolic blood pressure, and total cholesterol. OR = odds ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y

	OR	95% CI	p value
Age	1.07	1.06-1.08	<0.0001
Smoking			
Non-smoker *(reference)*			
Previous smoker	1.17	1.08-1.28	0.0003
Current smoker	1.59	1.41-1.80	<0.0001
BMI			
Normal *(reference)*			
Underweight	0.50	0.17-1.53	0.2178
Overweight	1.01	0.92-1.11	0.8010
Obese	0.97	0.86-1.09	0.5707
Diabetes			
Normoglycemic *(reference)*			
Pre-diabetes	1.01	0.91-1.12	0.9088
Diabetes mellitus	1.36	1.17-1.59	0.0001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.93	0.84-1.03	0.1618
Hypertension Stage 2	0.85	0.72-1.00	0.0509
Hypertensive crisis	0.87	0.17-6.43	0.8771
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.33	1.19-1.49	<0.0001
Hypertension Stage 2	1.95	1.69-2.26	<0.0001
Hypertensive crisis	2.39	1.25-4.85	0.0110
Total cholesterol	1.21	1.17-1.26	<0.0001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	0.95	0.81-1.13	0.5604
Substantial LOY	1.18	0.86-1.63	0.3126

Table 9. Multivariable adjusted logistic regression analysis for the prevalence of carotid plaques in the UK Biobank cohort

Multivariable adjusted logistic regression analysis testing an association between LOY in blood and carotid plaques (estimated as a carotid intima-media thickness > 1.5 mm). The model is adjusted for age, smoking, BMI, diabetes, diastolic blood pressure, systolic blood pressure, and total cholesterol. OR = odds ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y.

	OR	95%CI	p value
Age	1.06	1.02-1.11	0.003
Smoking			
Never (*reference*)			
Previous	0.7	0.38-1.22	0.216
Current	1.75	0.75-3.65	0.161
Diabetes	1.57	0.37-4.56	0.47
Total cholesterol	1.27	1.00-1.59	0.049
BMI			
Normal (*reference*)			
Underweight	0.0	0-89217	0.984
Overweight	1.46	0.78-2.89	0.252
Obese	1.68	0.75-3.75	0.198
Diastolic blood pressure			
Normal (*reference*)			
Hypertension Stage 1	1.02	0.53-2.01	0.959
Hypertension Stage 2	0.42	0.17-1.01	0.054
Hypertensive crisis	0.0	0.00-4e07	0.985
Systolic blood pressure			
Normal (*reference*)			
Hypertension Stage 1	1.76	0.74-4.37	0.205
Hypertension Stage 2	2.82	1.24-6.95	0.017
Hypertensive crisis	8.80	1.69-36.32	0.004
Hematopoietic Y loss			
No LOY (*reference*)			
Low LOY	0.88	0.38-1.80	0.742
Substantial LOY	2.10	0.88-4.47	0.069

Table 10. Cox proportional hazards regression analysis for atherosclerosis (ICD-10: I70 and I25.1) in the UK Biobank cohort: CVD-PRS adjusted

Multivariable adjusted logistic regression analysis exploring the risk of incident atherosclerosis (ICD-10: I70 and I25.1) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, systolic blood pressure, and PRS for CVD. Smoking violated the proportional hazards assumption and was therefore modeled with time-specific effects. HR = hazard ratio, CI = confidence interval, BMI = body mass index, CVD = cardiovascular disease, PRS = polygenic risk score, LOY = mosaic loss of chromosome Y.

	HR	95% CI	p value
Age	1.06	1.06-1.06	<0.001
Diabetes	1.86	1.77-1.95	<0.001
BMI			
Normal *(reference)*			
Underweight	1.04	0.72-1.51	0.835
Overweight	1.23	1.18-1.28	<0.001
Obese	1.52	1.45-1.59	<0.001
Cholesterol	1.06	1.05-1.08	<0.001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.89	0.85-0.92	<0.001
Hypertension Stage 2	0.91	0.87-0.96	<0.001
Hypertensive crisis	0.68	0.43-1.07	0.096
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.13	1.08-1.19	<0.001
Hypertension Stage 2	1.29	1.23-1.35	<0.001
Hypertensive crisis	1.49	1.37-1.64	<0.001
Smoking (1st time interval)			
Current smoker	1.78	1.65-1.92	<0.001
Previous smoker	1.25	1.19-1.32	<0.001
Non-smoker *(reference)*			
Smoking (2nd time interval)			
Current smoker	1.61	1.53-1.7	<0.001
Previous smoker	1.11	1.07-1.16	<0.001
Non-smoker *(reference)*			
CVD PRS	1.49	1.47-1.51	<0.001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.03	0.99-1.07	0.169
Substantial LOY	1.06	1.01-1.12	0.032

Table 11. Cox proportional hazards regression analysis for non-coronary atherosclerosis (I70) in the UK Biobank cohort

Multivariable adjusted logistic regression analysis exploring the risk of incident atherosclerosis (ICD-10: I70) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, systolic blood pressure, and PRS for CVD. Smoking violated the proportional hazards assumption and was therefore modeled with time-specific effects. HR = hazard ratio, CI = confidence interval, BMI = body mass index, CVD = cardiovascular disease, PRS = polygenic risk score, LOY = mosaic loss of chromosome Y.

	HR	95% CI	p value
Age	1.09	1.08-1.10	<0.001
Diabetes	2.84	2.51-3.22	<0.001
BMI			
Normal *(reference)*			
Underweight	2.03	1.01-4.09	0.048
Overweight	0.86	0.77-0.97	0.014
Obese	1.15	1.01-1.31	0.036
Cholesterol	0.95	0.91-0.99	0.022
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.78	0.69-0.87	<0.001
Hypertension Stage 2	0.72	0.63-0.83	<0.001
Hypertensive crisis	0.47	0.11-1.90	0.288
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.20	1.03-1.40	0.022
Hypertension Stage 2	1.68	1.46-1.95	<0.001
Hypertensive crisis	2.89	2.26-3.7	<0.001
Smoking (1st time interval)			
Current smoker	10.01	7.28-13.77	<0.001
Previous smoker	2.93	2.15-4.00	<0.001
Non-smoker *(reference)*			
Smoking (2nd time interval)			
Current smoker	4.25	3.69-4.89	<0.001
Previous smoker	1.86	1.65-2.10	<0.001
Non-smoker *(reference)*			
CVD PRS	1.29	1.24-1.36	<0.001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.16	1.04-1.31	0.011
Substantial LOY	1.40	1.21-1.60	<0.001

Table 12. Cox proportional hazards regression analysis for coronary atherosclerosis (I25.1) in the UK Biobank cohort

Multivariable adjusted logistic regression analysis exploring the risk of coronary atherosclerosis (ICD-10: I25.1) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, systolic blood pressure, and PRS for CVD. Smoking violated the proportional hazards assumption and was therefore modeled with time-specific effects. HR = hazard ratio, CI = confidence interval, BMI = body mass index, CVD = cardiovascular disease, PRS = polygenic risk score, LOY = mosaic loss of chromosome Y.

	HR	95% CI	p value
Age	1.06	1.06-1.06	<0.001
Diabetes	1.79	1.70-1.88	<0.001
BMI			
Normal *(reference)*			
Underweight	0.87	0.57-1.34	0.532
Overweight	1.27	1.22-1.32	<0.001
Obese	1.57	1.50-1.64	<0.001
Cholesterol	1.08	1.06-1.09	<0.001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.89	0.86-0.93	<0.001
Hypertension Stage 2	0.93	0.89-0.97	0.002
Hypertensive crisis	0.68	0.42-1.10	0.114
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.13	1.07-1.18	<0.001
Hypertension Stage 2	1.26	1.20-1.32	<0.001
Hypertensive crisis	1.40	1.28-1.54	<0.001
Smoking (1st time interval)			
Current smoker	1.61	1.49-1.74	<0.001
Previous smoker	1.22	1.15-1.29	<0.001
Non-smoker *(reference)*			
Smoking (2nd time interval)			
Current smoker	1.42	1.34-1.50	<0.001
Previous smoker	1.06	1.02-1.11	0.003
Non-smoker *(reference)*			
CVD PRS	1.51	1.48-1.53	<0.001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.01	0.97-1.06	0.529
Substantial LOY	1.02	0.97-1.08	0.427

Table 13. Multivariable logistic regression analysis for myocardial infarction in the UK Biobank cohort: CVD-PRS adjusted

Multivariable adjusted logistic regression analysis exploring the odds of myocardial infarction (algorithmically defined) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, systolic blood pressure, and PRS for CVD. OR = odds ratio, CI = confidence interval, BMI = body mass index, CVD = cardiovascular disease, PRS = polygenic risk score, LOY = mosaic loss of chromosome Y.

	OR	95% CI	p value
Age	1.07	1.06-1.07	<0.001
Smoking			
Non-smoker *(reference)*			
Previous smoker	1.34	1.29-1.39	<0.001
Current smoker	1.96	1.87-2.05	<0.001
Diabetes	1.54	1.47-1.62	<0.001
BMI			
Normal *(reference)*			
Underweight	0.92	0.63-1.31	0.667
Overweight	1.42	1.36-1.48	<0.001
Obese	1.95	1.87-2.05	<0.001
Cholesterol	0.78	0.77-0.79	<0.001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.79	0.75-0.82	<0.001
Hypertension Stage 2	0.80	0.77-0.85	<0.001
Hypertensive crisis	0.84	0.52-1.30	0.462
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	0.91	0.86-0.95	<0.001
Hypertension Stage 2	0.91	0.87-0.95	<0.001
Hypertensive crisis	1.08	0.97-1.19	0.149
CVD PRS	1.63	1.60-1.65	<0.001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.05	1.01-1.10	0.014
Substantial LOY	1.12	1.06-1.18	<0.001

Table 14. Multivariable logistic regression analysis for ischemic stroke in the UK Biobank cohort: CVD-PRS adjusted

Multivariable adjusted logistic regression analysis exploring the odds of ischemic stroke (algorithmically defined) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, systolic blood pressure, and PRS for CVD. OR = odds ratio, CI = confidence interval, BMI = body mass index, CVD = cardiovascular disease, PRS = polygenic risk score, LOY = mosaic loss of chromosome Y.

	OR	95% CI	p value
Age	1.08	1.08-1.09	<0.001
Smoking			
Non-smoker *(reference)*			
Previous smoker	1.08	1.02-1.14	0.007
Current smoker	1.82	1.69-1.95	<0.001
Diabetes	1.67	1.55-1.81	<0.001
BMI			
Normal *(reference)*			
Underweight	0.93	0.52-1.54	0.806
Overweight	1.01	0.94-1.07	0.875
Obese	1.22	1.14-1.31	<0.001
Cholesterol	0.87	0.85-0.89	<0.001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	1.05	0.99-1.12	0.132
Hypertension Stage 2	1.17	1.08-1.27	<0.001
Hypertensive crisis	3.26	2.06-4.98	<0.001
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	0.89	0.82-0.96	0.003
Hypertension Stage 2	1.04	0.97-1.12	0.277
Hypertensive crisis	1.51	1.31-1.73	<0.001
CVD PRS	1.25	1.22-1.28	<0.001
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.02	0.96-1.09	0.491
Substantial LOY	1.01	0.92-1.10	0.895

Table 15. Cox proportional hazards regression analysis for atherosclerosis (ICD-10: I70 and I25.1) in the UK Biobank cohort

Multivariable adjusted Cox hazards regression analysis exploring the risk of incident atherosclerosis (ICD-10: I70 and I25.1) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, and systolic blood pressure. Smoking violated the proportional hazards assumption and was therefore modeled with time-specific effects. HR = hazard ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y.

	HR	95% CI	p value
Age	1.06	1.06-1.06	<0.001
Diabetes	1.94	1.85-2.03	<0.001
BMI			
Normal *(reference)*			
Underweight	1.04	0.72-1.51	0.836
Overweight	1.24	1.19-1.29	<0.001
Obese	1.54	1.47-1.61	<0.001
Cholesterol	1.06	1.05-1.08	<0.001
Diastolic blood pressure			
Normal *(reference)*			
Hypertension Stage 1	0.89	0.85-0.92	<0.001
Hypertension Stage 2	0.92	0.87-0.96	<0.001
Hypertensive crisis	0.67	0.43-1.06	0.091
Systolic blood pressure			
Normal (reference)			
Hypertension Stage 1	1.16	1.10-1.21	<0.001
Hypertension Stage 2	1.36	1.30-1.42	<0.001
Hypertensive crisis	1.62	1.48-1.78	<0.001
Smoking (1st time interval)			
Current smoker	1.8	1.67-1.94	<0.001
Previous smoker	1.26	1.19-1.34	<0.001
Non-smoker *(reference)*			
Smoking (2nd time interval)			
Current smoker	1.62	1.54-1.71	<0.001
Previous smoker	1.12	1.08-1.16	<0.001
Non-smoker *(reference)*			
Hematopoietic Y loss			
No LOY *(reference)*			
Low LOY	1.03	0.99-1.07	0.195
Substantial LOY	1.05	1.00-1.11	0.055

Table 16. Multivariable logistic regression analysis for myocardial infarction in the UK Biobank cohort

Multivariable adjusted logistic regression analysis exploring the odds of myocardial infarction (algorithmically defined) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, and systolic blood pressure. OR = odds ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y.

	OR	95% CI	p value
Age	1.06	1.06-1.07	<0.001
Smoking status			
Never (*reference*)			
Previous	1.35	1.31-1.4	<0.001
Current	1.97	1.88-2.06	<0.001
Diabetes	1.58	1.50-1.65	<0.001
BMI			
Normal (*reference*)			
Underweight	0.91	0.62-1.28	0.596
Overweight	1.43	1.37-1.49	<0.001
Obese	1.98	1.89-2.08	<0.001
Total cholesterol	0.77	0.76-0.78	<0.001
Diastolic blood pressure			
Normal (*reference*)			
Hypertension Stage 1	0.78	0.75-0.81	<0.001
Hypertension Stage 2	0.80	0.76-0.84	<0.001
Hypertensive crisis	0.84	0.52-1.30	0.456
Systolic blood pressure			
Normal (*reference*)			
Hypertension Stage 1	0.93	0.89-0.97	0.001
Hypertension Stage 2	0.96	0.92-1.01	0.104
Hypertensive crisis	1.19	1.07-1.31	0.001
Hematopoietic Y loss			
No LOY (*reference*)			
Low LOY	1.05	1.01-1.09	0.026
Substantial LOY	1.11	1.05-1.17	<0.001

Table 17. Multivariable logistic regression analysis for ischemic stroke in the UK Biobank cohort

Multivariable adjusted logistic regression analysis exploring the odds of ischemic stroke (algorithmically defined) between men with LOY and men with no detectable LOY. The model is adjusted for age, smoking, diabetes, BMI, total cholesterol, diastolic blood pressure, and systolic blood pressure. OR = odds ratio, CI = confidence interval, BMI = body mass index, LOY = mosaic loss of chromosome Y.

	OR	95% CI	p value
Age	1.08	1.08-1.09	<0.001
Smoking status			
Never (*reference*)			
Previous	1.09	1.03-1.15	0.002
Current	1.84	1.71-1.97	<0.001
Diabetes	1.70	1.58-1.83	<0.001
BMI			
Normal (*reference*)			
Underweight	0.93	0.51-1.53	0.783
Overweight	1.01	0.95-1.08	0.716
Obese	1.23	1.15-1.33	<0.001
Total cholesterol	0.86	0.84-0.88	<0.001
Diastolic blood pressure			
Normal (*reference*)			
Hypertension Stage 1	1.05	0.98-1.12	0.181
Hypertension Stage 2	1.16	1.08-1.26	<0.001
Hypertensive crisis	3.25	2.05-4.96	<0.001
Systolic blood pressure			
Normal (*reference*)			
Hypertension Stage 1	0.90	0.83-0.97	0.008
Hypertension Stage 2	1.07	0.99-1.16	0.07
Hypertensive crisis	1.58	1.37-1.81	<0.001
Hematopoietic Y loss			
No LOY (*reference*)			
Low LOY	1.02	0.96-1.09	0.523
Substantial LOY	1.00	0.92-1.09	0.998

Table 18. Data fields for variable extraction in the SCAPIS cohort

A list of data fields used for data curation and statistical analyses in the SCAPIS cohort. Explanations of the data fields are provided in the variable column. CCTA = coronary computed tomography angiography.

Data field	Variable
CCTA_population_Circ21	Subjects included in CCTA analyses in SCAPIS (Bergström et al, Circulation 2021)
Atherosclerosis_Any	Atherosclerosis in any coronary segment
Above50_Any	Atherosclerosis in any coronary segment
SIS	Segment Involvement Score - total number of coronary segments with any atherosclerosis
CACS_Tot	Summed CACS (Coronary artery calcium score according to Agatston)
carotidplaque	Presence of any carotid artery plaque
AgeAtVisitOne	Age at first study visit
derived_smoke_status	Current smoking status (derived variable)
BMI	Body mass index
CholesterolFormattedResult	Cholesterol numerical result
DBP_Mean	Diastolic blood pressure, mean brachial
SBP_Mean	Systolic blood pressure, mean brachial
Diabetes	Classification of glycaemic status according to baseline examination results

Table 19. Data fields used for variable extraction in the UK Biobank cohort
A list of data fields used for data curation and statistical analyses in the UK Biobank cohort. Explanations of the data fields are provided in the variable column. IMT = intima-media thickness, PRS = polygenic risk score.

| Data field	Variable
53	Date of attending assessment centre
93	Systolic blood pressure, manual reading
94	Diastolic blood pressure, manual reading
2443	Diabetes diagnosed by doctor
4079	Diastolic blood pressure, automatic reading
4080	Systolic blood pressure, automatic reading
20116	Smoking status
21003	Age when attended assessment centre
22671	Mean carotid IMT at 120 degrees
22674	Mean carotid IMT at 150 degrees
22677	Mean carotid IMT at 210 degrees
22680	Mean carotid IMT at 240 degrees
23104	Body mass index by impedance
24120	Ascending aorta distensibility
26223	Standard PRS for cardiovascular disease (CVD)
30690	Cholesterol
41270	Diagnoses - ICD10
41280	Date of first in-patient diagnosis - ICD10
42000	Date of myocardial infarction
42006	Date of stroke
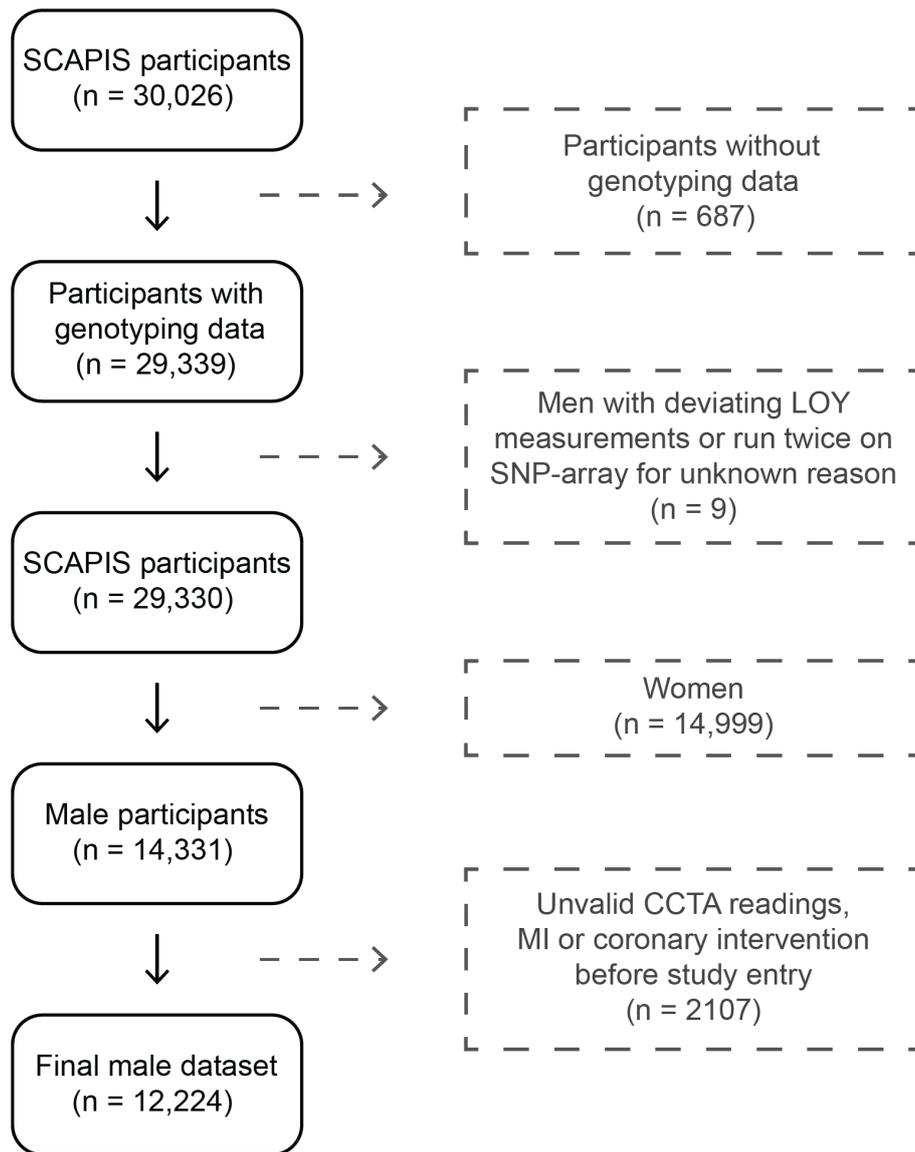
Figure 1. Inclusion criteria for the SCAPIS cohort

Overview of filtration steps applied to get the final dataset of 12,224 male participants from the SCAPIS cohort used for atherosclerosis analyses. Invalid CCTA readings refer to individuals with unsuccessful CCTA measures in any of the four proximal coronary segments.
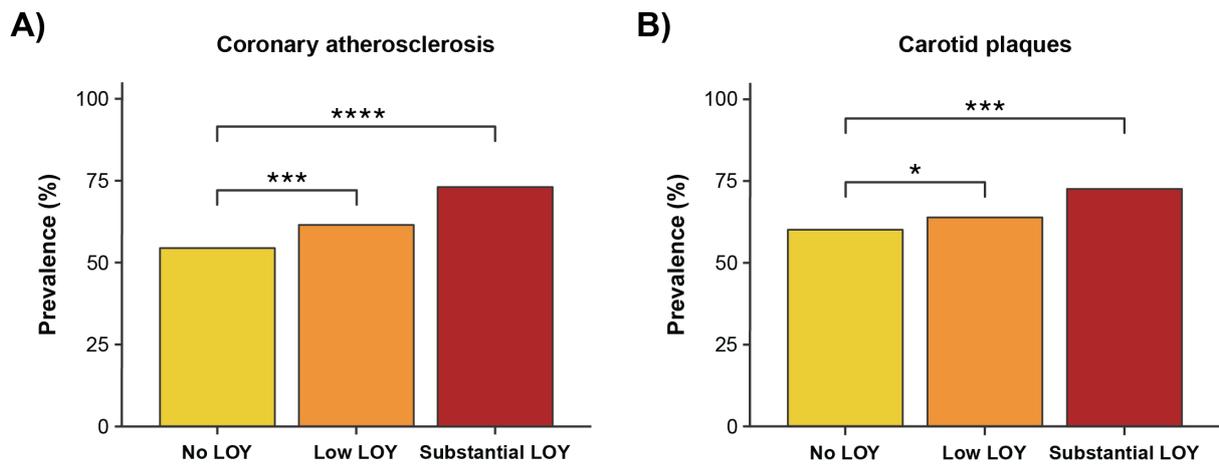
Figure 2. Prevalence of coronary and carotid atherosclerosis in the SCAPIS cohort
Coronary atherosclerosis (A) and carotid plaque (B) prevalence was compared among male SCAPIS participants, grouped based on their level of LOY measured in blood. The prevalence differences were tested using Fisher's exact test; p values are denoted as: $p < 0.05$ = *, $p < 0.001$ = ***, and $p < 0.0001$ = ****.
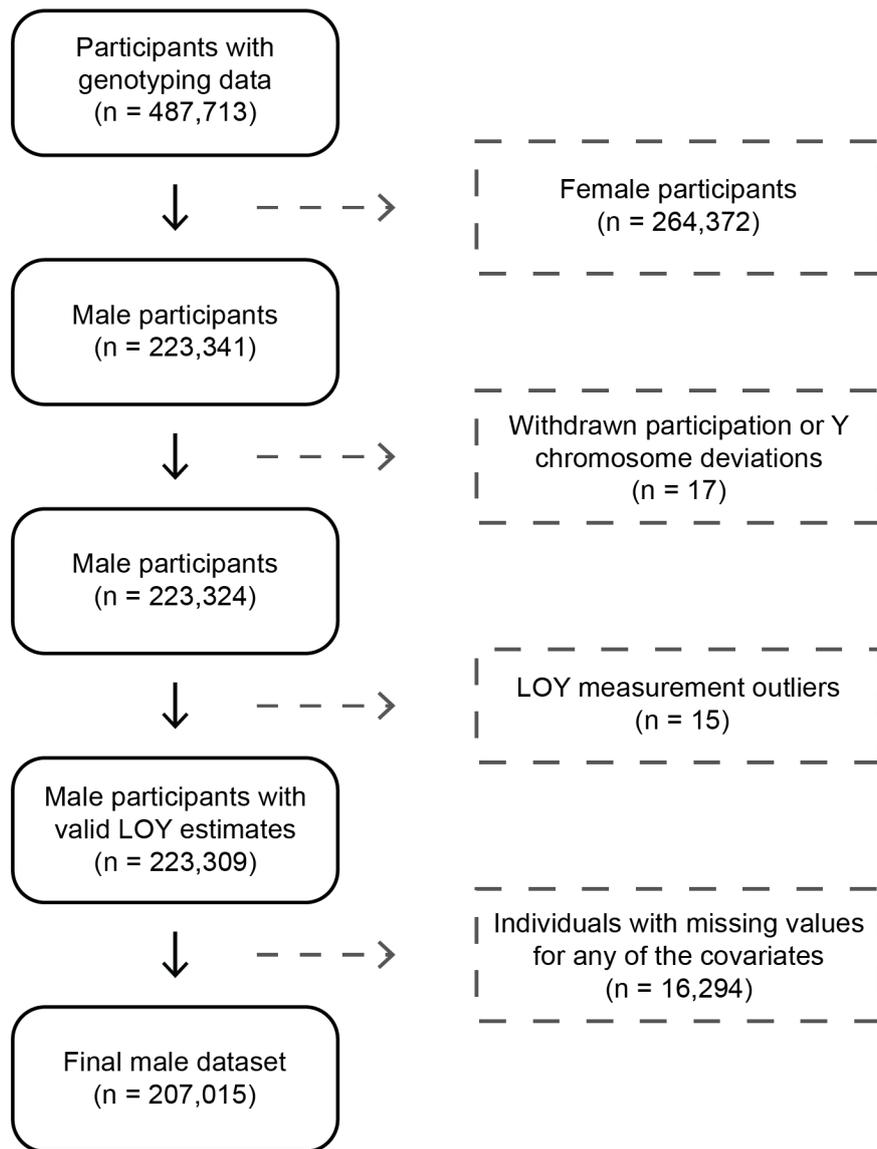
Figure 3. Inclusion criteria for the UK Biobank cohort
Overview of filtration steps applied to get the final dataset of 207,015 male participants from the UK Biobank cohort used in the analyses.
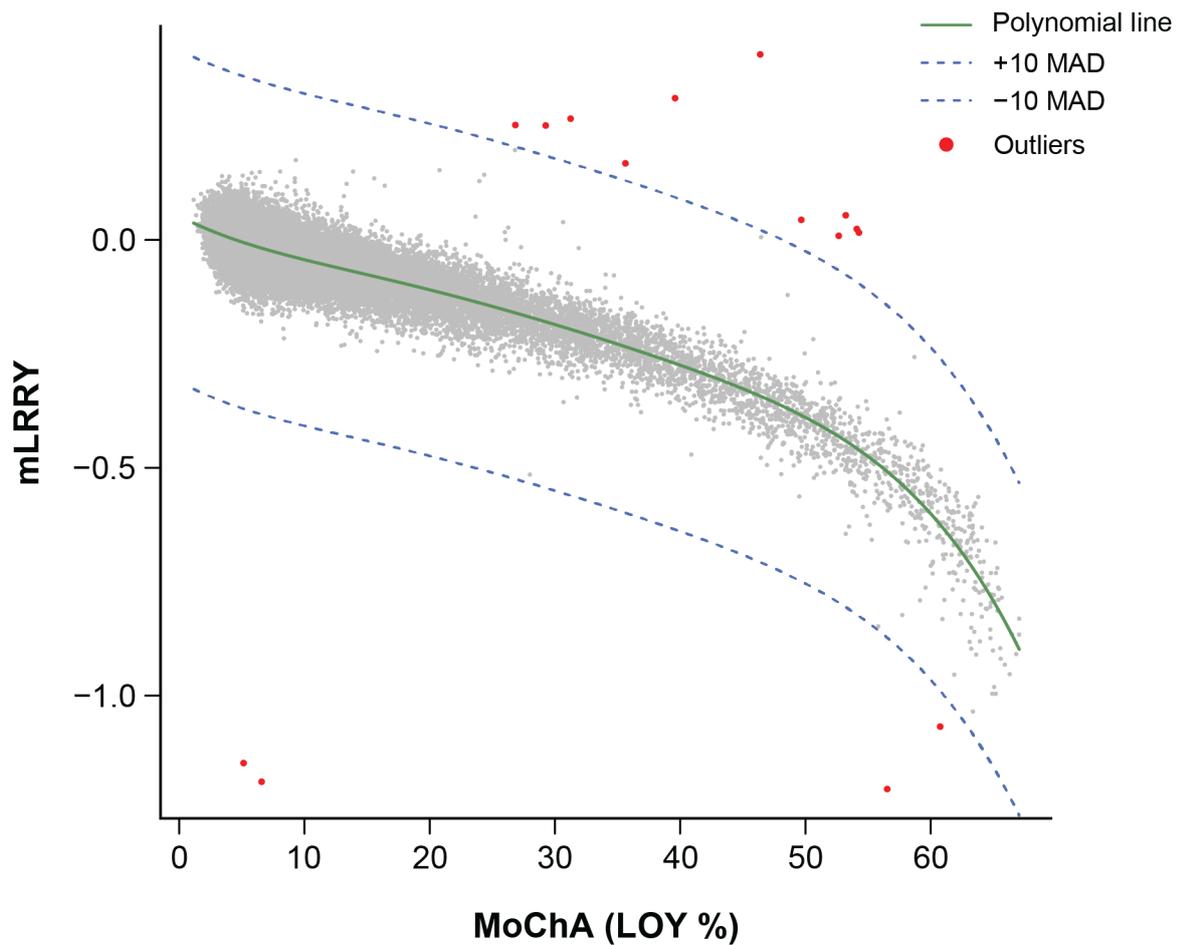
Figure 4. LOY estimation comparison and outlier detection in the UK Biobank cohort
Dotplot showing the distribution of median log R ratio for probes on the male-specific region of chromosome Y (mLRRY) values compared to MoChA values, presented as percentage of loss of chromosome Y (LOY). The green line shows a fitted 5th polynomial regression, and the dotted lines show the cutoff of ten times the median absolute deviation. Red dots are samples considered as outliers using this method.
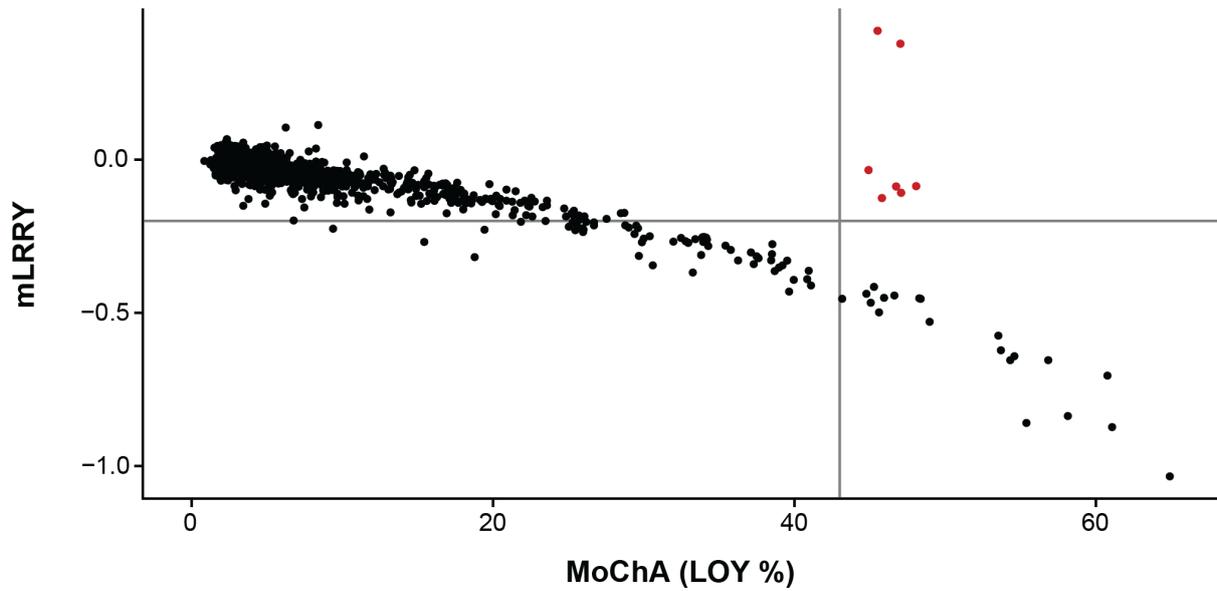
Figure 5. Comparison of LOY estimates and outlier detection in the SCAPIS cohort
A dotplot showing the comparison between loss of chromosome Y (LOY) measures estimated by the median log R ratio for probes on the male-specific region of chromosome Y (mLRRY) and the MoChA pipeline. Male samples marked in red were removed from the dataset due to deviating LOY measures between the two methods.
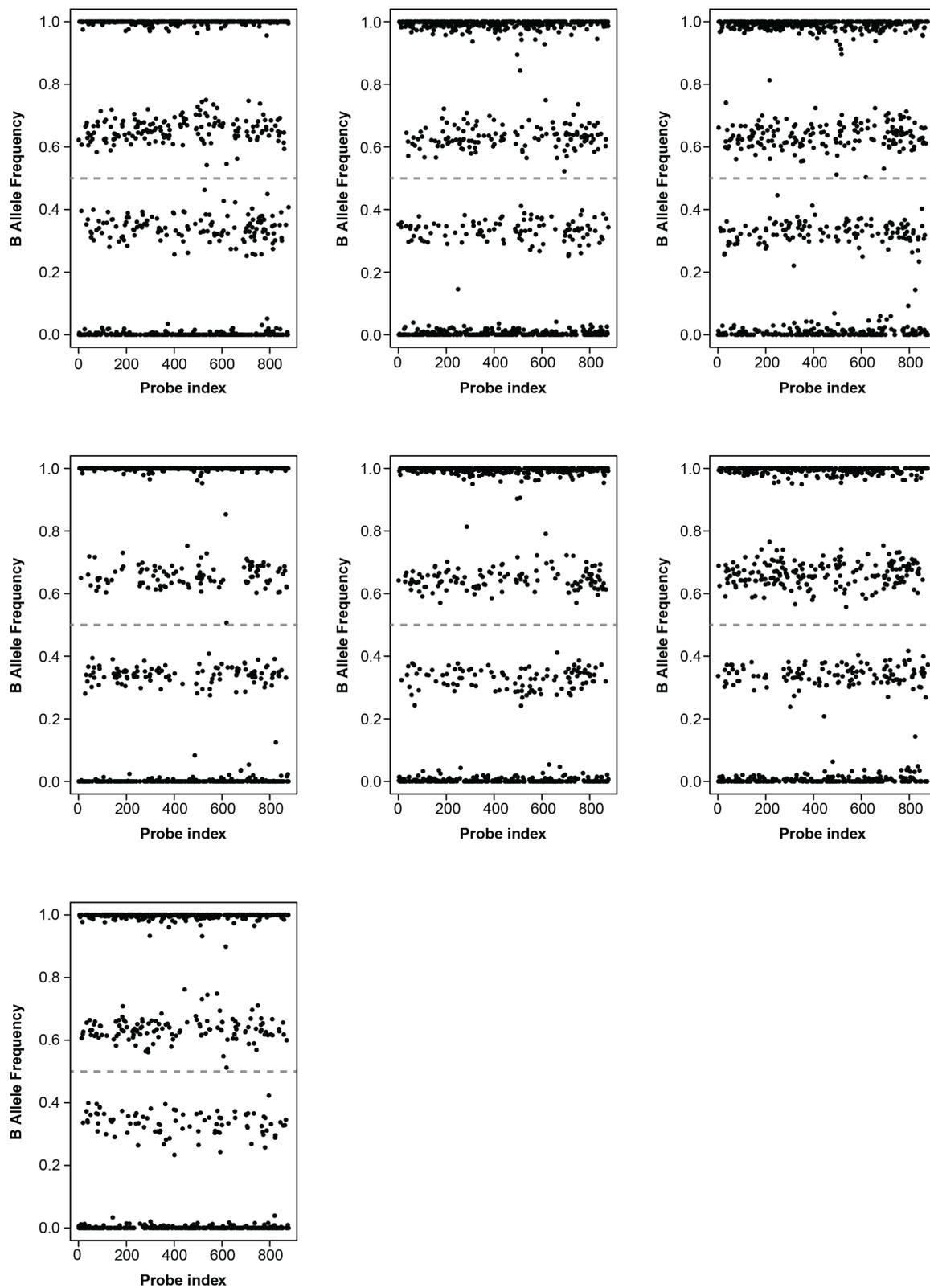
Figure 6. B Allele Frequency values for males with deviating LOY measures

The plots display B Allele Frequency (BAF) values for probes in the pseudoautosomal region 1 for seven males excluded from the analysis. The BAF values indicate that all seven men carry an additional sex chromosome (47,XXY or 47,XYY). The seven samples were run on different sequencing batches and came from several SCAPIS sites.
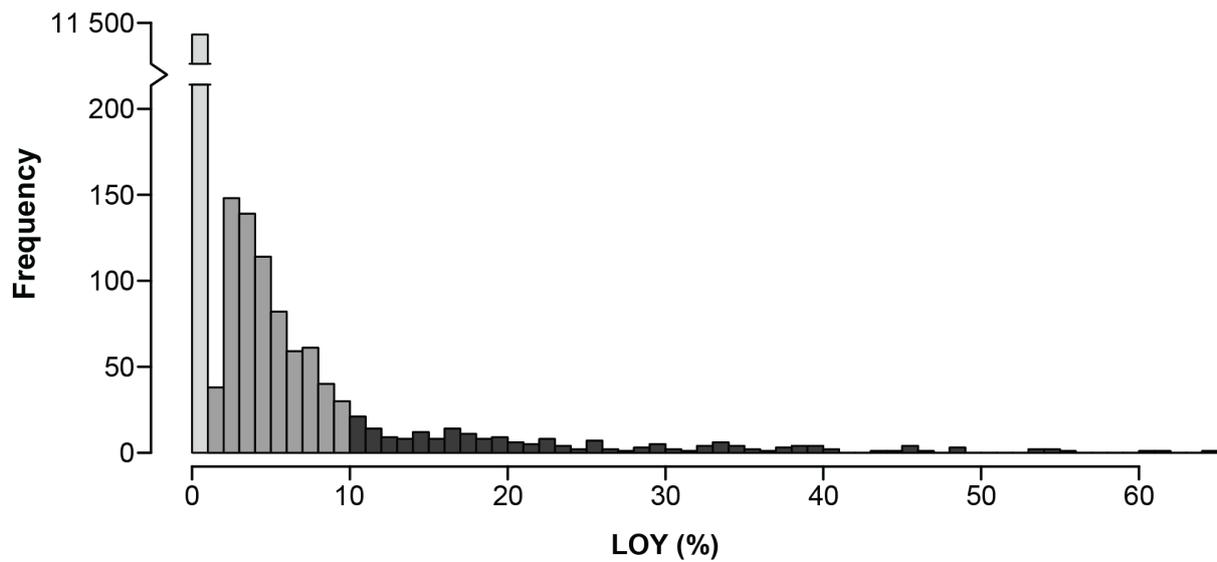
Figure 7. LOY groups in the SCAPIS cohort
The histogram shows the frequency of men with LOY in SCAPIS. Based on the percentage of Y loss measured in blood, men were categorized into three groups: no LOY (light grey), low LOY (≤10%, dark grey), and substantial LOY (>10%, black). These LOY levels were used for all statistical analyses for the SCAPIS cohort.
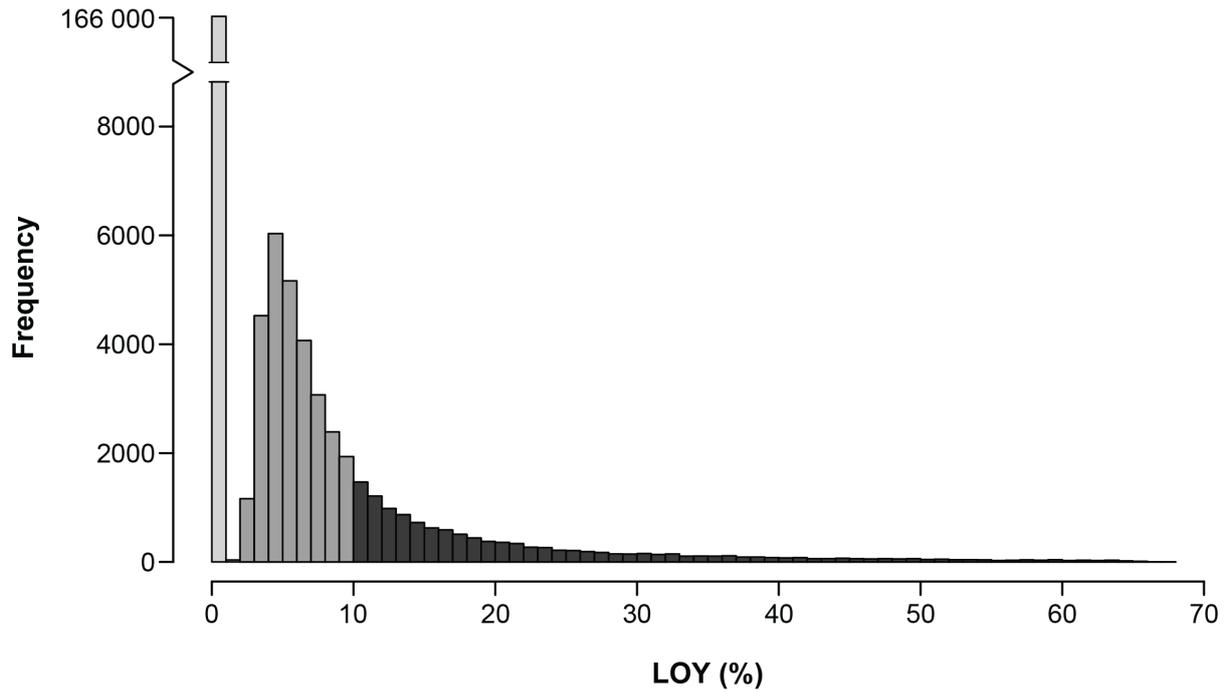
Figure 8. LOY groups in the UK Biobank cohort

The histogram shows the frequency of men with LOY in the UK Biobank. Based on the percentage of Y loss measured in blood, men were categorized into three groups: no LOY (light grey), low LOY (≤10%, dark grey), and substantial LOY (>10%, black). These LOY levels were used for all statistical analyses for the UK Biobank cohort.