








ORIGINAL RESEARCH

Associations Between Mosaic Loss of Sex Chromosomes and Incident Hospitalization for Atrial Fibrillation in the United Kingdom

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BACKGROUND: Mosaic loss of chromosome Y (mLOY) in leukocytes of men reflects genomic instability from aging, smoking, and environmental exposures. A similar mosaic loss of chromosome X (mLOX) occurs among women. However, the associations between mLOY, mLOX, and risk of incident heart diseases are unclear.

METHODS AND RESULTS: We estimated associations between mLOY, mLOX, and risk of incident heart diseases requiring hospitalization, including atrial fibrillation, myocardial infarction, ischemic heart disease, cardiomyopathy, and heart failure. We analyzed 190 613 men and 224 853 women with genotyping data from the UK Biobank. Among these participants, there were 37 037 men with mLOY and 13 978 women with mLOX detected using the Mosaic Chromosomal Alterations caller. Multivariable Cox regression was used to estimate hazard ratios (HRs) and 95% CIs of each incident heart disease in relation to mLOY in men and mLOX in women. Additionally, Mendelian randomization was conducted to estimate causal associations. Among men, detectable mLOY was associated with elevated risk of atrial fibrillation (HR, 1.06 [95% CI, 1.03–1.11]). The associations were apparent in both never smokers (HR, 1.07 [95% CI, 1.01–1.14]) and ever smokers (HR, 1.05 [95% CI, 1.01–1.11]) as well as men aged >60 and ≤60 years. Mendelian randomization analyses supported causal associations between mLOY and atrial fibrillation (HR_{MR-PRESSO}, 1.15 [95% CI, 1.13–1.18]). Among postmenopausal women, we found a suggestive inverse association between detectable mLOX and atrial fibrillation risk (HR, 0.90 [95% CI, 0.83–0.98]). However, associations with mLOY and mLOX were not found for other heart diseases.

CONCLUSIONS: Our findings suggest that mLOY and mLOX reflect sex-specific biological processes or exposure profiles related to incident atrial fibrillation requiring hospitalization.

Key Words: atrial fibrillation ■ heart disease ■ incident relative risk ■ mosaic loss of sex chromosomes ■ prospective cohort study

The Y chromosome contains genes that play crucial roles in biological processes involved in male sex determination, spermatogenesis, and sexual maturation. Furthermore, genetic variants on the Y chromosome have been linked to fundamental cellular housekeeping processes, including mitosis, cell

cycle regulation, DNA damage detection and repair, and apoptosis.¹ As such, alterations to the dosage of genes located on the Y chromosome can potentially influence the pathogenesis of chronic diseases that involve these underlying biological pathways. Mosaic loss of chromosome Y (mLOY) is a common genomic

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RESEARCH PERSPECTIVE

What Is New?

- Mosaic loss of chromosome Y (mLOY) in leukocytes of men reflects genomic instability from increasing age, smoking, and the burden of environmental exposures; a similar but less common mosaic loss of the X-chromosome (mLOX) occurs among women.
- In a population free of serious cardiovascular disease at baseline, we estimated associations between mLOY, mLOX, and risk of incident heart disease requiring hospitalization, including atrial fibrillation, myocardial infarction, ischemic heart disease, and cardiomyopathy/heart failure syndrome.
- We found that detectable mLOY was associated with elevated risk of atrial fibrillation among men; conversely, among postmenopausal women, we found a suggestive inverse association between detectable mLOX and atrial fibrillation risk.

What Question Should Be Addressed Next?

- Investigators should determine why mLOY and mLOX have potentially opposing associations with atrial fibrillation risk among men and women; furthermore, mechanistic studies are needed to address how mLOY and mLOX may be directly or indirectly involved in the pathogenesis of atrial fibrillation.

Nonstandard Abbreviations and Acronyms

BAF	B-allele frequency
IVW	inverse variance weighted
MR	Mendelian randomization
MR-PRESSO	Mendelian randomization pleiotropy residual sum and outlier
MR-RAPS	Mendelian randomization robust adjusted profile score
mCF	mosaic cell fraction
mLOX	mosaic loss of chromosome X
mLOY	mosaic loss of chromosome Y
PAR	pseudoautosomal region

alteration that manifests in a fraction of cells as men age. Depending on the study and calling methods, an estimated 7% to 57% of older men, generally aged

>65years, have detectable mLOY in circulating leukocytes.¹⁻⁷ Variation in mLOY has both genetic and environmental components, having associations reported with cigarette smoking, outdoor air pollution, and arsenic.^{1,4,7,8}

In population studies, mLOY has been linked to risk of various chronic diseases⁹⁻¹⁴; however, investigations into the contribution of mLOY to the pathogenesis of cardiovascular diseases (CVDs) are still in early stages.^{14,15} In the UK Biobank, mLOY in leukocytes was found to be cross-sectionally associated with prevalent diabetes and heart disease.¹⁵ Furthermore, recent analyses found that mLOY was associated with increased risk of death from both atrial fibrillation and heart failure syndrome.¹⁶ The biological mechanisms underlying these relationships with heart diseases in humans remain unclear. However, studies have suggested links between mLOY and increased total and bioavailable testosterone,¹⁷ metabolic biomarkers that we recently found to be associated with incident hospitalization for heart failure.¹⁸

The X chromosome contains essential housekeeping genes responsible for basic biological function.¹⁹ Among men, mosaic loss of chromosome X (mLOX) in leukocytes is poorly tolerated and rarely observed.²⁰ Among women, however, mLOX in leukocytes can change the dosage and allelic balance of genes on the maternal or paternal X chromosome. Given that 1 X chromosome is epigenetically inactivated in female diploid cells, the biological impact of mLOX is determined by which X chromosome is lost.²¹ Previous analyses found that mLOX preferentially affects the inactivated X chromosome.¹⁹ Recent meta-analyses of large genome-wide association studies (GWASs) conducted in multiple biobanks have identified 49 independent genetic variants associated with mLOX.²¹ However, little is known about its influence on the risk of heart diseases.

Despite a growing body of literature on the relationships between mosaic loss of sex chromosomes and prevalent CVD and CVD-related mortality, their associations with disease incidence are unclear. Investigating the impact of mosaic loss of sex chromosomes in leukocytes on risk of incident heart diseases is important for understanding the role of genomic instability and immune function in disease pathogenesis and could potentially have translational relevance toward risk prediction. To address these gaps in knowledge, we leveraged the extensive demographic, clinical, and GWAS data from the UK Biobank. In a population free of CVD at baseline, we evaluated the prospective associations between prediagnostic leukocyte mLOY among men, mLOX among women, and risk of incident atrial fibrillation, myocardial infarction, ischemic heart disease,

cardiomyopathy, and heart failure syndrome requiring hospitalization.

METHODS

Study Design

The UK Biobank is a prospective cohort study and has been described in detail (<http://www.ukbiobank.ac.uk/>).^{22,23} UK Biobank data are publicly available (<https://ams.ukbiobank.ac.uk/ams/>). Briefly, the source population included adults, aged 40 to 69 years, who lived ≤ 40 km of 22 study assessment centers across England, Wales, and Scotland. Nearly 9.2 million people registered in the National Health Service were mailed invitations to participate in the study, whereas 503 317 (5.5%) visited the assessment centers in 2006 to 2010 and were enrolled.²² The volunteers completed touchscreen questionnaires, underwent physical examinations, and provided blood samples for bioassays and genomic analyses. The UK Biobank is regularly updated, and our data set from August 2022 included 502 409 subjects (project number: 28072). The data fields used in our study are shown in [Table S1](#).

GWAS Data

GWAS data were available for 488 377 UK Biobank participants as described.²⁴ Briefly, genotyping was performed by the Affymetrix Research Services Laboratory (now part of Thermo Fisher Scientific) on 2 similar custom arrays. Among these subjects, 49 950 were scanned on the UK BiLEVE Axiom array, whereas the remaining 438 427 participants were scanned using the UK Biobank Axiom array. The GWAS data set combines results from both arrays, and there were 805 426 markers in the released genotype data set. Approximately 3% of eligible participants who consented to genetic analyses did not have sufficient extracted DNA to conduct the genotyping. Affymetrix used a custom genotype calling pipeline, and the genotype data were quality controlled. Furthermore, the data set was phased and nearly 96 million genotypes were imputed using computationally efficient methods combined with the Haplotype Reference Consortium and UK10K haplotype resources. Information on the quality control pipeline and population structure and relatedness has been described in detail.²⁴

Kinship coefficients were previously estimated for all pairs of individuals using KING software.²⁵ These estimates of relatedness are available in UK Biobank data field 22021. Furthermore, data field 22020 restricts to a maximal subset of unrelated (to the third degree) participants who were not sex discordant or outliers for missingness or heterozygosity. The genetic principal components (data field 22009) were generated as previously described in detail.²⁴

Detection of Mosaic Loss of Sex Chromosomes

Raw genotyping array intensity data were used to calculate B-allele frequencies (BAFs) and \log_2 R ratios, which were then analyzed using mosaic chromosomal alterations caller v2022-01-12 (<https://github.com/freeseek/mochawdl>) to detect mosaic chromosomal alteration regions as previously described.^{26–28} The mosaic chromosomal alteration calling was performed by Giulio Genovese (Broad Institute of Massachusetts Institute of Technology and Harvard). Mosaic chromosomal alterations caller uses Viterbi hidden Markov models to integrate \log_2 R ratios and BAFs, leveraging haplotype information to detect subtle imbalances between maternal and paternal allelic fractions in a cell population. SHAPEIT4 software was used for phasing to infer haplotypes. \log_2 R ratio was used to determine the status of events (ie, gain, loss, or copy neutral loss of heterozygosity). We focused on subjects with a sample call rate ≥ 0.97 and `baf_auto` ≤ 0.03 to ensure high-quality samples for subsequent analysis.

Postprocessing of the mosaic chromosomal alteration data to generate the mLOX and mLOY calls was performed at the National Cancer Institute. For mLOY calling, we identified male subjects exhibiting mLOY based on the established criteria outlined (<https://github.com/freeseek/mocha>). These criteria included a minimum event size >2 MB and a relative copy number <2.5 in the pseudoautosomal region 1 (PAR1) region. The proportion of cells with Y-chromosome loss (“mosaic cell fraction” [mCF]) was estimated using BAF values in the mLOY region. To improve mLOY detection, mosaic fraction estimates for Y-chromosome events were derived using BAF deviation on the pseudoautosomal 1 region. For the mLOX calling, we identified female subjects exhibiting mLOX based on the standard criteria specified (<https://github.com/freeseek/mocha>), including a minimum event size >100 MB and a relative copy number <2.5 on the X chromosome. The mCF with X-chromosome loss was estimated using BAF values in the mLOX region. Recently, mCF has emerged as an important consideration in mosaic chromosomal alteration analyses, as increased proportions reflect greater white blood cell aberrations and stronger disease associations have been found at mCFs $>10\%$.²⁹

Ascertainment of Heart Disease Cases

Heart disease cases were defined using inpatient hospital diagnoses coded according to *International Classification of Diseases, Ninth Revision* (ICD-9), and *International Classification of Diseases, Tenth Revision* (ICD-10). Atrial fibrillation was defined using ICD-10 (I48, I48.0, I48.1, I48.2, I48.3, I48.4, or I48.9) and ICD-9 (427.3). Myocardial infarction was defined using ICD-10 (I21, I22, or I23) and ICD-9 (412). Ischemic heart

disease/angina pectoris was defined using *ICD-10* (I20, I24, or I25) and *ICD-9* (411.1, 413.0, 413.1, 414.0, 414.8, or 414.9). Cardiomyopathy was defined using *ICD-10* (I25.5, I42.0, I42.5, I42.9, or I43) and *ICD-9* (425.4). Heart failure syndrome was defined using *ICD-10* (I42.8, I42.1, I50, I50.1, I50.9, I11.0, I13.0, or I13.2) and *ICD-9* (428.0, 428.1).

We conducted sensitivity analysis using a smaller subgroup of participants ($n \sim 229\,972$, 45% of study population) in which preliminary raw primary care data were collected (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf). These primary care data presumably capture more moderate cases that did not initially require hospitalization. Importantly, there is no national system for collecting or sharing primary care data, and the UK Biobank has worked with various data suppliers and other intermediaries to obtain primary care data. Participants provided written consent for linkage of primary care data to their health-related records. Here, for example, we defined atrial fibrillation using Clinical Terms Version 3 codes that correspond to a text search for “atrial fibrillation.” In the subset with primary care data, we analyzed incident outcomes as: (1) general practitioner–diagnosed specific heart disease, (2) hospitalization for specific heart disease, and (3) combined general practitioner and hospitalization for specific heart disease.

Inclusion/Exclusion Criteria

There were 502 409 participants at baseline. We considered self-reported sex (data field 31) acquired from the central registry at recruitment (with some data updated by the participant) as well as genetic sex (data field 22001) determined by genotyping array, then excluded 372 participants with discrepancy between genetic and self-reported sex because of potential data quality issues. Additionally, we excluded 40 who dropped out of the study, 2257 with prevalent heart failure syndrome, and 23 199 with prevalent CVD, which left 476 541 participants (Figure 1). Among these subjects, 463 082 had genotype data for detecting mLOY or mLOX (Table 1) and were considered for further analysis.

Follow-Up

For each participant, the prospective follow-up started at the date of visit to the assessment center in 2006 to 2010 and ended at the date of first incident diagnosis (hospitalization) of heart disease, death, or administrative censoring (ie, September 20, 2021, for England and Wales and October 31, 2021, for Scotland), whichever came first. Vital status and the primary underlying cause of death for participants were provided by the National Health Service Information Centre and the National Health Service Central Register. The

UK Biobank study was approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee. All participants provided electronic informed consent.

Main Analyses

Separate multivariable Cox regression models were used to estimate hazard ratios (HRs) and 95% CIs of incident hospitalization for atrial fibrillation, myocardial infarction, ischemic heart disease/angina pectoris, cardiomyopathy, and heart failure syndrome in relation to mLOY (detectable versus not detectable) among men and mLOX (detectable versus not detectable) among women. For mLOY analyses among men, we adjusted for potential confounders, including study assessment center, age at recruitment (continuous), self-reported race and ethnicity to indirectly adjust for culture-specific dietary patterns, environmental factors, social determinants of health (European, Black/African, mixed, South Asian, other groups [other participants who did not report themselves as European, Black/African, mixed, South Asian, or missing/unknown], or missing/unknown), 10 principal components for genetic ancestry, educational attainment (ie, qualifications), smoking status (never, former, or current, missing/unknown), body mass index (<18.5 , ≥ 18.5 to <25 , ≥ 25 to <30 , ≥ 30 to <35 , or ≥ 35 kg/m² or missing/unknown), material deprivation (Townsend deprivation index, socioeconomic status, or continuous), alcohol intake derived by combining drinking status and amount consumed per week calculated as the sum of all alcoholic beverages consumed on average per day (never, former, current occasional, current <1 drink/day, current 1–3 drinks/day, current >3 drinks/day, unknown, or missing/unknown), self-reported diabetes status (none, diabetic, or missing/unknown), glycosylated hemoglobin (mmol/mol, continuous), hypertension status based on average systolic and diastolic blood pressure at baseline (normal, elevated, stage 1 and 2 hypertension, hypertensive crisis, and unknown), total white blood cell count at enrollment, and any cancer diagnosis at enrollment. For mLOX analyses among women, we adjusted for the same covariates as men in addition to oral contraceptive use (never and ever), hormone replacement therapy use (never and ever), and menopausal status (premenopause, natural postmenopause, artificial menopause, and missing/unknown). We conducted additional analyses stratified by leukocyte mCFs, smoking status (never and ever), age groups (>60 and ≤ 60 years), menopausal status (premenopause and postmenopause) among women, as well as a sensitivity analysis restricted to European genetic ancestry participants determined using data field 22006 (participants who self-identified as “White British” in data field 21000 and have similar genetic ancestry based on a principal components analysis of genotypes). Categorical

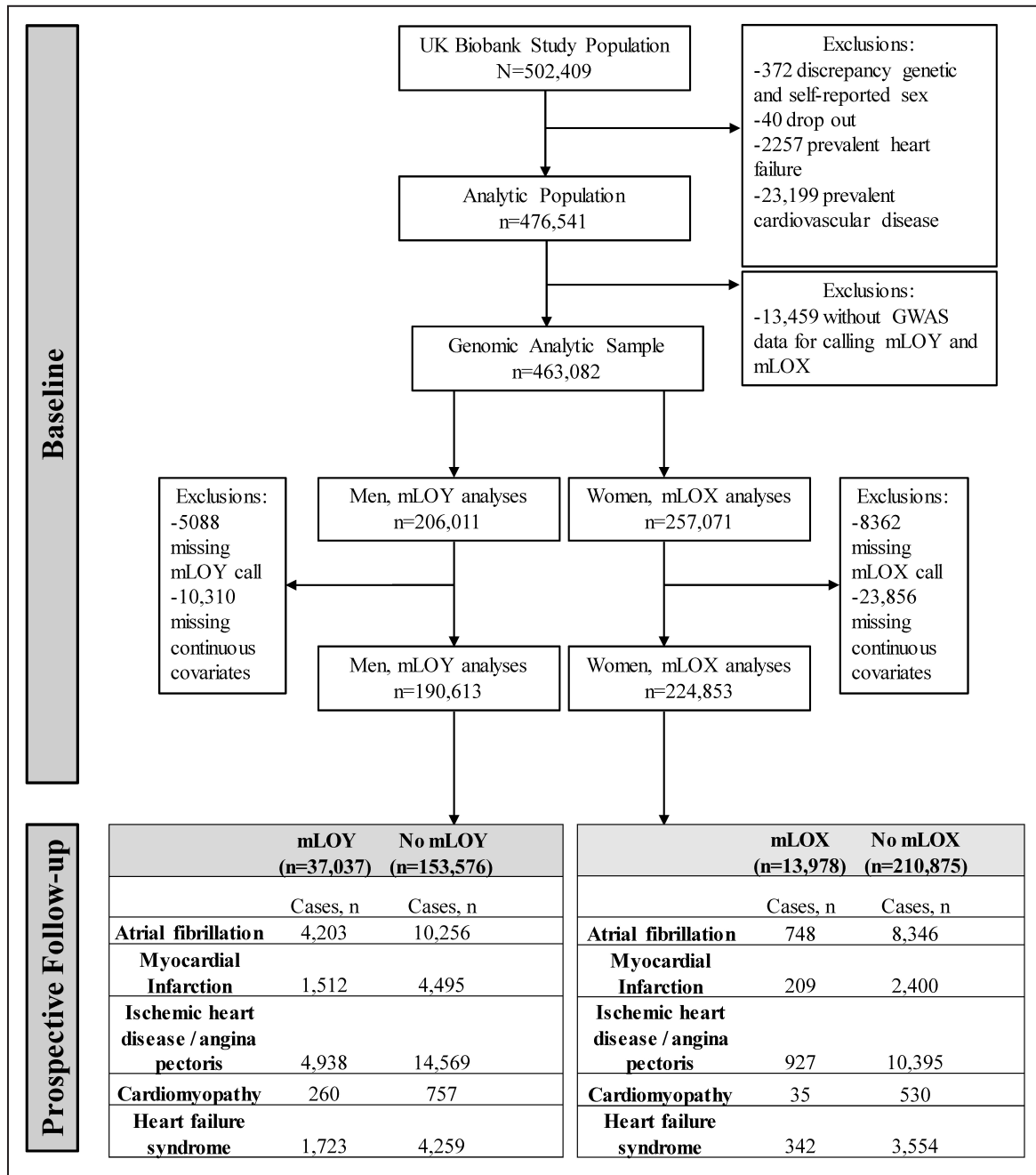


Figure 1. Analytical flowchart.

GWAS indicates genome-wide association study; mLOX, mosaic loss of chromosome X; and mLOY, mosaic loss of chromosome Y.

variables were coded with a category for missingness. We analyzed participants with complete data on continuous independent variables. Overall and within stratified and subgroup analyses, $P < 0.05$ was considered noteworthy, and those below a Bonferroni-corrected α threshold of 0.01 were considered statistically significant (ie, 0.05 divided by a family of 5 tests corresponding to each heart disease outcome). We checked for violations of proportional hazards assumptions by visually inspecting the Schoenfeld residuals over the follow-up time as

well as using cross-product terms between mLOY/mLOX and time. We did not find clear evidence of violations of proportional hazards assumptions. The P values for the cross-product terms with time were 0.34 for mLOY and 0.78 for mLOX.

Attenuation and Sensitivity Analyses

To tightly control potential residual confounding from smoking in the main analyses, we adjusted for a

Table 1. Baseline Characteristics of UK Biobank Study Population With and Without Mosaic Loss of Sex Chromosomes (n=463082)

Characteristic	Men					Women				
	Detectable mLOY (n=40043)		No mLOY (n=165968)			Detectable mLOX (n=15680)		No mLOX (n=241391)		
	No.	Mean (SD) or %	No.	Mean (SD) or %	P value	No.	Mean (SD) or %	No.	Mean (SD) or %	P value
Age at recruitment, y	40043	61.6 (6.0)	165968	55.1 (8.2)	<0.0001	15680	60.6 (6.6)	241391	55.9 (8.0)	
Body mass index, kg/m ²										
<18.5	90	0.2	365	0.2	<0.0001	99	0.63	1673	0.7	<0.0001
≥18.5 to <25	10213	25.5	40731	24.5		5521	35.21	93032	38.5	
≥25 to <30	20139	50.3	81156	48.9		6166	39.32	87774	36.4	
≥30 to <35	7254	18.1	31954	19.3		2532	16.15	36868	15.3	
≥35	1659	4.1	9257	5.6		1127	7.19	18237	7.6	
Missing/unknown	688	1.7	2505	1.5		235	1.50	3807	1.6	
Smoking status										
Never	16133	40.3	86637	52.2	<0.0001	8999	57.39	144230	59.7	<0.0001
Former	17039	42.6	59466	35.8		5345	34.09	74569	30.9	
Current	6674	16.7	19018	11.5		1257	8.02	21433	8.9	
Unknown	197	0.5	847	0.5		79	0.50	1159	0.5	
Self-reported race and ethnicity										
European	39023	97.5	154824	93.3	<0.0001	15369	98.02	227217	94.1	<0.0001
Mixed	96	0.2	913	0.6		51	0.33	1687	0.7	
South Asian	264	0.7	3426	2.1		60	0.38	3349	1.4	
Black/African	223	0.6	2949	1.8		88	0.56	4132	1.7	
Other groups	239	0.6	2919	1.8		61	0.39	4039	1.7	
Missing/unknown	198	0.5	937	0.6		51	0.33	967	0.4	
Townsend deprivation index (socioeconomic status)	40004	-1.5 (3.0)	165747	-1.2 (3.2)	<0.0001	15666	-1.6 (2.9)	241100	-1.4 (3.0)	
Education (qualifications)										
College or university degree	12180	30.4	59183	35.7	<0.0001	4008	25.6	77160	32.0	<0.0001
Advanced levels/Advanced Subsidiary levels or equivalent	3764	9.4	17693	10.7		1574	10.0	29013	12.0	
Ordinary levels/General Certificate of Secondary Education or equivalent	7153	17.9	31265	18.8		3825	24.4	56272	23.3	
Certificate of Secondary Education or equivalent	1343	3.4	10095	6.1		672	4.3	13243	5.5	
National Vocational Qualifications or Higher National Diploma or Higher National Certificate or equivalent	4010	10.0	14421	8.7		701	4.5	10702	4.4	
Other professional qualifications	2127	5.3	6886	4.1		1012	6.5	13695	5.7	
Unknown/missing/no answer	9466	23.6	26425	15.9		3888	24.8	41306	17.1	
Alcohol intake										
Never	827	2.1	4719	2.8	<0.0001	846	5.4	13701	5.7	0.02
Former	1371	3.4	5425	3.3		551	3.5	8471	3.5	
Current occasional	6007	15.0	26914	16.2		4292	27.4	67235	27.9	
Current <1 drink/day	7983	19.9	33641	20.3		4517	28.8	70209	29.1	
Current 1–3 drinks/day	17629	44.0	71479	43.1		4891	31.2	72539	30.1	
Current >3 drinks/day	6150	15.4	23251	14.0		556	3.5	8599	3.6	
Unknown	76	0.2	539	0.3		27	0.2	637	0.3	
Self-reported diabetes status										
None	37368	93.3	155269	93.6		15036	95.9	232269	96.2	
Diabetic	2507	6.3	9837	5.9	0.0018	593	3.8	8265	3.4	

(Continued)

Table 1. Continued

Characteristic	Men					Women					
	Detectable mLOY (n=40043)		No mLOY (n=165968)			Detectable mLOX (n=15680)		No mLOX (n=241391)			
	No.	Mean (SD) or %	No.	Mean (SD) or %	P value	No.	Mean (SD) or %	No.	Mean (SD) or %	P value	
Unknown	168	0.4	862	0.5		51	0.3	857	0.4		
Glycated hemoglobin, mmol/mol	38021	36.8 (7.1)	157700	36.1 (7.3)	<0.0001	14889	36.3 (5.6)	229328	35.6 (5.8)	0.05	
Hypertension status											
Normal	2467	6.2	13246	8.0	<0.0001	2052	13.1	46384	19.2	<0.0001	
Elevated	3680	9.2	17679	10.7		1768	11.3	28975	12.0		
Stage 1 or 2	29507	73.7	117793	71.0		10082	64.3	140702	58.3		
Hypertensive crisis	1201	3.0	3398	2.0		427	2.7	4340	1.8		
Unknown	3188	8.0	13852	8.3		1351	8.6	20990	8.7		
Menopausal status	N/A		N/A								
Premenopause						1455	9.3	60187	24.9	<0.0001	
Postmenopause						11726	74.8	143112	59.3		
Hysterectomy						2069	13.2	26680	11.1		
Bilateral oophorectomy						11	0.1	166	0.1		
Ever oral contraceptive use	Not applicable		Not applicable								
Yes					3691	23.5	43834	18.2	<0.0001		
No					11941	76.2	196495	81.4			
Ever hormone replacement therapy	Not applicable		Not applicable								
Yes					7801	49.8	151542	62.8	<0.0001		
No					7831	49.9	88628	36.7			

mLOX indicates mosaic loss of chromosome X; and mLOY, mosaic loss of chromosome Y.

27-category variable for smoking history and intensity.^{12,15} Additionally, to account for nonlinear relationships with age, we included polynomial terms for age in the models. We also conducted Fine and Gray models adjusted for the same covariates to account for competing risks by all-cause mortality and/or heart failure.

Mendelian Randomization Analyses

Among the measured mLOY, mLOX, and heart disease associations found to be statistically significant in the Cox regression analyses, we further assessed potential causal associations using several established Mendelian randomization (MR) methods. First, we used the inverse variance weighted (IVW) method, an effective approach when all included genetic variants are valid instrumental variables.³⁰ However, when horizontal pleiotropy is present, the estimate from IVW approach can be potentially biased with overestimation,^{30,31} and we therefore used additional approaches as sensitivity analyses. We used the weighted median approach, which has been shown to produce valid causal estimates if the invalid instrumental variables account for <50% of the weight of the studies.³⁰ Next, we used MR-Egger, which unlike other MR methods,

estimates the dose-response relationship between the genetic associations with mLOY and those with the heart disease outcome.³² A nonzero intercept from MR-Egger regression indicates potential horizontal pleiotropy, whereas the slope reflects the effect of mLOY on heart disease adjusted for horizontal pleiotropy.³³ Next, we used MR pleiotropy residual sum and outlier (MR-PRESSO), an approach that effectively accounts for horizontal pleiotropy by identifying instrumental variables that are outliers.³¹ By doing so, the method prevents potential horizontal pleiotropy and corrects the causal estimates.³¹ Last, we used robust adjusted profile score (RAPS), which maximizes the profile likelihood of the ratio estimates while accounting for weak instrument bias, pleiotropy, and extreme outliers.³⁴

We used the MendelianRandomization, MR-PRESSO, and mr.raps packages in R statistical software (version 4.2.2) to conduct MR analyses with summary GWAS data from a previously published landmark study and newly conducted analyses^{1,35} (Data S1). A 1-sample MR analysis was conducted using 156 previously identified independent variants (with $r^2 < 0.05$ in linkage disequilibrium (LD) clumping analyses) in the UK Biobank.¹ All 156 genetic variants

were previously found to be associated with mLOY below a standard genome-wide significance threshold of 5×10^{-8} in the discovery phase of the UK Biobank GWAS.¹ Notably, these genetic variants were previously validated in 757 114 men from separate European and Japanese populations.¹

RESULTS

Baseline Characteristics

The study population characteristics at baseline are shown in Table 1. Here, 19.4% of the male study participants had detectable mLOY, whereas 6.1% of the female study participants had detectable mLOX. On average, men with detectable mLOY were older (61.6 versus 55.1 years), had higher proportions of former (42.6% versus 35.8%) or current smokers (16.7% versus 11.5%), had lower proportions of non-Europeans, and had lower proportions of college/university degree holders (30.4% versus 35.7%; Table 1). Similarly, among women, those with detectable mLOX were older (60.6 versus 55.9 years) on average, had higher proportions of former smokers (34.09% versus 30.90%), had lower proportions of non-Europeans, and had lower proportions of college/university degree holders (25.6% versus 32.0%; Table 1).

Incident Heart Disease Cases

Among men, there were 14 459 incident cases (hospitalizations) of atrial fibrillation, 6007 cases of myocardial infarction, 19 507 cases of ischemic heart disease, 1017 cases of cardiomyopathy, and 5982 cases of heart failure syndrome during the follow-up (Table S2). Among women, there were 9094 incident cases of

atrial fibrillation, 2609 cases of myocardial infarction, 11 322 cases of ischemic heart disease, 565 cases of cardiomyopathy, and 3896 cases of heart failure syndrome during the follow-up (Table S2). The ages at first diagnosis (hospitalization) and the follow-up time to first diagnosis for each heart disease are shown in Table S2.

Associations of Age and Smoking With mLOY and mLOX

We conducted unadjusted analyses with age, smoking status, and sex chromosome loss at baseline to check the consistency with previous studies. Age was associated with increased prevalence odds of mLOY in men (odds ratio [OR], 1.13 per year [95% CI, 1.13–1.13]; $P < 0.0001$) and mLOX in women (OR, 1.09 per year [95% CI, 1.09–1.10]; $P < 0.0001$). As expected, among men, former smokers (OR, 1.54 [95% CI, 1.50–1.58]; $P < 0.0001$) and current smokers (OR, 1.88 [95% CI, 1.82–1.95]; $P < 0.0001$) had increased prevalence odds of mLOY compared with never smokers. Among postmenopausal women, former smoking (OR, 1.07 [95% CI, 1.03–1.11]; $P = 0.0014$) was associated with increased prevalence odds of mLOX, but not current smoking (OR, 0.97 [95% CI, 0.90–1.04]; $P = 0.3865$), which was similar to parallel analyses.²¹

mLOY Among Men and Future Risk of Heart Disease

Among men, having detectable mLOY in leukocytes was significantly associated with elevated risk of incident atrial fibrillation requiring hospitalization (HR, 1.06 [95% CI, 1.03–1.11]; $P = 0.0011$; Table 2), even after accounting for multiple comparisons. Furthermore,

Table 2. mLOY in Prediagnostic Leukocytes and Risk of Incident Heart Diseases in the UK Biobank

Outcome	Detectable mLOY (total n=37 037)	No mLOY (total n=153 576)	Censored deaths, n	HR	95% CI lower	95% CI upper	P value
	Cases, n	Cases, n					
Atrial fibrillation	4203	10 256	13 210	1.06	1.03	1.11	0.0011**
Myocardial infarction	1512	4 495	15 298	1.05	0.98	1.11	0.1448
Ischemic heart disease/angina pectoris	4938	14 569	13 387	1.00	0.96	1.03	0.8706
Cardiomyopathy	260	757	16 079	1.05	0.90	1.21	0.5579
Heart failure syndrome	1723	4 259	14 320	1.04	0.98	1.10	0.2115

Separate multivariable Cox regression models were used to estimate HRs and 95% CIs of newly diagnosed (incident) atrial fibrillation, myocardial infarction, ischemic heart disease/angina pectoris, cardiomyopathy, and heart failure syndrome in relation to mLOY (detectable vs not detectable) among men. We adjusted for potential confounders, including study assessment center, age at recruitment (continuous), self-reported race and ethnicity (European, Black/African, mixed, South Asian, other groups, or missing/unknown), 10 principal components for genetic ancestry, educational attainment (ie, qualifications), smoking status (never, former, current, or missing/unknown), body mass index (<18.5 , ≥ 18.5 to <25 , ≥ 25 to <30 , ≥ 30 to <35 , or ≥ 35 kg/m² or missing/unknown), material deprivation (Townsend deprivation index, socioeconomic status, or continuous), alcohol intake (never, former, current occasional, current <1 drink/day, current 1–3 drinks/day, current >3 drinks/day, or unknown/missing), diabetes status (none, diabetic, or missing/unknown), glycated hemoglobin (mmol/mol, continuous), and hypertension status based on average systolic and diastolic blood pressure at baseline (normal, elevated, stage 1 and 2 hypertension, hypertensive crisis, and missing/unknown), total white blood cell count at enrollment, and any cancer diagnosis at enrollment. HR indicates hazard ratio; and mLOY, mosaic loss of chromosome Y.

**P values below a Bonferroni-corrected P value of 0.01 (0.05 divided by a family of 5 tests). We analyzed participants with complete mLOY and covariate data.

the association with atrial fibrillation strengthened nonmonotonically as the mCF increased above 20% (HR_{mCF=0.20-<0.30}, 1.20 [95% CI, 1.07–1.35]; HR_{mCF=0.30-<0.40}, 0.95 [95% CI, 1.12–1.32]; HR_{mCF=0.40-<0.50}, 1.38 [95% CI, 1.13–1.69]; *P*=0.0015; HR_{mCF>0.50}, 1.44 [95% CI, 1.15–1.80]; *P*=0.0015; Figure 2). The association between

detectable mLOY and atrial fibrillation was consistent across subgroups, including those of European genetic ancestry (HR, 1.08 [95% CI, 1.04–1.12]; *P*=0.0002), those aged >60 years (HR, 1.08 [95% CI, 1.04–1.13]; *P*=0.0003), and those aged ≤60 years (HR, 1.07 [95% CI, 1.02–1.11]; *P*=0.0021; Table S3). The atrial fibrillation

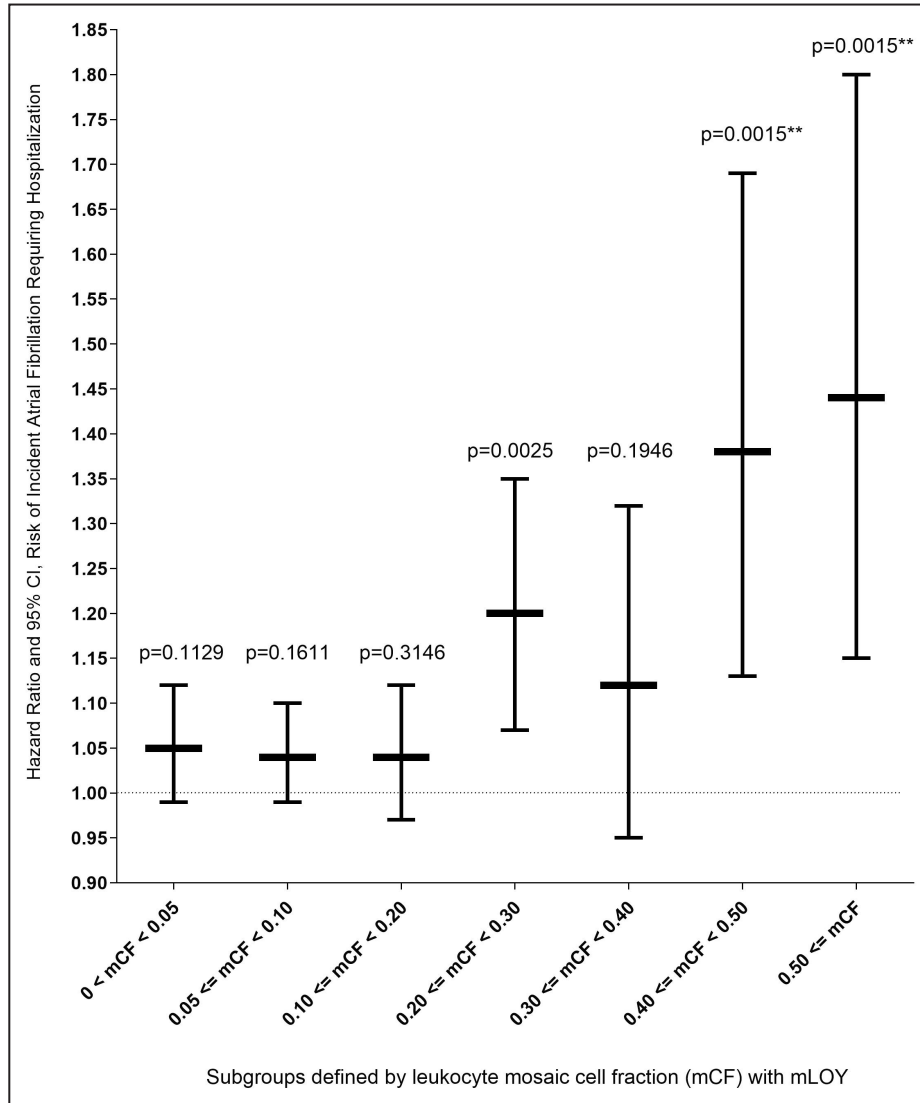


Figure 2. Mosaic loss of chromosome Y (mLOY) in prediagnostic leukocytes and risk of newly diagnosed atrial fibrillation, stratified by mosaic cell fractions (mCFs) with mLOY.

We analyzed participants with complete genotyping and covariate data. Multivariable Cox regression models were used to estimate hazard ratios and 95% CIs of newly diagnosed (incident) atrial fibrillation in relation to mLOY (detectable vs not detectable) among men. We adjusted for potential confounders, including study assessment center, age at recruitment, self-reported race and ethnicity, 10 principal components for genetic ancestry, educational attainment (ie, qualifications), smoking status, body mass index, material deprivation, alcohol, diabetes status, glycated hemoglobin (mmol/mol), and hypertension status based on average systolic and diastolic blood pressure at baseline, total white blood cell count at enrollment, and any cancer diagnosis at enrollment. Analytic subgroup sample sizes with complete data: no detectable mLOY (comparison group): 10245 cases/153367 men; 0<mCF<0.05: 1090 cases/11531 men; 0.05≤mCF<0.10: 1649 cases/14905 men; 0.10≤mCF<0.20: 843 cases/6703 men; 0.20≤mCF<0.30: 299 cases/1972 men; 0.30≤mCF<0.40: 141 cases/939 men; 0.40≤mCF<0.50: 98 cases/533 men; and mCF<0.50: 78 cases/418 men.

associations among never smokers (HR, 1.07 [95% CI, 1.01–1.14]; $P=0.0294$) and ever smokers (HR, 1.05 [95% CI, 1.01–1.11]; $P=0.0298$) were apparent, but nonsignificant, after Bonferroni correction (Table S3). Consistent associations were not found for myocardial infarction, ischemic heart disease/angina pectoris, cardiomyopathy, and heart failure syndrome in the overall (Table 2) and stratified analyses (Table S3).

Sensitivity and Attenuation Analyses

To tightly control potential residual confounding from smoking, we adjusted for a 27-category variable for smoking history and intensity.^{12,15} Here, the mLOY–atrial

fibrillation estimates were not considerably changed (HR, 1.06 [95% CI, 1.02–1.10]; $P=0.0016$). Additionally, we included a quadratic term for age; however, this parameter was nonsignificant ($P=0.19$), and the main mLOY–atrial fibrillation association remained statistically significant (HR, 1.06 [95% CI, 1.02–1.10]; $P=0.0014$).

There were 3254 men who were hospitalized with both incident atrial fibrillation and heart failure during the follow-up. Among these cases, 585 men (17.98%) had incident hospitalization for heart failure *before* atrial fibrillation, 1570 men (48.25%) had heart failure *after* atrial fibrillation, and 1099 men (33.77%) were hospitalized for both concurrently. The estimates from the Fine and Gray models for mLOY–atrial fibrillation associations

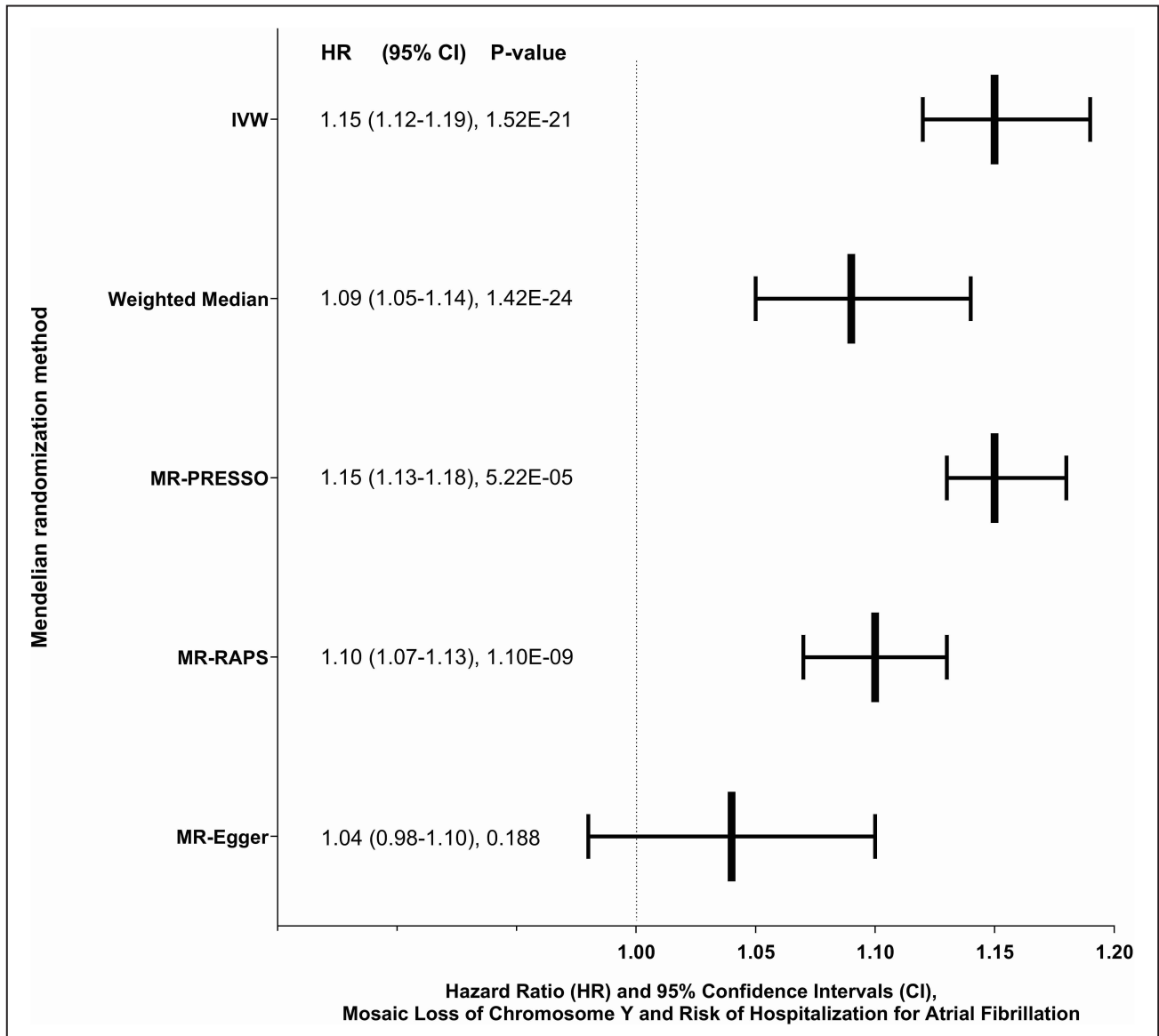


Figure 3. Mendelian randomization (MR) analyses to assess the potential causal associations between prediagnostic leukocyte mosaic loss of chromosome Y and risk of newly diagnosed atrial fibrillation in the UK Biobank.

IVW indicates inverse variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier; and MR-RAPS, MR robust adjusted profile score.

accounting for competing risks by all-cause mortality alone (Table S4), as well as heart failure and all-cause mortality together (data not shown), were not considerably different from the cause-specific Cox models.

When analyzing a subgroup of 87 041 participants who had primary care data and met our inclusion criteria, we found that the association between mLOY and *general practitioner diagnosed* incident atrial fibrillation had a similar effect size but was nonsignificant (605 cases/16749 with mLOY; 1470 cases/70292 without mLOY; HR, 1.08 [95% CI, 0.96–1.20]; $P=0.19$) compared with *incident hospitalization* for atrial fibrillation (1849 cases/16749 with mLOY; 4538 cases/70292 without mLOY; HR, 1.08 [95% CI, 1.02–1.14]; $P=8.1 \times 10^{-3}$). However, there was no evidence that these estimates were different (P -difference $Z_{\text{score.sign}}=1.00$). When combining general practitioner and hospitalization outcome ascertainment, the association between mLOY and atrial fibrillation risk was statistically significant (1933 cases/16749 with mLOY; 4746 cases/70292 without mLOY; HR, 1.09 [95% CI, 1.03–1.16]; $P=2.1 \times 10^{-3}$).

MR, mLOY, and Atrial Fibrillation Risk

We conducted MR analyses to assess potential causal associations between mLOY and atrial fibrillation risk among men. Using IVW, we found evidence supporting a causal relationship between mLOY and atrial fibrillation (HR_{IVW}, 1.15 [95% CI, 1.12–1.19]; $P=1.52 \times 10^{-21}$; Figure 3). We conducted sensitivity analyses with other MR methods and found that the weighted median (HR_{WM}, 1.09 [95% CI, 1.05–1.14]; $P=1.42 \times 10^{-24}$; Figure 3), MR-PRESSO (HR_{MR-PRESSO}, 1.15 [95% CI, 1.13–1.18]; $P=5.22 \times 10^{-5}$; Figure 3), and MR-RAPS approaches (HR_{MR}, 1.10 [95% CI, 1.07–1.13]; $P=1.10 \times 10^{-9}$; Figure 3) agreed with our main finding. Conversely, the MR-Egger slope was nonsignificant ($P=0.188$), and the intercept was nonzero ($\beta_0=0.011$, $P<0.001$), suggesting detection of pleiotropy.

mLOX Among Women and Future Risk of Heart Disease

Among women overall, having detectable mLOX in leukocytes was associated with decreased risk of atrial fibrillation requiring hospitalization before accounting for multiple testing; however, this association was nonsignificant after Bonferroni correction (HR, 0.91 [95% CI, 0.84–0.98]; $P=0.0130$; Table 3). The suggestive inverse association between mLOX and atrial fibrillation risk was observed only among postmenopausal women (HR, 0.90 [95% CI, 0.83–0.98]; $P=0.0151$; Table 3), who comprise most of the female participants. When further stratifying women into subgroups, the suggestive inverse association with atrial fibrillation was consistent among participants

of European ancestry (HR, 0.91 [95% CI, 0.84–0.98]; $P=0.0145$), and those aged >60 and ≤ 60 years at baseline (HR, 0.90 [95% CI, 0.83–0.98]; $P=0.0164$; and HR, 0.89 [95% CI, 0.82–0.96]; $P=0.0044$, respectively) before accounting for multiple testing, but was significant only among women aged ≤ 60 years after Bonferroni correction (Table S5).

There were 1835 women who were hospitalized with both incident atrial fibrillation and heart failure during the follow-up. Among these cases, 312 women (17.00%) had incident hospitalization for heart failure before atrial fibrillation, 952 women (51.88%) had heart failure after atrial fibrillation, and 571 women (31.12%) were hospitalized with both concurrently. After accounting for the influence of all-cause mortality alone (Table S4), as well as heart failure and all-cause mortality together as competing risks for atrial fibrillation (data not shown), the association between mLOX and atrial fibrillation was similar to the cause-specific Cox models.

DISCUSSION

In a large prospective cohort study from the United Kingdom, we investigated the associations between mLOY and mLOX in prediagnostic leukocytes collected at baseline and risk of incident heart disease requiring hospitalization. Among men, we found that mLOY was significantly associated with elevated risk of incident atrial fibrillation. This association was greatly strengthened among participants with increased mCF with mLOY and was largely consistent across subgroups defined by smoking, age, and race and ethnicity. Furthermore, most of the MR analyses supported causal associations between mLOY and atrial fibrillation. However, consistent associations between mLOY and other heart diseases were not detected. To our knowledge, we conducted the first study of mLOX among women and risk of newly diagnosed heart disease. Here, we found suggestive evidence for inverse associations between mLOX and atrial fibrillation risk that was nonsignificant after accounting for multiple comparisons. When stratifying by menopausal status, the suggestive association between mLOX and atrial fibrillation was only observed among postmenopausal women. Furthermore, given that mLOX is less frequent among younger women¹⁹ and that most female UK Biobank participants were aged >50 years, we did not have sufficient sample size to make sound inferences for premenopausal women. Additionally, consistent associations were not detected between mLOX and other heart diseases among women.

Our study examines the relationships between sex chromosome mosaicisms and CVD by focusing specifically on incident heart disease hospitalization, as opposed to prevalence and mortality as in other

Table 3. mLOX in Prediagnostic Leukocytes From Women and Risk of Incident Heart Diseases in the UK Biobank

Heart disease	Detectable mLOX	No mLOX	Censored deaths, n	HR	95% CI lower	95% CI upper	P value
	Cases, n	Cases, n					
Overall women (total n of subjects) θ	13978	210875					
Atrial fibrillation	748	8346	10351	0.91	0.84	0.98	0.0130*
Myocardial infarction	209	2400	11456	0.97	0.84	1.12	0.7012
Ischemic heart disease/angina pectoris	927	10395	10577	1.00	0.93	1.07	0.9477
Cardiomyopathy	35	530	11819	0.79	0.56	1.11	0.1752
Heart failure syndrome	342	3554	10795	0.99	0.89	1.11	0.8884
Postmenopause (total n of subjects)	10743	131193					
Atrial fibrillation	601	6534	8064	0.90	0.83	0.98	0.0151*
Myocardial infarction	170	1818	9004	0.98	0.84	1.15	0.7997
Ischemic heart disease/angina pectoris	727	7615	8326	1.00	0.93	1.08	0.9601
Cardiomyopathy	28	374	9297	0.84	0.57	1.23	0.3635
Heart failure syndrome	272	2750	8475	0.98	0.86	1.11	0.7473
Premenopause (total n of subjects)	1330	55054					
Atrial fibrillation	18	468	851	1.09	0.68	1.76	0.7160
Myocardial infarction	7	216	876	0.98	0.45	2.10	0.9527
Ischemic heart disease/angina pectoris	40	918	839	1.29	0.93	1.78	0.1248
Cardiomyopathy	2	62	893	1.12	0.27	4.66	0.8727
Heart failure syndrome	9	218	843	1.05	0.53	2.11	0.8884

θ Includes women in premenopause, postmenopause, and artificial menopause.

Separate multivariable Cox regression models were used to estimate HRs and 95% CIs of newly diagnosed (incident) atrial fibrillation, myocardial infarction, ischemic heart disease/angina pectoris, cardiomyopathy, and heart failure syndrome in relation to mLOX (detectable vs not detectable) among women. We adjusted for potential confounders, including study assessment center, age at recruitment (continuous), self-reported race and ethnicity (European, Black/African, mixed, South Asian, other groups, or missing/unknown), 10 principal components for genetic ancestry, educational attainment (ie, qualifications), smoking status (never, former, or current), body mass index (<18.5, ≥ 18.5 to <25, ≥ 25 to <30, ≥ 30 to <35, or ≥ 35 kg/m² or missing/unknown), material deprivation (Townsend deprivation index, socioeconomic status, or continuous), alcohol intake (never, former, current occasional, current <1 drink/day, current 1–3 drinks/day, current >3 drinks/day, or missing/unknown), diabetes status (none, diabetic, or unknown/missing), glycated hemoglobin (mmol/mol, continuous), and hypertension status based on average systolic and diastolic blood pressure at baseline (normal, elevated, stage 1 and 2 hypertension, hypertensive crisis, and unknown/missing), total white blood cell count at enrollment, ever use of oral contraceptive or hormone replacement therapy, and any cancer diagnosis at enrollment. HR indicates hazard ratio; and mLOX, mosaic loss of chromosome X.

* $P < 0.05$.

studies.^{15,16,36} We provide population-based evidence that mLOY and mLOX could be indirectly or directly involved in the biological processes leading to atrial fibrillation occurrence. Our investigation builds on previous studies conducted in human populations. Lofffield et al reported cross-sectional associations between prevalent heart disease and stroke and increased leukocyte mLOY at baseline.¹⁵ Furthermore, they reported no evidence for associations between mLOY and mortality from cardiovascular disease, ischemic heart disease, and stroke.¹⁵ Additionally, a recent study by Sano et al found evidence for associations between mLOY and death caused by diseases of the circulatory system, including hypertensive heart disease, atrial fibrillation, as well as heart failure syndrome.¹⁶

We note that our outcome ascertainment using national hospital registries potentially enriches for more serious cases of heart disease, which can be nonfatal or fatal. As such, we conducted analyses using a subset of participants with preliminary primary care data, in which the cases had moderate, nonfatal incident

heart disease. Here, we found that the associations between mLOY and general practitioner–diagnosed atrial fibrillation were similar in magnitude to the hospitalization data but were not statistically significant. This was likely attributable to limited statistical power from reduced case numbers. Important for consideration, these preliminary primary care data have not been validated or adjudicated, and we include these only for exploratory purposes and sensitivity analyses. When combining general practitioner–diagnosed and hospitalization cases in this subset, the mLOY–atrial fibrillation association was statistically significant.

Our MR analyses using IVW, weighted median, MR-PRESSO, and MR-RAPS strongly supported causal associations between mLOY and atrial fibrillation and had similar causal effect estimates. However, we found that the estimate from the older MR-Egger regression was nonsignificant, and the nonzero intercept suggested some pleiotropy. MR-Egger is different from other MR methods in that it estimates the causal effect as the slope from the weighted regression of the

variant-outcome associations on the variant-exposure associations, with the average pleiotropic effect estimated by the intercept. MR-Egger allows for the intercept to be nonzero, but this adds a degree of freedom that can decrease statistical efficiency compared with other methods. Furthermore, MR-Egger is problematic because the necessary instrument strength independent of direct effect (independence between the Egger regression intercept and slope) assumption is rarely satisfied. As such, the estimates from MR-Egger are sensitive to influential outliers and can be skewed, as well as lacking in precision when the variant-exposure associations are similar in magnitude. Newer methods like MR-PRESSO provide more precise and robust causal estimates by using global tests that detect horizontal pleiotropy; outlier-corrected causal estimates that correct for the detected horizontal pleiotropy; and distortion tests for which causal estimate is significantly different. Other newer methods like MR-RAPS downweights potential outlying genetic variants.

We detected associations with atrial fibrillation but not with other heart diseases. This may be because of fewer cases of myocardial infarction, cardiomyopathy, and heart failure syndrome. However, the associations for these outcomes trended in the same direction as atrial fibrillation. From a biological perspective, a plausible explanation is that mLOY or mLOX potentially reflects processes involving cardiac tissue itself, which would have greater impact on atrial fibrillation; whereas mLOY or mLOX may not reflect biological processes in vasculature, which contribute more to myocardial infarction, ischemic heart disease, and cardiomyopathy/heart failure syndrome. Mechanistic studies using mouse models provide some clues into this hypothesis. For instance, Sano et al demonstrated that mLOY promotes fibrotic phenotypes (“scarring”) in cardiac murine tissues, which potentially impairs cardiac function, such as tissue elasticity and electrical signal propagation.¹⁶ Along those lines, Horitani et al found evidence that mLOY in mice may disrupt the ubiquitously transcribed tetratricopeptide repeat containing, Y-linked gene, leading to epigenetic dysfunction and differentiation of profibrotic macrophages.³⁷ Ubiquitously transcribed tetratricopeptide repeat containing, Y-linked is found to be expressed in cardiac tissue in humans (www.gtexportal.org).

Other studies have posited additional mechanisms of action for mLOY. Analyses of sequencing data suggests that mLOY is genetically linked to clonal hematopoiesis of indeterminate potential,^{38–40} a mosaic expansion of hematopoietic stem cells driven by certain somatic mutations,⁴¹ which has been recently associated with risk of CVDs and heart failure syndrome.^{42–46} Additionally, it has been hypothesized that mLOY in leukocytes potentially reflects altered immunosurveillance and inflammatory processes, which can influence CVD pathogenesis.^{3,47}

We note that atrial fibrillation risk was positively associated with mLOY among men as expected but was potentially inversely associated with mLOX among women. It is possible that mLOY and mLOX operate in a distinctly sex-specific manner in reflecting genomic instability from the cumulative burden of age, genetic susceptibility, and environmental exposures. Furthermore, sex chromosomes Y and X contain PARs, which contain genes homologous to those found in autosomes. These PARs may contain either protective or detrimental genes relevant to the pathogenesis of atrial fibrillation. Loss of protective genes on the PAR of chromosome Y may contribute to increased risk, whereas loss of detrimental genes on the PAR of chromosome X may confer a protective effect. However, our population study was conducted using leukocytes, and whether these are surrogates for cardiac tissue is unclear.

A recent study found that atrial fibrillation risk was elevated among 2408 patients in South Korea with Turner syndrome compared with a control group.⁴⁸ However, we found a suggestive inverse association between mLOX and atrial fibrillation risk. A possible explanation for this difference is that we examined leukocyte DNA from a relatively healthy adult population, in which a subset of people had mosaic X-chromosome loss in a small fraction of white blood cells. This leukocyte mLOX increases with progressive age and potentially by environmental exposures. Leukocyte mLOX may be a surrogate marker for biological processes related to the pathogenesis of atrial fibrillation, but whether its directly involved is unclear. In contrast, Turner syndrome from monosomy X or partial X loss is largely a congenital disease and attributable to a random nondisjunction event during the formation of reproductive cells in an individual’s parent. This kind of X-chromosome loss would directly affect most tissues, including the heart, and a person’s phenotypes would be affected at birth. These 2 biological processes are distinct and may contribute to the pathogenesis of atrial fibrillation differently.

Our study had numerous strengths. First, we used mosaic chromosomal alterations caller to call chromosomal mosaicism from GWAS data, which is more sensitive compared with previous calling approaches.¹⁷ Second, the prospective cohort design strengthened our inferences and is robust against disease-effect bias of pre-diagnostic leukocyte mLOY and mLOX (ie, “reverse causation”). Third, we analyzed a large sample size of middle-aged and older adults, which improved statistical power to detect modest associations.

Our study had limitations. First, we had limited power to detect modest associations among younger premenopausal women. However, we did detect suggestive but nonsignificant associations for mLOX among postmenopausal women, which warrants further

exploration. Second, although we thoroughly adjusted for measured confounders, we cannot discount the possibility of unmeasured or residual confounding. However, our findings were consistent across never and ever smokers and age groups; supported by MR analyses; robust to adjustment for detailed smoking history; and consistent with previous studies.¹⁶ Third, the study population was predominantly of European ancestry. We included available ethnic minority populations in our main analyses; however, future studies are needed in more diverse populations. Fourth, we found some evidence of horizontal pleiotropy, but only with MR-Egger, which has been reported to be less statistically efficient and subject to skewed estimates⁴⁹ when the instrument strength independent of direct effect assumption is violated.³² As such, the MR-Egger results need to be taken together with those from the more robust MR-PRESSO and MR-RAPS methods, which did not detect pleiotropy. Fifth, UK Biobank did not have verified information on medication dose, duration, and history. Sixth, we acknowledge that some cryptic relatedness or closely related individuals may be in the study population; however, this is unlikely to influence the findings. Last, there is the possibility that healthy volunteer bias in the UK Biobank could limit generalizability; however, this does not affect the internal validity of our mechanistic study.

In conclusion, mLOY was significantly associated with elevated risk of atrial fibrillation among men. Conversely, we found suggestive evidence of an inverse association between mLOY and atrial fibrillation risk among postmenopausal women. Associations were not detected for other heart diseases. Caution is recommended when interpreting the findings, particularly for mLOY among women. Although the precise biological role of sex chromosome mosaicism in heart disease pathogenesis remains unclear, our findings support biologic processes related to or tagged by leukocyte mLOY and mLOY are related to atrial fibrillation occurrence in human populations. If our findings are confirmed across diverse populations, they support further consideration of mLOY in atrial fibrillation risk prediction and stratification analyses among men.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5

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