Predictors of mosaic chromosome Y loss and associations with mortality in the UK Biobank

Erikka Loftfield1, Weiyin Zhou1,2, Barry I. Graubard1, Meredith Yeager1,2, Stephen J. Chanock1, Neal D. Freedman1 & Mitchell J. Machiela1,3

Mosaic loss of the Y chromosome (mLOY) is the most commonly reported large structural somatic event. Previous studies have indicated age and cigarette smoking increase the risk of mLOY, but the relationship of other exposures with mLOY and mLOY with disease has not been adequately investigated. We characterized mLOY in a large cohort of 223,338 men from the UK Biobank by scanning for deviations in genotyping array median log, intensity ratios (mLRR) of the Y chromosome using a standard algorithm. A total of 3,789 (1.7%) men showed evidence for mLOY (mLRR < −0.15).

In multivariable-adjusted logistic regression models, we found that mLOY increases exponentially with age (overall P-value < 4.9 × 10−324; p-value for the quadratic term = 2.1 × 10−7), and observed a strong association with current smoking (P-value = 7.8 × 10−184). We observed less mLOY in men of African ancestry (0.4%) compared to men of European ancestry (1.8%, P-value = 0.003). Although mLOY was not associated with prevalent cancer (P-value = 0.61), associations were observed for diabetes (P-value = 0.003) and cardiovascular disease (P-value = 0.01). Using Cox proportional hazards regression models, mLOY was associated with all-cause mortality among men with a high proportion of cells affected (mLRR < −0.40; HR = 1.35, 95% CI = 1.08–1.70, P-value = 0.009). In conclusion, mLOY was associated with several health-related factors as well as with all-cause mortality. Further functional studies are warranted to understand how and in what way mLOY could influence adult male health.
mLRR < −0.40) to identify evidence for mLOY in a detectable percentage of circulating blood cells to better understand the determinants and distribution of mLOY in UK men.

Methods
Study design and participants. The design of the UK Biobank has been described in detail elsewhere. In brief, invitations were mailed to approximately 9.2 million individuals in the UK’s National Health Service, aged 40 to 69 years, who resided within 40 kilometers of 22 assessment centers across the UK. In total, 503,317 individuals visited an assessment center between 2006 and 2010 and provided baseline information on demographic, lifestyle and other health-related factors, biological samples, and physical measures. Genetic data from 223,507 male participants was made available by the UK Biobank for our study. We further excluded participants with sex discrepancies between the self-reported and inferred sex using X-chromosome heterozygosity (n = 167) as well as those with no follow-up time (n = 2), resulting in a final analytic cohort of N = 223,338 participants.

The UK Biobank study was approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicentre Research Ethics Committee. All participants provided signed informed consent at enrollment and all research was performed in accordance with relevant guidelines/regulations. All data used in this analysis is available through application to the UK Biobank.

Cohort follow-up. Follow-up time was counted from the date of assessment center visit, at which time blood was drawn and baseline information ascertained, until the date of death or the date of censor (i.e., January 31, 2016 for England and Wales and November 30, 2015 for Scotland), whichever came first. For cause-specific mortality analyses, individuals who died from other causes were censored at their date of death.

Ascertainment of death. Vital status, date, and primary cause of death were provided by the National Health Service (NHS) Information Centre for participants from England and Wales and by the NHS Central Register, Scotland for those from Scotland. For cause-specific mortality we used the International Classification of Diseases, edition 10 (ICD-10) codes to define all-causal (C00-D48) and all-cardiovascular disease (100-179) mortality. In addition, we further defined common causes of death (i.e., causes with >250 deaths) within these broad categories as follows: digestive system cancer (C15-C26 and C48), respiratory system cancer (C30-C39), ischemic heart diseases (I20-I25), and stroke (I60-I69).

Assessment of exposures. During the UK Biobank Assessment Centre visit, participants completed a touchscreen questionnaire that queried demographic, lifestyle, and other health-related factors. From this self-reported data, we created a 25-level detailed smoking history variable by combining data on smoking status, lifetime smoking, smoking intensity, time since quitting for former smokers, and type of tobacco smoked. We created a 6-level variable for alcohol drinking by combining data on drinking status and amount of alcohol consumed per week, calculated as the sum of all alcoholic beverages consumed on average per day, and we created a 4-level variable for physical activity by combining data on frequency of moderate or vigorous activity. Categories of body mass index (BMI), were defined according to the definition of the World Health Organization. Prior diagnoses of diabetes, cancer (other than non-melanoma skin cancer), and heart attack or stroke were obtained via self-report. For diabetes, the self-report questionnaire did not distinguish between type 1 and type 2 diabetes; however, fewer than 2% of cases were diagnosed earlier than age 44 suggesting the majority of cases were type 2 diabetes. Indicator variables were used to account for missing data in regression models.

UK Biobank participants were genotyped using genome-wide arrays. The initial 50,000 participants were genotyped using the Affymetrix UK BiLEVE Axiom array, and the remaining were genotyped using the Affymetrix UK Biobank Axiom array. Both arrays had 691 markers across male specific region of chromosome Y (MSY) (chrY:2658271-28767492, hg19/GRCh37). Quality control (QC) was performed centrally by the Wellcome Trust Centre for Human Genetics as described elsewhere. Each subject has a reported Log2 Intensity Ratio (LRR) and B-Allele Frequency (BAF) available. Y chromosome mosaicism was detected using LRR, which is the normalized measure of total signal intensity and provides data on relative copy number. Subjects were examined for deviations from expected median LRR (mLRR) for evidence of loss of the male specific region of chromosome Y (MSY). Evidence for loss is reflected by negative mLRR values, while evidence for gain is reflected by positive mLRR values. We defined mLLOX dichotomously using two different cut-points that have been previously cited in the literature: mLRR < −0.15 and mLRR < −0.40. These cutpoints represent cellular proportions of approximately 10% (1−2−0.15) and 24% (1−2−0.40), although molecular confirmation was not possible in the UK Biobank. A mLRR > +0.15 was used to define a Y chromosome gain event. For potential mLOY, each chromosome Y plot was then manually reviewed and suspect events were further excluded from subsequent analyses. For subjects with very low mLRR (<−0.95), their chromosome X plots were manually examined to confirm they are indeed males. We also performed analyses using continuous mLRR. For ease of interpretation we scaled the continuous mLRR variable by the standard deviation of the mLRR divided by 1 such that risk estimates are interpreted as a one standard deviation decrease in the mLRR. Frequency plots were generated in R using the binom package.

Statistical analysis. We tabulated our two definitions of mLOY and mLRR by demographic, lifestyle, and other health-related factors and used multivariable-logistic regression models to test for an association between each factor of interest and mLOY or mLRR, adjusting for continuous age and age-squared and the other variables in Table 1. We used multivariable Cox proportional hazard regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for all-cause and cause-specific mortality. Age was used as the underlying time metric since we expected the hazard to change more as a function of age than as a function of time enrolled in the study. We tested the proportional-hazards assumption by comparing the multivariable model with the interaction term between person-time and mLRR to the model without it using the likelihood ratio test. Detecting a deviation from this assumption for mLRR and all-cause mortality (P-value for likelihood ratio test = 0.005), we
|                        | Entire Cohort | mLOY (mLRR < −0.15) | mLOY (mLRR < −0.40) | mLRR |
|------------------------|---------------|----------------------|----------------------|-------|
|                        | N (%)         | N (%)                | Adj. P value^a       | N (%) | Adj. P value^a |
| **Age**                |               |                      |                      |       |
| <65 years              | 187,711 (84.0)| 1,991 (50.2)         | ref                  | 260 (43.6) | ref |
| ≥65 years              | 35,627 (16.0)| 1,888 (49.8)         | <4.9 × 10^{-13}     | 336 (56.4) | 4.6 × 10^{-9} | <4.9 × 10^{-13} |
| **Smoking status**     |               |                      |                      |       |
| Never smoker           | 108,859 (49.0)| 1,012 (26.9)         | ref                  | 126 (21.2) | ref |
| Former smoker          | 85,537 (38.5)| 1,808 (48.0)         | 2.8 × 10^{-24}      | 282 (47.5) | 2.8 × 10^{-4} | 0.003 ± 0.063 | 1.2 × 10^{-16} |
| Current smoker         | 27,748 (12.5)| 946 (25.1)           | 7.8 × 10^{-105}     | 186 (31.3) | 7.9 × 10^{-35} | 0.001 ± 0.076 | 1.0 × 10^{-28} |
| **Race/Ethnicity**     |               |                      |                      |       |
| White                  | 210,179 (94.6)| 3,679 (97.7)         | ref                  | 586 (98.5) | ref |
| Mixed Race             | 1,070 (0.5)  | 5 (0.1)              | 0.06                 | 1 (0.2) | 0.51 |
| Asian                  | 5,671 (2.6)  | 49 (1.3)             | 0.13                 | 6 (1) | 0.26 |
| Black                  | 3,285 (1.5)  | 12 (0.3)             | 0.003                | 0 (0) | 0.96 |
| Other                  | 1,882 (0.8)  | 19 (0.5)             | 0.77                 | 2 (0.3) | 0.62 |
| **Self-reported health status** | | |                      | | |
| Excellent              | 34,777 (15.7)| 480 (12.8)           | ref                  | 68 (11.5) | ref |
| Good                   | 124,573 (56.1)| 2,074 (55.1)        | 0.30                 | 316 (53.3) | 0.49 |
| Fair                   | 51,063 (23.3)| 971 (25.8)           | 0.03                 | 166 (28) | 0.08 |
| Poor                   | 11,527 (5.2) | 239 (6.4)            | 0.009                | 43 (7.3) | 0.06 |
| **Body mass index**    |               |                      |                      |       |
| Underweight (<18.5 kg/m²) | 483 (0.2) | 7 (0.2)              | 0.25                 | 1 (0.2) | 0.46 |
| Normal (18.5 to <25 kg/m²) | 53,505 (24.4)| 914 (24.7)         | ref                  | 151 (25.9) | ref |
| Overweight (25 to <30 kg/m²) | 108,768 (49.7)| 1,942 (52.5)        | 0.50                 | 310 (53.1) | 0.57 |
| Obese I (30 to <35 kg/m²) | 43,676 (19.9)| 167 (43.8)           | 0.0001               | 198 (16.8) | 0.01 |
| Obese II/III (≥35 kg/m²) | 12,609 (5.8) | 159 (4.3)           | 0.0006               | 24 (4.1) | 0.07 |
| **Physical activity (>10 minutes of moderate or vigorous activity)** | | |                      | | |
| 0 days/week            | 23,637 (11.4)| 430 (12.7)           | 0.21                 | 79 (15.0) | 0.08 |
| 1 or 2 days/week       | 28,237 (13.6)| 413 (12.2)           | 0.75                 | 57 (10.8) | 0.46 |
| 2 or 3 days/week       | 35,005 (16.8)| 569 (16.8)           | 0.91                 | 86 (16.3) | 0.91 |
| ≥5 days/week           | 121,165 (58.2)| 2,002 (59.1)        | ref                  | 304 (57.8) | ref |
| **Alcohol drinking status** | | |                      | | |
| Never drinker          | 6,243 (2.8)  | 78 (2.1)             | 0.40                 | 11 (1.8) | 0.69 |
| Former drinker         | 7,883 (3.5)  | 144 (3.8)            | 0.56                 | 23 (3.9) | 0.70 |
| Current drinker (1 to 2 drinks/week) | 36,187 (16.2)| 553 (14.6)        | 0.37                 | 88 (14.8) | 0.82 |
| Current drinker (≥3 to 4 drinks/week) | 44,922 (20.2)| 686 (18.2)           | 0.38                 | 111 (18.6) | 0.74 |
| **Education level**    |               |                      |                      |       |
| A levels/AS levels or equivalent | 22,915 (12.6)| 322 (12.3)          | 0.28                 | 60 (14.8) | 0.04 |
| O levels/GCSEs or equivalent | 41,341 (22.7)| 677 (25.8)         | 0.25                 | 100 (24.7) | 0.78 |
| O levels/GCSEs or equivalent | 12,048 (6.6)| 79 (3.0)             | 0.91                 | 14 (3.5) | 0.46 |
| SVQ or HND or HNC or equivalent | 20,204 (11.1)| 384 (14.6)        | 0.55                 | 64 (15.8) | 0.34 |
| Other qualifications   | 9,992 (5.5)  | 213 (8.1)            | 0.73                 | 34 (8.4) | 0.87 |
| **Diabetes diagnosis** |               |                      |                      |       |
| No                     | 206,681 (93.0)| 3,451 (91.5)        | ref                  | 545 (91.6) | ref |
| Yes                    | 15,507 (7.0) | 319 (8.5)            | 0.003                | 50 (8.4) | 0.14 |
| **Cancer (other than non-melanoma skin cancer) diagnosis** | | |                      | | |
| No                     | 211,208 (94.6)| 3,463 (91.4)        | ref                  | 541 (90.8) | ref |
| Yes                    | 12,130 (5.4) | 326 (8.6)            | 0.61                 | 55 (9.2) | 0.94 |
| **Heart attack or stroke diagnosis** | | |                      | | |
| No                     | 211,710 (94.8)| 3,399 (89.7)        | ref                  | 530 (88.9) | ref |
| Yes                    | 11,628 (5.2) | 390 (10.3)           | 0.01                 | 66 (11.1) | 0.32 |

Table 1. Baseline characteristics and mosaic loss of the Y chromosome. *Adjusted P-values (Adj. P-value) from multivariable logistic regression models are adjusted for all other covariates in Table 1. In this multivariable adjusted model, we fit parameters for continuous age and age-squared. Abbreviations: mLOY, mosaic loss of the Y chromosome; mLRR, median log intensity ratio of the Y chromosome.
evidence for an exponential increase in mLLOY with age such that a model including both age and age-squared
before 50 years of age and then rapidly increases with age (Fig. 1A). Supporting this observation, we observed
P-values of < 0.15). All statistical tests were two-sided and
outliers with a potential mosaic chromosome Y gain (mLRR
>−0.15). As previously reported, we observed a robust association between age and frequency of mLLOY (Methods,
Supplementary Fig. 1) for evidence of loss or gain of the male specific region of chromosome Y. Both a continu-
ous measure of chromosome Y loss (i.e., mLRR) and dichotomous indicators of Y loss (i.e., mLRR <−0.15 and
mLRR <−0.40) were created. Among the 223,338 males aged 37–73 (mean = 57, median = 58) in final analytic
cohort, a total of 3,789 men (mLRR <−0.15, 1.7%) had detectable mLLOY and of these men 596 (16%) had high
proportions of cells affected (mLRR <−0.40). We also found evidence of chromosome Y gain for 205 males
(mLRR >0.15, 0.09%).

As previously reported, we observed a robust association between age and frequency of mLLOY (mLRR
P-value < 4.9 × 10−324, Table 1). We note that the overall proportion of men with mLRR <−0.15 is negligible before
50 years of age and then rapidly increases with age (Fig. 1A). Supporting this observation, we observed
evidence for an exponential increase in mLLOY with age such that a model including both age and age-squared
(P-value = 2.1 × 10−4) fit the association better than a model with age alone.

A higher proportion of current smokers (3.4%) were affected by mLLOY (mLRR <−0.15) than former smok-
ers (2.1%) and non-smokers (0.9%). Marked differences by smoking status were consistent across increasing age
(Fig. 1B) (Table 1). Novel associations with self-reported ancestry, health, and body mass index (BMI) were
observed with mLLOY (mLRR <−0.15, Table 1). A lower percentage of black (0.4%) as compared with white
(1.8%) men were affected by mLLOY (P-value = 0.003). Men reporting poor health had a higher proportion of
mLOY than men reporting excellent health (2.1% vs 1.4%, P-value = 0.009). For BMI, a higher proportion of
mLOY was observed among men with a BMI in the normal range relative to men classified as obese class I
(1.7% vs. 1.5%, P-value = 0.0001) or obese class II/III (1.7% vs. and 1.3%, P-value = 0.0006). We also observed
higher proportions of mLLOY among men with a prior diagnosis of diabetes (2.6% vs. 1.6%, P-value = 0.003),
heart attack, or stroke (3.4% vs. 1.6%, P-value = 0.01). Similar associations were observed when using a more
extreme mLLOY threshold (mLRR <−0.40) or mLRR; however, the statistical significance of observed associations
varied considerably (Table 1).

Over 10 years of follow-up (median 7 years) and 1.5 million person-years, 8,401 deaths occurred. In our primary
analysis of mLLOY with all-cause mortality (Table 2), we observed an association with mLLOY with a higher
(mLRR <−0.40, HR = 1.35, 95% CI = 1.08–1.70, P-value = 0.009), but not a lower proportion of cells with mLLOY
(mLRR <−0.15, HR = 1.08, 95% CI = 0.97–1.21, P-value = 0.16). We also observed suggestive evidence of a linear
association with all-cause mortality (HR = 1.02, 95% CI = 1.00–1.03, P-value = 0.07) using the continuous var-
iable mLRR. These findings were supported by a spline analysis which visually presents the association between
mLLOY and mortality (Fig. 2). No association with mortality was observed for mosaic gain of the Y chromosome in
the small numbers available. For cause-specific mortality (Table 3), we found a higher risk of cancer death among
men with a higher proportion of affected cells (mLRR <−0.40, HR = 1.48, 95% CI = 1.10–1.99, P-value = 0.01).
We did not observe an association between mLLOY and cardiovascular disease mortality, although the number of
deaths among men with mLloyd was small (mLLOY <−0.15 = 77 deaths, mLLOY <−0.40 = 12 deaths).

In secondary analyses, HR estimates for mLLOY and all-cause mortality did not differ by self-reported health
status (P-value for interaction = 0.79). Associations with mortality were noted only in ever-smokers and were
stronger among younger participants, although differences by age (P-value for interaction = 0.38) and smoking
status (P-value for interaction = 0.46) were not statistically significant (Table 4). Excluding individuals with a Y
chromosome gain event did not markedly alter HR estimates (Supplementary Table 1). In a sensitivity analysis,
HR estimates were attenuated for the \(-0.15\) mLRR threshold when those with a prior diagnosis of diabetes, cancer, heart attack or stroke were excluded from the analysis (HR = 1.06, 95% CI = 0.91–1.22, P-value = 0.47) (Supplementary Table 2). Finally, the lag analysis indicated that baseline mLRR < \(-0.15\) was associated with deaths occurring in years 5 to 10 of follow-up (HR = 1.26, 95% CI = 1.06–1.49, P-value = 0.008), but not in the first five years of follow-up (HR = 1.00, 95% CI = 0.86–1.16, P-value = 0.98) (Supplementary Table 3). In contrast, associations with a mLRR < \(-0.40\) were similar in magnitude and direction among deaths occurring in the first five and later five years of follow-up, although due to small numbers was not statistically significant in the later five years of follow-up.

Discussion

We investigated mLOY in a large cohort of 223,338 men from the UK Biobank by scanning for deviations in mLRR of the Y-specific region of the male Y chromosome. We analyzed mLOY at mLRR < \(-0.15\) and mLRR < \(-0.40\) cutpoints as well as continuous mLRR. Our study is the largest to date, providing sufficiently strong statistical power to replicate prior cross-sectional associations for mLOY with age and smoking, as well as uncover new associations with ancestry, self-reported health, BMI, self-reported diabetes, and self-reported heart attack or stroke. Furthermore, men with a high proportion of cells with mLOY had a higher risk of mortality during follow-up.

The UK Biobank provides a unique opportunity to examine both the predictors and consequences of mLOY. Aging is associated with an accumulation of somatic mutations, so it is not surprising that rates of mLOY increase with age. Age-related mLOY has been previously reported, but existing datasets were smaller and had limited ability to test for non-linear associations. In this analysis, we report evidence that the frequency of mLOY increases exponentially with age (i.e., a quadratic rather than a linear relationship). The prevalence of mLOY appears to remain low until approximately 50 years of age after which the prevalence rapidly increases. Accelerated stochastic processes coupled with inherited variation in genome maintenance likely influence risk of mLOY. In combination with these mechanisms, it is possible that age-related changes in stem cell compartment diversity and reduced levels of immuno-surveillance permit sub-populations of cells with mLOY to increase in abundance. Previous studies of autosomal mosaicism support this possibility, suggesting the proportion of cells affected by mosaicism, while dynamic, increases with age.

In addition to age, we observed associations of mLOY with smoking, BMI, genetic ancestry, self-reported health, and a previous diagnosis of diabetes or cardiovascular disease. Smoking has been previously reported to be associated with increased mLOY risk. The large size of the current study adds to this previous literature, clearly indicating a higher prevalence of mLOY among current smokers of all ages. The decline of mLOY prevalence with cessation suggests that the association between smoking and mLOY could be reversible and that the mechanisms contributing to mLOY are potentially modifiable. The lower overall frequency of mLOY observed in the UK Biobank in relation to our previous study of mLOY is due to the combination of a younger overall age and lower proportion of current and former smokers in the UK Biobank; a comparison of age and smoking stratified frequencies suggests no meaningful differences in frequencies of mLOY (Supplementary Fig. 2).

The association with BMI, however, is new. Potential mechanisms linking obesity to reduced frequency of mLOY are unknown and residual confounding by other factors is possible. For example, despite careful adjustment, smoking may be responsible for some of the observed association between BMI and mLOY. A recent study in the UK Biobank observed that current smokers were less likely to be obese than never smokers, and that former...
smokers were more likely to be obese than current smokers and never smokers. Since smoking is an established risk factor for mLOY and is difficult to adjust for fully, the inverse association between mLOY and obesity may be confounded by higher frequencies of current smokers among normal weight men and higher frequencies of former smokers among obese men. The association between mLOY and ancestry has also not previously been

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### Table 2. Hazard ratios and 95% confidence intervals for mosaic loss of the Y chromosome (mLOY) and all-cause mortality using age as the underlying time metric (N = 223,338).

|          | mLOY (mLRR < −0.15) |          | mLOY (mLRR < −0.40) |          |
|----------|----------------------|----------|----------------------|----------|
|          | HR       | 95% CI   | P-value | HR       | 95% CI   | P-value | HR       | 95% CI   | P-value |
| N (%) with mLOY | 3,789 (1.70) |          |         | 596 (0.27) |          |         |
| No. deaths | 8401 |          |         | 8401 |          |         |
| No. deaths with mLOY | 334 |          |         | 75 |          |         |
| Age-adjusteda | 1.37 (1.23–1.53) | 1.7 × 10⁻⁸ | 1.88 (1.50–2.36) | 6.0 × 10⁻⁸ | 1.06 (1.04–1.08) | 9.0 × 10⁻¹² |
| Age- & smoking-adjustedb | 1.06 (0.95–1.18) | 0.31 | 1.35 (1.08–1.70) | 0.01 | 1.01 (0.99–1.03) | 0.24 |
| Multivariable-adjustedc | 1.08 (0.97–1.21) | 0.16 | 1.35 (1.08–1.70) | 0.009 | 1.02 (1.00–1.03) | 0.07 |

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**Figure 2.** Multivariable-adjusted Cox proportional hazards regression for mLRR and all-cause mortality, modeled with a restricted cubic spline with knots at the 1st, 25th, 50th, 75th, and 95th percentiles of mLRR, illustrating the relationship between mosaic loss of the Y chromosome and all-cause mortality (P-value of overall association = 0.01; P-value of nonlinear association = 0.12). Abbreviations: mLRR, median log₂ intensity ratio of the Y chromosome; mLOY, mosaic loss of the Y chromosome; mLRR, median log₂ intensity ratio of the Y chromosome.
Our analysis indicates mLOY is associated with several different risk factors for mortality and disease, including age, smoking, ancestry, and BMI. The associations, which are based on observational data, necessitate caution with regards to interpretation of the observed association between mLOY and mortality. Even with careful adjustment for age, smoking, and BMI, potential for residual confounding by these and other factors remains a concern.

Table 3. Hazard ratios and 95% confidence intervals for mosaic loss of the Y chromosome and cause-specific mortality using age as the underlying time metric (N = 223, 338). a Multivariable model is adjusted for age (as the underlying time metric), detailed smoking history (25-level variable incorporating current smoking status, smoking intensity (current and former smokers); time since quitting (former smokers), and cigar and pipe use (current and former smokers)); time to first cigarette among current smokers (≤5 minutes, 5 to 15 minutes, 15 minutes to 1 hour); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day); general health status (excellent, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m²); and physical activity (>10 minutes of moderate of vigorous activity 0, 1-2, 3-4, or ≥5 days/week). b Scaled by the (standard deviation) of mLRR such that the HR corresponds to a one standard deviation decrease in mLRR.

Abbreviations: CI, confidence interval; HR, hazard ratio; mLOY, mosaic loss of the Y chromosome; mLRR, median log2 intensity ratio of the Y chromosome.
<5 minutes, 5 to 15 minutes, 30 minutes to 1 hour, or >1 hour); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day); general health status (excellent, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m²); and physical activity (>10 minutes of moderate of vigorous activity 0, 1-2, 3-4, or ≥5 days/week). Smoking stratified models were not adjusted for detailed smoking history. ‘Self-reported health stratified models were not adjusted for self-reported health. ‘Scaled by the - (standard deviation) of mLRR such that the HR corresponds to a one standard deviation decrease in mLRR. Abbreviations: CI, confidence interval; HR, hazard ratio; mLOY, mosaic loss of the Y chromosome; mLRR, median log2 intensity ratio of the Y chromosome.

Table 4. Hazard ratios and 95% confidence intervals for mosaic loss of the Y chromosome and all-cause mortality using age as the underlying time metric and stratified by baseline characteristics. *Multivariable model is adjusted for age (as the underlying time metric), detailed smoking history (25-level variable incorporating current smoking status, smoking intensity (current and former smokers); time since quitting (former smokers), and cigar and pipe use (current and former smokers)); time to first cigarette among current smokers (<5 minutes, 5 to 15 minutes, 30 minutes to 1 hour, or >1 hour)); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day); general health status (excellent, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m²); and physical activity (>10 minutes of moderate of vigorous activity 0, 1-2, 3-4, or ≥5 days/week). Smoking stratified models were not adjusted for detailed smoking history. ‘Self-reported health stratified models were not adjusted for self-reported health. ‘Scaled by the - (standard deviation) of mLRR such that the HR corresponds to a one standard deviation decrease in mLRR. Abbreviations: CI, confidence interval; HR, hazard ratio; mLOY, mosaic loss of the Y chromosome; mLRR, median log2 intensity ratio of the Y chromosome.

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In conclusion, our analysis in the UK Biobank identifies intriguing predictors of mLOY and provides insight into potential health-related consequences of postzygotic loss of the male Y chromosome. These associations merit future epidemiologic and molecular investigations targeted at understanding the impact of mosaic Y loss on men’s health.

Data availability. All data used in this analysis is available through application to the UK Biobank.

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Author Contributions

E.L., W.Z., B.I.G., M.Y., S.J.C., N.D.F. and M.J.M. contributed to the study conception and design. E.L., N.D.F., M.J.M., S.J.C. contributed to the acquisition of data. E.L., W.Z. and M.J.M. contributed to the analysis of data. E.L., N.D.F. and M.J.M. drafted the first version of the manuscript. All authors contributed to the interpretation of the data and critically revised the manuscript and approved the final text.

Additional Information

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