

Supplementary Materials

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Table S1 Baseline characteristics of UKB participants

| | Non-carrier (N=173 786) | mLOY carrier (N=43 994) | P-value ^a |
|---|----------------------------|-------------------------------|----------------------|
| Age, years | 55.39 ± 8.18 | 61.98 ± 5.78 | <0.001 |
| Assessment center | | | <0.001 |
| England, n (%) | 193 447 (88.83) | 154 174 (88.71) | |
| Scotland, n (%) | 9111 (4.18) | 7279 (4.19) | |
| Wales, n (%) | 15 222 (6.99) | 12 333 (7.10) | |
| TDI | -1.23 ± 3.16 | -1.45 ± 3.06 | <0.001 |
| Missing, n (%) | 200 (0.13) | 43 (0.11) | |
| Ethnic background | | | <0.001 |
| White, n (%) | 162 438 (93.47) | 42 873 (97.45) | |
| Other, n (%) | 10 622 (6.11) | 942 (2.14) | |
| Missing, n (%) | 726 (0.42) | 179 (0.41) | |
| Qualification | | | <0.001 |
| College, n (%) | 60 753 (34.96) | 12 943 (29.42) | |
| Other, n (%) | 111 009 (63.88) | 30 480 (69.28) | |
| Missing, n (%) | 2024 (1.16) | 571 (1.30) | |
| Occupation | | | <0.001 |
| Agricultural and related work, n (%) | 1252 (0.72) | 268 (0.61) | |
| Industrial and related work, n (%) | 18 893 (10.87) | 3235 (7.35) | |
| Non-agricultural or industrial work, n (%) | 93 656 (53.89) | 14 694 (33.40) | |
| Retirement, n (%) | 45 070 (25.93) | 22 757 (51.73) | |
| Others, n (%) | 13 261 (7.63) | 2690 (6.11) | |
| Missing, n (%) | 1654 (0.95) | 350 (0.80) | |
| Smoking status | | | <0.001 |
| Non-smoker, n (%) | 89 652 (51.59) | 17 120 (38.91) | |

| | | | |
|--|---------------------------|---------------------------|--------|
| Former smoker, n (%) | 64 276 (36.99) | 19 510 (44.35) | |
| Current smoker, n (%) | 19 858 (11.43) | 7364 (16.74) | |
| Proportion of lifespan exposed to smoking, pack-years per year | 0.00 [0.00, 0.35] | 0.09 [0.00, 0.61] | <0.001 |
| Alcohol consumption | | | <0.001 |
| Daily or almost daily, n (%) | 42 479 (24.44) | 12 835 (29.17) | |
| Three or four times a week, n (%) | 45 845 (26.38) | 11 159 (25.36) | |
| Once or twice a week, n (%) | 45 826 (26.37) | 10 533 (23.94) | |
| One to three times a month, n (%) | 15 837 (9.11) | 3470 (7.89) | |
| Special occasions only, n (%) | 12 600 (7.25) | 3320 (7.55) | |
| Never, n (%) | 11 030 (6.35) | 2646 (6.01) | |
| Missing, n (%) | 169 (0.10) | 31 (0.07) | |
| MET, minutes per week | 1810.00 [799.00, 3712.00] | 1893.00 [840.00, 3871.00] | <0.001 |
| Missing, n (%) | 23 114 (15.26) | 6 026 (15.83) | |
| Healthy diet | | | <0.001 |
| Yes, n (%) | 146 292 (84.18) | 37 552 (85.36) | |
| No, n (%) | 21 748 (12.51) | 5068 (11.52) | |
| Missing, n (%) | 5746 (3.31) | 1374 (3.12) | |
| BMI, kg/m ² | 27.89 (4.30) | 27.60 (3.96) | <0.001 |
| Missing, n (%) | 665 (0.44) | 145 (0.38) | |
| Prevalent diabetes, n (%) | 13 654 (7.86) | 3844 (8.74) | <0.001 |
| Prevalent hypertension, n (%) | 103 650 (59.64) | 30 257 (68.78) | <0.001 |

mLOY, mosaic loss of chromosome Y; TDI, townsend deprivation index; MET, Metabolic Equivalent Task; BMI, body mass index

^a Both ANOVA and the Kruskal-Wallis H test were utilized to obtain p-values for continuous variables, while the χ^2 test was employed for categorical variables.

Table S2 Baseline characteristics of CKB participants

| | Non-carrier (N=40 401) | mLOY carrier (N=2,458) | P-value ^a |
|--|---------------------------|---------------------------|----------------------|
| Age, years | 54.30 ± 11.11 | 62.73 ± 9.83 | <0.001 |
| Region | | | <0.001 |
| Rural areas, n (%) | 23 723 (58.7) | 1194 (48.6) | |
| Urban areas, n (%) | 16 678 (41.3) | 1264 (51.4) | |
| Household income | | | 0.749 |
| <2,500 yuan, n (%) | 1537 (3.8) | 105 (4.3) | |
| 2,500-4,999 yuan, n (%) | 2976 (7.4) | 168 (6.8) | |
| 5,000-9,999 yuan, n (%) | 7370 (18.2) | 437 (17.8) | |
| 10,000-19,999 yuan, n (%) | 11 750 (29.1) | 727 (29.6) | |
| 20,000-34,999 yuan, n (%) | 9465 (23.4) | 577 (23.5) | |
| ≥35,000 yuan, n (%) | 7303 (18.1) | 444 (18.1) | |
| Qualification | | | 0.005 |
| College, n (%) | 1382 (3.4) | 111 (4.5) | |
| Other, n (%) | 39 019 (96.6) | 2347 (95.5) | |
| Occupation | | | <0.001 |
| Agricultural and related work, n (%) | 18 163 (45.0) | 885 (36.0) | |
| Industrial and related work, n (%) | 6630 (16.4) | 177 (7.2) | |
| Non-agricultural or industrial work, n (%) | 5952 (14.7) | 204 (8.3) | |
| Retirement, n (%) | 6361 (15.7) | 952 (38.7) | |
| Others, n (%) | 3295 (8.2) | 240 (9.8) | |
| Smoking status | | | <0.001 |
| Non-smoker, n (%) | 10 192 (25.2) | 532 (21.6) | |
| Former smoker, n (%) | 2765 (6.8) | 179 (7.3) | |
| Current smoker, n (%) | 27 444 (67.9) | 1747 (71.1) | |

| | | | |
|---|----------------------|----------------------|--------|
| Proportion of lifespan exposed to smoking, pack-years per year | 0.55 (0.53) | 0.57 (0.53) | 0.019 |
| Alcohol consumption | | | <0.001 |
| Non-daily drinkers, n (%) | 28 242 (69.9) | 1620 (65.9) | |
| Daily drinkers(<15g/day), n (%) | 354 (0.9) | 41 (1.7) | |
| Daily drinkers(15~30g/day), n (%) | 1617 (4.0) | 105 (4.3) | |
| Daily drinkers(30~60g/day), n (%) | 2704 (6.7) | 184 (7.5) | |
| Ex-excessive drinkers or daily drinkers(\geq 60g/day), n (%) | 7484 (18.5) | 508 (20.7) | |
| MET, minutes per week | 8769.60 (6388.20) | 6165.60 (5443.20) | <0.001 |
| Healthy diet | | | 0.268 |
| Yes, n (%) | 38 279 (94.7) | 2342 (95.3) | |
| No, n (%) | 2122 (5.3) | 116 (4.7) | |
| BMI, kg/m ² | 23.37 (3.34) | 22.99 (3.36) | <0.001 |
| Prevalent diabetes, n (%) | 2514 (6.2) | 200 (8.1) | <0.001 |
| Prevalent hypertension, n (%) | 5198 (12.9) | 441 (17.9) | <0.001 |

mLOY, mosaic loss of chromosome Y; MET, Metabolic Equivalent Task; BMI, body mass index

^aANOVA test was utilized to obtain p-values for continuous variables, while the χ^2 test was employed for categorical variables.

Table S3 Associations of mLOY subtypes with the risk of age-related lung diseases

| | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| All lung diseases | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 5129/27312 | 16.7 | 1.07 (1.03, 1.10) | 1.09 (1.05, 1.12) | 1.03 (0.99, 1.06) |
| CKB | 254/1349 | 18.6 | 0.92 (0.81, 1.04) | 0.92 (0.81, 1.05) | 0.90 (0.79, 1.02) |
| Combined | | | 1.00 (0.87, 1.16) | 1.01 (0.86, 1.19) | 0.98 (0.86, 1.11) |
| P for heterogeneity | | | 0.022 | 0.015 | 0.046 |
| Expanded mLOY | | | | | |
| UKB | 2809/10767 | 24.2 | 1.31 (1.26, 1.37) | 1.30 (1.25, 1.35) | 1.13 (1.09, 1.18) |
| CKB | 225/665 | 38.1 | 1.32 (1.15, 1.52) | 1.35 (1.18, 1.55) | 1.30 (1.13, 1.49) |
| Combined | | | 1.31 (1.26, 1.36) | 1.30 (1.24, 1.35) | 1.19 (1.04, 1.36) |
| P for heterogeneity | | | 0.919 | 0.530 | 0.049 |
| COPD | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 1764/30328 | 5.0 | 1.21 (1.14, 1.27) | 1.22 (1.15, 1.28) | 1.03 (0.97, 1.09) |
| CKB | 114/1366 | 8.0 | 0.96 (0.79, 1.16) | 1.00 (0.82, 1.21) | 0.97 (0.80, 1.17) |
| Combined | | | 1.10 (0.88, 1.37) | 1.13 (0.94, 1.35) | 1.02 (0.97, 1.08) |
| P for heterogeneity | | | 0.023 | 0.049 | 0.554 |

| | | | | | |
|--------------------------|------------|------|-------------------|-------------------|-------------------|
| Expanded mLOY | | | | | |
| UKB | 1199/11804 | 9.0 | 1.85 (1.74, 1.98) | 1.71 (1.61, 1.83) | 1.20 (1.12, 1.28) |
| CKB | 104/671 | 16.4 | 1.24 (1.01, 1.51) | 1.33 (1.09, 1.63) | 1.25 (1.02, 1.53) |
| Combined | | | 1.53 (1.04, 2.27) | 1.54 (1.20, 1.96) | 1.20 (1.13, 1.28) |
| P for heterogeneity | | | 0.002 | 0.024 | 0.708 |
| Lung cancer | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 566/31461 | 1.5 | 1.27 (1.15, 1.40) | 1.26 (1.14, 1.38) | 1.04 (0.94, 1.14) |
| CKB | 59/1622 | 3.5 | 1.16 (0.89, 1.51) | 1.14 (0.88, 1.49) | 1.07 (0.82, 1.40) |
| Combined | | | 1.26 (1.15, 1.38) | 1.24 (1.13, 1.35) | 1.04 (0.95, 1.14) |
| P for heterogeneity | | | 0.529 | 0.564 | 0.791 |
| Expanded mLOY | | | | | |
| UKB | 451/12462 | 3.1 | 2.19 (1.96, 2.44) | 1.98 (1.78, 2.21) | 1.32 (1.18, 1.47) |
| CKB | 52/820 | 6.6 | 1.61 (1.21, 2.14) | 1.58 (1.19, 2.11) | 1.47 (1.10, 1.95) |
| Combined | | | 1.93 (1.44, 2.60) | 1.84 (1.50, 2.25) | 1.34 (1.21, 1.48) |
| P for heterogeneity | | | 0.048 | 0.184 | 0.495 |
| IPF | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 332/31468 | 0.9 | 1.08 (0.95, 1.22) | 1.10 (0.97, 1.25) | 1.05 (0.93, 1.20) |
| Expanded mLOY | | | | | |

| | | | | | |
|-----|-----------|-----|-------------------|-------------------|-------------------|
| UKB | 231/12472 | 1.6 | 1.51 (1.31, 1.75) | 1.50 (1.30, 1.74) | 1.34 (1.16, 1.56) |
|-----|-----------|-----|-------------------|-------------------|-------------------|

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S4 Associations of mLOY with the risk of age-related lung diseases after excluding participants who experienced outcome events within two years of follow-up

| | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| All lung diseases | | | | | |
| UKB | 7259/37400 | 17.2 | 1.13 (1.10, 1.17) | 1.15 (1.11, 1.18) | 1.06 (1.03, 1.09) |
| CKB | 430/1985 | 22.0 | 1.06 (0.96, 1.17) | 1.07 (0.97, 1.18) | 1.04 (0.94, 1.15) |
| Combined | | | 1.11 (1.06, 1.17) | 1.13 (1.06, 1.20) | 1.06 (1.03, 1.09) |
| P for heterogeneity | | | 0.226 | 0.249 | 0.722 |
| COPD | | | | | |
| UKB | 2739/41908 | 5.6 | 1.39 (1.32, 1.46) | 1.37 (1.30, 1.43) | 1.08 (1.03, 1.14) |
| CKB | 196/2015 | 9.5 | 1.06 (0.91, 1.23) | 1.12 (0.97, 1.31) | 1.08 (0.93, 1.25) |
| Combined | | | 1.23 (0.94, 1.60) | 1.25 (1.04, 1.51) | 1.08 (1.03, 1.13) |
| P for heterogeneity | | | 0.001 | 0.017 | 0.991 |
| Lung cancer | | | | | |
| UKB | 903/43809 | 1.7 | 1.54 (1.41, 1.67) | 1.48 (1.36, 1.62) | 1.12 (1.03, 1.23) |
| CKB | 98/2429 | 3.9 | 1.33 (1.08, 1.65) | 1.32 (1.06, 1.63) | 1.23 (0.99, 1.53) |
| Combined | | | 1.48 (1.30, 1.68) | 1.46 (1.35, 1.58) | 1.14 (1.05, 1.23) |
| P for heterogeneity | | | 0.208 | 0.361 | 0.387 |
| IPF | | | | | |
| UKB | 533/43910 | 1.0 | 1.21 (1.08, 1.34) | 1.22 (1.10, 1.37) | 1.14 (1.02, 1.27) |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic

obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S5 Associations of mLOY subtypes with the risk of age-related lung diseases after excluding participants who experienced outcome events within two years of follow-up

| | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| All lung diseases | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 4694/26877 | 15.3 | 1.06 (1.03, 1.10) | 1.08 (1.05, 1.12) | 1.02 (0.99, 1.05) |
| CKB | 229/1324 | 16.8 | 0.91 (0.79, 1.04) | 0.91 (0.80, 1.04) | 0.89 (0.78, 1.01) |
| Combined | | | 1.00 (0.86, 1.15) | 1.00 (0.85, 1.18) | 0.97 (0.85, 1.10) |
| P for heterogeneity | | | 0.034 | 0.013 | 0.044 |
| Expanded mLOY | | | | | |
| UKB | 2565/10523 | 22.1 | 1.31 (1.25, 1.36) | 1.29 (1.24, 1.35) | 1.13 (1.08, 1.18) |
| CKB | 201/641 | 34.2 | 1.32 (1.14, 1.52) | 1.35 (1.17, 1.56) | 1.30 (1.12, 1.50) |
| Combined | | | 1.31 (1.26, 1.36) | 1.29 (1.24, 1.35) | 1.19 (1.04, 1.36) |
| P for heterogeneity | | | 0.921 | 0.499 | 0.072 |
| COPD | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 1629/30193 | 4.6 | 1.20 (1.13, 1.27) | 1.21 (1.14, 1.28) | 1.02 (0.97, 1.08) |
| CKB | 103/1355 | 7.2 | 0.95 (0.78, 1.16) | 0.99 (0.81, 1.21) | 0.96 (0.79, 1.18) |
| Combined | | | 1.09 (0.87, 1.36) | 1.12 (0.93, 1.34) | 1.02 (0.96, 1.07) |
| P for heterogeneity | | | 0.027 | 0.060 | 0.559 |

| | | | | | | |
|--------------------------|------------|------|-------------------|-------------------|-------------------|--|
| Expanded mLOY | | | | | | |
| UKB | 1110/11715 | 8.4 | 1.85 (1.73, 1.98) | 1.72 (1.61, 1.84) | 1.20 (1.12, 1.29) | |
| CKB | 93/660 | 14.7 | 1.22 (0.99, 1.51) | 1.33 (1.07, 1.64) | 1.24 (1.00, 1.54) | |
| Combined | | | 1.52 (1.01, 2.29) | 1.54 (1.20, 1.98) | 1.20 (1.13, 1.29) | |
| P for heterogeneity | | | <0.001 | 0.023 | 0.719 | |
| Lung cancer | | | | | | |
| Non-expanded mLOY | | | | | | |
| UKB | 506/31401 | 1.4 | 1.27 (1.14, 1.40) | 1.26 (1.13, 1.39) | 1.03 (0.93, 1.14) | |
| CKB | 54/1617 | 3.2 | 1.20 (0.91, 1.58) | 1.18 (0.89, 1.56) | 1.11 (0.84, 1.47) | |
| Combined | | | 1.26 (1.15, 1.39) | 1.24 (1.13, 1.37) | 1.04 (0.94, 1.14) | |
| P for heterogeneity | | | 0.706 | 0.746 | 0.574 | |
| Expanded mLOY | | | | | | |
| UKB | 397/12408 | 2.8 | 2.16 (1.93, 2.43) | 1.96 (1.75, 2.20) | 1.29 (1.15, 1.45) | |
| CKB | 44/812 | 5.6 | 1.56 (1.14, 2.13) | 1.54 (1.13, 2.11) | 1.43 (1.05, 1.96) | |
| Combined | | | 1.90 (1.39, 2.59) | 1.82 (1.47, 2.25) | 1.31 (1.17, 1.46) | |
| P for heterogeneity | | | 0.056 | 0.189 | 0.517 | |
| IPF | | | | | | |
| Non-expanded mLOY | | | | | | |
| UKB | 315/31451 | 0.8 | 1.07 (0.94, 1.22) | 1.10 (0.96, 1.25) | 1.05 (0.92, 1.19) | |
| Expanded mLOY | | | | | | |
| UKB | 218/12459 | 1.5 | 1.50 (1.29, 1.74) | 1.49 (1.28, 1.73) | 1.33 (1.14, 1.55) | |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic

obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S6 Associations of mLOY with the risk of IPF after adopting a broader definition of IPF

| | mLOY carrier | | HR (95% CI) | | |
|------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| IPF | | | | | |
| UKB | 644/43939 | 1.2 | 1.22 (1.11, 1.35) | 1.24 (1.13, 1.37) | 1.16 (1.05, 1.28) |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S7 Associations of mLOY subtypes with the risk of IPF after adopting a broader definition of IPF

| | mLOY carrier | | HR (95% CI) | | |
|--------------------------|----------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/ mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| IPF | | | | | |
| Non-expanded mLOY | | | | | |
| UKB | 392/31467 | 1.1 | 1.12 (0.99, 1.25) | 1.14 (1.02, 1.28) | 1.09 (0.97, 1.23) |
| Expanded mLOY | | | | | |
| UKB | 252/12472 | 1.7 | 1.46 (1.27, 1.68) | 1.46 (1.26, 1.67) | 1.30 (1.13, 1.50) |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S8 Associations of mLOY with the risk of age-related lung diseases after further adjusting for detailed smoking history

| | HR (95% CI) ^a | | |
|--------------------------|--------------------------|-------------------|-------------------|
| | All mLOY | Non-expanded mLOY | Expanded mLOY |
| All lung diseases | | | |
| UKB | 1.05 (1.02, 1.08) | 1.02 (0.99, 1.05) | 1.13 (1.08, 1.17) |
| CKB | 1.05 (0.95, 1.15) | 0.90 (0.79, 1.02) | 1.29 (1.13, 1.48) |
| Combined | 1.05 (1.02, 1.08) | 0.97 (0.86, 1.10) | 1.19 (1.05, 1.35) |
| P for heterogeneity | 0.999 | 0.061 | 0.065 |
| COPD | | | |
| UKB | 1.08 (1.03, 1.13) | 1.02 (0.97, 1.08) | 1.18 (1.11, 1.26) |
| CKB | 1.08 (0.94, 1.25) | 0.97 (0.81, 1.18) | 1.24 (1.01, 1.52) |
| Combined | 1.08 (1.03, 1.13) | 1.02 (0.97, 1.07) | 1.19 (1.12, 1.26) |
| P for heterogeneity | 0.998 | 0.615 | 0.650 |
| Lung cancer | | | |
| UKB | 1.12 (1.04, 1.22) | 1.03 (0.93, 1.13) | 1.29 (1.16, 1.44) |
| CKB | 1.22 (0.99, 1.49) | 1.07 (0.82, 1.39) | 1.45 (1.09, 1.94) |
| Combined | 1.13 (1.05, 1.22) | 1.03 (0.94, 1.13) | 1.31 (1.18, 1.45) |
| P for heterogeneity | 0.445 | 0.791 | 0.457 |
| IPF | | | |
| UKB | 1.15 (1.03, 1.28) | 1.05 (0.93, 1.20) | 1.34 (1.15, 1.55) |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

^a adjusted for age, age-squared, assessment center, ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, top 10 principal components, and detailed smoking history (smoking status, smoking intensity, time since quitting, type of tobacco currently smoked, and exposure to

second-hand smoke).

Table S9 Associations of mLOY with the risk of age-related lung diseases after excluding participants with missing information at baseline in UKB

| | Cases/mLOY carriers | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|--|
| | | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c | |
| All lung diseases | | | | | | |
| UKB | 6125/30823 | 17.8 | 1.14 (1.10, 1.17) | 1.14 (1.11, 1.18) | 1.05 (1.02, 1.09) | |
| COPD | | | | | | |
| UKB | 2191/34058 | 5.5 | 1.39 (1.32, 1.46) | 1.36 (1.29, 1.44) | 1.07 (1.01, 1.13) | |
| Lung cancer | | | | | | |
| UKB | 755/35382 | 1.8 | 1.48 (1.35, 1.63) | 1.43 (1.30, 1.57) | 1.09 (1.00, 1.19) | |
| IPF | | | | | | |
| UKB | 439/35396 | 1.1 | 1.27 (1.12, 1.43) | 1.28 (1.13, 1.44) | 1.18 (1.05, 1.34) | |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S10 Associations of mLOY subtypes with the risk of age-related lung diseases after excluding participants with missing information at baseline in UKB

| | Cases/mLOY carriers | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|--|----------------------|----------------------|----------------------|
| | | Incident cases per 1,000 person-years | | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| All lung diseases | | | | | | |
| Non-expanded mLOY | | | | | | |
| UKB | 3961/22179 | 15.8 | | 1.06 (1.03, 1.10) | 1.08 (1.04, 1.12) | 1.02 (0.98, 1.06) |
| Expanded mLOY | | | | | | |
| UKB | 2164/8644 | 23.1 | | 1.31 (1.25, 1.37) | 1.29 (1.23, 1.35) | 1.13 (1.08, 1.18) |
| COPD | | | | | | |
| Non-expanded mLOY | | | | | | |
| UKB | 1311/24598 | 4.5 | | 1.21 (1.13, 1.29) | 1.21 (1.14, 1.29) | 1.02 (0.95, 1.08) |
| Expanded mLOY | | | | | | |
| UKB | 880/9460 | 8.2 | | 1.83 (1.69, 1.97) | 1.69 (1.56, 1.82) | 1.17 (1.09, 1.27) |
| Lung cancer | | | | | | |
| Non-expanded mLOY | | | | | | |
| UKB | 423/25454 | 1.4 | | 1.22 (1.09, 1.37) | 1.21 (1.08, 1.35) | 0.98 (0.88, 1.10) |
| Expanded mLOY | | | | | | |
| UKB | 332/9928 | 2.9 | | 2.09 (1.84, 2.37) | 1.90 (1.68, 2.16) | 1.27 (1.12, 1.44) |
| IPF | | | | | | |
| Non-expanded mLOY | | | | | | |
| UKB | 260/25457 | 0.9 | | 1.13 (0.98, 1.30) | 1.15 (0.99, 1.32) | 1.09 (0.94, 1.26) |

Expanded mLOY

| | | | | | |
|-----|----------|-----|-------------------|-------------------|-------------------|
| UKB | 179/9939 | 1.6 | 1.56 (1.32, 1.85) | 1.54 (1.31, 1.83) | 1.37 (1.15, 1.62) |
|-----|----------|-----|-------------------|-------------------|-------------------|

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S11 Associations of mLOY with the co-occurrence of lung diseases

| | | Number of diseases | Cases/N | Beta | Se | P-value |
|-----|-------------------|-----------------------|---------------|--------|-------|---------|
| UKB | mLOY | 0 | 30023 / 38046 | 0.019 | 0.003 | <0.001 |
| | | 1 | 5084 / 38046 | | | |
| | | 2 | 2568 / 38046 | | | |
| | | 3 | 371 / 38046 | | | |
| | Non-expanded mLOY | 0 | 22111 / 27294 | 0.003 | 0.003 | 0.458 |
| | | 1 | 3482 / 27294 | | | |
| | | 2 | 1500 / 27294 | | | |
| | | 3 | 201 / 27294 | | | |
| | Expanded mLOY | 0 | 7912 / 10752 | 0.064 | 0.005 | <0.001 |
| | | 1 | 1602 / 10752 | | | |
| | | 2 | 1068 / 10752 | | | |
| | | 3 | 170 / 10752 | | | |
| CKB | mLOY | 0 | 1729 / 2014 | 0.011 | 0.006 | 0.078 |
| | | 1 | 274 / 2014 | | | |
| | | 2 | 11 / 2014 | | | |
| | Non-expanded mLOY | 0 | 1200 / 1349 | -0.006 | 0.008 | 0.424 |
| | | 1 | 144 / 1349 | | | |
| | | 2 | 5 / 1349 | | | |
| | Expanded mLOY | 0 | 529 / 665 | 0.049 | 0.011 | <0.001 |
| | | 1 | 130 / 665 | | | |
| | | 2 | 6 / 665 | | | |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank

Table S12 Associations of mLOY events and mLOY subtypes with the risk of asthma

| | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| mLOY | | | | | |
| UKB | 1032/38258 | 2.3 | 1.05 (0.98, 1.13) | 1.08 (1.00, 1.16) | 1.05 (0.98, 1.14) |
| CKB | 32/2427 | 1.3 | 1.10 (0.76, 1.59) | 1.12 (0.77, 1.62) | 1.09 (0.75, 1.59) |
| Combined | | | 1.05 (0.98, 1.13) | 1.08 (1.01, 1.16) | 1.05 (0.98, 1.13) |
| P for heterogeneity | | | 0.808 | 0.850 | 0.848 |
| Non-expanded mLOY | | | | | |
| UKB | 686/27433 | 2.1 | 0.99 (0.91, 1.08) | 1.03 (0.94, 1.12) | 1.01 (0.93, 1.10) |
| CKB | 19/1611 | 1.1 | 1.08 (0.68, 1.73) | 1.09 (0.69, 1.75) | 1.07 (0.67, 1.71) |
| Combined | | | 0.99 (0.91, 1.08) | 1.03 (0.95, 1.12) | 1.01 (0.93, 1.10) |
| P for heterogeneity | | | 0.719 | 0.815 | 0.781 |
| Expanded mLOY | | | | | |
| UKB | 346/10825 | 2.8 | 1.21 (1.08, 1.36) | 1.21 (1.08, 1.36) | 1.17 (1.04, 1.31) |
| CKB | 13/816 | 1.6 | 1.12 (0.63, 1.97) | 1.16 (0.66, 2.04) | 1.13 (0.64, 1.98) |
| Combined | | | 1.21 (1.08, 1.35) | 1.21 (1.08, 1.35) | 1.17 (1.04, 1.31) |
| P for heterogeneity | | | 0.795 | 0.886 | 0.906 |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S13 Associations of mLOY events and mLOY subtypes with the risk of pneumonia

| | mLOY carrier | | HR (95% CI) | | |
|--------------------------|---------------------|---------------------------------------|----------------------|----------------------|----------------------|
| | Cases/mLOY carriers | Incident cases per 1,000 person-years | Model 1 ^a | Model 2 ^b | Model 3 ^c |
| mLOY | | | | | |
| UKB | 4272/43994 | 8.4 | 1.13 (1.09, 1.17) | 1.14 (1.10, 1.19) | 1.05 (1.02, 1.10) |
| CKB | 310/2458 | 12.8 | 1.02 (0.90, 1.14) | 1.02 (0.91, 1.15) | 1.00 (0.89, 1.13) |
| Combined | | | 1.09 (0.99, 1.20) | 1.09 (0.98, 1.22) | 1.05 (1.02, 1.09) |
| P for heterogeneity | | | 0.104 | 0.078 | 0.467 |
| Non-expanded mLOY | | | | | |
| UKB | 2707/31506 | 7.4 | 1.05 (1.01, 1.10) | 1.07 (1.03, 1.12) | 1.01 (0.97, 1.06) |
| CKB | 177/1631 | 10.6 | 0.95 (0.81, 1.10) | 0.95 (0.81, 1.10) | 0.93 (0.80, 1.09) |
| Combined | | | 1.03 (0.95, 1.11) | 1.03 (0.93, 1.15) | 1.00 (0.96, 1.05) |
| P for heterogeneity | | | 0.217 | 0.142 | 0.315 |
| Expanded mLOY | | | | | |
| UKB | 1565/12488 | 11.1 | 1.31 (1.24, 1.39) | 1.30 (1.23, 1.37) | 1.14 (1.08, 1.21) |
| CKB | 133/827 | 17.5 | 1.13 (0.95, 1.35) | 1.14 (0.95, 1.36) | 1.11 (0.93, 1.33) |
| Combined | | | 1.25 (1.09, 1.43) | 1.25 (1.11, 1.41) | 1.14 (1.08, 1.20) |
| P for heterogeneity | | | 0.117 | 0.169 | 0.781 |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank

^a Model 1 adjusted for age, age-squared, and assessment center.

^b Model 2 further adjusted for ethnic background (only in UKB), socioeconomic status, qualification, occupation, alcohol consumption, total MET minutes per week for all activities, healthy diet, BMI, prevalent health conditions (diabetes and hypertension), genotyping batch, and top 10 principal components.

^c Model 3 additionally adjusted for smoking status and smoking intensity.

Table S14 Interactions between mLOY subtypes and smoking status on the effect of lung diseases

| | Non-expand mLOY | | Expand mLOY | | P for interaction |
|--------------------------|---------------------|---------------------|---------------------|---------------------|-------------------|
| Current-smoker | RERI (97.5% CI) | AP (97.5% CI) | RERI (97.5% CI) | AP (97.5% CI) | |
| All lung diseases | | | | | |
| UKB | 0.04 (-0.09, 0.18) | 0.03 (-0.05, 0.11) | 0.16 (0.00, 0.32) | 0.09 (0.00, 0.17) | 0.176 |
| CKB | -0.04 (-0.35, 0.27) | -0.04 (-0.35, 0.26) | 0.04 (-0.43, 0.50) | 0.03 (-0.28, 0.33) | 0.980 |
| COPD | | | | | |
| UKB | 0.24 (-0.09, 0.57) | 0.07 (-0.02, 0.17) | 0.01 (-0.37, 0.40) | 0.00 (-0.11, 0.12) | 0.129 |
| CKB | -0.15 (-0.73, 0.43) | -0.11 (-0.57, 0.34) | -0.31 (-1.15, 0.53) | -0.19 (-0.72, 0.35) | 0.463 |
| Lung cancer | | | | | |
| UKB | 0.06 (-0.59, 0.70) | 0.02 (-0.16, 0.19) | 0.28 (-0.49, 1.05) | 0.06 (-0.10, 0.23) | 0.155 |
| CKB | 0.09 (-0.84, 1.01) | 0.05 (-0.50, 0.61) | 0.82 (-0.38, 2.02) | 0.34 (-0.10, 0.78) | 0.591 |
| IPF | | | | | |
| UKB | -0.27 (-0.75, 0.21) | -0.23 (-0.70, 0.23) | 0.02 (-0.60, 0.64) | 0.01 (-0.34, 0.37) | 0.598 |

mLOY, mosaic loss of chromosome Y; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; UKB, UK biobank; CKB, China Kadoorie biobank.

Table S15 Joint association of mLOY subtypes and smoking status with the risk of lung diseases

| | HR (95% CI) | | | |
|-----------------------|-------------------|-------------------|--------------------|-------------------|
| | All lung diseases | COPD | Lung cancer | IPF |
| UKB | | | | |
| Never smoker | | | | |
| non carrier | Ref. | Ref. | Ref. | Ref. |
| non expanded | 1.01 (0.95, 1.06) | 0.88 (0.76, 1.02) | 0.90 (0.67, 1.22) | 1.09 (0.84, 1.40) |
| expanded | 1.05 (0.97, 1.14) | 1.04 (0.84, 1.28) | 0.97 (0.62, 1.52) | 1.51 (1.09, 2.09) |
| Former smoker | | | | |
| non carrier | 1.09 (1.05, 1.13) | 2.07 (1.92, 2.23) | 2.54 (2.18, 2.96) | 1.84 (1.58, 2.15) |
| non expanded | 1.12 (1.07, 1.18) | 2.12 (1.93, 2.23) | 2.67 (2.22, 3.21) | 2.01 (1.65, 2.44) |
| expanded | 1.25 (1.17, 1.33) | 2.65 (2.38, 2.96) | 3.70 (3.03, 4.51) | 2.37 (1.90, 2.97) |
| Current smoker | | | | |
| non carrier | 1.67 (1.60, 1.75) | 5.19 (4.77, 5.64) | 7.22 (6.14, 8.48) | 2.09 (1.69, 2.59) |
| non expanded | 1.75 (1.64, 1.88) | 5.67 (5.12, 6.28) | 7.62 (6.30, 9.21) | 1.84 (1.35, 2.52) |
| expanded | 1.99 (1.84, 2.14) | 6.02 (5.38, 6.73) | 9.08 (7.47, 11.02) | 2.79 (2.07, 3.76) |
| CKB | | | | |
| Never smoker | | | | |
| non carrier | Ref. | Ref. | Ref. | |

| | | | |
|-----------------------|-------------------|-------------------|-------------------|
| non expanded | 0.88 (0.66, 1.18) | 1.11 (0.71, 1.75) | 1.01 (0.45, 2.30) |
| expanded | 1.68 (1.24, 2.26) | 1.98 (1.21, 3.23) | 1.72 (0.75, 3.92) |
| Former smoker | | | |
| non carrier | 1.01 (0.90, 1.14) | 1.08 (0.87, 1.33) | 1.28 (0.94, 1.73) |
| non expanded | 1.02 (0.66, 1.58) | 1.02 (0.45, 2.30) | 1.36 (0.50, 3.70) |
| expanded | 0.76 (0.45, 1.30) | 1.08 (0.51, 2.29) | 0.38 (0.05, 2.74) |
| Current smoker | | | |
| non carrier | 1.16 (1.07, 1.26) | 1.42 (1.24, 1.63) | 1.68 (1.34, 2.09) |
| non expanded | 1.03 (0.88, 1.21) | 1.34 (1.05, 1.71) | 1.81 (1.28, 2.57) |
| expanded | 1.50 (1.27, 1.78) | 1.68 (1.30, 2.16) | 2.63 (1.83, 3.77) |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

Table S16 The distribution of the number of participants when categorized into 9 groups according to the smoking status and mLOY subtypes

| | All lung diseases | | COPD | | Lung cancer | | IPF | |
|-----------------------|--------------------------|--|-------------|--|--------------------|--|------------|--|
| | Cases/N | Incident cases per 1,000 person-years | Cases/N | Incident cases per 1,000 person-years | Cases/N | Incident cases per 1,000 person-years | Cases/N | Incident cases per 1,000 person-years |
| UKB | | | | | | | | |
| Never smoker | | | | | | | | |
| non carrier | 7670/78751 | 8.2 | 1033/88382 | 1.0 | 229/89603 | 0.2 | 285/89603 | 0.3 |
| non expanded | 1609/11687 | 11.9 | 210/13024 | 1.3 | 52/13273 | 0.3 | 78/13273 | 0.5 |
| expanded | 598/3389 | 15.5 | 93/3769 | 2.1 | 21/3838 | 0.5 | 43/3835 | 0.9 |
| Former smoker | | | | | | | | |
| non carrier | 8737/55439 | 13.7 | 2818/62102 | 3.8 | 802/64160 | 1.0 | 606/64198 | 0.8 |
| non expanded | 2405/11643 | 18.6 | 843/12973 | 5.6 | 261/13568 | 1.6 | 204/13577 | 1.3 |
| expanded | 1336/5006 | 24.8 | 511/5524 | 8.9 | 196/5891 | 2.9 | 130/5898 | 1.9 |
| Current smoker | | | | | | | | |
| non carrier | 3472/17237 | 18.0 | 1920/18945 | 8.8 | 614/19835 | 2.6 | 152/19841 | 0.6 |
| non expanded | 1115/3982 | 26.3 | 711/4331 | 14.9 | 253/4620 | 4.8 | 50/4618 | 0.9 |
| expanded | 875/2372 | 36.6 | 555/2511 | 21.2 | 234/2733 | 7.8 | 58/2739 | 1.9 |
| CKB | | | | | | | | |
| Never smoker | | | | | | | | |

| | | | | | | |
|-----------------------|------------|------|------------|------|-----------|-----|
| non carrier | 1147/9188 | 11.3 | 354/9265 | 3.4 | 118/10150 | 1.0 |
| non expanded | 47/302 | 14.9 | 20/307 | 6.1 | 6/357 | 1.6 |
| expanded | 46/145 | 35.3 | 17/146 | 12 | 6/171 | 3.6 |
| Former smoker | | | | | | |
| non carrier | 404/2456 | 15.4 | 131/2476 | 4.8 | 74/2753 | 2.4 |
| non expanded | 21/95 | 22.3 | 6/96 | 6 | 4/107 | 3.5 |
| expanded | 14/65 | 22.0 | 7/65 | 10.6 | 1/71 | 1.3 |
| Current smoker | | | | | | |
| non carrier | 3818/23863 | 14.8 | 1655/24001 | 6.2 | 734/27360 | 2.4 |
| non expanded | 186/952 | 19.5 | 88/963 | 8.9 | 49/1158 | 4.1 |
| expanded | 165/455 | 41.6 | 80/460 | 18.7 | 45/578 | 8.2 |

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; UKB, UK biobank; CKB, China Kadoorie biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

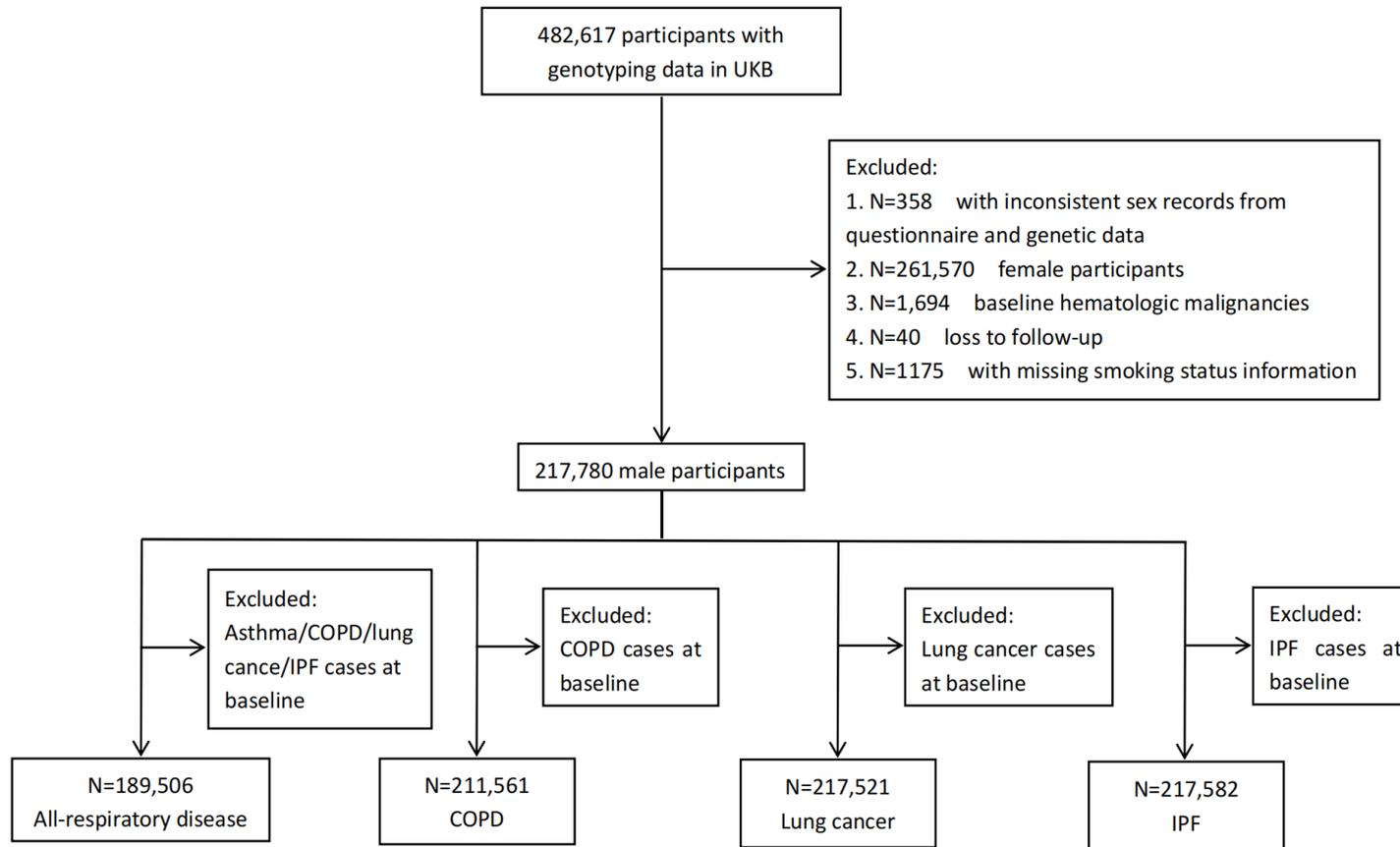


Figure S1 Flow chart of the study in UKB

UKB, UK Biobank; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

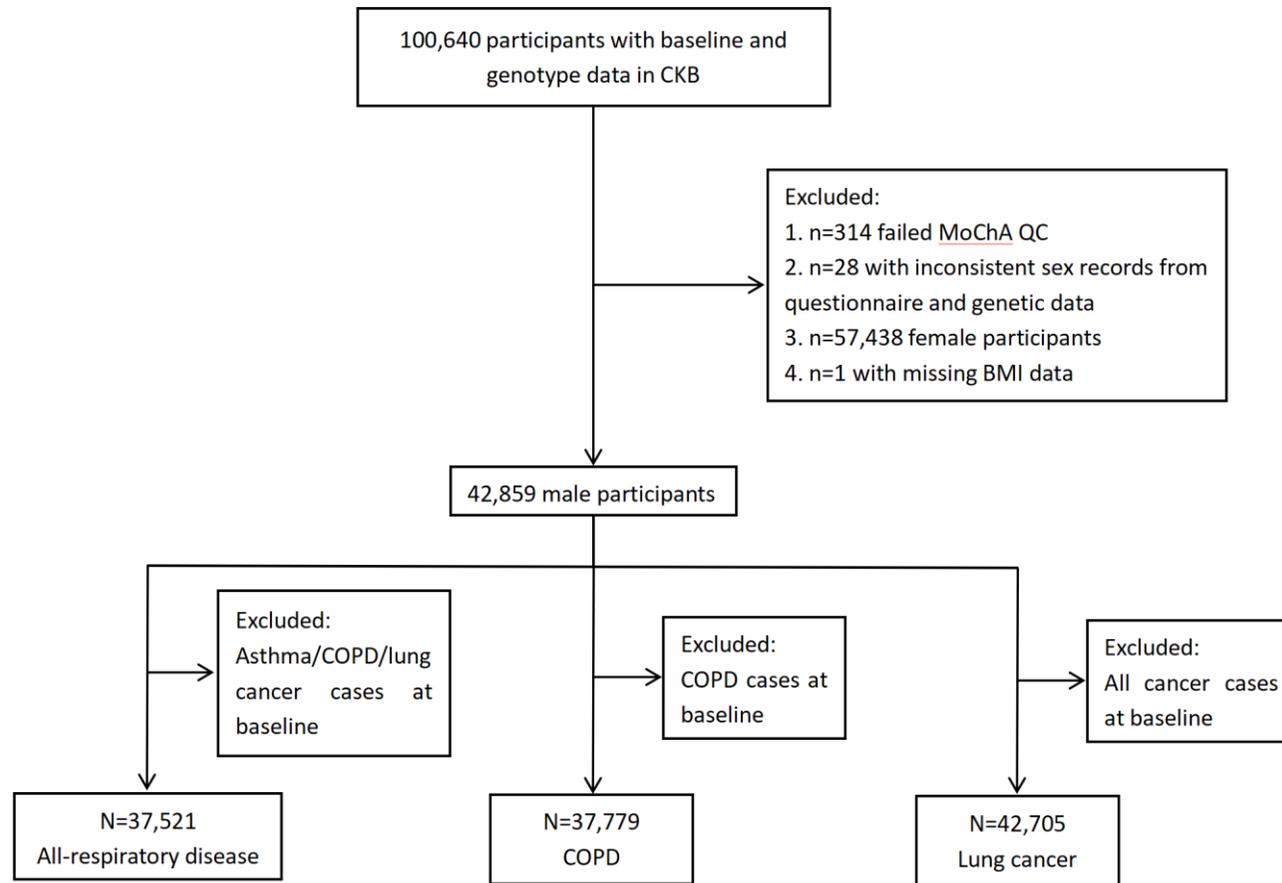


Figure S2 Flow chart of the study in CKB

CKB, China Kadoorie Biobank; MoChA, mosaic Chromosomal Alterations; QC, quality control; BMI, body mass index; COPD, chronic obstructive pulmonary disease

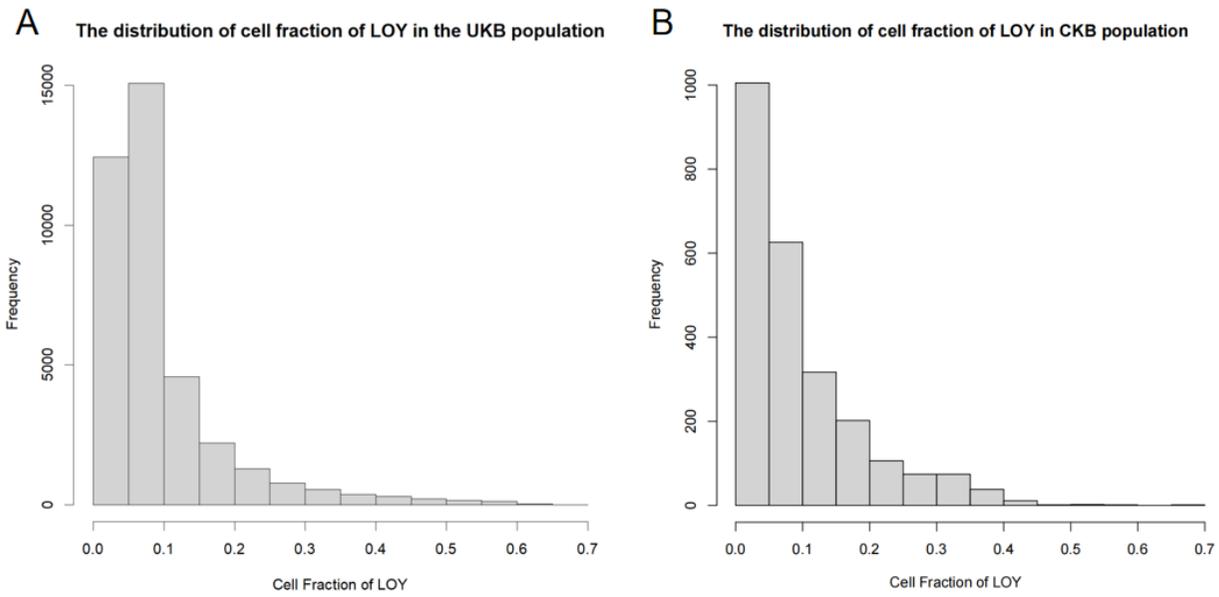


Figure S3 The distribution of cell fraction of mLOY in the UKB and CKB cohorts
 LOY, mosaic loss of chromosome Y; UKB, UK Biobank; CKB, China Kadoorie Biobank

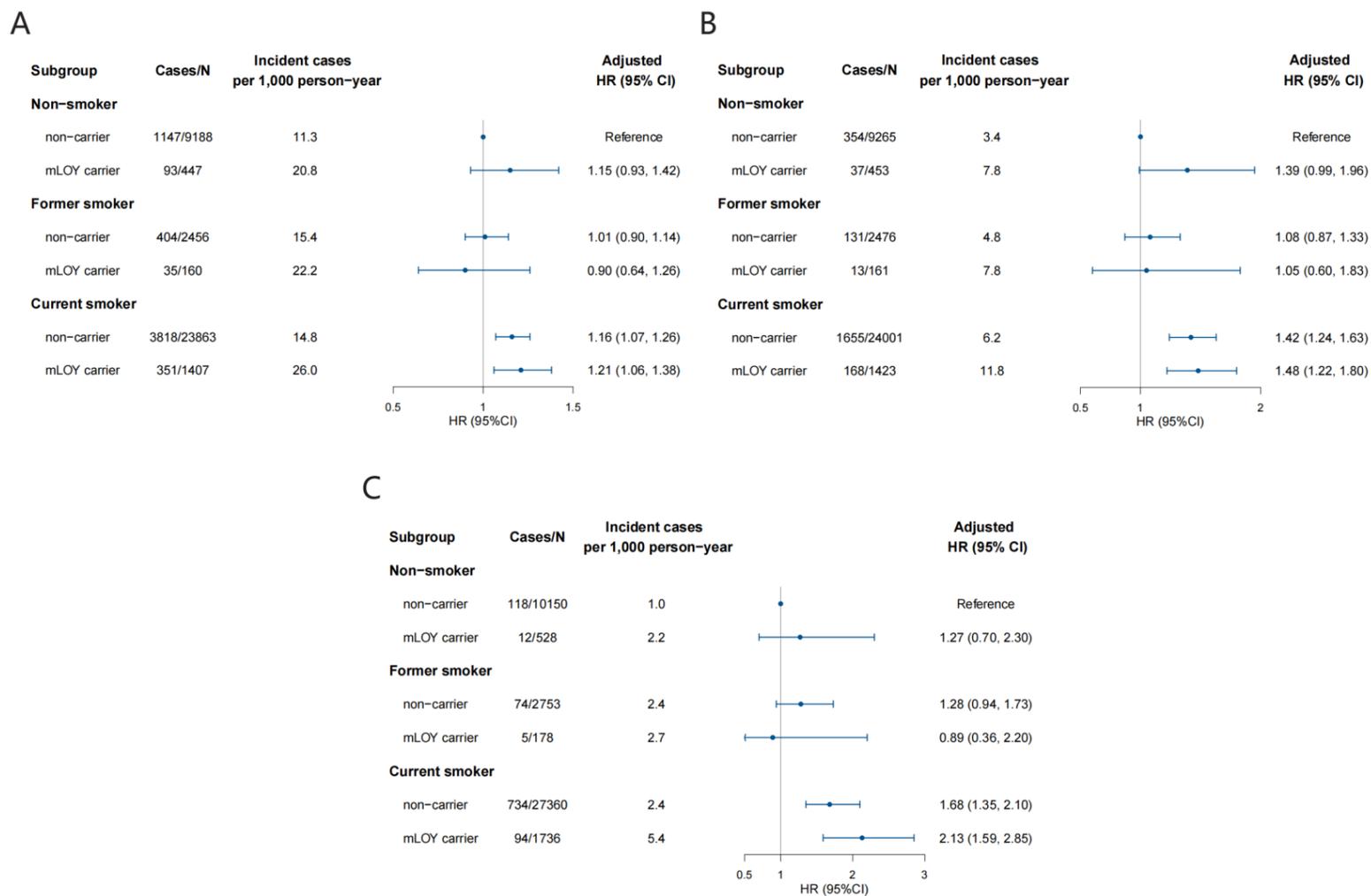


Figure S4 Joint association of mLOY and smoking status with the risk of lung diseases in CKB

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease

A) all lung diseases; B) chronic obstructive pulmonary disease; C) lung cancer

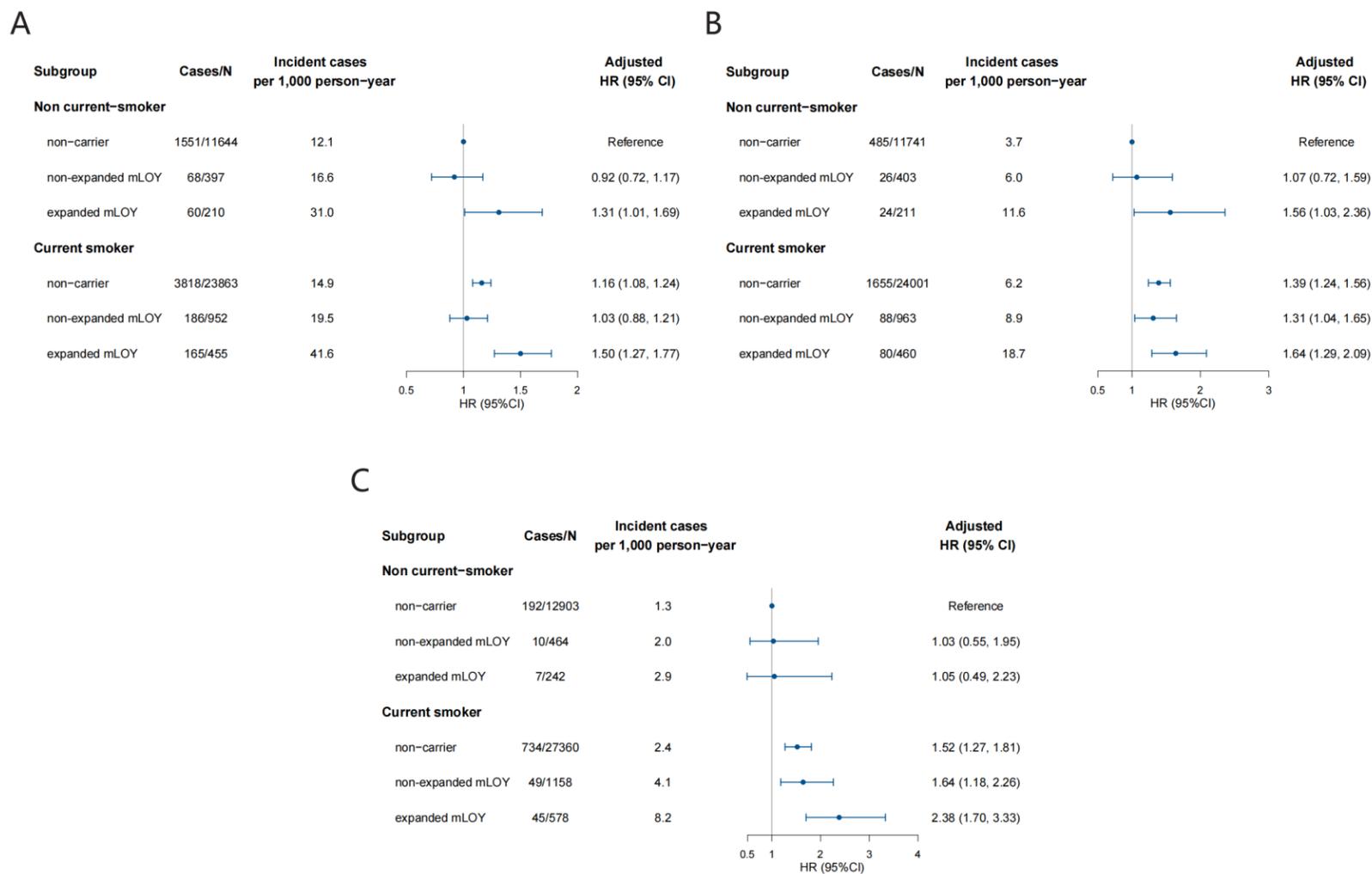


Figure S5 Joint association of mLOY subtypes and smoking status with the risk of lung diseases in CKB

mLOY, mosaic loss of chromosome Y; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease

A) all lung diseases; B) chronic obstructive pulmonary disease; C) lung cancer