

## Supplementary Materials for

### **Mendelian randomization supports bidirectional causality between telomere length and clonal hematopoiesis of indeterminate potential**

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## Supplementary Text

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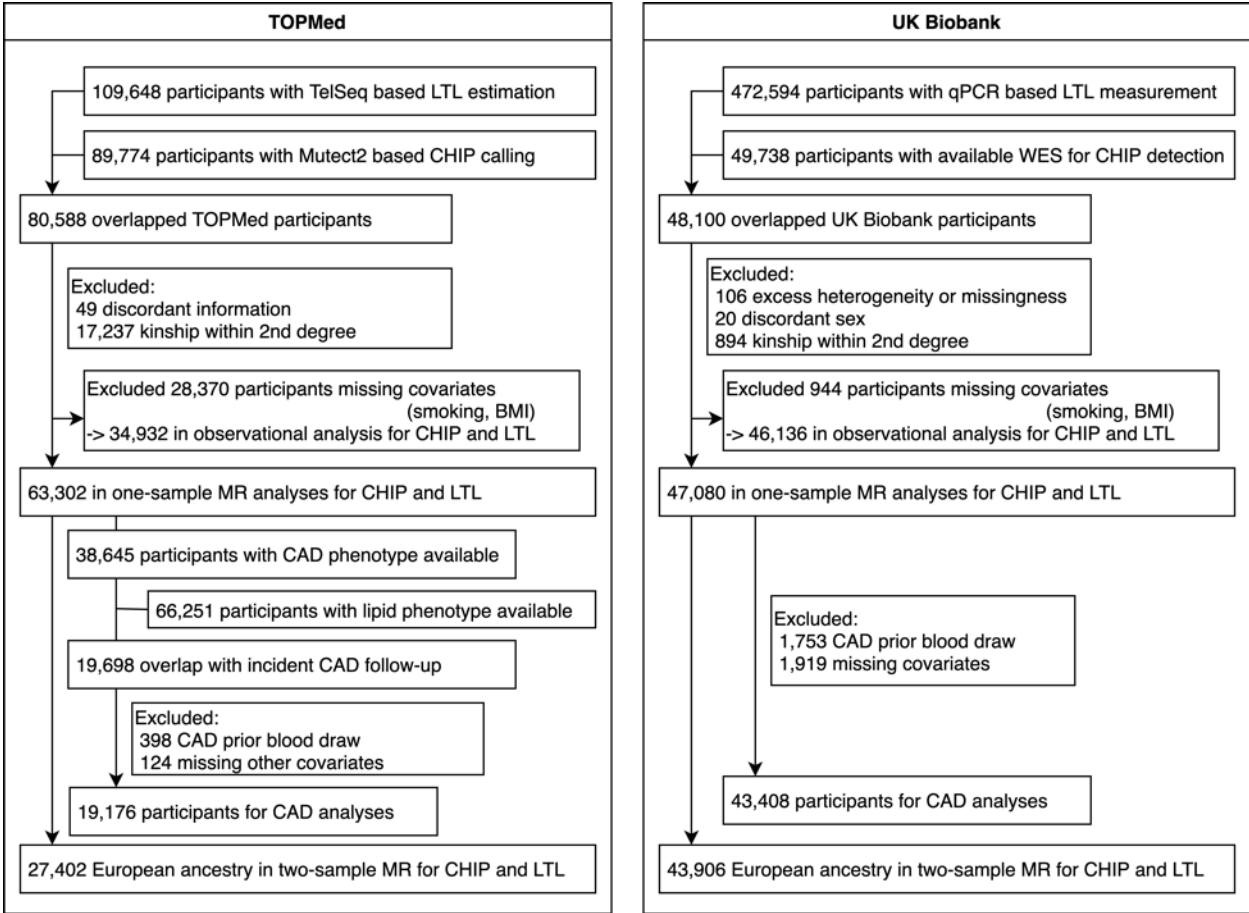
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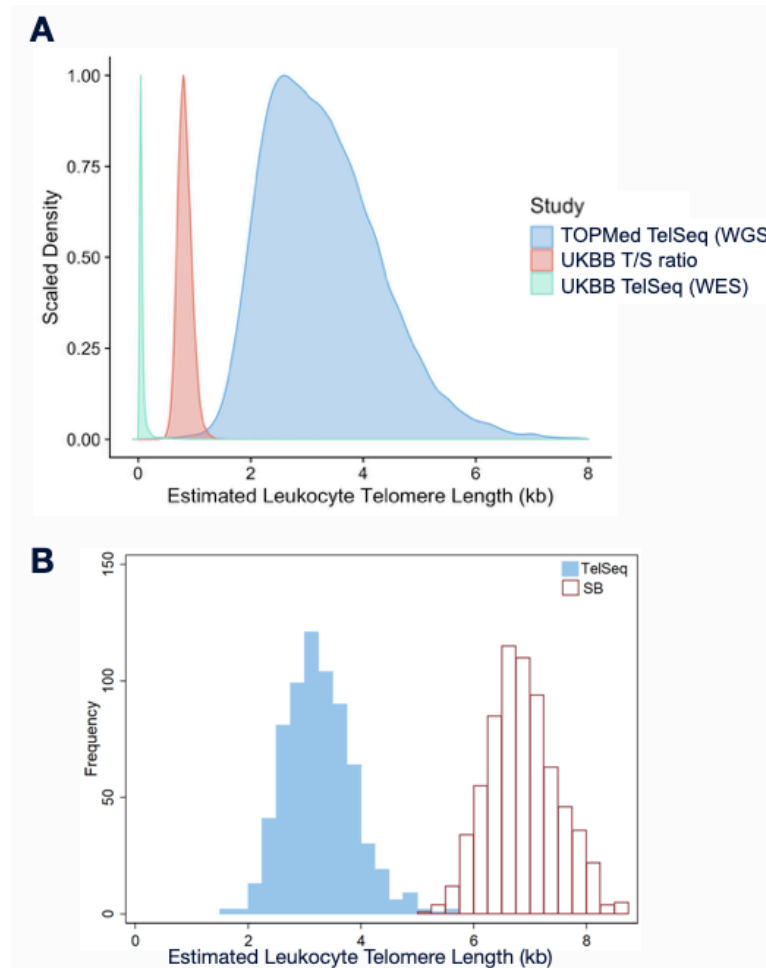
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**Fig. S1. Generation of the study population.**



The flow chart for generating the study population used for observational and Mendelian randomization studies in TOPMed and UK Biobank. CAD: coronary artery disease, CHIP: Clonal hematopoiesis of indeterminate potential, LTL: Leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine, WES: Whole-exome sequencing.

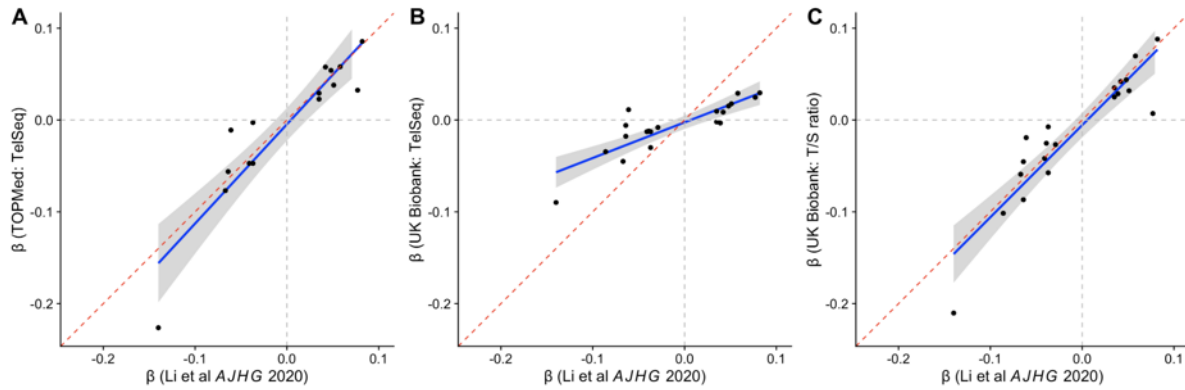
**Fig. S2. Comparison of the measurements for leukocyte telomere length.**



**A** Telomere length estimated by TelSeq (31) using whole-genome sequence (WGS) data in TOPMed ( $n = 63,302$ ) and UK Biobank ( $n = 48,658$ ) using whole-exome sequencing (WES), and T/S ratio in UK Biobank ( $n = 472,594$ ). **B** Estimated LTL by TelSeq using WGS is shorter than the measurement by southern blot when directly compared in the same individuals in a subset of WHI cohort ( $n = 686$ ). kb: kilo base, LTL: Leukocyte telomere length, SB: Southern blot, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, WHI: Women's Health Initiative.



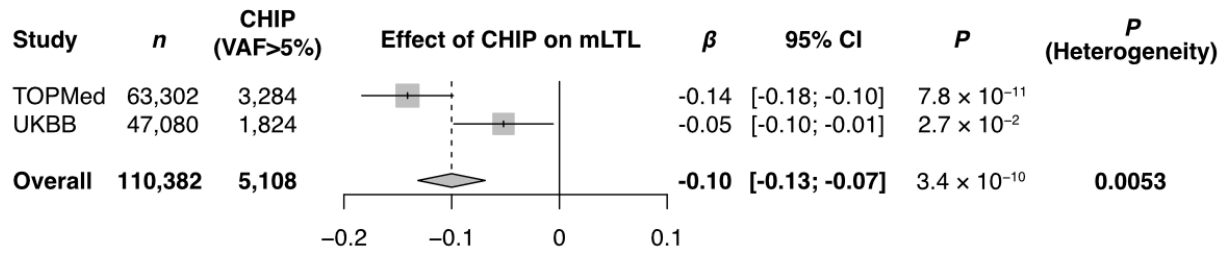
**Fig. S3. SNPs' effect sizes for associations with mLTL strongly correlated with the previous report across estimation methods.**



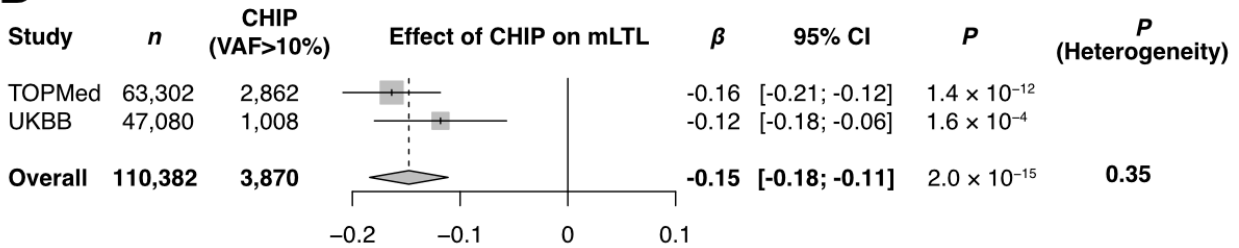
Correlation of estimates in the effect of variants for mLTL between our data from TOPMed and UK Biobank, and previous report (11). Effect sizes for minor alleles were calculated in subsets of European ancestry population in both TOPMed ( $n = 27,402$ ) and UK Biobank ( $n = 43,906$ ) with adjustment by age, sex, first 11 genetic principal components, sequencing center or batch, and study in TOPMed. Red dotted lines represent equality between both data ( $x=y$ ). AJHG: The American Journal of Human Genetics, mLTL: Measured leukocyte telomere length, SNP: Single nucleotide polymorphism, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank.

**Fig. S4. Longer mLTL is associated with reduced CHIP prevalence.**

**A**

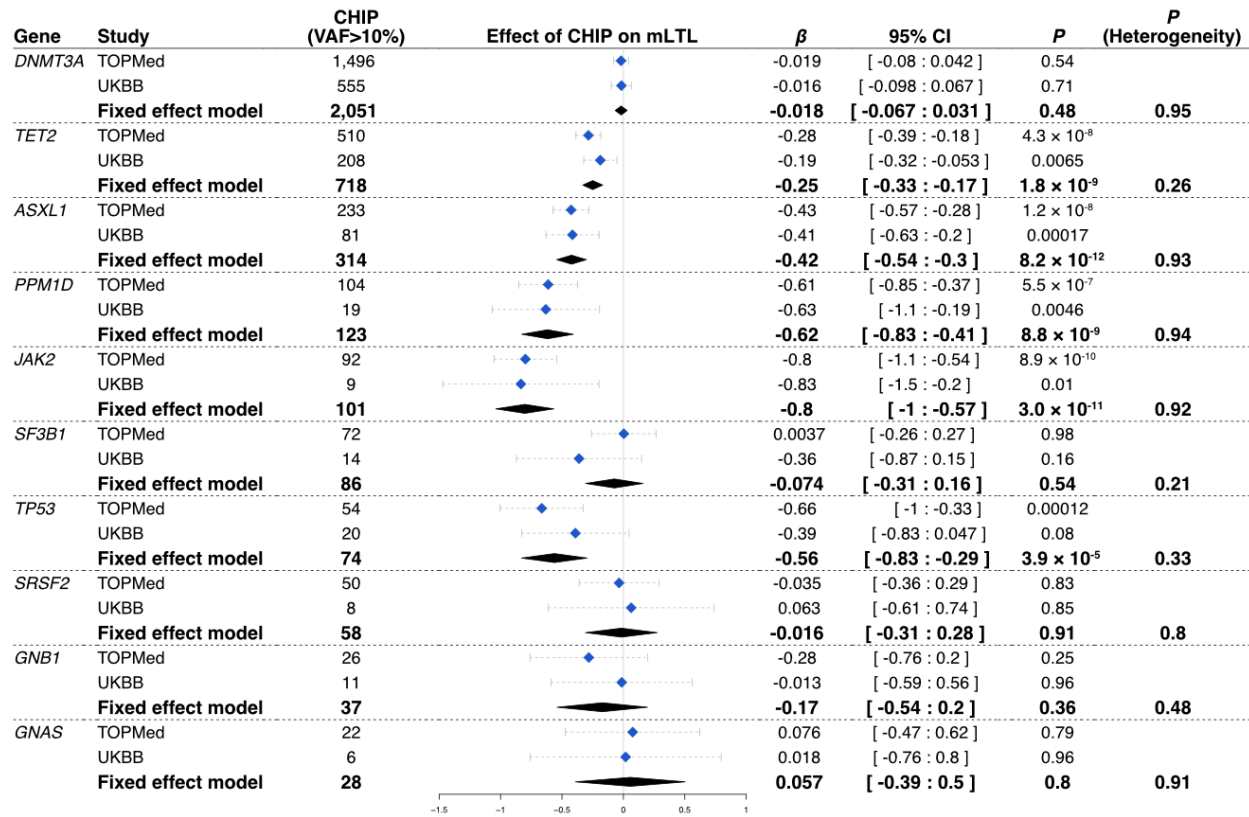


**B**



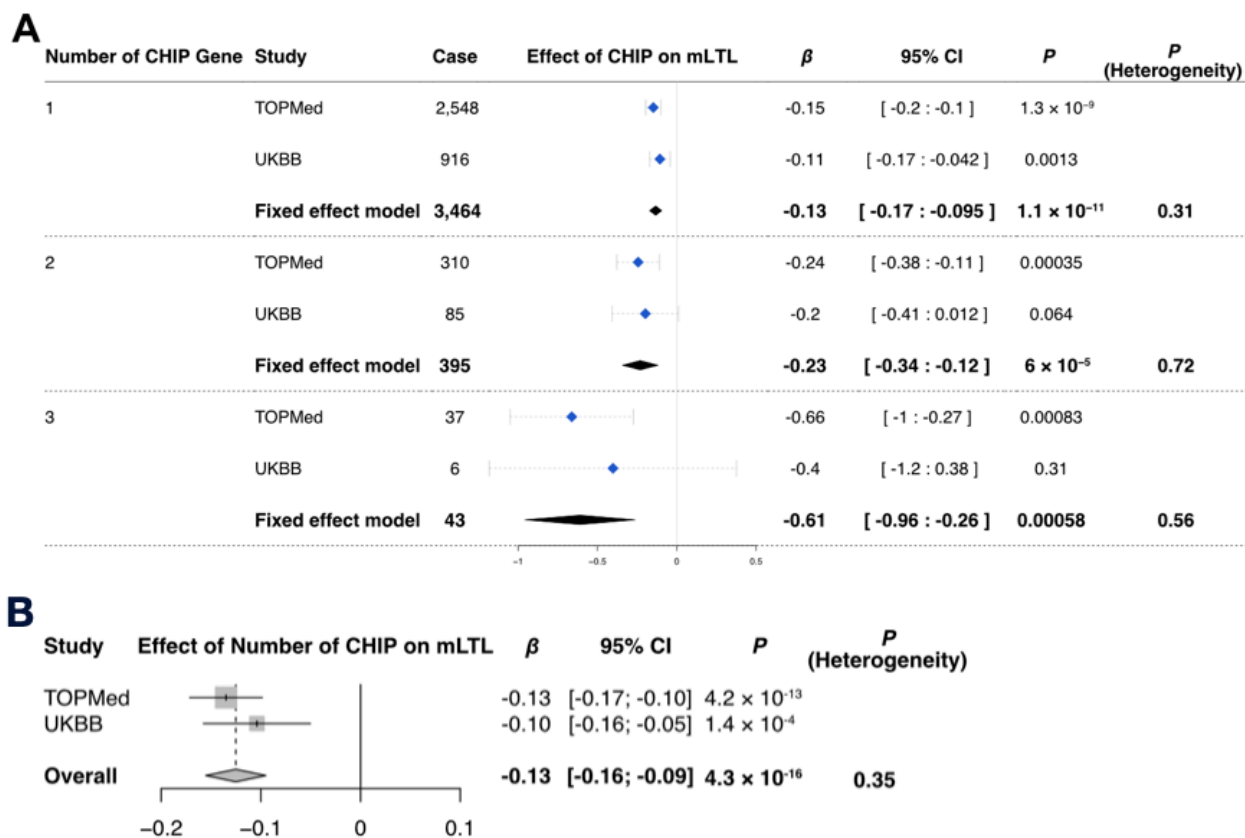
**A,B** For the outcomes **A** any CHIP (VAF > 5%) and **B** CHIP with VAF > 10%, the associations with LTL were assessed by linear regression model both in TOPMed and UK Biobank, then meta-analyzed. Both models were adjusted with age, sex, ever smoking, body mass index, first 11 principal components, sequencing center or batch, and study in TOPMed. CHIP: Clonal hematopoiesis of indeterminate potential, CI: Confidence interval, mLTL: Measured leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, VAF: Variant allele frequency.

**Fig. S5. Effect of CHIP (VAF>10%) on mLTL per CHIP gene (most frequently mutated 10 genes).**



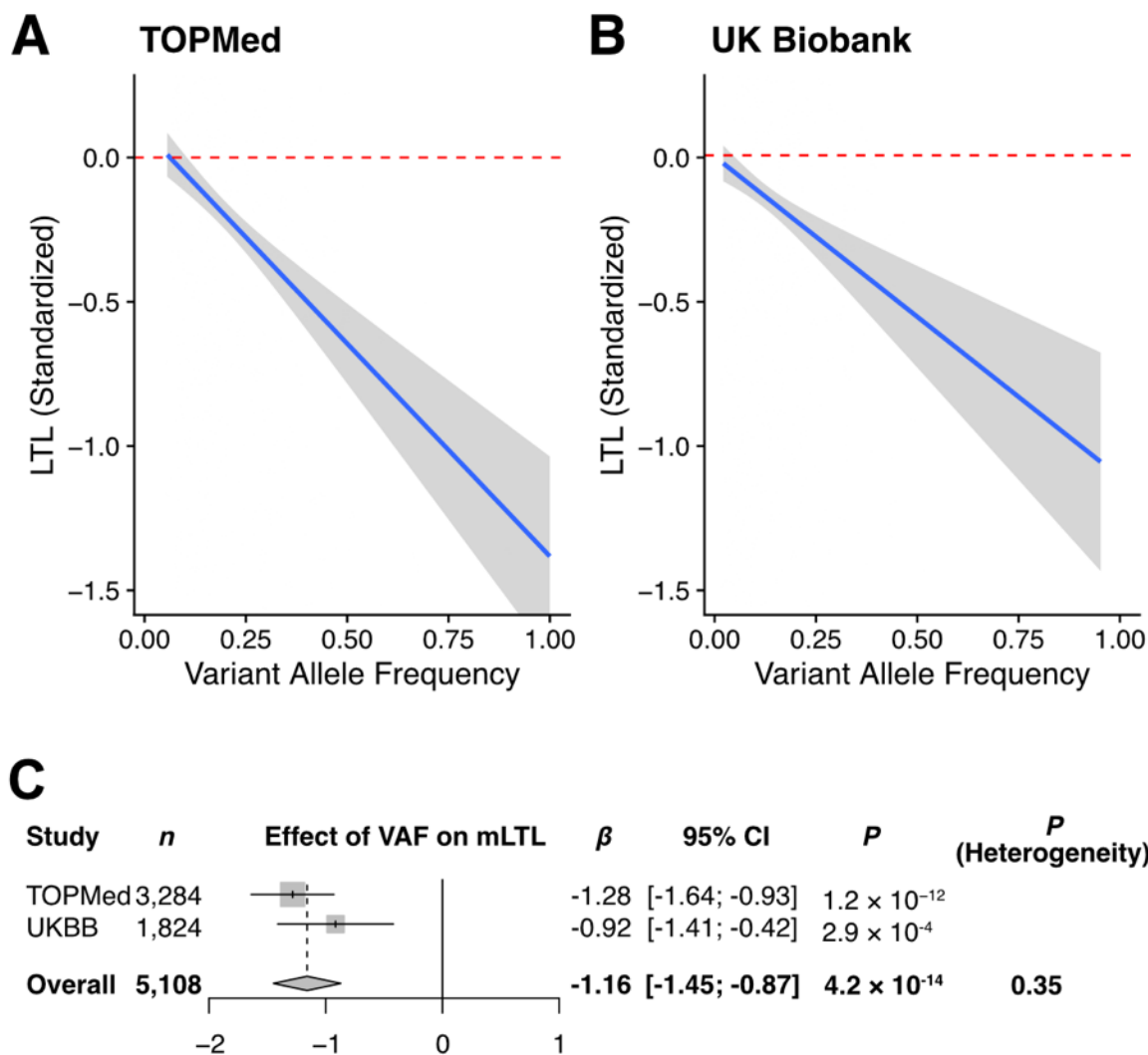
Effect estimate of large clone size CHIP (VAF > 10 %) on mLTL was assessed in each CHIP gene. Linear regression model was adjusted with age, sex, smoking, body mass index, first 11 genetic principal components, sequencing center or batch, and study in TOPMed and meta-analyzed using fixed effect model. The 10 most frequently mutated genes are displayed. Data for the other CHIP genes is reported in Table S2. CHIP: Clonal hematopoiesis of indeterminate potential, CI: Confidence interval, mLTL: Measured leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, VAF: Variant allele frequency.

**Fig. S6. Association of CHIP with mLTL per number of genes affected by CHIP mutations.**



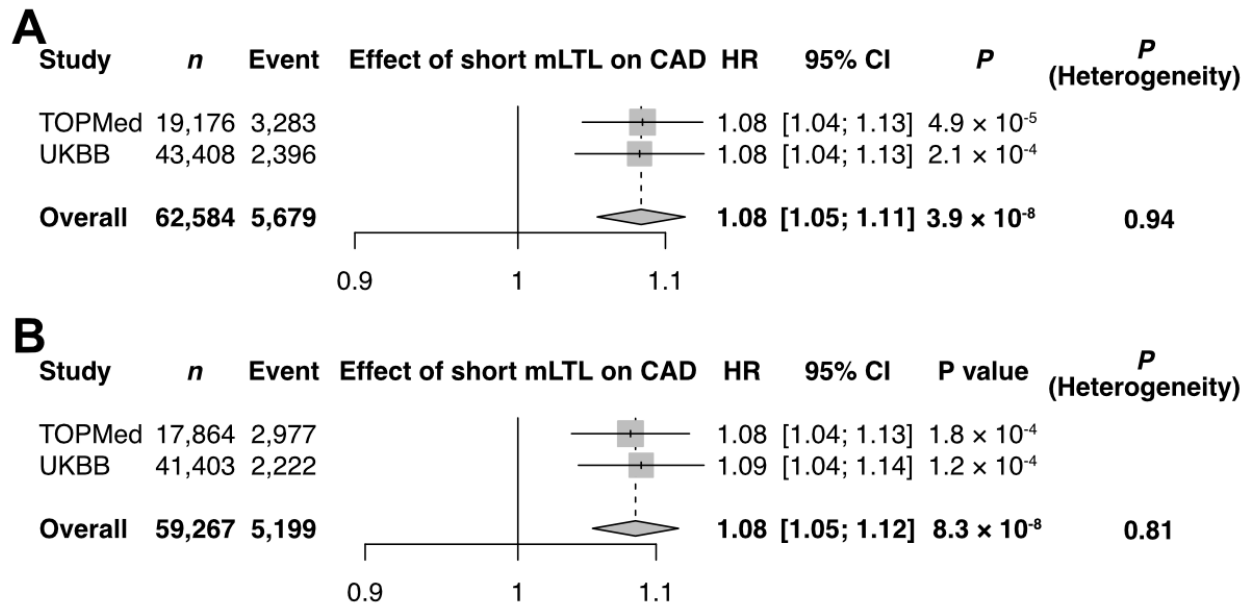
**A** The effect of CHIP on LTL was assessed by the number of CHIP related mutations. Linear regression model was adjusted with age, sex, smoking, body mass index, first 11 genetic principal components, sequencing center or batch, and study in TOPMed in both cohorts and meta-analyzed using fixed effect model. **B** The effect of the number of CHIP related mutations on LTL. CHIP: Clonal hematopoiesis of indeterminate potential, CI: Confidence interval, mLTL: Measured leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, VAF: Variant allele frequency.

**Fig. S7. VAF of CHIP is inversely correlated with mLTL in both TOPMed and UK Biobank.**



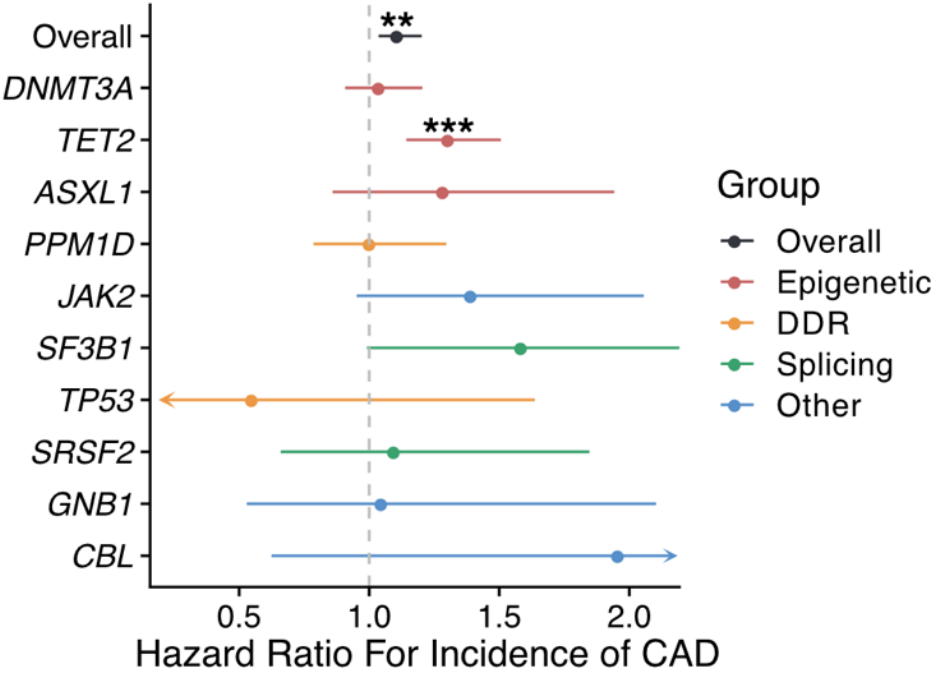
The association of VAF of CHIP with LTL was assessed by linear regression model both in **A** TOPMed and **B** UK Biobank, then **C** meta-analyzed. Linear regression models were adjusted with age, sex, ever smoking, body mass index, first 11 principal components, sequencing center or batch, and study in TOPMed. CHIP with VAF > 5% was included in the meta-analysis (**C**). CHIP: Clonal hematopoiesis of indeterminate potential, CI: Confidence interval, mLTL: Measured leukocyte telomere length, PC: principal component, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, VAF: Variant allele frequency.

**Fig. S8. Effect of shorter mLTL on CAD.**



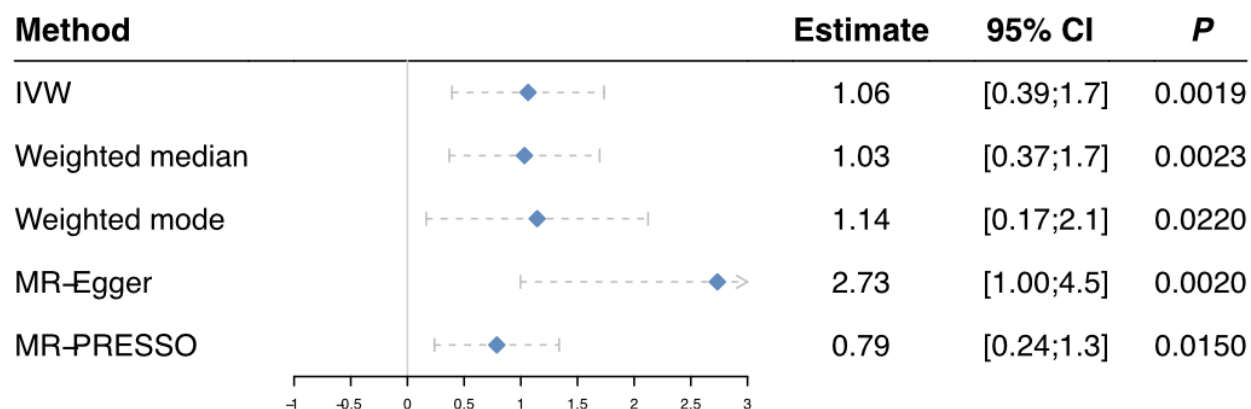
The effect of shorter mLTL on CAD incidence was assessed in Cox Proportional Hazard model in both cohorts for all participants (**A**) and for those without CHIP (**B**). The model was adjusted by age, sex, ever smoking, hypercholesterolemia, body mass index, sequencing center or batch, and first 11 genetic principal components, and study in TOPMed. Effects were combined using fixed effects meta-analysis. CAD: Coronary artery disease, CI: Confidence interval, HR: Hazard ratio, mLTL: Measured leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank.

**Fig. S9. Effect of overall and each CHIP gene on CAD.**



Effect of each CHIP gene on CAD. Cox proportional hazard model was fitted with adjustment for age, age squared, sex, ever smoking, total cholesterol, body mass index, principal components 1 to 11, sequencing center or batch, and TOPMed study (if applicable) in TOPMed and UK Biobank, and meta analyzed. \*\*:  $P < 0.01$ , \*\*\*:  $P < 0.001$ . CAD: coronary artery disease, CHIP: clonal hematopoiesis of indeterminate potential.

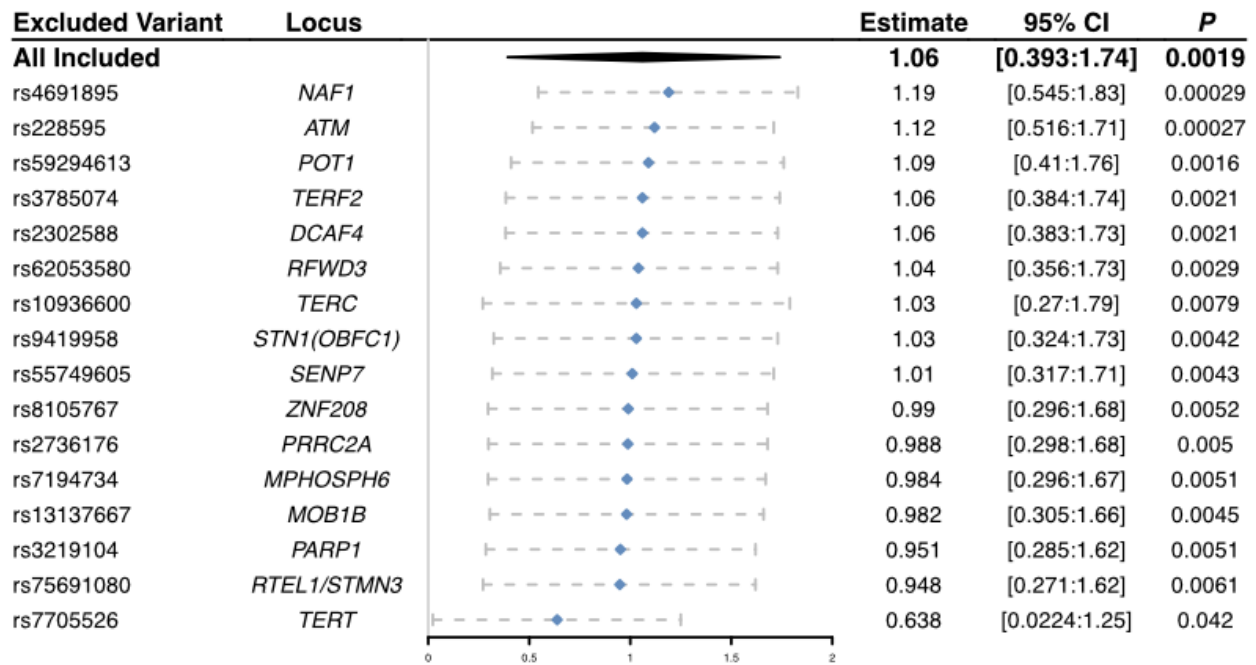
**Fig. S10. Two-sample Mendelian randomization studies for LTL on CHIP.**



Two-sample Mendelian randomization study for LTL on CHIP was performed to infer the causal effect of LTL on CHIP. IVs were derived from previous report (11) in all analyses for LTL on CHIP and clumped as 10 Mb apart and in linkage disequilibrium ( $R^2 > 0.001$  calculated in European ancestry from 1000 Genome project) resulting in 16 IVs. We used previous GWAS summary statistics for LTL (11) for the exposure and white British subset of UK Biobank for the outcome. In addition to the conventional inverse-variance weighted (IVW) method, weighted median, weighted mode, MR-Egger, and MR-PRESSO were performed as sensitivity analyses. MR-PRESSO excluded *TERT* and *ATM* loci variants as outliers. Used IVs are reported in Tables S7. CHIP: Clonal hematopoiesis of indeterminate potential, CI: Confidence interval, IV: Instrumental variable, LTL: Leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank.

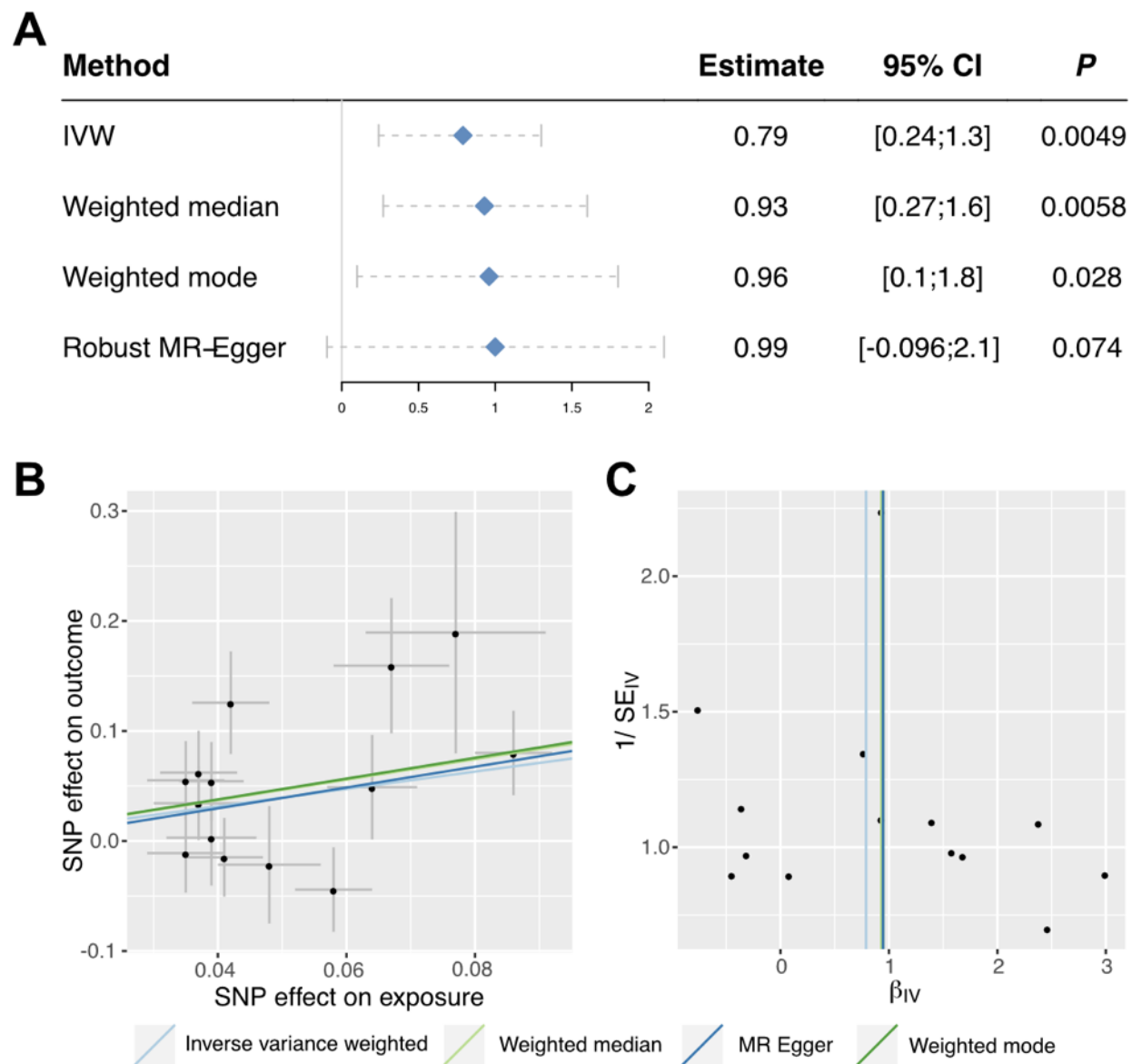


**Fig. S11. Leave-one-out analysis in two-sample MR of LTL on CHIP.**



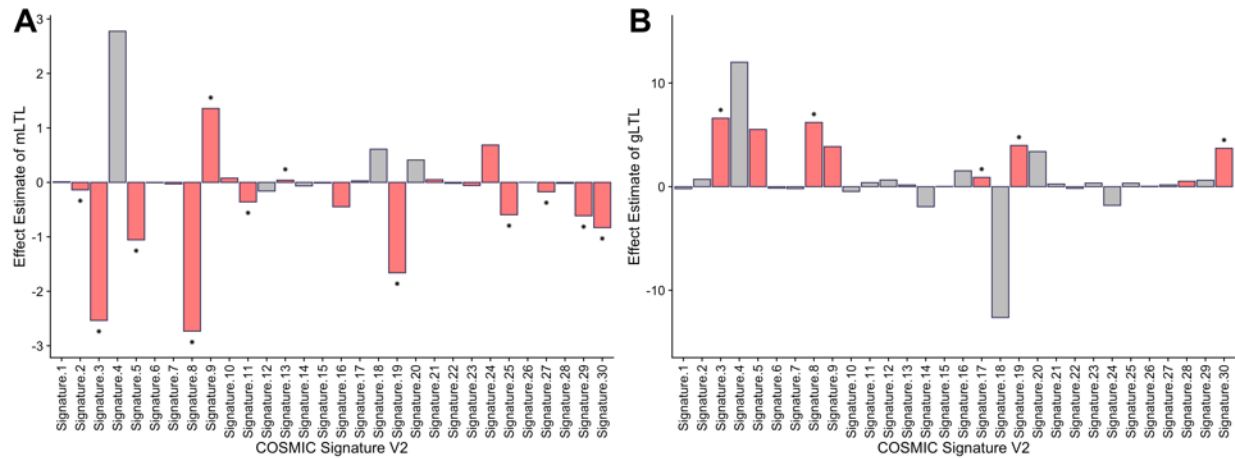
Leave-one-out analysis was performed by simple inverse variance weighted method. CHIP: Clonal hematopoiesis of indeterminate potential, LTL: Leukocyte telomere length, MR: Mendelian randomization.

Fig. S12. Two-sample MR using 14 IVs excluding *TERT* and *ATM* loci.



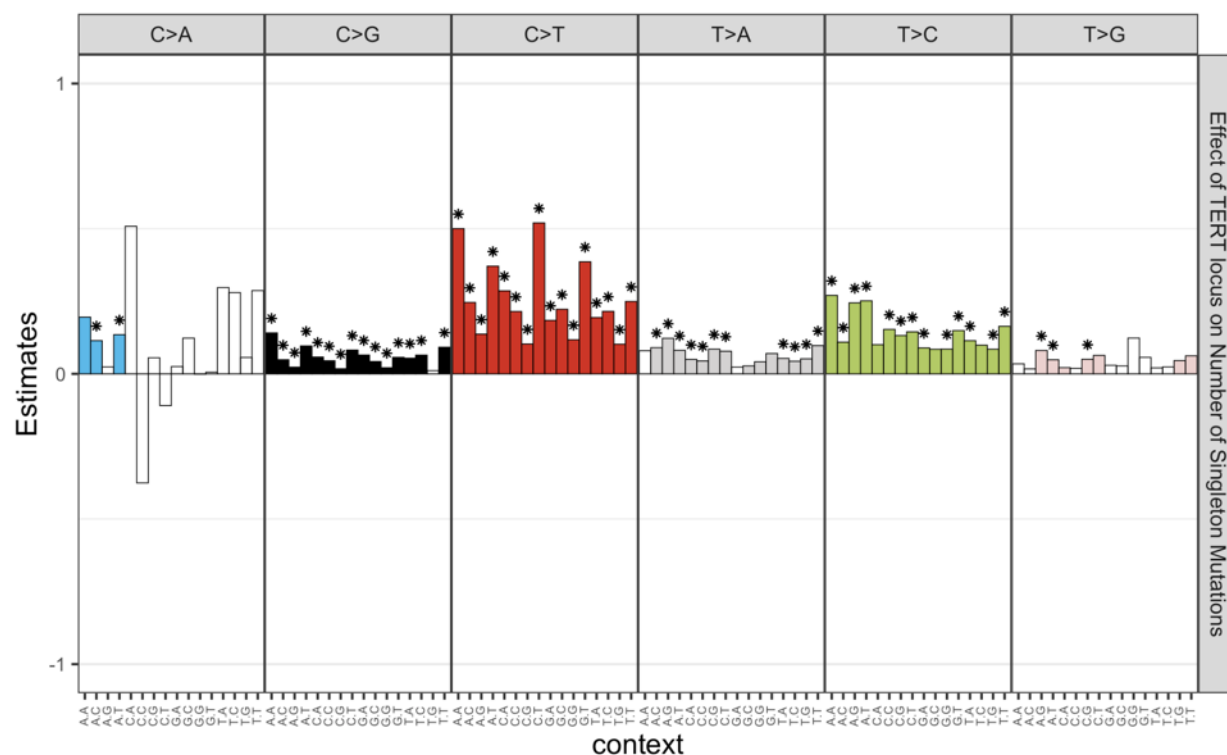
Two-sample MR was performed using 14 IVs excluding outliers detected by MR-PRESSO. **A** Estimates from various methods using distinct assumptions. **B** Scatter plot and **C** Funnel plot for each IVs are displayed. IV: Instrumental variables, IVW: Inverse variance weighted, MR: Mendelian randomization

**Fig. S13. Effect of mLTL and gLTL for COSMIC mutational signatures.**



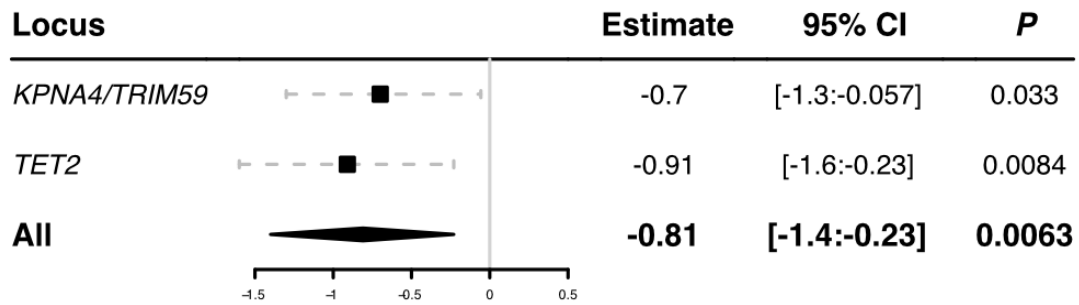
Effect estimates of **A** mLTL and **B** gLTL on COSMIC mutational signature version 2 ([https://cancer.sanger.ac.uk/cosmic/signatures\\_v2](https://cancer.sanger.ac.uk/cosmic/signatures_v2)) in TOPMed. *MutationalPattern* package in R was used to calculate the absolute contribution of each signature in each sample. The association with mLTL and gLTL were assessed by linear models with adjustment by age, age squared, sex, sequencing center or batch, and TOPMed study. Effect estimate of gLTL was calculated by one-sample MR using two-stage least-square method with outlier-excluded 14 IVs. The same adjustment was implemented with observational model. Effect estimates with  $P < 0.05$  are colored. \* denotes  $FDR < 0.05$ . mLTL: Measured leukocyte telomere length, gLTL: Genetically imputed leukocyte telomere length, MR: Mendelian randomization, TOPMed: Trans-Omics for Precision Medicine.

**Fig. S14. Effect of *TERT* locus for mutational occurrence and signature.**



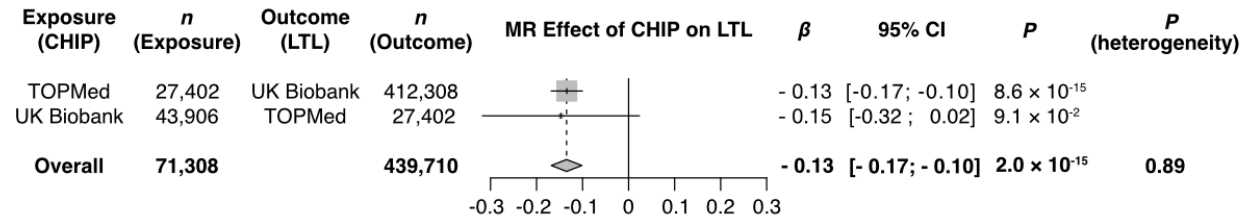
Effect estimates of *TERT* variant (rs7705526) on singleton mutation occurrence. The vcf files were generated by Mutect2 from 56,266 CRAM files in TOPMed with appropriate filters and single base substitutions were extracted, stratified by trinucleotide context. IVs were selected as one-sample Mendelian randomization for LTL (Figure 3) with outlier exclusion. Effect estimates with  $P < 0.05$  are colored. \* denotes surviving from Bonferroni's correction. LTL: Leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine.

**Fig. S15. Single instrumental variable tests of one-sample Mendelian randomization for CHIP on LTL in TOPMed.**



One-sample Mendelian randomization for CHIP on LTL using each variant separately in TOPMed. CHIP: Clonal hematopoiesis of indeterminate potential, CI: Confidence interval, LTL: Leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine.

**Fig. S16. Two-sample Mendelian randomization for CHIP on LTL.**



Two-sample Mendelian randomization with rs58322641 for European subsets of TOPMed and UK Biobank indicated an inverse causal effect of CHIP on LTL. CHIP: Clonal hematopoiesis of indeterminate potential, LTL: Leukocyte telomere length, TOPMed: Trans-Omics for Precision Medicine.

**Table S1. Baseline characteristics**

|                               | TOPMed ( <i>n</i> = 63,302)     |                                   |                                     |          | UK Biobank ( <i>n</i> = 47,080) |                                     |                                     |          |
|-------------------------------|---------------------------------|-----------------------------------|-------------------------------------|----------|---------------------------------|-------------------------------------|-------------------------------------|----------|
|                               | No CHIP<br>( <i>n</i> = 60,018) | CHIP VAF<0.1<br>( <i>n</i> = 422) | CHIP VAF≥0.1<br>( <i>n</i> = 2,862) | <i>P</i> | No CHIP<br>( <i>n</i> = 44,874) | CHIP VAF<0.1<br>( <i>n</i> = 1,198) | CHIP VAF≥0.1<br>( <i>n</i> = 1,008) | <i>P</i> |
| Age at blood draw (mean (SD)) | 53.65 (18.12)                   | 66.50 (11.03)                     | 67.68 (10.64)                       | <0.001   | 56.35 (8.01)                    | 60.33 (6.65)                        | 60.83 (6.58)                        | <0.001   |
| Sex (Male, %)                 | 25,581 (42.6)                   | 141 (33.4)                        | 1,073 (37.5)                        | <0.001   | 20,412 (45.5)                   | 532 (44.4)                          | 488 (48.4)                          | 0.134    |
| Race (%)                      |                                 |                                   |                                     | <0.001   |                                 |                                     |                                     | 0.004    |
| European                      | 29,171 (64.6)                   | 269 (73.7)                        | 1,854 (75.6)                        |          | 41,806 (93.2)                   | 1,133 (94.6)                        | 968 (96.0)                          |          |
| African                       | 12,006 (26.6)                   | 76 (20.8)                         | 490 (20.0)                          |          | 927 (2.1)                       | 19 (1.6)                            | 15 (1.5)                            |          |
| Asian                         | 2,665 (5.9)                     | 14 (3.8)                          | 69 (2.8)                            |          | 990 (2.2)                       | 16 (1.3)                            | 10 (1.0)                            |          |
| Other                         | 1,347 (3.0)                     | 6 (1.6)                           | 40 (1.6)                            |          | 1,151 (2.6)                     | 30 (2.5)                            | 15 (1.5)                            |          |
| Smoking (%)                   |                                 |                                   |                                     | <0.001   |                                 |                                     |                                     | <0.001   |
| Never                         | 11,745 (19.6)                   | 113 (26.8)                        | 749 (26.2)                          |          | 24,988 (55.9)                   | 604 (50.8)                          | 470 (46.8)                          |          |
| Previous                      | 40,089 (66.8)                   | 257 (60.9)                        | 1,738 (60.7)                        |          | 15,724 (35.2)                   | 467 (39.2)                          | 425 (42.3)                          |          |
| Current                       | 8,184 (13.6)                    | 52 (12.3)                         | 375 (13.1)                          |          | 4,019 (9.0)                     | 119 (10.0)                          | 110 (10.9)                          |          |
| BMI, kg/m2 (mean (SD))        | 28.55 (6.01)                    | 28.18 (5.74)                      | 28.24 (5.75)                        | 0.04     | 27.41 (4.80)                    | 27.54 (4.71)                        | 27.73 (4.79)                        | 0.077    |
| mLTL (TelSeq), kb (mean (SD)) |                                 |                                   |                                     | <0.001   |                                 |                                     |                                     | <0.001   |
| Unadjusted                    | 3.28 (1.01)                     | 3.24 (0.98)                       | 3.14 (0.98)                         |          | 0.83 (0.13)                     | 0.82 (0.13)                         | 0.80 (0.12)                         |          |
| Adjusted                      | 0.02 (1.00)                     | -0.18 (0.98)                      | -0.33 (0.97)                        | <0.001   | 0.01 (1.00)                     | -0.06 (1.00)                        | -0.23 (1.00)                        | <0.001   |
| Type 2 Diabetes (%)           | 1,946 (12.7)                    | 22 (18.2)                         | 111 (13.6)                          | 0.154    | 3,327 (7.4)                     | 112 (9.3)                           | 89 (8.8)                            | 0.011    |
| Hypercholesterolemia (%)      | 6,062 (10.1)                    | 74 (17.5)                         | 372 (13.0)                          | <0.001   | 10,502 (23.4)                   | 323 (27.0)                          | 306 (30.4)                          | <0.001   |

BMI: Body mass index, CHIP: Clonal hematopoiesis of indeterminate potential, mLTL: Measured leukocyte telomere length, SD: Standard deviation,

TOPMed: Trans-Omics for Precision Medicine, VAF: Variant allele frequency.

Continuous variables were compared using ANOVA, and categorical variable associations were estimated using the chi-square test. Samples missing each information were excluded.

Table S2. Effect estimates of each CHIP gene with VAF &gt; 10 % on mLTL

| Gene          | Study   | Control | CHIP  | $\beta$ | SE    | P        | P (Heterogeneity) |
|---------------|---------|---------|-------|---------|-------|----------|-------------------|
| <i>DNMT3A</i> | TOPMed  | 60,018  | 1,496 | -0.019  | 0.031 | 0.544    |                   |
|               | UKBB    | 44,874  | 555   | -0.016  | 0.042 | 0.706    |                   |
|               | Overall | 104,892 | 2,051 | -0.018  | 0.025 | 0.477    | 0.95              |
| <i>TET2</i>   | TOPMed  | 60,018  | 510   | -0.285  | 0.052 | 4.33E-08 |                   |
|               | UKBB    | 44,874  | 208   | -0.188  | 0.069 | 6.47E-03 |                   |
|               | Overall | 104,892 | 718   | -0.250  | 0.041 | 1.81E-09 | 0.26              |
| <i>ASXL1</i>  | TOPMed  | 60,018  | 233   | -0.426  | 0.075 | 1.15E-08 |                   |
|               | UKBB    | 44,874  | 81    | -0.415  | 0.110 | 1.69E-04 |                   |
|               | Overall | 104,892 | 314   | -0.422  | 0.062 | 8.18E-12 | 0.93              |
| <i>PPM1D</i>  | TOPMed  | 60,018  | 104   | -0.613  | 0.122 | 5.53E-07 |                   |
|               | UKBB    | 44,874  | 19    | -0.632  | 0.223 | 4.65E-03 |                   |
|               | Overall | 104,892 | 123   | -0.617  | 0.107 | 8.81E-09 | 0.94              |
| <i>JAK2</i>   | TOPMed  | 60,018  | 92    | -0.798  | 0.130 | 8.93E-10 |                   |
|               | UKBB    | 44,874  | 9     | -0.834  | 0.324 | 0.010    |                   |
|               | Overall | 104,892 | 101   | -0.803  | 0.121 | 2.99E-11 | 0.92              |
| <i>SF3B1</i>  | TOPMed  | 60,018  | 72    | 0.004   | 0.135 | 0.978    |                   |
|               | UKBB    | 44,874  | 14    | -0.361  | 0.260 | 0.165    |                   |
|               | Overall | 104,892 | 86    | -0.074  | 0.120 | 0.538    | 0.21              |
| <i>TP53</i>   | TOPMed  | 60,018  | 54    | -0.665  | 0.173 | 1.21E-04 |                   |
|               | UKBB    | 44,874  | 20    | -0.391  | 0.223 | 0.080    |                   |
|               | Overall | 104,892 | 74    | -0.562  | 0.137 | 3.93E-05 | 0.33              |
| <i>SRSF2</i>  | TOPMed  | 60,018  | 50    | -0.035  | 0.166 | 0.833    |                   |
|               | UKBB    | 44,874  | 8     | 0.063   | 0.344 | 0.854    |                   |
|               | Overall | 104,892 | 58    | -0.016  | 0.149 | 0.913    | 0.80              |
| <i>GNB1</i>   | TOPMed  | 60,018  | 26    | -0.281  | 0.244 | 0.250    |                   |
|               | UKBB    | 44,874  | 11    | -0.013  | 0.293 | 0.964    |                   |
|               | Overall | 104,892 | 37    | -0.171  | 0.188 | 0.361    | 0.48              |
| <i>GNAS</i>   | TOPMed  | 60,018  | 22    | 0.076   | 0.279 | 0.787    |                   |
|               | UKBB    | 44,874  | 6     | 0.018   | 0.397 | 0.963    |                   |
|               | Overall | 104,892 | 28    | 0.057   | 0.228 | 0.804    | 0.91              |
| <i>CBL</i>    | TOPMed  | 60,018  | 17    | 0.248   | 0.279 | 0.375    |                   |
|               | UKBB    | 44,874  | 10    | 0.222   | 0.307 | 0.470    |                   |
|               | Overall | 104,892 | 27    | 0.236   | 0.207 | 0.253    | 0.95              |
| <i>BRCC3</i>  | TOPMed  | 60,018  | 16    | -0.128  | 0.260 | 0.621    |                   |
|               | UKBB    | 44,874  | 4     | -1.223  | 0.562 | 0.029    |                   |
|               | Overall | 104,892 | 20    | -0.322  | 0.236 | 0.173    | 0.08              |
| <i>NFI</i>    | TOPMed  | 60,018  | 13    | -0.807  | 0.411 | 0.050    |                   |
|               | UKBB    | 44,874  | 7     | 0.131   | 0.367 | 0.720    |                   |
|               | Overall | 104,892 | 20    | -0.285  | 0.274 | 0.297    | 0.09              |
| <i>PRPF8</i>  | TOPMed  | 60,018  | 15    | 0.046   | 0.381 | 0.905    |                   |
|               | UKBB    | 44,874  | 2     | 0.079   | 0.687 | 0.909    |                   |
|               | Overall | 104,892 | 17    | 0.053   | 0.333 | 0.873    | 0.97              |
| <i>KRAS</i>   | TOPMed  | 60,018  | 11    | 0.238   | 0.381 | 0.532    |                   |
|               | UKBB    | 44,874  | 4     | -0.615  | 0.486 | 0.206    |                   |
|               | Overall | 104,892 | 15    | -0.086  | 0.300 | 0.774    | 0.17              |
| <i>ASXL2</i>  | TOPMed  | 60,018  | 8     | -0.585  | 0.450 | 0.194    |                   |
|               | UKBB    | 44,874  | 4     | 0.721   | 0.486 | 0.138    |                   |
|               | Overall | 104,892 | 12    | 0.018   | 0.330 | 0.957    | 0.05              |
| <i>CUX1</i>   | TOPMed  | 60,018  | 6     | -0.281  | 0.712 | 0.693    |                   |
|               | UKBB    | 44,874  | 3     | -0.166  | 0.561 | 0.768    |                   |
|               | Overall | 104,892 | 9     | -0.210  | 0.441 | 0.634    | 0.90              |
| <i>IDH2</i>   | TOPMed  | 60,018  | 6     | -0.159  | 0.450 | 0.724    |                   |
|               | UKBB    | 44,874  | 3     | 0.455   | 0.561 | 0.417    |                   |
|               | Overall | 104,892 | 9     | 0.082   | 0.351 | 0.816    | 0.39              |
| <i>SETD2</i>  | TOPMed  | 60,018  | 5     | -0.341  | 1.007 | 0.735    |                   |
|               | UKBB    | 44,874  | 4     | 0.207   | 0.486 | 0.670    |                   |
|               | Overall | 104,892 | 9     | 0.104   | 0.438 | 0.813    | 0.62              |
| <i>BCORL1</i> | TOPMed  | 60,018  | 7     | -0.521  | 0.381 | 0.171    |                   |
|               | UKBB    | 44,874  | 1     | -0.190  | 0.972 | 0.845    |                   |
|               | Overall | 104,892 | 8     | -0.477  | 0.354 | 0.179    | 0.75              |
| <i>BCOR</i>   | TOPMed  | 60,018  | 6     | 0.095   | 0.581 | 0.870    |                   |
|               | UKBB    | 44,874  | 1     | -0.182  | 0.972 | 0.851    |                   |
|               | Overall | 104,892 | 7     | 0.022   | 0.499 | 0.964    | 0.81              |
| <i>ETNK1</i>  | TOPMed  | 60,018  | 5     | 0.136   | 0.503 | 0.786    |                   |
|               | UKBB    | 44,874  | 2     | -0.253  | 0.687 | 0.713    |                   |
|               | Overall | 104,892 | 7     | 0.000   | 0.406 | 0.999    | 0.65              |
| <i>ETV6</i>   | TOPMed  | 60,018  | 5     | 0.234   | 0.581 | 0.687    |                   |
|               | UKBB    | 44,874  | 2     | 0.764   | 0.687 | 0.266    |                   |
|               | Overall | 104,892 | 7     | 0.455   | 0.444 | 0.305    | 0.56              |
| <i>RAD21</i>  | TOPMed  | 60,018  | 5     | 0.100   | 0.712 | 0.889    |                   |
|               | UKBB    | 44,874  | 2     | -2.218  | 0.972 | 0.023    |                   |
|               | Overall | 104,892 | 7     | -0.709  | 0.574 | 0.217    | 0.05              |
| <i>KDM6A</i>  | TOPMed  | 60,018  | 4     | -1.204  | 0.581 | 0.038    |                   |
|               | UKBB    | 44,874  | 1     | -1.837  | 0.972 | 0.059    |                   |
|               | Overall | 104,892 | 5     | -1.371  | 0.499 | 0.006    | 0.58              |
| <i>NRAS</i>   | TOPMed  | 60,018  | 3     | 0.397   | 0.712 | 0.578    |                   |
|               | UKBB    | 44,874  | 2     | -0.627  | 0.687 | 0.362    |                   |
|               | Overall | 104,892 | 5     | -0.133  | 0.494 | 0.788    | 0.30              |
| <i>SMC3</i>   | TOPMed  | 60,018  | 2     | -0.946  | 0.712 | 0.184    |                   |
|               | UKBB    | 44,874  | 3     | 1.493   | 0.561 | 0.008    |                   |
|               | Overall | 104,892 | 5     | 0.558   | 0.441 | 0.206    | 0.01              |
| <i>MPL</i>    | TOPMed  | 60,018  | 2     | -2.680  | 1.007 | 0.008    |                   |
|               | UKBB    | 44,874  | 2     | -0.356  | 0.687 | 0.605    |                   |
|               | Overall | 104,892 | 4     | -1.094  | 0.568 | 0.054    | 0.06              |
| <i>EP300</i>  | TOPMed  | 60,018  | 2     | -2.572  | 1.007 | 0.011    |                   |
|               | UKBB    | 44,874  | 1     | -0.587  | 0.972 | 0.546    |                   |
|               | Overall | 104,892 | 3     | -1.545  | 0.699 | 0.027    | 0.16              |
| <i>SUZ12</i>  | TOPMed  | 60,018  | 2     | -0.058  | 0.712 | 0.935    |                   |
|               | UKBB    | 44,874  | 1     | -2.102  | 0.972 | 0.031    |                   |
|               | Overall | 104,892 | 3     | -0.772  | 0.574 | 0.179    | 0.09              |
| <i>BRAF</i>   | TOPMed  | 60,018  | 1     | 1.660   | 1.007 | 0.099    |                   |
|               | UKBB    | 44,874  | 1     | 1.071   | 0.972 | 0.270    |                   |
|               | Overall | 104,892 | 2     | 1.355   | 0.699 | 0.053    | 0.67              |

CHIP: Clonal hematopoiesis of indeterminate potential, mLTL: Measured leukocyte telomere length, SE: Standard error, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, VAF: Variant allele frequency.



**Table S3. Coronary artery disease definition in UK Biobank.**

| <b>Dianosis</b>     | <b>Disease</b>                       | <b>Data Field</b>          | <b>Code</b>  |
|---------------------|--------------------------------------|----------------------------|--|
| Self reported       | Heart attack/Myocardial infarction   | 20002                      | 1075   |
|                     | Coronary angioplasty/bypass grafting | 20004                      | 1070, 1095, 1523   |
| Diagnosed by doctor | Heart attack                         | 6150                       | 1  |
| ICD9                | Myocardial infarction                | 41203, 41205               | 410, 412, 4129   |
|                     | Other ischemic heart disease         | 41203, 41205               | 411, 4119, 4140, 4148, 4149  |
| ICD10               | Myocardial infarction                | 40001, 40002, 41202, 41204 | I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I25.2   |
|                     | Other ischemic heart disease         | 40001, 40002, 41202, 41204 | I24, I24.8, I24.9, I25.1, I25.5, I25.6, I25.8, I25.9   |
| OPCS                | Coronary angioplasty/bypass grafting | 41200, 41210               | K40, K40.1, K40.2, K40.3, K40.4, K40.8, K40.9, K41, K41.1, K41.2, K41.3, K41.4, K41.8, K41.9, K42, K42.1, K42.2, K42.3, K42.4, K42.8, K42.9, K43, K43.1, K43.2, K43.3, K43.4, K43.8, K43.9, K44, K44.1, K44.2, K44.8, K44.9, K45.1, K45.2, K45.3, K45.4, K45.5, K45.6, K45.8, K45.9, K46, K46.1, K46.2, K46.3, K46.4, K46.5, K46.8, K46.9, K49.1, K49.2, K49.3, K49.4, K49.8, K49.9, K50.1, K50.2, K50.4, K75.1, K75.2, K75.3, K75.4, K75.8, K75.9 |

Table S7. Effect estimates of each CHIP gene with VAF > 10 % on mLTL conditioned with previous CAD

| Gene          | Study   | Control | CHIP  | $\beta$ | SE    | P        | P (Heterogeneity) |
|---------------|---------|---------|-------|---------|-------|----------|-------------------|
| <i>DNMT3A</i> | TOPMed  | 19,504  | 669   | 0.005   | 0.037 | 0.888    |                   |
|               | UKBB    | 44,341  | 536   | -0.025  | 0.042 | 0.548    |                   |
|               | Overall | 63,845  | 1,205 | -0.008  | 0.028 | 0.769    | 0.59              |
| <i>TET2</i>   | TOPMed  | 19,504  | 244   | -0.263  | 0.061 | 1.80E-05 |                   |
|               | UKBB    | 44,341  | 199   | -0.197  | 0.069 | 0.004    |                   |
|               | Overall | 63,845  | 443   | -0.234  | 0.046 | 3.20E-07 | 0.48              |
| <i>ASXL1</i>  | TOPMed  | 19,504  | 104   | -0.359  | 0.093 | 1.19E-04 |                   |
|               | UKBB    | 44,341  | 76    | -0.421  | 0.111 | 1.50E-04 |                   |
|               | Overall | 63,845  | 180   | -0.385  | 0.071 | 7.24E-08 | 0.67              |
| <i>PPM1D</i>  | TOPMed  | 19,504  | 41    | -0.479  | 0.148 | 1.24E-03 |                   |
|               | UKBB    | 44,341  | 19    | -0.639  | 0.222 | 0.004    |                   |
|               | Overall | 63,845  | 60    | -0.529  | 0.123 | 1.83E-05 | 0.55              |
| <i>SF3B1</i>  | TOPMed  | 19,504  | 35    | 0.060   | 0.161 | 0.707    |                   |
|               | UKBB    | 44,341  | 14    | -0.317  | 0.259 | 0.221    |                   |
|               | Overall | 63,845  | 49    | -0.045  | 0.136 | 0.744    | 0.22              |
| <i>JAK2</i>   | TOPMed  | 19,504  | 36    | -0.658  | 0.158 | 3.25E-05 |                   |
|               | UKBB    | 44,341  | 9     | -0.896  | 0.322 | 0.005    |                   |
|               | Overall | 63,845  | 45    | -0.704  | 0.142 | 7.23E-07 | 0.51              |
| <i>TP53</i>   | TOPMed  | 19,504  | 19    | -0.152  | 0.218 | 0.486    |                   |
|               | UKBB    | 44,341  | 18    | -0.418  | 0.228 | 0.067    |                   |
|               | Overall | 63,845  | 37    | -0.279  | 0.157 | 0.077    | 0.40              |
| <i>SRSF2</i>  | TOPMed  | 19,504  | 20    | 0.169   | 0.212 | 0.426    |                   |
|               | UKBB    | 44,341  | 8     | 0.039   | 0.342 | 0.909    |                   |
|               | Overall | 63,845  | 28    | 0.133   | 0.180 | 0.462    | 0.75              |
| <i>GNB1</i>   | TOPMed  | 19,504  | 7     | -0.551  | 0.359 | 0.125    |                   |
|               | UKBB    | 44,341  | 11    | -0.042  | 0.292 | 0.886    |                   |
|               | Overall | 63,845  | 18    | -0.244  | 0.226 | 0.280    | 0.27              |
| <i>CBL</i>    | TOPMed  | 19,504  | 4     | 0.969   | 0.474 | 0.041    |                   |
|               | UKBB    | 44,341  | 10    | 0.141   | 0.306 | 0.645    |                   |
|               | Overall | 63,845  | 14    | 0.384   | 0.257 | 0.135    | 0.14              |
| <i>G5</i>     | TOPMed  | 19,504  | 7     | 0.271   | 0.358 | 0.449    |                   |
|               | UKBB    | 44,341  | 6     | 0.052   | 0.395 | 0.896    |                   |
|               | Overall | 63,845  | 13    | 0.172   | 0.265 | 0.516    | 0.68              |
| <i>NFI</i>    | TOPMed  | 19,504  | 4     | -0.662  | 0.474 | 0.163    |                   |
|               | UKBB    | 44,341  | 7     | 0.144   | 0.366 | 0.693    |                   |
|               | Overall | 63,845  | 11    | -0.156  | 0.290 | 0.590    | 0.18              |
| <i>BRCC3</i>  | TOPMed  | 19,504  | 7     | 0.097   | 0.359 | 0.788    |                   |
|               | UKBB    | 44,341  | 3     | -1.215  | 0.560 | 0.030    |                   |
|               | Overall | 63,845  | 10    | -0.285  | 0.302 | 0.345    | 0.05              |
| <i>ASXL2</i>  | TOPMed  | 19,504  | 4     | -0.739  | 0.474 | 0.119    |                   |
|               | UKBB    | 44,341  | 4     | 0.622   | 0.485 | 0.199    |                   |
|               | Overall | 63,845  | 8     | -0.074  | 0.339 | 0.828    | 0.04              |
| <i>KRAS</i>   | TOPMed  | 19,504  | 3     | 0.271   | 0.547 | 0.620    |                   |
|               | UKBB    | 44,341  | 4     | -0.705  | 0.484 | 0.145    |                   |
|               | Overall | 63,845  | 7     | -0.277  | 0.362 | 0.445    | 0.18              |
| <i>IDH2</i>   | TOPMed  | 19,504  | 3     | -0.313  | 0.547 | 0.568    |                   |
|               | UKBB    | 44,341  | 3     | 0.453   | 0.558 | 0.417    |                   |
|               | Overall | 63,845  | 6     | 0.063   | 0.391 | 0.872    | 0.33              |
| <i>PRPF8</i>  | TOPMed  | 19,504  | 4     | -0.103  | 0.474 | 0.827    |                   |
|               | UKBB    | 44,341  | 2     | 0.138   | 0.684 | 0.841    |                   |
|               | Overall | 63,845  | 6     | -0.025  | 0.390 | 0.948    | 0.77              |
| <i>ETNK1</i>  | TOPMed  | 19,504  | 3     | 0.076   | 0.548 | 0.890    |                   |
|               | UKBB    | 44,341  | 2     | -0.018  | 0.684 | 0.978    |                   |
|               | Overall | 63,845  | 5     | 0.039   | 0.427 | 0.927    | 0.91              |
| <i>BCORL1</i> | TOPMed  | 19,504  | 3     | 0.054   | 0.547 | 0.921    |                   |
|               | UKBB    | 44,341  | 1     | -0.065  | 0.968 | 0.947    |                   |
|               | Overall | 63,845  | 4     | 0.025   | 0.476 | 0.958    | 0.91              |
| <i>CUX1</i>   | TOPMed  | 19,504  | 1     | 0.042   | 0.948 | 0.965    |                   |
|               | UKBB    | 44,341  | 3     | -0.262  | 0.558 | 0.638    |                   |
|               | Overall | 63,845  | 4     | -0.184  | 0.481 | 0.702    | 0.78              |
| <i>NRAS</i>   | TOPMed  | 19,504  | 2     | 0.385   | 0.670 | 0.565    |                   |
|               | UKBB    | 44,341  | 2     | -0.673  | 0.684 | 0.325    |                   |
|               | Overall | 63,845  | 4     | -0.133  | 0.479 | 0.780    | 0.27              |
| <i>SMC3</i>   | TOPMed  | 19,504  | 1     | -0.335  | 0.948 | 0.724    |                   |
|               | UKBB    | 44,341  | 3     | 1.532   | 0.558 | 0.006    |                   |
|               | Overall | 63,845  | 4     | 1.051   | 0.481 | 0.029    | 0.09              |
| <i>KDM6A</i>  | TOPMed  | 19,504  | 2     | -0.993  | 0.670 | 0.139    |                   |
|               | UKBB    | 44,341  | 1     | -2.092  | 0.967 | 0.031    |                   |
|               | Overall | 63,845  | 3     | -1.350  | 0.551 | 0.014    | 0.35              |
| <i>MPL</i>    | TOPMed  | 19,504  | 1     | -2.729  | 0.948 | 0.004    |                   |
|               | UKBB    | 44,341  | 2     | -0.460  | 0.684 | 0.502    |                   |
|               | Overall | 63,845  | 3     | -1.236  | 0.555 | 0.026    | 0.05              |
| <i>BRAF</i>   | TOPMed  | 19,504  | 1     | 1.542   | 0.948 | 0.104    |                   |
|               | UKBB    | 44,341  | 1     | 1.146   | 0.967 | 0.236    |                   |
|               | Overall | 63,845  | 2     | 1.348   | 0.677 | 0.046    | 0.77              |

CAD: Coronary artery disease, CHIP: Clonal hematopoiesis of indeterminate potential, mLTL: Measured leukocyte telomere length, SE: Standard error, TOPMed: Trans-Omics for Precision Medicine, UKBB: UK Biobank, VAF: Variant allele frequency.

**Table S8. Instrumental variable used in Mendelian randomization studies for LTL on CHIP.**

| <b>rsid</b> | <b>Gene</b>  | <b>Chromosome</b> | <b>Position (GRCh38)</b> | <b>RSSobs</b> | <b>P</b> |
|-------------|--------------|-------------------|--------------------------|---------------|----------|
| rs3219104   | PARP1        | 1                 | 226374920                | 1.40E-05      | 0.29     |
| rs55749605  | SENP7        | 3                 | 101513249                | 2.47E-07      | 1        |
| rs10936600  | TERC         | 3                 | 169796797                | 8.29E-07      | 1        |
| rs13137667  | MOB1B        | 4                 | 70908630                 | 1.75E-05      | 1        |
| rs4691895   | NAF1         | 4                 | 163127047                | 2.22E-05      | 0.13     |
| rs7705526   | TERT         | 5                 | 1285859                  | 4.90E-05      | 0.0016   |
| rs2736176   | PRRC2A       | 6                 | 31619784                 | 2.22E-06      | 1        |
| rs59294613  | POT1         | 7                 | 124914213                | 1.12E-05      | 0.528    |
| rs9419958   | STN1 (OBFC1) | 10                | 103916188                | 8.97E-07      | 1        |
| rs228595    | ATM          | 11                | 108234866                | 2.45E-05      | 0.0048   |
| rs2302588   | DCAF4        | 14                | 72938044                 | 5.82E-06      | 1        |
| rs3785074   | TERF2        | 16                | 69373083                 | 4.78E-06      | 1        |
| rs62053580  | RFWD3        | 16                | 74646176                 | 8.79E-06      | 1        |
| rs7194734   | MPHOSPH6     | 16                | 82166375                 | 6.10E-07      | 1        |
| rs8105767   | ZNF208       | 19                | 22032639                 | 2.43E-07      | 1        |
| rs75691080  | RTEL1/STMN3  | 20                | 63638397                 | 7.38E-06      | 1        |

CHIP: Clonal hematopoiesis of indeterminate potential, LTL: Leukocyte telomere length,

*P*: Heterogeneity test assessed by MR-PRESSO, RSSobs: Observed residual sum of squares calculated by MR-PRESSO.

**Table S9. Instrumental variables used in one-sample Mendelian randomization of CHIP on LTL**

| SNP ID      | Chromosome | Position  | Gene                | F value for CHIP | R square for CHIP | R square for LTL | Steiger test           |          |          |
|-------------|------------|-----------|---------------------|------------------|-------------------|------------------|------------------------|----------|----------|
|             |            |           |                     |                  |                   |                  | Steiger test Direction | <i>t</i> | <i>P</i> |
| rs58322641  | 3          | 160497760 | <i>KPNA4/TRIM59</i> | 38.681           | 9.50E-04          | 7.06E-05         | TRUE                   | 4.68     | 2.90E-06 |
| rs114420266 | 4          | 104838707 | <i>TET2</i>         | 36.303           | 1.62E-04          | 8.23E-06         | TRUE                   | 2.06     | 0.0399   |
| rs7705526   | 5          | 1285859   | <i>TERT</i>         |                  | 0.00124           | 0.00225          | FALSE                  | -2.56    | 0.0105   |

CHIP: Clonal hematopoiesis of indeterminate potential, LTL: Leukocyte telomere length, SNP: Single nucleotide polymorphism.

### **Legends for Tables S4 to S6**

Table S4: TOPMed cohorts included in this study.

Table S5: Sensitivity analysis for observational association of CHIP and mLTL with CAD incidence in Cox proportional hazard model.

Table S6: Sensitivity analysis for observational association of CHIP and previous CAD with mLTL in linear regression model.