SUPPLEMENTAL MATERIAL

Age at menopause, leukocyte telomere length, and coronary artery disease in postmenopausal women

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Study cohorts

Participants from two population-based studies, the UK Biobank and Women's health initiative (WHI), were considered for inclusion in the current study. The UK Biobank is a cohort study of approximately 500,000 adults in the United Kingdom.[42] Individuals aged 40-70 years enrolled between 2006-2010 and are followed prospectively via linkage to national health records. Participants provided informed consent and were assessed for demographic information, lifestyle factors, health history, and medication use. In addition, participants underwent measurement of vital signs and anthropomorphic features, as well as blood sampling for analysis of DNA and other biomarkers. Follow-up in the UK Biobank occurred through March 2020.

The WHI is a prospective study of postmenopausal women aged 50-79 years, recruited from 40 centers across the United States between 1993 and 1998.[43,44] Participants enrolled in one or more clinical trials (hormone therapy, calcium/vitamin D supplementation, or dietary modification) or in an observational study. At baseline, participants provided information on demographics, medical history, health behaviors, and reproductive history, and underwent measurements of anthropometric characteristics and vital signs. The present study included a subsample of WHI participants who underwent whole genome sequencing through the NHLBI Trans-Omics for Precision Medicine (TOPMed) program.[45] Follow-up for incident outcomes in the WHI continued through March 2019.

For both the UK Biobank and WHI, women who were postmenopausal at baseline with complete data on reproductive history, available leukocyte telomere length (LTL) measurements, and no missing covariates for the primary analysis were included in the final study population (**Figure S1**). To control for the potential effects of study treatments on outcomes in the WHI cohort, women in the hormone therapy trial who had their blood drawn ≥2 years after the screening visit were excluded (*n*=486). To mitigate the possibility of immortal time bias affecting study outcomes,[45] women aged <50 years at the time of blood draw were excluded from the final UK Biobank cohort (*n*=4,239), aligning the lower age bound across cohorts.

The UK Biobank received approval from the North West Multi-center Research Ethics Committee. UK Biobank data were accessed under application number 7089. The WHI received approval from the institutional review boards at each clinical center. All participants provided written informed consent, and the Mass General Brigham Institutional Review Board approved secondary analyses using these data.

Exposures and covariates

The primary exposure was continuous age at menopause, ascertained by participant self-report. Given prior work suggesting important differences between natural and surgical menopause,[5,9] secondary analyses tested the effects of menopausal age separately among women with and without a history of gynecologic surgery (defined as bilateral oophorectomy and/or hysterectomy, as done previously).[9] Additional secondary exposures included premature menopause, defined as natural or surgical menopause before age 40 years,[7,8] as well as natural premature menopause and surgical premature menopause separately. Surgical premature menopause was defined as menopause occurring before age 40 years resulting from gynecologic surgery, whereas natural premature menopause was defined as menopause occurring before age 40 years not resulting from gynecologic surgery.[9] Exploratory analyses tested age at menarche (≤11, 12, 13 [reference], 14, and ≥15 years) and reproductive lifespan (i.e., the difference between age at menopause and age at menarche; <33, 33-35, 36-38 [reference], 39-41, and ≥42 years) as separate categorical exposures, as done previously.[47]

Medical history, health behaviors, and medication use including hormone therapy were systematically obtained at enrollment in the UK Biobank and WHI. Anthropometric data and vital signs were measured by trained study staff as described previously.[42-44] Self-reported race/ethnicity was collected at baseline and dichotomized as White vs. non-White in analysis. The Townsend deprivation index—a census-based score that incorporates home ownership, automobile ownership, employment, and household overcrowding—was used as a composite measure of material deprivation for UK Biobank participants. Type 2 diabetes status was defined by self-report or qualifying *International Classification of Diseases* (ICD) codes in the UK Biobank (**Table S1**), and by self-report of any treated diabetes in the WHI.

In addition, because previous work suggests that premature menopause is associated with a higher prevalence of CHIP,[9] and that CHIP may contribute to accelerated telomere shortening,[15] we examined the potential role of CHIP in any associations of age at menopause with LTL. UK Biobank exomes were sequenced from whole blood-derived DNA at the Regeneron Genetics Center (Tarrytown, NY).[48] WHI genomes were sequenced from whole blood-derived DNA at the Broad Institute of Harvard and MIT (Cambridge, MA). In brief, CHIP status was defined by the presence of somatic variants in at least one of 58 previously curated myeloid driver genes (**Table S2**)[49] with variant allele frequency ≥2%.[50] Variant calling was performed using the Mutect2 tool from the Genome Analysis ToolKit (GATK),[51,52] and sequencing artifacts and germline variants were removed as described previously.[49]

Outcomes

Primary analyses tested the association between age at menopause and LTL. In the UK Biobank, DNA was extracted from peripheral blood leukocytes as part of a cohort-wide array genotyping project.[53] LTL was measured using quantitative PCR as the ratio of telomere repeat copy number to single-copy gene copy number (T/S ratio) relative to a standard sample.[54] Raw T/S ratio estimates were adjusted for the influence of technical parameters, as detailed before.[55] In the WHI, LTL was estimated from whole genome sequences using TelSeq, which estimates individual telomere length from counts of sequencing reads that contain a fixed number of repeats of the telomeric nucleotide motif TTAGGG.[56] These read counts were corrected for potential technical artifacts, as described previously.[57] In both cohorts, technically adjusted LTL estimates were log-transformed to obtain a normal distribution and expressed as Z-scores to enable comparisons across the UK Biobank and WHI.

Additional models tested the association of LTL with incident coronary artery disease (CAD). Incident CAD was defined as a composite of myocardial infarction or coronary artery revascularization in both cohorts.[9] In the UK Biobank, incident CAD events were identified using ICD or *Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures* (OPCS) codes corresponding to myocardial infarction or coronary artery revascularization (**Table S3**) as used previously.[5,9,58] In the WHI, incident CAD was similarly defined as a composite outcome of myocardial infarction or coronary artery revascularization using a standardized physician review, classification, and adjudication process.[59]

Statistical analysis

The Shapiro-Wilk test was used to evaluate whether continuous variables followed a normal distribution (**Table S4**). Continuous variables were compared between women with vs. those without a history of premature menopause using the Kruskal-Wallis test for skewed variables. Categorical variables were compared between groups using the Pearson chi-squared test.

Linear regression models

Primary analyses tested the association of age at menopause with LTL using multivariable-adjusted linear regression models. Minimally adjusted models included age, age², the first ten principal components of genetic ancestry, and race/ethnicity as covariates. Fully adjusted models further included current/former smoking status, body mass index, prevalent diabetes, prevalent CAD, and current hormone therapy use as covariates. WHI models additionally adjusted for inverse probability of sampling weights to account for the nonrandom selection of women in the whole genome sequencing cohort,[60] while UK Biobank models also adjusted for Townsend deprivation index. Multivariable-adjusted models were run for each cohort separately and meta-analyzed with a fixed-effects model using the *rmeta* package (version 3.0) in R. In sensitivity analyses, we excluded participants with prevalent CAD, excluded participants with a history of cancer, excluded individuals with a history of hysterectomy without bilateral oophorectomy, stratified by age at blood collection (<65 vs. ≥65 years), stratified by self-reported race/ethnicity (Black vs. White), further adjusted for history of prior hormone therapy use, stratified by history of hormone therapy use, and further adjusted for age at menarche. Additionally, to investigate the potential role of CHIP in the association between age at menopause and LTL, we performed linear regression analyses that were further adjusted for CHIP status or stratified by CHIP status.

Cox proportional hazards models

Additional models tested the association of LTL with incident CAD using Cox proportional hazards models adjusted for age, age², the first ten components of genetic ancestry, race/ethnicity, current/former smoking status, body mass index, prevalent diabetes, current hormone therapy use, antihypertensive medication use, cholesterol-lowering medication use, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, inverse probability of sampling weights (for the WHI cohort), and Townsend deprivation index (for the UK Biobank cohort). In addition, to evaluate the joint association of LTL and history of premature menopause, participants were grouped by LTL and menopause history, and these groups were incorporated as a nonordered categorical variable in Cox proportional hazards models. Cox proportional hazards models were run for each cohort separately and meta-analyzed using fixed-effects models. Crude CAD incidence was visualized using cumulative incidence plots for the individual cohorts as well as for both cohorts combined using pooled time-to-event data. Participants with prevalent CAD at the time of blood draw were excluded from any incident CAD analyses. Follow-up started at the time of blood draw and was truncated when ≤10% of participants remained in the time-to-event models for the separate cohorts or ≤5% of participants remained in the pooled time-to-event model. The proportional hazards assumption was tested by plotting Schoenfeld residuals against time. Missing systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels were imputed using the *predict()* function in R, incorporating any covariates significantly associated with missingness, along with age and race/ethnicity, in linear regression models to predict these variables. Sensitivity analyses to assess the robustness of the association of LTL with incident CAD included stratification by age at blood collection (<65 vs. ≥65 years), further adjustment for history of hormone therapy use, stratification by history of hormone therapy, and exclusion of participants with imputed covariates.

Mediation analyses

To evaluate potential mediation by LTL for the association of age at menopause with incident CAD, we performed mediation analyses using the *mediation* package (version 4.5.0)

in R.[61] In brief, mediation analysis partitions the effects of an exposure (i.e., age at menopause) on an outcome (i.e., incident CAD) into direct and indirect effects, with the indirect effects working through the mediator of interest (i.e., LTL) and the direct effects working through other mechanisms, thereby estimating how much of the exposure-outcome association works through that mediator.[62] All mediator (i.e., LTL) models were adjusted for age, age^2, the first ten components of genetic ancestry, race/ethnicity, current/former smoking status, body mass index, prevalent diabetes, hormone therapy use, inverse probability of sampling weights (for the WHI cohort), and Townsend deprivation index (for the UK Biobank cohort); outcome (i.e., incident CAD) models using the *survreg()* function with a Weibull distribution were further adjusted for antihypertensive medication use, cholesterol-lowering medication use, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol. We excluded individuals with prevalent CAD at baseline from all mediation analysis models. Mediation analyses were conducted separately for women with and without previous gynecologic surgery, using a quasi-Bayesian approach with 1,000 simulations to estimate confidence intervals.

In addition, we performed mediation analyses to explore which risk factors other than LTL mediated the association of age at menopause with incident CAD among those with vs. without a history of gynecologic surgery. Ever-smoking, body mass index, diabetes mellitus, systolic blood pressure, total cholesterol, HDL cholesterol, C-reactive protein, and triglycerides were considered as candidate mediators. For consistency with the framework of causal mediation, we performed mediation analyses if (1) age at menopause was significantly associated with the candidate risk factor; (2) the candidate risk factor was significantly associated with incident coronary artery disease; and (3) the associations between earlier age at menopause, the indicated risk factor, and incident CAD were directionally consistent.[63]

Genetic correlation and Mendelian randomization (MR) analyses

Next, we tested for shared genetic architecture (i.e., genetic correlation) and causal associations between LTL and age at natural menopause. Linkage disequilibrium (LD) score regression[64] was performed to quantify genetic correlation between LTL and age at natural menopause, using LD scores calculated from European-ancestry samples included in the 1000 Genomes reference panel. In order to restrict to a set of common and well-imputed variants, we only retained variants included in the HapMap 3 reference panel, as recommended.[64] In addition, we used MR to test causal associations between LTL and age at natural menopause. MR is a method that evaluates the causality between an exposure (i.e., LTL or age at natural menopause) and outcome (i.e., age at natural menopause or LTL) by treating genetic variants—which are randomly allocated at conception—as instrumental variables. Causal inference using MR relies on three central assumptions: (1) genetic instruments must be associated with the exposure of interest (i.e., relevance assumption); (2) there must be no unmeasured confounders affecting the associations between the selected genetic variants and outcomes (i.e., independence assumption); and (3) the selected genetic variants must not affect the outcome through pathways other than the exposure of interest. Methods used to test and control for these assumptions are described below.

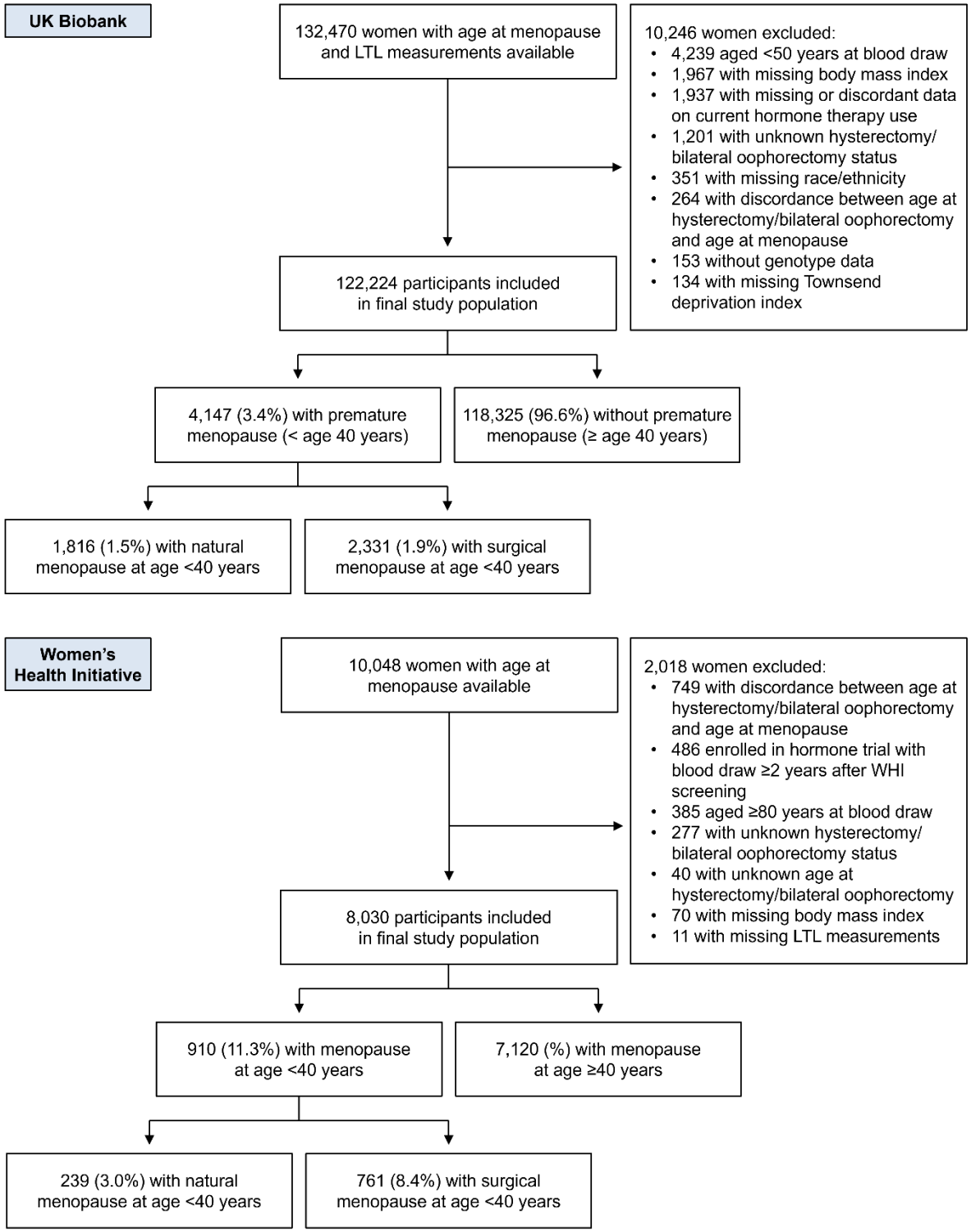
Summary statistics used in genetic correlation and MR analyses were obtained from genome-wide association studies comprising 472,174 participants for LTL[23] and 69,360 for age at natural menopause.[19] Genetic association data for LTL were obtained from UK Biobank participants with LTL measurements and no mismatch in self-reported and genetic sex.[23] LTL was measured as described previously and log-transformed and *Z*-standardized prior to genetic association analyses.[23,55] Approximately 19.4 million variants with a mean allele frequency of ≥0.1% and imputation score of ≥0.3 ascertained from imputed genotypes were tested using BOLT-LMM, adjusting for age, sex, genotyping array, and ten principal components of genetic ancestry. A total of 33 studies contributed genome-wide association data on self-reported age at menopause, as detailed previously.[19] Imputation schemes and

study-specific covariates varied across the included studies. Approximately 2.6 million variants with mean allele frequency ≥1% and imputation score ≥0.4 were retained for meta-analysis. The final set of genetic variants underwent inverse-variance-weighted meta-analysis, implemented using METAL; Day *et al*. did not find any significant between-study heterogeneity for the 54 independent signals identified using approximate conditional analysis.[19] Genetic association data for LTL and age at natural menopause were obtained in individuals of European ancestry, and there was no overlap between both study cohorts. Ethics committee approval and participant informed consent were obtained in the original studies contributing genetic data to the selected genome-wide assocaition studies.[19,23]

Instrumental variables were constructed using genome-wide significant ($P<5.0\times10^{-8}$) single-nucleotide variants (SNVs) that were present in both the exposure and outcome datasets. Genome-wide significant variants were clumped into independent loci using a window size of 20 megabases and LD R^2 threshold of 1.0×10^{-4}. Primary MR analyses used the inverse-variance-weighted MR method. Sensitivity analyses used the MR with robust adjusted profile score (MR-RAPS) and median-based MR methods, both of which are robust to potential pleiotropy (i.e., effects of the selected SNVs through pathways other than the exposure of interest). We also incorporated sensitivity analyses that used Steiger filtering, which tests whether SNVs explain more variance in the exposure than the outcome and excludes SNVs that do not satisfy this criterion (i.e., potential "reverse causal" SNVs), as well as analyses that used more lenient *P*-value and LD R^2 thresholds for instrumental variable selection. The presence of horizontal pleiotropy was tested using the MR-Egger intercept test, and the relevance assumption was tested by estimating *F*-statistics for the genetic variants included in our genetic instruments. The instruments used in our primary analyses only included variants with *F*-statistics >10, with median *F*-statistics ranging from 39.6 to 65.2 across main and sensitivity analyses, suggesting low risk for weak instrument bias.

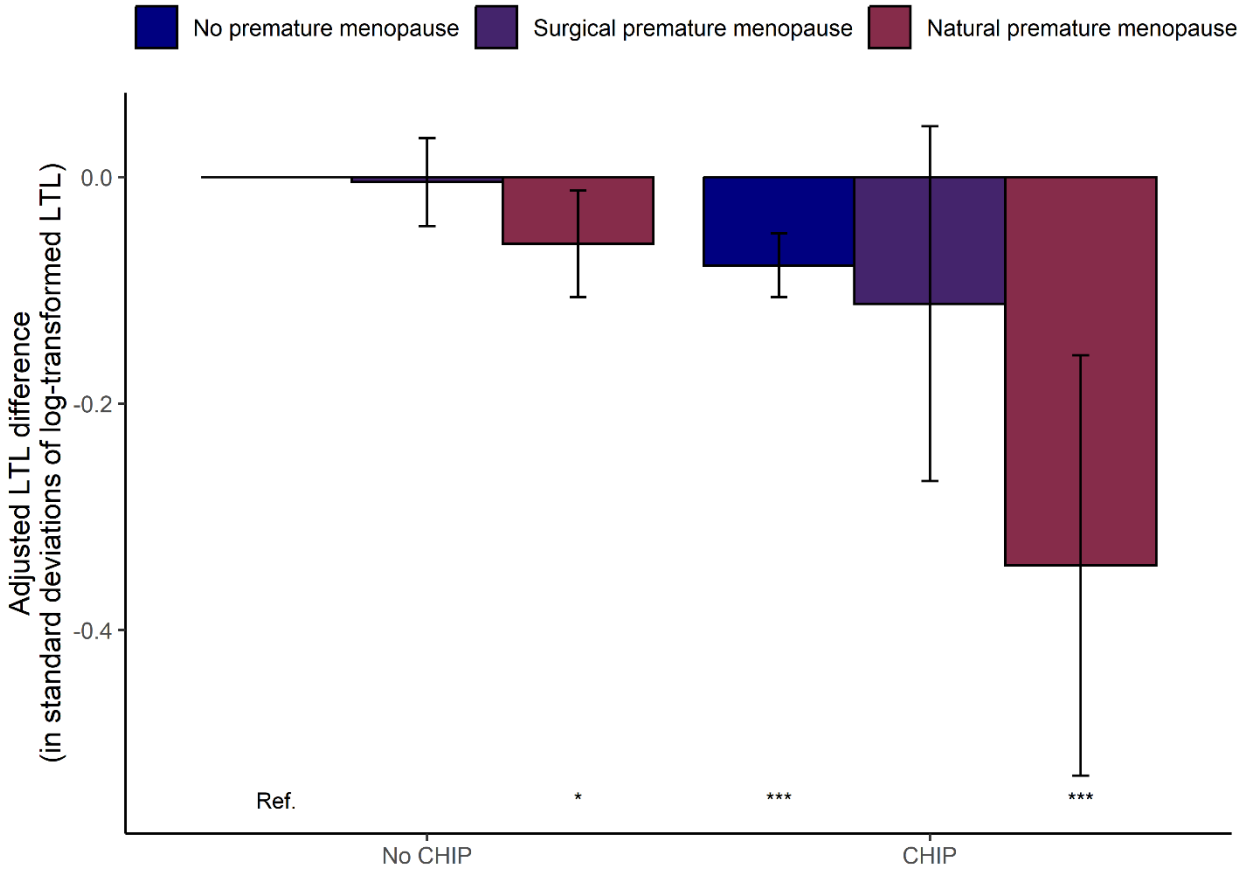
LD score regression was performed using *ldsc* (version 1.0.1),[64] while MR analyses were performed using the *TwoSampleMR* (version 0.5.6) and *mr.raps* (version 0.2) packages in R.[65,66]

SUPPLEMENTAL FIGURES
Figure S1. Study flowchart.



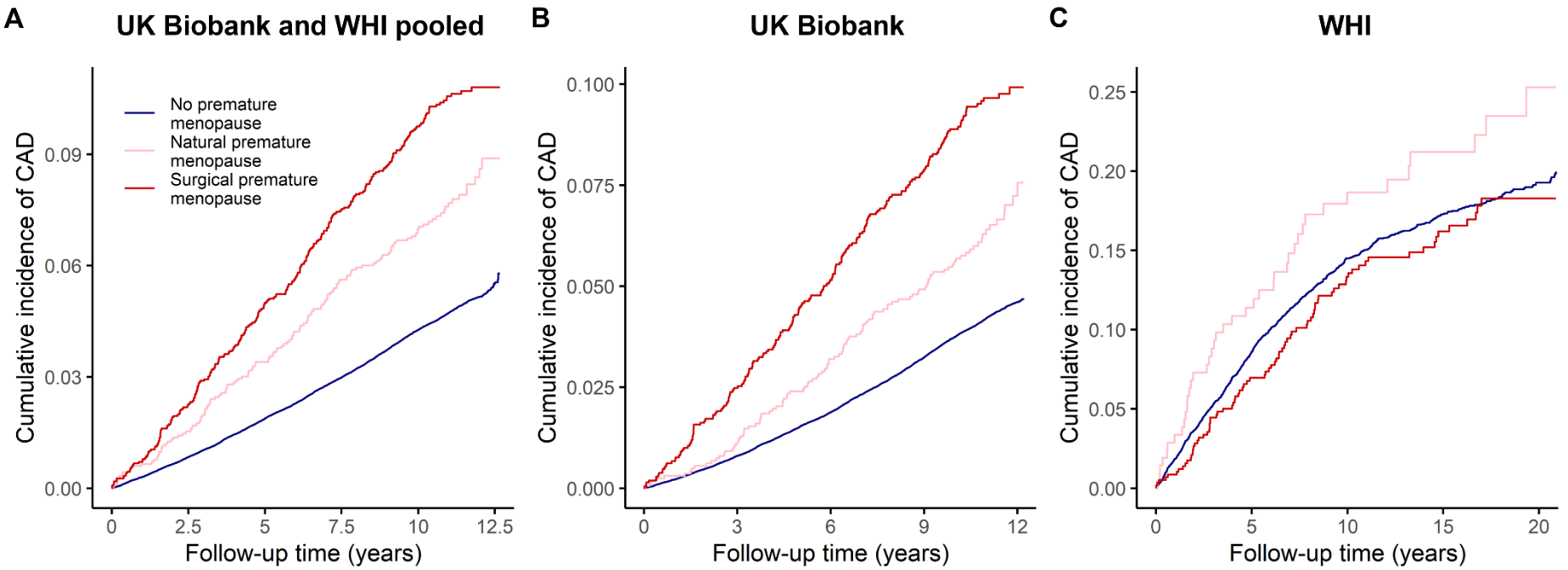
LTL indicates leukocyte telomere length.

Figure S2. Meta-analyzed adjusted differences in leukocyte telomere length (LTL) by clonal hematopoiesis of indeterminate potential (CHIP) status across menopause categories.



Each bar represents the meta-analyzed effect size of each menopause category on LTL, calculated using linear regression models adjusted for age, age², race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. Analyses in the WHI were further adjusted for inverse probability of sampling weights, while those in the UK Biobank were further adjusted for Townsend deprivation index. Combined menopause and CHIP status categories were incorporated as a categorical nonordered variable, with women with age at menopause ≥45 years and no CHIP constituting the reference group. The error bars indicate 95% confidence intervals. No corrections for multiple comparisons were made. ***$P<1.0\times10^{-3}$, **$P<1.0\times10^{-2}$.

Figure S3. Cumulative incidence of coronary artery disease (CAD) events by menopause category in the UK Biobank and Women's Health Initiative (WHI).



The UK Biobank cohort included 119,600 women without prevalent CAD at baseline, of whom 5,224 experienced incident CAD events during a follow-up period truncated at 12.2 years. The WHI cohort included 7,183 women without prevalent CAD at baseline, of whom 1,130 experienced incident CAD events during a follow-up period truncated at 20.9 years. The follow-up duration for the pooled model was truncated at 12.7 years.

Figure S4. Cumulative incidence of coronary artery disease (CAD) events by leukocyte telomere length (LTL) in the UK Biobank and Women's Health Initiative (WHI).

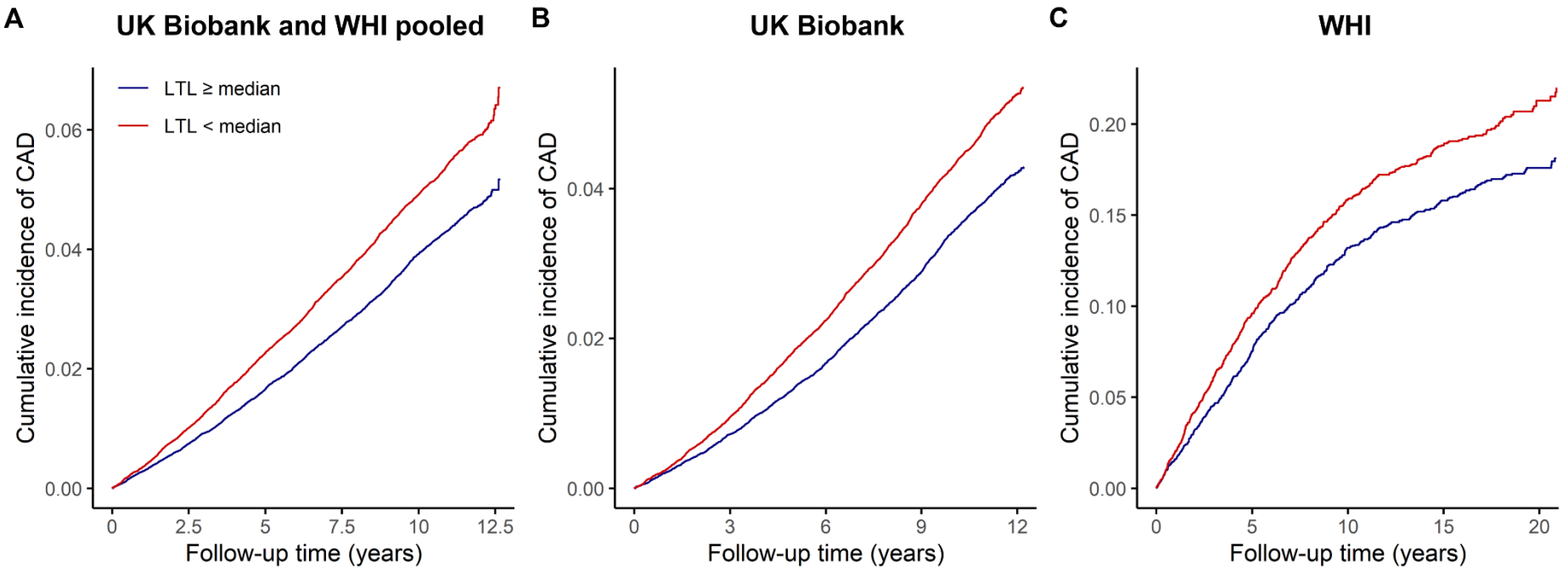


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Figure S5. Cumulative incidence of coronary artery disease (CAD) events by menopause category and leukocyte telomere length (LTL) in the UK Biobank and Women's Health Initiative (WHI).

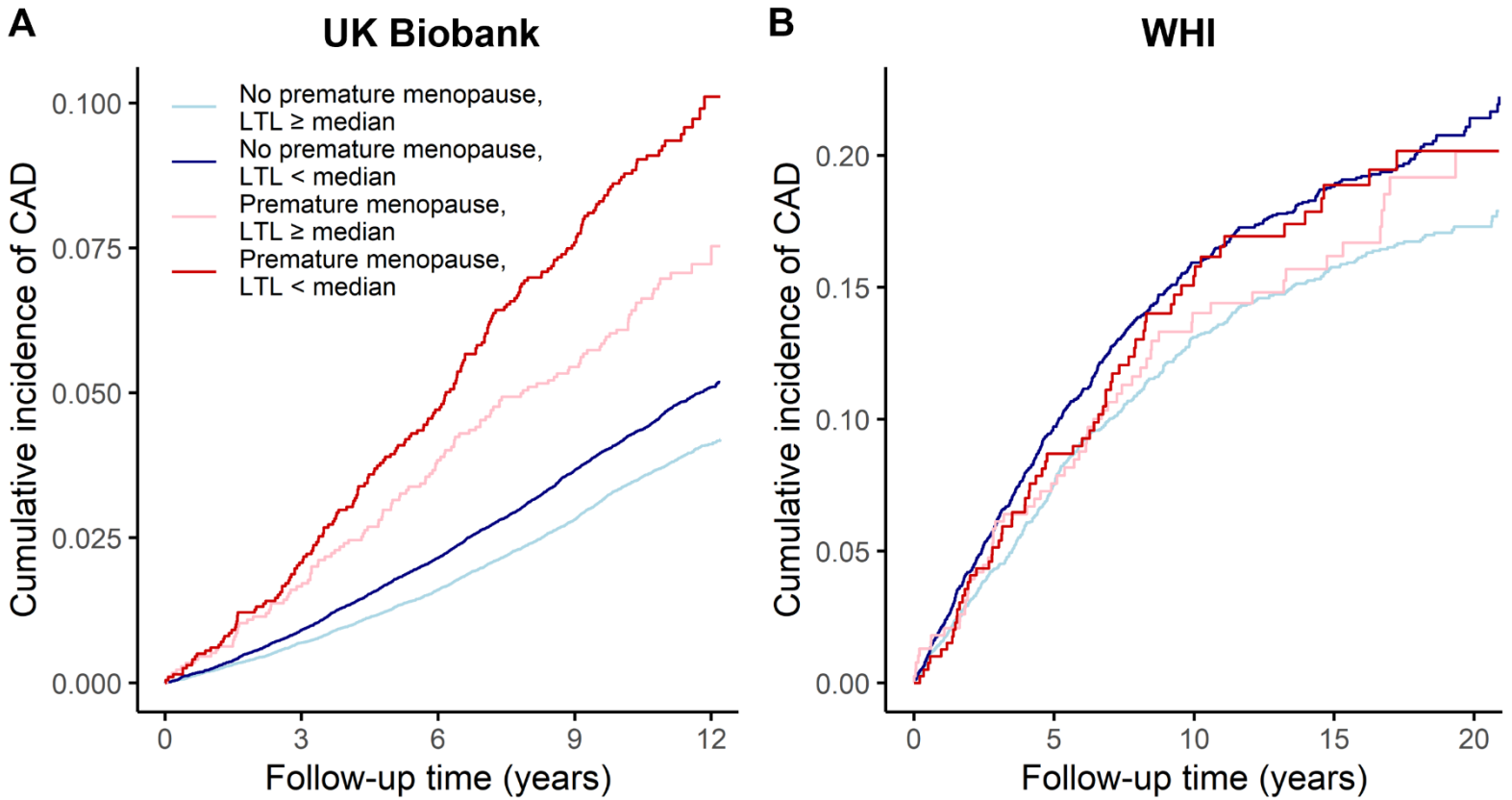

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Figure S6. Cumulative incidence of coronary artery disease (CAD) events by menopause category and leukocyte telomere length (LTL) among women without a history of gynecologic surgery in the UK Biobank and Women's Health Initiative (WHI).

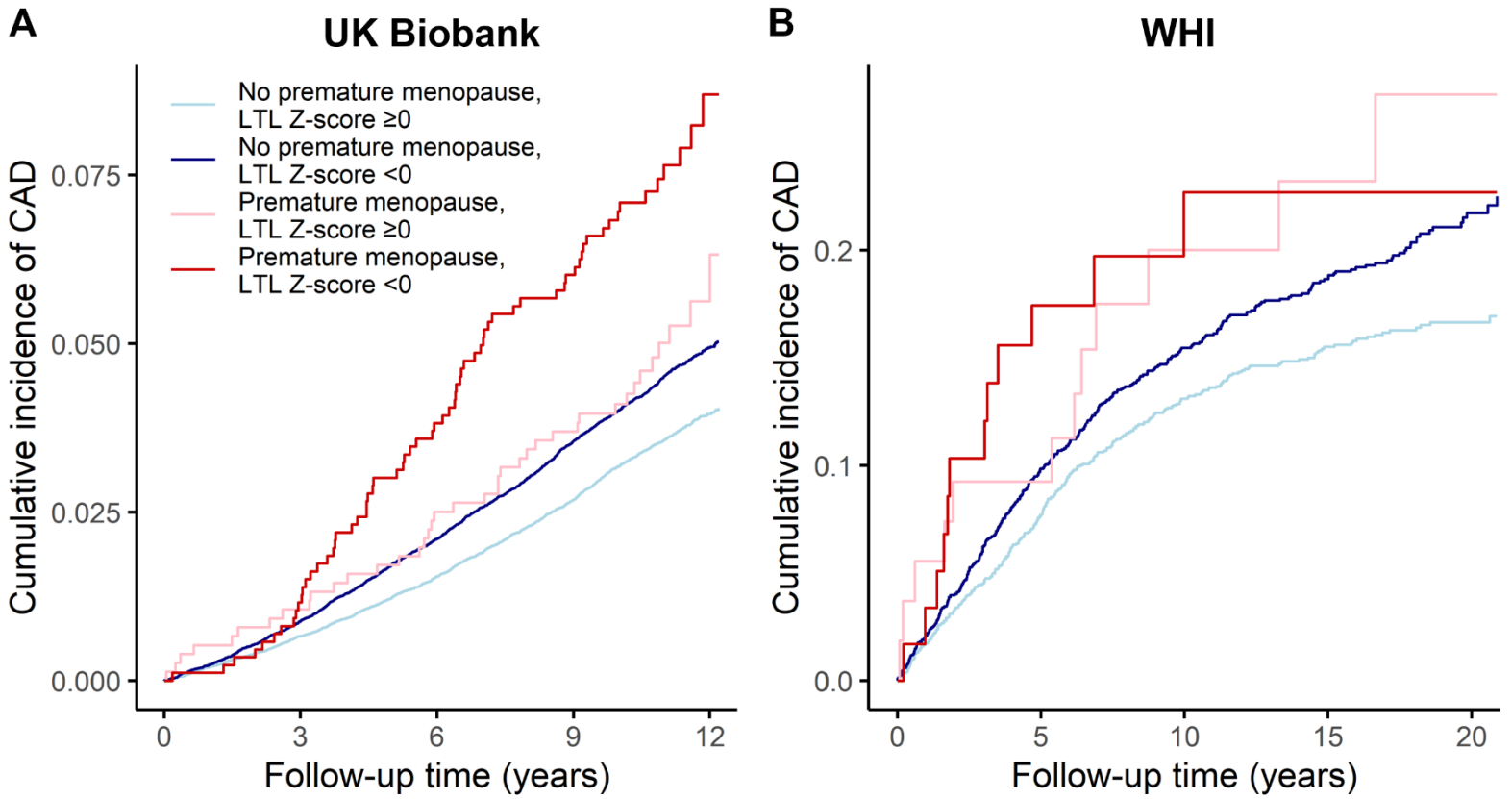

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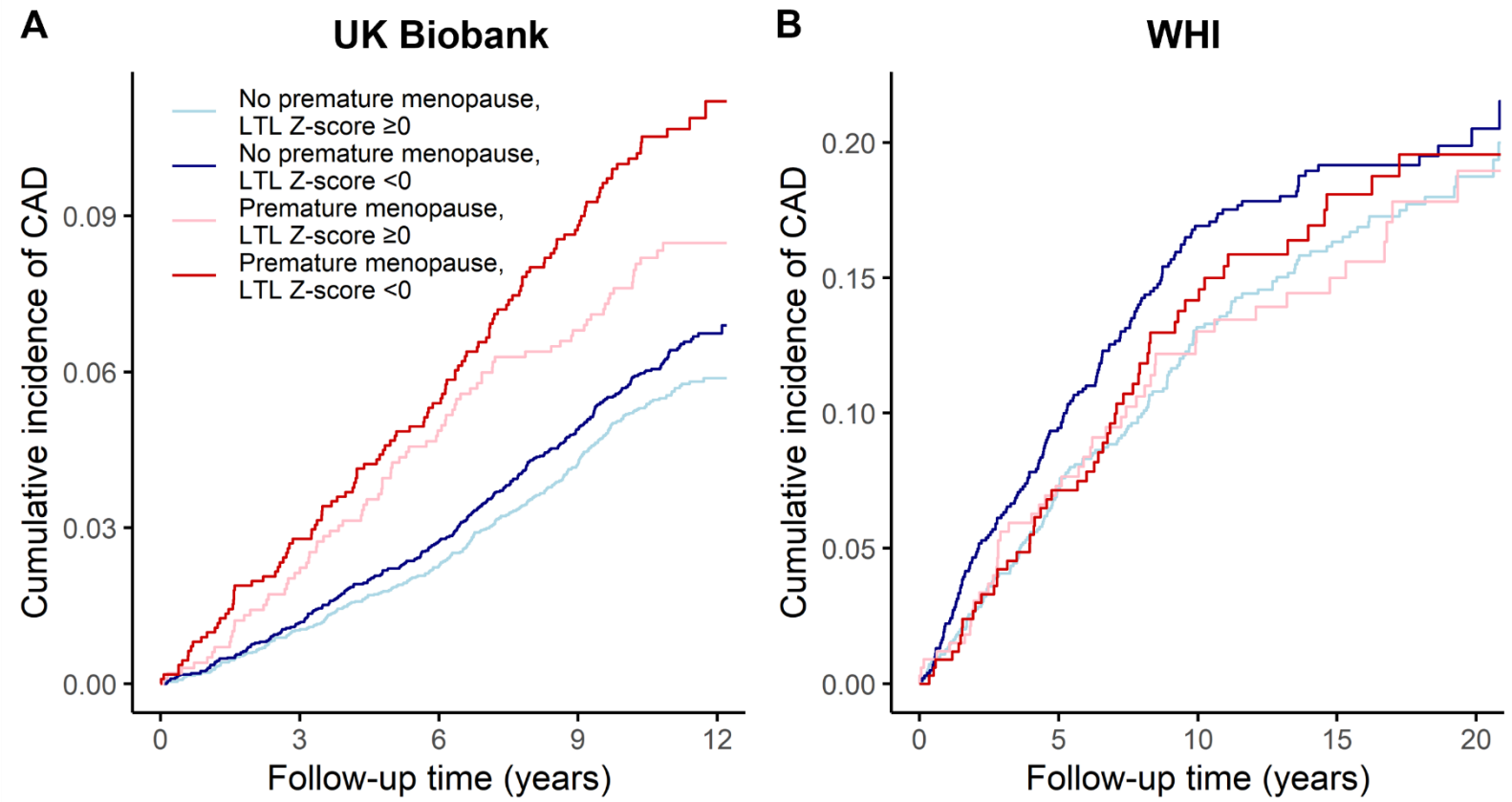
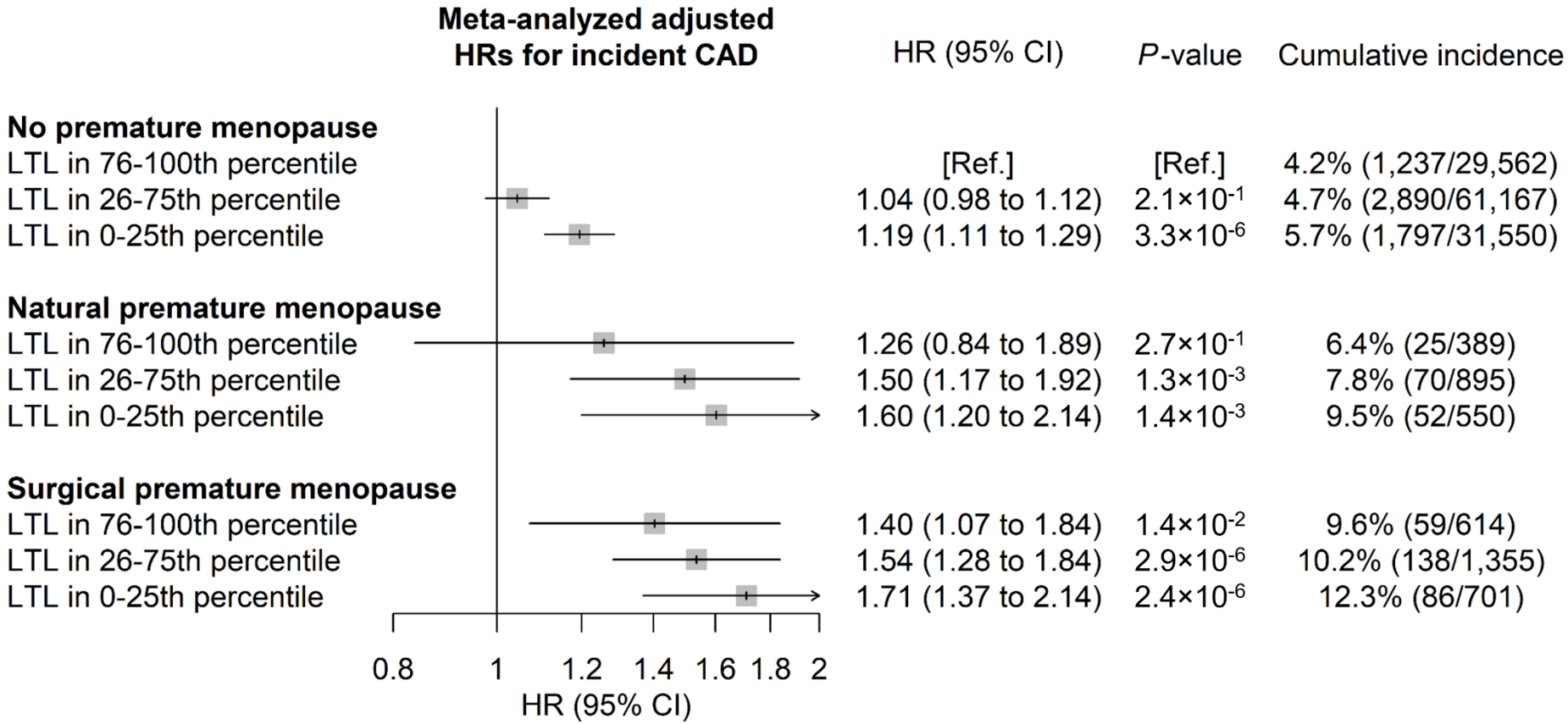
Figure S7. Cumulative incidence of coronary artery disease (CAD) events by menopause category and leukocyte telomere length (LTL) among women with a history of gynecologic surgery in the UK Biobank and Women's Health Initiative (WHI).



The UK Biobank cohort included 119,600 women without prevalent CAD at baseline, of whom 5,224 experienced incident CAD events during a follow-up period truncated at 12.2 years. The WHI cohort included 7,183 women without prevalent CAD at baseline, of whom 1,130 experienced incident CAD events during a follow-up period truncated at 20.9 years. The follow-up duration for the pooled model was truncated at 12.7 years.

Figure S8. Multivariable-adjusted associations of menopause and leukocyte telomere length (LTL) categories with incident coronary artery disease (CAD) events.



P-values correspond to Cox regression models adjusted for age, age², the first ten principal components of genetic ancestry, race/ethnicity, current/former smoking status, body mass index, diabetes status, current hormone therapy use, antihypertensive medication use, cholesterol-lowering medication use, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol. Analyses in the WHI were further adjusted for inverse probability of sampling weights, while those in the UK Biobank were further adjusted for Townsend deprivation index. Menopause status and LTL were included as combined nonordered, categorical variables, with women without premature menopause and above-median LTL constituting the reference category. No corrections for multiple comparisons were made.

SUPPLEMENTAL TABLES

Table S1. *International Classification of Diseases* (ICD) codes used to define prevalent type 2 diabetes status in the UK Biobank.

Diagnosis	**ICD codes**
Diabetes mellitus	ICD 9: 2500, 25000, 25001, 25009, 25011, 25019, 2503, 2504, 2505, 25099 ICD-10: E11, E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.9, E11.9

Table S2. Driver genes and variants queried for the detection of CHIP.

Gene name	Reported mutations for variant calling
ASXL1	Frameshift/nonsense/splice-site in exon 11-12
ASXL2	Frameshift/nonsense/splice-site in exon 11-12
BCOR	Frameshift/nonsense/splice-site
BCORL1	Frameshift/nonsense/splice-site
BRAF	G464E, G464V, G466E, G466V, G469R, G469E, G469A, G469V, V471F, V472S, L485W, N581S, I582M, I592M, I592V, D594N, D594G, D594V, D594E, F595L, F595S, G596R, L597V, L597S, L597Q, L597R, A598V, V600M, V600L, V600K, V600R, V600E, V600A, V600G, V600D, K601E, K601N, R603*, W604R, W604G, S605G, S605F, S605N, G606E, G606A, G606V, H608R, H608L, G615R, S616P, S616F, L618S, L618W
BRCC3	Frameshift/nonsense/splice-site
CBL	RING finger missense p.381-421
CBLB	RING finger missense p.372-412
CEBPA	Frameshift/nonsense/splice-site
CREBBP	Frameshift/nonsense/splice-site, D1435E, R1446L, R1446H, R1446C, Y1450C, P1476R, Y1482H, H1487Y, W1502C, Y1503D, Y1503H, Y1503F, S1680del
CSF3R	T615A, T618I, truncating c.741-791
CTCF	Frameshift/nonsense, R377C, R377H, P378A, P378L
CUX1	Frameshift/nonsense
DNMT3A	Frameshift/nonsense/splice-site, F290I, F290C, V296M, P307S, P307R, R326H, R326L, R326C, R326S, G332R, G332E, V339A, V339M, V339G, L344Q, L344P, R366P, R366H, R366G, A368T, A368V, R379H, R379C, I407T, I407N, I407S, F414L, F414S, F414C, A462V, K468R, C497G, C497Y, Q527H, Q527P, Y533C, S535F, C537G, C537R, G543A, G543S, G543C, L547H, L547P, L547F, M548I, M548K, G550R, W581R, W581G, W581C, R604Q, R604W, R635W, R635Q, S638F, G646V, G646E, L653W, L653F, I655N, V657A, V657M, R659H, Y660C, V665G, V665L, M674V, R676W, R676Q, G685R, G685E, G685A, D686Y, D686G, R688H, G699R, G699S, G699D, P700L, P700S, P700R, P700Q, P700T, P700A, D702N, D702Y, V704M, V704G, I705F, I705T, I705S, I705N, G707D, G707V, C710S, C710Y, S714C, V716D, V716F, V716I, N717S, N717I, P718L, R720H, R720G, K721R, K721T, Y724C, R729Q, R729W, R729G, F731C, F731L, F731Y, F731I, F732del, F732C, F732S, F732L, E733G, E733A, F734L, F734C, Y735C, Y735N, Y735S, R736H, R736C, R736P, L737H, L737V, L737F, L737R, A741V, P742P, P743R, P743L, R749C, R749L, R749H, R749G, F751L, F751C, F752del, F752C, F752L, F752I, F752V, W753G, W753C, W753R, L754P, L754R, L754H, F755S, F755I, F755L, M761I, M761V, G762C, V763I, S770L, S770W, S770P, R771Q, F772I, F772V, L773R, L773V,

	E774K, E774D, E774G, I780T, D781G, R792H, W795C, W795L, G796D, G796V, N797Y, N797H, N797S, P799S, P799R, P799H, R803S, R803W, P804L, P804S, K826R, S828N, K829R, T835M, N838D, K841Q, Q842E, P849L, D857N, W860R, E863D, F868S, G869S, G869V, M880V, S881R, S881I, R882H, R882P, R882C, R882G, A884P, A884V, Q886R, L889P, L889R, G890D, G890R, G890S, V895M, P896L, V897G, V897D, R899L, R899H, R899C, L901R, L901H, P904L, F909C, P904Q, A910P, C911R, C911Y
EED	Frameshift/nonsense/splice-site, L240Q, I363M
EP300	Frameshift/nonsense/splice_site, VF1148_1149del, D1399N, D1399Y, P1452L, Y1467N, Y1467H, Y1467C, R1627W, A1629V
ETNK1	N155(244)S, N155(244)T, N155(244)K
ETV6	Frameshift/nonsense/splice-site
EZH2	Frameshift/nonsense/splice-site, Q62R, N102S, F145S, F145C, F145Y, F145L, G159R, E164D, R202Q, K238E, E244K, R283Q, H292R, P488S, R497Q, R561H, T568I, K629E, Y641N, Y641H, Y641S, Y641C, Y641F, D659Y, D659G, V674M, A677G, A677V, R679C, R679H, R685C, R685H, A687V, N688I, N688K, H689Y, S690P, I708V, I708T, I708M, E720K, E740K
FLT3	V579A, V592A, V592I, F594L, FY590-591GD, D835Y, D835H, D835E, del835
GATA2	Frameshift/nonsense/splice-site, R293Q, N317H, A318T, A318V, A318G, G320D, L321P, L321F, L321V, Q328P, R330Q, R361L, L359V, A372T, R384G, R384K
GNAS	R201S, R201C, R201H, R201L, Q227K, Q227R, Q227L, Q227H, R374C
GNB1	K57N, K57M, K57E, K57T, I80T, I80N
IDH1	R132C, R132G, R132H, R132L, R132P, R132V, V178I
IDH2	R140W, R140Q, R140L, R140G, R172W, R172G, R172K, R172T, R172M, R172N, R172S
IKZF1	Frameshift/nonsense
JAK2	N533D, N533Y, N533S, H538R, K539E, K539L, I540T, I540V, V617F, R683S, R683G, del/ins537-539L, del/ins538-539L, del/ins540-543MK, del/ins540-544MK, del/ins541-543K, del542-543, del543-544, ins11546-547
KDM6A	Frameshift/nonsense/splice-site, del419
KIT	ins503, V559A, V559D, V559G, V559I, V560D, V560A, V560G, V560E, del560, E561K, del579, P627L, P627T, R634W, K642E, K642Q, V654A, V654E, H697Y, H697D, E761D, K807R, D816H, D816Y, D816F, D816I, D816V, D816H, del551-559
KRAS	G12D, G12A, G12E, G12V, G13D, G13C, G13Y, G13F, G13R, G13A, G13V, G13E, V14I, T58I, G60D, G60A, G60V, Q61K, Q61E, Q61P, Q61R, Q61L, Q61H, K117E, K117N, A146T, A146P, A146V
MPL	S505G, S505N, S505C, L510P, del513, W515A, W515R, W515K, W515S, W515L, A519T, A519V, Y591D, W515-518KT
NF1	Frameshift/nonsense

NPM1	Frameshift p.W288fs (insertion at c.859_860, 860_861, 862_863, 863_864)
NRAS	G12S, G12R, G12C, G12N, G12P, G12Y, G12D, G12A, G12V, G12E, G13S, G13R, G13C, G13N, G13P, G13Y, G13D, G13A, G13V, G13E, G60E, G60R, Q61R, Q61L, Q61K, Q61P, Q61H, Q61Q
PDS5B	Frameshift/nonsense/splice-site, R1292Q
PHF6	Frameshift/nonsense/splice-site, A40D, M125I, S246Y, F263L, R274Q, C297Y, H302Y, H329L
PHIP	Frameshift/nonsense/splice-site
PPM1D	Frameshift/nonsense, exon 5 or 6
PRPF40B	Frameshift/nonsense/splice-site, P15H, M58I, P405L, P562S,
PRPF8	M1307I, C1594W, D1598Y, D1598N, D1598V
PTPN11	G60V, G60R, G60A, D61Y, D61V, D61G, Y63C, E69K, E69G, E69D, E69Q, F71L, F71K, A72T, A72V, A72D, T73I, E76K, E76Q, E76M, E76A, E76G, E139G, E139D, N308D, N308T, N339S, P491L, S502P, S502A, S502L, G503V, G503G, G503A, G503E, Q506P, T507A, T507K
RAD21	Frameshift/nonsense/splice-site, R65Q, H208R, Q474R
RUNX1	Frameshift/nonsense/splice-site, S73F, H78Q, H78L, R80C, R80P, R80H, L85Q, P86L, P86H, S114L, D133Y, L134P, R135G, R135K, R135S, R139Q, R142S, A165V, R174Q, R177L, R177Q, A224T, D171G, D171V, D171N, R205W, R223C
SETBP1	D868N, D868T, S869N, G870S, I871T, D880N, D880Q
SETD2	Frameshift/nonsense, V1190M
SETDB1	Frameshift/nonsense, K715E
SF3B1	G347V, R387W, R387Q, E592K, E622D, Y623C, R625L, R625C, R625G, H662Q, H662D, T663I, K666N, K666T, K666E, K666R, K700E, V701F, A708T, G740R, G740E, A744P, D781G, E783K, R831Q, L833F, E862K, R957Q
SRSF2	Y44H, P95H, P95L, P95T, P95R, P95A, P107H, P95fs
SMC1A	K190T, R586W, M689V, R807H, R1090H, R1090C
SMC3	Frameshift/nonsense, R155I, Q367E, D392V, K571R, R661P, G662C
STAG2	Frameshift/nonsense/splice-site
SUZ12	Frameshift/nonsense
TET2	Frameshift/nonsense/splice-site, missense mutations in catalytic domains (p.1104-1481 and 1843-2002)
TP53	Frameshift/nonsense/splice-site, S46F, G105C, G105R, G105D, G108S, G108C, R110L, R110C, T118A, T118R, T118I, S127F, S127Y, L130V, L130F, K132Q, K132E, K132W, K132R, K132M, K132N, F134V. F134L, F134S,

	C135W, C135S, C135F, C135G, C135Y, Q136K, Q136E, Q136P, Q136R, Q136L, Q136H, A138P, A138V, A138A, A138T, T140I, C141R, C141G, C141A, C141Y, C141S, C141F, C141W, V143M, V143A, V143E, L145Q, W146C, W146L, L145R, V147G, P151T, P151A, P151S, P151H, P151R, P152S, P152R, P152L, T155P, T155A, V157F, R158H, R158L, A159V, A159P, A159S, A159D, A161T, A161D, Y163N, Y163H, Y163D, Y163S, Y163C, K164E, K164M, K164N, K164P, H168Y, H168P, H168R, H168L, H168Q, M169I, M169T, M169V, E171K, E171Q, E171G, E171A, E171V, E171D, V172D, V173M, V173L, V173G, R174W, R175G, R175C, R175H, C176R, C176G, C176Y, C176F, C176S, P177R, P177R, P177L, H178D, H178P, H178Q, H179Y, H179R, H179Q, R181C, R181Y, D186G, G187S, P190L, P190T, H193N, H193P, H193L, H193R, L194F, L194R, I195F, I195N, I195T, R196P, V197L, G199V, Y205N, Y205C, Y205H, D208V, R213Q, R213P, R213L, R213Q, H214D, H214R, S215G, S215I, S215R, V216M, V217G, Y220N, Y220H, Y220S, Y220C, E224D, I232F, I232N, I232T, I232S, Y234N, Y234H, Y234S, Y234C, Y236N, Y236H, Y236C, M237V, M237K, M237I, C238R, C238G, C238Y, C238W, N239T, N239S, S241Y, S241C, S241F, C242G, C242Y, C242S, C242F, G244S, G244C, G244D, G245S, G245R, G245C, G245D, G245A, G245V, G245S, M246V, M246K, M246R, M246I, N247I, R248W, R248G, R248Q, R249G, R249W, R249T, R249M, P250L, I251N, L252P, I254S, I255F, I255N, I255S, L257Q, L257P, E258K, E258Q, D259Y, S261T, G262D, G262V, L265P, G266R, G266E, G266V, R267W, R267Q, R267P, E271K, V272M, V272L, R273S, R273G, R273C, R273H, R273P, R273L, V274F, V274D, V274A, V274G, V274L, C275Y, C275S, C275F, A276P, C277F, C277Y, P278T, P278A, P278S, P278H, P278R, P278L, G279E, R280G, R280K, R280T, R280I, R280S, D281N, D281H, D281Y, D281G, D281E, R282G, R282W, R282Q, R282P, E285K, E285V, E286G, E286V, E286K, K320N, L330R, G334V, R337C, R337L, A347T, L348F, T377P
U2AF1	D14G, S34F, S34Y, R35L, R156H, R156Q, Q157R, Q157P
U2AF2	R18W, Q143L, M144I, L187V, Q190L
WT1	Frameshift/nonsense/splice-site
ZRSR2	Frameshift/nonsense, R126P, E133G, C181F, H191Y, I202N, F239V, F239Y, N261Y, C280R, C302R, C326R, H330R, N382K

Table S3. *International Classification of Diseases* (ICD) and procedure codes used to define incident coronary artery disease events in the UK Biobank.

Diagnosis	ICD codes
Coronary artery disease	ICD-9: 410, 4109, 411, 4119, 412, 4129, 4140, 4148, 4149 ICD-10: 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, I24.0, I24.1, I24.8, I24.9, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9 OPCS4: 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 S4. Results from the Shapiro-Wilk test to evaluate whether continuous variables followed a normal distribution.

	UK Biobank (*N*=122,224)	**Women's Health Initiative (*N* =8,030)**
Age at blood draw, years	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Townsend deprivation index	$<2.2\times10^{-16}$	-
Age at menarche, years	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Age at menopause, years	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Parity	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Age at hysterectomy, years	4.1×10^{-4}	$<2.2\times10^{-16}$
Age at bilateral oophorectomy, years	3.3×10^{-3}	$<2.2\times10^{-16}$
Body mass index, kg/m²	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Systolic blood pressure, mmHg	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Total cholesterol, mg/dL	3.5×10^{-14}	$<2.2\times10^{-16}$
Low-density lipoprotein cholesterol, mg/dL	6.4×10^{-14}	$<2.2\times10^{-16}$
High-density lipoprotein cholesterol, mg/dL	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
Triglycerides, mg/dL	$<2.2\times10^{-16}$	$<2.2\times10^{-16}$
C-reactive protein, mg/L	$<2.2\times10^{-16}$	-

All values represent *P*-values obtained using the Shapiro-Wilk test to evaluate whether the indicated continuous variables followed a normal distribution. All tests were run using the *shapiro.test()* function in R using a randomly selected sample of 5,000 participants (i.e., the limit up to which this function accepts samples) in the UK Biobank and WHI.

Table S5. Baseline characteristics of the study sample.

	UK Biobank (*N*=122,224)			Women's Health Initiative (*N* =8,030)		
	Menopause at age <40 years (*n*=3,899)	**Menopause at age ≥40 years (*n*=118,325)**	***P*-value**	**Menopause at age <40 years (*n*=910)**	**Menopause at age ≥40 years (*n*=7,120)**	***P*-value**
Age at blood draw, years	61 (57 to 65)	61 (57 to 64)	1.5×10^{-3}	68 (63 to 72)	69 (64 to 74)	5.1×10^{-8}
Race, *n* • White • Black • Asian • Other	 3,727 (95.6%) 55 (1.4%) 65 (1.7%) 52 (1.3%)	 113,768 (96.1%) 1,176 (1.0%) 1,995 (1.7%) 1,386 (1.2%)	9.4×10^{-2}	 677 (74.4%) 179 (19.7%) 12 (1.3%) 42 (4.6%)	 5,990 (84.1%) 730 (10.3%) 144 (2.0%) 256 (3.6%)	1.5×10^{-16}
Townsend deprivation index	-1.88 (-3.44 to 0.98)	-2.33 (-3.72 to 0.10)	$<2.2\times10^{-16}$	-	-	-
Age at menarche, years	13 (11 to 14)	13 (12 to 14)	1.0×10^{-5}	12 (11 to 13)	13 (12 to 13)	3.0×10^{-4}
Age at menopause, years	36 (34 to 38)	51 (48 to 53)	$<2.2\times10^{-16}$	35 (32 to 37)	50 (46 to 53)	$<2.2\times10^{-16}$
Parity	2 (1 to 3)	2 (1 to 3)	1.9×10^{-1}	3 (2 to 4)	3 (2 to 4)	1.4×10^{-7}
Nulliparity, *n*	653 (16.8%)	19,252 (16.3%)	4.5×10^{-1}	37 (4.8%)	137 (2.1%)	9.4×10^{-6}
History of hysterectomy, *n*	2,178 (55.9%)	9,841 (8.3%)	$<2.2\times10^{-16}$	765 (84.1%)	2,374 (33.3%)	$<2.2\times10^{-16}$
Age at hysterectomy, years	36 (32 to 38)	49 (45 to 55)	$<2.2\times10^{-16}$	35-39 (30-34 to 35-39)	45-49 (40-44 to 50-54)	$<2.2\times10^{-16}$
History of bilateral oophorectomy, *n*	494 (12.9%)	5,609 (4.7%)	$<2.2\times10^{-16}$	495 (54.4%)	1,416 (19.9%)	$<2.2\times10^{-16}$
Age at bilateral oophorectomy, years	36 (32 to 38)	52 (47 to 57)	$<2.2\times10^{-16}$	35-39 (30-34 to 35-39)	45-49 (40-44 to 50-54)	$<2.2\times10^{-16}$
Ever-use of hormone therapy, *n*	2,817 (72.4%)	52,015 (44.0%)	$<2.2\times10^{-16}$	698 (79.0%)	4,126 (59.2%)	$<2.2\times10^{-16}$
Current use of hormone therapy, *n*	414 (10.6%)	5,425 (4.6%)	$<2.2\times10^{-16}$	160 (17.5%)	1,215 (17.1%)	7.3×10^{-1}
Current or former smoking, *n*	1,960 (50.3%)	49,153 (41.5%)	$<2.2\times10^{-16}$	481 (53.2%)	3,424 (48.7%)	1.3×10^{-2}
Type 2 diabetes mellitus, *n*	117 (3.0%)	2,017 (1.7%)	1.8×10^{-09}	112 (12.3%)	550 (7.7%)	2.3×10^{-5}
Coronary artery disease, *n*	178 (4.6%)	2,446 (2.1%)	$<2.2\times10^{-16}$	127 (14.0%)	720 (10.1%)	7.9×10^{-5}
History of cancer, *n*	577 (14.9%)	12,040 (10.2%)	$<2.2\times10^{-16}$	98 (10.9%)	460 (6.5%)	1.8×10^{-6}
Antihypertensive medication use, *n*	1,044 (26.8%)	24,492 (20.7%)	$<2.2\times10^{-16}$	385 (42.3%)	2,318 (32.6%)	5.7×10^{-9}
Cholesterol-lowering medication use, *n*	945 (24.2%)	18,091 (15.3%)	$<2.2\times10^{-16}$	151 (16.6%)	1,051 (14.8%)	1.6×10^{-1}
Body mass index, kg/m²	27.4 (24.3 to 31.1)	26.2 (23.6 to 29.6)	$<2.2\times10^{-16}$	28.9 (25.1 to 33.7)	27.4 (24.2 to 31.7)	1.1×10^{-11}

Systolic blood pressure, mmHg	139 (127 to 154)	139 (126 to 153)	5.5×10^{-1}	131 (120 to 145)	130 (119 to 143)	4.0×10^{-2}
Total cholesterol, mg/dL	229.0 (198.7 to 259.4)	233.7 (205.6 to 262.6)	7.4×10^{-11}	225 (198 to 254)	226 (203.0 to 252.0)	2.6×10^{-1}
Low-density lipoprotein cholesterol, mg/dL	141.8 (116.8 to 165.6)	144.0 (122.0 to 167.1)	4.3×10^{-7}	137.0 (114.0 to 165.0)	141.0 (118.0 to 166.0)	1.1×10^{-1}
High-density lipoprotein cholesterol, mg/dL	58.3 (49.8 to 68.7)	61.4 (52.4 to 71.9)	$<2.2\times10^{-16}$	53.0 (44.0 to 64.8)	54.0 (45.0 to 65.0)	6.6×10^{-2}
Triglycerides, mg/dL	138.7 (100.1 to 194.1)	124.4 (91.2 to 173.7)	$<2.2\times10^{-16}$	140.0 (97.5 to 195.0)	135.0 (95.0 to 185.0)	1.1×10^{-1}
C-reactive protein, mg/L	1.90 (0.89 to 4.10)	1.40 (0.69 to 2.92)	$<2.2\times10^{-16}$	-	-	-
Any Women's Health Initiative clinical trial, *n*	-	-	-	514 (56.5%)	3,946 (55.4%)	5.7×10^{-1}
Women's Health Initiative hormone trial, *n*	-	-	-	300 (33.0%)	2,328 (32.7%)	9.0×10^{-1}
Clonal hematopoiesis of indeterminate potential, *n*	169/3,633 (4.7%)	4,403/110,567 (4.0%)	4.7×10^{-2}	93 (10.2%)	596 (8.4%)	7.0×10^{-2}

Continuous variables are summarized as median (IQR), while categorical characteristics are summarized as number (%). Continuous characteristics were compared using the Kruskal-Wallis test given evidence of skewed distributions (**Table S4**). Categorical characteristics were compared using the Pearson chi squared test. No corrections for multiple comparisons were made.

Table S6. Baseline characteristics in women with below-median vs. above-median LTL.

	UK Biobank (*N*=122,224)			Women's Health Initiative (*N* =8,030)		
	LTL < median (*n*=61,111)	**LTL ≥ median (*n*=61,113)**	***P*-value**	**LTL < median (*n*=4,015)**	**LTL ≥ median (*n*=4,015)**	***P*-value**
Age at blood draw, years	61 (57 to 65)	60 (56 to 64)	$<2.2\times10^{-16}$	70 (65 to 74)	68 (62 to 73)	$<2.2\times10^{-16}$
Race, *n* • White • Black • Asian • Other	 59,120 (96.7%) 397 (0.6%) 979 (1.6%) 615 (1.0%)	 58,375 (95.5%) 834 (1.4%) 1,081 (1.8%) 823 (1.3%)	$<2.2\times10^{-16}$	 3,433 (85.5%) 389 (9.7%) 70 (1.7%) 123 (3.1%)	 3,234 (80.5%) 520 (13.0%) 86 (2.1%) 175 (4.4%)	9.4×10^{-8}
Townsend deprivation index	-2.31 (-3.70 to 0.13)	-2.32 (-3.73 to 0.12)	1.0×10^{-1}	-	-	-
Age at menarche, years	13 (12 to 14)	13 (12 to 14)	7.2×10^{-2}	13 (12 to 13)	13 (12 to 13)	5.9×10^{-1}
Age at menopause, years	50 (48 to 53)	51 (48 to 53)	1.4×10^{-8}	50 (45 to 52)	50 (45 to 52)	3.9×10^{-1}
Parity	2 (1 to 3)	2 (1 to 2)	6.6×10^{-8}	3 (2 to 4)	3 (2 to 4)	8.6×10^{-1}
Nulliparity, *n*	9,548 (15.6%)	10,357 (17.0%)	3.7×10^{-10}	93 (2.5%)	81 (2.2%)	4.2×10^{-1}
History of hysterectomy, *n*	6,062 (9.9%)	5,957 (9.7%)	3.2×10^{-1}	1,534 (38.2%)	1,605 (40.0%)	1.1×10^{-1}
Age at hysterectomy, years	47 (40 to 54)	47 (41 to 53)	8.7×10^{-1}	45-49 (40-44 to 50-54)	45-49 (40-44 to 50-54)	5.5×10^{-1}
History of bilateral oophorectomy, *n*	3,025 (4.9%)	3,078 (5.0%)	5.0×10^{-1}	936 (23.3%)	975 (24.3%)	3.2×10^{-1}
Age at bilateral oophorectomy, years	51 (46 to 57)	50 (46 to 56)	2.4×10^{-3}	45-49 (40-44 to 50-54)	45-49 (40-44 to 50-54)	7.2×10^{-1}
Ever-use of hormone therapy, *n*	28,628 (46.9%)	26,204 (43.0%)	$<2.2\times10^{-16}$	2,421 (61.6%)	2,403 (61.2%)	7.3×10^{-1}

Current use of hormone therapy, *n*	2,901 (4.7%)	2,938 (4.8%)	6.3×10^{-1}	666 (16.6%)	709 (17.7%)	2.1×10^{-1}
Current or former smoking, *n*	26,043 (42.6%)	25,070 (41.0%)	1.7×10^{-8}	1,952 (49.2%)	1,953 (49.3%)	9.4×10^{-1}
Type 2 diabetes mellitus, *n*	1,140 (1.9%)	994 (1.6%)	1.5×10^{-3}	324 (8.1%)	338 (8.4%)	6.0×10^{-1}
Coronary artery disease, *n*	1,473 (2.4%)	1,151 (1.9%)	2.4×10^{-10}	463 (11.5%)	384 (9.6%)	4.6×10^{-3}
History of cancer, *n*	6,466 (10.6%)	6,151 (10.1%)	3.4×10^{-3}	296 (7.4%)	262 (6.6%)	1.4×10^{-1}
Antihypertensive medication use, *n*	13,291 (21.7%)	12,245 (20.0%)	1.9×10^{-13}	1,340 (33.4%)	1,363 (33.9%)	6.0×10^{-1}
Cholesterol-lowering medication use, *n*	10,337 (16.9%)	8,699 (14.2%)	$<2.2\times10^{-16}$	626 (15.6%)	576 (14.3%)	1.3×10^{-1}
Body mass index, kg/m²	26.3 (23.7 to 29.9)	26.0 (23.5 to 29.4)	$<2.2\times10^{-16}$	27.6 (24.4 to 31.9)	27.4 (24.2 to 31.9)	2.5×10^{-1}
Systolic blood pressure, mmHg	139 (127 to 154)	139 (126 to 153)	1.2×10^{-9}	131 (120 to 144)	130 (119 to 143)	2.2×10^{-1}
Total cholesterol, mg/dL	233.0 (204.6 to 262.0)	234.1 (206.1 to 263.0)	5.1×10^{-7}	226.0 (202.0 to 253.0)	225.0 (203.O to 252.0)	6.8×10^{-1}
Low-density lipoprotein cholesterol, mg/dL	143.4 (121.0 to 166.5)	144.4 (122.7 to 167.6)	1.7×10^{-9}	141.0 (117.2 to 165.0)	141.0 (117.0 to 166.0)	8.6×10^{-1}
High-density lipoprotein cholesterol, mg/dL	61.2 (52.2 to 71.7)	61.3 (52.4 to 71.8)	2.1×10^{-1}	54.0 (45.0 to 64.8)	54.0 (45.0 to 65.0)	4.8×10^{-1}
Triglycerides, mg/dL	125.9 (92.3 to 175.9)	123.7 (90.6 to 173.0)	1.0×10^{-10}	135.0 (95.0 to 190.0)	130.0 (95.0 to 185.0)	2.3×10^{-2}
C-reactive protein, mg/L	1.49 (0.73 to 3.07)	1.35 (0.66 to 2.83)	$<2.2\times10^{-16}$	-	-	-
Any Women's Health Initiative clinical trial, *n*	-	-	-	2,106 (52.5%)	2,354 (58.6%)	2.9×10^{-8}
Women's Health Initiative hormone trial, *n*	-	-	-	1,254 (31.2%)	1,374 (34.2%)	4.6×10^{-3}

Clonal hematopoiesis of indeterminate potential, *n*	2,445/57,219 (4.3%)	2,127/56,981 (3.7%)	3.5×10^{-6}	374 (9.3%)	315 (7.8%)	2.1×10^{-2}

Continuous variables are summarized as median (IQR), while categorical characteristics are summarized as number (%). Continuous characteristics were compared using the Kruskal-Wallis test given evidence of skewed distributions (**Table S4**). Categorical characteristics were compared using the Pearson chi squared test. No corrections for multiple comparisons were made.

Table S7. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) in the UK Biobank and Women's Health Initiative (minimally adjusted models).

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	$<2.2\times10^{-16}$	0.00 (-0.02 to 0.02)	0.92×10^{-1}	-0.02 (-0.03 to -0.02)	3.0×10^{-15}	2.9×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.00)	4.3×10^{-2}	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	5.2×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.03 to -0.01)	4.6×10^{-3}	0.00 (-0.02 to 0.02)	9.6×10^{-1}	-0.01 (-0.03 to 0.00)	1.3×10^{-2}	1.7×10^{-1}
Premature menopause[a]	-0.05 (-0.08 to -0.02)	1.6×10^{-3}	-0.02 (-0.09 to 0.05)	6.2×10^{-1}	-0.04 (-0.07 to -0.02)	2.1×10^{-3}	3.8×10^{-1}
Natural premature menopause[a]	-0.09 (-0.14 to -0.04)	2.5×10^{-4}	-0.06 (-0.19 to 0.07)	3.4×10^{-1}	-0.09 (-0.13 to -0.04)	1.7×10^{-4}	6.9×10^{-1}
Surgical premature menopause[a]	-0.02 (-0.06 to 0.02)	3.0×10^{-2}	-0.00 (-0.08 to 0.08)	9.7×10^{-1}	-0.02 (-0.05 to 0.02)	3.5×10^{-1}	6.5×10^{-1}

Analyses represent linear regression models adjusted for age, age², race/ethnicity, and the first ten principal components of genetic ancestry. The UK Biobank sample included 112,224 women, of whom 12,531 had a history of gynecologic surgery. The WHI sample included 8,030 women, of whom 3,170 had a history of gynecologic surgery. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S8. Adjusted differences in leukocyte telomere length by age at menopause among women with and without a history of gynecologic surgery.

	UK Biobank		Women's Health Initiative		Meta-analysis		
Age at menopause	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
No history of gynecologic surgery	-	-	-	-	-	-	-
≥55	0.03 (0.02 to 0.05)	5.1×10^{-5}	-0.01 (-0.08 to 0.06)	8.1×10^{-1}	0.03 (0.02 to 0.05)	9.7×10^{-5}	2.6×10^{-1}
50-54	Ref.	-	Ref.	-	Ref.	-	-
45-49	-0.04 (-0.06 to -0.03)	1.5×10^{-8}	-0.05 (-0.12 to 0.02)	1.9×10^{-1}	-0.04 (-0.06 to -0.03)	6.2×10^{-9}	9.0×10^{-1}
40-44	-0.07 (-0.10 to -0.05)	2.8×10^{-9}	-0.08 (-0.19 to 0.03)	1.4×10^{-1}	-0.07 (-0.10 to -0.05)	9.4×10^{-10}	9.1×10^{-1}
<40	-0.08 (-0.13 to -0.03)	$<2.2\times10^{-16}$	-0.11 (-0.28 to 0.06)	2.1×10^{-1}	-0.08 (-0.13 to -0.04)	5.2×10^{-4}	7.4×10^{-1}
History of gynecologic surgery	-	-	-	-	-	-	-
≥55	-0.02 (-0.09 to 0.05)	6.1×10^{-1}	-0.09 (-0.24 to 0.05)	2.0×10^{-1}	-0.03 (-0.10 to 0.03)	3.0×10^{-1}	3.6×10^{-1}
50-54	Ref.	-	Ref.	-	Ref.	-	-
45-49	0.00 (-0.05 to 0.05)	9.5×10^{-1}	0.02 (-0.08 to 0.12)	6.9×10^{-1}	0.00 (-0.04 to 0.05)	9.1×10^{-1}	7.0×10^{-1}
40-44	0.02 (-0.03 to 0.07)	4.5×10^{-1}	0.03 (-0.08 to 0.14)	5.9×10^{-1}	0.02 (-0.02 to 0.07)	3.6×10^{-1}	8.7×10^{-1}
<40	-0.06 (-0.12 to -0.01)	2.8×10^{-2}	-0.04 (-0.15 to 0.06)	4.4×10^{-1}	-0.06 (-0.11 to -0.01)	2.1×10^{-2}	7.4×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI

models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. No corrections for multiple comparisons were made. CI indicates confidence interval.

Table S9. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) after exclusion of participants with prevalent coronary artery disease.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	1.2×10^{-13}	0.00 (-0.02 to 0.01)	6.6×10^{-1}	-0.02 (-0.03 to -0.01)	8.4×10^{-13}	4.7×10^{-2}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.00)	6.6×10^{-2}	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	5.8×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.03 to 0.00)	1.4×10^{-2}	-0.01 (-0.04 to 0.01)	4.2×10^{-1}	-0.02 (-0.03 to 0.00)	1.1×10^{-2}	6.5×10^{-1}
Premature menopause (age <40 y)[a]	-0.04 (-0.07 to -0.01)	1.5×10^{-2}	-0.03 (-0.11 to 0.04)	4.0×10^{-1}	-0.04 (-0.07 to -0.01)	1.0×10^{-2}	8.4×10^{-1}
Natural premature menopause[a]	-0.09 (-0.14 to -0.04)	5.1×10^{-4}	-0.05 (-0.19 to 0.08)	4.6×10^{-1}	-0.08 (-0.13 to -0.04)	4.2×10^{-4}	6.5×10^{-1}
Surgical premature menopause[a]	0.00 (-0.05 to 0.04)	8.4×10^{-1}	-0.02 (-0.11 to 0.06)	5.8×10^{-1}	-0.01 (-0.05 to 0.03)	6.6×10^{-1}	6.8×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, and current hormone therapy use. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 119,600 women without prevalent coronary artery disease (CAD). The Women's Health Initiative sample included 7,183 women without prevalent CAD. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S10. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) after exclusion of participants with a history of cancer.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	3.6×10^{-13}	0.00 (-0.01 to 0.02)	6.3×10^{-1}	-0.02 (-0.03 to -0.01)	3.0×10^{-11}	2.8×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.0)	5.7×10^{-3}	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	5.1×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.03 to 0.00)	2.7×10^{-2}	0.00 (-0.02 to 0.03)	7.0×10^{-1}	-0.01 (-0.02 to 0.00)	9.0×10^{-2}	1.4×10^{-1}
Premature menopause (age <40 y)[a]	-0.03 (-0.07 to 0.00)	6.8×10^{-2}	0.00 (-0.07 to 0.07)	9.7×10^{-1}	-0.03 (-0.06 to 0.00)	1.0×10^{-1}	4.5×10^{-1}
Natural premature menopause[a]	-0.08 (-0.13 to -0.03)	1.7×10^{-3}	-0.05 (-0.18 to 0.08)	4.8×10^{-1}	-0.08 (-0.12 to -0.03)	1.4×10^{-3}	6.3×10^{-1}
Surgical premature menopause[a]	0.01 (-0.04 to 0.05)	7.3×10^{-1}	0.02 (-0.07 to 0.10)	7.0×10^{-1}	0.01 (-0.03 to 0.05)	6.3×10^{-1}	8.7×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 119,600 women without prevalent coronary artery disease (CAD). The Women's Health Initiative sample included 7,183 women without prevalent CAD. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S11. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) after exclusion of participants with a history of hysterectomy only (without bilateral oophorectomy).

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.03 (-0.04 to -0.02)	$<2.2\times10^{-16}$	0.00 (-0.02 to 0.02)	8.3×10^{-1}	-0.03 (-0.03 to -0.02)	$<2.2\times10^{-16}$	1.6×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.00)	4.7×10^{-2}	-0.04 (-0.04 to 0.03)	$<2.2\times10^{-16}$	5.8×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.01 (-0.03 to 0.02)	6.4×10^{-1}	-0.01 (-0.04 to 0.02)	6.1×10^{-1}	-0.01 (-0.02 to 0.01)	5.0×10^{-1}	8.7×10^{-1}
Premature menopause (age <40 y)[a]	-0.04 (-0.08 to 0.00)	6.7×10^{-2}	-0.01 (-0.09 to 0.07)	7.8×10^{-1}	-0.03 (-0.07 to 0.00)	7.8×10^{-2}	5.6×10^{-1}
Natural premature menopause[a]	-0.07 (-0.12 to -0.03)	2.8×10^{-3}	-0.08 (-0.23 to 0.08)	3.3×10^{-1}	-0.07 (-0.12 to -0.03)	1.6×10^{-3}	9.5×10^{-1}
Surgical premature menopause[a]	0.08 (-0.01 to 0.16)	9.2×10^{-2}	0.01 (-0.08 to 0.10)	8.2×10^{-1}	0.05 (-0.02 to 0.11)	1.7×10^{-1}	3.2×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. After exlucding those witha history of hysterectomy only, the UK Biobank sample included 115,796 women. After excluding those with a history of hysterectomy only, the Women's Health Initiative sample included 6,771 women. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S12. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) stratified by age <65 years vs. ≥65 years at blood draw.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Age <65 years	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.01)	2.5×10^{-9}	0.00 (-0.03 to 0.03)	8.2×10^{-1}	-0.02 (-0.03 to -0.01)	4.3×10^{-9}	2.9×10^{-1}
Per 5 years of earlier natural menopause	-0.03 (-0.04 to -0.03)	2.3×10^{-16}	-0.06 (-0.12 to -0.01)	2.8×10^{-2}	-0.03 (-0.04 to -0.03)	$<2.2\times10^{-16}$	3.3×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	0.02 (-0.03 to 0.00)	3.3×10^{-2}	0.01 (-0.04 to 0.05)	8.1×10^{-1}	-0.02 (-0.03 to 0.00)	5.2×10^{-2}	3.6×10^{-1}
Premature menopause (age <40 y)[a]	-0.03 (-0.07 to 0.01)	1.2×10^{-1}	0.00 (-0.12 to 0.12)	9.6×10^{-1}	-0.03 (-0.06 to 0.01)	1.3×10^{-1}	6.8×10^{-1}
Natural premature menopause[a]	-0.07 (-0.13 to -0.02)	1.0×10^{-2}	-0.07 (-0.30 to 0.17)	5.8×10^{-1}	-0.07 (-0.12 to -0.02)	8.6×10^{-3}	9.6×10^{-1}
Surgical premature menopause[a]	0.00 (-0.04 to 0.05)	8.4×10^{-1}	0.02 (-0.12 to 0.15)	8.1×10^{-1}	0.01 (-0.04 to 0.05)	7.9×10^{-1}	8.7×10^{-1}
Age ≥65 years	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.02 (-0.04 to -0.01)	9.0×10^{-6}	0.00 (-0.01 to 0.02)	6.1×10^{-1}	-0.02 (-0.03 to -0.01)	3.5×10^{-4}	7.3×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.05 to -0.03)	1.5×10^{-9}	-0.02 (-0.05 to 0.01)	2.8×10^{-1}	-0.04 (-0.05 to -0.03)	2.0×10^{-9}	1.9×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.01 (-0.03 to 0.01)	4.3×10^{-1}	0.00 (-0.03 to 0.03)	9.7×10^{-1}	-0.01 (-0.02 to 0.01)	5.7×10^{-1}	5.8×10^{-1}
Premature menopause (age <40 y)[a]	-0.05 (-0.11 to 0.02)	1.4×10^{-1}	-0.01 (-0.10 to 0.07)	7.3×10^{-1}	-0.04 (-0.08 to 0.01)	1.7×10^{-1}	5.5×10^{-1}
Natural premature menopause[a]	-0.09 (-0.19 to 0.01)	7.0×10^{-2}	-0.05 (-0.20 to 0.10)	5.3×10^{-1}	-0.08 (-0.16 to 0.00)	6.4×10^{-2}	6.3×10^{-1}

Surgical premature menopause[a]	-0.02 (-0.10 to 0.06)	6.4×10^{-1}	0.00 (-0.10 to 0.09)	9.7×10^{-1}	-0.01 (-0.07 to 0.05)	7.0×10^{-1}	7.9×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 93,389 women with age <65 years and 28,835 women with age ≥65 years at blood draw. The Women's Health Initiative sample included 2,191 women with age <65 years and 5,839 with age ≥65 years at blood draw. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S13. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) stratified by self-reported race (White vs. Black).

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Self-reported race/ethnicity: White	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	2.3×10^{-13}	0.00 (-0.02 to 0.02)	8.8×10^{-1}	-0.02 (-0.03 to -0.01)	2.6×10^{-12}	2.9×10^{-2}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.00)	3.1×10^{-2}	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	8.3×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.01 (-0.03 to 0.00)	4.0×10^{-2}	0.00 (-0.02 to 0.03)	8.5×10^{-1}	-0.01 (-0.02 to 0.00)	8.4×10^{-2}	2.6×10^{-1}
Premature menopause (age <40 y)[a]	-0.03 (-0.07 to -0.00)	4.6×10^{-2}	-0.01 (-0.08 to 0.07)	9.0×10^{-1}	-0.03 (-0.06 to 0.00)	5.9×10^{-2}	5.2×10^{-1}
Natural premature menopause[a]	-0.07 (-0.12 to -0.03)	3.0×10^{-3}	-0.05 (-0.20 to 0.10)	4.9×10^{-1}	-0.07 (-0.12 to -0.03)	2.4×10^{-3}	7.7×10^{-1}
Surgical premature menopause[a]	-0.00 (-0.04 to 0.04)	9.3×10^{-1}	0.01 (-0.08 to 0.10)	8.1×10^{-1}	0.00 (-0.04 to 0.04)	9.8×10^{-1}	8.0×10^{-1}
Self-reported race/ethnicity: Black	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.05 (-0.11 to 0.00)	5.6×10^{-2}	0.01 (-0.03 to 0.06)	6.5×10^{-1}	-0.02 (-0.05 to 0.02)	4.0×10^{-1}	7.6×10^{-2}
Per 5 years of earlier natural menopause	-0.06 (-0.13 to 0.01)	1.0×10^{-1}	-0.04 (-0.13 to 0.04)	3.4×10^{-1}	-0.05 (-0.11 to 0.00)	6.2×10^{-2}	7.5×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.13 (-0.26 to 0.00)	4.6×10^{-2}	0.00 (-0.07 to 0.06)	9.0×10^{-1}	-0.03 (-0.09 to 0.03)	3.1×10^{-1}	8.2×10^{-2}
Premature menopause (age <40 y)[a]	-0.29 (-0.56 to -0.02)	3.4×10^{-2}	-0.02 (-0.19 to 0.16)	8.5×10^{-1}	-0.10 (-0.24 to 0.05)	1.9×10^{-1}	9.3×10^{-2}
Natural premature menopause[a]	-0.45 (-0.88 to -0.03)	3.8×10^{-2}	-0.05 (-0.36 to 0.25)	7.3×10^{-1}	-0.19 (-0.44 to 0.06)	1.3×10^{-1}	1.4×10^{-1}

Surgical premature menopause[a]	-0.19 (-0.53 to 0.15)	2.7×10^{-1}	-0.00 (-0.20 to 0.19)	9.8×10^{-1}	-0.05 (-0.22 to 0.12)	5.7×10^{-1}	3.5×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 117,495 women who reported to be White and 1,231 who reported to be Black. The Women's Health Initiative sample included 6,667 women who reported to be White and 909 who reported to be Black. Women with other self-reported races/ethnicities were excluded from the present analysis. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S14. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) after further adjustment for history of hormone therapy use.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.01)	1.4×10^{-11}	0.01 (-0.01 to 0.02)	5.2×10^{-1}	-0.02 (-0.02 to -0.01)	7.8×10^{-10}	4.0×10^{-3}
Per 5 years of earlier natural menopause	-0.03 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.02 (-0.05 to 0.00)	1.0×10^{-1}	-0.03 (-0.04 to -0.03)	$<2.2\times10^{-16}$	4.6×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.03 to 0.00)	2.4×10^{-2}	0.00 (-0.02 to 0.03)	7.6×10^{-1}	-0.01 (-0.02 to 0.00)	7.0×10^{-2}	1.7×10^{-1}
Premature menopause (age <40 y)[a]	-0.03 (-0.06 to 0.01)	1.1×10^{-1}	-0.01 (-0.08 to 0.06)	8.0×10^{-1}	-0.02 (-0.05 to 0.01)	1.1×10^{-1}	6.6×10^{-1}
Natural premature menopause[a]	-0.07 (-0.12 to -0.02)	3.8×10^{-3}	-0.05 (-0.18 to 0.08)	4.3×10^{-1}	-0.07 (-0.11 to -0.02)	2.8×10^{-3}	7.9×10^{-1}
Surgical premature menopause[a]	0.01 (-0.03 to 0.05)	7.2×10^{-1}	0.01 (-0.07 to 0.09)	8.9×10^{-1}	0.01 (-0.03 to 0.04)	7.0×10^{-1}	9.7×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, prevalent coronary artery disease, and prior hormone therapy use. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S15. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) stratified by ever- vs. never-use of hormone therapy.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
No prior use of hormone therapy	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.03 (-0.04 to -0.02)	2.0×10^{-12}	-0.01 (-0.04 to 0.02)	5.5×10^{-1}	-0.03 (-0.04 to -0.02)	4.9×10^{-12}	1.4×10^{-1}
Per 5 years of earlier natural menopause	-0.04 (-0.05 to -0.03)	$<2.2\times10^{-16}$	-0.04 (-0.08 to 0.00)	7.8×10^{-2}	-0.04 (-0.05 to -0.03)	$<2.2\times10^{-16}$	7.6×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.01 (-0.03 to 0.02)	6.8×10^{-1}	-0.02 (-0.08 to 0.03)	3.8×10^{-1}	-0.01 (-0.03 to 0.01)	4.6×10^{-1}	5.3×10^{-1}
Premature menopause (age <40 y)[a]	-0.05 (-0.11 to 0.01)	1.1×10^{-1}	0.02 (-0.12 to 0.17)	7.8×10^{-1}	-0.04 (-0.09 to 0.02)	1.6×10^{-1}	3.8×10^{-1}
Natural premature menopause[a]	-0.11 (-0.19 to -0.03)	8.1×10^{-3}	-0.03 (-0.28 to 0.22)	8.3×10^{-1}	-0.10 (-0.18 to -0.02)	9.9×10^{-3}	5.3×10^{-1}
Surgical premature menopause[a]	0.02 (-0.07 to 0.10)	6.8×10^{-1}	0.04 (-0.13 to 0.22)	6.2×10^{-1}	0.02 (-0.05 to 0.10)	5.6×10^{-1}	7.9×10^{-1}
Prior use of hormone therapy	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.01 (-0.02 to 0.00)	5.0×10^{-3}	0.01 (-0.01 to 0.03)	2.7×10^{-1}	-0.01 (-0.02 to 0.00)	2.7×10^{-2}	3.9×10^{-2}
Per 5 years of earlier natural menopause	-0.03 (-0.04 to -0.02)	1.6×10^{-7}	-0.01 (-0.05 to 0.03)	5.0×10^{-1}	-0.02 (-0.03 to -0.02)	1.5×10^{-7}	5.4×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.04 to 0.00)	1.7×10^{-2}	0.01 (-0.02 to 0.04)	4.8×10^{-1}	-0.01 (-0.03 to 0.00)	9.5×10^{-2}	6.5×10^{-2}
Premature menopause (age <40 y)[a]	-0.02 (-0.05 to 0.02)	3.9×10^{-1}	-0.01 (-0.09 to 0.07)	7.2×10^{-1}	-0.02 (-0.05 to 0.02)	3.5×10^{-1}	9.7×10^{-1}
Natural premature menopause[a]	-0.05 (-0.11 to 0.01)	1.1×10^{-1}	-0.05 (-0.20 to 0.10)	5.4×10^{-1}	-0.05 (-0.10 to 0.01)	8.5×10^{-2}	9.9×10^{-1}

Surgical premature menopause[a]	0.00 (-0.04 to 0.05)	6.4×10^{-1}	0.00 (-0.09 to 0.09)	9.3×10^{-1}	0.00 (-0.04 to 0.04)	9.1×10^{-1}	8.7×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 67,159 women who reported never having used hormone therapy (HT) and 54,832 women with ever-use of HT. The Women's Health Initiative sample included 3,031 women who reported never having used HT and 4,824 women with ever-use of HT. [a]Reference group is women with age at menopause ≥40 years. No corrections for multiple comparisons were made. CI indicates confidence interval.

Table S16. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) after further adjustment for age at menarche.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	8.1×10^{-13}	0.00 (-0.01 to 0.02)	5.9×10^{-1}	-0.02 (-0.02 to -0.01)	6.2×10^{-11}	2.8×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.05 to 0.00)	6.2×10^{-2}	-0.03 (-0.04 to -0.03)	$<2.2\times10^{-16}$	5.3×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.03 to 0.00)	2.8×10^{-2}	0.00 (-0.02 to 0.03)	7.7×10^{-1}	0.01 (-0.02 to 0.00)	7.8×10^{-2}	1.7×10^{-1}
Premature menopause (age <40 y)[a]	-0.03 (-0.06 to 0.00)	6.8×10^{-2}	-0.01 (-0.08 to 0.06)	8.5×10^{-1}	-0.03 (-0.05 to 0.00)	8.2×10^{-2}	5.5×10^{-1}
Natural premature menopause[a]	-0.07 (-0.12 to -0.02)	4.4×10^{-3}	-0.05 (-0.17 to 0.08)	4.8×10^{-1}	-0.07 (-0.11 to -0.02)	3.6×10^{-3}	7.3×10^{-1}
Surgical premature menopause[a]	0.00 (-0.04 to 0.04)	9.8×10^{-1}	0.01 (-0.07 to 0.09)	8.6×10^{-1}	0.00 (-0.03 to 0.04)	9.1×10^{-1}	8.8×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, prevalent coronary artery disease, and prior hormone therapy use. The UK Biobank sample included 119,627 women with available data on age at menarche. The Women's Health Initiative sample included 8,015 women with available data on age at menarche. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. [a]Reference group is women with age at menopause ≥40 years. No corrections for multiple comparisons were made. CI indicates confidence interval.

Table S17. Associations of age at menarche and reproductive lifespan with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length).

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Age at menarche	-	-	-	-	-	-	-
≤11 years	-0.03 (-0.05 to -0.01)	2.3×10^{-4}	-0.02 (-0.09 to 0.04)	4.4×10^{-1}	-0.03 (-0.05 to -0.02)	1.7×10^{-4}	8.2×10^{-1}
12 years	0.00 (-0.02 to 0.01)	7.0×10^{-1}	0.04 (-0.02 to 0.10)	1.6×10^{-1}	0.00 (-0.02 to 0.02)	9.7×10^{-1}	1.4×10^{-1}
13 years	Ref.	-	Ref.	-	Ref.	-	-
14 years	-0.01 (-0.03 to 0.01)	2.2×10^{-1}	0.05 (-0.02 to 0.12)	1.9×10^{-1}	-0.01 (-0.02 to 0.01)	3.8×10^{-1}	1.2×10^{-1}
≥15 years	-0.01 (-0.03 to 0.01)	4.0×10^{-1}	-0.02 (-0.10 to 0.06)	6.6×10^{-1}	-0.01 (-0.03 to 0.01)	3.6×10^{-1}	8.1×10^{-1}
Reproductive lifespan	-	-	-	-	-	-	-
<33 years	-0.03 (-0.05 to -0.01)	3.1×10^{-4}	0.01 (-0.05 to 0.07)	7.0×10^{-1}	-0.03 (-0.05 to -0.01)	7.8×10^{-4}	1.7×10^{-1}
33-35 years	-0.01 (-0.03 to 0.01)	3.7×10^{-1}	0.03 (-0.04 to 0.11)	3.5×10^{-1}	-0.01 (-0.02 to 0.01)	5.1×10^{-1}	2.6×10^{-1}
36-38 years	Ref.	-	Ref.	-	Ref.	-	-
39-41 years	0.01 (-0.00 to 0.03)	6.6×10^{-2}	0.04 (-0.03 to 0.10)	3.2×10^{-1}	0.02 (0.00 to 0.03)	4.4×10^{-2}	5.7×10^{-1}
≥42 years	0.03 (0.01 to 0.05)	7.5×10^{-4}	-0.03 (-0.10 to 0.05)	4.9×10^{-1}	0.03 (0.01 to 0.04)	1.9×10^{-3}	1.4×10^{-1}

Analyses represent linear regression models adjusted for age, age², race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI analyses were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend

deprivation index. The UK Biobank sample included 119,627 women with available data on age at menarche. The Women's Health Initiative sample included 8,015 women with available data on age at menarche. No corrections for multiple comparisons were made. CI indicates confidence interval.

Table S18. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length) after further adjustment for CHIP.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	4.1×10^{-14}	0.00 (-0.01 to 0.01)	6.7×10^{-1}	-0.02 (-0.03 to -0.01)	4.3×10^{-12}	2.2×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.00)	4.7×10^{-2}	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	5.3×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.01 (-0.03 to 0.00)	3.3×10^{-2}	0.00 (-0.02 to 0.02)	9.2×10^{-1}	-0.01 (-0.02 to 0.00)	7.5×10^{-2}	2.5×10^{-1}
Premature menopause[a]	-0.04 (-0.07 to 0.00)	3.3×10^{-2}	-0.01 (-0.07 to 0.06)	8.6×10^{-1}	-0.03 (-0.06 to 0.00)	4.5×10^{-2}	4.5×10^{-1}
Natural premature menopause[a]	-0.07 (-0.12 to -0.02)	3.4×10^{-3}	-0.04 (-0.17 to 0.08)	4.9×10^{-1}	-0.07 (-0.12 to -0.02)	2.9×10^{-3}	6.7×10^{-1}
Surgical premature menopause[a]	0.00 (-0.05 to 0.04)	7.6×10^{-1}	0.01 (-0.07 to 0.09)	8.5×10^{-1}	0.00 (-0.04 to 0.03)	8.6×10^{-1}	7.5×10^{-1}

Analyses represent linear regression models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, prevalent coronary artery disease, and clonal hematopoiesis of indeterminate potential (CHIP) status. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 114,200 women with whole exome sequences available, of whom 4,572 were identified as having clonal hematopoiesis of indeterminate potential (CHIP). The Women's Health Initiative sample had available whole genome sequences for all participants and included 689 women with CHIP. [a]Reference group is women with age at menopause ≥40 years. No corrections for multiple comparisons were made. CI indicates confidence interval.

Table S19. Association of age at menopause with leukocyte telomere length (in standard deviations of log-transformed leukocyte telomere length), stratified by clonal hematopoiesis of indeterminate potential (CHIP) status.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***β* (95% CI)**	***P*-value**	***P*(heterogeneity)**
Women without CHIP	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.02 (-0.03 to -0.02)	$<7.9\times10^{-13}$	0.00 (-0.01 to 0.02)	7.7×10^{-1}	-0.02 (-0.03 to -0.01)	3.4×10^{-11}	6.2×10^{-3}
Per 5 years of earlier natural menopause	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	-0.03 (-0.06 to 0.00)	5.2×10^{-2}	-0.04 (-0.04 to -0.03)	$<2.2\times10^{-16}$	6.5×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	-0.02 (-0.03 to 0.00)	2.8×10^{-2}	0.00 (-0.02 to 0.03)	7.5×10^{-1}	-0.01 (-0.02 to 0.00)	8.1×10^{-2}	1.7×10^{-1}
Premature menopause (age <40 y)[a]	-0.03 (-0.06 to 0.00)	7.6×10^{-2}	-0.01 (-0.08 to 0.06)	8.5×10^{-1}	-0.03 (-0.06 to 0.00)	9.1×10^{-2}	5.7×10^{-1}
Natural premature menopause[a]	-0.07 (-0.12 to -0.01)	1.2×10^{-2}	-0.02 (-0.15 to 0.12)	8.2×10^{-1}	-0.06 (-0.11 to -0.01)	1.5×10^{-2}	5.0×10^{-1}
Surgical premature menopause[a]	0.00 (-0.05 to 0.04)	8.5×10^{-1}	0.00 (-0.09 to 0.08)	9.2×10^{-1}	0.00 (-0.04 to 0.03)	8.3×10^{-1}	$>9.9\times10^{-1}$
Women with CHIP	-	-	-	-	-	-	-
Per 5 years of earlier menopause, overall	-0.04 (-0.07 to -0.02)	2.5×10^{-3}	0.00 (-0.06 to 0.05)	9.4×10^{-1}	-0.03 (-0.06 to -0.01)	8.6×10^{-3}	1.3×10^{-1}
Per 5 years of earlier natural menopause	-0.07 (-0.10 to -0.03)	9.7×10^{-5}	-0.03 (-0.12 to 0.07)	5.8×10^{-1}	-0.06 (-0.10 to -0.03)	1.2×10^{-4}	4.0×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	0.00 (-0.06 to 0.07)	9.2×10^{-1}	-0.01 (-0.09 to 0.07)	7.7×10^{-1}	0.00 (-0.05 to 0.05)	9.1×10^{-1}	7.7×10^{-1}
Premature menopause (age <40 y)[a]	-0.17 (-0.33 to -0.02)	2.8×10^{-2}	-0.01 (-0.24 to 0.22)	9.5×10^{-1}	-0.12 (-0.24 to 0.01)	6.3×10^{-2}	2.4×10^{-1}

Natural premature menopause[a]	-0.26 (-0.49 to -0.03)	2.6×10^{-3}	-0.24 (-0.60 to 0.12)	1.9×10^{-1}	-0.25 (-0.45 to -0.06)	9.7×10^{-3}	9.3×10^{-1}
Surgical premature menopause[a]	-0.10 (-0.31 to 0.10)	3.3×10^{-1}	0.12 (-0.15 to 0.40)	3.9×10^{-1}	-0.02 (-0.19 to 0.14)	7.9×10^{-1}	2.0×10^{-1}

Analyses represent linear regression models adjusted for age, age², race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, and prevalent coronary artery disease. WHI analyses were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. The UK Biobank sample included 114,200 women with whole exome sequences available, of whom 4,572 were identified as having clonal hematopoiesis of indeterminate potential (CHIP). The Women's Health Initiative sample had available whole genome sequences for all participants and included 689 women with CHIP. No corrections for multiple comparisons were made. [a]Reference group is women with age at menopause ≥40 years. CI indicates confidence interval.

Table S20. Single-nucleotide variants (SNVs) included in the genetic instrument for leukocyte telomere length (LTL).

SNV	Chromosome	Position	Effect allele	Other allele	*β* (LTL)	SE (LTL)	*β* (ANM)	SE (ANM)	*F*-statistic	Excluded after Steiger filtering
rs10156169	7	128684571	A	G	0.02019	0.002112	0.07	0.02	91.4	No
rs1023767	8	95530969	G	A	0.018373	0.002348	-0.04	0.02	61.2	No
rs10840270	11	9629553	C	G	-0.01438	0.002125	0	0.02	45.8	No
rs10845387	12	11757743	G	A	0.014121	0.002094	0	0.03	45.5	No
rs11579626	1	146741960	A	C	-0.02651	0.003578	-0.02	0.04	54.9	No
rs11672788	19	33752731	G	A	-0.0223	0.003489	0.03	0.04	40.8	No
rs1233596	6	28727673	T	C	0.017237	0.002011	0.01	0.03	73.5	No
rs12372756	12	122815130	A	G	0.015129	0.00232	0.07	0.02	42.5	Yes
rs13230646	7	23930316	T	C	0.017328	0.002324	0.02	0.02	55.6	No
rs1332941	13	41695100	A	G	-0.02566	0.002732	-0.02	0.03	88.2	No
rs1609812	11	5247141	G	A	-0.04661	0.002735	-0.04	0.03	290.5	No
rs17464525	1	114443899	G	A	0.032442	0.002593	-0.02	0.03	156.5	No
rs17803849	2	210673445	C	T	-0.02732	0.002035	-0.03	0.02	180.3	No
rs1907702	12	88955469	G	A	-0.01502	0.002427	0.01	0.03	38.3	No
rs2072671	1	20915701	A	C	0.017373	0.002119	0.03	0.02	67.2	No

rs2180885	14	91949499	A	G	-0.01908	0.002002	-0.04	0.02	90.8	No
rs2230590	3	49936102	T	C	0.015802	0.002008	0	0.02	61.9	No
rs2282764	4	2255063	A	G	0.022423	0.002894	0.01	0.03	60	No
rs2293579	11	47440758	G	A	0.012915	0.002055	0.03	0.02	39.5	No
rs2303262	16	82203758	C	T	0.046949	0.002399	-0.03	0.03	382.9	No
rs2616	15	42045660	A	G	-0.01846	0.002324	0.02	0.02	63.1	No
rs2763979	6	31794592	C	T	0.027771	0.002081	0.17	0.02	178.1	Yes
rs2852772	18	42262869	G	A	0.023915	0.002699	-0.01	0.03	78.5	No
rs3093872	14	20811332	C	T	0.028251	0.004488	0	0.04	39.6	No
rs3785074	16	69406986	A	G	-0.02386	0.002205	0	0.02	117.2	No
rs38664	7	76390970	T	C	0.012247	0.002064	-0.04	0.03	35.2	No
rs4695407	4	48843372	A	G	-0.01415	0.001999	-0.08	0.02	50.1	Yes
rs5742915	15	74336633	T	C	-0.01934	0.002029	0.04	0.02	90.8	No
rs6054257	20	66370	G	A	0.014168	0.002477	-0.07	0.03	32.7	Yes
rs611646	11	108177097	T	A	0.036831	0.002035	0.02	0.02	327.4	No
rs6587577	1	151402045	A	G	0.018215	0.002636	0.03	0.03	47.8	No

rs6590343	11	128500215	A	G	-0.01217	0.002014	0.07	0.02	36.5	Yes
rs6659669	1	185315067	C	T	0.011709	0.002052	0.01	0.02	32.6	No
rs6669563	1	32279629	G	A	-0.01824	0.002025	-0.01	0.02	81.1	No
rs6873104	5	78954121	A	T	0.024533	0.003354	-0.02	0.03	53.5	No
rs728739	14	96182062	A	G	-0.02054	0.002695	-0.03	0.03	58.1	No
rs762679	8	48885436	T	A	-0.03101	0.00285	0.02	0.03	118.4	No
rs7790856	7	124459852	C	T	0.04372	0.002205	0.01	0.02	393	No
rs8053839	16	48390512	G	T	0.013921	0.002046	0.03	0.02	46.3	No
rs8102497	19	57370055	G	A	0.014965	0.002023	0	0.02	54.7	No
rs8105767	19	22215441	A	G	-0.03284	0.002201	-0.02	0.02	222.6	No
rs932002	1	226577306	C	T	0.040205	0.002797	0.08	0.03	206.7	No
rs9419958	10	105675946	T	C	0.08101	0.002938	0	0.03	760	No

Single-nucleotide variant (SNV) positions are expressed in hg37. ANM indicates age at natural menopause; SE, standard error.

Table S21. Single-nucleotide variants (SNVs) included in the genetic instrument for age at natural menopause.

SNV	Chromosome	Position	Effect allele	Other allele	*β* (ANM)	SE (ANM)	*β* (LTL)	SE (LTL)	*F*-statistic	Excluded after Steiger filtering
rs1046089	6	31602967	A	G	-0.22	0.02	-0.02706	0.002087	121	No
rs1054875	15	89879126	A	T	0.19	0.02	-0.00146	0.002059	90.3	No
rs10852344	16	12016919	T	C	-0.16	0.02	-0.00952	0.00205	64	No
rs10905065	10	5769827	A	G	-0.11	0.02	-0.01818	0.002044	30.3	No
rs10957156	8	61629401	A	G	-0.14	0.02	-0.00304	0.002333	49	No
rs11031006	11	30226528	A	G	0.22	0.03	-0.00464	0.002894	53.8	No
rs11668344	19	55833664	A	G	0.41	0.02	-0.00292	0.002081	420.3	No
rs11804189	1	46839995	A	G	0.11	0.02	0.001301	0.002171	30.3	No
rs12196873	6	111598058	A	C	-0.16	0.03	-0.00276	0.002889	28.4	No
rs12824058	12	130804334	A	G	0.14	0.02	0.008401	0.002054	49	No
rs13040088	20	61549202	A	G	0.16	0.02	-0.01101	0.002445	64	No
rs1411478	1	180962282	A	G	-0.13	0.02	-0.00516	0.00203	42.3	No
rs16858210	3	183624010	A	G	0.14	0.02	0.000698	0.002313	49	No
rs16991615	20	5948227	A	G	0.88	0.04	0.003866	0.004112	484	No
rs1713460	14	20933615	A	G	0.14	0.02	0.005101	0.002156	49	No

rs1799949	17	41245466	A	G	0.14	0.02	-0.01604	0.00213	49	No
rs1800932	2	48018081	A	G	-0.17	0.03	-0.00549	0.002562	32.1	No
rs2277068	5	175916249	T	C	-0.12	0.02	5.92E-05	0.002049	36	No
rs2277339	12	57146069	T	G	0.31	0.03	-0.01256	0.003239	106.8	No
rs2720044	8	37980587	A	C	-0.29	0.03	-0.00244	0.002736	93.4	No
rs2941505	17	37832704	A	G	-0.13	0.02	0.001899	0.002151	42.3	No
rs349306	19	950694	A	G	0.23	0.04	0.006291	0.003042	33.1	No
rs365132	5	176378574	T	G	0.24	0.02	-0.00384	0.002008	144	No
rs4246511	1	39380385	T	C	0.22	0.02	0.00028	0.002213	121	No
rs427394	5	6745875	A	G	0.13	0.02	-0.00041	0.002028	42.3	No
rs4693089	4	84373622	A	G	-0.2	0.02	0.000224	0.002004	100	No
rs4879656	9	33012382	A	C	-0.12	0.02	-0.00312	0.002072	36	No
rs4886238	13	61113739	A	G	0.18	0.02	0.002678	0.002137	81	No
rs6856693	4	185748806	A	G	-0.16	0.02	-0.00013	0.002019	64	No
rs6899676	6	10895260	A	G	-0.23	0.03	0.003747	0.002494	58.8	No
rs704795	2	27716494	A	G	-0.16	0.02	-0.00743	0.002044	64	No

rs7259376	19	22507705	A	G	-0.11	0.02	-0.01802	0.002011	30.3	No
rs763121	22	38879940	A	G	0.16	0.02	-0.00692	0.002106	64	No
rs8070740	17	5331896	A	G	-0.15	0.02	-0.00212	0.002328	56.3	No
rs930036	2	171941018	A	G	-0.19	0.02	-0.0018	0.002063	90.3	No

ANM indicates age at natural menopause; SE, standard error; LTL, leukocyte telomere length.

Table S22. Multivariable-adjusted associations of age at menopause with incident coronary artery disease events.

	UK Biobank		Women's Health Initiative		Meta-analysis		
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	***P*(heterogeneity)**
Per 5 years of earlier menopause, overall	1.13 (1.10 to 1.16)	$<2.2\times10^{-16}$	1.02 (0.98 to 1.07)	3.1×10^{-1}	1.10 (1.08 to 1.13)	$<2.2\times10^{-16}$	7.3×10^{-5}
Per 5 years of earlier natural menopause	1.10 (1.07 to 1.14)	4.0×10^{-9}	1.10 (1.02 to 1.18)	1.4×10^{-2}	1.10 (1.07 to 1.13)	1.8×10^{-10}	9.2×10^{-1}
Per 5 years of earlier menopause, history of gynecologic surgery	1.15 (1.10 to 1.21)	2.7×10^{-8}	1.01 (0.94 to 1.07)	8.8×10^{-1}	1.09 (1.05 to 1.14)	8.4×10^{-6}	8.7×10^{-4}
Premature menopause[a]	1.64 (1.46 to 1.84)	$<2.2\times10^{-16}$	1.01 (0.14 to 7.27)	9.3×10^{-1}	1.64 (1.46 to 1.84)	$<2.2\times10^{-16}$	6.3×10^{-1}
Natural premature menopause[a]	1.42 (1.17 to 1.72)	3.9×10^{-4}	1.33 (0.97 to 1.82)	7.4×10^{-2}	1.39 (1.18 to 1.64)	7.7×10^{-5}	7.4×10^{-1}
Surgical premature menopause[a]	1.79 (1.55 to 2.06)	1.1×10^{-15}	0.90 (0.72 to 1.13)	3.6×10^{-1}	1.47 (1.31 to 1.66)	2.7×10^{-10}	5.0×10^{-7}

Analyses represent Cox proportional hazards models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, cholesterol-lowering medication use, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index.
[a]Reference group is women with age at menopause ≥40 years. No corrections for multiple comparisons were made. CI indicates confidence interval; HR, hazard ratio.

Table S23. Sensitivity analyses of the association between leukocyte telomere length (per standard deviation decrease of log-transformed leukocyte telomere length) and incident coronary artery disease events during follow-up.

	UK Biobank		Women's Health Initiative		Meta-analysis		
Sensitivity analysis	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	***P*(heterogeneity)**
Stratification by age at blood collection	-	-	-	-	-	-	-
Age at blood collection <65 years	1.07 (1.03 to 1.11)	2.6×10^{-4}	1.12 (0.98 to 1.28)	9.6×10^{-2}	1.07 (1.04 to 1.11)	7.6×10^{-5}	4.9×10^{-1}
Age at blood collection ≥65 years	1.07 (1.02 to 1.11)	2.9×10^{-3}	1.08 (1.01 to 1.16)	3.0×10^{-2}	1.07 (1.03 to 1.11)	2.4×10^{-4}	7.6×10^{-1}
Further adjusted for history of hormone therapy use	1.07 (1.04 to 1.10)	3.1×10^{-6}	1.10 (1.03 to 1.17)	3.2×10^{-3}	1.07 (1.05 to 1.10)	4.9×10^{-8}	3.9×10^{-1}
Stratification by history of hormone therapy	-	-	-	-	-	-	-
No history of hormone therapy	1.05 (1.01 to 1.09)	2.0×10^{-2}	1.10 (1.00 to 1.22)	4.6×10^{-2}	1.06 (1.02 to 1.10)	3.6×10^{-3}	3.4×10^{-1}
History of hormone therapy	1.08 (1.04 to 1.12)	3.3×10^{-5}	1.11 (1.02 to 1.20)	1.7×10^{-2}	1.08 (1.05 to 1.12)	1.8×10^{-6}	6.2×10^{-1}
Exclusion of participants with imputed covariates	1.07 (1.04 to 1.10)	9.5×10^{-6}	1.06 (0.99 to 1.13)	1.1×10^{-2}	1.07 (1.04 to 1.10)	2.6×10^{-6}	7.9×10^{-1}

Analyses represent Cox proportional hazards models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, cholesterol-lowering medication use, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. No corrections for multiple comparisons were made. CI indicates confidence interval; HR, hazard ratio.

Table S24. Complete results of multivariable-adjusted Cox proportional hazards regression models including age at menopause, clonal hematopoiesis of indeterminate potential (CHIP) status and leukocyte telomere lenth (LTL) as covariates for incident coronary artery disease.

	UK Biobank		Women's Health Initiative		Meta-analysis		
Variable	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	***P*(heterogeneity)**
Age (per year)	0.90 (0.78 to 1.03)	1.2×10^{-1}	1.32 (1.09 to 1.59)	3.9×10^{-3}	1.03 (0.92 to 1.15)	6.3×10^{-1}	1.2×10^{-3}
Age² (per year²)	1.00 (1.00 to 1.00)	1.2×10^{-1}	1.00 (1.00 to 1.00)	8.2×10^{-3}	1.00 (1.00 to 1.00)	7.9×10^{-1}	2.7×10^{-4}
Race (non-White vs. White)	1.18 (0.81 to 1.75)	3.8×10^{-1}	0.56 (0.32 to 0.98)	4.3×10^{-2}	0.93 (0.68 to 1.28)	6.7×10^{-1}	3.1×10^{-2}
Smoking status (current or former vs. never)	1.29 (1.21 to 1.36)	$<2.2\times10^{-16}$	1.22 (1.09 to 1.38)	8.3×10^{-4}	1.27 (1.21 to 1.34)	$<2.2\times10^{-16}$	4.7×10^{-1}
Body mass index (per kg/m²)	1.02 (1.01 to 1.03)	8.3×10^{-11}	1.00 (0.99 to 1.01)	7.3×10^{-1}	1.01 (1.01 to 1.02)	3.2×10^{-8}	6.2×10^{-4}
Townsend deprivation index (per unit)	1.71 (1.49 to 1.95)	7.3×10^{-15}	-	-	-	-	-
Diabetes mellitus (yes vs. no)	1.04 (1.03 to 1.05)	1.9×10^{-14}	2.05 (1.68 to 2.51)	3.0×10^{-12}	1.04 (1.03 to 1.05)	1.6×10^{-15}	3.7×10^{-11}
Antihypertensive medication use (yes vs. no)	1.57 (1.47 to 1.68)	$<2.2\times10^{-16}$	1.22 (1.07 to 1.39)	3.4×10^{-3}	1.49 (1.40 to 1.58)	$<2.2\times10^{-16}$	7.1×10^{-4}
Systolic blood pressure (per mmHg)	1.00 (1.00 to 1.01)	8.5×10^{-09}	1.01 (1.01 to 1.01)	5.1×10^{-8}	1.01 (1.00 to 1.01)	6.8×10^{-14}	9.5×10^{-3}
Cholesterol-lowering medication use (yes vs. no)	1.71 (1.58 to 1.84)	$<2.2\times10^{-16}$	1.19 (1.01 to 1.40)	3.4×10^{-2}	1.60 (1.49 to 1.71)	$<2.2\times10^{-16}$	7.7×10^{-5}
Total cholesterol (per mg/dL)	1.00 (1.00 to 1.00)	6.7×10^{-11}	1.00 (1.00 to 1.01)	3.2×10^{-6}	1.00 (1.00 to 1.00)	4.9×10^{-15}	8.4×10^{-2}
HDL cholesterol (per mg/dL)	0.99 (0.98 to 0.99)	$<2.2\times10^{-16}$	0.99 (0.98 to 0.99)	1.8×10^{-7}	0.99 (0.98 to 0.99)	$<2.2\times10^{-16}$	9.0×10^{-1}

Current hormone therapy use (yes vs. no)	1.19 (1.04 to 1.36)	1.2×10^{-1}	0.84 (0.72 to 0.98)	2.8×10^{-2}	1.03 (0.93 to 1.13)	6.3×10^{-1}	9.2×10^{-4}
Inverse probability of sample weight (per unit)	-	-	0.98 (0.98 to 0.99)	2.8×10^{-12}	-	-	-
CHIP (yes vs. no)	1.08 (0.95 to 1.23)	2.5×10^{-1}	1.17 (0.96 to 1.42)	1.3×10^{-1}	1.10 (0.99 to 1.23)	7.4×10^{-2}	5.2×10^{-1}
Age at menopause (per 5-year decrease)	1.14 (1.11 to 1.17)	$<2.2\times10^{-16}$	1.02 (0.98 to 1.07)	3.5×10^{-1}	1.11 (1.08 to 1.13)	$<2.2\times10^{-16}$	1.7×10^{-5}
Leukocyte telomere length (per SD decrease)	1.06 (1.03 to 1.09)	3.2×10^{-05}	1.09 (1.02 to 1.16)	6.8×10^{-3}	1.07 (1.04 to 1.09)	9.5×10^{-7}	4.5×10^{-1}

Analyses represent Cox proportional hazards models adjusted for all variables listed in the left-hand column along with the first ten principal components of genetic ancestry. The UK Biobank sample included 114,429 women with whole exome sequences available. No corrections for multiple comparisons were made. CI indicates confidence interval; HR, hazard ratio.

Table S25. Proportions of the association between age at menopause and incident coronary artery disease (CAD) mediated by selected risk factors in women without a history of gynecologic surgery.

	UK Biobank			Women's Health Initiative		
Risk factor	**Association of earlier meno-pause with risk factor (95% CI)[a]**	**Association of risk factor with incident CAD (95% CI)[b]**	**Proportion mediated (95% CI)[d]**	**Association of earlier meno-pause with risk factor (95% CI)[a]**	**Association of risk factor with incident CAD (95% CI)[b]**	**Proportion mediated (95% CI)[d]**
Current/former smoking (yes vs. no)	0.12 (0.11 to 0.14)***	0.22 (0.16 to 0.28)***	6.1% (3.9 to 10.3%)***	0.08 (0.02 to 0.14)**	0.18 (0.03 to 0.33)*	2.9% (-32.5 to 34.6%)
Body mass index (per kg/m²)	-0.08 (-0.12 to -0.05)***	0.02 (0.01 to 0.03)***	–[d]	-0.01 (-0.17 to 0.16)	0.00 (-0.01 to 0.02)	–[d]
Diabetes mellitus (yes vs. no)	0.057 (0.004 to 0.109)*	0.53 (0.39 to 0.68)***	0.7% (-0.1 to 2.4%)	0.00 (-0.12 to 0.12)	0.69 (0.42 to 0.95)***	–[d]
Systolic blood pressure (per mmHg)	-0.41 (-0.55 to -0.27)***	0.005 (0.003 to 0.006)***	–[d]	-0.22 (-0.72 to 0.28)	0.01 (0.01 to 0.01)***	–[d]
Total cholesterol(per mg/dL)	-0.39 (-0.69 to -0.09)*	0.003 (0.002 to 0.004)***	–[d]	0.93 (-0.35 to 2.22)	0.004 (0.002 to 0.006)***	–[d]
HDL cholesterol (per mg/dL)	-0.26 (-0.37 to -0.16)***	-0.01 (-0.02 to -0.01)***	4.1% (2.3 to 7.3%)***	-0.11 (-0.57 to 0.35)	-0.011 (-0.017 to -0.005)***	–[d]
C-reactive protein (per mg/dL)	0.09 (0.07 to 0.12)***	0.018 (0.013 to 0.024)***	1.7% (0.9 to 3.1%)***	–[e]	–[e]	–[e]
Triglycerides (per mg/dL)	0.94 (0.42 to 1.45)***	0.0001 (-0.0004 to 0.0005)	–[d]	-0.07 (-2.54 to 2.41)	0.004 (0.003 to 0.005)***	–[d]
LTL (per SD)	-0.04 (-0.04 to -0.03)***	-0.07 (-0.1 to -0.04)***	2.8% (1.6 to 4.7%)***	-0.028 (-0.056 to 0.000)*	-0.10 (-0.18 to -0.02)*	2.6% (-0.1 to 12.3%)

[a]Calculated using linear or logistic regression models adjusted for age, age², the first ten components of genetic ancestry, race/ethnicity, current/former smoking status, body mass index, prevalent diabetes, hormone therapy use, prevalent coronary artery disease, inverse probability of sampling weights (for the WHI cohort), and Townsend deprivation index (for the UK Biobank cohort); expressed as β per 5-year decrease in age at menopause. [b]Calculated using Cox proportional hazards models further adjusted for antihypertensive medication use, cholesterol-lowering medication use, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol; expressed as log(hazard ratio) per 1-unit increase in risk factor. [c]Individuals with prevalent CAD at baseline were excluded from all mediation analysis models. [d]Mediation analysis was not performed due to nonsignificant or directionally inconsistent associations between age at menopause, the indicated risk factor, and incident coronary artery disease. [e]C-reactive protein measurements were not available in the WHI cohort. No corrections for multiple comparisons were made. * indicates $P<5.0\times10^{-2}$; **, $P<1.0\times10^{-2}$; ***, $P<1.0\times10^{-3}$.

Table S26. Proportions of the association between age at menopause and incident coronary artery disease (CAD) mediated by selected risk factors in women with a history of gynecologic surgery.

	UK Biobank			Women's Health Initiative		
Variable	**Association of earlier meno-pause with risk factor (95% CI)[a]**	**Association of risk factor with incident CAD (95% CI)[b]**	**Proportion mediated (95% CI)[c]**	**Association of earlier meno-pause with risk factor (95% CI)[a]**	**Association of risk factor with incident CAD (95% CI)[b]**	**Proportion mediated (95% CI)**
Current/former smoking (yes vs. no)	0.09 (0.07 to 0.12)***	0.43 (0.28 to 0.57)***	6.2% (2.0 to 12.4%)**	0.08 (0.03 to 0.13)***	0.24 (0.04 to 0.43)*	7.2% (-197.7 to 335.2%)
Body mass index (per kg/m²)	0.17 (0.10 to 0.23)***	0.017 (0.003 to 0.031)*	1.9% (0.4 to 4.4%)**	0.14 (0.00 to 0.28)*	-0.01 (-0.03 to 0.01)	–[d]
Diabetes mellitus (yes vs. no)	0.02 (-0.06 to 0.10)	0.51 (0.22 to 0.80)***	–[d]	0.05 (-0.04 to 0.14)	0.74 (0.42 to 1.05)***	–[d]
Systolic blood pressure (per mmHg)	-0.05 (-0.31 to 0.21)	0.004 (0.000 to 0.008)*	–[d]	0.33 (-0.09 to 0.75)	0.007 (0.002 to 0.013)*	–[d]
Total cholesterol(per mg/dL)	-0.05 (-0.64 to 0.54)	0.001 (-0.001 to 0.003)	–[d]	-1.06 (-2.17 to 0.05)	0.003 (0.000 to 0.006)*	–[d]
HDL cholesterol (per mg/dL)	-0.11 (-0.30 to 0.07)	-0.02 (-0.02 to -0.01)***	–[d]	-0.07 (-0.49 to 0.34)	-0.01 (-0.02 to -0.01)***	–[d]
C-reactive protein (per mg/dL)	0.02 (-0.04 to 0.08)	0.016 (0.003 to 0.028)*	–[d]	–[e]	–[e]	–[e]
Triglycerides (per mg/dL)	1.51 (0.45 to 2.58)**	0.000 (-0.001 to 0.001)	–[d]	0.74 (-1.57 to 3.04)	0.001 (-0.001 to 0.003)	–[d]
LTL (per SD)	-0.015 (-0.028 to -0.002)*	-0.01 (-0.08 to 0.05)	–[d]	0.00 (-0.02 to 0.02)	-0.07 (-0.17 to 0.03)	–[d]

[a]Calculated using linear or logistic regression models adjusted for age, age², the first ten components of genetic ancestry, race/ethnicity, current/former smoking status, body mass index, prevalent diabetes, hormone therapy use, prevalent coronary artery disease, inverse probability of sampling weights (for the WHI cohort), and Townsend deprivation index (for the UK Biobank cohort); expressed as β per 5-year decrease in age at menopause. [b]Calculated using Cox proportional hazards models further adjusted for antihypertensive medication use, cholesterol-lowering medication use, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol; expressed as log(hazard ratio) per 1-unit increase in risk factor. [c]Individuals with prevalent CAD at baseline were excluded from all mediation analysis models. [d]Mediation analysis was not performed due to nonsignificant or directionally inconsistent associations between age at menopause, the indicated risk factor, and incident coronary artery disease. [e]C-reactive protein measurements were not available in the WHI cohort. No corrections for multiple comparisons were made. * indicates $P<5.0\times10^{-2}$; **, $P<1.0\times10^{-2}$; ***, $P<1.0\times10^{-3}$.

Table S27. Associations of selected risk factors with incident coronary artery disease (CAD) stratified by history of premature menopause.

	History of premature menopause			No history of premature menopause			Interaction[b]	
Variable	**Meta-analyzed HR (95% CI)[a]**	***P*-value[a]**	***P*(hetero-geneity)[a]**	**Meta-analyzed HR (95% CI)[a]**	***P*-value[a]**	***P*(hetero-geneity)[a]**	***P*(inter-action)[b]**	***P*(hetero-geneity)[a]**
Current/former smoking (yes vs. no)	1.55 (1.27 to 1.90)	1.7×10^{-5}	4.8×10^{-1}	1.27 (1.20 to 1.33)	$<2.2\times10^{-16}$	5.3×10^{-1}	8.6×10^{-2}	4.1×10^{-1}
Body mass index (per kg/m²)	1.01 (0.99 to 1.03)	2.8×10^{-1}	1.2×10^{-1}	1.02 (1.01 to 1.02)	7.4×10^{-9}	2.0×10^{-3}	6.9×10^{-1}	5.9×10^{-1}
Diabetes mellitus (yes vs. no)	1.04 (1.00 to 1.08)	3.4×10^{-2}	1.8×10^{-4}	1.04 (1.03 to 1.05)	1.4×10^{-15}	1.8×10^{-8}	8.8×10^{-1}	6.3×10^{-1}
Systolic blood pressure (per mmHg)	0.998 (0.993 to 1.003)	4.8×10^{-1}	2.4×10^{-1}	1.006 (1.004 to 1.007)	$<2.2\times10^{-16}$	1.0×10^{-3}	4.1×10^{-4}	4.5×10^{-2}
Total cholesterol (per mg/dL)	1.004 (1.001 to 1.006)	6.1×10^{-3}	6.0×10^{-1}	1.003 (1.002 to 1.003)	3.7×10^{-14}	1.4×10^{-1}	5.3×10^{-1}	6.4×10^{-1}
HDL cholesterol (per mg/dL)	0.98 (0.98 to 0.99)	3.1×10^{-4}	7.5×10^{-1}	0.99 (0.98 to 0.99)	$<2.2\times10^{-16}$	9.5×10^{-1}	9.3×10^{-1}	6.5×10^{-1}
C-reactive protein (per mg/dL)	1.01 (0.99 to 1.03)	2.7×10^{-1}	–	1.02 (1.01 to 1.02)	7.4×10^{-13}	–	6.4×10^{-1}	–
Triglycerides (per mg/dL)	1.0016 (1.0002 to 1.0030)	2.4×10^{-2}	5.9×10^{-1}	1.0004 (1.0000 to 1.0008)	7.3×10^{-2}	3.3×10^{-7}	3.4×10^{-1}	1.3×10^{-2}
Leukocyte telomere length (per SD decrease)	1.07 (0.97 to 1.18)	2.0×10^{-1}	4.8×10^{-1}	1.07 (1.04 to 1.10)	2.7×10^{-7}	3.0×10^{-1}	8.3×10^{-1}	5.7×10^{-1}

Analyses represent Cox proportional hazards models adjusted for age, age^2, race/ethnicity, the first ten principal components of genetic ancestry, current/former smoking status, body mass index, diabetes status, current hormone therapy use, cholesterol-lowering medication use, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, age at menopause, and leukocyte telomere length. WHI models were further adjusted for inverse probability of sampling weights, while UK Biobank models were further adjusted for Townsend deprivation index. [a]All reported hazard ratios (HRs) were meta-analyzed across cohorts for women with and without a history of premature menopause, respectively. *P*(heterogeneity) corresponds to the heterogeneity between estimates from the UK Biobank and WHI cohorts. [b]*P*(interaction) corresponds to the meta-analyzed interaction between the indicated risk factor and premature menopause status on incident CAD. No corrections for multiple comparisons were made. CI indicates confidence interval; HR, hazard ratio.