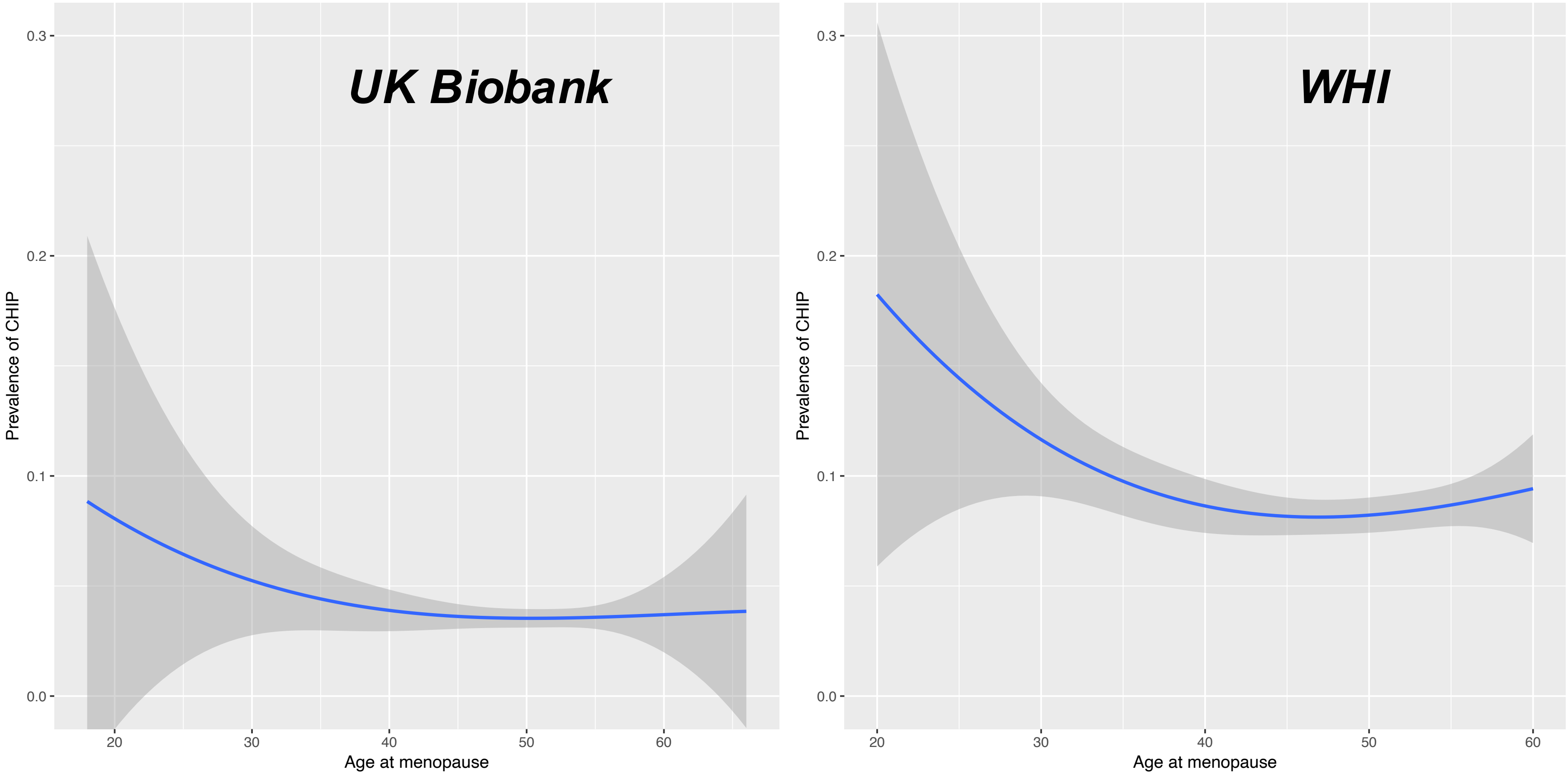
SUPPLEMENTAL MATERIAL

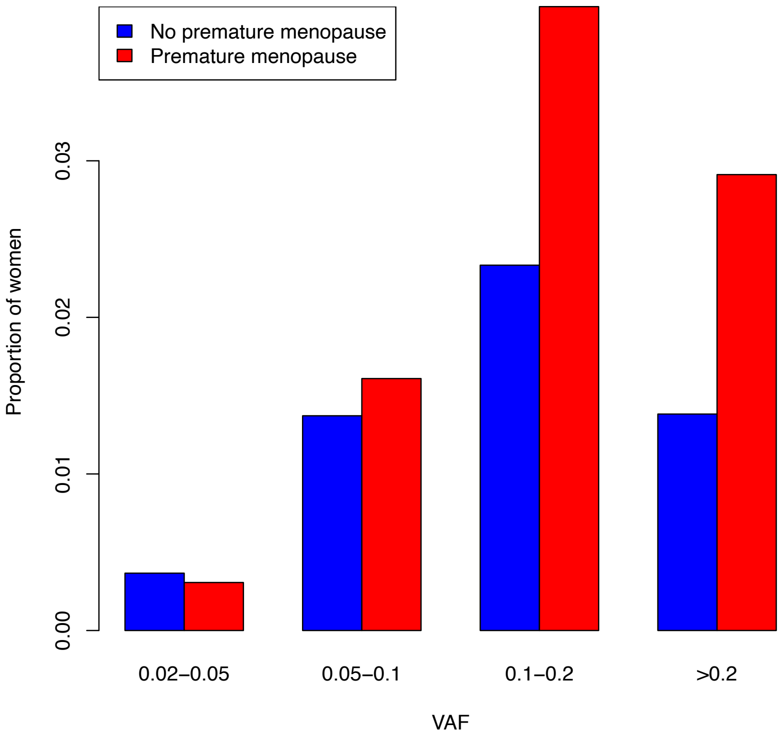
Honigberg MC, Zekavat SM, Niroula A, et al. Premature Menopause, Clonal Hematopoiesis, and Coronary Artery Disease in Postmenopausal Women.

Supplemental Figure I. Prevalence of CHIP by age at menopause in the UK Biobank and Women's Health Initiative.



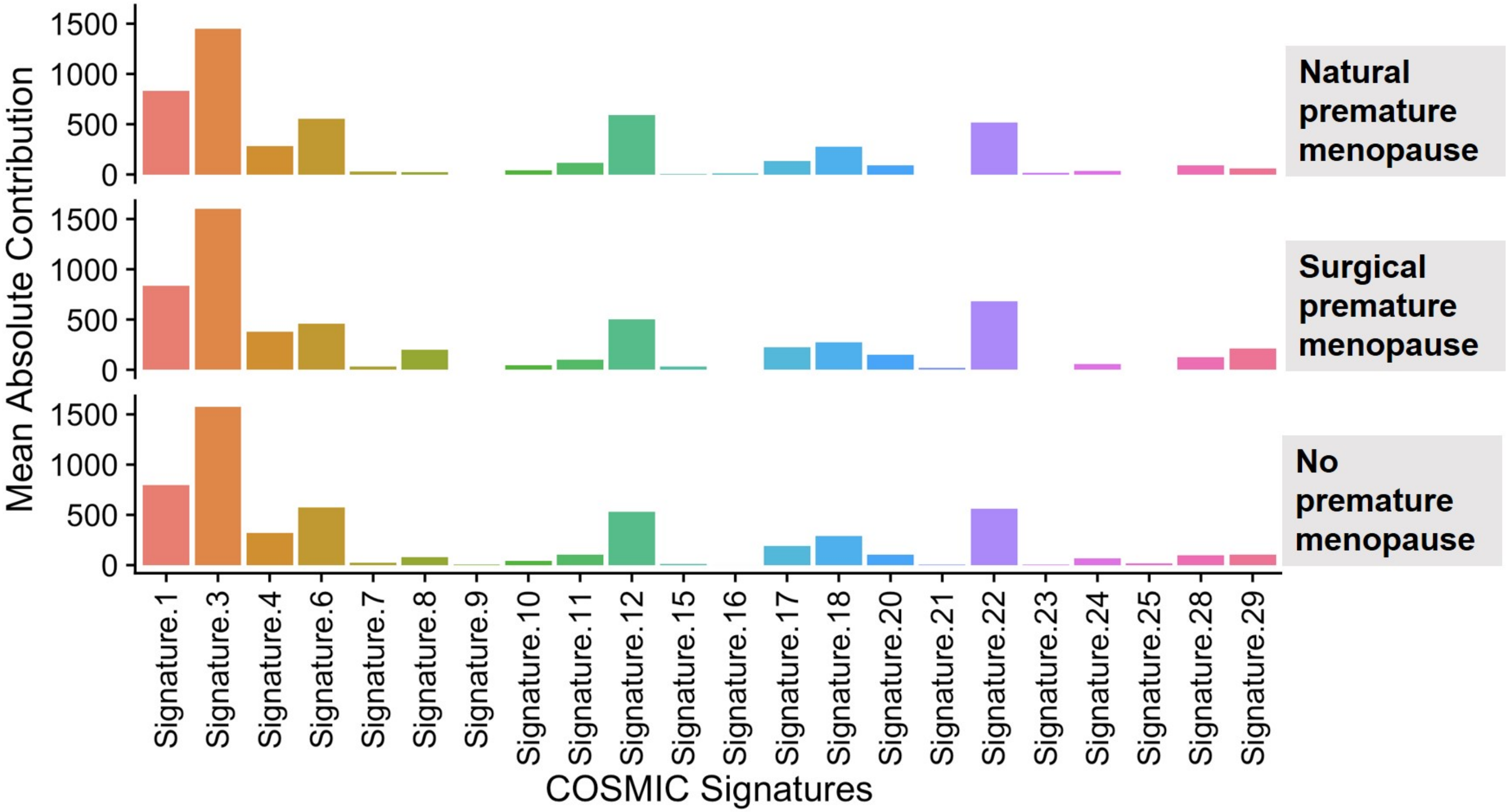
CHIP prevalence increased with progressively younger age at menopause. Plots were generated with the 'ggplot2' package in R using a cubic spline with 3 knots. The shaded band represents the modeled 95% confidence band. CHIP = clonal hematopoiesis of indeterminate potential; WHI = Women's Health Initiative.

Supplemental Figure II. Prevalence of CHIP in women with vs. without premature menopause by variant allele frequency.

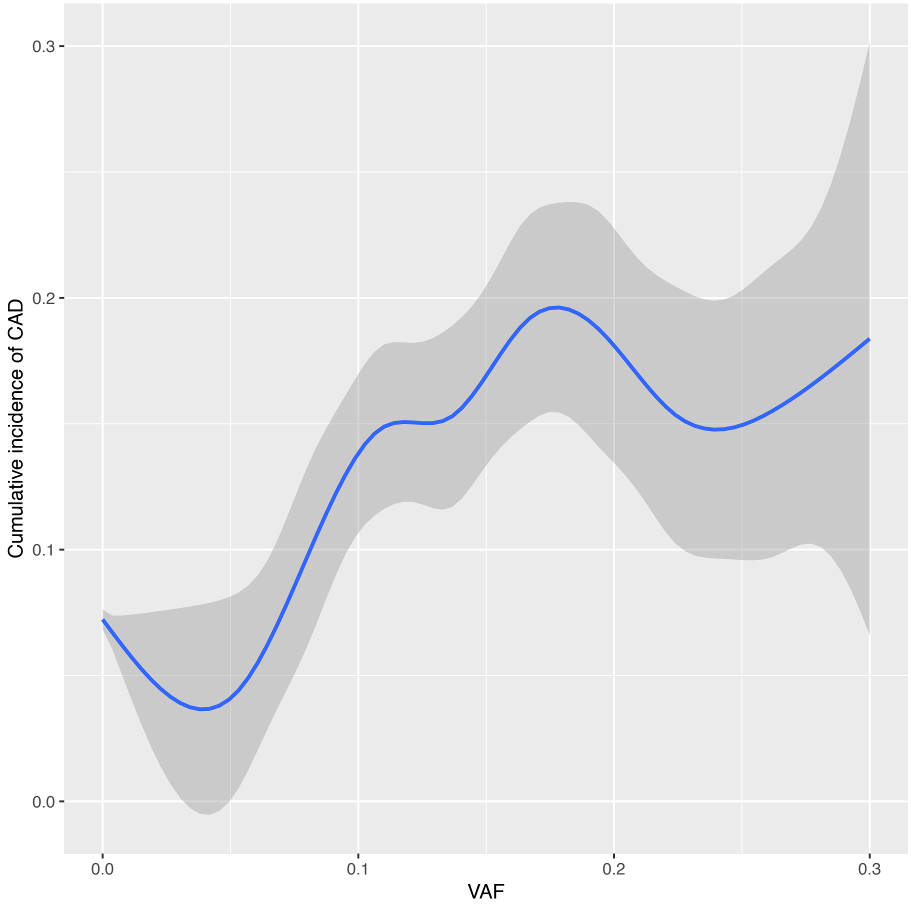


Prevalence of CHIP in the pooled cohort of the UK Biobank and Women's Health Initiative (total N=19,606) grouped by CHIP VAF. Differences in CHIP prevalence between women with (n=1,305) vs. without (n=18,301) premature menopause were more pronounced for CHIP with VAF >0.1. CHIP = clonal hematopoiesis of indeterminate potential; VAF = variant allele frequency.

Supplemental Figure III. Mutational signatures observed in UK Biobank subjects with CHIP by premature menopause status.



Supplemental Table IV. Cumulative incidence of coronary artery disease events by variant allele frequency.



Cumulative incidence of coronary artery disease by VAF among individuals in the pooled cohort of the UK Biobank and Women's Health Initiative with CHIP (N=18,451 without prevalent coronary artery disease). Data are fit using the generalized additive model in the 'ggplot2' package in R version 3.6.0. The shaded band represents the modeled 95% confidence band. CHIP = clonal hematopoiesis of indeterminate potential; CAD = coronary artery disease; VAF = variant allele frequency.

Supplemental Table I. CHIP variants queried in the UK Biobank.

Gene name	Accession	Reported mutations used for variant calling
DNMT3A	NM_022552	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
TET2	NM_001127208	Frameshift/nonsense/splice-site, missense mutations in catalytic domains (p.1104-1481 and 1843-2002)

Supplemental Table II. CHIP variants queried in the Women's Health Initiative.

Gene name	Accession	Reported mutations used for variant calling
ASXL1	NM_015338	Frameshift/nonsense/splice-site in exon 11-12
ASXL2	NM_018263	Frameshift/nonsense/splice-site in exon 11-12
BCOR	NM_001123385	Frameshift/nonsense/splice-site
BCORL1	NM_021946	Frameshift/nonsense/splice-site
BRAF	NM_004333	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	NM_024332	Frameshift/nonsense/splice-site
CBL	NM_005188	RING finger missense p.381-421
CBLB	NM_170662	RING finger missense p.372-412
CEBPA	NM_004364	Frameshift/nonsense/splice-site
CREBBP	NM_004380	Frameshift/nonsense/splice-site, D1435E, R1446L, R1446H, R1446C, Y1450C, P1476R, Y1482H, H1487Y, W1502C, Y1503D, Y1503H, Y1503F, S1680del
CSF1R	NM_005211	L301F, L301S, Y969C, Y969N, Y969F, Y969H, Y969D
CSF3R	NM_000760	T615A, T618I, truncating c.741-791
CTCF	NM_006565	Frameshift/nonsense, R377C, R377H, P378A, P378L
CUX1	NM_181552	Frameshift/nonsense
DNMT3A	NM_022552	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	NM_003797	Frameshift/nonsense/splice-site, L240Q, I363M
EP300	NM_001429	Frameshift/nonsense/splice-site, VF1148_1149del, D1399N, D1399Y, P1452L, Y1467N, Y1467H, Y1467C, R1627W, A1629V
ETNK1	NM_018638	N244S, N244T, N244K
ETV6	NM_001987	Frameshift/nonsense/splice-site
EZH2	NM_001203247	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	NM_004119	V579A, V592A, V592I, F594L, FY590-591GD, D835Y, D835H, D835E, del835
GATA1	NM_002049	Frameshift/nonsense/splice-site
GATA2	NM_001145661	Frameshift/nonsense/splice-site, R293Q, N317H, A318T, A318V, A318G, G320D, L321P, L321F, L321V, Q328P, R330Q, R361L, L359V, A372T, R384G, R384K
GATA3	NM_001002295	Frameshift/nonsense/splice-site ZNF domain, R276W, R276Q, N286T, L348V,
GNA13	NM_006572	I34T, G57S, S62F, M68K, Q134R, Y145F, L152F, E167D, Q169H, R264H, E273K, V322G, V362G, L371F
GNAS	NM_000516	R201(844)S, R201(844)C, R201(844)H, R201(844)L, Q227(870)K, Q227(870)R, Q227(870)L, Q227(870)H, R374(1017)C
GNB1	NM_002074	K57N, K57M, K57E, K57T, I80T, I80N
IDH1	NM_005896	R132C, R132G, R132H, R132L, R132P, R132V, V178I
IDH2	NM_002168	R140W, R140Q, R140L, R140G, R172W, R172G, R172K, R172T, R172M, R172N, R172S
IKZF1	NM_006060	Frameshift/nonsense
IKZF2	NM_016260	Frameshift/nonsense
IKZF3	NM_012481	Frameshift/nonsense
JAK1	NM_002227	T478A, T478S, V623A, A634D, L653F, R724H, R724Q, R724P, T782M, L783F
JAK2	NM_004972	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
JAK3	NM_000215	M511T, M511I, A572V, A572T, A573V, R657Q, V715I, V715A
KDM6A	NM_021140	Frameshift/nonsense/splice-site, del419
KIT	NM_000222	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	NM_033360	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
LUC7L2	NM_016019	Frameshift/nonsense/splice-site
MLL	NM_005933	Frameshift/nonsense
MLL2	NM_003482	Frameshift/nonsense
MPL	NM_005373	S505G, S505N, S505C, L510P, del513, W515A, W515R, W515K, W515S, W515L, A519T, A519V, Y591D, W515-518KT
NF1	NM_000267	Frameshift/nonsense
NPM1	NM_002520	Frameshift p.W288fs (insertion at c.859_860, 860_861, 862_863, 863_864)
NRAS	NM_002524	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	NM_015032	Frameshift/nonsense/splice-site, R1292Q
PDSS2	NM_020381	Frameshift/nonsense
PHF6	NM_001015877	Frameshift/nonsense/splice-site, A40D, M125I, S246Y, F263L, R274Q, C297Y, H302Y, H329L
PHIP	NM_017934	Frameshift/nonsense/splice-site
PPM1D	NM_003620	Frameshift/nonsense, exon 5 or 6
PRPF40B	NM_001031698	Frameshift/nonsense/splice-site, P15H, M58I, P405L, P562S,
PRPF8	NM_006445	M1307I, C1594W, D1598Y, D1598N, D1598V (ADD MORE VARS)
PTEN	NM_000314	Frameshift/nonsense/splice-site, D24G, R47G, F56V, L57W, H61R, K66N, Y68H, C71Y, F81C, Y88C, D92G, D92V, D92E, H93Y, H93D, H93Q, N94I, P95L, I101T, C105F, C105S, D107Y, L112V, H123Y, C124R, C124S, K125E, A126D, K128N, R130G, R130Q, R130L, G132D, I135V, I135K, C136R, C136F, K144Q, A151T, D153Y, D153N, Y155H, Y155C, R159K, R159S, R161K, R161I, G165R, G165E, S170N, S170I, R173C, Y174D, Y177C, H196Y, R234W, G251C, D252Y, F271S, D326G
PTPN11	NM_002834	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	NM_006265	Frameshift/nonsense/splice-site, R65Q, H208R, Q474R
RUNX1	NM_001001890	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	NM_015559	D868N, D868T, S869N, G870S, I871T, D880N, D880Q
SETD2	NM_014159	Frameshift/nonsense, V1190M
SETDB1	NM_001145415	Frameshift/nonsense, K715E
SF1	NM_004630	Frameshift/nonsense/splice-site, T454M, Y476C, A508G
SF3A1	NM_005877	Frameshift/nonsense/splice-site, A57S, M117I, K166T, Y271C

SF3B1	NM_012433	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	NM_003016	Y44H, P95H, P95L, P95T, P95R, P95A, P107H, P95fs
SMC1A	NM_006306	K190T, R586W, M689V, R807H, R1090H, R1090C
SMC3	NM_005445	Frameshift/nonsense, R155I, Q367E, D392V, K571R, R661P, G662C
STAG1	NM_005862	Frameshift/nonsense/splice-site, H1085Y
STAG2	NM_006603	Frameshift/nonsense/splice-site
SUZ12	NM_015355	Frameshift/nonsense
TET2	NM_001127208	Frameshift/nonsense/splice-site, missense mutations in catalytic domains (p.1104-1481 and 1843-2002)
TP53	NM_001126112	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	NM_006758	D14G, S34F, S34Y, R35L, R156H, R156Q, Q157R, Q157P
U2AF2	NM_007279	R18W, Q143L, M144I, L187V, Q190L
WT1	NM_024426	Frameshift/nonsense/splice-site
ZRSR2	NM_005089	Frameshift/nonsense, R126P, E133G, C181F, H191Y, I202N, F239V, F239Y, N261Y, C280R, C302R, C326R, H330R, N382K

Supplemental Table III. *International Classification of Diseases* codes used to ascertain prevalent type 2 diabetes mellitus, incident coronary artery disease, and myeloid dysplasia and neoplasia in the UK Biobank.

Diagnosis	**ICD codes**
Type 2 diabetes mellitus	ICD 9: 2500, 25000, 25001, 25009, 25011, 25019, 2503, 2504, 2505, 25099 ICD 10: E10, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E10.9, E11, E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E11.9, E12, E12.1, E12.8, E12.9, E13, E13.1, E13.2, E13.3, E13.5, E13.6, E13.7, E13.8, E13.9, E14, E14.1, E14.2, E14.3, E14.4, E14.5, E14.6, E14.7, E14.8, E14.9
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
Myeloid dysplasia and neoplasia	ICD 9: 2050, 2051, 2059 ICD 10: C92.0, C92.1, C92.3, C92.4, C92.5, C92.7, C92.9, D45, D46.9, D47.1, D47.3

Supplemental Table IV. Case counts of CHIP in the UK Biobank and Women's Health Initiative study cohorts.

	UK Biobank (N=11,495)	**Women's Health Initiative (N=8,111)**
Any CHIP	415 (3.6%)	698 (8.6%)
CHIP with VAF ≤0.1	243 (2.1%)	100 (1.2%)
CHIP with VAF >0.1	172 (1.5%)	598 (7.4%)
DNMT3A	342 (3.0%)	404 (5.0%)
TET2	73 (0.6%)	129 (1.6%)
ASXL1	--	51 (0.6%)
JAK2	--	26 (0.3%)
Other CHIP driver	--	88 (1.1%)

CHIP = clonal hematopoiesis of indeterminate potential; VAF = variant allele frequency

Supplemental Table V. Association of race/ethnicity with CHIP in the Women's Health Initiative cohort.

Racial/ethnic group	Number with CHIP	Adjusted odds ratio (95% CI)	P-value
White	600 / 6,733 (8.9%)	*Reference*	--
Black	66 / 918 (7.2%)	1.33 (0.41-4.31)	0.64
Hispanic/Latina	16 / 217 (7.4%)	1.13 (0.44-2.93)	0.80
Asian/Pacific Islander	8 / 157 (5.1%)	0.48 (0.007-31.03)	0.73
American Indian/Alaskan Native	5 / 28 (17.9%)	2.56 (0.86-7.67)	0.09
Unknown	3 / 58 (5.2%)	0.67 (0.20-2.22)	0.51

Model is adjusted for age, PC 1-10, ever-smoking, diabetes mellitus, use of hormone therapy, enrollment in the WHI observational study vs. clinical trial, and randomization to hormone therapy vs. placebo. CHIP = clonal hematopoiesis of indeterminate potential.

Supplemental Table VI. Association of premature menopause, premature menopause subtypes, and other reproductive factors with CHIP.

	UK Biobank		Women's Health Initiative	
	All CHIP	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
All premature menopause	1.35 (0.83-2.17)	2.07 (1.10-3.88)*	1.36 (1.07-1.73)*	1.32 (1.01-1.71)*
Natural premature menopause	1.66 (0.86-3.18)	2.72 (1.17-6.29)*	1.77 (1.18-2.63)**	1.75 (1.13-2.69)*
Surgical premature menopause	1.11 (0.56-2.20)	1.60 (0.65-3.98)	1.22 (0.92-1.62)	1.17 (0.86-1.60)
• Bilateral oophorectomy ± hysterectomy	1.23 (0.30-5.16)	1.61 (0.22-11.91)	1.21 (0.87-1.65)	1.09 (0.75-1.55)
• Hysterectomy only	1.08 (0.50-2.34)	1.60 (0.58-4.41)	1.27 (0.71-2.13)	1.41 (0.77-2.39)
Age at menarche, per year	0.99 (0.93-1.06)	0.99 (0.90-1.09)	0.97 (0.91-1.02)	0.97 (0.91-1.03)
Age at menopause (continuous), per year	0.99 (0.97-1.01)	0.97 (0.94-0.99)*	0.99 (0.98-1.00)	0.99 (0.98-1.00)
Duration of menopause, per year	1.01 (0.99-1.03)	1.03 (1.002-1.06)*	1.01 (0.998-1.02)	1.01 (0.995-1.02)
Parity, per live birth	0.96 (0.87-1.05)	0.91 (0.80-1.05)	0.94 (0.89-1.00)	0.94 (0.88-1.00)
Nulliparity	1.11 (0.85-1.44)	1.15 (0.77-1.72)	0.85 (0.44-1.48)	0.84 (0.41-1.53)

*P<0.05, **P<0.01

All models are adjusted for age at blood draw, the first 10 principal components of ancestry, current or former smoking, diabetes mellitus, and prior use of hormone therapy. WHI models are additionally adjusted for race/ethnicity, enrollment in the WHI observational study vs. clinical trials, and randomization to hormone therapy vs. placebo.

Supplemental Table VII. Association of premature menopause with CHIP, further adjusted for body-mass index.

	UK Biobank		**Women's Health Initiative**	
	All CHIP	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
All premature menopause	1.39 (0.86-2.24)	2.09 (1.11-3.94)*	1.30 (1.02-1.66)*	1.26 (0.96-1.64)
Natural premature menopause	1.70 (0.98-3.27)	2.76 (1.19-6.40)*	1.69 (1.13-2.54)*	1.73 (1.12-2.66)*
Surgical premature menopause	1.15 (0.58-2.28)	1.61 (0.65-4.02)	1.17 (0.88-1.56)	1.10 (0.80-1.51)

*P<0.05

All models are adjusted for age at blood draw, the first 10 principal components of ancestry, current or former smoking, diabetes mellitus, prior use of hormone therapy, and body-mass index. WHI models are additionally adjusted for race/ethnicity, enrollment in the WHI observational study vs. clinical trials, and randomization to hormone therapy vs. placebo.

Supplemental Table VIII. Sensitivity analyses: Associations between premature menopause and CHIP, excluding women with history of cancer, women with history of gynecologic surgery, and women enrolled in the Women's Health Initiative hormone trial.

	UK Biobank		**Women's Health Initiative**	
	All CHIP	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Excluding 1,308 women from UK Biobank and 625 women from WHI with a history of cancer or missing cancer history				
All premature menopause	1.50 (0.90-2.50)	2.26 (1.16-4.40)*	1.38 (1.07-1.78)*	1.35 (1.02-1.78)*
Natural premature menopause	1.57 (0.76-3.26)	2.60 (1.04-6.53)*	1.97 (1.30-2.88)***	1.96 (1.26-2.96)**
Surgical premature menopause	1.44 (0.73-2.87)	2.00 (0.80-5.00)	1.19 (0.87-1.60)	1.14 (0.91-1.58)
Excluding 1,187 women from UK Biobank and 3,203 women from WHI with any history of hysterectomy or bilateral oophorectomy				
Natural premature menopause	1.85 (0.96-3.57)	3.16 (1.35-7.36)**	1.65 (0.93-2.94)	1.67 (0.90-3.10)
Excluding women in 2.649 women in WHI enrolled in the hormone therapy clinical trial				
All premature menopause	--	--	1.37 (1.02-1.83)*	1.30 (0.94-1.79)
Natural premature menopause	--	--	1.95 (1.19-3.07)**	1.79 (1.02-2.94)*
Surgical premature menopause	--	--	1.17 (0.81-1.64)	1.13 (0.76-1.64)

*P<0.05, **P<0.01, ***P<0.001

All models are adjusted for age at blood draw, the first 10 principal components of ancestry, current or former smoking, diabetes mellitus, and prior use of hormone therapy. WHI models are additionally adjusted for race/ethnicity, enrollment in the WHI observational study vs. clinical trials, and randomization to hormone therapy vs. placebo.

Supplemental Table IX. Associations between premature menopause and CHIP in the Women's Health Initiative, stratified by age at blood draw <70 years vs. ≥70 years.

	All CHIP	**CHIP with VAF >0.1**
	OR (95% CI)	*OR (95% CI)*
Women <70 years old at blood draw (N=4,251)		
All premature menopause	1.54 (1.09-2.13)*	1.50 (1.02-2.15)*
Natural premature menopause	1.92 (1.05-3.28)*	2.13 (1.14-3.71)*
Surgical premature menopause	1.41 (0.94-2.05)	1.29 (0.81-1.97)
Women ≥70 years old at blood draw (N=3,860)		
All premature menopause	1.23 (0.86-1.71)	1.16 (0.79-1.67)
Natural premature menopause	1.66 (0.91-2.84)	1.41 (0.70-2.58)
Surgical premature menopause	1.07 (0.70-1.60)	1.08 (0.68-1.65)

*P<0.05

All models are adjusted for age at blood draw, race/ethnicity, the first 10 principal components of ancestry, current or former smoking, diabetes mellitus, prior use of hormone therapy, enrollment in the WHI observational study vs. clinical trials, and randomization to hormone therapy vs. placebo.

Supplemental Table X. Association between premature menopause and specific CHIP mutations.

	DNMT3A				***TET2***				***ASXL1***	
	UK Biobank		**Women's Health Initiative**		**UK Biobank**		**Women's Health Initiative**		**Women's Health Initiative**	
	All CHIP	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**	**All CHIP**	**CHIP with VAF >0.1**
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
All premature menopause	1.38 (0.82-2.32)	2.01 (0.96-4.19)	1.30 (0.94-1.75)	1.30 (0.91-1.81)	1.18 (0.37-3.82)	2.12 (0.64-7.01)	1.38 (0.78-2.31)	1.32 (0.71-2.28)	1.73 (0.74-3.59)	1.35 (0.51-3.03)
Natural premature menopause	1.83 (0.92-3.63)	3.07 (1.22-7.69)*	2.05 (1.25-3.20)**	2.08 (1.20-3.39)**	0.89 (0.12-6.51)	1.62 (0.22-11.98)	1.33 (0.40-3.24)	1.09 (0.26-2.95)	0.82 (0.46-3.89)	0.90 (0.50-4.24)
Surgical premature menopause	1.05 (0.49-2.26)	1.27 (0.40-4.08)	1.04 (0.69-1.50)	1.02 (0.65-1.54)	1.41 (0.34-5.87)	2.52 (0.59-10.67)	1.40 (0.72-2.49)	1.41 (0.70-2.56)	2.06 (0.83-4.42)	1.50 (0.51-3.57)

*P<0.05, **P<0.01

Models are adjusted for age, the first 10 principal components of ancestry, current or former smoking, diabetes mellitus, and prior use of hormone therapy. WHI models are additionally adjusted for race/ethnicity, enrollment in the WHI observational study vs. clinical trials, and randomization to hormone therapy vs. placebo.

Supplemental Table XI. Laboratory values by CHIP and premature menopause status in the UK Biobank cohort (N=11,495).

Laboratory value	**Premature menopause and CHIP (n=19)**	**CHIP and no premature menopause (n=396)**	**Premature menopause and no CHIP (n=371)**	**No premature menopause or CHIP (n=10,709)**	**P-value**
White blood cells (10^9 cells/L)	6.85 (2.28)	6.83 (1.78)	7.26 (1.90)	6.84 (2.18)	0.004
Neutrophils (10^9 cells/L)	4.17 (1.59)	4.15 (1.41)	4.38 (1.47)	4.11 (1.32)	0.002
Lymphocytes (10^9 cells/L)	2.32 (0.83)	2.04 (0.59)	2.18 (0.75)	2.08 (1.40)	0.40
Monocytes (10^9 cells/L)	0.41 (0.13)	0.44 (0.16)	0.47 (0.16)	0.45 (0.20)	0.12
Eosinophils (10^9 cells/L)	0.16 (0.08)	0.16 (0.15)	0.18 (0.15)	0.16 (0.13)	0.12
Basophils (10^9 cells/L)	0.03 (0.02)	0.04 (0.05)	0.04 (0.06)	0.04 (0.06)	0.82
Hemoglobin (g/dL)	13.8 (1.2)	13.7 (0.9)	13.6 (1.0)	13.7 (0.9)	0.57
Hematocrit (%)	40.6 (3.5)	40.0 (2.8)	39.9 (2.9)	40.0 (2.7)	0.57
Mean corpuscular volume (fL)	91.5 (5.6)	91.9 (4.5)	91.6 (4.3)	92.0 (4.0)	0.26
Mean corpuscular hemoglobin concentration (g/dL)	34.1 (0.8)	34.3 (1.1)	34.2 (0.8)	34.2 (0.9)	0.22
Red blood cell distribution width (%)	13.9 (1.3)	13.5 (0.9)	13.6 (1.2)	13.5 (0.9)	<0.001
Platelets (10^9 cells/L)	242.5 (61.1)	254.2 (59.6)	261.9 (60.7)	252.7 (56.0)	0.02
C-reactive protein, mg/L (median [IQR])	1.84 [0.82, 2.97]	1.43 [0.76, 2.80]	2.10 [0.93, 4.14]	1.34 [0.66, 2.81]	<0.001

Values are displayed as mean (SD) unless otherwise specified. P-values were calculated using analysis of variance (for normally distributed variables) or the Kruskal-Wallis test (for non-normally distributed variables).

Supplemental Table XII. Association of premature menopause with mosaic chromosomal alterations in the UK Biobank.

	Any mosaicism*		**Mosaicism with cell fraction >0.1**	
	OR (95% CI)	P-value	OR (95% CI)	P-value
All chromosomal mosaicism				
All premature menopause	1.09 (0.99-1.19)	0.07	1.31 (1.01-1.70)	0.04
Natural premature menopause	1.13 (0.98-1.29)	0.08	1.28 (0.86-1.89)	0.22
Surgical premature menopause	1.06 (0.94-1.19)	0.36	1.34 (0.96-1.87)	0.09
Autosomes only				
All premature menopause	1.10 (0.95-1.26)	0.21	1.15 (0.85-1.56)	0.36
Natural premature menopause	1.14 (0.93-1.40)	0.21	1.03 (0.64-1.67)	0.90
Surgical premature menopause	1.06 (0.88-1.28)	0.54	1.25 (0.85-1.83)	0.27
Chromosome X only				
All premature menopause	1.07 (0.96-1.20)	0.20	1.76 (1.09-2.86)	0.02
Natural premature menopause	1.11 (0.95-1.31)	0.19	2.07 (1.06-4.04)	0.03
Surgical premature menopause	1.04 (0.90-1.21)	0.56	1.53 (0.78-3.00)	0.21

Models are adjusted for age, race/ethnicity, the first 10 principal components of ancestry, current or former smoking, diabetes mellitus, and prior use of hormone therapy.

*Mosaic chromosomal alterations were detectable at cell fractions as low as 1%.

Supplemental Table XIII. Association between use of hormone therapy before study enrollment and CHIP, stratified by age at menopause.

	Age at menopause					
	<40 years	**40-44 years**	**45-49 years**	**50-54 years**	**≥55 years**	
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*P(trend)*$^+$
UK Biobank						
Ever-use of hormone therapy at study enrollment	0.63 (0.22-1.76)	1.14 (0.56-2.32)	1.21 (0.77-1.91)	1.27 (0.96-1.70)	1.71 (1.01-2.89)*	<0.001
Current use of hormone therapy at study enrollment	0.94 (0.18-4.79)	1.60 (0.53-4.86)	1.69 (0.76-3.79)	1.91 (1.18-3.09)**	2.94 (1.39-6.21)**	<0.001
Women's Health Initiative						
Ever-use of hormone therapy at study enrollment	1.33 (0.76-2.47)	1.21 (0.72-2.10)	0.91 (0.64-1.30)	1.06 (0.80-1.39)	1.22 (0.82-1.84)	0.67
Current use of hormone therapy at study enrollment	0.75 (0.45-1.22)	1.09 (0.66-1.78)	0.87 (0.59-1.27)	1.19 (0.86-1.63)	1.10 (0.71-1.68)	0.41

*P<0.05, **P<0.01

$^+$P-value for trend calculated using the Mantel-Haenszel chi-squared test of trend

All models are adjusted for age at blood draw, the first 10 principal components, current or former smoking, and diabetes mellitus. WHI models are additionally adjusted for race/ethnicity, enrollment in the WHI observational study vs. clinical trials, and randomization to hormone therapy vs. placebo.

Supplemental Table XIV. Association of CHIP with incident coronary artery disease.

	Number of women without prevalent CAD	Events / woman-years at risk	Adjusted hazard ratio (95% CI)	P-value
UK Biobank				
No CHIP	10,792	448 / 108,757	*Reference*	--
All CHIP	403	25 / 4,002	1.31 (0.87-1.99)	0.20
CHIP with VAF ≤0.1	236	13 / 2,370	1.13 (0.64-2.02)	0.67
CHIP with VAF >0.1	167	12 / 1,633	1.56 (0.88-2.78)	0.13
Women's Health Initiative (overall)				
No CHIP	6,640	1,036 / 84,007	*Reference*	--
All CHIP	616	110 / 7,173	1.19 (0.97-1.45)	0.10
CHIP with VAF ≤0.1	84	13 / 985	1.15 (0.66-1.99)	0.62
CHIP with VAF >0.1	532	97 / 6,188	1.19 (0.96-1.48)	0.11
Women's Health Initiative, women <70 years old at blood draw				
No CHIP	3,637	510 / 51,541	*Reference*	--
All CHIP	256	50 / 3,521	1.38 (1.03-1.86)	0.03
CHIP with VAF ≤0.1	37	4 / 495	0.89 (0.33-2.39)	0.82
CHIP with VAF >0.1	219	36 / 3,026	1.45 (1.07-1.98)	0.02
Women's Health Initiative, women ≥70 years old at blood draw				
No CHIP	3,003	526 / 32,467	*Reference*	--
All CHIP	360	60 / 3,652	1.07 (0.81-1.41)	0.65
CHIP with VAF ≤0.1	47	9 / 491	1.32 (0.68-2.56)	0.41
CHIP with VAF >0.1	313	51 / 3,162	1.03 (0.76-1.39)	0.85

Cox proportional hazard models are adjusted for age, the first 10 principal components of ancestry, current or former tobacco use, prevalent diabetes mellitus, systolic blood pressure, antihypertensive medication use, cholesterol-lowering medication use, body-mass index, prior hysterectomy, and a history of prior hormone therapy use; WHI models are further adjusted for race/ethnicity, enrollment in the WHI observational study vs. clinical trial, whether women were randomized to hormone therapy vs. placebo, and an inverse probability weight to account for the non-random selection of women for whole-genome sequencing in WHI.