Supplementary Online Content

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eResults

This supplementary material has been provided by the authors to give readers additional information about their work.

eResults.

Missing data: Laboratory values (non-HDL-C [15%] and C-reactive protein [7%]) were the most common missing covariates. Antihypertensive medication use was found to be associated with missing non-HDL-C (P=0.02). BMI (P<0.001), systolic blood pressure (P=0.005), and antihypertensive medication use (P=0.004) were associated with missing C-reactive protein. In secondary analyses, these variables were in turn incorporated as covariates in prediction models, along with age and sex, to impute missing data values.

Sensitivity analyses:

Primary and secondary cardiovascular outcomes: Sensitivity analysis incorporating non-cardiovascular death as a competing risk yielded nearly identical hazards (**eTable 2**). Models using imputed data to replace missing covariates also yielded similar results (**eTable 3**). Sensitivity analyses excluding women with incident heart failure (**eTable 4**), history of cancer (**eTable 5**), and current or prior menopausal hormone therapy (MHT) use >1 year (**eTable 6**) yielded similar results, as did analysis excluding women with history of ever-hysterectomy from the natural premature menopause group (**eTable 7**). In models stratified by BMI category, risks associated with premature menopause were not restricted to a particular BMI subset (**eTable 8**). Results of sensitivity analyses restricted to women aged ≥ 55 years old at enrollment (**eTable 9**) and with ≥5 years of prior MHT (**eTable 10**) use also recapitulated results of the primary and secondary analyses. In addition, results were consistent when incorporating premenopausal women in the UK Biobank as the reference group (**eTable 11**).

Incident cardiovascular risk factors: Results were similar when competing risk regression was used, incorporating death as a competing risk (**eTable 16**). In sensitivity analyses to assess possible reverse causation, similar hazards were observed after excluding women with any incident cardiovascular disease (**eTable 17**). An inverse dose-responsive relationship was observed between age at menopause and risk for acquiring cardiovascular disease risk factors (**eTable 18**).

eTable 1. Complete Results of Fully Adjusted Cox Proportional Hazards Model for Time-to-First Cardiovascular Diagnosis (Primary Outcome).

Variable	Hazard ratio (95% CI)	P-value
Surgical premature menopause	1.87 (1.36-2.58)	<0.001
Natural premature menopause	1.36 (1.19-1.56)	<0.001
Age (years)	0.88 (0.79-0.99)	0.03
Age^2 ($years^2$)	1.002 (1.00-1.003)	<0.001
Non-white race	0.91 (0.78-1.07)	0.27
Prevalent type 2 diabetes mellitus	1.65 (1.41-1.93)	<0.001
Ever-smoking	1.20 (1.13-1.28)	<0.001
Systolic blood pressure at study enrollment (mmHg)	1.004 (1.002-1.005)	<0.001
Antihypertensive medication use at enrollment	1.43 (1.33-1.53)	<0.001
Non-high-density lipoprotein cholesterol (mg/dL)	1.03 (1.00-1.06)	0.04
Cholesterol-lowering medication use at enrollment	1.37 (1.26-1.49)	<0.001
Body-mass index (kg/m^2)	1.02 (1.02-1.03)	<0.001
Log-transformed C-reactive protein	1.18 (1.15-1.22)	<0.001
Ever-use of menopausal hormone therapy	1.04 (0.98-1.11)	0.20

The primary outcome was a composite of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism.

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from a Cox proportional hazard model. The model was adjusted for all covariates listed in the left-hand column.

eTable 2. Sensitivity Analysis: Sub-distribution Hazards for Incident Cardiovascular Disease Derived From Fine-Gray Competing Risk Regression Models, Incorporating Noncardiovascular Death as a Competing Risk.

	Surgical premature menopause		Natural premature menopause	
	Sub-distribution hazard (95% CI)	P-value	Sub-distribution hazard (95% CI)	P-value
First cardiovascular disease diagnosis*	1.87 (1.35-2.60)	<0.001	1.36 (1.18-1.56)	<0.001
Coronary artery disease	2.52 (1.46-4.35)	<0.001	1.38 (1.06-1.81)	0.02
Heart failure	2.49 (1.17-5.29)	0.02	1.21 (0.80-1.84)	0.36
Aortic stenosis	2.92 (0.95-9.01)	0.06	2.38 (1.48-3.83)	<0.001
Mitral regurgitation	4.13 (1.64-10.35)	0.003	0.71 (0.33-1.53)	0.38
Atrial fibrillation	1.61 (0.90-2.87)	0.11	1.25 (1.00-1.58)	0.06
Ischemic stroke	0.44 (0.06-3.15)	0.41	1.50 (1.01-2.29)	0.04
Peripheral artery disease	1.36 (0.33-5.58)	0.67	1.33 (0.75-2.25)	0.29
Venous thromboembolism	2.76 (1.48-5.17)	0.001	1.71 (1.27-2.29)	<0.001

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from competing risk regression models.

Models adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 3. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women, With and Without Imputed Data to Replace Missing Covariates in Fully Adjusted Models.

	Surgical premature menopause				Natural premature menopause			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	1.87 (1.36-2.58)	<0.001	1.84 (1.38-2.44)	<0.001	1.36 (1.19-1.56)	<0.001	1.41 (1.25-1.58)	<0.001
Coronary artery disease	2.52 (1.48-4.29)	<0.001	2.80 (1.79-4.36)	<0.001	1.39 (1.06-1.82)	0.02	1.51 (1.20-1.90)	<0.001
Heart failure	2.57 (1.21-5.47)	0.01	2.36 (1.22-4.58)	0.01	1.21 (0.81-1.82)	0.35	1.39 (1.01-1.93)	0.04
Aortic stenosis	2.91 (0.92-9.15)	0.06	2.79 (1.03-7.54)	0.04	2.37 (1.47-3.82)	<0.001	2.15 (1.39-3.31)	<0.001
Mitral regurgitation	4.13 (1.69-10.11)	0.002	3.16 (1.30-7.69)	0.01	0.73 (0.34-1.55)	0.41	0.90 (0.49-1.65)	0.73
Atrial fibrillation	1.60 (0.91-2.83)	0.11	1.61 (0.98-2.64)	0.06	1.25 (1.00-1.58)	0.05	1.30 (1.06-1.59)	0.01
Ischemic stroke	0.43 (0.06-3.12)	0.41	0.99 (0.32-3.07)	0.98	1.50 (1.01-2.25)	0.04	1.43 (1.00-2.05)	0.05
Peripheral artery disease	1.34 (0.33-5.41)	0.68	1.55 (0.49-4.85)	0.45	1.34 (0.79 - 2.26)	0.27	1.47 (0.94-2.29)	0.09
Venous thromboembolism	2.73 (1.46-5.14)	0.002	2.26 (1.24-4.11)	0.008	1.70 (1.27-2.29)	<0.001	1.56 (1.19-2.04)	0.001

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use, excluding 30,975 women with missing covariates

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use, using imputed data to replace missing covariates

eTable 4. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women With History of Premature Natural and Surgical Menopause (< 40 Years), Eliminating 772 Women With Incident Heart Failure and 46 Women With Missing Heart Failure Data (n = 143,442).

	Premature surgical menopause				Premature natural menopause			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.1 (1.6-2.9)	<0.001	1.9 (1.3-2.7)	<0.001	1.6 (1.4-1.8)	<0.001	1.4 (1.2-1.6)	<0.001
Coronary artery disease	3.2 (2.0-5.4)	<0.001	2.4 (1.3-4.5)	0.006	1.8 (1.4-2.3)	<0.001	1.3 (0.9-1.8)	0.11
Aortic stenosis	2.1 (0.5-8.5)	0.30	2.4 (0.6-9.8)	0.22	2.3 (1.4-3.8)	<0.001	2.1 (1.2-3.6)	0.01
Mitral regurgitation	3.8 (1.4-10.2)	0.008	3.7 (1.2-11.8)	0.02	0.9 (0.5-1.9)	0.88	0.9 (0.4-2.0)	0.78
Atrial fibrillation	1.8 (1.0-3.0)	0.04	1.7 (0.9-3.2)	0.09	1.5 (1.2-1.9)	<0.001	1.4 (1.1-1.7)	0.02

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age at enrollment and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 5. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women With History of Premature Natural and Surgical Menopause (< 40 Years), Eliminating 15,017 Women With Any Prevalent Cancer at Enrollment and 436 Women With Missing Data on Prevalent Cancer Diagnosis at Enrollment (n = 128,807).

	Premature surgical menopause				Premature natural menopause			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.2 (1.6-3.1)	<0.001	1.9 (1.3-2.9)	0.001	1.6 (1.4-1.8)	<0.001	1.4 (1.2-1.6)	<0.001
Coronary artery disease	3.5 (2.1-5.9)	<0.001	2.2 (1.1-4.4)	0.03	1.9 (1.5-2.4)	<0.001	1.4 (1.1-2.0)	0.02
Heart failure	2.4 (1.0-5.7)	0.06	2.0 (0.6-6.2)	0.24	1.4 (1.0-2.1)	0.06	1.1 (0.6-1.8)	0.75
Aortic stenosis	3.7 (1.2-11.5)	0.02	3.0 (0.7-12.2)	0.12	2.5 (1.6-4.0)	<0.001	2.3 (1.3-4.0)	0.003
Mitral regurgitation	2.9 (0.9-8.9)	0.07	2.5 (0.6-10.2)	0.20	1.0 (0.6-2.0)	0.90	0.9 (0.4-2.0)	0.89
Atrial fibrillation	1.9 (1.1-3.4)	0.02	1.6 (0.8-3.2)	0.18	1.4 (1.1-1.7)	0.008	1.2 (0.9-1.6)	0.19
Ischemic stroke	1.1 (0.3-4.5)	0.87	0.7 (0.1-5.2)	0.75	1.6 (1.1-2.4)	0.02	1.6 (1.0-2.5)	0.04
Peripheral artery disease	2.0 (0.5-8.1)	0.32	2.1 (0.5-8.5)	0.30	1.9 (1.1-3.0)	0.01	1.1 (0.6-2.2)	0.74
Venous thromboembolism	2.5 (1.2-5.3)	0.02	1.8 (0.7-4.8)	0.24	1.8 (1.4-2.5)	<0.001	1.7 (1.2-2.5)	0.001

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 6. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women With History of Premature Natural and Surgical Menopause (< 40 years), Eliminating 39,281 Women With >1 Year of Menopausal Hormone Therapy Use, 9,456 With Current Menopausal Hormone Therapy Use at Study Enrollment, 4,441 Women With Missing Data on Duration of Prior Menopausal Hormone Therapy Use, and 345 Women With Missing Data on Ever-Use of Menopausal Hormone Therapy (n = 90,737).

	Premature surgical menopause (n = 161)				Premature natural menopause (n = 1,851)			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.5 (1.5-4.2)	<0.001	2.6 (1.4-4.7)	0.002	1.5 (1.3-1.9)	<0.001	1.4 (1.2-1.9)	<0.001
Coronary artery disease	4.2 (1.9-9.3)	<0.001	4.1 (1.7-9.8)	0.002	1.9 (1.3-2.7)	<0.001	1.8 (1.2-2.8)	0.005
Heart failure	5.8 (2.4-14.0)	<0.001	6.9 (2.6-18.6)	<0.001	1.6 (1.0-2.7)	0.07	1.8 (1.0-3.2)	0.04
Aortic stenosis	3.0 (0.4-21.2)	0.28	4.2 (0.6-30.0)	0.16	2.5 (1.3-4.9)	0.008	3.5 (1.7-6.9)	<0.001
Mitral regurgitation	8.1 (2.6-25.3)	<0.001	8.3 (2.0-33.8)	0.003	0.3 (0-1.8)	0.17	0.4 (0-2.6)	0.31
Atrial fibrillation	2.5 (1.1-5.7)	0.02	2.4 (0.9-6.5)	0.08	1.3 (1.0-1.9)	0.09	1.3 (0.9-2.0)	0.16
Ischemic stroke	2.9 (0.7-11.5)	0.14	NA	NA	0.4 (0.1-1.2)	0.11	0.5 (0.2-1.7)	0.30
Peripheral artery disease	2.7 (0.4-19.1)	0.33	3.2 (0.4-23.1)	0.25	2.4 (1.3-4.6)	0.006	1.5 (0.6-3.7)	0.36
Venous thromboembolism	2.7 (0.9-8.5)	0.08	1.2 (0.2-8.8)	0.83	2.0 (1.3-2.9)	0.001	2.1 (1.3-3.3)	0.001

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, and C-reactive protein

eTable 7. Sensitivity Analysis: Hazards of Incident Cardiovascular Disease Diagnoses Associated With **Natural Premature Menopause** (i.e., Menopause Before Age 40), Comparing Model Results With and Without Inclusion of 2,524 Women With Prior Hysterectomy in the Group With Natural Premature Menopause.

	No exclusion of women with hysterectomy				Excluding 2,540 women with prior hysterectomy			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First cardiovascular disease diagnosis*	1.60 (1.42-1.80)	<0.001	1.36 (1.19-1.56)	<0.001	1.61 (1.34-1.92)	<0.001	1.34 (1.08-1.66)	0.008
Coronary artery disease	1.81 (1.44-2.28)	<0.001	1.39 (1.06-1.82)	0.02	1.79 (1.27-2.53)	<0.001	1.38 (0.90-2.11)	0.14
Heart failure	1.56 (1.14-2.16)	0.006	1.21 (0.81-1.82)	0.35	1.78 (1.13-2.79)	0.01	1.52 (0.87-2.65)	0.14
Aortic stenosis	2.48 (1.62-3.80)	<0.001	2.37 (1.47-3.82)	<0.001	2.33 (1.19-4.54)	0.01	2.53 (1.24-5.17)	0.01
Mitral regurgitation	0.95 (0.52-1.74)	0.87	0.73 (0.34-1.55)	0.41	0.60 (0.19-1.88)	0.38	0.73 (0.23-2.29)	0.59
Atrial fibrillation	1.44 (1.18-1.77)	<0.001	1.25 (1.00-1.58)	0.05	1.25 (0.90-1.74)	0.18	1.15 (0.79-1.69)	0.46
Ischemic stroke	1.59 (1.12-2.28)	0.01	1.50 (1.01-2.25)	0.04	2.13 (1.33-3.41)	0.002	2.04 (1.19-3.49)	0.009
Peripheral artery disease	1.96 (1.27-3.03)	0.002	1.34 (0.79 - 2.26)	0.27	1.93 (1.00-3.75)	0.05	0.91 (0.34-2.45)	0.85
Venous thromboembolism	1.68 (1.29-2.20)	<0.001	1.70 (1.27-2.29)	<0.001	1.62 (1.08-2.43)	0.02	1.60 (1.01-2.53)	0.04

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age at enrollment and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 8. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses, Stratified by Body-Mass Index (BMI) at Study Enrollment.

	Surgical premature menopause			Natural premature menopause		
Body-mass index at study enrollment	<25 (n = 174)	≥25 and <30 (n = 238)	≥30 (n = 217)	<25 (n = 1,551)	≥25 and <30 (n = 1,856)	≥30 (n = 1,407)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
First incident cardiovascular diagnosis[+]	1.50 (0.67-3.36)	1.73 (1.02-2.94)*	2.13 (1.33-3.40)**	1.78 (1.37-2.29)***	1.23 (0.81-1.55)	1.25 (0.99-1.57)
Coronary artery disease	2.65 (0.84-8.30)	1.59 (0.59-4.30)	3.37 (1.58-7.20)**	1.56 (0.92-2.63)	1.46 (0.95-2.23)	1.22 (0.76-1.94)
Heart failure	4.22 (1.03-17.28)*	1.88 (0.46-7.67)	2.54 (0.80-8.03)	2.84 (1.51-5.31)**	1.20 (0.61-2.35)	0.53 (0.22-1.28)
Aortic stenosis	6.00 (0.81-44.34)	NA	4.85 (1.16-20.34)*	1.32 (0.32-5.51)	2.75 (1.36-5.55)**	2.37 (1.12-4.99)*
Mitral regurgitation	2.80 (0.38-20.39)	6.79 (2.09-22.00)	2.33 (0.31-17.09)	0.98 (0.31-3.11)	0.29 (0.04-2.09)	0.95 (0.30-2.06)
Atrial fibrillation	1.45 (0.36-5.84)	1.38 (0.51-3.69)	1.89 (0.84-4.23)	1.42 (0.89-2.29)	1.12 (0.75-1.66)	1.29 (0.90-1.84)
Ischemic stroke	NA	1.08 (0.15-7.78)	NA	2.17 (1.05-4.49)*	1.34 (0.68-2.62)	1.3 (0.66-2.57)
Peripheral artery disease	2.34 (0.32-17.23)	1.48 (0.20-10.76)	NA	1.51 (0.55-4.17)	1.34 (0.59-3.09)	1.16 (0.46-2.90)
Venous thromboembolism	2.69 (0.66-11.00)	1.50 (0.37-6.09)	3.74 (1.64-8.49)**	2.36 (1.38-4.06)**	1.65 (1.01-2.71)*	1.39 (0.83-2.32)

*P<0.05; **P<0.01; ***P<0.001

[+] Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Models adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 9. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women Who Were ≥55 Years Old at Study Enrollment (n = 118,971).

	Surgical premature menopause				Natural premature menopause			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.31 (1.71-3.12)	<0.001	1.93 (1.36-2.73)	<0.001	1.56 (1.37-1.77)	<0.001	1.34 (1.16-1.55)	<0.001
Coronary artery disease	3.97 (2.49-6.32)	<0.001	2.62 (1.48-4.64)	<0.001	1.82 (1.43-2.31)	<0.001	1.40 (1.06-1.86)	0.02
Heart failure	3.10 (1.54-6.22)	0.001	2.75 (1.22-6.16)	0.01	1.35 (0.93-1.95)	0.12	1.06 (0.67-1.67)	0.82
Aortic stenosis	2.94 (0.94-9.17)	0.06	2.28 (0.56-9.24)	0.25	2.37 (1.50-3.73)	<0.001	2.20 (1.31-3.69)	0.002
Mitral regurgitation	4.18 (1.73-10.13)	0.002	5.26 (2.16-12.82)	<0.001	0.91 (0.47-1.76)	0.77	0.75 (0.33-1.70)	0.49
Atrial fibrillation	1.83 (1.08-3.10)	0.02	1.52 (0.81-2.83)	0.19	1.47 (1.20-1.81)	<0.001	1.28 (1.01-1.62)	0.04
Ischemic stroke	1.39 (0.45-4.32)	0.57	0.53 (0.07-3.75)	0.52	1.68 (1.17-2.43)	0.005	1.58 (1.04-2.36)	0.03
Peripheral artery disease	2.47 (0.79-7.69)	0.12	1.55 (0.38-6.24)	0.54	1.84 (1.16-2.92)	0.01	1.26 (0.72-2.21)	0.42
Venous thromboembolism	2.75 (1.43-5.30)	0.003	2.97 (1.47-5.97)	0.002	1.57 (1.16-2.12)	0.003	1.62 (1.16-2.25)	0.004

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 10. Sensitivity Analysis: Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women Who Used Menopausal Hormone Therapy for ≥5 Years Prior to Study Enrollment, Not Including Women Using Menopausal Hormone Therapy at Study Enrollment (n = 28,083).

	Surgical premature menopause				Natural premature menopause			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.08 (1.36-3.18)	<0.001	1.54 (0.92-2.58)	0.10	1.58 (1.30-1.94)	<0.001	1.34 (1.07-1.69)	0.01
Coronary artery disease	4.69 (2.62-8.39)	<0.001	2.85 (1.33-6.09)	0.007	1.63 (1.10-2.43)	0.02	1.33 (0.83-2.13)	0.24
Heart failure	2.03 (0.63-6.45)	0.23	0.82 (0.11-5.9)	0.84	1.22 (0.66-2.27)	0.52	0.65 (0.27-1.61)	0.35
Aortic stenosis	3.33 (0.78-14.2)	0.10	1.55 (0.20-12.16)	0.68	2.73 (1.33-5.60)	0.006	1.61 (0.66-3.90)	0.29
Mitral regurgitation	NA	NA	NA	NA	1.53 (0.70-3.33)	0.28	1.09 (0.39-3.02)	0.87
Atrial fibrillation	1.76 (0.83-3.73)	0.14	1.47 (0.60-3.56)	0.40	1.56 (1.12-2.17)	0.008	1.27 (0.86-1.87)	0.23
Ischemic stroke	0.80 (0.11-5.76)	0.82	0.83 (0.12-6.03)	0.86	1.98 (1.16-3.40)	0.01	1.86 (1.04-3.35)	0.04
Peripheral artery disease	1.41 (0.20-10.1)	0.73	1.55 (0.21-11.28)	0.66	1.72 (0.83-3.56)	0.14	1.61 (0.73-3.53)	0.24
Venous thromboembolism	3.23 (1.42-7.36)	0.005	3.00 (1.21-7.43)	0.02	1.40 (0.84-2.35)	0.20	1.25 (0.70-2.21)	0.45

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, and C-reactive protein

eTable 11. Hazard Ratios for Incident Cardiovascular Diagnoses in Postmenopausal Women Compared With a Reference Group of Women Who Were Premenopausal at Study Enrollment.

	Surgical premature menopause				Natural premature menopause				Postmenopausal without premature menopause			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.6 (1.9-3.5)	<0.001	2.0 (1.4-2.9)	<0.001	1.8 (1.6-2.2)	<0.001	1.5 (1.2-1.8)	<0.001	1.1 (1.0-1.3)	0.04	1.1 (0.9-1.3)	0.26
Coronary artery disease	3.8 (2.3-6.3)	<0.001	2.2 (1.2-3.9)	0.01	1.8 (1.3-2.5)	<0.001	1.2 (0.8-1.8)	0.38	1.0 (0.8-1.3)	0.95	0.9 (0.6-1.2)	0.31
Heart failure	4.5 (2.2-9.5)	<0.001	4.2 (1.8-9.8)	0.001	2.5 (1.6-4.1)	<0.001	1.9 (1.1-3.5)	0.03	1.6 (1.1-2.3)	0.02	1.6 (1.0-2.5)	0.04
Aortic stenosis	7.2 (2.1-24.8)	0.002	5.6 (1.4-23.0)	0.02	5.2 (2.2-12.4)	<0.001	4.5 (1.7-11.8)	0.002	2.1 (1.0-4.5)	0.07	1.9 (0.8-4.6)	0.14
Mitral regurgitation	4.1 (1.5-11.2)	0.005	5.3 (1.9-14.9)	0.002	1.1 (0.5-2.4)	0.74	0.9 (0.4-2.3)	0.84	1.2 (0.7-2.0)	0.53	1.2 (0.7-2.2)	0.49
Atrial fibrillation	2.2 (1.3-3.8)	0.005	1.9 (1.0-3.5)	0.04	1.7 (1.2-2.3)	<0.001	1.5 (1.0-2.1)	0.03	1.2 (0.9-1.5)	0.22	1.2 (0.9-1.5)	0.26
Ischemic stroke	1.4 (0.4-4.5)	0.62	0.5 (0.1-3.6)	0.47	1.8 (1.1-3.1)	0.03	1.6 (0.9-2.9)	0.12	1.1 (0.7-1.7)	0.59	1.1 (0.7-1.7)	0.80
Peripheral artery disease	2.0 (0.6-6.9)	0.26	1.2 (0.3-5.2)	0.84	1.8 (1.0-3.5)	0.07	1.2 (0.5-2.5)	0.68	0.9 (0.6-1.6)	0.79	0.9 (0.5-1.6)	0.72
Venous thromboembolism	3.3 (1.7-6.3)	<0.001	3.2 (1.6-6.2)	<0.001	2.1 (1.5-3.1)	<0.001	2.0 (1.3-2.9)	0.001	1.2 (1.0-1.6)	0.10	1.2 (0.9-1.6)	0.33

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 12. Sensitivity Analysis: Comparison of Models With and Without Adjustment for Ever Use of Menopausal Hormone Therapy.

	Premature surgical menopause				Premature natural menopause			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First incident cardiovascular diagnosis*	2.1 (1.5-2.9)	<0.001	2.0 (1.4-2.7)	<0.001	1.4 (1.2-1.6)	<0.001	1.4 (1.2-1.6)	<0.001
Coronary artery disease	2.9 (1.6-4.9)	<0.001	2.7 (1.6-4.8)	<0.001	1.4 (1.0-1.8)	0.04	1.3 (1.0-1.8)	0.05
Heart failure	2.7 (1.2-6.0)	0.02	2.6 (1.2-5.9)	0.02	1.2 (0.7-1.8)	0.52	1.2 (0.7-1.8)	0.53
Aortic stenosis	3.4 (1.1-10.6)	0.04	3.3 (1.0-10.4)	0.04	2.4 (1.5-3.9)	<0.001	2.4 (1.5-3.9)	<0.001
Mitral regurgitation	4.2 (1.6-11.3)	0.005	3.7 (1.4-10.0)	0.01	0.9 (0.4-1.8)	0.69	0.8 (0.4-1.7)	0.55
Atrial fibrillation	1.7 (1.0-3.1)	0.07	1.7 (0.9-3.0)	0.10	1.3 (1.0-1.7)	0.02	1.3 (1.0-1.6)	0.04
Ischemic stroke	0.5 (0.1-3.9)	0.54	0.5 (0.1-3.6)	0.49	1.7 (1.1-2.5)	0.01	1.6 (1.1-2.4)	0.02
Peripheral artery disease	1.6 (0.4-6.4)	0.52	1.5 (0.4-6.2)	0.54	1.4 (0.8-2.4)	0.22	1.4 (0.8-2.4)	0.25
Venous thromboembolism	2.2 (1.0-2.6)	0.04	2.1 (1.0-4.5)	0.04	1.7 (1.2-2.3)	<0.001	1.7 (1.2-2.3)	0.001

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Model 1: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, and C-reactive protein

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 13. Associations of Use of Menopausal Hormone Therapy With Incident Cardiovascular Outcomes. Values displayed are hazard ratio (95% confidence interval).

	Premature surgical menopause	Premature natural menopause	Ever-use of MHT	Current use of MHT	Duration of MHT use	Delayed initiation of MHT (≥5 years after menopause)
First incident cardiovascular diagnosis[+]						
Model 1	2.2 (1.7-2.9)***	1.6 (1.4-1.8)***	1.06 (1.0-1.1)*			
Model 2	2.3 (1.7-3.0***	1.6 (1.4-1.8)***		0.98 (0.87-1.09)		
Model 3	2.6 (1.9-3.7)***	1.6 (1.4-1.9)***			0.99 (0.99-1.0)	
Model 4	2.3 (1.7-3.1)***	1.7 (1.4-1.9)***				1.1 (0.9-1.3)
Model 5	2.6 (1.9-3.7)***	1.6 (1.4-1.9)***			0.99 (0.98-1.002)	1.06 (0.9-1.3)
Coronary artery disease						
Model 1	3.6 (2.3-5.5)***	1.8 (1.4-2.2)***	1.2 (1.0-1.3)**			
Model 2	3.7 (2.4-5.8)***	1.8 (1.4-2.3)***		1.06 (0.9-1.3)		
Model 3	4.5 (2.6-7.5)***	1.8 (1.3-2.5)***			0.99 (0.97-1.01)	
Model 4	3.5 (2.1-5.9)***	1.8 (1.4-2.4)***				1.1 (0.8-1.5)
Model 5	4.5 (1.6-7.5)***	1.8 (1.3-2.5)***			0.99 (0.97-1.01)	1.0 (0.7-1.4)
Atrial fibrillation						
Model 1	1.8 (1.1-3.0**	1.4 (1.2-1.8)***	1.07 (0.99-1.17)			
Model 2	1.9 (1.2-3.1)*	1.5 (1.2-1.8)***		0.9 (0.7-1.1)		
Model 3	2.6 (1.4-4.6)**	1.6 (1.2-2.1)**			0.98 (0.97-0.997)*	
Model 4	2.1 (1.2-3.6)**	1.5 (1.2-1.9)**				1.2 (0.9-1.5)
Model 5	2.6 (1.4-4.6)**	1.5 (1.2-2.0)**			0.98 (0.97-0.998)*	1.2 (0.9-1.5)
Venous thromboembolism						
Model 1	2.7 (1.5-5.0)***	1.7 (1.3-2.3)***	0.96 (0.8-1.1)			
Model 2	2.8 (1.5-5.0)***	1.7 (1.3-2.3)***		0.86 (0.7-1.1)		
Model 3	3.8 (1.9-7.8)***	1.6 (1.0-2.4)*			0.98 (0.96-0.998)*	
Model 4	2.7 (1.4-5.2)**	1.5 (1.1-2.2)*				1.06 (0.7-1.5)
Model 5	3.8 (1.9-7.8)***	1.6 (1.0-2.4)*			0.98 (0.96-0.998)*	0.94 (0.6-1.5)

MHT = menopausal hormone therapy

[+] Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

All models adjusted for age at enrollment and race

*P<0.05; **P<0.01; ***P<0.001

eTable 14. Hazard Ratios Associated With Different Menopausal Age Thresholds for First Incident Cardiovascular Diagnosis and Eight Separate Cardiovascular Disease Diagnoses, Compared With a Reference Group of Women With Menopause ≥ 50 Years.

	Surgical menopause				**Natural menopause**			
	Model 1		Model 2		Model 1		Model 2	
Age at menopause	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
	First incident cardiovascular diagnosis*							
	P(trend) = 0.03				P(trend) <0.001			
<30	3.4 (1.8-6.6)	<0.001	2.3 (1.0-5.2)	0.04	1.6 (1.0-2.4)	0.03	1.3 (0.8-2.2)	0.23
<35	3.0 (2.1-4.5)	<0.001	2.3 (1.5-3.7)	<0.001	1.7 (1.4-2.1)	<0.001	1.5 (1.2-2.0)	<0.001
<40	2.4 (1.8-3.2)	<0.001	2.1 (1.5-2.9)	<0.001	1.7 (1.5-2.0)	<0.001	1.4 (1.2-1.7)	<0.001
<45	1.7 (1.4-2.1)	<0.001	1.4 (1.2-1.8)	0.001	1.5 (1.4-1.6)	<0.001	1.3 (1.2-1.4)	<0.001
<50	1.5 (1.3-1.7)	<0.001	1.2 (1.0-1.4)	0.02	1.3 (1.2-1.4)	<0.001	1.2 (1.1-1.3)	<0.001
	Coronary artery disease							
	P(trend) = 0.004				P(trend) = 0.02			
<30	6.5 (2.4-17.3)	<0.001	2.7 (0.7-11.1)	0.16	2.5 (1.2-4.9)	0.01	1.6 (0.7-3.9)	0.31
<35	5.4 (3.0-9.8)	<0.001	3.5 (1.6-7.4)	0.001	2.0 (1.3-3.0)	0.001	1.6 (1.0-2.6)	0.07
<40	4.2 (2.7-6.6)	<0.001	2.9 (1.6-5.0)	<0.001	2.0 (1.6-2.5)	<0.001	1.4 (1.0-1.9)	0.03
<45	1.8 (1.3-2.6)	0.002	1.4 (0.9-2.2)	0.15	1.6 (1.4-1.8)	<0.001	1.3 (1.1-1.6)	0.01
<50	1.6 (1.2-2.0)	0.001	1.2 (0.9-1.7)	0.22	1.4 (1.2-1.5)	<0.001	1.3 (1.1-1.5)	<0.001
	Heart failure							
	P(trend) = 0.20				P(trend) = 0.77			
<30	5.3 (1.3-21.7)	0.02	3.3 (0.5-23.7)	0.24	1.1 (0.3-4.3)	0.94	1.3 (0.3-5.4)	0.69
<35	3.4 (1.3-9.1)	0.02	2.2 (0.5-9.0)	0.27	1.1 (0.5-2.3)	0.83	1.0 (0.4-2.4)	0.96
<40	3.1 (1.6-6.0)	0.001	3.0 (1.3-6.9)	0.008	1.8 (1.3-2.5)	<0.001	1.3 (0.8-2.1)	0.25
<45	1.8 (1.1-2.9)	0.02	1.7 (1.0-3.1)	0.07	1.4 (1.2-1.8)	<0.001	1.2 (0.9-1.5)	0.29
<50	1.7 (1.2-2.4)	0.004	1.5 (1.0-2.3)	0.07	1.5 (1.3-1.7)	<0.001	1.3 (1.1-1.6)	0.004
	Aortic stenosis							
	P(trend) = 0.004				P(trend) = 0.04			
<30	16.8 (5.1-55.1)	<0.001	17.9 (5.4-59.1)	<0.001	3.6 (1.1-11.5)	0.03	3.6 (1.1-11.6)	0.03
<35	5.3 (1.7-17.3)	0.005	6.3 (1.9-20.9)	0.003	1.4 (0.5-3.8)	0.53	1.5 (0.5-4.2)	0.44
<40	3.4 (1.2-9.1)	0.02	3.1 (1.0-9.8)	0.06	2.5 (1.6-3.9)	<0.001	2.3 (1.4-3.9)	0.001
<45	2.3 (1.2-4.6)	0.01	2.1 (1.0-4.6)	0.06	1.6 (1.1-2.2)	0.005	1.4 (0.9-2.1)	0.09
<50	1.1 (0.6-2.1)	0.83	1.0 (0.5-2.2)	0.93	1.3 (1.0-1.6)	0.04	1.1 (0.8-1.5)	0.38

	Surgical menopause				Natural menopause			
	Model 1		Model 2		Model 1		Model 2	
Age at menopause	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
	Mitral regurgitation							
	P(trend) = 0.08				P(trend) = 0.85			
<30	6.4 (0.9-46.2)	0.06	8.0 (1.1-57.7)	0.04	1.3 (0.2-9.1)	0.81	1.6 (0.2-11.4)	0.65
<35	8.1 (3.0-21.9)	<0.001	7.8 (2.4-24.9)	<0.001	1.1 (0.3-3.4)	0.89	1.4 (0.4-4.4)	0.57
<40	4.2 (1.7-10.3)	0.002	4.8 (1.7-13.1)	0.002	1.1 (0.6-2.1)	0.66	1.0 (0.5-2.1)	0.97
<45	2.1 (1.1-4.2)	0.03	1.9 (0.8-4.4)	0.13	1.4 (1.0-1.9)	0.04	1.5 (1.0-2.2)	0.03
<50	1.6 (1.0-2.8)	0.06	1.2 (0.6-2.4)	0.64	1.5 (1.2-1.8)	<0.001	1.5 (1.2-2.0)	0.001
	Atrial fibrillation							
	P(trend) = 0.44				P(trend) = 0.04			
<30	2.8 (0.9-8.6)	0.08	3.0 (1.0-9.4)	0.06	1.4 (0.7-2.9)	0.30	1.6 (0.8-3.2)	0.20
<35	1.7 (0.8-3.8)	0.20	1.6 (0.7-3.9)	0.29	1.5 (1.1-2.2)	0.02	1.5 (1.0-2.3)	0.03
<40	1.9 (1.2-3.2)	0.008	1.6 (0.9-3.0)	0.11	1.5 (1.2-1.8)	<0.001	1.3 (1.0-1.6)	0.04
<45	1.6 (1.2-2.1)	0.002	1.3 (0.9-1.9)	0.16	1.3 (1.2-1.5)	<0.001	1.2 (1.0-1.4)	0.04
<50	1.3 (1.0-1.6)	0.03	1.0 (0.7-1.3)	0.96	1.2 (1.1-1.3)	<0.001	1.1 (1.0-1.2)	0.03
	Ischemic stroke							
	P(trend) = 0.75				P(trend) = 0.19			
<30	NA	NA	NA	NA	1.3 (0.3-5.2)	0.72	1.5 (0.4-6.2)	0.55
<35	1.0 (0.1-7.1)	0.99	1.2 (0.2-8.4)	0.88	1.8 (1.0-3.4)	0.06	2.2 (1.1-4.1)	0.02
<40	1.3 (0.4-4.0)	0.66	0.5 (0.1-3.9)	0.54	1.7 (1.2-2.5)	0.004	1.7 (1.1-2.6)	0.01
<45	1.9 (1.1-3.2)	0.02	1.6 (0.8-3.0)	0.18	1.3 (1.0-1.7)	0.02	1.2 (0.9-1.6)	0.21
<50	1.4 (0.9-2.1)	0.14	1.1 (0.6-1.9)	0.73	1.2 (1.0-1.4)	0.04	1.2 (1.0-1.5)	0.04
	Peripheral artery disease							
	P(trend) = 0.62				P(trend) = 0.06			
<30	7.0 (1.0-50.1)	0.05	NA	NA	3.9 (1.3-12.3)	0.02	2.7 (0.7-11.2)	0.16
<35	2.1 (0.3-14.9)	0.46	NA	NA	2.9 (1.4-5.9)	0.003	2.3 (1.0-5.2)	0.05
<40	2.6 (0.8-8.2)	0.10	1.9 (0.5-7.9)	0.36	2.3 (1.5-3.6)	<0.001	1.7 (0.9-2.9)	0.08
<45	2.0 (1.0-4.0)	0.06	1.4 (0.6-3.3)	0.51	2.1 (1.6-2.8)	<0.001	1.7 (1.2-2.4)	0.001
<50	1.7 (1.0-2.8)	0.05	1.5 (0.8-2.8)	0.17	1.6 (1.3-2.0)	<0.001	1.4 (1.1-1.8)	0.01

	Surgical menopause				Natural menopause			
	Model 1		Model 2		Model 1		Model 2	
Age at menopause	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
	Venous thromboembolism							
	P(trend) = 0.36				P(trend) = 0.08			
<30	2.1 (0.3-14.9)	0.46	2.4 (0.3-17.5)	0.37	0.8 (0.2-3.2)	0.76	0.5 (0.1-3.5)	0.47
<35	5.0 (2.5-10.1)	<0.001	3.1 (1.1-8.4)	0.03	1.9 (1.2-3.1)	0.009	1.6 (0.9-2.9)	0.10
<40	2.9 (1.6-5.3)	<0.001	2.3 (1.1-5.0)	0.03	1.9 (1.4-2.5)	<0.001	1.8 (1.3-2.5)	<0.001
<45	1.9 (1.3-2.8)	0.002	1.6 (0.9-2.6)	0.08	1.5 (1.3-1.8)	<0.001	1.6 (1.3-1.9)	<0.001
<50	2.0 (1.5-2.6)	<0.001	1.5 (1.1-2.2)	0.02	1.3 (1.2-1.5)	<0.001	1.2 (1.1-1.5)	0.005

* Comprised of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.

Groups are inclusive of all women with menopausal age below the listed cutoff.

Model 1: Adjusted for age and race

Model 2: Adjusted for age, race, prevalent type 2 diabetes mellitus, ever-smoking, systolic blood pressure, use of anti-hypertensive medication, non-HDL cholesterol, use of cholesterol-lowering medication, body-mass index, C-reactive protein, and history of menopausal hormone therapy use

eTable 15. Incident Development of Hypertension, Hyperlipidemia, and Type 2 Diabetes, Stratified by Age at Study Enrollment (5-Year Age Categories).

		Premature surgical menopause		Premature natural menopause	
	Age at enrollment (years)	HR (95% CI)	P-value	HR (95% CI)	P-value
Hypertension*	40-44	3.7 (0.8-17.5)	0.10	1.4 (0.4-5.5)	0.61
	45-49	1.5 (0.4-6.4)	0.56	2.7 (1.5-4.9)	<0.001
	50-54	2.5 (0.9-6.7)	0.07	1.7 (1.1-2.7)	0.02
	55-59	1.7 (0.6-4.6)	0.28	1.4 (1.0-2.0)	0.06
	60-64	2.4 (1.2-4.6)	0.01	1.4 (1.1-1.8)	0.005
	65-69	1.7 (0.9-3.3)	0.11	1.2 (0.9-1.6)	0.32
Hyperlipidemia**	40-44	NA	NA	0.9 (0.2-3.9)	0.85
	45-49	1.1 (0.2-8.3)	0.91	2.1 (0.9-4.5)	0.07
	50-54	2.8 (1.1-7.7)	0.04	1.8 (1.0-3.0)	0.03
	55-59	3.7 (1.7-7.7)	<0.001	1.2 (0.8-1.8)	0.47
	60-64	2.3 (1.1-4.6)	0.02	1.3 (1.0-1.8)	0.09
	65-69	1.6 (0.8-3.4)	0.20	1.2 (0.8-1.6)	0.41
Type 2 diabetes mellitus***	40-44	NA	NA	1.6 (0.2-12.3)	0.67
	45-49	2.4 (0.6-10.2)	0.23	1.6 (0.6-3.8)	0.33
	50-54	1.3 (0.3-5.0)	0.75	1.6 (1.0-2.7)	0.08
	55-59	2.5 (1.0-5.9)	0.04	0.9 (0.5-1.7)	0.77
	60-64	4.7 (2.6-8.5)	<0.001	1.6 (1.2-2.2)	0.001
	65-69	1.3 (0.5-3.1)	0.58	1.4 (1.1-2.0)	0.02

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.
*Models adjusted for age at study enrollment, race, body-mass index, prevalent hyperlipidemia, and prevalent type 2 diabetes mellitus
**Models adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent type 2 diabetes mellitus
***Models adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent hyperlipidemia

eTable 16. Sensitivity Analysis: Subdistribution Hazards for Incident Hypertension, Hyperlipidemia, and Type 2 Diabetes From Fine-Gray Competing Risk Regression Models, Incorporating Death as a Competing Risk.

	Surgical premature menopause		Natural premature menopause	
	Sub-distribution hazard (95% CI)	P-value	Sub-distribution hazard (95% CI)	P-value
Hypertension*	2.09 (1.46-2.98)	<0.001	1.42 (1.22-1.65)	<0.001
Hyperlipidemia**	2.19 (1.49-3.23)	<0.001	1.30 (1.09-1.55)	0.004
Type 2 diabetes mellitus***	2.14 (1.43-3.22)	<0.001	1.43 (1.19-1.74)	<0.001

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from competing risk regression models.
*Model adjusted for age at study enrollment, race, body-mass index, prevalent hyperlipidemia, and prevalent type 2 diabetes mellitus
**Model adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent type 2 diabetes mellitus
***Model adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent hyperlipidemia

eTable 17. Sensitivity Analysis: Incident Development of Cardiovascular Risk Factors, Excluding 5,756 Women With Any Incident Cardiovascular Disease Diagnosis (n = 138,504).

	Premature surgical menopause		Premature natural menopause	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Hypertension*	2.09 (1.46-3.00)	<0.001	1.45 (1.24-1.69)	<0.001
Hyperlipidemia**	1.93 (1.25-2.96)	0.003	1.35 (1.12-1.62)	0.002
Type 2 diabetes mellitus***	2.34 (1.55-3.55)	<0.001	1.54 (1.27-1.87)	<0.001

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.
*Model adjusted for age at study enrollment, race, body-mass index, prevalent hyperlipidemia, and prevalent type 2 diabetes mellitus
**Model adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent type 2 diabetes mellitus
***Model adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent hyperlipidemia

eTable 18. Hazards of Incident Hypertension, Hyperlipidemia, and Type 2 Diabetes by Age at Menopause Compared With Women With Menopause ≥ Age 50.

Age at menopause (years)	Surgical menopause		Natural menopause	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Hypertension*				
	P(trend) = 0.01		P(trend) < 0.001	
<30	3.1 (1.4-6.9)	0.007	1.4 (0.8-2.4)	0.23
<35	2.6 (1.6-4.2)	<0.001	1.9 (1.5-2.4)	<0.001
<40	2.0 (1.4-2.9)	<0.001	1.4 (1.2-1.7)	<0.001
<45	1.7 (1.4-2.1)	<0.001	1.3 (1.2-1.4)	<0.001
<50	1.5 (1.2-1.7)	<0.001	1.2 (1.1-1.2)	<0.001
Hyperlipidemia**				
	P(trend) = 0.003		P(trend) < 0.001	
<30	2.6 (1.1-6.2)	0.04	1.7 (1.0-2.9)	0.06
<35	2.3 (1.3-4.2)	0.003	1.8 (1.3-2.4)	<0.001
<40	2.3 (1.6-3.4)	<0.001	1.4 (1.1-1.7)	<0.001
<45	1.6 (1.3-2.1)	<0.001	1.3 (1.2-1.4)	<0.001
<50	1.4 (1.2-1.7)	<0.001	1.2 (1.1-1.3)	<0.001
Type 2 diabetes mellitus***				
	P(trend) = 0.24		P(trend) < 0.001	
<30	1.5 (0.4-6.1)	0.59	1.7 (0.9-3.0)	0.08
<35	2.0 (1.1-3.9)	0.03	1.7 (1.2-2.3)	0.001
<40	2.3 (1.5-3.4)	<0.001	1.5 (1.3-1.9)	<0.001
<45	2.1 (1.6-2.6)	<0.001	1.3 (1.1-1.4)	<0.001
<50	1.8 (1.5-2.2)	<0.001	1.2 (1.1-1.3)	<0.001

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values are derived from Cox proportional hazard models.
Groups are inclusive of all women with menopausal age below the listed cutoff.
*Model adjusted for age at study enrollment, race, body-mass index, prevalent hyperlipidemia, and prevalent type 2 diabetes mellitus
**Model adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent type 2 diabetes mellitus
***Model adjusted for age at study enrollment, race, body-mass index, prevalent hypertension, and prevalent hyperlipidemia

eAppendix. *ICD* Codes Used to Identify Women With Congenital Heart Disease and to Ascertain Diagnoses of Cardiovascular Risk Factors and Cardiovascular Diseases.

Diagnosis	ICD codes
Congenital heart disease (exclusion)	ICD 9: 745, 7455, 746, 7464, 7468, 74687, 7469, 74693, 74699 ICD 10: K04, K04.1, K04.2, K04.4, K07, K07.8, K07.9, K09, K09.1, K09.2, K09.3, K09.5, K09.9, K10, K10.1, K10.2, K10.3, K10.4, K10.5, K10.8, K10.9, K11, K11.1, K11.2, K11.4, K11.5, K11.9, K12, K12.1, K12.2, K12.4, K12.8, K13, K13.1, K13.2, K13.3, K13.4, K.16.3, K16.5, K18, K18.3, K18.4, K18.8, K19, K19.1, K19.3, K20, K20.1, K20.2, Q20, Q20.1, Q20.2, Q20.3, Q20.4, Q20.5, Q20.6, Q20.8, Q20.9, Q21, Q21.0, Q21.1, Q21.2, Q21.3, Q21.4, Q21.8, Q21.9, Q22, Q22.1, Q22.2, Q22.4, Q22.5, Q22.8, Q22.9, Q23, Q23.0, Q23.1, Q23.2, Q23.3, Q23.4, Q23.8, Q23.9, Q24, Q24.0, Q24.3, Q24.4, Q24.5, Q24.6, Q24.8, Q24.9, Q22.5
Hypertension	ICD 9: 401, 4010, 4011, 4019, 402, 4020, 4021, 4029, 403, 4031, 4039, 404, 4040, 4041, 4049, 405, 4050, 4051, 4059 ICD 10: I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9
Hyperlipidemia	ICD 10: E78.0, E78.1, E78.2, E78.4, E78.5
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
Heart failure	ICD 9: 4254, 4280, 4281, 4289 ICD 10: I11.0 I11.3, I13.2, I25.5, I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, I50, I50.1, I50.9
Aortic stenosis	ICD 10: I06.0, I06.2, I35.0, I35.2

Diagnosis	ICD codes
Mitral regurgitation	ICD 9: 3942 ICD 10: I05.1, I05.2, I34.0
Atrial fibrillation or flutter	ICD 9: 4273, ICD 10: I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Ischemic stroke [adjudicated centrally by UK Biobank staff using listed ICD codes]	ICD 9: 434, 43401, 43411, 43491, 436 ICD 10: I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64
Peripheral arterial disease	ICD 9: 4400, 4402, 4438, 4439 ICD 10: I70.0, I70.00, I70.01, I70.2, I70.20, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8, I73.9
Venous thromboembolism	ICD 9: 4151, 4511 ICD 10: 126, I26.0, I26.9, I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, I81, I82.0, I82.2, D68, D68.0, D68.1, D68.2, D68.3, D68.4, D68.5, D68.6, D68.8, D68.9