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eSupplementary table 2. Association between reproductive lifespan, age at menarche, age at menopause, and risk of non-fatal CHD and stroke events

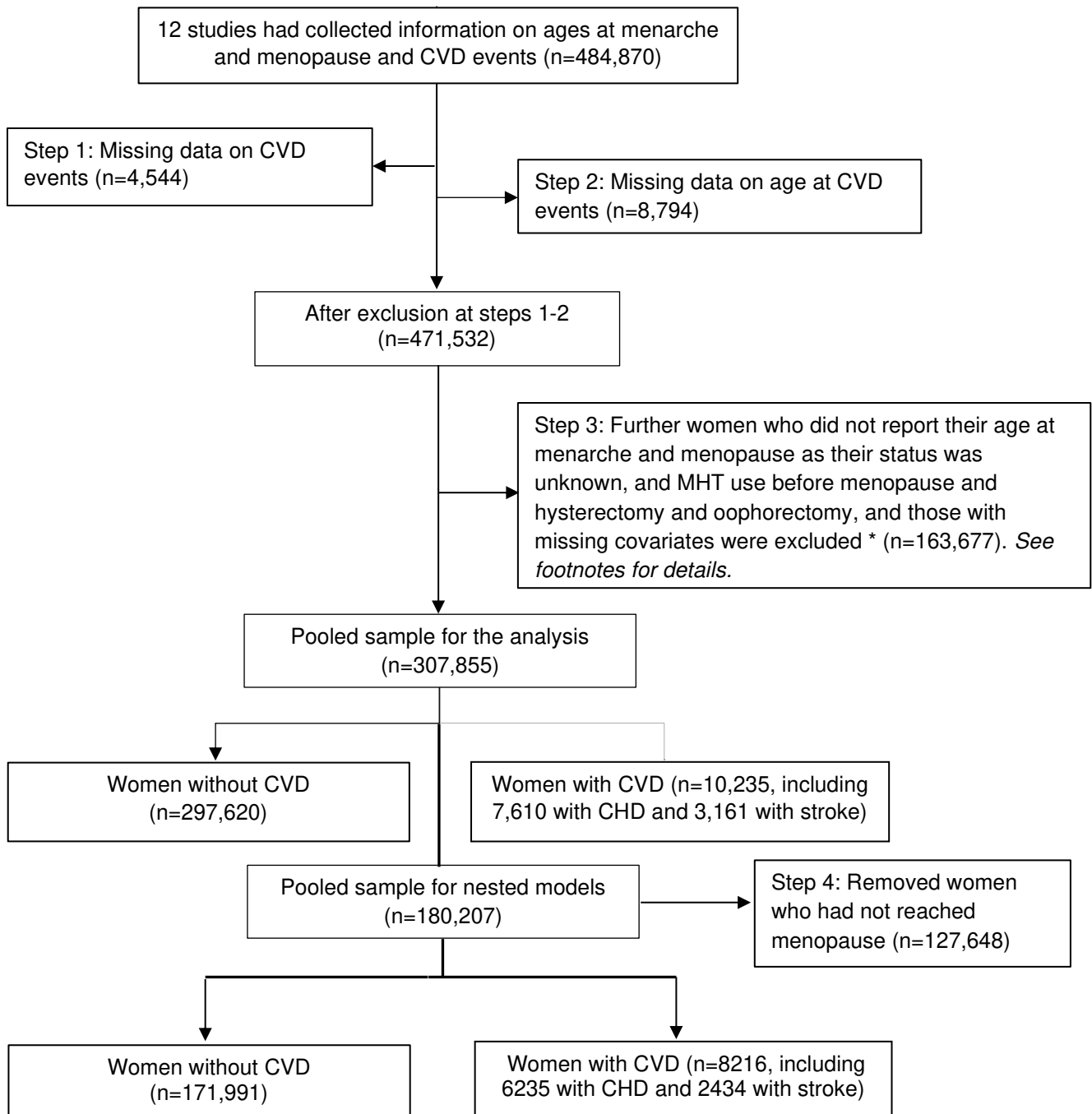
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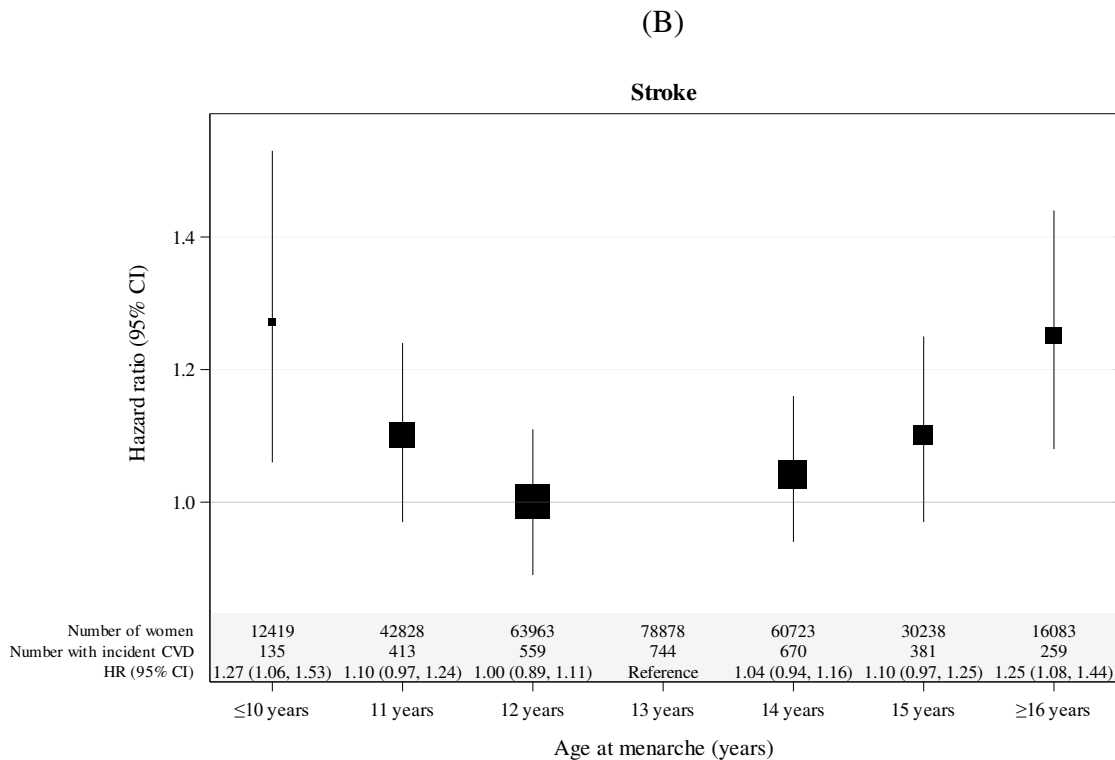
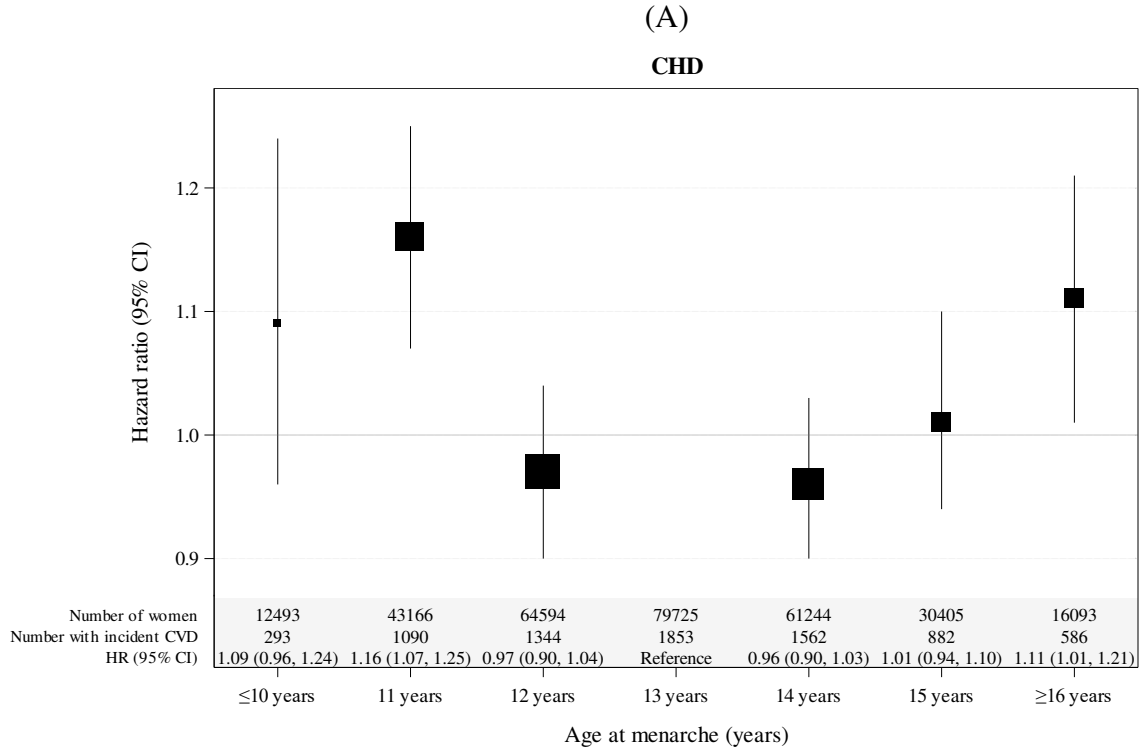
eSupplementary table 6. Sensitivity analysis for the association between reproductive lifespan, age at menarche, age at menopause, and diagnosed CVD events using hospital registry data (N=142,763)

eSupplementary figure 1. Flow diagram of sample for analysis of the associations between reproductive lifespan and non-fatal CVD events in the InterLACE consortium.



*Women who did not report their age at menarche and menopause as their status was unknown (n=56,232), and those who were using menopausal hormone therapy before menopause, and experienced hysterectomy and oophorectomy were excluded (n=70,597). Further, 36,848 records were excluded at step 3 due to missing data on covariates: women's year at birth (n=1,397), age at last follow-up (n=1,402), education (n=4,688), smoking status at baseline (n=5,164), BMI at baseline (n=8,400), age at first birth (n=18,795), number of children (n=7,194), and menopausal hormone therapy use (n=4,508). Women who were excluded from the analysis were more often from Caucasian (European) background and had body mass index ≥ 30 kg/m² at baseline and were current smoker and aged ≥ 65 years at last follow up than women included (data not shown).

eSupplementary figure 2. Hazard ratio and 95% confidence interval (CI) of incident (A) coronary heart disease (CHD) and (B) stroke by age at menarche. The estimates used in the figure are shown in eTable 2. The hazard ratios were fully adjusted for women’s year at birth, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth, and MHT use. Reference category was menarche at 13 years of age. The area of the square was inversely proportional to the variance of log hazard ratio.



eSupplementary table 1. Baseline characteristics according to reproductive lifespan and occurrence of first non-fatal CVD events (N=307,855).

Variables	Reproductive lifespan (years)							CVD		
	Pre- or peri- menoapuse (n=127,648)	<30 years (n=11,442)	30-32 years (n=14,075)	33-35 years (n=29,046)	36-38 years (n=51,552)	39-41 years (n=45,647)	42-44 years (n=21,901)	≥45 years (n=6,544)	Yes (n=10,235)	No (n=297,620)
Year at birth										
<1940	181 (0.69)	1999 (7.65)	2533 (9.69)	4748 (18.2)	7553 (28.9)	5890 (22.5)	2493 (9.54)	733 (2.81)	3398 (13.0)	22732 (87.0)
1940-49	9677 (9.44)	4954 (4.83)	6328 (6.17)	12855 (12.5)	25189 (24.6)	24522 (23.9)	13958 (13.6)	5014 (4.89)	4363 (4.26)	98134 (95.7)
≥1950	117790 (65.7)	4489 (2.50)	5214 (2.91)	11443 (6.38)	18810 (10.5)	15235 (8.50)	5450 (3.04)	797 (0.44)	2474 (1.38)	176754 (98.6)
Age group at last follow-up (years)										
<60	125937 (61.7)	5285 (2.59)	6433 (3.15)	14337 (7.03)	24314 (11.9)	19825 (9.71)	7004 (3.43)	946 (0.46)	3318 (1.63)	200763 (98.4)
60-64	1187 (2.23)	2788 (5.25)	3367 (6.34)	6804 (12.8)	13435 (25.3)	13931 (26.2)	8531 (16.1)	3072 (5.78)	2080 (3.92)	51035 (96.1)
≥65	524 (1.03)	3369 (6.65)	4275 (8.44)	7905 (15.6)	13803 (27.2)	11891 (23.5)	6366 (12.6)	2526 (4.99)	4837 (9.55)	45822 (90.5)
Mean (SD)	44.6 (6.2)	59.7 (8.7)	60.3 (8.2)	60.0 (7.5)	60.6 (6.8)	61.1 (5.9)	62.2 (5.1)	63.7 (4.3)	62.8 (10.7)	53.8 (10.2)
Race/ethnicity (region)										
Caucasian (Australian/NZ)	2657 (17.3)	868 (5.66)	1046 (6.82)	2008 (13.1)	3561 (23.2)	3180 (20.7)	1593 (10.4)	430 (2.80)	1314 (8.56)	14029 (91.4)
Caucasian (European)	83930 (35.1)	9850 (4.12)	11980 (5.01)	24763 (10.4)	43987 (18.4)	39498 (16.5)	19237 (8.05)	5861 (2.45)	8261 (3.45)	230845 (96.5)
Caucasian (American)	986 (36.6)	51 (1.89)	78 (2.90)	220 (8.17)	561 (20.8)	538 (20.0)	212 (7.87)	47 (1.75)	89 (3.30)	2604 (96.7)
Asian	37199 (83.2)	398 (0.89)	633 (1.42)	1471 (3.29)	2591 (5.79)	1774 (3.97)	535 (1.20)	122 (0.27)	362 (0.81)	44361 (99.2)
Other	2876 (48.0)	275 (4.59)	338 (5.64)	584 (9.75)	852 (14.2)	657 (11.0)	324 (5.41)	84 (1.40)	209 (3.49)	5781 (96.5)
Education (years)										
≤10	29734 (26.1)	6253 (5.49)	6899 (6.05)	13553 (11.9)	23334 (20.5)	20638 (18.1)	10285 (9.02)	3270 (2.87)	4993 (4.38)	108973 (95.6)
11-12	16382 (44.2)	1229 (3.31)	1522 (4.10)	3137 (8.46)	5954 (16.1)	5525 (14.9)	2610 (7.04)	726 (1.96)	1007 (2.72)	36078 (97.3)
>12	81532 (52.0)	3960 (2.53)	5654 (3.61)	12356 (7.88)	22264 (14.2)	19484 (12.4)	9006 (5.74)	2548 (1.62)	4235 (2.70)	152569 (97.3)
Smoking status at baseline										
Never	77676 (42.9)	5762 (3.18)	7270 (4.01)	15726 (8.68)	29722 (16.4)	27470 (15.2)	13624 (7.52)	3933 (2.17)	4679 (2.58)	176504 (97.4)
Past	30788 (35.0)	3745 (4.26)	4562 (5.19)	9102 (10.4)	16213 (18.4)	14338 (16.3)	6912 (7.86)	2247 (2.56)	3634 (4.13)	84273 (95.9)
Current	19184 (49.5)	1935 (4.99)	2243 (5.79)	4218 (10.9)	5617 (14.5)	3839 (9.90)	1365 (3.52)	364 (0.94)	1922 (4.96)	36843 (95.0)

Variables	Reproductive lifespan (years)								CVD	
	Pre- or peri-menopause (n=127,648)	<30 years (n=11,442)	30-32 years (n=14,075)	33-35 years (n=29,046)	36-38 years (n=51,552)	39-41 years (n=45,647)	42-44 years (n=21,901)	≥45 years (n=6,544)	Yes (n=10,235)	No (n=297,620)
BMI at baseline (kg/m²)										
<18.5	4803 (69.6)	200 (2.90)	249 (3.61)	460 (6.67)	662 (9.59)	358 (5.19)	142 (2.06)	26 (0.38)	160 (2.32)	6740 (97.7)
18.5-22.9	55288 (55.8)	2857 (2.88)	3677 (3.71)	8089 (8.16)	13652 (13.8)	10613 (10.7)	4058 (4.09)	925 (0.93)	2227 (2.25)	96932 (97.8)
23.0-24.9	23967 (39.9)	2155 (3.59)	2724 (4.54)	6008 (10.0)	10697 (17.8)	9239 (15.4)	4128 (6.88)	1079 (1.80)	1760 (2.93)	58237 (97.1)
25.0-29.9	28915 (31.4)	3826 (4.16)	4883 (5.30)	9514 (10.3)	17551 (19.1)	16395 (17.8)	8415 (9.14)	2554 (2.77)	3412 (3.71)	88641 (96.3)
≥30.0	14675 (29.5)	2404 (4.83)	2542 (5.11)	4975 (10.0)	8990 (18.1)	9042 (18.2)	5158 (10.4)	1960 (3.94)	2676 (5.38)	47070 (94.6)
Mean (SD)	24.3 (4.9)	26.4 (5.2)	26.1 (4.9)	25.9 (4.9)	26.0 (4.8)	26.5 (5.0)	27.2 (5.0)	28.1 (5.4)	27.2 (5.7)	25.5 (5.0)
Age at first birth (years)										
No children	30028 (50.3)	2318 (3.88)	2691 (4.51)	5271 (8.83)	7005 (16.0)	6857 (11.5)	3003 (5.03)	841 (1.41)	1491 (2.50)	58176 (97.5)
≤20	8689 (32.2)	1388 (5.14)	1511 (5.60)	2854 (10.6)	8658 (14.5)	4442 (16.5)	2357 (8.73)	789 (2.92)	1451 (5.38)	25536 (94.6)
21-25	32788 (36.8)	3641 (4.08)	4405 (4.94)	9049 (10.1)	4957 (18.4)	14229 (16.0)	6975 (7.82)	2240 (2.51)	3710 (4.16)	85498 (95.8)
26-30	36442 (41.4)	2728 (3.10)	3608 (4.09)	7906 (8.97)	15881 (17.8)	13820 (15.7)	6677 (7.58)	1892 (2.15)	2484 (2.82)	85640 (97.2)
>30	19701 (44.9)	1367 (3.12)	1860 (4.24)	3966 (9.04)	15051 (17.1)	6299 (14.4)	2889 (6.59)	782 (1.78)	1099 (2.51)	42770 (97.5)
Number of children										
No children	30028 (50.3)	2318 (3.88)	2691 (4.51)	5271 (8.83)	8658 (14.5)	6857 (11.5)	3003 (5.03)	841 (1.41)	1491 (2.50)	58176 (97.5)
1 child	17475 (44.4)	1661 (4.22)	1863 (4.73)	3863 (9.81)	6141 (15.6)	5222 (13.3)	2418 (6.14)	737 (1.87)	1276 (3.24)	38104 (96.8)
2 children	49835 (39.0)	4399 (3.44)	5695 (4.46)	12060 (9.44)	22347 (17.5)	20516 (16.1)	9941 (7.78)	3022 (2.36)	3710 (2.90)	124105 (97.1)
3 children	23419 (39.4)	2065 (3.48)	2580 (4.35)	5604 (9.44)	10282 (17.3)	9355 (15.8)	4677 (7.88)	1387 (2.34)	2359 (3.97)	57010 (96.0)
≥4 children	6891 (31.9)	999 (4.62)	1246 (5.76)	2248 (10.4)	4124 (19.1)	3697 (17.1)	1862 (8.61)	557 (2.58)	1399 (6.47)	20225 (93.5)
MHT-use*										
Never	125880 (51.9)	5851 (2.41)	8278 (3.41)	19118 (7.88)	34982 (14.4)	31063 (12.8)	13856 (5.71)	3586 (1.48)	7116 (2.93)	235498 (97.1)
Past	1768 (3.39)	4117 (7.90)	4403 (8.45)	7608 (14.6)	13134 (25.2)	11808 (22.7)	6768 (13.0)	2515 (4.83)	2459 (4.72)	49662 (95.3)
Current	0 (0.00)	1474 (11.2)	1394 (10.6)	2320 (17.7)	3436 (26.2)	2776 (21.2)	1277 (9.73)	443 (3.38)	660 (5.03)	12460 (95.0)

Data were presented as n (%). All p-values <0.0001 between women with and without the disease outcome and between the reproductive lifespan categories based on chi-square tests. Abbreviations: BMI: body mass index; CVD: cardiovascular disease; MHT: menopausal hormone therapy; SD: standard deviation.

* Most studies had data on MHT use at baseline, but few studies (DNC, NSHD, NCDS, ELSA) only had data at follow-up surveys.

eSupplementary table 2. Association between reproductive lifespan, age at menarche, age at menopause, and risk of non-fatal CHD and stroke events.

Variable	Number of women	Number. of CVD events	Person years at risk	No. of events per 10,000 person-years	Partially adjusted model ^b	Fully adjusted model ^s
					HR (95%CI)	HR (95%CI)
CHD (n=307,720)						
Reproductive lifespan (years)						
pre- or peri-menopause	127631	1375	5687019	2.4	0.28 (0.25,0.31)	0.26 (0.23,0.28)
<30	11432	681	678430	10.0	1.69 (1.54,1.85)	1.66 (1.52,1.82)
30-32	14065	681	844725	8.1	1.35 (1.23,1.48)	1.34 (1.23,1.47)
33-35	29020	1119	1737189	6.4	1.16 (1.08,1.25)	1.16 (1.08,1.25)
36-38	51526	1676	3115040	5.4	ref	ref
39-41	45619	1320	2781277	4.7	0.90 (0.84,0.97)	0.91 (0.85,0.98)
42-44	21887	594	1358816	4.4	0.79 (0.72,0.87)	0.80 (0.73,0.88)
≥45	6540	164	416061	3.9	0.63 (0.53,0.74)	0.64 (0.54,0.75)
Trend P value ^δ					<0.001	<0.001
Age at menarche (years)						
≤10	12493	293	658478	4.4	1.10 (0.97,1.24)	1.09 (0.96,1.24)
11	43166	1090	2302676	4.7	1.17 (1.08,1.26)	1.16 (1.07,1.25)
12	64594	1344	3401655	4.0	0.98 (0.91,1.05)	0.97 (0.90,1.04)
13	79725	1853	4287972	4.3	ref	ref
14	61244	1562	3357123	4.7	0.97 (0.90,1.04)	0.96 (0.90,1.03)
15	30405	882	1698910	5.2	1.03 (0.95,1.12)	1.01 (0.94,1.10)
≥16	16093	586	911741	6.4	1.12 (1.02,1.23)	1.11 (1.01,1.21)
Age at menopause (years)						
pre- or peri-menopause	127631	1375	5687019	2.4	0.27 (0.25,0.30)	0.25 (0.23,0.28)
<40	3362	209	193842	10.8	1.94 (1.67,2.24)	1.89 (1.64,2.19)
40-44	13173	704	784233	9.0	1.59 (1.45,1.74)	1.57 (1.44,1.72)
45-49	45076	1746	2680910	6.5	1.21 (1.13,1.30)	1.22 (1.14,1.31)
50-51	44050	1432	2671642	5.4	ref	ref
52-53	35716	1065	2179509	4.9	0.92 (0.85,1.00)	0.93 (0.86,1.01)
54-55	24178	685	1499673	4.6	0.82 (0.74,0.89)	0.82 (0.75,0.90)
≥56	14534	394	921727	4.3	0.71 (0.64,0.80)	0.72 (0.65,0.81)
Trend P value ^δ					<0.001	<0.001
Stroke (n=305,132)						

Reproductive lifespan (years)							
pre- or peri-menopause	127048	727	5653343	1.3	0.25 (0.22,0.29)	0.22 (0.19,0.26)	
<30	11305	283	673709	4.2	1.78 (1.55,2.05)	1.75 (1.52,2.01)	
30-32	13905	241	838541	2.9	1.19 (1.03,1.38)	1.18 (1.02,1.37)	
33-35	28622	441	1718721	2.6	1.15 (1.02,1.29)	1.14 (1.01,1.29)	
36-38	50904	674	3085110	2.2	ref	ref	
39-41	45043	516	2753321	1.9	0.87 (0.78,0.98)	0.88 (0.78,0.99)	
42-44	21768	224	1353835	1.7	0.74 (0.63,0.86)	0.75 (0.64,0.87)	
≥45	6537	55	416204	1.3	0.54 (0.41,0.71)	0.56 (0.43,0.74)	
Trend P value ^δ					<0.001	<0.001	
Age at menarche (years)							
≤10	12419	135	655247	2.1	1.28 (1.06,1.54)	1.27 (1.06,1.53)	
11	42828	413	2287237	1.8	1.11 (0.98,1.25)	1.10 (0.97,1.24)	
12	63963	559	3369572	1.7	1.00 (0.90,1.12)	1.00 (0.89,1.11)	
13	78878	744	4245461	1.8	ref	ref	
14	60723	670	3331853	2.0	1.05 (0.95,1.17)	1.04 (0.94,1.16)	
15	30238	381	1690932	2.3	1.12 (0.99,1.27)	1.10 (0.97,1.25)	
≥16	16083	259	912481	2.8	1.27 (1.10,1.46)	1.25 (1.08,1.44)	
Age at menopause (years)							
pre- or peri-menopause	127048	727	5653343	1.3	0.25 (0.22,0.29)	0.22 (0.19,0.26)	
<40	3312	86	192090	4.5	2.05 (1.63,2.57)	1.98 (1.57,2.48)	
40-44	13014	267	777859	3.4	1.50 (1.30,1.73)	1.49 (1.28,1.72)	
45-49	44358	682	2647311	2.6	1.18 (1.06,1.32)	1.18 (1.06,1.32)	
50-51	43664	578	2653831	2.2	ref	ref	
52-53	35203	407	2154233	1.9	0.86 (0.76,0.98)	0.87 (0.77,0.99)	
54-55	24004	257	1491912	1.7	0.74 (0.64,0.86)	0.75 (0.65,0.87)	
≥56	14529	157	922205	1.7	0.70 (0.59,0.84)	0.72 (0.60,0.86)	
Trend P value ^δ					<0.001	<0.001	

Abbreviations: CHD: coronary heart disease. [‡]Adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, and baseline BMI. [§]Additionally adjusted for number of children, age at first birth, and menopausal hormone therapy (MHT) use

eSupplementary table 3. Nested models between reproductive lifespan, age at menarche, age at menopause, and risk of non-fatal CHD and stroke events.

Variable	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 HR (95%CI)	Model 6 HR (95%CI)
CHD (n=180,089)						
<i>—log likelihood</i>	65749	65738	65892	65717	65732	65726
Reproductive lifespan (years)						
<30	1.64 (1.50,1.80)			1.65 (1.51,1.81)	1.20 (1.01,1.42)	
30-32	1.34 (1.23,1.47)			1.34 (1.23,1.47)	1.11 (0.98,1.25)	
33-35	1.17 (1.08,1.26)			1.17 (1.08,1.26)	1.05 (0.96,1.14)	
36-38	ref			ref	ref	
39-41	0.90 (0.84,0.97)			0.86 (0.80,0.93)	1.00 (0.92,1.10)	
42-44	0.78 (0.71,0.85)			0.72 (0.66,0.80)	0.95 (0.83,1.10)	
≥45	0.59 (0.50,0.70)			0.53 (0.45,0.63)	0.77 (0.61,0.96)	
Age at menarche (years)						
≤10		1.09 (0.95,1.26)		1.29 (1.12,1.48)		1.09 (0.95,1.25)
11		1.16 (1.07,1.27)		1.28 (1.17,1.39)		1.15 (1.06,1.25)
12		0.97 (0.90,1.05)		1.02 (0.94,1.11)		0.97 (0.90,1.05)
13		ref		ref		ref
14		0.97 (0.90,1.05)		0.93 (0.86,1.00)		0.97 (0.90,1.05)
15		1.05 (0.96,1.14)		0.95 (0.87,1.04)		1.05 (0.96,1.15)
≥16		1.13 (1.02,1.25)		0.96 (0.86,1.06)		1.13 (1.02,1.25)
Age at menopause (years)						
<40			1.88 (1.62,2.17)		1.58 (1.26,1.96)	1.86 (1.60,2.15)
40-44			1.55 (1.42,1.70)		1.35 (1.15,1.58)	1.55 (1.41,1.69)
45-49			1.23 (1.15,1.32)		1.18 (1.08,1.29)	1.23 (1.14,1.32)
50-51			ref		ref	ref
52-53			0.93 (0.86,1.00)		0.94 (0.86,1.03)	0.93 (0.86,1.00)
54-55			0.81 (0.74,0.89)		0.84 (0.74,0.94)	0.81 (0.74,0.88)
≥56			0.69 (0.61,0.77)		0.79 (0.66,0.94)	0.68 (0.61,0.77)
Stroke (n=178,084)						
<i>—log likelihood</i>	25711	25777	25711	25703	25703	25705
Reproductive lifespan (years)						
<30	1.75 (1.52,2.01)			1.74 (1.51,2.01)	1.37 (1.04,1.80)	
30-32	1.18 (1.02,1.37)			1.17 (1.01,1.36)	1.00 (0.82,1.21)	
33-35	1.14 (1.01,1.29)			1.13 (1.00,1.28)	1.02 (0.88,1.17)	
36-38	ref			ref	ref	

Variable	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 HR (95%CI)	Model 6 HR (95%CI)
39-41	0.88 (0.78,0.98)			0.85 (0.76,0.96)	1.00 (0.87,1.16)	
42-44	0.73 (0.63,0.85)			0.70 (0.60,0.82)	0.88 (0.70,1.11)	
≥45	0.52 (0.40,0.69)			0.48 (0.36,0.63)	0.60 (0.41,0.87)	
Age at menarche (years)						
≤10		1.18 (0.95,1.48)		1.42 (1.13,1.77)		1.17 (0.94,1.46)
11		1.13 (0.98,1.30)		1.25 (1.08,1.43)		1.12 (0.97,1.28)
12		1.01 (0.89,1.15)		1.06 (0.93,1.20)		1.01 (0.89,1.15)
13		ref		ref		ref
14		1.06 (0.94,1.20)		1.01 (0.90,1.14)		1.07 (0.95,1.20)
15		1.15 (1.00,1.32)		1.05 (0.91,1.21)		1.16 (1.01,1.33)
≥16		1.28 (1.09,1.50)		1.08 (0.92,1.27)		1.27 (1.08,1.49)
Age at menopause (years)						
<40			2.02 (1.61,2.53)		1.48 (1.04,2.10)	2.00 (1.59,2.51)
40-44			1.48 (1.28,1.72)		1.22 (0.95,1.58)	1.48 (1.28,1.71)
45-49			1.19 (1.06,1.33)		1.17 (1.02,1.35)	1.19 (1.06,1.33)
50-51			ref		ref	ref
52-53			0.87 (0.77,0.99)		0.88 (0.76,1.01)	0.87 (0.77,0.99)
54-55			0.74 (0.64,0.86)		0.79 (0.65,0.95)	0.74 (0.64,0.85)
≥56			0.69 (0.58,0.82)		0.89 (0.67,1.17)	0.68 (0.57,0.82)

Abbreviations: CHD: coronary heart disease.

Model 1-3 (three separate models) was adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, baseline BMI, number of children, age at first birth, and menopausal hormone therapy (MHT) use.

Model 4 (one model) included both reproductive lifespan and age at menarche, and the covariates.

Model 5 (one model) included both reproductive lifespan and age at menopause, and the covariates.

Model 6 (one model) included both reproductive lifespan, age at menarche and age at menopause, and the covariates.

eSupplementary table 4. Reproductive lifespan in combination with age at menarche and the risk of non-fatal CVD events (N=180,207).

Variable	Age at menopause Mean (SD)	N	No. of CVD events	Person years at risk	No. of events per 10,000 person-years	AHR ^a (95%CI)
Reproductive lifespan <33 years & age at menarche ≤11 years	40.1 (2.9)	2781	221	140290	15.8	2.06 (1.76,2.41)
Reproductive lifespan 33-35 years & age at menarche ≤11 years	45.0 (0.8)	3078	168	156559	10.7	1.41 (1.18,1.67)
Reproductive lifespan 36-38 years & age at menarche ≤11 years	47.9 (0.9)	5179	251	262230	9.6	1.35 (1.16,1.57)
Reproductive lifespan 39-41 years & age at menarche ≤11 years	50.7 (0.9)	10913	469	568531	8.2	1.15 (1.02,1.30)
Reproductive lifespan ≥42 years & age at menarche ≤11 years	54.7 (1.9)	10519	362	564582	6.4	0.81 (0.71,0.93)
Reproductive lifespan <33 years & age at menarche 12 years	40.9 (3.2)	3055	188	154893	12.1	1.56 (1.32,1.84)
Reproductive lifespan 33-35 years & age at menarche 12 years	45.9 (0.9)	4022	202	205303	9.8	1.28 (1.09,1.50)
Reproductive lifespan 36-38 years & age at menarche 12 years	49.3 (0.8)	10431	426	542067	7.9	1.02 (0.90,1.16)
Reproductive lifespan 39-41 years & age at menarche 12 years	52.0 (0.7)	9944	337	519791	6.5	0.90 (0.78,1.03)
Reproductive lifespan ≥42 years & age at menarche 12 years	55.4 (1.5)	7258	235	393452	6.0	0.72 (0.62,0.84)
Reproductive lifespan <33 years & age at menarche 13 years	42.4 (3.1)	5890	385	302301	12.7	1.48 (1.30,1.69)
Reproductive lifespan 33-35 years & age at menarche 13 years	47.3 (0.8)	6439	308	328120	9.4	1.21 (1.05,1.39)
Reproductive lifespan 36-38 years & age at menarche 13 years	50.1 (0.7)	14374	558	748093	7.5	ref
Reproductive lifespan 39-41 years & age at menarche 13 years	52.8 (0.8)	12450	446	659914	6.8	0.87 (0.77,0.99)
Reproductive lifespan ≥42 years & age at menarche 13 years	56.1 (1.4)	6431	220	353181	6.2	0.72 (0.62,0.85)
Reproductive lifespan <33 years & age at menarche 14 years	43.0 (3.1)	6076	410	317009	12.9	1.35 (1.19,1.54)
Reproductive lifespan 33-35 years & age at menarche 14 years	48.2 (0.7)	6334	280	327780	8.5	1.05 (0.91,1.21)
Reproductive lifespan 36-38 years & age at menarche 14 years	50.9 (0.9)	13866	651	737251	8.8	1.05 (0.94,1.17)
Reproductive lifespan 39-41 years & age at menarche 14 years	54.0 (0.8)	7794	286	420002	6.8	0.79 (0.69,0.91)
Reproductive lifespan ≥42 years & age at menarche 14 years	57.2 (1.4)	3010	120	167374	7.2	0.76 (0.62,0.93)
Reproductive lifespan <33 years & age at menarche ≥15 years	44.2 (3.6)	7715	577	403807	14.3	1.50 (1.33,1.68)
Reproductive lifespan 33-35 years & age at menarche ≥15 years	49.7 (1.0)	9173	517	487607	10.6	1.16 (1.03,1.31)
Reproductive lifespan 36-38 years & age at menarche ≥15 years	52.4 (1.0)	7702	335	412695	8.1	0.89 (0.78,1.02)
Reproductive lifespan 39-41 years & age at menarche ≥15 years	55.1 (0.9)	4546	214	248551	8.6	0.97 (0.83,1.14)
Reproductive lifespan ≥42 years & age at menarche ≥15 years	58.4 (1.4)	1227	50	69191	7.2	0.72 (0.54,0.96)

Abbreviations: AHR: adjusted hazard ratio, CVD: cardiovascular disease, SD: standard deviation.

^a Adjusted for women's year at birth, age, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth and MHT use.

eSupplementary table 5 (A). Sensitivity analysis for the association between reproductive lifespan, age at menarche, age at menopause, and incident CVD events disaggregated by onset of CVD at 5-years after menopause (n=136,267).

		N	No. of CVD events	No. of events per 10,000 person-years	Model 1	Model 2	Model 3	Model 4	Model 5
					HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
<i>—log likelihood</i>					69469	69728	69462	69435	69336
Reproductive lifespan (years)									
<30	10833	861	15.3	1.88 (1.73,2.04)			1.90 (1.75,2.07)	1.36 (1.17,1.59)	
30-32	12535	807	12	1.40 (1.29,1.52)			1.41 (1.30,1.53)	1.17 (1.05,1.31)	
33-35	23645	1283	10.1	1.19 (1.11,1.28)			1.20 (1.12,1.29)	1.08 (0.99,1.18)	
36-38	39252	1828	8.5	ref			ref	ref	
39-41	31759	1331	7.5	0.88 (0.82,0.94)			0.84 (0.78,0.91)	0.99 (0.91,1.08)	
42-44	14382	523	6.4	0.71 (0.64,0.78)			0.66 (0.60,0.73)	0.91 (0.79,1.05)	
≥45	3861	109	4.9	0.46 (0.38,0.56)			0.41 (0.34,0.50)	0.63 (0.49,0.81)	
Age at menarche (years)									
≤10	5375	232	8		1.05 (0.92,1.21)		1.30 (1.13,1.50)		
11	19168	903	8.7		1.14 (1.05,1.23)		1.27 (1.17,1.38)		
12	25806	1104	7.9		0.96 (0.89,1.04)		1.02 (0.95,1.10)		
13	34053	1589	8.5		ref		ref		
14	28399	1487	9.5		1.00 (0.93,1.07)		0.94 (0.88,1.01)		
15	15148	847	10.1		1.04 (0.95,1.13)		0.92 (0.85,1.01)		
≥16	8318	580	12.5		1.15 (1.04,1.27)		0.93 (0.84,1.03)		
Age at menopause (years)									
<40	3245	261	16			2.16 (1.90,2.47)		1.62 (1.32,1.98)	
40-44	12218	865	13.5			1.70 (1.56,1.84)		1.35 (1.17,1.56)	
45-49	36666	1979	10.1			1.23 (1.15,1.32)		1.15 (1.06,1.25)	
50-51	33941	1577	8.5			ref		ref	
52-53	24961	1106	8			0.90 (0.84,0.98)		0.93 (0.85,1.02)	
54-55	16466	645	6.9			0.74 (0.68,0.81)		0.81 (0.72,0.92)	
≥56	8770	309	6.1			0.59 (0.52,0.66)		0.78 (0.65,0.93)	

Abbreviations: CVD: cardiovascular disease.

Model 1-3 (three separate models) was adjusted for women's year at birth, age, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth and MHT use.

Model 4 (one model) included both reproductive lifespan and age at menarche, and the covariates. Model 5 (one model) included both reproductive lifespan and age at menopause, and the covariates.

eSupplementary table 5 (B). Sensitivity analysis for the association between reproductive lifespan, age at menarche, age at menopause, and incident CVD events disaggregated by onset of CVD at 7-years after menopause (N=116,305).

		N	No. of CVD events	No. of events per 10,000 person-years	Model 1	Model 2	Model 3	Model 4	Model 5
					HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
<i>—log likelihood</i>					61010	61270	61000	60977	60829
Reproductive lifespan (years)									
<30	10428	835	15.2	1.99 (1.83,2.17)			2.03 (1.86,2.21)	1.37 (1.17,1.60)	
30-32	11705	758	11.9	1.43 (1.31,1.56)			1.45 (1.33,1.58)	1.17 (1.04,1.31)	
33-35	21090	1189	10.3	1.22 (1.13,1.31)			1.23 (1.14,1.33)	1.09 (1.00,1.19)	
36-38	33702	1620	8.6	ref			ref	ref	
39-41	26128	1137	7.7	0.88 (0.82,0.95)			0.84 (0.78,0.91)	1.01 (0.92,1.11)	
42-44	10758	404	6.5	0.68 (0.61,0.76)			0.63 (0.57,0.71)	0.89 (0.76,1.04)	
≥45	2494	80	5.4	0.46 (0.37,0.58)			0.41 (0.33,0.52)	0.63 (0.47,0.85)	
Age at menarche (years)									
≤10	4522	201	8.1		1.06 (0.91,1.23)		1.31 (1.13,1.53)		
11	16281	792	8.8		1.14 (1.04,1.24)		1.28 (1.17,1.40)		
12	21890	965	8		0.95 (0.87,1.03)		1.01 (0.93,1.10)		
13	28919	1422	8.8		ref		ref		
14	24394	1348	9.8		1.00 (0.93,1.08)		0.94 (0.87,1.01)		
15	13093	758	10.3		1.02 (0.93,1.11)		0.90 (0.82,0.98)		
≥16	7206	537	13.1		1.15 (1.04,1.27)		0.91 (0.83,1.01)		
Age at menopause (years)									
<40	3152	256	16.1			2.34 (2.05,2.68)		1.74 (1.42,2.14)	
40-44	11656	830	13.4			1.79 (1.64,1.95)		1.42 (1.22,1.65)	
45-49	32647	1833	10.3			1.26 (1.18,1.35)		1.18 (1.08,1.28)	
50-51	29373	1399	8.5			ref		ref	
52-53	20851	949	8			0.90 (0.83,0.98)		0.94 (0.86,1.03)	
54-55	12660	516	7			0.72 (0.65,0.80)		0.80 (0.70,0.91)	
≥56	5966	240	6.8			0.60 (0.52,0.69)		0.81 (0.67,0.99)	

Abbreviations: CVD: cardiovascular disease.

Model 1-3 (three separate models) was adjusted for women's year at birth, age, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth and MHT use.

Model 4 (one model) included both reproductive lifespan and age at menarche, and the covariates.

Model 5 (one model) included both reproductive lifespan and age at menopause, and the covariates.

eSupplementary table 5 (C). Sensitivity analysis for the association between reproductive lifespan, age at menarche, age at menopause, and incident CVD events disaggregated by onset of CVD at 10-years after menopause (n=87,832).

				Model 1	Model 2	Model 3	Model 4	Model 5
				HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
	N	No. of CVD events	No. of events per 10,000 person-years					
<i>—log likelihood</i>				48185	48445	48174	48154	47931
Reproductive lifespan (years)								
<30	9639	779	15.1	2.17 (1.98,2.37)			2.22 (2.03,2.43)	1.40 (1.18,1.66)
30-32	10382	694	12.1	1.53 (1.39,1.68)			1.56 (1.42,1.71)	1.20 (1.06,1.36)
33-35	17125	1023	10.6	1.26 (1.16,1.37)			1.28 (1.18,1.39)	1.11 (1.00,1.22)
36-38	25789	1294	8.7	ref			ref	ref
39-41	17836	820	7.8	0.85 (0.78,0.93)			0.81 (0.74,0.88)	0.99 (0.89,1.10)
42-44	6046	255	7	0.66 (0.58,0.75)			0.60 (0.53,0.69)	0.87 (0.72,1.05)
≥45	1015	43	6.8	0.47 (0.35,0.64)			0.42 (0.31,0.57)	0.62 (0.42,0.91)
Age at menarche (years)								
≤10	3296	150	8.1		1.04 (0.88,1.24)		1.31 (1.10,1.56)	
11	12075	620	9.1		1.15 (1.05,1.27)		1.31 (1.19,1.45)	
12	16384	773	8.3		0.95 (0.87,1.04)		1.03 (0.94,1.13)	
13	21533	1148	9.3		ref		ref	
14	18741	1121	10.4		1.00 (0.92,1.09)		0.94 (0.87,1.02)	
15	10164	629	10.7		1.02 (0.92,1.12)		0.88 (0.80,0.97)	
≥16	5639	467	14.2		1.17 (1.05,1.31)		0.90 (0.81,1.01)	
Age at menopause (years)								
<40	2954	238	15.6			2.58 (2.24,2.97)		1.78 (1.43,2.21)
40-44	10634	773	13.4			1.96 (1.78,2.14)		1.44 (1.22,1.69)
45-49	26719	1583	10.5			1.31 (1.21,1.41)		1.15 (1.05,1.27)
50-51	22766	1115	8.5			ref		ref
52-53	14442	707	8.3			0.88 (0.80,0.96)		0.91 (0.82,1.01)
54-55	7521	348	7.7			0.68 (0.61,0.77)		0.77 (0.66,0.90)
≥56	2796	144	8.3			0.61 (0.51,0.73)		0.82 (0.64,1.05)

Abbreviations: CVD: cardiovascular disease.

Model 1-3 (three separate models) was adjusted for women's year at birth, age, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth and MHT use.

Model 4 (one model) included both reproductive lifespan and age at menarche, and the covariates.

Model 5 (one model) included both reproductive lifespan and age at menopause, and the covariates.

eSupplementary table 6. Sensitivity analysis for the association between reproductive lifespan, age at menarche, age at menopause, and diagnosed CVD events using hospital registry data (N=142,763*).

	N	No. of CVD events	No. of events per 10,000 person-years	Model 1	Model 2	Model 3	Model 4	Model 5
				HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
<i>—log likelihood</i>				40542	40673	40533	40525	40508
Reproductive lifespan (years)								
<30	8883	444	9.9	1.83 (1.64,2.05)			1.84 (1.65,2.06)	1.23 (1.00,1.51)
30-32	11003	441	7.8	1.26 (1.12,1.40)			1.25 (1.12,1.40)	1.00 (0.87,1.16)
33-35	22675	746	6.4	1.11 (1.02,1.22)			1.11 (1.01,1.22)	0.99 (0.89,1.11)
36-38	40403	1119	5.3	ref			ref	ref
39-41	36320	857	4.5	0.90 (0.82,0.98)			0.87 (0.80,0.96)	1.03 (0.92,1.14)
42-44	17911	324	3.4	0.68 (0.60,0.77)			0.65 (0.57,0.74)	0.88 (0.73,1.05)
≥45	5568	87	2.8	0.51 (0.41,0.63)			0.47 (0.38,0.59)	0.66 (0.49,0.89)
Age at menarche (years)								
≤10	5638	125	4.3		1.18 (1.00,1.39)		1.38 (1.17,1.63)	
11	20517	502	4.7		1.11 (1.01,1.22)		1.20 (1.09,1.32)	
12	27007	658	4.7		1.01 (0.93,1.11)		1.06 (0.97,1.15)	
13	35583	929	5.0		ref		ref	
14	29470	895	5.8		0.97 (0.90,1.05)		0.94 (0.86,1.01)	
15	16003	543	6.4		0.99 (0.90,1.09)		0.91 (0.82,1.00)	
≥16	8545	366	8.1		1.07 (0.96,1.20)		0.93 (0.83,1.04)	
Age at menopause (years)								
<40	2479	106	8.8			2.02 (1.65,2.47)		1.67 (1.25,2.22)
40-44	10297	466	8.9			1.71 (1.53,1.92)		1.53 (1.26,1.85)
45-49	34964	1144	6.4			1.17 (1.07,1.28)		1.19 (1.07,1.32)
50-51	34801	944	5.2			ref		ref
52-53	28306	724	4.9			0.94 (0.85,1.04)		0.94 (0.85,1.05)
54-55	19659	400	3.8			0.71 (0.63,0.79)		0.74 (0.64,0.86)
≥56	12257	234	3.5			0.63 (0.55,0.73)		0.80 (0.64,1.00)

*Data from three studies (DNC: 1695 cases, WLH: 821 cases, UK Biobank: 2661 cases) were used for this analysis. Abbreviations: CVD: cardiovascular disease.

Model 1-3 (three separate models) was adjusted for women's year at birth, age, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth and MHT use.

Model 4 (one model) included both reproductive lifespan and age at menarche, and the covariates.

Model 5 (one model) included both reproductive lifespan and age at menopause, and the covariates.

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