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Supplementary appendix

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Appendix 1. Characteristics of individual studies in the InterLACE consortium

Study	Country	N	Age at baseline (years), Mean (SD),	Age at last follow-up (years), Mean (SD)	Women's year of birth			
					<1930	1930-39	1940-49	1950+
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	7316	47.6 (1.4)	63.1 (3.4)	.	.	74.9	25.1
Healthy Ageing of Women Study (HOW)	Australia	306	54.8 (2.8)	62.6 (3.9)	.	.	86.6	13.4
Melbourne Collaborative Cohort Study (MCCS)	Australia	12 276	58.1 (7.5)	67.9 (7.7)	33.8	41.8	20.8	3.6
Danish Nurse Cohort Study (DNC)	Scandinavia	9128	59.4 (7.9)	70.1 (9.2)	28.9	50.2	20.9	0.0
Women's Lifestyle and Health Study (WLH)	Scandinavia	23 110	40.0 (5.8)	51.1 (5.9)	.	.	37.3	62.7
Hilo Women's Healthy Study (HILO)	USA	643	50.7 (6.2)	50.7 (6.2)	.	0.2	24.4	75.4
Study of Women's Health Across the Nation (SWAN)	USA	2209	46 (2.7)	55.9 (2.7)	.	.	42.6	57.4
Japan Nurses' Health Study (JNHS)	Japan	42 917	41.9 (7.8)	41.9 (7.8)	.	0.2	9.31	90.5
MRC National Survey of Health and Development (NSHD)*	UK	710	47.0	54.1 (1.1)	.	.	100.0	.
National Child Development Study (NCDS)*	UK	2905	50.0	54.7 (1.2)	.	.	.	100.0
English Longitudinal Study of Ageing (ELSA)	UK	1781	59.6 (10)	71 (9.7)	22.4	28.1	36.4	13.1
UK Women's Cohort Study (UKWCS)	UK	11 105	53.4 (9.3)	56.7 (8.9)	8.8	28.9	34.3	28.1
Whitehall II study (WHITEHALL II)	UK	1695	45.9 (6.2)	63.7 (6.5)	0.1	47.3	42.4	10.2
Southall And Brent REvisited (SABRE)	UK	592	53.7 (6.7)	60.5 (11.8)	15.0	50.5	33.1	1.4
UK Biobank (UK Biobank)	UK	184 745	55.7 (8)	56.2 (8.1)	.	2.9	39.6	57.5
All		301 438	52.3 (9.9)	57.0 (10.3)	2.7	6.6	34.6	56.1

* NSHD (1946 British Birth Cohort) and NCDS (1958 British Birth Cohort) first collected information on women's health in 1993 (aged 47) and 2008 (aged 50), respectively, so we used 1993 and 2008 as the baseline year for the InterLACE.

Abbreviations: InterLACE, International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events; SD, standard deviation.

Appendix 1 (Continued). Characteristics of individual studies in the InterLACE consortium

Study	Country	Baseline survey year	Last survey year used	Number of CVD events	Person-years	Incidence rate (%)	Average age at natural menopause, mean (SD)	Average age at natural menopause, median (Q1, Q3)
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	1996	2013	826	214672.7	3.8	50.9 (4.3)	51 (49, 54)
Healthy Ageing of Women Study (HOW)	Australia	2001	2011	29	8929.5	3.2	50.5 (4.4)	50 (48, 54)
Melbourne Collaborative Cohort Study (MCCS)	Australia	1990-1994	2003-2006	1401	413275.6	3.4	49.7 (4.5)	50 (47, 53)
Danish Nurse Cohort Study (DNC)	Scandinavia	1993	1999	1374	334386.0	4.1	49.4 (3.7)	50 (48, 52)
Women's Lifestyle and Health Study (WLH)	Scandinavia	1991-1992	2003-2004	1163	412579.0	2.8	50.2 (3.8)	50 (48, 53)
Hilo Women's Healthy Study (HILO)	USA	2004-2005	2005	35	11392.3	3.1	49.2 (4.3)	50 (47.5, 52)
Study of Women's Health Across the Nation (SWAN)	USA	1996	2006	163	47015.0	3.5	51 (2.6)	51 (49, 53)
Japan Nurses' Health Study (JNHS)	Japan	2001-2007	2007	380	379005.0	1.0	49.8 (3.5)	50 (48, 52)
MRC National Survey of Health and Development (NSHD)*	UK	1993	2000	87	15410.9	5.6	50.7 (3.4)	51.1 (49.2, 52.9)
National Child Development Study (NCDS)*	UK	2008	2013	19	7539.0	2.5	48.8 (3.9)	49 (47, 52)
English Longitudinal Study of Ageing (ELSA)	UK	2002	2010-2011	500	62883.0	8.0	49.9 (5)	50 (48, 53)
UK Women's Cohort Study (UKWCS)	UK	1995-1998	1999-2004	481	264770.5	1.8	49.3 (4.6)	50 (47, 52)
Whitehall II study (WHITEHALL II)	UK	1985-1988	2006	321	48323.7	6.6	50.1 (4)	50 (48, 53)
Southall And Brent REvisited (SABRE)	UK	1988-1991	2008-2012	136	15931.0	8.5	48.9 (4.6)	50 (47, 52)
UK Biobank (UK Biobank)	UK	2006-2010	2013 [†]	7339	4303440.0	1.7	50.4 (4.3)	51 (48, 53)
All				14254	6539553.2	2.2	50.2 (4.3)	50 (48, 53)

* NSHD (1946 British Birth Cohort) and NCDS (1958 British Birth Cohort) first collected information on women's health in 1993 (aged 47) and 2008 (aged 50), respectively, so we used 1993 and 2008 as the baseline year for the InterLACE.

Abbreviations: InterLACE, International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events; SD, standard deviation.

[†] There were 20 000-25 000 people were included in the repeated assessment.

Appendix 2. The combined effect of age at menopause and MHT on the incident CVD, CHD and stroke*

	Age at menopause combined with MHT status [†]	N	No. of CVD events	Sum of person years	No. of event per 1000 person-years	Adjusted hazard ratio (95% CI)
CVD	<40 years + MHT	1946	168	46 783.4	3.6	1.75 (1.49, 2.04)
	<40 years + No MHT	1478	178	38 178.2	4.7	1.53 (1.31, 1.78)
	40-44 years + MHT	6836	556	181 261.3	3.1	1.39 (1.27, 1.53)
	40-44 years + No MHT	7202	660	190 881.5	3.5	1.30 (1.19, 1.43)
	45-49 years + MHT	18 777	1435	516 517.4	2.8	1.24 (1.16, 1.33)
	45-49 years + No MHT	29 284	1881	753 317.5	2.5	1.10 (1.03, 1.17)
	50-51 years + MHT	17 159	1190	490 060.8	2.4	1.10 (1.02, 1.18)
	50-51 years + No MHT	30 232	1826	813 815.2	2.2	Ref
	52-54 years + MHT	18 399	1266	531 391.7	2.4	1.07 (1.00, 1.15)
	52-54 years + No MHT	32 597	1880	898 491.7	2.1	0.96 (0.90, 1.02)
	≥55 years + MHT	12 468	880	375 719.3	2.3	1.00 (0.92, 1.08)
	≥55 years + No MHT	16 194	1042	477 057.2	2.2	0.92 (0.86, 1.00)
CHD	<40 years + MHT	1942	113	47 010.4	2.4	1.64 (1.35, 1.99)
	<40 years + No MHT	1477	140	38 403.7	3.6	1.62 (1.36, 1.93)
	40-44 years + MHT	6828	402	181 757.6	2.2	1.41 (1.26, 1.57)
	40-44 years + No MHT	7194	479	191 659.9	2.5	1.38 (1.19, 1.54)
	45-49 years + MHT	18 756	1047	517 874.0	2.0	1.28 (1.18, 1.39)
	45-49 years + No MHT	29 260	1371	755 046.1	1.8	1.12 (1.04, 1.21)
	50-51 years + MHT	17 146	873	491 329.1	1.8	1.13 (1.04, 1.23)
	50-51 years + No MHT	30 216	1307	816 168.0	1.6	Ref
	52-54 years + MHT	18 373	918	531 968.5	1.7	1.10 (1.01, 1.20)
	52-54 years + No MHT	32 571	1342	900 355.7	1.5	0.96 (0.89, 1.04)
	≥55 years + MHT	12 452	615	376 636.6	1.6	0.98 (0.89, 1.08)
	≥55 years + No MHT	16 176	762	477 784.3	1.6	0.94 (0.86, 1.03)
Stroke	<40 years + MHT	1940	67	47 314.1	1.4	2.06 (1.52, 2.52)
	<40 years + No MHT	1472	59	39 160.7	1.5	1.45 (1.11, 1.89)
	40-44 years + MHT	6822	187	182 906.6	1.0	1.34 (1.14, 1.57)
	40-44 years + No MHT	7171	229	193 193.2	1.2	1.13 (1.03, 1.22)
	45-49 years + MHT	18 742	465	521 348.7	0.9	1.15 (1.02, 1.30)
	45-49 years + No MHT	29 150	613	758 116.1	0.8	1.03 (0.92, 1.15)
	50-51 years + MHT	17 142	385	494 539.6	0.8	1.02 (0.90, 1.16)
	50-51 years + No MHT	30 159	633	819 666.5	0.8	Ref
	52-54 years + MHT	18 375	419	535 859.5	0.8	1.02 (0.90, 1.15)
	52-54 years + No MHT	32 493	629	903 857.4	0.7	0.92 (0.82, 1.02)
	≥55 years + MHT	12 461	317	379 295.3	0.8	1.06 (0.92, 1.21)
	≥55 years + No MHT	16 183	335	481 643.0	0.7	0.87 (0.76, 0.99)

*Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, and hypertension status.

[†] Pre or perimenopause group was not included because only less than 3% pre or perimenopause women with MHT. Abbreviations: MHT, menopausal hormone therapy; CVD, cardiovascular disease; CHD, coronary heart disease.

Appendix 3. The combined effect of age at menopause and duration of MHT, time of initiation of MHT on the incident CVD*

	N	No. of CVD events	Sum of person years	No. of event per 1000 person-years	Adjusted hazard ratio (95% CI)
Duration, years					
<40 + No MHT	839	86	20321.7	4.2	2.03 (1.63, 2.53)
<40 + Duration <10	754	55	16377.3	3.4	1.98 (1.51, 2.59)
<40 + Duration ≥10	687	48	17074.6	2.8	1.66 (1.24, 2.21)
40-44 + No MHT	5000	354	122146.7	2.9	1.44 (1.28, 1.63)
40-44 + Duration <10	3184	214	77309.2	2.8	1.52 (1.31, 1.76)
40-44 + Duration ≥10	1750	128	49760.7	2.6	1.43 (1.19, 1.72)
45-49 + No MHT	21247	984	512137	1.9	1.13 (1.04, 1.24)
45-49 + Duration <10	9583	561	246983.2	2.3	1.31 (1.18, 1.45)
45-49 + Duration ≥10	3095	224	93879.3	2.4	1.09 (0.94, 1.26)
50-51 + No MHT	23025	989	589606.9	1.7	Ref
50-51 + Duration <10	9760	496	267442.1	1.9	1.03 (0.93, 1.15)
50-51 + Duration ≥10	2360	171	73276.1	2.3	1.03 (0.88, 1.22)
52-54 + No MHT	25209	1080	667879.5	1.6	0.94 (0.86, 1.03)
52-54 + Duration <10	11053	588	310125.1	1.9	1.05 (0.95, 1.16)
52-54 + Duration ≥10	2122	150	65258.7	2.3	1.04 (0.87, 1.24)
≥55 + No MHT	13306	666	381793.5	1.7	0.89 (0.81, 0.99)
≥55 + Duration <10	7135	429	210949.6	2.0	0.99 (0.88, 1.11)
≥55 + Duration ≥10	2416	176	74251.5	2.4	1.17 (1.01, 1.34)
Time since menopause, years					
<40 + No MHT	841	86	20363.7	4.22	2.03 (1.63, 2.53)
<40 + Initiated MHT before menopause	211	31	5428.7	5.71	1.98 (1.39, 2.84)
<40 + Initiated MHT in < 1 year after menopause	413	20	8680.9	2.30	1.68 (1.08, 2.62)
<40 + Initiated MHT in ≥ 1 year of menopause	1000	78	24402.6	3.20	1.75 (1.39, 2.2)
40-44 + No MHT	5020	355	122570.7	2.90	1.44 (1.28, 1.63)
40-44 + Initiated MHT before menopause	1123	126	30226.2	4.17	1.87 (1.55, 2.25)
40-44 + Initiated MHT in <1 year after menopause	1593	89	38581.2	2.31	1.36 (1.16, 1.59)
40-44 + Initiated MHT in ≥ 1 year of menopause	2798	194	74840.9	2.59	1.43 (1.15, 1.78)
45-49 + No MHT	21347	999	514073	1.94	1.14 (1.04, 1.24)
45-49 + Initiated MHT before menopause	4891	363	130833.4	2.77	1.35 (1.2, 1.52)
45-49 + Initiated MHT in <1 year after menopause	3847	206	102205.9	2.02	1.19 (1.02, 1.38)
45-49 + Initiated MHT in ≥ 1 year of menopause	5492	362	151808.2	2.38	1.2 (1.06, 1.35)
50-51 + No MHT	23132	1010	591723.9	1.71	Ref
50-51 + Initiated MHT before menopause	6237	437	171525.9	2.55	1.27 (1.14, 1.42)
50-51 + Initiated MHT in <1 year after menopause	3690	181	105847	1.71	0.93 (0.79, 1.09)
50-51 + Initiated MHT in ≥ 1 year of menopause	3616	179	104465.9	1.71	0.87 (0.74, 1.02)
52-54 + No MHT	25342	1094	670590.67	1.63	0.94 (0.86, 1.03)
52-54 + Initiated MHT before menopause	9270	561	260268.63	2.16	1.12 (1.01, 1.24)
52-54 + Initiated MHT in <1 year after menopause	2430	132	70652.5	1.87	1 (0.83, 1.2)
52-54 + Initiated MHT in ≥ 1 year of menopause	2888	163	85276.4	1.91	0.96 (0.82, 1.14)

≥55 + No MHT	13342	671	382575·92	1·75	0·89 (0·81, 0·98)
≥55 + Initiated MHT before menopause	8783	569	260782·5	2·18	1·03 (0·93, 1·14)
≥55 + Initiated MHT in <1 year after menopause	1155	60	35611·5	1·68	0·82 (0·63, 1·07)
≥55 + Initiated MHT in ≥ 1 year of menopause	915	55	28218·5	1·95	0·83 (0·63, 1·09)
Age at Initiation, years					
<45 + No MHT	5861	441	142934·4	3·09	1·56 (1·4, 1·73)
<45 + MHT initiation at age < 60 year	6985	521	177290·3	2·94	1·53 (1·37, 1·71)
<45 + MHT initiation at age ≥ 60 y	153	17	4870·2	3·49	1·93 (1·12, 3·05)
45-49 + No MHT	21347	999	514073	1·94	1·14 (1·04, 1·24)
45-49 + MHT initiation at age < 60 year	13760	896	370554·7	2·42	1·25 (1·14, 1·37)
45-49 + MHT initiation at age ≥ 60 y	470	35	14292·8	2·45	1·27 (0·73, 1·94)
50-51 + No MHT	23132	1010	591723·9	1·71	Ref
50-51 + MHT initiation at age < 60 year	12851	754	360696·5	2·09	1·07 (0·98, 1·18)
50-51 + MHT initiation at age ≥ 60 y	692	43	21142·3	2·03	1·12 (0·68, 1·68)
52-54 + No MHT	25342	1094	670590·67	1·63	0·94 (0·86, 1·02)
52-54 + MHT initiation at age < 60 year	13048	762	370247·53	2·06	0·79 (0·42, 1·47)
52-54 + MHT initiation at age ≥ 60 y	1540	94	45950	2·05	1·07 (0·98, 1·18)
≥ 55 + No MHT	13342	671	382575·92	1·75	0·89 (0·81, 0·98)
≥ 55 + MHT initiation at age < 60 year	8006	524	237047·5	2·21	1 (0·9, 1·1)
≥ 55 + MHT initiation at age ≥ 60 y	2847	160	87565	1·83	1·06 (0·77, 1·35)

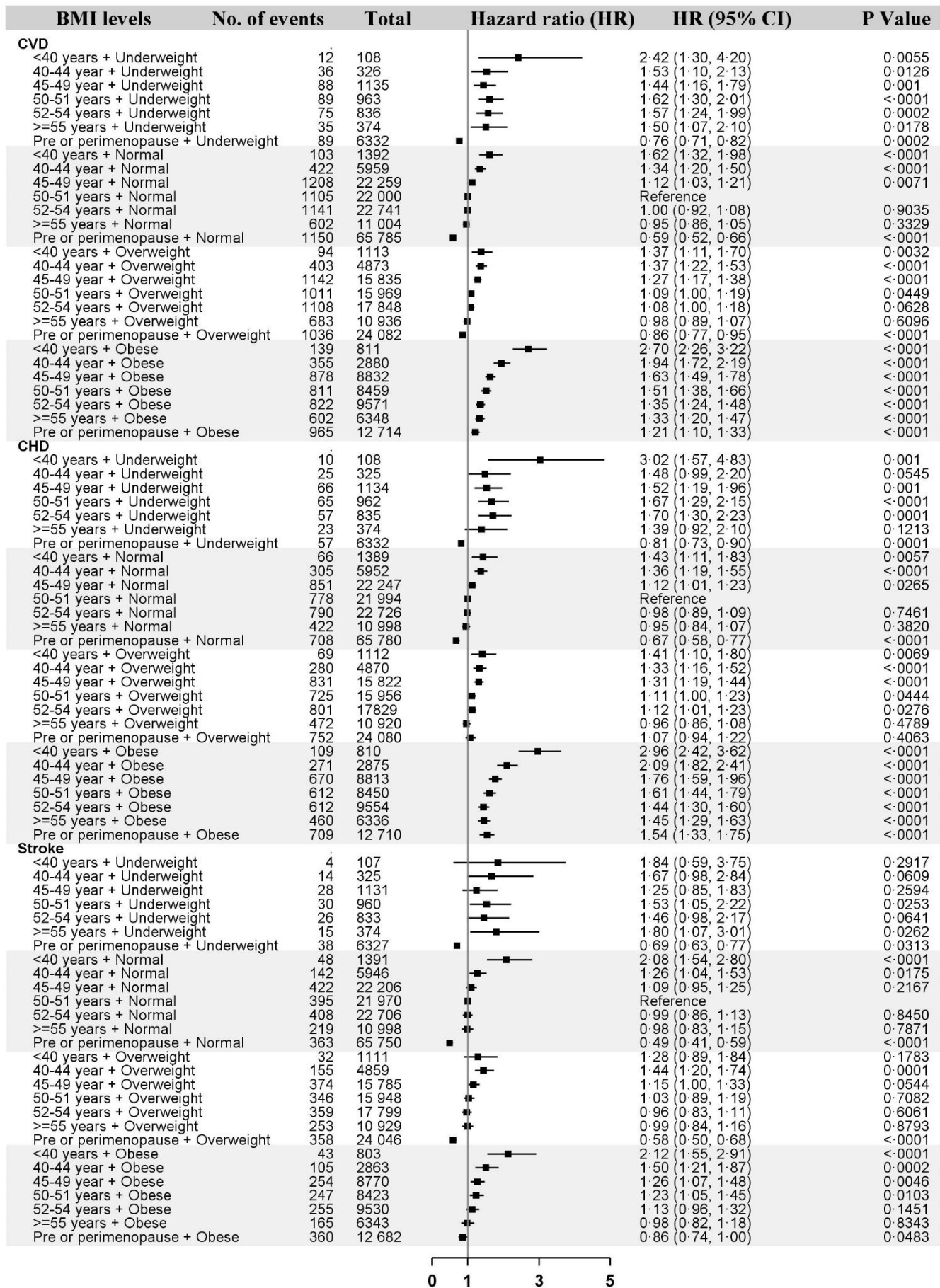
*Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, and hypertension status.

Appendix 4. The combined effect of age at menopause and smoking status on the incident CVD, CHD and stroke events*

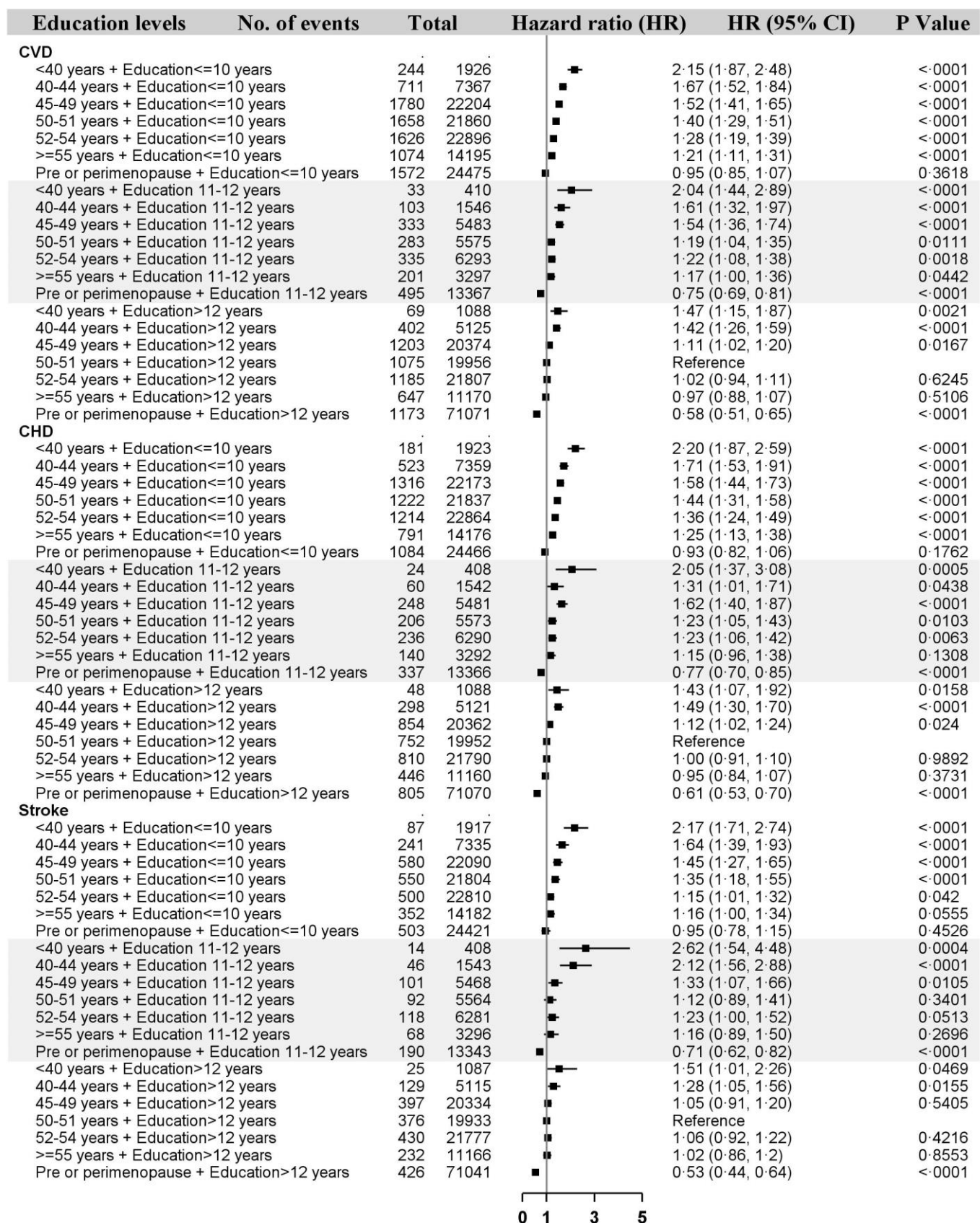
	Age at menopause combined with smoking status	N	No. of CVD events	Sum of person years	No. of event per 1000 person-years	Adjusted hazard ratio (95% CI)
CVD	<40 years + Current smoker	635	84	15 280·6	5·5	3·15 (2·53, 3·92)
	<40 years + Former smoker	1080	121	27 337·5	4·4	2·19 (1·83, 2·63)
	<40 years + Never smokers	1709	141	42 343·5	3·3	1·52 (1·28, 1·80)
	40-44 years + Current smoker	2301	284	59 128·8	4·8	2·78 (2·45, 3·16)
	40-44 years + Former smoker	4565	415	123 207·0	3·4	1·69 (1·51, 1·89)
	40-44 years + Never smokers	7172	517	189 806·9	2·7	1·34 (1·21, 1·48)
	45-49 years + Current smoker	7183	704	186 720·0	3·8	2·28 (2·08, 2·50)
	45-49 years + Former smoker	15 049	1169	402 114·5	2·9	1·57 (1·45, 1·69)
	45-49 years + Never smokers	25 829	1443	681 000·4	2·1	1·14 (1·05, 1·22)
	50-51 years + Current smoker	5110	530	140 313·5	3·8	2·16 (1·95, 2·38)
	50-51 years + Former smoker	14 809	1071	410 244·2	2·6	1·40 (1·29, 1·52)
	50-51 years + Never smokers	27 472	1415	753 318·4	1·9	Ref
	52-54 years + Current smoker	4524	433	127 710·7	3·4	1·87 (1·67, 2·08)
	52-54 years + Former smoker	15 980	1118	448 117·8	2·5	1·34 (1·24, 1·45)
	52-54 years + Never smokers	30 492	1595	854 054·8	1·9	1·01 (0·94, 1·08)
	≥55 years + Current smoker	1908	195	56 740·3	3·4	1·79 (1·55, 2·08)
	≥55 years + Former smoker	9382	664	279 250·9	2·4	1·19 (1·08, 1·30)
	≥55 years + Never smokers	17 372	1063	516 785·2	2·1	1·00 (0·92, 1·08)
	Pre or perimenopause + Current smoker	15 426	545	295 505·9	1·8	1·07 (0·92, 1·24)
	Pre or perimenopause + Former smoker	24 458	1071	796 697·8	1·3	0·70 (0·63, 0·78)
Pre or perimenopause + Never smoker	70 736	1624	1719 610·4	0·9	0·51 (0·46, 0·56)	
CHD	<40 years + Current smoker	634	60	15 371·3	3·9	3·12 (2·40, 4·04)
	<40 years + Former smoker	1079	88	27 570·0	3·2	2·35 (1·89, 2·92)
	<40 years + Never smokers	1706	105	42 472·8	2·5	1·80 (1·47, 2·20)
	40-44 years + Current smoker	2299	217	59 381·5	3·7	2·54 (2·20, 2·95)
	40-44 years + Former smoker	4557	302	123 607·5	2·4	1·73 (1·52, 1·97)
	40-44 years + Never smokers	7166	362	190 428·5	1·9	1·35 (1·20, 1·52)
	45-49 years + Current smoker	7177	516	187 403·2	2·8	1·93 (1·74, 2·15)
	45-49 years + Former smoker	15 029	859	403 072·0	2·1	1·56 (1·43, 1·71)
	45-49 years + Never smokers	25 810	1043	682 444·8	1·5	1·16 (1·06, 1·26)
	50-51 years + Current smoker	5105	395	140 759·6	2·8	1·86 (1·65, 2·09)
	50-51 years + Former smoker	14 801	778	411 725·9	1·9	1·36 (1·24, 1·49)
	50-51 years + Never smokers	27 456	1007	755 011·6	1·3	Ref
	52-54 years + Current smoker	4516	320	127 976·6	2·5	1·64 (1·45, 1·86)
	52-54 years + Former smoker	15 960	804	448 828·1	1·8	1·33 (1·22, 1·46)
	52-54 years + Never smokers	30 468	1136	855 519·5	1·3	1·00 (0·92, 1·09)
	≥55 years + Current smoker	1907	139	56 958·1	2·4	1·62 (1·36, 1·93)
	≥55 years + Former smoker	9370	500	279 678·1	1·8	1·24 (1·12, 1·38)
	≥55 years + Never smokers	17 351	738	517 784·8	1·4	1·00 (0·91, 1·10)
	Pre or perimenopause + Current smoker	15 423	384	308 607·8	1·2	1·31 (1·14, 1·51)

	Pre or perimenopause + Former smoker	24 455	781	826 953.9	0.9	0.89 (0.74, 1.07)
	Pre or perimenopause + Never smoker	70 730	1061	1646 492.6	0.6	0.66 (0.54, 0.80)
	<40 years + Current smoker	634	33	15 635.6	2.1	3.41 (2.39, 4.84)
	<40 years + Former smoker	1072	48	27 707.2	1.7	2.61 (1.94, 3.50)
	<40 years + Never smokers	1706	45	43 132.0	1.0	1.53 (1.12, 2.07)
	40-44 years + Current smoker	2289	95	59 921.9	1.6	2.26 (1.81, 2.81)
	40-44 years + Former smoker	4550	140	124 669.2	1.1	1.64 (1.36, 1.98)
	40-44 years + Never smokers	7154	181	191 508.8	0.9	1.39 (1.17, 1.64)
	45-49 years + Current smoker	7137	238	187 995.4	1.3	1.82 (1.56, 2.13)
	45-49 years + Former smoker	14 993	368	405 981.3	0.9	1.37 (1.20, 1.57)
	45-49 years + Never smokers	25 762	472	685 488.1	0.7	1.08 (0.95, 1.23)
	50-51 years + Current smoker	5092	172	141 707.4	1.2	1.65 (1.39, 1.96)
Stroke	50-51 years + Former smoker	14 775	363	413 744.1	0.9	1.32 (1.15, 1.51)
	50-51 years +Never smokers	27 434	483	758 754.7	0.6	Ref
	52-54 years + Current smoker	4507	141	128 840.0	1.1	1.47 (1.22, 1.77)
	52-54 years + Former smoker	15 936	375	451 744.9	0.8	1.29 (1.13, 1.47)
	52-54 years +Never smokers	30 425	532	859 132.0	0.6	0.98 (0.87, 1.11)
	≥55 years + Current smoker	1906	70	57 478.4	1.2	1.70 (1.32, 2.18)
	≥55 years + Former smoker	9379	207	282 269.8	0.7	1.07 (0.91, 1.26)
	≥55 years + Never smokers	17 359	375	521 190.1	0.7	1.06 (0.93, 1.22)
	Pre or perimenopause + Current smoker	15 412	224	411 462.4	0.5	0.86 (0.77, 0.95)
	Pre or perimenopause + Former smoker	24 413	375	1120 071.0	0.3	0.52 (0.45, 0.59)
	Pre or perimenopause + Never smoker	70 685	520	1510 749.9	0.3	0.41 (0.35, 0.49)

*Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), hypertension status, and postmenopausal menopausal hormone therapy (MHT) status or oral contraception pills use in pre-or perimenopause group. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.



Appendix 5: The combined effect of age at menopause and body mass index (BMI) levels on the incident CVD, CHD and stroke events. Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, smoking, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.



Appendix 6: The combined effect of age at menopause and education levels on the incident CVD, CHD and stroke. Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, body mass index (BMI), smoking status, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Appendix 7. The associations between age at menopause and incident CVD – Only cases with hospital record of diagnosis were included (based on 3 studies: DNC, WLH, and UK Biobank) *

	Age at natural menopause (years) †	Adjusted hazard ratio (95% CI)			
		Overall	Stratified by age at first CVD event (years)		
			<60	65-69	70+
CVD	<40	1.64 (1.39, 1.94)	2.05 (1.71, 2.45)	1.34 (1.17, 1.54)	1.50 (1.01, 2.25)
	40-44	1.43 (1.30, 1.56)	1.49 (1.34, 1.67)	1.25 (0.94, 1.65)	1.13 (0.93, 1.38)
	45-49	1.14 (1.07, 1.22)	1.17 (1.07, 1.27)	1.14 (1.03, 1.27)	1.04 (0.91, 1.19)
	50-51	1.00	1.00	1.00	1.00
	52-54	1.02 (0.95, 1.09)	0.91 (0.84, 1.00)	1.05 (0.95, 1.17)	1.01 (0.87, 1.16)
	≥55	0.89 (0.82, 0.96)	0.81 (0.73, 0.89)	0.91 (0.81, 1.02)	1.01 (0.85, 1.20)
CHD	<40	1.56 (1.28, 1.90)	2.09 (1.68, 2.60)	1.38 (1.17, 1.63)	0.86 (0.45, 1.61)
	40-44	1.44 (1.30, 1.60)	1.49 (1.30, 1.71)	1.26 (0.91, 1.76)	1.11 (0.87, 1.41)
	45-49	1.13 (1.04, 1.23)	1.23 (1.11, 1.37)	1.17 (1.03, 1.33)	0.95 (0.8, 1.12)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.98 (0.91, 1.07)	0.94 (0.84, 1.04)	1.03 (0.91, 1.17)	0.93 (0.79, 1.11)
	≥55	0.86 (0.79, 0.95)	0.86 (0.77, 0.97)	0.86 (0.74, 0.99)	0.83 (0.67, 1.03)
Stroke	<40	1.84 (1.39, 2.45)	1.88 (1.39, 2.55)	1.26 (0.8, 1.99)	2.38 (1.47, 3.87)
	40-44	1.43 (1.22, 1.68)	1.48 (1.24, 1.78)	1.27 (1.00, 1.6)	1.26 (0.93, 1.72)
	45-49	1.16 (1.03, 1.31)	1.05 (0.91, 1.21)	1.06 (0.89, 1.26)	1.18 (0.95, 1.47)
	50-51	1.00	1.00	1.00	1.00
	52-54	1.11 (0.98, 1.25)	0.85 (0.74, 0.98)	1.09 (0.92, 1.29)	1.18 (0.94, 1.48)
	≥55	0.94 (0.82, 1.08)	0.67 (0.56, 0.80)	1.00 (0.83, 1.20)	1.39 (1.09, 1.78)

* Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Appendix 8. The associations between age at menopause and incident CVD – after excluding UK Biobank study*

	Age at natural menopause [†] (years)	Adjusted hazard ratio (95% CI)			
		Overall	Stratified by age at first CVD event (years) [†]		
			<60	60-69	70+
CVD	<40	1.61 (1.25, 2.06)	-	-	-
	40-44	1.36 (1.16, 1.59)	2.06 (1.55, 2.74)	1.33 (1.09, 1.61)	1.09 (0.90, 1.32)
	45-49	1.15 (0.99, 1.34)	1.70 (1.22, 2.37)	1.04 (0.92, 1.18)	1.09 (0.88, 1.36)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.94 (0.89, 0.99)	1.10 (0.85, 1.42)	1.08 (0.98, 1.19)	0.98 (0.86, 1.12)
	55+	0.82 (0.71, 0.94)	0.86 (0.64, 1.17)	1.05 (0.93, 1.18)	0.96 (0.78, 1.17)
CHD	<40	1.68 (1.29, 2.20)	-	-	-
	40-44	1.35 (1.15, 1.59)	2.31 (1.71, 3.11)	1.24 (1.12, 1.37)	1.19 (1.04, 1.36)
	45-49	1.13 (0.95, 1.33)	1.73 (1.21, 2.46)	1.02 (0.86, 1.21)	1.04 (0.81, 1.34)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.93 (0.86, 1.00)	1.21 (0.93, 1.56)	1.03 (0.92, 1.17)	0.99 (0.89, 1.10)
	55+	0.82 (0.69, 0.97)	1.07 (0.78, 1.47)	1.05 (0.95, 1.16)	0.90 (0.76, 1.08)
Stroke	<40	1.74 (1.24, 2.43)	-	-	-
	40-44	1.29 (1.15, 1.46)	1.77 (0.99, 3.16)	1.26 (0.69, 2.31)	1.02 (0.62, 1.68)
	45-49	1.19 (1.05, 1.35)	1.74 (1.28, 2.36)	1.06 (0.76, 1.48)	1.17 (0.90, 1.51)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.97 (0.84, 1.13)	0.84 (0.32, 1.72)	1.16 (0.77, 1.75)	0.94 (0.82, 1.08)
	55+	0.87 (0.71, 1.06)	0.38 (0.13, 1.08)	1.21 (0.73, 2.02)	1.00 (0.69, 1.45)

* Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status.

[†] When stratified by age at first CVD event, menopause at <40 and 40-44 years were combined as <45 years to get sufficient number of women.

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Appendix 9. The associations between age at menopause and incident CVD - only include CVD events which occurred at least three years after menopause

	Age at natural menopause [†] (years)	Adjusted hazard ratio (95% CI)			
		Overall	Stratified by age at first CVD event (years)		
			<60	60-69	70+
CVD	<40	2.01 (1.79, 2.26)	1.89 (1.62, 2.20)	1.35 (1.10, 1.66)	1.26 (0.95, 1.67)
	40-44	1.61 (1.50, 1.73)	1.40 (1.27, 1.54)	1.30 (1.16, 1.46)	1.09 (0.93, 1.28)
	45-49	1.25 (1.18, 1.32)	1.17 (1.09, 1.25)	1.07 (0.98, 1.17)	1.11 (0.99, 1.24)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.91 (0.85, 0.96)	0.91 (0.85, 0.98)	0.99 (0.91, 1.08)	1.03 (0.92, 1.16)
	55+	0.68 (0.63, 0.73)	0.82 (0.75, 0.89)	0.91 (0.83, 1.00)	0.96 (0.83, 1.10)
CHD	<40	1.97 (1.72, 2.26)	1.85 (1.55, 2.21)	1.43 (1.13, 1.80)	1.04 (0.73, 1.47)
	40-44	1.62 (1.49, 1.76)	1.38 (1.23, 1.54)	1.33 (1.16, 1.52)	1.07 (0.89, 1.29)
	45-49	1.26 (1.18, 1.35)	1.19 (1.10, 1.30)	1.10 (0.99, 1.22)	1.04 (0.91, 1.19)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.90 (0.84, 0.97)	0.93 (0.86, 1.01)	0.99 (0.89, 1.10)	0.98 (0.85, 1.12)
	55+	0.67 (0.61, 0.73)	0.86 (0.78, 0.95)	0.92 (0.82, 1.03)	0.86 (0.73, 1.02)
Stroke	<40	2.14 (1.77, 2.60)	1.93 (1.48, 2.52)	1.32 (0.91, 1.89)	1.94 (1.33, 2.83)
	40-44	1.56 (1.38, 1.76)	1.44 (1.22, 1.70)	1.23 (1.01, 1.50)	1.20 (0.93, 1.55)
	45-49	1.18 (1.07, 1.30)	1.11 (0.98, 1.26)	0.99 (0.85, 1.15)	1.22 (1.01, 1.46)
	50-51	1.00	1.00	1.00	1.00
	52-54	0.90 (0.82, 1.00)	0.85 (0.75, 0.96)	0.98 (0.85, 1.14)	1.14 (0.94, 1.38)
	55+	0.72 (0.64, 0.81)	0.69 (0.60, 0.81)	0.90 (0.76, 1.06)	1.16 (0.94, 1.44)

* Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Appendix 10. The associations between age at natural menopause and specific types of CHD and stroke (based on 11 studies) *

Age at natural menopause (years)	CHD: Adjusted hazard ratio (95% CI)		Stroke: Adjusted hazard ratio (95% CI)	
	Heart attack	Angina pectoris	Ischemic stroke	Haemorrhagic stroke
<40	1.62 (1.27, 2.07)	1.58 (1.34, 1.87)	1.81 (1.04, 3.17)	1.94 (1.06, 3.56)
40-44	1.61 (1.40, 1.86)	1.31 (1.18, 1.45)	1.44 (1.03, 2.00)	1.63 (1.15, 2.32)
45-49	1.17 (1.04, 1.30)	1.10 (1.02, 1.19)	1.19 (0.92, 1.54)	1.16 (0.87, 1.54)
50-51	1.00	1.00	1.00	1.00
52-54	1.00 (0.89, 1.12)	0.96 (0.89, 1.03)	1.27 (1.00, 1.63)	1.11 (0.85, 1.46)
≥55	0.96 (0.84, 1.10)	0.91 (0.83, 0.99)	1.22 (0.93, 1.58)	0.83 (0.60, 1.15)
Pre- or perimenopause	0.61 (0.54, 0.70)	0.67 (0.62, 0.73)	0.85 (0.63, 1.15)	1.00 (0.74, 1.36)

* Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), hypertension status, and postmenopausal menopausal hormone therapy (MHT) status. Abbreviations: CHD, coronary heart disease.

Appendix 11. Comparison of women's characteristics in complete dataset used for analysis and the dataset with missing values

	Complete Dataset used		Missing data	
	n	%	n	%
Race/ethnicity				
Caucasian-Australian	14651	4.86	1167	2.82
Caucasian-European	229962	76.28	35823	86.56
Asian	48199	15.99	3162	7.64
Others	8673	2.87	1233	2.98
Body mass index (kg/m²)				
Underweight<18.5	10074	3.34	6932	16.75
Normal[18.5,25.0)	151140	50.13	20221	48.86
Overweight[25.0,30.0)	90656	30.07	9452	22.84
Obese>=30	49615	16.46	4780	11.55
Smoking status				
never	179840	59.65	17804	47.1
past	84868	28.15	11805	31.23
current	36777	12.2	8191	21.67
Education level (years)				
≤10	114923	38.12	14393	36.74
11-12	35971	11.93	5210	13.3
>12	150591	49.95	19572	49.96
Age at last follow-up (years)				
<60	191085	63.38	33728	81.67
60-64	56089	18.6	2742	6.64
65-69	38991	12.93	2395	5.8
70+	15320	5.08	2437	5.9
Hypertension status				
No	243896	80.9	4711	78.79
Yes	57589	19.1	1268	21.21
Postmenopausal MHT users				
No	222446	73.78	18835	74.86
Yes	79039	26.22	6325	25.14
Number of children				
0	56717	19.57	4866	12.53
1	37598	12.97	5296	13.64
2	120310	41.51	16481	42.45
3+	75222	25.95	12182	31.38
Age at menarche (years)				
≤11	53297	18.39	5311	13.93
12	60813	20.98	8035	21.08
13	74118	25.57	11275	29.57
14	57665	19.89	7941	20.83
≥15	43954	15.16	5562	14.59

Appendix 12. The associations (adjusted HR, 95%CI) between age at natural menopause and incident CVD - after missing covariates were imputed *

	Age at natural menopause	Overall	Age at first CVD: <60 years	Age at first CVD: 60-69 years	Age at first CVD: 70+ years
CVD	<40	1.53 (1.37, 1.71)	1.80 (1.55, 2.09)	1.34 (1.09, 1.65)	1.25 (0.95, 1.66)
	40-44	1.27 (1.19, 1.35)	1.34 (1.22, 1.48)	1.28 (1.14, 1.44)	1.08 (0.93, 1.27)
	45-49	1.11 (1.06, 1.17)	1.15 (1.07, 1.23)	1.08 (0.99, 1.17)	1.11 (1.00, 1.24)
	50-51	1.0	1.0	1.0	1.0
	52-54	0.97 (0.92, 1.02)	0.93 (0.86, 1)	1.02 (0.94, 1.11)	1.03 (0.92, 1.16)
	≥55	0.89 (0.84, 0.95)	0.82 (0.75, 0.89)	0.94 (0.85, 1.03)	0.96 (0.83, 1.10)
	CHD	<40	1.53 (1.37, 1.71)	1.79 (1.55, 2.11)	1.47 (1.17, 1.86)
40-44		1.27 (1.17, 1.37)	1.32 (1.18, 1.48)	1.31 (1.15, 1.5)	1.07 (0.89, 1.29)
45-49		1.13 (1.06, 1.19)	1.18 (1.09, 1.28)	1.11 (1, 1.23)	1.04 (0.91, 1.19)
50-51		1.0	1.0	1.0	1.0
52-54		0.97 (0.91, 1.03)	0.94 (0.86, 1.02)	1.01 (0.91, 1.12)	0.98 (0.85, 1.12)
≥55		0.88 (0.82, 0.94)	0.83 (0.76, 0.92)	0.93 (0.83, 1.04)	0.86 (0.73, 1.02)
Stroke		<40	1.62 (1.35, 1.96)	1.88 (1.44, 2.44)	1.28 (0.89, 1.83)
	40-44	1.27 (1.14, 1.43)	1.39 (1.18, 1.64)	1.21 (0.99, 1.48)	1.2 (0.93, 1.55)
	45-49	1.07 (0.98, 1.17)	1.1 (0.97, 1.24)	0.98 (0.84, 1.14)	1.22 (1.01, 1.46)
	50-51	1.0	1.0	1.0	1.0
	52-54	0.96 (0.88, 1.04)	0.86 (0.76, 0.98)	1.01 (0.87, 1.18)	1.14 (0.94, 1.38)
	≥55	0.9 (0.82, 1)	0.71 (0.6, 0.82)	0.95 (0.81, 1.12)	1.16 (0.94, 1.44)

* Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status.

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Appendix 13. The associations between age at menopause and incident CVD - after type 2 diabetes was further adjusted in 12 studies

	Age at natural menopause [†] (years)	Adjusted hazard ratio (95% CI)			
		Overall	Stratified by age at first CVD event (years)		
			<60	60-69	70+
CVD	<40	1.56 (1.39, 1.74)	1.88 (1.61, 2.2)	1.35 (1.1, 1.67)	1.26 (0.95, 1.67)
	40-44	1.31 (1.22, 1.4)	1.39 (1.26, 1.54)	1.3 (1.16, 1.47)	1.09 (0.93, 1.28)
	45-49	1.11 (1.06, 1.17)	1.16 (1.07, 1.25)	1.08 (0.98, 1.18)	1.11 (0.99, 1.24)
	50-51	1.0	1.0	1.0	1.0
	52-54	0.96 (0.91, 1.01)	0.93 (0.86, 1)	0.98 (0.9, 1.08)	1.03 (0.92, 1.16)
	55+	0.92 (0.86, 0.97)	0.83 (0.76, 0.91)	0.92 (0.84, 1.02)	0.96 (0.83, 1.1)
CHD	<40	1.5 (1.31, 1.71)	1.81 (1.5, 2.18)	1.42 (1.12, 1.81)	1.07 (0.89, 1.29)
	40-44	1.3 (1.2, 1.41)	1.37 (1.22, 1.55)	1.33 (1.16, 1.53)	1.04 (0.73, 1.47)
	45-49	1.12 (1.06, 1.19)	1.19 (1.09, 1.3)	1.1 (0.99, 1.22)	1.04 (0.91, 1.19)
	50-51	1.0	1.0	1.0	1.0
	52-54	0.97 (0.91, 1.03)	0.96 (0.88, 1.05)	0.99 (0.89, 1.1)	0.98 (0.85, 1.12)
	55+	0.92 (0.86, 0.99)	0.88 (0.79, 0.98)	0.95 (0.84, 1.06)	0.86 (0.73, 1.02)
Stroke	<40	1.74 (1.44, 2.1)	1.94 (1.48, 2.55)	1.32 (0.91, 1.92)	1.94 (1.33, 2.83)
	40-44	1.32 (1.17, 1.48)	1.44 (1.21, 1.71)	1.22 (0.99, 1.51)	1.2 (0.93, 1.55)
	45-49	1.08 (0.98, 1.18)	1.08 (0.95, 1.24)	1 (0.85, 1.17)	1.22 (1.01, 1.46)
	50-51	1.0	1.0	1.0	1.0
	52-54	0.93 (0.85, 1.02)	0.84 (0.74, 0.96)	0.96 (0.82, 1.12)	1.14 (0.94, 1.38)
	55+	0.9 (0.81, 1)	0.71 (0.61, 0.84)	0.89 (0.75, 1.06)	1.16 (0.94, 1.44)

* Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for age at last follow up, race/ethnicity, education, body mass index (BMI), smoking status, hypertension status, and postmenopausal menopausal hormone therapy (MHT) status. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

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