Menopause and Heart Disease

Association of menopausal characteristics and risk of coronary heart disease: a pan-European case–cohort analysis

Veerle Dam [iD] ,[1,2] Yvonne T van der Schouw [iD] ,[1]*
N Charlotte Onland-Moret,[1] Rolf HH Groenwold,[1] Sanne AE Peters,[3]
Stephen Burgess [iD] ,[4,5] Angela M Wood,[5] Maria-Dolores Chirlaque,[6,7]
Karel GM Moons,[1] Clare Oliver-Williams,[8,9] Ewoud Schuit [iD] ,[1]
Kaja Tikk,[10,11] Elisabete Weiderpass [iD] ,[12,13,14,15] Marianne Holm,[16]
Anne Tjønneland,[16] Tilman Kühn,[17] Renée T Fortner,[17]
Antonia Trichopoulou,[18,19] Anna Karakatsani,[18,20] Carlo La Vecchia,[18,21]
Pietro Ferrari,[22] Marc Gunter,[22] Giovanna Masala,[23] Sabina Sieri,[24]
Rosario Tumino,[25] Salvatore Panico,[26] Jolanda MA Boer,[27]
WM Monique Verschuren,[1,27] Elena Salamanca-Fernández,[7,28]
Larraitz Arriola,[7,29] Conchi Moreno-Iribas,[30,31] Gunnar Engström [iD] ,[32]
Olle Melander,[32] Maria Nordendahl,[33] Patrik Wennberg,[33]
Timothy J Key,[34] Sandra Colorado-Yohar,[35,36] Giuseppe Matullo,[37,38]
Kim Overvad,[39] Francoise Clavel-Chapelon,[40] Heiner Boeing,[41]
J Ramon Quiros,[42] Emanuele di Angelantonio,[4] Claudia Langenberg,[43]
Michael J Sweeting,[4] Elio Riboli,[44] Nicholas J Wareham,[43]
John Danesh[43] and Adam Butterworth[5,45]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Netherlands Heart Institute, Utrecht, The Netherlands, [3]The George Institute for Global Health, University of Oxford, Oxford, UK, [4]MRC Biostatistics Unit, University of Cambridge, Cambridge, UK, [5]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK, [6]Department of Epidemiology, Regional Health Authority, IMIB-Arraxaca, Murcia University, Murcia, Spain, [7]Department of Epidemiology, CIBER de Epidemiología y Salud Pública (CIBERESP),Madrid, Spain, [8]Cardiovascular Epidemiology Unit, Department of Public Health & Primary Care, University of Cambridge, Cambridge, UK, [9]Homerton College, Cambridge, UK, [10]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany, [11]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany, [12]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway, [13]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [14]Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland, [15]Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway, [16]Department of Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark, [17]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [18]2nd Pulmonary Medicine Department, Hellenic Health

Foundation, Athens, Greece, [19]Department of Hygiene, Epidemiology and Medical Statistics, WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [20]2nd Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, 'ATTIKON' University Hospital, Haidari, Greece, [21]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy, [22]International Agency for Research on Cancer, Lyon, France, [23]Cancer Risk Factors and Life-Style Epidemiology Unit, Cancer Research and Prevention Institute, ISPO, Florence, Italy, [24]Epidemiology and Prevention Unit, Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy, [25]Cancer Registry and Histopathology Department, 'Civic-M.P.Arezzo' Hospital, ASP Ragusa, Ragusa, Italy, [26]Dipartimento di Medicina Clinica E Chirurgia, Federico II University, Naples, Italy, [27]Center for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, [28]Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria ibs, Granada, Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain, [29]Public Health Division of Gipuzkoa, Instituto BIO-Donostia, Basque Government, Donostia, Spain, [30]Instituto de Salud Pública de Navarra, IdiSNA, Navarre Institute for Health Research, Pamplona, Spain, [31]Red de Servicios de Salud Orientados a Enfermedades Crónicas, REDISSEC, Pamplona, Spain, [32]Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [33]Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Umeå, Sweden, [34]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK, [35]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain, [36]Research Group on Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia, [37]Department of Medical Sciences, University of Torino, Turin, Italy, [38]Department Medical Sciences, Italian Institute for Genomic Medicine –IIGM/HuGeF, Turin, Italy, [39]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark, [40]INSERM, Centre for Research in Epidemiology and Population Health (CESP), U1018, Nutrition, Hormones, and Women's Health Team, Institut Gustave Roussy, Villejuif, France, [41]Department of Epidemiology, German Institute of Human Nutrition (DIfE), Potsdam-Rehbrücke, Germany, [42]Public Health Directorate, Asturias, Spain, [43]MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK, [44]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK and [45]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK

*Corresponding author. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Huispostnr. STR 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: Y.T.vanderSchouw@umcutrecht.nl

Abstract

Background: Earlier age at menopause has been associated with increased risk of coronary heart disease (CHD), but the shape of association and role of established cardiovascular risk factors remain unclear. Therefore, we examined the associations between menopausal characteristics and CHD risk; the shape of the association between age at menopause and CHD risk; and the extent to which these associations are explained by established cardiovascular risk factors.

Methods: We used data from EPIC-CVD, a case–cohort study, which includes data from 23 centres from 10 European countries. We included only women, of whom 10 880 comprise the randomly selected sub-cohort, supplemented with 4522 cases outside the sub-cohort. We conducted Prentice-weighted Cox proportional hazards regressions with age as the underlying time scale, stratified by country and adjusted for relevant confounders.

Results: After confounder and intermediate adjustment, post-menopausal women were not at higher CHD risk compared with pre-menopausal women. Among post-

menopausal women, earlier menopause was linearly associated with higher CHD risk [$HR_{\text{confounder and intermediate adjusted}}$ per-year decrease = 1.02, 95% confidence interval (CI) = 1.01–1.03, $p = 0.001$]. Women with a surgical menopause were at higher risk of CHD compared with those with natural menopause ($HR_{\text{confounder-adjusted}} = 1.25$, 95% CI = 1.10–1.42, $p < 0.001$), but this attenuated after additional adjustment for age at menopause and intermediates (HR = 1.12, 95% CI = 0.96–1.29, $p = 0.15$). A proportion of the association was explained by cardiovascular risk factors.

Conclusions: Earlier and surgical menopause were associated with higher CHD risk. These associations could partially be explained by differences in conventional cardiovascular risk factors. These women might benefit from close monitoring of cardiovascular risk factors and disease.

Key words: Menopause, coronary disease, ageing, Epidemiology, women, risk factors

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Key Messages

- Age at menopause has an inverse dose–response relationship with coronary heart disease (CHD) risk.
- Surgical menopause is associated with an increased CHD risk, even after accounting for age at menopause.
- A proportion of the risk appears to be explained by cardiovascular risk factors.
- As a residual association between menopausal characteristics and CHD remains and the mechanism is not fully understood, this merits further research.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in men and women from Western countries, with 17.5 million deaths worldwide in 2012, representing 31% of all global deaths.[1] Approximately 7.4 million of these were due to coronary heart disease (CHD). CHD risk increases in women after the age of 50 years, leading to suggestions that menopause may be a contributing factor.[2–4] A recent meta-analysis suggested that women who had early menopause (before age 45 years) are at 50% higher CHD risk compared with those with later menopause.[5] However, that analysis was not able to include 9 studies out of the 14 studies they found examining the association between age at menopause and CHD, nor was it able to examine whether there is a (non-)linear dose–response relationship or threshold effect or whether type of menopause (surgical or natural) was associated with CHD risk.

The biological mechanisms through which menopause might influence CHD risk are postulated to include reductions in oestrogen levels, but rises in conventional cardiovascular risk factors (e.g. major lipids and blood pressure) around the time of menopause may also play a role.[6–8] However, the extent to which the association between menopausal characteristics and CHD can be explained by such factors remains unclear.

We conducted a large pan-European prospective case–cohort study (EPIC-CVD) with an average of 11 years of follow-up to quantify the associations of menopausal status, age at menopause and type of menopause with risk of CHD; we also examined the shape of the relationship between age at menopause (as a continuous exposure) and risk of CHD; and we assessed the extent to which the associations of menopausal characteristics with risk of CHD could be explained by established cardiovascular risk factors.

Methods

Participants

We used data from female participants in the EPIC-CVD study—a case–cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study.[9] EPIC consists of 519 978 adults (366 521 women), aged between 35 and 70 years at baseline, and recruited from 23 centres across 10 European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the UK) between 1992 and 2000. Baseline questionnaires included questions on diet, lifestyle, reproductive and medical factors. Blood samples were collected for approximately 70% of the participants and stored in liquid nitrogen at −196°C. For EPIC-CVD, a representative

sub-cohort of 18 249 participants was selected by simple random sampling, stratified by centre, from participants who had available stored blood and buffy coat samples.[10,11] After exclusion of 609 participants with a prior history of myocardial infarction or stroke at baseline, 17 640 sub-cohort members remained. After subsequent exclusion of the 6760 men, a sub-cohort of 10 880 women remained, of whom 231 had a CHD event. Subsequently, incident CHD cases in women outside the sub-cohort were added to the study sample using the same exclusion criteria ($N = 4522$).

EPIC complies with the Declaration of Helsinki, and all participants gave written informed consent before participating in this study. The study was approved by the local ethics committees of the participating centres and the Institutional Review Board of the International Agency for Research on Cancer (IARC, Lyon).

Menopausal status, timing and type of menopause

Menopause was assessed by questionnaire at baseline. Women were categorized as *pre-menopausal* if they had experienced menses over the past 12 months before recruitment and by design, for women with missing or incomplete questionnaires, if they were 54 years or younger at recruitment. The pre-menopausal group also includes the peri-menopausal women, since numbers were too small to analyse them as a separate group. Women were categorized as *post-menopausal* if they had experienced no menses for 12 months or longer due to natural or surgical menopause and by design, for women with missing or incomplete questionnaire data, if they were 55 years or older at recruitment.[12]

Post-menopausal women were classified as having had a natural or surgical menopause, where surgical menopause was defined as having had a hysterectomy, unilateral or bilateral oophorectomy, only when age at surgery preceded or was equal to age at menopause. In the Malmö centre, since the age at removal of a woman's womb and/or one or both ovaries was not recorded, women were classified as having had a surgical menopause regardless of age at surgery and age at menopause was then imputed (see below). For naturally post-menopausal women, age at menopause was defined as the age at which they had their last menstruation. For surgically post-menopausal women, their age at surgery was used instead. Since most other studies compare early menopause with late menopause, we present risk associations for decreases (rather than increases) in age at menopause, by multiplying age at menopause by –1.

Covariate measurement

Baseline questionnaires included questions on age, smoking status (current, former, never), highest education level (no schooling/primary school, secondary school, vocational education/university), age at menarche ($\leq$10, 11, 12, 13, 14, 15, 16, $\geq$17 years), full-term pregnancy (yes/no) and whether participants had ever used post-menopausal hormones (yes/no). All centres used trained professionals to measure height and weight except the French centre, for which self-reported measures were used for a subset of participants, and Oxford, for which recalibrated self-reported measures were used based on a comparison between self-reported and measured data in a subset of participants. Both height and weight were adjusted for clothing worn.[9,13] Body mass index (BMI) was calculated as weight divided by the square of height in metres and was categorized ($\leq$20, >20 to <25, $\geq$25 to <30, $\geq$30 kg/m^2). Physical activity was categorized using the Cambridge Physical Activity Index into inactive, moderately inactive, moderately active and active.[14] Baseline systolic and diastolic blood pressure measurements were available in 62% of participants.[11] Therefore, to maximize the availability of information, we used a composite variable ('high blood pressure', available in 98% of participants) defined as any of self-reported hypertension, self-reported use of anti-hypertensive medication, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

Serum biomarkers were measured in baseline non-fasted samples at Stichting Huisartsen Laboratorium (Etten-Leur, The Netherlands) and included high-sensitivity C-reactive protein (hsCRP), total cholesterol, high-density lipoprotein cholesterol (HDL-c) and triglycerides. Erythrocyte haemoglobin A1c (HbA1c) was measured using the Tosoh-G8 HPLC analyser (Tosoh Bioscience, Japan); all other biomarkers were measured using a Cobas enzymatic assay (Roche Diagnostics, Mannheim, Germany) on a Roche HitachiModular P analyser.

First fatal or non-fatal CHD event

First fatal or non-fatal CHD events were defined by codes 410–414 of the International classification of diseases Ninth Edition (ICD-9) and codes I20–I25 of the Tenth Edition (ICD-10). Methods used in the recruitment centres to determine first non-fatal CHD events included self-report and linkage with morbidity or hospital registries. Non-fatal CHD events were further validated by a review of medical records and/or linkage with registries. Fatal CHD events were generally determined through mortality registries.[11] The final year of follow-up for CHD events varied between centres from 2003 to 2010 and median follow-up time was 11 years.

Statistical analyses

Missing values in the exposures and covariates were imputed with multiple imputation using the package MICE in

R[15] with 10 imputations and 50 iterations (Supplementary Appendix 1, available as Supplementary data at *IJE* online). Women from Norway were excluded prior to imputation due to high levels of missing data. Hazard ratios were estimated using Prentice-weighted Cox proportional hazards regression, with age as the underlying time scale and with country-stratified baseline hazards.[16] Robust standard errors were used to construct 95% confidence intervals (CIs). In order to study the association between menopausal characteristics and CHD, three levels of covariate adjustment were applied: adjustment for age at baseline only (age-adjusted model), further adjustment for CHD and reproductive risk factors: smoking status, BMI, HbA1c, education level, physical activity, age at menarche, full-term pregnancy and ever hormone use (confounder-adjusted model). The third model—the confounder- and intermediate-adjusted model—additionally includes the established cardiovascular risk factors that might mediate the association between menopausal characteristics and CHD (total cholesterol, HDL-c, triglycerides, high blood pressure and C-reactive protein). Since the association between menopausal age and CHD may vary depending on smoking and obesity status,[17] we also assessed effect-modification by including interaction terms between menopausal age and smoking status and between menopausal age and obesity status, respectively, in the confounder-adjusted model. Surgically post-menopausal women tend to have an earlier age at menopause.[18–20] Thus, the analysis of type of menopause was also adjusted for age at menopause (Model 3b).

To verify the expected linear relationship between age at menopause and CHD, we used floating absolute risks to display the hazard ratios (HRs) for age at menopause categories [<40, 40–44, 45–49, 50–54, >55 years (reference)] and CHD risk in the confounder-adjusted model. Instead of using a fixed value for the reference group, floating absolute risks redistribute the overall variance across the groups, which results in a reference category with a CI and narrower CIs for the other categories.[21]

To estimate the proportion of the association between menopause and CHD risk that could be explained by potential mediators that were also CVD risk factors, we used the difference method[22,23] for which two regression coefficients of the exposure–outcome association are required: the direct effect (i.e. with adjustment for the possible mediators or established CVD risk factors) and the total effect (without adjustment). First, the total effect of each menopausal characteristic on CHD was estimated based on Model 1 (adjusted for age). Subsequently, for each model of adjustment separately, we estimated the direct effect when removing the indirect via the added risk factors. The proportion of the effect explained (PE) by the mediators

was then calculated as: PE = (total effect – direct effect)/total effect, where effects were considered on the logarithmic scale, i.e. log(HR). Thereafter, we performed the same analyses for each separate risk factor. Bootstrap re-sampling (1000 bootstrap samples) was used to obtain 95% CIs around the PE (Supplementary Appendix 1, available as Supplementary data at *IJE* online).

We performed three sensitivity analyses: (i) restricting to women who had never used hormone therapy, since age at menopause may be difficult to determine under hormone use and the effects of surgical menopause on CHD are attenuated in women using hormone therapy (HT)[24–26]; (ii) excluding the first 2 years of follow-up to reduce the likelihood of reverse causality; (iii) excluding women with unilateral oophorectomy or hysterectomy from the surgical menopause category to reflect alternative definitions of surgical menopause used previously. We also conducted a complete case analysis and compared results with the multiple imputation approach. All analyses were performed on each imputed dataset separately and the estimates were pooled using Rubin's rules,[27] with R version 3.2.0.[28]

Results

After exclusions, there were 10 880 women in the sub-cohort and 4753 incident CHD cases (231 of whom were also in the sub-cohort) comprising a total of 15 402 participants, of whom 5486 were pre-menopausal and 9916 were post-menopausal. Compared with pre-menopausal women, post-menopausal women in the sub-cohort were older, less likely to be smokers, less educated, more likely to have a history of high blood pressure and had higher total cholesterol levels and BMI (Table 1). Mean age at menopause was 49.2 years [standard deviation (SD) 4.5] for women with a natural menopause and 45.1 years (SD 5.8) for women with a surgical menopause. Within post-menopausal women, natural post-menopausal women more often had a high blood pressure, less often used HT and they had a higher age at menopause compared with surgical post-menopausal women (Supplementary Appendix Table 1, available as Supplementary data at *IJE* online).

Post-menopausal women had a higher CHD risk compared with pre-menopausal women (age-adjusted model HR = 1.23, 95% CI: 1.08–1.40, *p*-value = 0.002) (Table 2), but this attenuated in the confounder- and intermediate-adjusted model (HR = 1.08, 95% CI: 0.93–1.26, *p*-value = 0.29).

Age at menopause had an approximately linear association with CHD risk, with women in the lowest category (menopausal age <40 years) having a 51% (confounder-adjusted model HR = 1.51, 95% CI: 1.15–1.98), *p* = 0.003) higher risk than those in the highest category

Table 1. Baseline characteristics of women in the sub-cohort of the EPIC-CVD case–cohort study

	Pre-menopausal ($N = 5486$)	Post-menopausal ($N = 9916$)
CHD risk factors		
Age at baseline (years)	44.8 ± 6.5	59.7 ± 6.8
Smoking status		
Never	2788 (51.7%)	5386 (55.0%)
Former	1133 (21.0%)	2141 (21.9%)
Current	1474 (27.3%)	2266 (23.1%)
Body mass index (kg/m^2)[a]		
≤20	390 (7.2%)	418 (4.2%)
>20 to <25	2543 (46.7%)	3653 (37.0%)
≥25 to <30	1679 (30.9%)	3739 (37.9%)
≥30	828 (15.2%)	2057 (20.8%)
Physical activity		
Inactive	1448 (26.8%)	3155 (32.2%)
Moderately inactive	1871 (34.6%)	3313 (33.9%)
Moderately active	1188 (22.0%)	1798 (18.4%)
Active	894 (16.6%)	1517 (15.5%)
Education level		
No schooling/primary school	1926 (35.9%)	4926 (52.0%)
Secondary school	1065 (19.8%)	1174 (12.4%)
Vocational/university	2376 (44.3%)	3380 (35.7%)
High blood pressure (history)	1249 (23.0%)	5201 (53.4%)
HbA1c (%)[b]	5.4 (5.1-5.5)	5.6 (5.4-5.8)
hsCRP (mg/L)[b]	1.0 (0.4-2.2)	1.5 (0.7-3.3)
Total cholesterol (mmol/L)	5.6 ± 1.0	6.4 ± 1.2
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.5 ± 0.4
Triglycerides (mmol/L)[b]	0.9 (0.7-1.3)	1.2 (0.9-1.8)
Reproductive factors		
Age at menopause (years)[c]	–	47.6 ± 5.6
Full-term pregnancy (Yes)	4415 (87.0%)	8562 (88.5%)
Ever hormone use (Yes)	444 (9.4%)	3006 (33.8%)
Age at menarche (years)		
≤10	209 (4.1%)	271 (2.8%)
11	698 (13.6%)	1006 (10.4%)
12	1270 (24.7%)	1733 (18.0%)
13	1330 (25.8%)	2228 (23.1%)
14	1051 (20.4%)	2235 (23.2%)
15	375 (7.3%)	1208 (12.5%)
16	156 (3.0%)	595 (6.2%)
≥17	57 (1.1%)	365 (3.8%)
Follow-up		
Number of events	679 (12.4%)	4074 (41.1%)
Age at event	56.4 ± 7.1	69.8 ± 7.0

Mean ± standard deviation.
[a]Adjusted for clothing.
[b]Median (Q1–Q3).
[c]Only post-menopausal women.

(menopausal age ≥55 years) (Figure 1). In addition, Table 3 showed that, for each 1-year decrease in age at menopause, CHD risk was 2% higher (HR$_{\text{confounder and intermediate adjusted}}$ = 1.02, 95% CI: 1.01–1.03, $p < 0.001$) and, for each SD decrease (7.9 years) in age at menopause, risk was 14%

higher (HR$_{\text{confounder and intermediate adjusted}}$ = 1.14, 95% CI: 1.05–1.22, $p = 0.001$).

Post-menopausal women with a surgical menopause had a higher risk of CHD compared with women with a natural menopause (HR$_{\text{confounder-adjusted}}$ = 1.25, 95% CI:

Table 2. Hazard ratio (HR) and 95% confidence intervals (CIs) for the association between menopausal status and any first CHD event

Model	Post-menopausal vs pre-menopausal		
	HR (95% CI)	*p*-value	PE% (95% CI)[a]
Age-adjusted model	1.23 (1.08–1.40)	0.002	/
Confounder-adjusted model[b]	1.13 (0.98–1.30)	0.09	40.5 (30.4–54.6)
Confounder- and intermediate-adjusted model[c]	1.08 (0.93–1.26)	0.29	60.7 (54.4–80.6)

N (*N* of events): post-menopausal 9916 (4074), pre-menopausal 5486 (679).

[a]PE, proportion explained.

[b]Adjusted for baseline age, smoking status, BMI, HbA1c, education level, physical activity, full-term pregnancy, age at menarche and ever hormone use.

[c]Additionally adjusted for high-sensitivity C-reactive protein, total cholesterol, HDL-cholesterol, triglycerides and high blood pressure.
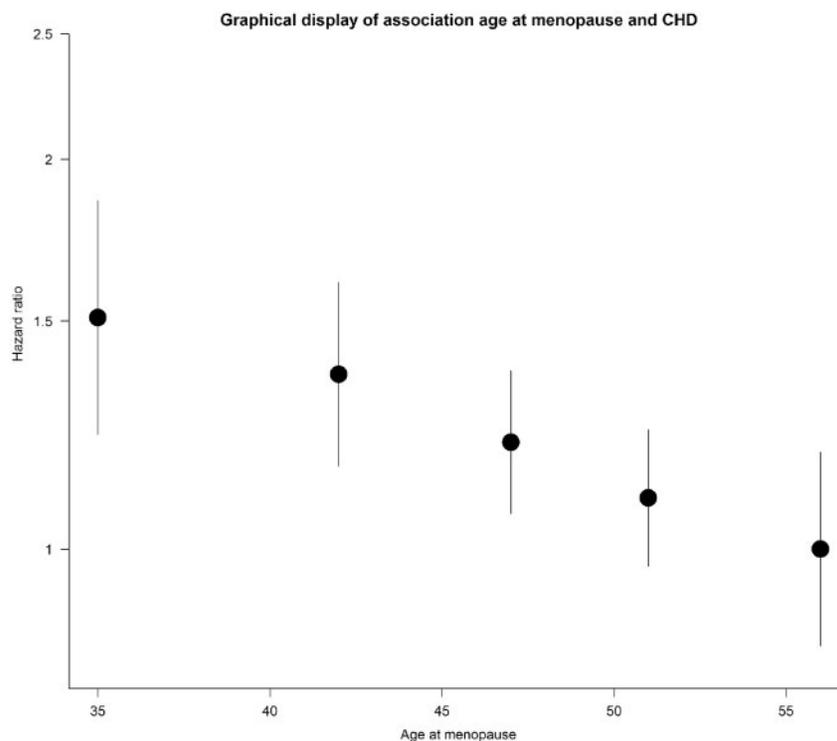
Figure 1. Graphical display of the linear relationship between age at menopause and CHD using floating absolute risks to display the hazard ratios (HRs) for age at menopause categories [<40, 40–44, 45–49, 50–54, ≥55 years (reference), with 364, 551, 1284, 1563, 312 CHD events, respectively]. HRs were plotted against the mean age at menopause of each category, which are 34, 42, 47, 51 and 57 accordingly.

1.10–1.42, $p < 0.001$), which attenuated on further adjustment for age at menopause ($HR_{confounder-adjusted(b)} = 1.15$, 95% CI: 1.00–1.33, $p = 0.05$) and intermediates ($HR_{confounder\ and\ intermediate\ adjusted} = 1.12$, 95% CI: 0.96–1.29, $p = 0.15$) (Table 4).

In the association between age at menopause and CHD, BMI was an effect modifier ($p = 0.003$) where smoking was not ($p = 0.56$). The BMI stratified results (Supplementary Appendix Table 2, available as Supplementary data at *IJE* online) showed that, in women with a BMI of 25 or higher, each 1-year decrease in age at menopause resulted in a 2 or 4% higher CHD risk ($HR_{confounder\ and\ intermediate\ adjusted}$

[BMI ≥ 25–<30] 1.02, 95% CI: 1.01–1.04, p-value = 0.01; $HR_{confounder\ and\ intermediate\ adjusted}$[BMI ≥ 30] 1.04, 95% CI: 1.02–1.06, p-value < 0.001). Women with a BMI between >20 and <25 had no increased CHD risk ($HR_{confounder\ and\ intermediate\ adjusted} = 1.00$, 95% CI: 0.99–1.02, $p = 0.66$) and women with a BMI ≤20 had a 1% increase in CHD risk for each 1-year decrease in age at menopause ($HR_{confounder\ and\ intermediate\ adjusted} = 1.01$, 95% CI: 0.97–1.07, p-value = 0.56).

Finally, in all analyses, we added possible mediators for the associations in Model 4. For post-menopausal compared with pre-menopausal women, we found that adding the

Table 3. Hazard ratio (HR) and 95% confidence intervals (CIs) for the association between age at menopause and any first CHD event in post-menopausal women

Model	HR per-year decrease in age at menopause		HR per SD decrease in age at menopause		
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	PE% (95% CI)[a]
Age-adjusted model	1.03 (1.02–1.04)	<0.001	1.23 (1.15–1.33)	<0.001	–
Confounder-adjusted model[b]	1.02 (1.01–1.03)	<0.001	1.16 (1.08–1.25)	<0.001	28.6 (23.2–34.5)
Confounder- and intermediate-adjusted model[c]	1.02 (1.01–1.03)	0.001	1.14 (1.05–1.23)	0.001	38.7 (30.4–44.6)

N (*N* of events): 9916 (4074).

[a]PE, proportion explained.

[b]Adjusted for baseline age, smoking status, BMI, HbA1c, education level, physical activity, full-term pregnancy, age at menarche and ever hormone use.

[c]Additionally adjusted for high-sensitivity C-reactive protein, total cholesterol, HDL-cholesterol, triglycerides and high blood pressure.

Table 4. Hazard ratio (HR) and 95% confidence intervals (CIs) for the association between type of menopause and any first CHD event in post-menopausal women

Surgical vs natural menopause

Model	HR (95% CI)	*p*-value	PE% (95% CI)[a]
Age-adjusted model	1.31 (1.16–1.47)	<0.001	/
Confounder-adjusted model[b]	1.25 (1.10–1.42)	<0.001	17.6 (10.4–25.4)
Confounder-adjusted model(b)[c]	1.15 (1.00–1.33)	0.05	47.2 (37.3–59.1)
Confounder- and intermediate-adjusted model[d]	1.12 (0.96–1.29)	0.15	59.2 (46.6–73.5)

N (*N* of events): surgical 2206 (935), natural 7710 (3139).

[a]PE, proportion explained.

[b]Adjusted for baseline age, smoking status, BMI, HbA1c, education level, physical activity, full-term pregnancy, age at menarche and ever hormone use.

[c]Additionally adjusted for age at menopause.

[d]Additionally adjusted for high-sensitivity C-reactive protein, total cholesterol, HDL-cholesterol, triglycerides and high blood pressure.

established risk factors in Model 4 explains an additional 20% of the association compared with the confounder-adjusted Model 3 (Table 2). In the association with age at menopause, the possible mediators or established risk factors explained an additional 10% of the association compared with the confounder-adjusted model, although the HR only slightly changes (Table 4). Finally, for types of menopause, the possible mediators explained an additional part of the association of approximately 10% compared with model confounder and age at menopause adjusted model. However, in this case, it seemed that age at menopause explained the largest part of the association (Table 3). Furthermore, Supplementary Appendix Table 3, available as Supplementary data at *IJE* online, shows the proportion explained of all the risk factors separately.

Sensitivity analyses

Similar results were obtained in analyses that were restricted to women who never used HT (Supplementary Appendix Tables 4–6, available as Supplementary data at *IJE* online) and that excluded the first 2 years of follow-up (Supplementary Appendix Tables 7–9, available as Supplementary data at *IJE* online). When surgical menopause was defined as bilateral oophorectomy only, the risk estimates for menopausal status attenuated compared with the main analyses ($HR_{confounder\ and\ intermediate\ adjusted} = 0.95$, 95% CI: 0.82–1.10, $p = 0.50$) as did the results for type of menopause ($HR_{confounder\ and\ intermediate\ adjusted} = 0.92$, 95% CI = 0.74–1.15, $p = 0.47$) (Supplementary Appendix Tables 10 and 11, available as Supplementary data at *IJE* online). The complete case analysis (data not shown) gave similar results to those from the multiple imputation approach.

Discussion

Our study has shown that age at menopause has an inverse dose–response relationship with risk of CHD. Surgical menopause is also associated with an increased CHD risk, even once the earlier age at menopause is accounted for. A proportion of the risk appears to be explained by cardiovascular risk factors that have been postulated to mediate the associations of menopausal characteristics with risk of CHD.

Our finding that the higher risk of CHD in post-menopausal women attenuated upon adjustment for conventional cardiovascular risk factors and reproductive factors is in line with a previous meta-analysis[29] that also found an increased risk for post-menopausal women. These analyses could be challenging, since one might expect both pre- and post-menopausal women to have their events around the same age in their post-menopausal period. However, the age at event in our study was 56.4 ± 7.1 years for pre-menopausal women and 69.8 ± 7.0 years for post-menopausal women, indicating enough dispersion to show a robust effect. Similarly, our finding that earlier menopause is associated with a higher CHD risk is also consistent with a recent meta-analysis[5] that showed a higher CHD risk for women with an age at menopause before 45 years. However, our access to individual participant data (rather than literature-based summary results) meant that we were able to amplify previous findings by showing that the relationship is continuous and approximately linear across the range in age at menopause. Hence, there is no clear age threshold below which early menopause appears to be of intrinsic concern, within the approximate mean ages of the earliest (34 years) and latest (56 years) categories of menopausal age. Age at menopause might be harder to recall when women used HT, but the results of the sensitivity analysis excluding women using HT barely changed, indicating that this did not influence our results. We identified BMI as an effect modifier and the stratified results appeared similar to the findings of a smaller study,[18] which suggested that age at menopause has a stronger association with CHD in obese women compared with non-obese women.

Previous evidence on the associations of surgical and natural menopause with CHD is conflicting.[2,3,24,30,31] Comparison of these studies is difficult, since the definition of surgical menopause and inclusion of women using HT differs by study. Notably, none of the studies on surgical menopause adjusted for age at menopause in their analysis, notwithstanding the fact that a surgical menopause occurs consistently earlier than a natural menopause. Our study shows that the association between surgical menopause and CHD risk is largely explained by the earlier age at menopause, but residual risk remains. Excluding women using HT only slightly altered the results. However, when we defined surgical menopause as bilateral oophorectomy only, the results attenuated towards the null, suggesting that the effect of surgical menopause might be smaller than previously thought.

As conventional cardiovascular risk factors such as blood pressure, lipids and C-reactive protein (CRP) rise around the age of menopause, we specifically examined the extent to which these potential mediators explained the associations we observed in Model 4. Our analyses suggested that these factors can explain part of the association between menopausal characteristics and higher risk of CHD, because the greatest difference in the percentage of proportion explained was found between Model 3 and Model 4 in each association. This concurs with the findings of several other studies, which showed the greatest changes in lipid levels around the time of menopausal transition.[7,8,32–36] Our results should be interpreted with caution, as measurement error might exist in the mediators that could distort the adjustment.[37] Furthermore, as EPIC-CVD has only a single measure of these risk factors at baseline (i.e. after the menopause in post-menopausal women), it is not possible to reliably distinguish whether the attenuations seen are due to mediation or confounding.[38]

Our study has several strengths. We used data from a large prospective study encompassing diverse European populations with a long duration of follow-up and a substantial number of validated incident CHD events. The availability of a wide range of cardiovascular and reproductive risk factors allowed us to systematically examine the effects of accounting for these factors. We were also able to examine the impact of HT use, which has not been possible in many previous studies. Potential limitations include missing or incomplete menopause data, which may have led to non-differential misclassification resulting in under-estimation of the true associations[39]; self-reported menopausal characteristics, although studies show that the validity is rather good for menopausal status and age and varies for surgical menopause[40–42]; the possibility of residual confounding; and measurement error in the intermediates. As EPIC-CVD did not have measures of sex hormones, we were not able to evaluate the contribution of oestrogen. The fact that there are HT users among pre-menopausal women can be explained by the inclusion of peri-menopausal women in this category. Finally, a substantial number of the pre-menopausal women would likely have become post-menopausal during the follow-up period. Therefore, our associations may have been slightly underestimated.

In conclusion, earlier age at menopause and surgical menopause are both associated with higher risk of CHD, which might suggest that these women need close monitoring in clinical practice. The excess risk is, in part, explained by conventional cardiovascular risk factors. Therefore, these risk factors should play an important role in the monitoring of these women. However, there is still a residual association between menopausal characteristics and CHD, of which the mechanism is not fully understood and which merits further research.

Supplementary Data

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