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Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality
A Systematic Review and Meta-analysis

Taulant Muka, MD, PhD; Clare Oliver-Williams, PhD; Setor Kunutsor, MD, PhD; Joop S. E. Laven, MD, PhD; Bart C. J. M. Fauser, MD, PhD; Rajiv Chowdhury, MD, PhD; Maryam Kavousi, MD, PhD; Oscar H. Franco, MD, PhD

IMPORTANCE As many as 10% of women experience natural menopause by the age of 45 years. If confirmed, an increased risk of cardiovascular disease (CVD) and all-cause mortality associated with premature and early-onset menopause could be an important factor affecting risk of disease and mortality among middle-aged and older women.

OBJECTIVE To systematically review and meta-analyze studies evaluating the effect of age at onset of menopause and duration since onset of menopause on intermediate CVD end points, CVD outcomes, and all-cause mortality.

DATA SOURCES Medical databases (ie, Medline, EMBASE, and Web of Science) until March 2015.

STUDY SELECTION Studies (ie, observational cohort, case-control, or cross-sectional) that assessed age at onset of menopause and/or time since onset of menopause as exposures as well as risk of cardiovascular outcomes and intermediate CVD end points in perimenopausal, menopausal, or postmenopausal women.

DATA EXTRACTION AND SYNTHESIS Studies were sought if they were observational cohort, case-control, or cross-sectional studies; reported on age at onset of menopause and/or time since onset of menopause as exposures; and assessed associations with risk of CVD-related outcomes, all-cause mortality, or intermediate CVD end points. Data were extracted by 2 independent reviewers using a predesigned data collection form. The inverse-variance weighted method was used to combine relative risks to produce a pooled relative risk using random-effects models to allow for between-study heterogeneity.

MAIN OUTCOMES AND MEASURES Cardiovascular disease outcomes (ie, composite CVD, fatal and nonfatal coronary heart disease [CHD], and overall stroke and stroke mortality), CVD mortality, all-cause mortality, and intermediate CVD end points.

RESULTS Of the initially identified references, 32 studies were selected that included 310 329 nonoverlapping women. Outcomes were compared between women who experienced menopause younger than 45 years and women 45 years or older at onset; the relative risks (95% CIs) were 1.50 (1.28-1.76) for overall CHD, 1.11 (1.03-1.20) for fatal CHD, 1.23 (0.98-1.53) for overall stroke, 0.99 (0.92-1.07) for stroke mortality, 1.19 (1.08-1.31) for CVD mortality, and 1.12 (1.03-1.21) for all-cause mortality. Outcomes were also compared between women between 50 and 54 years at onset of menopause and women younger than 50 years at onset; there was a decreased risk of fatal CHD (relative risk, 0.87; 95% CI, 0.80-0.96) and no effect on stroke. Time since onset of menopause in relation to risk of developing intermediate cardiovascular traits or CVD outcomes was reported in 4 observational studies with inconsistent results.

CONCLUSIONS AND RELEVANCE The findings of this review indicate a higher risk of CHD, CVD mortality, and overall mortality in women who experience premature or early-onset menopause.

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Author Affiliations: Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands (Muka, Kavousi, Franco); Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, England (Oliver-Williams, Kunutsor, Chowdhury); Department of Obstetrics and Gynaecology, Erasmus University Medical Center, Rotterdam, The Netherlands (Laven); Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands (Fauser).

Corresponding Author: Taulant Muka, MD, PhD, Department of Epidemiology, Erasmus University Medical Center, PO Box 2040, Dr Molewaterplein 50, Office NA29-14, 3000 CA Rotterdam, The Netherlands (t.muka@erasmusmc.nl).

Risk of cardiovascular disease (CVD) increases with age, and because women tend to live longer than men, the absolute number of women living with and dying of CVD is greater than the number of men.[1] Therefore, early recognition of women at high risk for CVD and timely implementation of appropriate lifestyle or therapeutic interventions are of tremendous public health importance.

Adverse changes in cardiovascular risk factors occur around the menopausal transition,[2-4] highlighting the need for CVD risk assessment during this period and the introduction of appropriate preventive or treatment modalities. While the average age at onset of menopause is 51 years,[5] this age varies significantly among women aged 40 to 60 years. Women with premature or early-onset menopause may not only be at risk from a younger age but may also live more years of their lives at an increased risk of adverse outcomes.[6-8] This highlights the need to evaluate the role of both age at and time since onset of menopause as risk factors for CVD.

Age at onset of menopause may be a marker for not only reproductive aging but also for general health and somatic aging.[9] Menopause has been proposed as the first step of a causal pathway that, because of hormonal changes, eventually results in organ dysfunction.[10] A hormonal change cited as an important determinant in CVD development after menopause is the decrease of endogenous estrogen synthesis.[11] In health vessels, estrogens are involved in the relaxation and expansion of blood vessels, helping to accommodate blood flow; consequently, decreased levels of estrogen result in stiffer blood vessels.[12] Furthermore, loss of the ovarian function through menopause is associated with the activation of the renin-angiotensin-aldosterone system, leading to downstream endothelial dysfunction, inflammation, and immune dysfunction.[13] These processes are associated with obesity, diabetes, and hypertension.[13] Thus, premature and early-onset menopause, which occur in women younger than 40 years and aged 40 to 44 years, respectively, have been hypothesized to be detrimental to cardiovascular health because of the early cessation of the protective effect of endogenous estrogen. Therefore, a greater time since the onset of menopause would result in a greater risk of intermediate and hard CVD outcomes.

However, the extent to which age at onset of menopause and time since onset of menopause is associated with the risk of death and CVD and its intermediate risk factors remains unclear. A previous review[14] investigated the association of age at onset of menopause with CVD but did not include years since onset and was based on few studies that lacked sufficient detail (eg, associations of different age categories at onset of menopause with CVD outcomes and the effect with CVD subtypes or all-cause mortality). Therefore, a need exists for an adequately powered, comprehensive assessment of onset of menopause in association with subsequent adverse cardiovascular outcomes.

We conducted a systematic review and meta-analysis of available observational evidence to quantify the associations of age at onset of menopause and time since onset of menopause with (1) primarily clinical CVD outcomes and intermediate vascular traits and (2) all-cause mortality.

Key Points

Question Are age at onset of menopause and years since onset of menopause associated with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality?

Findings In this meta-analysis of 32 observational studies, premature or early-onset menopause in women younger than 45 years were associated with an increased risk of coronary heart disease and all-cause mortality. Time since onset of menopause in relation to vascular outcomes was reported in 4 studies and showed inconsistent results.

Meaning Our findings underscore a potential increased risk of adverse cardiovascular outcomes in women who experience premature or early-onset menopause.

Methods

This review was conducted in accordance with PRISMA and Meta-analysis of Observational Studies in Epidemiology guidelines (eAppendix 1 and 2 in the Supplement). Two independent reviewers, in duplication, sought studies published up to March 2015 using Medline, EMBASE, and Web of Science electronic databases. The computer-based searches combined terms related to the exposure (eg, *age at menopause* and *duration from onset of menopause*) and outcomes (eg, *inflammation*, *cardiovascular disease*, and *mortality*), without any language restriction. Details on the search strategy are provided in eAppendix 3 in the Supplement.

Study selection and eligibility criteria, data extraction and quality assessment, and data synthesis and analysis are described in detail in eAppendix 4 in the Supplement.

Results

Identification of Relevant Studies

The search strategy identified 9444 citations. Following initial screening based on titles and abstracts, full texts of 73 articles were evaluated further. Of these articles, 40 articles were excluded (**Figure 1**). The remaining 33 articles, based on 32 unique studies, met inclusion criteria and were included in the review.

General Characteristics of the Included Studies

eTables 1 and 2 in the Supplement summarize the key characteristics of the included studies. All studies except one evaluated risk in relation to the age at onset of menopause, with 4 additionally evaluating risk in relation to time since onset of menopause. In aggregate, 342 284 women were included in this review. However, not all studies provided relevant data that could be meta-analyzed, and it was not possible to combine any results related to time since onset of menopause, although an analysis of age at onset of menopause was possible. Consequently, there were 297 496 participants in the analysis of age at onset of menopause, which included 44 962 instances of CVD and/or deaths. Twenty-four studies were prospective cohort studies, 2 were case-control studies, and 6 were

cross-sectional studies. Overall, age at onset of menopause in relation to risk of developing CVD intermediate end points or outcomes or all-cause mortality was reported in 31 studies. Among the prospective cohort and case-control studies, 14 studies were judged to be at low risk of bias, 10 were at medium risk, and 2 were at high risk (eTables 1 and 2 in the Supplement).

Association of Age at Onset of Menopause With CVD, CHD, and Stroke

There was only 1 study[15] that examined the association between age at onset of menopause and incidence of CVD, which showed a relative risk (RR; 95% CI) of 1.56 (1.08-2.26) for women who experienced menopause younger than 45 years compared with 45 years or older. In our pooled meta-analysis of 50 125 participants and 1217 CHD events, which compared women with an age at onset of menopause younger than 45 years with women 45 years or older at onset and adjusted for several established CVD risk factors and other potential confounders (eg, age, smoking status, lipid levels, hypertension, body mass index, history of cardiometabolic disease, and hormone therapy), the RR (95% CI) was 1.50 (1.28-1.76) for coronary heart disease risk (**Figure 2**A). The corresponding pooled result based on our meta-analysis of 49 246 participants and 770 stroke events was 1.23 (0.98-1.53) for stroke risk (Figure 2B). There was little evidence of between-study heterogeneity in these meta-analyses (CHD: I^2 = 0%; P = .65; stroke: I^2 = 51%; P = .09).

Comparing women aged 45 to 49 years at onset of menopause with women aged 50 years or older at onset yielded adjusted pooled RRs (95% CI) of 1.12 (0.95-1.31) for CHD risk based on 36 483 participants and 784 events and 0.95 (0.74-1.23) for stroke risk based on 109 928 participants and 536 stroke events (eFigures 1 and 2 in the Supplement). There was no evidence of between-study heterogeneity in these analyses (CHD: I^2 = 0%; P = .37; stroke: I^2 = 0%; P = .78).

Figure 1. PRISMA Flow Diagram

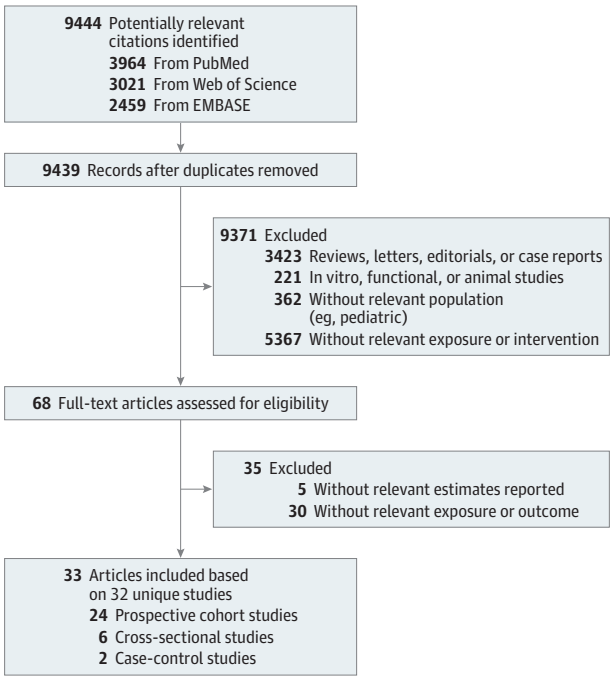
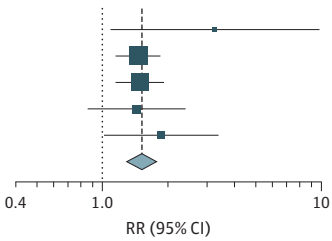


Figure 2. Risk of Coronary Heart Disease and Stroke for Women Younger Than 45 Years at Onset of Menopause vs Women 45 Years and Older at Onset

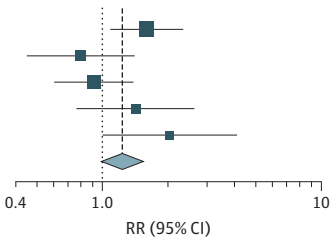
A Coronary heart disease risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cooper et al,[16] 1999	≥51	867	3.24 (1.08-9.79)[a]
Hu et al,[17] 1999	50-54	35 616	1.45 (1.14-1.83)[b]
Løkkegard et al,[18] 2006	>45	10 533	1.47 (1.14-1.90)[b]
Pfeifer et al,[15] 2014	>45	600	1.42 (0.85-2.39)[b]
Wellons et al,[19] 2012	≥46	2509	1.85 (1.01-3.37)[b]
Overall			1.50 (1.28-1.76)



B Stroke risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Baba et al,[20] 2010	45-49	4790	1.58 (1.08-2.32)[b]
Choi et al,[21] 2005	50-54	5731	0.79 (0.45-1.40)[b]
Hu et al,[17] 1999	50-54	35 616	0.91 (0.60-1.38)[b]
Pfeifer et al,[15] 2014	>45	600	1.41 (0.76-2.62)[a]
Wellons et al,[19] 2012	≥46	2509	2.03 (1.00-4.10)[b]
Overall			1.23 (0.98-1.53)



A, There was no evidence of between-study heterogeneity for incident coronary heart disease (χ^2 = 2.49; I^2 = 0%; 95% CI, 0-79; P = .65). B, There was evidence of between-study heterogeneity for total stroke (χ^2 = 8.12; I^2 = 51%; 95% CI, 0-82; P = .09). RR indicates relative risk. Error bars indicate 95% CIs. The size of the data markers are proportional to the inverse of the variance of the effect estimate.

[a] Adjusted for age.

[b] Adjusted for vascular risk factors (covariates are listed in eTable 1 in the Supplement).

Because of differences in age categories, it was not possible to include one study in these meta-analyses. Lisabeth et al[22] evaluated the risk of ischemic stroke for women aged 42 to 54 years at onset of menopause compared with women with premature menopause (younger than 42 years). They found a decreased risk of ischemic stroke (RR, 0.50; 95% CI, 0.29-0.89) for women aged 42 to 54 years at onset. An additional lower risk was found for women 55 years and older at onset (RR, 0.31; 95% CI, 0.13-0.76).[22]

Association of Age at Menopause With All-Cause CVD, CHD, and Stroke Mortality

The risk for different mortality outcomes was estimated for women who experienced menopause younger than 45 years relative to women 45 years or older and adjusted for several established CVD risk factors and other potential confounders. Pooled results yielded combined RRs (95% CIs) of 1.12 (1.03-1.21) for all-cause mortality based on 109 898 participants and 31 427 all-cause deaths, 1.19 (1.08-1.31) for CVD mortality based on 65 653 participants and 6979 CVD deaths, 1.11 (1.03-1.20) for CHD mortality based on 118 150 participants and 8737 CHD deaths, and 0.99 (0.92-1.07) for stroke mortality based on 143 833 participants and 6706 stroke deaths (**Figure 3**). There was evidence of between-study heterogeneity for all-cause mortality analysis (I^2 = 63%; 95% CI, 20-83; P = .009), whereas little evidence of between-study heterogeneity was found for the other analyses (Figure 3). Corresponding pooled RRs (95% CIs) for women aged 45 to 49 years at onset of menopause compared with women 50 years or older were 1.03 (1.00-1.05) for all-cause mortality based on 90 691 participants and 28 188 all-cause deaths, 0.99 (0.92-1.07) for CVD mortality based on 62 995 participants and 5786 CVD deaths, 0.98 (0.93 -1.04) for CHD mortality based on 121 444 participants and 5954 CHD deaths, and 1.03 (0.91 -1.16) for stroke mortality based on 141 175 participants and 6320 stroke deaths (**Figure 4**; eFigures 1-4 in the Supplement).

Comparing women who experienced menopause at 50 to 54 years with women younger than 50 years at onset yielded pooled RRs (95% CIs) of 1.02 (0.89-1.15) for all-cause mortality based on 7341 participants and 1408 all-cause deaths, 0.96 (0.74-1.24) for CVD mortality based on 12 108 participants and 2256 CVD deaths, 0.87 (0.80-0.96) for CHD mortality based on 31 417 participants and 3279 CHD deaths, and 1.19 (0.93-1.52) for stroke mortality based on 12 108 participants and 623 stroke deaths (eFigures 5-8 in the Supplement). There was little evidence of between-study heterogeneity in these analyses (Figure 4; eFigures 1-8 in the Supplement). Because of differences in age categories, it was not possible to include one study in the pooled results.[30] Wu et al[30] reported an increased risk of all-cause mortality (RR, 1.16; 95% CI, 1.04-1.29) for women younger than 46.64 years at onset of menopause compared with women aged 48.80 to 50.15 years at onset (eTable 3 in the Supplement).

Association of Age at Onset of Menopause With Intermediate Cardiovascular Traits

Only 2 studies[31,32] were identified that evaluated risk for carotid atherosclerosis. Pooled RR (95% CI) for the risk of carotid atherosclerosis for 3388 participants was 0.74 (0.63-0.87) when comparing women 50 years or older with women younger than 50 years at onset of menopause (eFigure 9 in the Supplement). However, there was evidence of between-study heterogeneity (I^2 = 69%; 95% CI, 0-93; P = .07). Three studies[30,33,34] could not be included in the meta-analysis of intermediate cardiovascular traits (eTable 3 in the Supplement). These studies evaluated risk of diabetes relative to age at onset of menopause. Two of the studies[30,33] found no higher risk for Chinese women who experienced menopause younger or older than 50 years relative to women aged approximately 50 years at onset. The same findings were observed in a study of European women[34] in which women younger than 45 years at onset of menopause, aged 45 to 49 years at onset, and older than 55 years at onset were not at greater risk for diabetes than women aged 50 to 54 years at onset.

Association of Years Since Onset of Menopause With CVD Outcomes and Intermediate Cardiovascular Traits

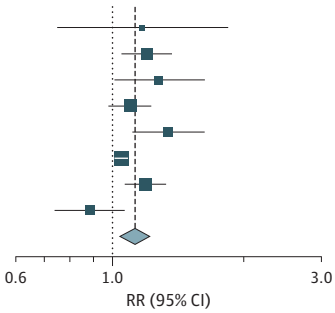
Time since onset of menopause in relation to risk of developing intermediate cardiovascular traits or CVD outcomes was reported in 4 observational studies.[32,35-37] Of these, 2 studies[35,36] reported risk of overall CVD outcomes, and 3 studies[32,36,37] estimated risk of intermediate cardiovascular traits. The age at baseline ranged from 40 to 81 years. Two studies, conducted in Italy[35] and China,[36] evaluated the risk of CVD outcomes, including CHD, stroke, and composite CVD outcomes (eTable 4 in the Supplement), and 3 studies assessed the risk of intermediate cardiovascular traits, including metabolic syndrome, obesity or high body mass index, and hypertension (eTable 5 in the Supplement) in Korean,[37] Chinese,[36] and German[32] populations. Owing to a substantial heterogeneity in the comparison groups used across these studies, no quantitative synthesis could be performed. Therefore, the findings of these studies were only qualitatively reviewed. In a Chinese population study,[13] women 2 to 6 years postmenopause were at a greater risk of CVD than women less than 1 year postmenopause, with evidence of an increased risk after 6 years. In the same study, there was also evidence of a greater risk of CHD and stroke for women more than 1 year postmenopause.[13] However, these findings were in contrast to those in an Italian population study,[14] which found no increased risk of myocardial infarction in postmenopausal women less than 10 years, 10 to 20 years, or more than 20 years postmenopause compared with pre- or perimenopausal women. Stöckl et al[32] found no association between time since onset of menopause and the presence of carotid atherosclerosis. However, time since onset of menopause was dichotomized into broad groups, comparing women less than 15 years postmenopause with women more than 15 years postmenopause.

Relative to premenopausal women, Korean women were at greater risk of metabolic syndrome after menopause, and this risk increased with time since onset of menopause, with the greatest risk found in women between 10 and 14 years after menopause.[22] Within the same population, there was evidence of increased risk of hypertension, abdominal obesity, and high glucose levels in postmenopausal women; however, risk did not vary with duration since onset of menopause.[22] Conversely, no increased risk of obesity, hypertension, or diabetes

Figure 3. Risk of Mortality for Women Younger Than 45 Years at Onset of Menopause vs Women 45 Years and Older at Onset

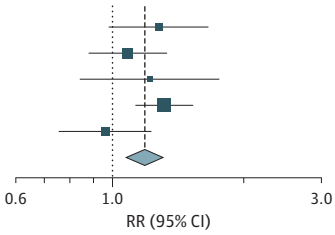
A All-cause mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Amagai et al,[23] 2006	45-49	4683	1.16 (0.74-1.83)
Hong et al,[24] 2007	45-49	2658	1.19 (1.04-1.36)
Cooper et al,[16] 1998	≥50	3191	1.27 (1.00-1.62)[a]
Jacobsen et al,[7] 1999	49-51	6182	1.09 (0.97-1.22)
Li et al,[25] 2013	50-54	11212	1.33 (1.10-1.62)
Mondul et al,[26] 2005	50-54	68154	1.04 (1.00-1.08)
Ossewarde et al,[27] 2005	50-54	12134	1.18 (1.06-1.32)
Tom et al,[28] 2012	50-54	1684	0.88 (0.73-1.06)
Overall			1.12 (1.03-1.21)



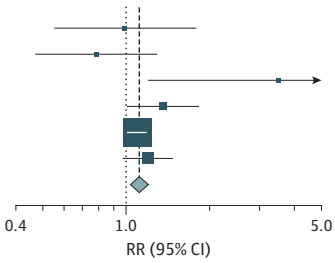
B Cardiovascular disease mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Hong et al,[24] 2007	45-49	2658	1.28 (0.98-1.67)
Cui et al,[29] 2006	≥51	37965	1.08 (0.88-1.34)
Li et al,[25] 2013	50-54	11212	1.22 (0.84-1.77)
Ossewarde et al,[27] 2005	50-54	12134	1.32 (1.13-1.54)
Tom et al,[28] 2012	50-54	1684	0.96 (0.75-1.23)
Overall			1.19 (1.08-1.31)



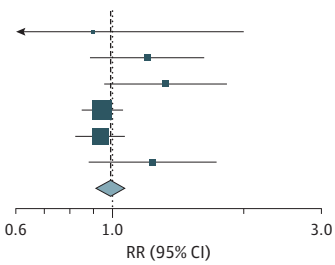
C Coronary heart disease mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cooper et al,[16] 1998	≥50	3191	0.98 (0.55-1.77)
Cui et al,[29] 2006	≥51	37965	0.78 (0.47-1.29)
Hong et al,[24] 2007	45-49	2658	3.52 (1.19-10.43)
Jacobsen et al,[7] 1999	49-51	6182	1.35 (1.00-1.82)
Mondul et al,[26] 2005	50-54	68154	1.09 (1.00-1.18)
Ossewarde et al,[27] 2005	50-54	12134	1.19 (0.97-1.47)
Overall			1.11 (1.03-1.20)



D Stroke mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cooper et al,[16] 1998	≥50	3191	0.90 (0.40-2.02)
Cui et al,[29] 2006	≥51	37965	1.21 (0.89-1.64)
Hong et al,[24] 2007	45-49	2658	1.33 (0.96-1.85)
Jacobsen et al,[7] 1999	50-52	19731	0.95 (0.85-1.06)
Mondul et al,[26] 2005	50-54	68154	0.94 (0.82-1.07)
Ossewarde et al,[27] 2005	50-54	12134	1.24 (0.88-1.75)
Overall			0.99 (0.92-1.07)



All relative risks (RRs) adjusted for vascular risk factors (covariates are listed in eTable 1 in the Supplement). A, There was evidence of between-study heterogeneity for all-cause mortality (χ^2 = 18.80; I^2 = 63%; 95% CI, 20-83; P = .009). B, There was evidence of between-study heterogeneity for cardiovascular disease mortality (χ^2 = 5.74; I^2 = 30%; 95% CI, 0-73; P = .22). C, There was evidence of between-study heterogeneity for coronary heart disease mortality (χ^2 = 8.65; I^2 = 42%; 95% CI, 0-77; P = .12). D, There was evidence of between-study heterogeneity for stroke mortality (χ^2 = 7.59; I^2 = 34%; 95% CI, 0-74; P = .18). Error bars indicate 95% CIs. The size of the data markers are proportional to the inverse of the variance of the effect estimate.

[a] Adjusted only for age.

was found in Chinese women more than 2 years after menopause compared with women less than 1 year after menopause.[13] Similarly, within the same study, systolic and diastolic blood pressures, body mass index, waist-hip ratio, and glucose levels did not vary with time since onset of menopause.

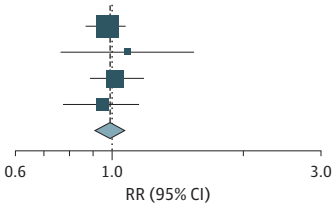
Sensitivity Analysis and Publication Bias

The effect estimates for the association between premature or early-onset menopause and coronary heart disease, stroke, all-cause mortality, cardiovascular mortality, and coronary heart disease mortality remained broadly similar

Figure 4. Risk of Cardiovascular Disease and All-Cause Mortality for Women Aged 45 to 49 Years at Onset of Menopause vs Women 50 Years and Older at Onset

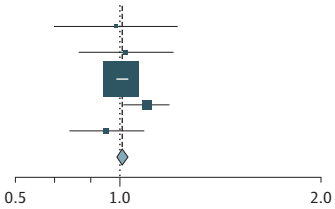
A Cardiovascular disease mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cui et al,[29] 2006	≥51	37965	0.98 (0.87-1.08)
Li et al,[25] 2013	50-54	11212	1.09 (0.76-1.56)
Ossewarde et al,[27] 2005	50-54	12134	1.02 (0.89-1.19)
Tom et al,[28] 2012	50-54	1684	0.95 (0.77-1.16)
Overall			0.99 (0.92-1.07)



B All-cause mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cooper et al,[16] 1998	≥50	3191	1.00 (0.78-1.28)[a]
Li et al,[25] 2013	50-54	11212	1.04 (0.86-1.26)
Mondul et al,[26] 2005	50-54	64154	1.02 (1.00-1.05)
Ossewarde et al,[27] 2005	50-54	12134	1.13 (1.03-1.24)
Tom et al,[28] 2012	50-54	1684	0.96 (0.83-1.12)
Overall			1.03 (1.00-1.05)



All relative risks (RRs) adjusted for vascular risk factors (covariates are listed in eTable 1 in the Supplement). A, There was no evidence of between-study heterogeneity for cardiovascular disease (χ^2 = 0.62; I^2 = 0%; 95% CI, 0-85; P = .89). B, There was some evidence of between-study heterogeneity for all-cause mortality (χ^2 = 5.19; I^2 = 23%; 95% CI, 0-68; P = .27). Error bars indicate 95% CIs. The size of the data markers are proportional to the inverse of the variance of the effect estimate.

[a] Adjusted only for age.

when studies were grouped by location and type of menopause as well as by adjustment for socioeconomic status or hormone replacement therapy (**Table**). Under visual examination, Begg funnel plots for those analyses that included a minimum of 5 studies were mostly symmetrical (eFigure 10 in the Supplement), with possible exception of studies evaluating overall CHD risk and CHD mortality risk in women with premature or early-onset menopause. However, there was no statistical evidence of publication bias based on the Egger test, which was nonsignificant (P > .05) for all analyses that involved 5 or more studies.

Discussion

Overall, we found that women who experienced premature or early-onset menopause appeared to have a greater risk of CHD, CVD mortality, and all-cause mortality but no association with stroke risk. By contrast, an age of 45 to 49 years at onset of menopause compared with 50 years or older at onset had no apparent association with adverse outcomes except for an increased risk of carotid atherosclerosis. Only a few studies evaluating risk in relation to time since onset of menopause could be found, reporting conflicting results.

Interpretation of Findings

The current study supports previous findings that there is an increased risk of CVD with premature or early-onset menopause, specifically identifying a greater risk of CHD and potentially with carotid atherosclerosis. These findings generally concur with and further extend a previous review,[14] which reported an increased risk of CVD for women 50 years or younger at onset of menopause compared with women 51 years or older at onset. However, the findings of the previous review were only based on 7 prospective cohort studies, and the authors were not able to compare other age categories with the risk of CVD. In addition, our study examined the association between age at onset of menopause with all-cause mortality and CVD subtypes, providing a more detailed assessment of the nature and magnitude of the association between menopause and risk of disease and mortality in women. Despite the 12108 participants included, our finding on an association between premature or early-onset menopause with carotid atherosclerosis needs to be interpreted with some caution; to our knowledge, a relatively small number of studies are currently available, some of which have between-study heterogeneity.

The association between premature and early-onset menopause and CHD risk may have several mechanistic interpretations. Early loss of the ovarian function through menopause may lead to long-term activation of the renin-angiotensin-aldosterone system, leading to endothelial dysfunction, inflammation, and immune dysfunction and therefore causing vascular damage.[13,38] This process may be partially mediated via the transmembrane G protein-coupled estrogen receptor.[13] Additionally, menopause marks the start of a biological mechanism, led by hormonal changes, that causes tissue damage and organ dysfunction.[10] The multiorgan effect of menopause proposed by this theory, and supported by findings of an increased risk of depression, dementia, and osteoporosis,[39-41] seems to be consistent with the increased risk of all-cause mortality found in the current analysis.

Alternatively, there may be shared risk factors—either genetic or environmental—that result in premature or

Table. Relative Risks of Cardiovascular Outcomes and Mortality by Study Characteristics and Type of Menopause

Study Characteristics	No. of Studies	Relative Risk (95% CI)	*P* Value[a]
Age <45 y at onset of menopause and risk of CHD vs age ≥45 y at onset			
Location			
Europe	1	1.47 (1.14-1.90)	.83
North America	4	1.52 (1.25-1.86)	
Adjusted for SES			
Yes	0	NA	NA
No	5	1.50 (1.28-1.76)	
Adjusted for HRT			
Yes	2	1.52 (1.20-1.93)	.89
No	3	1.49 (1.21-1.84)	
Menopause type			
Natural	3	1.49 (1.21-1.83)	.96
Unnatural	2	1.87 (0.26-13.39)	
Age <45 y at onset of menopause and risk of stroke vs age ≥45 y at onset			
Location			
North America	3	1.29 (0.80-2.06)	.78
Asia	2	1.16 (0.59-2.27)	
Adjusted for SES			
Yes	0	NA	NA
No	5	1.23 (0.98-1.53)	
Adjusted for HRT			
Yes	1	2.03 (1.00-4.11)	.22
No	4	1.14 (0.81-1.60)	
Menopause type			
Natural	3	0.93 (0.70-1.24)	.19
Unnatural	2	1.50 (0.79-2.83)	
Age <45 y at onset of menopause and risk of mortality vs age ≥45 y at onset			
Location			
Europe	1	1.18 (1.06-1.32)	.62
North America	5	1.09 (0.98-1.21)	
Asia	2	1.19 (1.04-1.35)	
Adjusted for SES			
Yes	4	1.10 (0.94-1.28)	.46
No	4	1.15 (1.08-1.23)	
Adjusted for HRT			
Yes	4	1.07 (0.95-1.21)	.23
No	4	1.16 (1.08-1.25)	
Menopause type			
Natural	6	1.09 (0.99-1.20)	.35
Unnatural	2	1.23 (1.20-1.53)	
Age <45 y at onset of menopause and risk of CVD vs age ≥45 y at onset			
Location			
Europe	1	1.32 (1.13-1.54)	.18
North America	5	1.04 (0.83-1.29)	
Asia	2	1.15 (0.98-1.36)	
Adjusted for SES			
Yes	4	1.10 (0.97-1.26)	.08
No	4	1.32 (1.13-.54)	
Adjusted for HRT			
Yes	4	1.10 (0.83-1.46)	.48
No	4	1.22 (1.07-1.39)	
Menopause type			
Natural	NA	NA	NA
Unnatural	NA	NA	

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HRT, hormone replacement therapy; NA, not applicable; SES, socioeconomic status.

[a] *P* value for heterogeneity was evaluated using random-effects meta-regression.

early-onset menopause and increase the risk of adverse health outcomes.[10] In this case, early menopause could be considered only as a marker of risk. In support of a shared genetic basis, a large-scale genome-wide association study[42] of age at onset of menopause identified a number of loci, including the ones relevant to CVD, that were involved in inflammatory response, oxidative stress, and genome stability. Speculative environmental factors could include obstetric history, such as parity or having a past stillbirth. However, these explanations are not necessarily mutually exclusive, and a combination of these mechanisms may be responsible for the observed increase in CVD and all-cause mortality risk.

Strengths and Limitations

To our knowledge, this is the first comprehensive quantitative review of observational evidence that assessed both the associations of age at onset of menopause and time since onset of menopause with clinical CVD outcomes, intermediate cardiovascular traits, and all-cause mortality. Our analyses included more than 300 000 women and evaluated the risk of a wide range of outcomes in relation to various age groups. However, strengths and limitations in the current study merit careful consideration. First, all systematic reviews are prone to reporting bias, owing to the possibility that studies with more extreme results are more likely to be published. Nonetheless, as demonstrated by Egger test estimates, there was little evidence of publication bias in the current analyses. Additionally, all meta-analyses are limited by the quality of the individual published studies. However, the majority of studies included in the current analyses were of high quality, with a low risk of bias.

To allow for a uniform analysis, it was necessary to combine some overlapping age groups for some studies (eg, studies that reported estimates for women who experienced menopause at 50 to 54 years and those that reported data for women older than 50 years). This might have introduced some heterogeneity into the analyses. Additionally, owing to differential categorization of age at onset of menopause in various studies and the few studies evaluating a particular outcome (eg, carotid atherosclerosis), some of our analysis are based on a small number of studies. Therefore, these results need to be interpreted with caution, particularly those that yielded moderate between-study heterogeneity estimates. Furthermore, the lack of studies evaluating risk in relation to time since onset of menopause limited us from performing any meaningful quantitative synthesis using this exposure.

Most studies that were identified adjusted for a range of relevant confounders, although one study was entirely unadjusted[43] and 3 were only adjusted for age.[16,31,44] Many studies did not examine the effect of important determinants of age at onset of menopause, such as socioeconomic factors, number of births, and lifestyle factors (eg, smoking status, alcohol intake, and level of physical activity). Therefore, the risk of residual confounding cannot be entirely ruled out. A specific concern is confounding from hormone therapy use, which particularly may vary depending on the age at onset of menopause. Women who experience menopause at a younger age may be more likely to start hormone therapy than women who reach menopause in their 50s. Consequently, hormone therapy use may confound the association between age at menopause and CVD risk. Indeed, hormone therapy was only adjusted for in a minority of identified studies.[18,33,35,45,46] Moreover, because the number of available studies in some of our analyses was small, it precluded our ability to comprehensively assess the effect of type of menopause in our results. However, the complex interplay between exogenous hormones and CVD risk is not fully understood, and the results regarding hormone replacement therapy and CVD risk are conflicting.[47-49]

Clinical and Scientific Implications

This review underscores a potential increased risk of adverse cardiovascular outcomes in women who experience premature or early-onset menopause, which may have important clinical and public health implications. This study also identified a number of gaps in the literature concerning the associations between time since onset of menopause, age at onset of menopause, and intermediate cardiovascular traits and CVD outcomes. To our knowledge, few studies focused on intermediate cardiovascular end points, leading to conflicting results and impeding meaningful interpretation. These intermediate factors are of potential importance in the interpretation of the observed higher cardiovascular risk; further research focusing on intermediate cardiovascular traits is required. Finally, other areas of interest are the association between age at onset of menopause and time since onset of menopause and whether there are common determinants for premature menopause and CVD. The observed link between premature or early menopause and CVD risk may be modified by differing times since the onset of menopause. The higher CHD risk may be driven in part by a longer time since the onset of menopause in women with premature or early-onset menopause. Alternatively, the increased RR found with early-onset menopause may be present only in the first years after menopause, ameliorating over time. To our knowledge, the known risk factors for premature menopause include genetics,[41] reproductive factors (eg, parity and age at menarche),[18] and lifestyle factors (eg, smoking status, alcohol intake, and body mass index).[18,50] However, the role of these factors in mediating the association between an early onset of menopause and CVD remains unclear and therefore warrants further research.

Conclusions

The findings of this review indicate a higher risk of CHD, cardiovascular mortality, and overall mortality in women who experience premature or early-onset menopause when younger than 45 years. However, this review also highlights important gaps in the existing literature and calls for further research to reliably establish whether cardiovascular risk varies in relation to the time since onset of menopause and the mechanisms leading early menopause to cardiovascular outcomes and mortality.

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Invited Commentary

Reproductive Health as a Marker of Subsequent Cardiovascular Disease

The Role of Estrogen

JoAnn E. Manson, MD, DrPH; Teresa K. Woodruff, PhD

Cardiovascular disease (CVD) kills 1 in 3 women worldwide,[1] and the risk of CVD increases markedly after the cessation of ovarian function at menopause.[2] Although the dramatic decline in estrogen levels following menopause has been implicated in the loss of cardioprotection in women, the association between the decline in ovarian function and vascular disease may be even more complex.[2] The menopausal transition is associated with significant changes in the vascular system, distribution of body fat, blood pressure, and blood lipid levels,[3] all of which increase the risk of CVD. However, the possibility of shared risk factors, including genetic, lifestyle, and environmental, for both early menopause and elevated CVD risk warrants consideration. Key questions are whether early cessation of reproductive function etiologically increases risk of CVD or whether latent cardiovascular disease causes reproductive aging and accelerates the onset of menopause (or both).

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Menopause occurs at an average age of 51 years in Western populations, but the range of age at onset is wide, with most women experiencing menopause between ages 40 and 60 years.[3,4] Approximately 10% of women experience menopause younger than 45 years and consequently have a shorter total duration of premenopausal estrogen exposure than women with later-onset menopause. As shown in the meta-analysis in this issue of *JAMA Cardiology* by Muka et al,[5] women with early menopause have an increased risk of overall coronary heart disease, fatal coronary heart disease, CVD mortality, and all-cause mortality. However, most studies are unable to assess directionality of the association between early natural menopause and CVD risk. The potential for pre- or perimenopausal cardiovascular risk factor status to predict early menopause was addressed in the Framingham Heart Study,[6] which found that increases in cholesterol, systolic and diastolic blood pressures, and other vascular risk factors prior to menopause were each associated with future menopause at a significantly younger age, even after adjusting for smoking. Such data provide intriguing support for the hypothesis that cardiovascular health may contribute to the timing of menopause but do not preclude a bidirectional association. Shared risk factors, such as smoking, which has been associated with both early menopause and increased CVD risk, other risk factors, and shared gene variants for both outcomes may also be contributory.[3,4]

An additional line of evidence for an adverse effect of early loss of ovarian hormones on vascular outcomes derives from research on women with early surgical menopause and bilateral oophorectomy. Oophorectomy before menopause leads to an abrupt reduction in endogenous estrogen and androgen production.[3,4] In a meta-analysis of observational studies,[7] early bilateral oophorectomy was associated with more than double the risk of CVD (relative risk, 2.62; 95% CI, 2.05-3.35).