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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.

Muka T¹, Oliver-Williams C², Kunutsor S², Laven JS³, Fauser BC⁴, Chowdhury R², Kavousi M¹, Franco OH¹.

Abstract

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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