

Early menopause and risk of cardiovascular disease: an issue for young women



Despite an overall reduction in cardiovascular disease mortality in the past 40 years, cardiovascular disease remains the leading cause of death worldwide, with gender disparities. Women tend to present with cardiovascular disease up to 10 years later than men, although age-adjusted rates of cardiovascular disease mortality in women are similar to men, and account for more deaths than any other cause. Since women have a longer life expectancy than men, the absolute number of cardiovascular disease deaths is higher among women than men and increasing cardiovascular disease mortality rates have been observed in women younger than 55 years.¹ Although gender differences with regard to risk factors, aetiology, and outcomes of cardiovascular disease are well established, a unique group of sex-specific risk factors associated with reproductive health have been identified in women. Previous evidence is inconsistent, but a number of factors including early menarche or menopause have been associated with future cardiovascular disease events in women.² Up to 10% of women have early natural menopause,³ indicating a potentially important target population for early and tailored risk stratification. In *The Lancet Public Health*, Dongshan Zhu and colleagues⁴ report one of the largest studies to date to investigate the association between age at menopause and onset and timing of incident cardiovascular disease.

The study by Zhu and colleagues adds to the findings of a previous review of 32 studies that identified key gaps in the evidence with regard to the effect of early menopause on cardiovascular disease risk, including the importance of age at menopause, interactions between traditional cardiovascular disease risk factors, and whether the cardiovascular disease risk associated with early menopause persists or dissipates over time as women age.⁵ To address these questions, Zhu and colleagues pooled individual-level data on reproductive health and chronic diseases from 15 studies included in the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) consortium. This large-scale observational study included 301438 women from five different countries and regions. The mean age of

the women at last follow-up was 57.0 years (SD 10.3), by which time 192 525 (64.0%) of 301438 women were postmenopausal, with menopause occurring at a mean age of 50.2 years (4.4). Compared with women who had menopause at age 50–51 years, a dose-response relationship was identified between each lower menopausal age category and increasing cardiovascular disease risk: 45–49 years (relatively early menopause; hazard ratio [HR] 1.12, 95% CI 1.07–1.18); 40–44 years (early menopause; HR 1.30, 1.22–1.39); and younger than 40 years (premature menopause; HR 1.55, 1.38–1.73). These associations were similar when coronary heart disease and stroke were examined separately. Stratification by age at first non-fatal cardiovascular disease event showed that the excess risk of incident cardiovascular disease associated with younger menopausal age was highest before age 60 years (HR 1.40, 95% CI 1.27–1.54 for women with early menopause; 1.88, 1.62–2.20 for women with premature menopause). This higher risk of cardiovascular events was attenuated between age 60–69 years, with no significant association observed at older ages (≥ 70 years). Furthermore, the increased risk of developing cardiovascular disease in women with early or premature menopause persisted after adjustment for smoking status and body-mass index, and was not affected by postmenopausal hormone therapy use. After stratification by these key variables, the associations between younger age at menopause and cardiovascular disease risk was stronger in women who smoked, were underweight or obese, and women who had a low level of education.

These findings have important public health and clinical implications. The doubling of cardiovascular disease risk in women below the age of 60 years who have premature menopause is concerning and indicates an urgent need to raise awareness of cardiovascular disease risk in younger women. A common misconception already exists among health professionals and the general public, that cardiovascular disease predominantly affects men, at least until older age.⁶ This sex-bias needs to be addressed, with emphasis on the increasing risk in younger women, in addition to

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new sex-specific preventative and therapeutic strategies for reducing and managing cardiovascular disease in women.⁷ Sex-specific risk factors provide a unique opportunity for early identification of women with increased cardiovascular disease risk, however, these risk factors are not included in cardiovascular disease risk algorithms such as QRISK or the Framingham Risk Score, which focus on traditional cardiovascular disease risk factors. The study by Zhu and colleagues shows that early menopause was an independent predictor of cardiovascular disease after adjusting for traditional risk factors. Although unmeasured confounding cannot be ruled out, these findings demonstrate the potential for including sex-based factors to improve current prognostic models for women. The finding that the cardiovascular disease risk associated with early menopause increased in smokers, women who were underweight or with obesity, and those with lower socioeconomic status, indicates a potential interaction between menopause and traditional cardiovascular disease risk factors, which also requires further exploration and consideration in risk assessment and management. These findings add to previous evidence showing increased influence of some traditional cardiovascular disease risk factors in women compared with men⁸ and further emphasizes the need for risk stratification by sex. Notably, most women included in the InterLACE consortium studies were white. Ethnic variation in age at menopause, cardiovascular disease risk profiles, and timing of cardiovascular disease, have been reported previously.⁹ To develop tailored guidelines, the heterogeneity that exists among women must be considered and further research is needed to understand whether the association between early or premature menopause and incident cardiovascular disease differs by ethnicity.

Research such as that done by Zhu and colleagues is timely and underpins the importance of precision

medicine across the cardiovascular disease life course. Differences in cardiovascular disease pathogenesis between men and women originate from both genetic and biological mechanisms and complex interactions between behavioural and socioeconomic factors. Studies further elucidating the mechanisms that underpin the complex associations between sex and cardiovascular disease risk are essential to inform the redesign of primary and secondary prevention guidelines and make the necessary shift away from a one-size-fits-all approach to a more patient centred approach, to target the increasing global burden of cardiovascular disease.

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We declare no competing interests.

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