

## EDITORIAL COMMENT

# Menopause and Cardiovascular Risk

## Cause or Consequence?\*

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In the developed world, mean life expectancy for women since 1900 has increased from 50.0 to 81.7 years (1). Given an average age at menopause of 51.4 years, women in developed countries thus live over one-third of their lives in the postmenopausal state (2). Although life expectancy at birth varies by country owing to varying rates of infant and child mortality, life expectancy for women at age 50 years is quite similar throughout the world (range 27 to 32 years) (3). Global population projections predict a marked increase in the number of postmenopausal women from 467 million in 1990 to 1,200 million in 2030 (3). Understanding the impact of menopause on women's health is thus becoming increasingly important.

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Determinants of age at menopause are incompletely understood. The age at menopause correlates between mothers and daughters and between sisters. A study of twins suggested 63% heritability of menopausal age (4). A common polymorphism in the estrogen receptor alpha has been associated with earlier onset of menopause, as has the Factor V Leiden mutation (5,6). Smoking is the only environmental factor that has been consistently associated with earlier menopause (7).

Although it is clear that coronary heart disease (CHD) incidence and prevalence are higher in postmenopausal compared with premenopausal women, the impact of menopause and loss of endogenous estrogen distinct from that of advancing age remains controversial. Perimenopausal metabolic changes seen in longitudinal studies are reminiscent of the metabolic syndrome (8). Despite these adverse changes in the cardiovascular risk profile, CHD mortality rates do not accelerate at or after natural menopause, and the apparent increase in CHD risk among women with premature natural menopause seems to be secondary to confounding by smoking (9–11). Serum levels of endogenous sex hormones do not correlate with severity

of atherosclerosis or coronary events, and attempts to pharmacologically replace estrogens in postmenopausal women have not improved coronary morbidity or mortality (9,12–14).

Kok et al. (15), in a very provocative paper in this issue of the *Journal*, suggest that it is not menopause that adversely affects cardiovascular risk but rather that cardiovascular risk factors determine the age at menopause, possibly by inducing ischemic damage in the ovaries or through direct effects on the endocrine system. The authors analyzed data on 695 premenopausal women in the Framingham cohort who reached natural menopause during the study. With serial data obtained at the biannual exams, the authors estimated the values of total cholesterol, relative weight, and blood pressure at age 43 through linear regression models for each participant and determined whether each risk factor had increased, decreased, or remained the same during the premenopausal years. Framingham risk score was estimated in a subset of women at age 35 years with an assumed normal high-density lipoprotein (HDL) cholesterol level. Analyses were adjusted for smoking status at the exam closest to menopause.

Mean menopausal age was 49.9 years, approximately 1.5 years earlier than reported for the U.S. population (2), possibly due to the very high smoking rate of 42% in this study. Earlier age at menopause was associated with higher cholesterol levels at age 43 years, increase in cholesterol and blood pressure before menopause, and both increases and decreases in relative weight. Improvements in cholesterol and systolic blood pressure were associated with a later menopause. A 1% higher 10-year risk for CHD at age 35 years was associated with a decrease in menopausal age of  $-1.8$  years (95% confidence interval  $-2.72$  to  $-0.92$ ).

A major strength of the current study is the use of prospectively collected longitudinal risk-factor data and modeling that allowed estimation of risk factors at a specific age, thus permitting an analysis not confounded by age. Because of the frequency of exams, the authors were also able to determine age at cessation of menstruation quite accurately and distinguish between natural and surgical menopause, excluding the latter from this analysis. What is less clear, however, is that cessation of menstruation at younger ages in this cohort necessarily represented “menopause.” It is likely that some of the younger women had secondary amenorrhea and some might have had hypothalamic hypoestrogenemia, a condition that has been associated with angiographic coronary disease among women undergoing diagnostic angiography for suspected myocardial ischemia (16).

The authors assume in their modeling that the relationship between cholesterol and menopausal age is linear throughout the range of values measured. If serum cholesterol adversely influences ovarian function through vascular injury, an exponential model analogous to the relationship between cholesterol and CHD might have been more

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appropriate. Similar concerns apply to the other risk-factor relationships. Although estimating Framingham risk with assumed "normal" HDL cholesterol levels is not ideal, this is unlikely to have had a major impact, because Framingham risk estimates for a 35-year-old woman are relatively insensitive to the HDL cholesterol levels entered into the equations.

In the U.S., cardiovascular risk-factor prevalence increases with advancing age. In this Framingham cohort, cholesterol decreased in 15% of women, weight in 14%, and systolic blood pressure in 24% despite advancing age and in the absence of pharmacologic therapy. Such spontaneous and unexplained "risk-factor improvement" raises concern about underlying diseases that could have confounded the relationship to menopausal age. Even if the changes were due to improvement in diet and/or physical activity level, confounding is still a possibility, because the reason for the lifestyle change could have been related to age at menopause. Such confounding might explain the puzzling finding that both increases and decreases in relative weight related to earlier age at menopause.

Prevalence of cardiovascular risk factors varies widely by country. If risk factors have a substantial influence on age at menopause, one would expect the same between-country heterogeneity in menopausal ages as in risk-factor prevalence and in CHD morbidity and mortality. Cross-cultural comparisons of menopausal age suggest that average age at menopause is not highly variable. The range of average age at menopause reported among almost 19,000 women in 11 countries in Europe, the Americas, Asia, Australia, and Africa was only 49 to 52 years (mean 50 years) (17). A study conducted in menopausal women in seven Southeast Asian countries similarly revealed a median age at menopause of 51 years (18). Secular trends might also provide information about the relationship of cardiovascular risk factors and menopausal age. McKinlay et al. (19) tabulated results from 13 studies conducted in Europe and the U.S. between the 1960s and 1980s and did not find significant differences in average menopausal age between countries or between time periods. Historical reviews have even suggested that average age at menopause has not changed since antiquity (20). While ecologic comparisons such as these have significant limitations and do not rule out a causal relationship between cardiovascular risk factors and menopausal age in an individual woman, the lack of heterogeneity in menopausal ages across markedly different cardiovascular risk environments suggests, however, that the effect of cardiovascular risk factors on menopausal age is at most modest.

The Stages of Reproductive Aging Workshop (STRAW) distinguished three reproductive stages (early, peak, late), two stages of menopausal transition (early, late), and two postmenopausal stages (early, late) (21). The late reproductive stage that is characterized by fertility decline and progressive hormonal changes generally falls into the fourth decade of life around age 35 years and beyond (i.e., typically 10 to 15 years before the final menstrual period). Vasomotor

symptoms and other symptoms generally attributed to menopause might start in this late reproductive stage as well, suggesting that changes in the hypothalamic-pituitary-ovarian axis have a physiologic impact beyond the reproductive system. The risk-factor trends calculated by Kok et al. (15) are based on an average of 4.9 measurements (range 2 to 10) before menopause, corresponding to an average of 10 years of observation before the final menstrual period (range 4 to 20 years). These risk-factor trends were thus measured in the late reproductive phase (i.e., at a time when endocrine changes in the reproductive system were already in progress). We do not know whether endocrine changes and risk-factor changes simply occurred concurrently, whether risk-factor changes influenced the endocrine changes in progress and thus changed menopausal age as the authors hypothesize, or whether endocrine changes caused both a change in risk-factor levels over time and determined menopausal age.

Although the hypothesis put forward by Kok et al. (15) is intriguing, the current study design cannot provide a definitive answer. Longitudinal studies such as the Study of Women's Health Across the Nation (SWAN) (22), which collect detailed demographic and clinical data, data on cardiovascular risk factors, health behaviors, and psychosocial factors as well as serial markers of ovarian function, will be in a better position to further our understanding of the relationship between cardiovascular risk and menopause.

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