Menopause, Age, and Cardiovascular Risk
A Complex Relationship*

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The incidence and prevalence of coronary heart disease and atherosclerotic diseases in noncoronary beds are higher in post-menopausal than in pre-menopausal women. Whether this higher cardiovascular risk is a function of aging, a consequence of menopause and its associated loss of endogenous estrogen, or both has been debated in the literature for many years (1–3). To add to the complexity, investigators recently suggested that the timing of menopause itself could be influenced by the cardiovascular risk milieu (4).

Trying to sort out the relative contribution of 2 concurrent and intimately linked processes such as aging and menopause (ovarian aging) to cardiovascular disease, which is multifactorial in origin, is methodologically challenging. Cross-sectional studies cannot distinguish between the 2 processes. Previous longitudinal studies often had limitations relating to the definition of menopause; the exact timing of the final menstrual period; the lack of concurrent measurement of hypothalamic and reproductive hormones to distinguish menopause from other causes of amenorrhea; inadequate capture of multiple risk markers at frequent intervals in the critical period between late pre-menopause, perimenopause, and early menopause; and the lack of concurrent measurement of covariates that could influence the relationship between menopause and cardiovascular risk factors including lifestyle measures and medications. Importantly, previous studies were generally limited to samples of Caucasian women.

In this issue of the Journal, Matthews et al. (5) attempt to disentangle the influence of aging and menopause on cardiovascular risk factors in a subset of 1,054 women enrolled in SWAN (Study of Women’s Health Across the Nation), a multicenter, prospective cohort study of initially pre-menopausal or early perimenopausal women of diverse ethnicity. SWAN participants included in the current analysis were not taking hormone therapy before menopause; ranged in age from 42 to 52 years; were free of stroke, heart disease, and diabetes at entry; were followed for 9 years; and reached their final menstrual period during follow-up. The authors serially measured blood pressure, lipids and lipoproteins, hemostatic factors, insulin and glucose, and high-sensitivity C-reactive protein and concluded that only total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B) demonstrated increases in the 1-year interval before and after the final menstrual period that were consistent with menopause-induced changes. High-density lipoprotein cholesterol (HDL-C) and apo A-I changes were also better described by the menopause model than by the aging model, but the greatest increase in HDL-C and apo A-I levels occurred before the 1-year interval surrounding the final menstrual period. The other risk factors changed in a linear pattern consistent with chronologic aging: triglycerides, lipoprotein (a), insulin, factor VIIc, and systolic blood pressure increased; diastolic blood pressure, tissue plasminogen activator antigen, fibrinogen, and high-sensitivity C-reactive protein did not change; and, somewhat unexpectedly, glucose and plasminogen activator inhibitor decreased over time. Importantly, the investigators did not find any heterogeneity by ethnic group. Major strengths of the present analysis include the careful prospective characterization of the timing of the final menstrual period, frequent assessment of risk factors in multiple domains, ability to adjust for many covariates that could confound the analysis, the multiethnic composition of the cohort, and the use of sophisticated modeling that allows unequal times between measurements and unequal numbers of measurements across women.

The lipid changes attributable to menopause reported in this study deserve a closer look. Figure 2A and 2B of Matthews et al. (5) shows the changes in LDL-C and apo B over time and nicely demonstrate that both measures increase from pre-menopausal levels and that the changes are not linear (i.e., not consistent with an aging model). It is noteworthy, however, that the curves for the 2 measures seem to diverge after year 1 after the final menstrual period.
with a continued subtle increase in LDL-C but a decrease in apo B. This finding suggests that composition of the low-density lipoprotein (LDL) particles changed after the final menstrual period and that the particle number decreased while the cholesterol content per particle increased. This is an unexpected finding because previous cross-sectional studies suggested a shift toward smaller, denser LDL particles during the menopausal transition (6,7). It is of note that the women in the previous studies had lower apo B levels both pre-menopausally and post-menopausally than seen in the current study. Whether the impact of menopause on LDL-C and LDL particle number differs by baseline apo B level is unknown. A similar discrepancy between cholesterol and apoprotein trajectories is evident for HDL-C and apo A-I, where apo A-I continues to increase after the final menstrual period while HDL-C levels decline (Fig. 2C and 2D of Matthews et al. [5]). These findings require confirmation in other contemporary longitudinal data sets. Assuming that there are discrepant changes in cholesterol and apoprotein levels after cessation of menses, how should we best assess a woman’s cardiovascular risk? Computation of the apo B/A-I ratio post-menopause would convey a lower risk than computation of the LDL-C/HDL-C ratio. It will be critically important to closely follow the women in the SWAN study long term to determine which of these 2 measures better relates to actual cardiovascular events. Such follow-up could also tell us whether we need to only focus on the risk factor values achieved after the menopausal transition is completed or whether the degree and slope of change during the transition carry additional prognostic information.

Triglycerides in this cohort increased 1.75% annually in a pattern consistent with chronologic aging. Given that metabolism of HDL and triglyceride-rich lipoproteins is closely linked in general and significantly influenced by estrogen, it is a bit puzzling that changes in HDL-C and apo A-I would be related to menopause, whereas triglyceride changes would be driven solely by chronologic aging. It is possible that the greater variability in triglyceride measurements could have masked a menopausal effect, but metabolic changes that alter the relationship between triglycerides and HDL at the time of menopause cannot be excluded and deserve further exploration in detailed longitudinal kinetic studies.

Blood pressure, hemostatic markers, high-sensitivity C-reactive protein, and glucose and insulin were not influenced by menopause in this cohort. Should we then conclude that the impact of menopause is limited to adverse effects on lipids and that CHD risk in post-menopausal women is otherwise driven by chronologic aging? I believe that this would be premature. Both in vitro studies and in vivo studies in animals and humans show that estrogens have vascular effects (genomic and nongenomic) that could influence susceptibility to atherosclerosis and future cardiovascular events (8). Reproductive hormones also have a major impact on bone remodeling and calcium homeostasis and could thus influence vascular calcification independent of alterations in serum markers measured in the current study (9,10). To determine the relative contributions of chronologic aging and menopause to overall cardiovascular risk, future studies should not only assess cardiovascular risk factors but also assess vascular structure and function longitudinally in the context of careful characterization of the menopausal transition and while controlling for important covariates.

For now, the major take-home point for the clinician is that risk factor levels do indeed change around the time of menopause, some related to chronologic aging and some related to the menopausal transition itself. Women should be made aware that their cardiovascular risk is likely to increase during this period and should be counseled to emphasize therapeutic lifestyle changes to combat such increases. It may be prudent to increase the frequency of risk factor monitoring during this time to identify women in a timely fashion who may benefit from pharmacologic management of their risk factors beyond lifestyle modification.

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REFERENCES


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