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Are Changes in Cardiovascular Disease Risk Factors in Midlife Women Due to Chronological Aging or to the Menopausal Transition?

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Objectives This prospective study examined whether changes in traditional and novel coronary heart disease (CHD) risk factors are greater within a year of the final menstrual period (FMP), relative to changes that occur before or after that interval, in a multiethnic cohort.

Background Understanding the influence of menopause on CHD risk remains elusive and has been evaluated primarily in Caucasian samples.

Methods SWAN (Study of Women's Health Across the Nation) is a prospective study of the menopausal transition in 3,302 minority (African American, Hispanic, Japanese, or Chinese) and Caucasian women. After 10 annual examinations, 1,054 women had achieved an FMP not due to surgery and without hormone therapy use before FMP. Measured CHD risk factors included lipids and lipoproteins, glucose, insulin, blood pressure, fibrinogen, and C-reactive protein. We assessed which of 2 models provided a better fit with the observed risk factor changes over time in relation to the FMP: a linear model, consistent with chronological aging, or a piecewise linear model, consistent with ovarian aging.

Results Only total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B demonstrated substantial increases within the 1-year interval before and after the FMP, consistent with menopause-induced changes. This pattern was similar across ethnic groups. The other risk factors were consistent with a linear model, indicative of chronological aging.

Conclusions Women experience a unique increase in lipids at the time of the FMP. Monitoring lipids in perimenopausal women should enhance primary prevention of CHD. (J Am Coll Cardiol 2009;54:2366–73) © 2009 by the American College of Cardiology Foundation

Understanding the influence of the menopausal transition on women's risk of coronary heart disease (CHD) remains elusive (1). Women who experience early menopause, especially due to surgical oophorectomy, are at increased risk of CHD events compared with age-matched pre-menopausal women (2). Further, adverse risk factor profiles can account for the increased risk of CHD events associated with hysterectomy and oophorectomy in the Women's Health Initiative (3) and for an earlier age at menopause in the Framingham cohort (4). Women's rates of CHD do not increase dramatically during perimenopause, but start to climb exponentially in the post-menopausal years (1). On the other hand, the post-menopausal increase in CHD rates may reflect the cumulative impact of earlier alterations in CHD risk factors beginning during the menopausal transition. Taken together,

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these disparate findings have contributed to controversy about whether menopause accelerates CHD risk or whether increased CHD risk leads to earlier menopause (5).

One approach to understanding the directionality of the effect is to evaluate changes in risk factors for CHD during perimenopause and early post-menopause. Epidemiological studies suggest that the menopause is associated with increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C), whereas increases in blood pressure and weight during midlife are more linear and appear to reflect chronological aging (6–11). However, almost all studies were based on Caucasian samples and did not measure risk factors simultaneously with changes in menopausal status. Thus, the designs were not optimal to determine associations between changes in menopausal status and changes in risk factors. Many of the studies were also conducted before the identification of emerging risk factors, such as C-reactive protein (CRP) and fibrinogen. The aim of this report is to describe the changes in a wide array of risk factors, including lipids and lipoproteins, blood pressure, insulin, glucose, and hemostatic and inflammatory factors in women before and after their final menstrual period (FMP) and to ascertain whether changes in these risk factors were related to ovarian aging or chronological aging. The sample was composed of African-American, Chinese, Japanese, Hispanic, and Caucasian women, allowing a secondary aim of evaluating ethnic differences in the patterns of risk factor change over time in relation to the FMP.

Abbreviations and Acronyms

AIC = Akaike information criterion
Apo = apolipoprotein
CHD = coronary heart disease
CRP = C-reactive protein
FSH = follicle-stimulating hormone
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
Lp(a) = lipoprotein(a)
PAI-1 = plasminogen activator inhibitor type 1
t-PA-ag = tissue-type plasminogen activator antigen

Methods

Participants. The study sample was composed of 1,054 women who had their FMP by the end of 9 years of follow-up in SWAN (Study of Women's Health Across the Nation), a longitudinal, multisite, community-based study of 3,302 initially pre-menopausal and early perimenopausal women (12). A screening survey was conducted in 16,065 women from 1995 to 1997 to assess eligibility and to collect health, reproductive, demographic, and lifestyle data. Each of 7 sites recruited at least 450 eligible women into the longitudinal cohort: Caucasian women and women from 1 specified minority group (African Americans in Pittsburgh, Pennsylvania; Boston, Massachusetts; Detroit area, Michigan; and Chicago, Illinois; Japanese in Los Angeles, California; Chinese in the Oakland East Bay region, California; and Hispanic women in Newark, New Jersey). Eligibility criteria for the longitudinal cohort were age 42 to 52 years, having an intact uterus, having at least 1 menstrual period and not using exogenous reproductive hormones in the 3 months before the baseline interview, and having self-identified with the site's designated race/ethnic groups. The institutional review board at each participating site approved the study protocol.

Women's menstrual bleeding status, including the date of the most recent menstrual period, was assessed annually. The FMP was defined as the date of the participant's FMP before 12 consecutive months of amenorrhea and was assigned retrospectively, after at least 12 months of amenorrhea. For each annual observation, the years remaining until the FMP or years elapsed since the FMP were computed for observations occurring before or after the FMP, respectively. For a woman with 1 or 2 consecutive missed annual visits that encompassed her FMP, the date of the FMP was imputed based on her menopausal status at the preceding annual visit. Omitted from the analysis were 189 women with a missing FMP date or covariates; 645 women were lost to follow-up before the FMP; and 1,034 women with an indeterminate FMP date because of hormone therapy (HT) use (n = 801) or surgical menopause (n = 233; some because of both) before final menses (those with HT use or surgical menopause after the FMP were included in the analytic sample). Relative to the 645 women lost to follow-up before the FMP, the women in the analytic sample were less likely to be Hispanic and more likely to be Chinese or Japanese; the site that followed Hispanics was closed due to administrative reasons unrelated to the study's scientific goals.

Procedures. SWAN participants were questioned annually about health, lifestyle, and psychosocial factors. Anthropometric measurements and phlebotomy procedures were obtained with standardized protocols. At each examination, the fasting blood draw was targeted to the early follicular phase of the menstrual cycle (days 2 to 5) in menstruating women and before 10 AM to allow for a standardized hormonal milieu. All samples were maintained at 4°C until separated and then were frozen at −80°C and shipped in dry ice to a central certified laboratory (Medical Research Laboratories, Highland Heights, Kentucky). Assays were not undertaken at follow-up years 2, 8, and 9 for all risk factors, and, in addition, for fibrinogen and factor VIIc at follow-up years 4 and 6 for budget reasons.

Cardiovascular risk factor measurement. Risk factors were selected for measurement in the SWAN study if they were predictors of CHD in women or if they were influenced by ovarian hormones. All lipid and lipoprotein fractions were analyzed on ethylenediamine tetraacetic acid-treated plasma. Total cholesterol and triglycerides were (13) analyzed by enzymatic methods and high-density lipoprotein cholesterol (HDL-C) was isolated using heparin-2M manganese chloride (14,15). Serum insulin was measured using a radioimmunoassay (DPC Coat-a-Count, Diagnostic Products Corporation, Los Angeles, California) procedure and monitored as part of the monthly quality assurance program by the Diabetes Diagnostic Laboratory at the University of

Missouri. Glucose was measured using a hexokinase-coupled reaction on a Hitachi 747-200 (Boehringer Mannheim Diagnostics, Indianapolis, Indiana). Lipoprotein(a) [Lp(a)] was quantified by competitive enzyme-linked immunosorbent assay. Fibrinogen and factor VIIc were measured in frozen citrated plasma using a clot-based turbidometric detection system, with the factor VII assay using factor VII-deficient plasma in preparing the standard curve. Tissue-type plasminogen activator antigen (t-PA-ag) was measured in plasma using a double antibody in an enzyme-linked immunosorbent assay (American Diagnostica, Greenwich, Connecticut), with a human single chain t-PA-ag as a standard calibrated against an international standard (National Institute for Biological Standards and Control, Hertfordshire, United Kingdom). Plasminogen activator inhibitor type 1 (PAI-1) was measured using a solid phased monoclonal antibody and a second enzyme-labeled goat antiserum for detection (American Diagnostica). CRP measured using ultrasensitive rate immunonephelometry (Dade-Behring, Marburg, Germany).

Other variables. Age, race/ethnicity, and education (high school degree or less, some college/vocational training, college degree or more) were obtained at the baseline examination. Dietary data were collected at years 0 and 5 (16); the within-woman correlation for dietary variables ranged from 0.45 for the percentage of calories from fat to 0.66 for calories from alcohol. Information on physical activity associated with routine activities, sports/leisure, and household/child care was collected at baseline and at years 3, 5, and 6 (17). The within-woman correlation for these variables ranged from 0.57 for household and child care-related activity to 0.67 for sports-related activity. Information on medication use including HT, health history, smoking (current, past, never), menopausal status, and body mass index was obtained at each examination. Body mass index (kg/m^2) was calculated from measurements of weight and height, which were obtained with a calibrated scale and a stadiometer.

Statistical analyses. The analytic sample was compared using chi-square and *t* tests with the subgroup of SWAN participants who still had not reached their full FMP at the ninth annual follow-up visit, that is, no previous or current use of HT, no hysterectomy or bilateral oophorectomy, and fewer than 12 consecutive months of amenorrhea.

We evaluated the magnitude of change in each risk factor by dividing the transition into 3 time periods relative to the FMP. The 3 segments were based on the timing of changes seen for follicle-stimulating hormone (FSH), which is tightly linked to the menopausal transition, independent of chronological age: 1) more than 12 months before the FMP; 2) within 12 months before and after the FMP; and 3) more than 12 months after the FMP. A risk factor change (slope) that is similar across all 3 segments is consistent with chronological aging, with no impact of the menopausal transition. Differences in rates of risk factor change across the 3 segments, with a steeper slope in segment 2 than in 1 and 3, as observed for FSH (18,19), is consistent with changes driven by ovarian aging, independent of chronological aging.

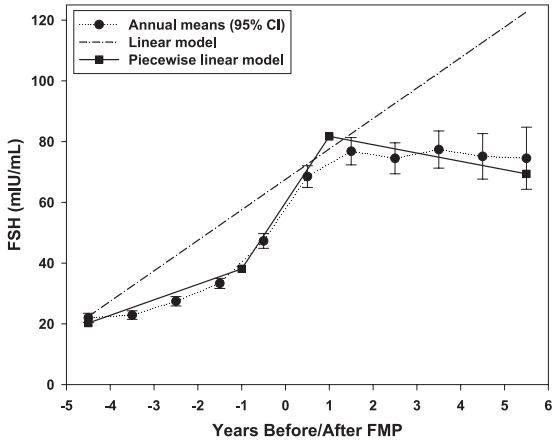

Figure 1 FSH Annual and Estimated Means

Pattern of follicle-stimulating hormone (FSH) across the SWAN (Study of Women's Health Across the Nation) follow-up period showing the annual covariate adjusted mean values compared with estimated values by the better fitting piecewise linear model (menopause related) and the linear model (aging related); relative Akaike information criterion fit for piecewise linear versus linear models is 0.6640 (95% confidence interval [CI]: 0.6096 to 0.7184).

To test this statistically, we fit 2 longitudinal models for each risk factor: 1) a linear model that assumes a constant slope across the 3 time periods; and 2) a piecewise linear model that allows the slope to differ across the 3 segments. To demonstrate, Figure 1 shows the annual mean SWAN values of FSH from 5 years before to 5 years after the FMP, as well as the estimates from both the linear and piecewise linear models. The piecewise linear model tracks the annual mean values closely, with a steep positive slope in segment 2 that differs significantly from the slopes in segments 1 and 3. Because the model fit is better for the piecewise linear model than for the linear model, we conclude that changes in FSH are driven by ovarian aging rather than solely by chronological aging.

Separate longitudinal mixed models were estimated for each risk factor as a function of years before/after the FMP, separately for the linear and piecewise linear models (20); this technique accommodates within-subject correlation, unequal numbers of observations per subject, and unequal intervals between measures. Model fit was assessed using the Akaike information criterion (AIC), with the best fit indicated by the lowest AIC (21). Relative fit compared the AIC values of the linear model and the piecewise model (22). Confidence intervals indicate whether the relative fit is statistically different from 1 (i.e., equivalent fit for the 2 models) at $p < 0.05$. For risk factors in which the piecewise linear model provided a better fit than the linear model, the

Table 1 Age-Adjusted Baseline Characteristics of the Analytic Sample With the Final Menstrual Period by Follow-Up 09 Compared With Women Not Yet Post-Menopausal

Characteristic	Baseline Analytic Sample (n = 1,054)	Women Not Yet Post-Menopausal (n = 380)
Ethnicity, %		
African American	29.0	26.6
Caucasian	44.9	46.5
Chinese	10.8	10.7
Hispanic	4.7	0.0
Japanese	11.1	14.2
Age (yrs), mean (95% CI)*†	47.1 (46.9–47.2)	44.3 (44.1–44.6)
Smoking status, %*		
Never	57.3	65.7
Past	23.9	26.1
Current	18.8	8.2
Weight, kg, mean (95% CI)*	72.3 (71.0–73.5)	74.5 (72.3–76.7)
Total dietary intake (kcal), mean (95% CI)	1,827.6 (1,784.9–1,870.3)	1,838.4 (1,763.3–1,913.5)
Percentage of calories from fat, mean (95% CI)	32.7 (32.3–33.2)	31.8 (31.0–32.6)
Any alcohol consumption, %	49.4	47.4
Calories from alcohol, mean (95% CI)‡	42.3 (38.3–46.8)	44.9 (37.6–53.7)
Physical activity, mean (95% CI)		
Sports*	2.6 (2.5–2.7)	2.8 (2.7–2.9)
Leisure/routine	2.4 (2.4–2.5)	2.4 (2.3–2.5)
Household/child care	2.7 (2.6–2.7)	2.7 (2.6–2.8)
Lipid-lowering medication, % (n)	0.9 (9)	0.3 (1)
Antihypertensive medication, % (n)	10.1 (106)	8.5 (32)
Age at final menstrual period (yrs), mean (95% CI)	51.2 (51.0–51.4)	—
Lipids and lipoproteins, mean (95% CI)		
Cholesterol, mg/dl§	191.8 (189.8–193.8)	193.0 (189.4–196.5)
LDL, mg/dl§	113.6 (111.7–115.4)	115.8 (112.6–119.1)
Apo B, mg/dl§	108.1 (106.4–109.9)	110.5 (107.4–113.6)
HDL, mg/dl*§	57.5 (56.6–58.4)	55.4 (53.9–57.0)
Apo A-I, mg/dl§	151.0 (149.5–152.5)	148.0 (145.3–150.7)
Triglycerides, mg/dl§	90.2 (87.5–93.0)	95.1 (90.2–100.3)
Lp(a)	14.6 (13.5–15.9)	15.5 (13.3–17.9)
Glucose and insulin, mean (SE)		
Glucose, mg/dl§	91.6 (91.0–92.3)	92.3 (91.2–93.4)
Insulin, uIU/ml§	8.8 (8.5–9.1)	8.8 (8.3–9.3)
Blood pressure (mm Hg), mean (95% CI)		
Systolic blood pressure§	114.9 (113.9–116.0)	114.2 (112.4–116.0)
Diastolic blood pressure§	74.1 (73.4–74.8)	73.7 (72.5–74.8)
Hemostatic factors, mean (95% CI)		
t-PA-ag, ng/ml	6.8 (6.6–7.0)	6.9 (6.5–7.2)
PAI-1, ng/ml	19.1 (18.2–20.0)	20.4 (18.7–22.2)
Fibrinogen, mg/ml	283.4 (279.5–287.4)	288.0 (281.0–295.1)
Factor VIIc, %	113.7 (111.9–115.6)	114.0 (110.8–117.3)
hs-CRP, mg/l*	1.4 (1.3–1.5)	1.6 (1.4–1.9)

*p value for between-group differences <0.05, using logistic regression for categorical variables and analysis of covariance for continuous variables. †Not adjusted for age. ‡Drinkers only. §Untreated measurements only.

Apo = apolipoprotein; CI = confidence interval; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); PAI-1 = plasminogen activator inhibitor type 1; t-PA-ag = tissue-type plasminogen activator antigen.

slopes in the 3 segments based on time intervals surrounding the FMP were compared.

Models adjusted for age at the FMP; ethnicity; site; baseline height; baseline log weight and change in log weight; concurrent smoking (never, past, current); concurrent relevant medication use (antihypertensive use for analyses of blood pressure and pulse pressure, insulin use for analyses of glucose and insulin, lipid-lowering medications for analyses of lipids and lipoproteins); total calories, percentage of calories from fat, and calories from alcohol; and physical activity from routine activities, sports/leisure, and household/child care from the most recent measurement. With the exception of smoking, which was used as a time-invariant covariate because of its stability (baseline smoking), all other annually measured variables were used as time-varying covariates.

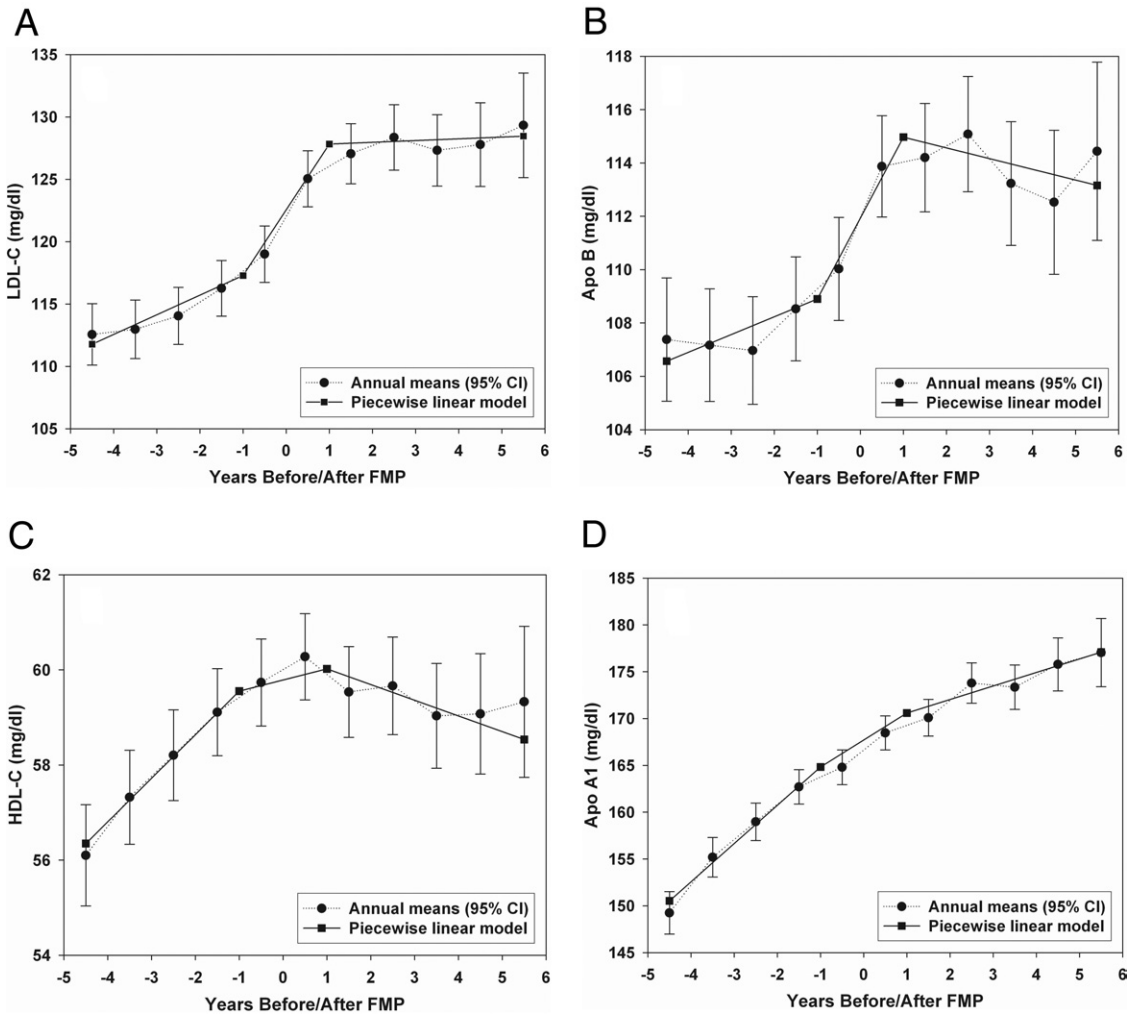

Figure 2 **Lipids Annual and Estimated Means**

Pattern of low-density lipoprotein cholesterol (LDL-C) **(A)**, apolipoprotein (Apo) B **(B)**, high-density lipoprotein cholesterol (HDL-C) **(C)**, and Apo A-I **(D)** across the SWAN study follow-up period showing the annual covariate adjusted mean values compared with estimated values by the better fitting piecewise linear model (menopause related); relative Akaike information criterion fit for the piecewise linear versus linear models, 1.0430 (95% CI: 1.0130 to 1.0730), 1.0340 (95% CI: 1.0092 to 1.0588), 1.0486 (95% CI: 1.0203 to 1.0769), and 1.0255 (95% CI: 1.0036 to 1.0474), respectively. Abbreviations as in Figure 1.

Right-skewed outcomes were log-transformed for analyses and back-transformed for presentation. Analyses excluded observations concurrent with HT use or a 6-month HT washout period; note that in the analytic sample, any of these deleted observations would have occurred only after a woman's FMP because women who used HT or had a hysterectomy/bilateral oophorectomy before the FMP were not included in the analytic sample. The total number of observations available for analysis ranged from 4,507 (LDL-C) to 5,739 (blood pressure). The figures presented in the following are truncated at −5 and +6 years around the FMP because of the smaller number of observations at the extremes and the larger SEs. We tested whether risk factor changes with respect to the FMP varied significantly by ethnicity, after first estimating ethnic-specific models to confirm that the same functional form for the model—linear or piecewise linear—was appropriate for each ethnic group. These analyses were conducted in the full sample and repeated in the largest ethnic groups only (African Americans and Caucasians). Power to detect interactions by ethnicity showed that an annual difference of 0.08 SD in LDL-C could be detected between the smallest groups (Hispanics and Japanese) and 0.03 SD between the largest ethnic groups. We also tested for interactions between baseline weight and status for those cardiovascular risk factors that fit the piecewise linear models because in the full SWAN cohort, women who were in the highest tertile of baseline weight did not show an effect of menopausal status on lipids through year 7 (23).

Table 2 Segment-Specific Slopes for Years Before/After the FMP for Cardiovascular Risk Factors Where Piecewise Linear Trajectory Fits Better Than Linear Trajectory (Relative Fit >1)

Outcome, mg/dl (No. of Observations/ No. of Women)	Segment-Specific Slope (SE)			p Value for Pairwise Difference in Segment-Specific Slopes			Overall p Value for Differences in Segment-Specific Slopes
	Segment 1: >12 Months Before FMP	Segment 2: Within 12 Months of FMP	Segment 3: >12 Months After FMP	Segment 1 vs. 2	Segment 1 vs. 3	Segment 2 vs. 3	
Total cholesterol (4,725/1,022)	2.98 (0.37)	6.47 (0.62)	−0.16 (0.36)	<0.0001	<0.0001	<0.0001	<0.0001
LDL-C (4,507/1,012)	1.57 (0.32)	5.20 (0.55)	0.14 (0.32)	<0.0001	0.0007	<0.0001	<0.0001
Apo B (4,709/1,021)	0.67 (0.28)	3.24 (0.45)	−0.40 (0.25)	<0.0001	0.0025	<0.0001	<0.0001
HDL-C (4,724/1,022)	0.92 (0.13)	0.40 (0.21)	−0.33 (0.12)	0.0823	<0.0001	0.0142	<0.0001
Apo A-I (4,709/1,021)	4.09 (0.32)	2.16 (0.54)	1.44 (0.29)	0.0102	<0.0001	0.3398	<0.0001

Apo = apolipoprotein; FMP = final menstrual period; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Results

Baseline characteristics of women who had an FMP. The 1,054 women who had an observed FMP were approximately 47 years of age at baseline and on average had their FMP approximately 3 years after study entry (Table 1). The proportion of ethnic groups with an FMP was generally consistent with proportions recruited in those groups at baseline, with the largest proportion being Caucasian, followed by African American and the remaining ethnic groups. Relative to 380 women who still had not reached their FMP after visit 9, women in the analytic sample at baseline were older, leaner, and more often current smokers and reported lower sports-related physical activity; they also had higher HDL-C and lower CRP levels. No other differences in age-adjusted risk factors were observed.

Changes in cardiovascular risk factors in relation to the FMP. LIPIDS AND LIPOPROTEINS. The mean adjusted changes across time in total cholesterol, LDL-C, apolipoprotein (Apo) B, HDL-C, and Apo A-I were fit better by the piecewise linear model than by the linear model (Fig. 2). The increases in total cholesterol, LDL-C, and Apo B were substantial around the FMP and were significantly greater than the increases in total cholesterol, LDL-C, and Apo B before and after the FMP interval (Table 2). The greatest increase in HDL-C and Apo A-I levels occurred before the 1-year interval surrounding the FMP and then leveled off or declined. The absence of interactions between ethnicity and the slopes generated from the piecewise linear model indicated that all ethnic groups changed in a similar manner around the FMP; tests only in African-American and Caucasian women also showed no significant interaction effects. A linear model fit log-transformed triglycerides across time, consistent with the effects of chronological aging rather than ovarian aging.

Effect modification by baseline weight was statistically significant for total cholesterol and LDL-C and Apo B, largely due to a flattening of lipids in heavier women after the FMP. The steep upward incline around the FMP occurred in all 3 weight tertiles (Fig. 3).

GLUCOSE, INSULIN, BLOOD PRESSURE, LP(A), AND HEMOSTATIC FACTORS. Linear models provided a better fit than did piecewise models for the changes across time in glucose, t-PA-ag, PAI-1, and fibrinogen, relative AIC fits <1. Linear and piecewise models were of equivalent fit for systolic and diastolic blood pressure, Lp(a), insulin, factor VIIc, and CRP trajectories, relative AIC fits included 1. Examination of the percentage of annual change showed that the following increased: triglycerides (1.75%), Lp(a) (2.48%), insulin (2.84%), and factor VIIc (1.40%); systolic blood pressure increased on average 0.26 mm Hg annually. Glucose (−2.21%) and PAI-1 (−6.75%) decreased. Diastolic blood pressure, t-PA-ag, fibrinogen, and CRP did not change across time.

Discussion

The aims of the study were to evaluate the change in CHD risk factors in relation to the FMP, independent of age and other confounders, among women who experienced a natural menopause and to examine the extent of ethnic differences in those patterns. The results showed significant increases in total cholesterol, LDL-C, and Apo B within a year of the FMP, relative to the observed increase over time intervals before or after. These FMP-related increases were similar in women classified into tertiles by baseline weight. Importantly, the rate of change relative to FMP did not vary by ethnicity, suggesting that menopause had a uniform influence on lipids. The influence of the interval surrounding the FMP on total cholesterol, LDL-C, and Apo B was independent of age as well as the many covariates that vary by ethnicity, including weight, weight gain, and medications. The present analysis is the first to document the effects of the natural menopausal transition anchored prospectively by the FMP with sufficient follow-up, annual assessment of risk factors, accurate and detailed timing of

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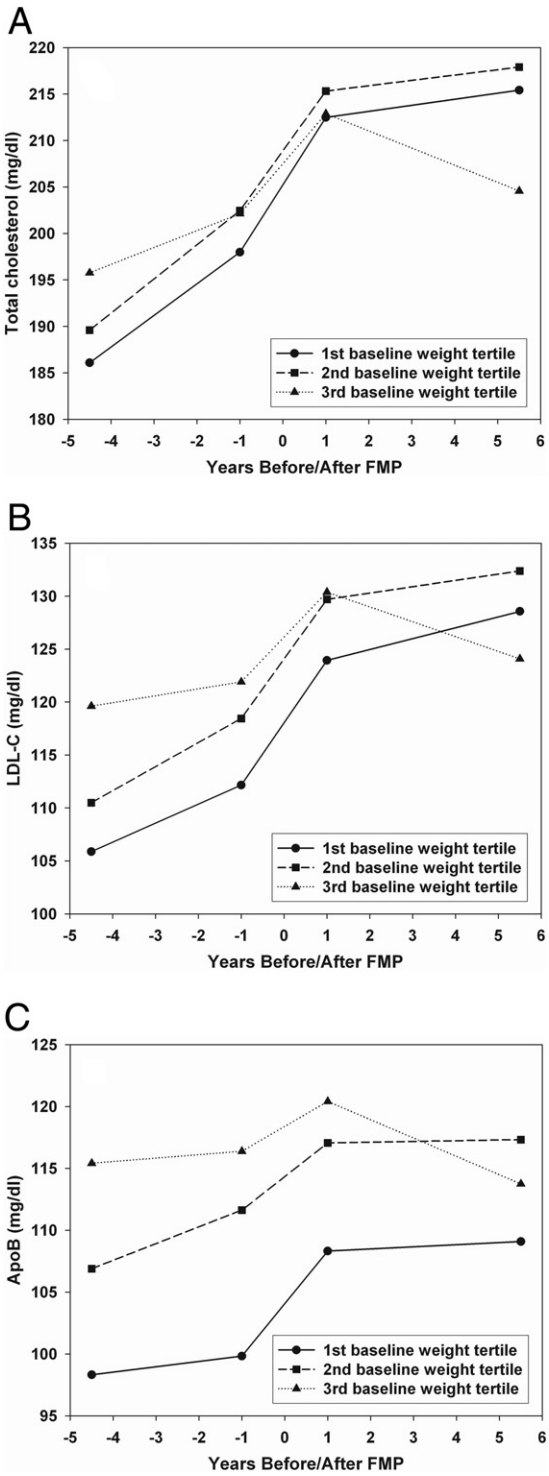

Figure 3 Lipid Annual Means According to Baseline Weight

Pattern of total cholesterol **(A)**, LDL-C **(B)**, and Apo B **(C)** across the SWAN study follow-up period showing the annual covariate adjusted mean values in women categorized by baseline weight tertiles. Slopes around the FMP interval were identical in the 3 groups for total cholesterol, LDL-C, and Apo B (p values >0.28, respectively), whereas slopes more than 1 year after the FMP differed (p values <0.01, respectively). FMP = final menstrual period; other abbreviations as in Figure 2.

menopause, and extensive covariate adjustment. It is also the first to report the absence of detectable ethnic differences in the influence of menopause on lipids and lipoproteins. These findings are consistent with the hypothesis that the increase in CHD in post-menopausal women may in part be related to the earlier changes in lipids associated with the menopausal transition. The analyses showed no influence of the FMP on blood pressure, insulin, glucose, Lp(a), and hemostatic and inflammatory factors. These null menopause results are consistent with other SWAN analyses of the relationship between reproductive hormones and changes in risk factors and with earlier reports of changes in menopause based on bleeding patterns (6–10,24). Taking these findings together, it is unlikely that the increase in CHD risk in the post-menopausal years is due to menopause-induced increases in these factors.

Like SWAN, the Melbourne Midlife Women's Health Project reported that HDL-C increased steadily until the FMP, peaked at the FMP, and declined thereafter, resulting in little net change in HDL-C across the transition (25,26). Thus, the acute increase in HDL-C before the FMP is unlikely to be protective for women. In contrast to HDL-C, log-transformed triglycerides increased in a linear fashion across the study period, perhaps because HDL-C and log-transformed triglycerides had different associations with log weight gain over time in our sample ($r = -0.06$, and $r = 0.20$, respectively). Changes in HDL and very low density particle concentration with aging may also play a role (27).

Study limitations. Results are based on women who had a natural FMP by 9 years. These women, as in other studies (23,28–32), were smokers and leaner. The bias that this may introduce is not clear, given that smoking status, weight, change in weight, medications, and many other relevant covariates were adjusted for at each year before and after the FMP. Second, the results are based on the subset of women who did not use HT before the FMP or who had not reported undergoing a hysterectomy. Women who take HT or have had a hysterectomy or bilateral oophorectomy are undoubtedly different from women who have had a natural menopause. Third, approximately 25% of women were lost to follow-up. One site that followed Hispanics was closed due to administrative reasons. Finally, financial constraints precluded the assay of stored samples in years 2, 8, and 9. Only blood pressure was measured annually.

Clinical implications. Our findings have potential clinical implications because identification of modifiable risk factors and early intervention may reduce women's increased risk of CHD after menopause. Although an increase in LDL-C and a decrease in HDL-C between pre-menopause and post-menopause have been previously reported in healthy Caucasian women (8), our data specifically identify the critical time period, the year immediately around the FMP, as the time of the most adverse changes in the lipid profile in all ethnic groups. This study underscores the need to closely monitor lipid profiles of pre-menopausal and peri-menopausal women, and the importance of emphasizing

proven lifestyle measures and therapeutic interventions before the menopause transition to counter and possibly prevent this adverse change in lipids associated with menopause itself. Although absolute levels of LDL-C were within what is considered the normal range, even lipids in the normal range during the pre-menopausal and perimenopausal transition predict later coronary calcification and carotid intima media thickness (33–35). Whether the threshold levels for lipid-lowering therapy should change around the time of menopause or whether the absolute or relative degree of change in lipids (independent of premenopausal levels) predicts future CHD events merits further study. The menopause-associated changes in total cholesterol, LDL-C, and Apo B observed here may play an important role in women's increased risk of CHD in the post-menopausal years.

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