Progression of Metabolic Syndrome Severity During the Menopausal Transition

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Background—After menopause, women exhibit a higher prevalence of the metabolic syndrome (MetS) and higher risk of cardiovascular disease. However, the timing of changes in MetS severity over the menopausal transition and whether these changes differ by racial/ethnic group remain unclear.

Methods and Results—We assessed data from 1470 women from the Atherosclerosis Risk in Communities cohort who experienced transition in menopausal status over 10 years (visits 1–4). We used linear mixed models to evaluate changes by menopausal status (premenopause, perimenopause, and postmenopause) in a MetS severity Z-score and in the individual MetS components. While there were gradual increases in MetS severity over time across menopause stages, black women in particular exhibited more rapid progression in MetS severity during the premenopausal and perimenopausal periods than during the postmenopausal period. In the postmenopausal period (compared with prior periods), white women exhibited unfavorable decreases in high-density lipoprotein, while black women exhibited favorable alterations in the rate of change for waist circumference, triglycerides, high-density lipoprotein, and glucose, contributing to the slowed progression of MetS severity. These changes were all observed after adjusting for hormone replacement treatment.

Conclusions—During menopausal transition, women exhibited rapid increases in MetS severity during the premenopausal and perimenopausal periods, with black women having significant reductions in this increase in severity during the postmenopausal period. These data suggest that the higher prevalence of MetS in postmenopausal women may be caused more by changes during the menopausal transition than by postmenopause. These findings may thus have implications regarding the timing of cardiovascular risk relative to menopause. (J Am Heart Assoc. 2016;5:e003609 doi: 10.1161/JAHA.116.003609)

Key Words: cardiovascular disease risk factors • menopause • metabolic syndrome • race and ethnicity • type 2 diabetes mellitus

T he transition through menopause has been implicated in a significant increase in risk for cardiovascular disease (CVD) to a point where postmenopausal women have rates of CVD equal to or greater than those seen in men.1,2 Many have hypothesized that this higher CVD risk is related to an increase in the metabolic syndrome (MetS) during the menopausal transition, beyond what is seen from aging alone.3. Cross-sectional studies have demonstrated that compared with premenopausal women, postmenopausal women have significantly more visceral obesity4 and MetS.5 However, it remains unclear whether these processes progress more rapidly during the transition through menopause or during the postmenopausal period.3

Longitudinal studies that followed premenopausal women and compared changes in visceral adiposity between those who did and did not progress through menopause noted significant advances in visceral adiposity6,7 and the prevalence of MetS among those who became postmenopausal during the study period. However, close examination of the data reveals that those who remained premenopausal at follow-up had advances in these measures of similar or greater degree than those who completed menopause.1,6,7 In some cases, the rate of change of components of MetS or insulin sensitivity appeared to be slower after menopausal transition—even among women who did not take hormone replacement.1,7 Janssen et al reported that among 1644 women followed through the menopausal transition, the...
yearly change in triglyceride levels slowed significantly after the final menstrual period, while systolic blood pressure decreased after menopause. Conversely, high-density lipoprotein (HDL) cholesterol levels unfavorably decreased after menopause, while the rate of change in waist circumference did not differ. Finally, among these women, blacks were less likely than whites to develop MetS over the menopausal transition (odds ratio 0.74), though this failed to reach statistical significance. Thus, the overall change in MetS during the menopausal transition, its timing, and any racial/ethnic difference in these changes remain unclear.

We recently developed a MetS severity score that is linked to long-term risk of CVD and diabetes. We noted that the rate of increase in MetS severity was significantly higher among middle-aged women than among middle-aged men. The goal of the current project was to assess participants of the Atherosclerosis Risk in Communities (ARIC) study for changes in the rate of progression of MetS severity during the menopausal transition, including whether these rates varied by race/ethnicity. We hypothesized that given the potential for women to have greater visceral fat after menopause (because of insufficient estrogen levels), MetS would worsen more rapidly after menopause compared with before or during perimenopausal years. Such data could clarify the timing of change in a key CVD risk factor among postmenopausal women.

**Methods**

ARIC is a large community-based epidemiological cohort study that started in 1987–1989 across 4 field centers in the United States. Further details regarding study design and objectives are published elsewhere. A total of 5943 white women and 2464 black women were enrolled. The institutional review boards of the following participating institutions approved the study: University of Mississippi Medical Center, Jackson State University, Tougaloo College, University of North Carolina, University of Minnesota, Johns Hopkins University, and University of Florida. All participants provided written informed consent.

Menopausal status among women who reported having had menstrual periods (ie, those without primary amenorrhea) was categorized following the technique of Nabulsi for this cohort. At each visit, women were asked, “Have you had any menstrual periods during the past 2 years?” and “Have you reached menopause?” They were also asked questions related to the surgical removal of ovaries and uterus. Women who had a menstrual period within the previous 2 years but denied current menopause were classified as “premenopausal.” Women who had a menstrual period within the previous 2 years and answered “yes” or “uncertain” to the question regarding current menopause were classified as “perimenopausal.” Women who had not had a menstrual period within the previous 2 years and did not have surgical removal of ovaries or uterus were classified as natural “postmenopausal.” Our analysis data set included only those women 60 years and younger at baseline with fasting laboratory values, baseline menopause information, and no history of coronary heart disease or diabetes at baseline (see Figure S1). Because we were interested specifically in changes in MetS severity during the menopausal transition, we restricted our primary analysis to women who progressed in their menopausal stage over the course of the 4 visits, either from premenopausal to perimenopausal, premenopausal to postmenopausal, or perimenopausal to postmenopausal. As an overall comparison of the rate of change in MetS severity, we also assessed for MetS changes in women who were postmenopausal at baseline. The minimum entry age for ARIC (45 years) precluded our ability to assess women who remained premenopausal through all 4 visits.

Women were asked regarding use of current hormonal replacement therapy (regardless of route of administration) at each visit; these data were categorized as estrogen, estrogen plus progesterone, or none in assessing the relationship between current hormone replacement therapy as related to the change in MetS severity. We did not find significant differences in the change in MetS over time between estrogen and estrogen plus progesterone and thus grouped these together in the final analysis to maximize power.

MetS severity Z scores were calculated for participants at all 4 visits by using sex- and race-based formulas. As described elsewhere, these scores were derived by using a confirmatory factor analysis approach for the 5 traditional MetS components (waist circumference, triglycerides, HDL cholesterol, systolic blood pressure, fasting glucose) to determine the weighted contribution of each of these components to a latent MetS “factor” on a sex- and race/ethnicity-specific basis. Confirmatory factor analysis was performed among adults aged 20 to 64 years from the National Health and Nutrition Examination Survey (NHANES) with categorization into 6 subgroups based on sex and the following self-identified race/ethnicities: non-Hispanic white, non-Hispanic black, and Hispanic. For each of these 6 population subgroups, loading coefficients for the 5 MetS components were determined toward a single MetS factor. These loading coefficients were used to generate equations to calculate a standardized MetS severity score for each subgroup (http://mets.health-outcomes-policy.ufl.edu/calculator/). The resulting MetS severity scores are Z scores (normally distributed and ranging from theoretical negative infinity to theoretical positive infinity with mean=0 and SD=1) of relative MetS severity on a sex- and race/ethnicity-specific basis. These scores are highly correlated to other surrogate markers of MetS risk, including high-sensitivity C-reactive
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protein, uric acid, the Homeostasis Model of Insulin Resistance, and adiponectin, and type 2 diabetes mellitus (T2DM) risk in the Princeton Lipid Research Cohort Study. These scores were also examined descriptively over time in ARIC. All statistical analyses were performed by using SAS Version 9.4, and statistical significance was set to \( \alpha = 0.05 \). Descriptive statistics were calculated at baseline and across the 4 visits of the study. The primary outcome was MetS severity as measured by the Z-score described earlier. The traditional MetS components (waist circumference, HDL, triglycerides, fasting glucose, systolic blood pressure) that compose the Z-score were also examined individually. Linear mixed models were used to model MetS Z-score over time (as a function of years postbaseline) among women who progressed in their menopausal stage at some level during ARIC, including a random intercept and random slope to effectively account for the correlation among observations from each participant. Our focus on only women who had \( \geq 1 \) menopausal transition during the study naturally limited our analysis to primarily women who remained in the study. Nonetheless, missing MetS scores at follow-up visits was possible, and the mixed-model approach allows for this missingness assuming a random missing mechanism. A linear spline approach with 2 knots was used among the mixed-models to account for the correlation in MetS scores across visits. The increase in MetS severity that would represent a decrease in the rate of MetS progression from the perimenopausal period relative to earlier periods. For white women, there was a decrease in the rate of MetS progression from the perimenopausal period to the postmenopausal period (from 0.076 to 0.062), but this failed to reach statistical significance (\( P = 0.106 \)). Compared with white women, black women had a slower progression of MetS Z-scores during the postmenopausal period relative to earlier periods. For white women, there was a decrease in the rate of MetS progression from the perimenopausal period to the postmenopausal period (from 0.076 to 0.062), but this failed to reach statistical significance (\( P = 0.106 \)). Compared with white women, black women had a
### Table 1. Baseline Descriptive Characteristics of the Women Who Observed Menopausal Transition During the Follow-up Period

|                                | Whites   | Blacks   | P Value* |
|--------------------------------|----------|----------|----------|
|                                | (n=1216) | (n=285)  |          |
| **Baseline menopausal status** |          |          | 0.763    |
| Premenopausal, n (%)           | 822 (67.6) | 190 (66.7) |          |
| Perimenopausal, n (%)          | 394 (32.4) | 95 (33.3)  |          |
| **Metabolic syndrome components** |          |          |          |
| Waist circumference, cm, mean (SD) | 90.3 (14.3) | 99.4 (17.6) | <0.001  |
| Triglycerides, mg/dL, mean (SD) | 102.2 (54.1) | 91.7 (44.4) | <0.001  |
| High-density lipoprotein, mg/dL, mean (SD) | 57.8 (15.6) | 58.3 (17.5) | 0.609   |
| Systolic blood pressure, mm Hg, mean (SD) | 112.5 (16.0) | 122.7 (19.2) | <0.001  |
| Glucose, mg/dL, mean (SD)      | 95.6 (8.4)  | 98.1 (9.8)  | <0.001  |
| **Metabolic syndrome Z-score, mean (SD)** | 0.3 (0.7)  | 0.1 (0.8)  | <0.001  |
| Age, y, mean (SD)              | 49.3 (3.2)  | 48.7 (3.0)  | 0.014   |
| Hormonal use, n (%)            | 163 (13.9)  | 18 (6.4)   | 0.001   |
| Current smoking, n (%)         | 247 (20.3)  | 63 (22.1)  | 0.501   |
| Income status, n (%)           |          |          | <0.001  |
| <$25 000                       | 200 (17.2)  | 169 (64.5) |          |
| $25 000 to <$50 000            | 520 (44.8)  | 68 (26.0)  |          |
| >$50 000                       | 441 (38.0)  | 25 (9.5)   |          |
| **Education, n (%)**           |          |          | <0.001  |
| Basic or no education          | 112 (9.2)   | 74 (26.0)  |          |
| Intermediate education         | 600 (49.4)  | 91 (31.9)  |          |
| Advanced education             | 503 (41.4)  | 120 (42.1) |          |
| Hypertension, n (%)            | 190 (15.7)  | 127 (44.7) | <0.001  |
| **Transition category during study, n (%)** |          |          | 0.0059  |
| Premenopausal to perimenopausal | 191 (15.7)  | 39 (13.7)  |          |
| Perimenopausal to postmenopausal | 394 (32.4) | 95 (33.3)  |          |
| Premenopausal to postmenopausal | 283 (23.3) | 91 (31.9)  |          |
| Premenopausal to perimenopausal to postmenopausal | 348 (28.6) | 60 (21.1)  |          |

* t test for continuous variables; χ² test for categorical variables.
† Basic education was defined as 0 years of education, grade school or high school but no degree; Intermediate education was defined as high school graduate or vocational school; Advanced education was defined as college or graduate/professional school.

### Table 2. Mixed-Model Parameter Estimates: MetS Z-Score Over Time

| Model Parameter          | Estimate | 95% CI       | P Value |
|--------------------------|----------|--------------|---------|
| Intercept                | -1.668   | -2.268 to -1.068 | <0.001  |
| Baseline age, y          | 0.029    | 0.017 to 0.041 | <0.001  |
| Black                    | 0.424    | 0.324 to 0.524 | <0.001  |
| Linear slope for whites  |          |              |         |
| Premenopausal            | 0.065    | 0.058 to 0.072 | <0.001  |
| Perimenopausal           | 0.072    | 0.065 to 0.080 | <0.001  |
| Postmenopausal           | 0.051†   | 0.042 to 0.060 | <0.001  |
| Linear slope for blacks  |          |              |         |
| Premenopausal            | 0.107    | 0.092 to 0.121 | <0.001  |
| Perimenopausal           | 0.090    | 0.073 to 0.108 | <0.001  |
| Postmenopausal           | 0.037†   | 0.017 to 0.056 | 0.365   |

Blacks vs Whites slope comparisons (P-values): premenopausal: P=0.001; perimenopausal: P=0.072; postmenopausal: P=0.182.
*Significantly (P<0.05) different than premenopausal slope.
†Significantly (P<0.05) different than perimenopausal slope.

A higher increase in MetS severity during the premenopausal and perimenopausal periods (P<0.001 and P=0.036, respectively). As a comparison, women who were postmenopausal at study entry (mean age 54 years) exhibited a rate of change in MetS severity Z-scores of 0.057 (0.052, 0.062) per year for white women and 0.061 (0.053, 0.069) per year for black women (Tables S1 and S2), while women who remained premenopausal throughout the study (mean age 45 years) had a rate of change of 0.057 (0.039, 0.074) for white women and 0.115 (0.080, 0.150) for black women (Table S3). Use of estrogen replacement therapy was not associated with slope in MetS severity during any of the menopausal stages. A sensitivity analysis that excluded women who had menopause because of surgical removal of ovaries resulted in similar results.

Figure 2 shows model-based mean levels and average change in the individual components of MetS from models that included age, socioeconomic variables, and hormone use. Among white women, the rate of change was slower during the postmenopausal period (compared with both premenopausal and perimenopausal periods for triglycerides and glucose; P<0.05, P<0.01). Among black women, there were significant decreases in the rates of change during the postmenopausal period (versus the premenopausal and perimenopausal period) for waist circumference (P<0.001) and glucose (P<0.001), while the rate of change of triglycerides (P<0.05) was slower for the postmenopausal period compared with the premenopausal period (P<0.05), and the rate of change for systolic blood pressure (P<0.05) was greater during the
The proportion of participants taking estrogen replacement therapy after menopause were high in this study, with higher use among white (13.8%) versus black (6.6%) women, raising potential that this discrepancy in hormone replacement could account for the racial differences in MetS progression among postmenopausal women in the study. Oral (but not transdermal or vaginal) administration of estrogen suppresses fat oxidation, contributing to increased body fat while.
administration of transdermal estrogen did not change levels of body fat over time.\textsuperscript{21–23} While we lacked data regarding the route of estrogen administration during the study, visit 4 of ARIC completed in 1998, at which point >75\% of estrogen replacement was oral.\textsuperscript{24} Topical or vaginal estrogen replacement, as is more common currently, was found to improve lean body mass without affecting fat mass.\textsuperscript{21–23} We did not note differences in the rate of change in MetS severity by current estrogen use—although we lacked data regarding dose and adherence to estrogen use, which may have further influenced any effect. Overall, however, hormone replacement did not appear to explain the racial differences in MetS severity.

The mechanisms behind the slower rate progression of MetS severity after menopause are unclear but could be related to changes in estrogen levels and related action of adipocytes and hepatic function.\textsuperscript{3,25,26} Tepper et al demonstrated that while there is an overall decline in estradiol levels between 6 years before and 1 year after the final menstrual period (when estradiol levels stabilize), the pattern of this decline is variable. In 60\% of white and 25\% of black women, there is an initial rise in estradiol to 50\% above baseline.\textsuperscript{27} While we lacked estradiol levels among the women in ARIC, the duration of these fluctuations in estradiol before stabilization coincides temporally with the time frame of more rapid MetS changes during the menopausal transition. As mentioned previously, oral estradiol decreases fatty acid oxidation.\textsuperscript{23} Nevertheless, it remains unclear why endogenous increases and then decreases in estradiol would be involved in a rise in triglycerides and/or other MetS components.

Many of the changes in MetS during the menopausal transition have previously been attributed to the effect of decreasing levels of estradiol on the transition between gynecoid and android body habitus. Women exhibit a tendency toward visceral fat accumulation during the menopausal transition, though it is difficult to separate the influence of menopause from the natural tendency toward fat accumulation with age.\textsuperscript{6,28} Certainly, mice that are deficient in estradiol (because of a genetic deletion of the gene for aromatase) exhibit an increase in visceral fat and resultant insulin resistance compared with their wild-type counterparts.\textsuperscript{29} Contrary to our hypothesis, we found that the rate of change in waist circumference was not significantly different during the stages of the menopausal transition among white women, while black women in the sample exhibited a slower rate of change in waist circumference after menopause. These findings are consistent with data from prior clinical studies.\textsuperscript{1,30} Sowers et al noted an increase in waist circumference the year after the final menstrual period followed by a stabilization (or even decrease) in waist circumference.\textsuperscript{30} Janssen et al noted steady increases in waist circumference over a period including 6 years before and 6 years after menopause.\textsuperscript{1} Thus, the effect of decreased estrogen on visceral fat mass may be less significant than the overall tendency toward weight gain by age.
Figure 2. Model-generated MetS components over time and rate of change by menopausal status. Mean and 95% confidence intervals are shown for white (light grey) and black (dark grey) participants who exhibited menopausal transition over the 4 visits of ARIC. All models included age, education, family income and hormone use. Significance between race: *P<0.05; **P<0.01; ***P<0.001. For significance in differences in rate of change between menopausal period within races, see text.
This study had several limitations. We relied on a composite assessment of menopause, in which perimenopausal women were classified on the basis of having had a menstrual period in the 2 years before study visit but answered “yes” or “uncertain” regarding whether they had undergone menopause, while postmenopause was classified only among women who had not had a menstrual period for 2 years. Because menopause is most commonly categorized after 1 year without menses, the “perimenopausal” group included some women who had experienced menopause (as it is usually characterized) up to 1 year earlier. Nevertheless, we did not believe that this classification detracted significantly from our assessment because this study focused on changes observed during the years surrounding the menopausal transition. Indeed, the heterogeneous nature of women in the perimenopausal group could have been expected to bias the study toward a higher degree of variability and less likely to identify the changes that we observed. In addition, our findings of a slower rate of progression of MetS postmenopause remained true, even ignoring the perimenopausal classification and only comparing directly to the premenopausal group. Owing to the age of women at study entry and length of follow-up, we lacked a group of women who were not in the age range for being near the timing of menopause, though the women in the study who remained premenopausal had similar rates to the perimenopausal women. While the mixed models we used allowed for missing data, it is possible that dropout was nonignorable, as women who remained in the study may have been healthier than those who dropped out. However, the relatively low rates of dropout given the nature of the primary sample most likely does not bias the slope comparisons between whites and blacks. This study had significant strengths in following a large cohort longitudinally and assessing novel markers of MetS severity.

In conclusion, we found that the progression of MetS is rapid during the course of the menopausal transition but slows afterward among black women. This appears to be unrelated to hormone replacement and may have bearing on the higher prevalence of MetS among postmenopausal women and related cardiovascular and diabetes risk. Further research is needed to determine whether interventions during the menopausal transition such as diet, exercise, and insulin-sensitizing medication could slow this rate of progression of MetS severity and lower risk of future disease.

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Disclosures
None.

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Table S1. Descriptive characteristics of women who did not transition (pre-menopausal throughout the study, or post-menopausal at baseline)

| Metabolic Syndrome Components | Pre-Menopausal Women | Post-Menopausal Women | p-value* |
|------------------------------|----------------------|-----------------------|----------|
|                              | Whites (n = 168)     | African-Americans (n = 72) |          |
| Waist Circumference cm, mean(SD) | 89.2 (15.1) | 99.5 (18.4) | < 0.001 |
| Triglycerides mg/dl, mean(SD) | 105.0 (54.7) | 95.0 (42.5) | 0.008 |
| HDL mg/dl, mean(SD) | 58.8 (16.9) | 57.2 (14.4) | 0.500 |
| Systolic BP mmHg, mean(SD) | 114.7 (16.9) | 128.2 (25.5) | < 0.001 |
| Glucose mg/dl, mean(SD) | 95.4 (8.3) | 96.2 (10.5) | < 0.001 |
| Metabolic Syndrome z-score, mean | -0.3 (0.8) | 0.1 (0.8) | 0.002 |
| Age years, mean(SD) | 47.6 (3.4) | 47.4 (2.1) | 0.500 |
| Hormonal Use, n (%) | 26 (15.9%) | 0 (0%) | < 0.001 |
| Current Smoking, n (%) | 40 (23.8%) | 22 (30.6%) | 0.274 |
| Income Status, n (%) |          |          | < 0.001 |
| < $25,000 | 17 (10.8%) | 48 (72.7%) | < 0.001 |
| $25,000 - < $50,000 | 66 (41.8%) | 11 (16.7%) | 594 (31.0%) | 467 (74.5%) |
| > $50,000 | 75 (47.5%) | 7 (10.6%) | 806 (42.0%) | 124 (19.8%) |
| Education, n (%)** |          |          | < 0.001 |
| Basic or no education | 4 (2.4%) | 23 (32.4%) | 349 (17.4%) | 269 (38.1%) |
| Intermediate education | 85 (50.9%) | 24 (33.8%) | 1052 (52.4%) | 203 (28.8%) |
| Advanced education | 78 (46.7%) | 24 (33.8%) | 607 (30.2%) | 234 (33.1%) |
| Hypertension, n (%) | 23 (13.7%) | 20 (27.8%) | 475 (23.7%) | 383 (54.6%) |

* t-test for continuous variables; chi-square test for categorical variables.

**Basic education was defined as 0 years of education, grade school or high school but no degree; Intermediate education was defined as high school graduate or vocational school; Advanced education was defined as college or graduate/professional school.

Abbreviations: BP, blood pressure; SD standard deviation.
Table S2: Mixed Model Parameter Estimates: MetS Z-score Over Time (Post-Menopausal Women Only)

Adjusted for Hormone Use and other SES Variables

| Model Parameter                                      | Estimate  | 95% Confidence Interval | p-value |
|------------------------------------------------------|-----------|-------------------------|---------|
| Intercept                                            | -0.941    | (-1.376, -0.505)        | < 0.001 |
| Baseline Age (Years)                                 | 0.014     | (0.006, 0.022)          | < 0.001 |
| African American                                     | 0.196     | (0.119, 0.273)          | < 0.001 |
| Baseline Education (vs. Advanced Education)          |           |                         |         |
| Basic or No Education                                | 0.262     | (0.173, 0.350)          | < 0.001 |
| Intermediate Education                               | 0.089     | (0.019, 0.159)          | 0.013   |
| Baseline Annual Income (vs. > $50,000)               |           |                         |         |
| < $25,000                                            | 0.138     | (0.050, 0.227)          | 0.002   |
| $25,000 - $50,000                                    | 0.076     | (-0.004, 0.156)         | 0.063   |
| Hormone Use                                          | -0.103    | (-0.148, -0.058)        | < 0.001 |
| Hormone Use Change in Slope                          | -0.006    | (-0.013, 0.001)         | 0.114   |
| Linear Slope for Whites:                             | 0.057     | (0.052, 0.062)          | < 0.001 |
| Linear Slope for African-Americans:                  | 0.061     | (0.053, 0.069)          | < 0.001 |

*African-American vs. Whites Slope Comparison p-value = 0.409*
Table S3: Mixed Model Parameter Estimates: MetS Z-score Over Time (Pre-Menopausal Women Only (n = 240))

Adjusted for SES Variables

| Model Parameter                                      | Estimate | 95% Confidence Interval | p-value |
|-------------------------------------------------------|----------|--------------------------|---------|
| Intercept                                             | -1.096   | (-2.705, 0.514)          | 0.502   |
| Baseline Age (Years)                                  | 0.011    | (-0.022, 0.045)          | 0.502   |
| African American                                      | 0.232    | (-0.060, 0.524)          | 0.119   |
| Baseline Education (vs. Advanced Education)           |          |                          |         |
| Basic or No Education                                 | 0.455    | (0.071, 0.839)           | 0.020   |
| Intermediate Education                                | 0.332    | (0.117, 0.547)           | 0.003   |
| Baseline Annual Income (vs. > $50,000)                |          |                          |         |
| < $25,000                                             | 0.171    | (-0.147, 0.489)          | 0.290   |
| $25,000 - $50,000                                     | 0.160    | (-0.077, 0.397)          | 0.184   |
| Linear Slope for Whites:                              | 0.057    | (0.039, 0.074)           | < 0.001 |
| Linear Slope for African-Americans:                   | 0.115    | (0.080, 0.150)           | < 0.001 |

*African-American vs. Whites Slope Comparison p-value = 0.004*
Recruited: N = 15,792

Consented: 15,391

White & African American women: N = 8,407

Men, non-white, non-African American women: N = 6,984

Not consented/enrolled: N = 401

Menopausal data at baseline and disease-free: N = 4,529

At baseline: no menopausal data N = 1,069; CHD N = 185; diabetes N = 999; under age 50 years N = 1,770

Remained:
pre-menopausal: N = 240; peri-menopausal N = 70; post-menopausal N = 2,716

Experienced menopausal transition: N = 1,501
Figure S1: Consort diagram of analytic data set. Abbreviation: CHD = coronary heart disease.