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Consistent Ovulation May Not Be Enough to Make You Healthy when Approaching Menopause: An Update from the Study of Women's Health Across the Nation (SWAN)

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Abstract

Objective—Test the hypothesis that consistently ovulatory pre/perimenopausal women have a more favorable cardiometabolic profile than anovulatory women.

Methods—The first four collections from the Study of Women's Health Across the Nation (SWAN) Daily Hormone Study (DHS) were used. DHS enrollees annually completed a daily collection of first morning voided urine for an entire menstrual cycle or up to 50 days (whichever comes first). Consistent ovulation (COA) was defined as four ovulatory cycles, or 2–3 ovulatory cycles followed by the Final Menstrual Period [FMP]). A woman was categorized as not consistently ovulatory annually (nCOA) if at least 1 anovulatory year was observed. Cross sectional and longitudinal differences were compared between COA and nCOA women. Data were centered at FMP, and adjusted for age and BMI.

Results—636 DHS participants (mean age 47.3 years $\pm$ 2.5; mean body mass index (BMI) 27.4 $\pm$ 7.1), were included. 36% were COA. At the fourth follow-up collection, COA women had lower high density lipoprotein than nCOA women [55.7mg/dL (54.0, 57.4) vs. 59.5mg/dL (57.9, 61.0), $p=0.002$, respectively] which persisted after adjustment. Among 460 women with FMP, 39% were COA. COA women were slightly older (52.9 years vs. 52.0 $p=0.002$) and of lower BMI

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(Geometric Mean: 26.1kg/m² vs. 27.5, p=0.06) than nCOA women at FMP. Other cardiometabolic factors did not significantly differ by COA status through FMP.

Conclusions—Consistent ovulation across the menopausal transition does not appear to reflect superior cardiometabolic health.

Keywords

SWAN; DHS; menopause; HDL; consistent ovulation

INTRODUCTION

The final menstrual period (FMP), a woman's entry into menopause, is defined after 1 year of amenorrhea; the period of time leading up to menopause, perimenopause, varies widely between women. Perimenopause typically lasts 4–8 years and can be characterized by variable cycle length or occasional skipped cycles in its early stage. Two or more skipped cycles (i.e. 60 days of amenorrhea) define the late stage¹. As menses become irregular, they also are more likely to be anovulatory. The progression of menstrual cycle types (regular to irregular) as women transition to menopause denotes a shift in ovarian activity to anovulatory cycles and then to eventual hypogonadism². Luteal phase production of progesterone likewise decreases over time³. The characteristics of reproductively aged women with respect to menstrual cycle irregularity are partially documented in the literature^{4, 5}. Some evidence suggests that persistent anovulation, reflective of poor ovarian function, is associated with inferior cardiometabolic health and thus poorer systemic health.

The Women's Ischemia Syndrome Evaluation (WISE) study⁶ demonstrated that women with irregular and infrequent menstrual periods have a greater prevalence of angiographically-proven coronary artery disease; however as WISE participants were a special pre-selected population with chest discomfort referred for angiographic testing, they differ from the general population. Others have shown that women who undergo early menopause have a worse cardiometabolic profile⁷ and are more likely to die at a younger age from heart disease⁸. Taken together, these data imply that consistent estrogen exposure in during final reproductive years is cardioprotective. Whether menstrual irregularity or lower overall estrogen exposure per cycle are associated with adverse cardiometabolic indicators have not been addressed definitively. Neither has it been addressed, to our knowledge, whether there is an effect of menstrual irregularity on cardiometabolic risk factors of previously normally cycling women who become irregular when approaching menopause. In a recent cross sectional study of 951 middle aged women, diminished ovarian reserve, as measured by antimüllerian hormone (AMH) levels, was associated with a worse cardiometabolic profile⁹.

We hypothesized that consistently ovulatory cycles during the menopausal transition would identify women with a more favorable cardiometabolic profile when compared to women observed as anovulatory prior to menopause. To test this hypothesis, we utilized data from the Study of Women's health Across the Nation (SWAN)'s Daily Hormone Study (DHS), which includes a large, multi-ethnic cohort.

METHODS

Study Sample

The DHS is an annual sub study of SWAN that began in the second SWAN follow-up year. SWAN is an ongoing multicenter, multiethnic, longitudinal study of women as they transition from pre- to postmenopause. The SWAN study began in 1994; details about the sampling frame and strategies have been previously published¹⁰. Screening surveys were administered by telephone based on random digit dialing (Los Angeles, Pittsburgh, Newark, NJ) or household lists (Boston, Chicago, Detroit, Oakland). At each site, $\frac{1}{3}$ to $\frac{1}{2}$ of the women were of a pre-specified ethnicity (African American, Chinese, Japanese, or Hispanic); the remainder were non-Hispanic Whites, who were recruited at each site. Eligibility criteria included age 42–52, at least one menstrual period and no hormone therapy within the prior 3 months, no current pregnancy or breast-feeding, intact uterus, and at least one ovary. Written informed consent was obtained from all participants. All appropriate institutional review boards approved the study.

In addition to the core SWAN measurements, which are taken annually, DHS enrollees annually complete a collection of first morning voided urine daily for either an entire menstrual cycle or up to 50 days (whichever comes first). DHS participants did not collect urine samples in years they were taking exogenous hormone therapy. DHS participants completed the study protocol by either having an FMP, or collecting annually through the 10th year. The DHS was stopped at that point in time. Currently, data are available through the 4th annual DHS collection.

Laboratory and Anthropometric Measurements

Chemiluminescent assays were developed to measure urinary luteinizing hormone (LH) and Follicle-stimulating hormone (FSH), as well as metabolites of estradiol [estrone conjugates (E1c)] and progesterone [pregnanediol glucuronide (Pdg)]¹¹. All hormones were normalized for creatinine¹². Cycles were assessed for evidence of luteal activity and the day of luteal transition using previously developed algorithms¹³, and from this ovulatory status was determined for each of up to 4 annual DHS visits.

A woman was categorized as consistently ovulatory annually (COA) if annual collections from the DHS year 1 (abbreviated “H1”) through the fourth year (abbreviated “H4”) prior to menopause were observed as ovulatory, and if menopause occurred no earlier than the 3rd year of the DHS. A woman was categorized as not consistently ovulatory annually (nCOA) if at least 1 anovulatory year was observed.

Menopausal status was determined annually in SWAN based on reports about frequency, regularity of menstrual bleeding and use of hormone therapy as follows: 1) Premenopause: monthly bleeding with no perceived change in cycle interval, 2) Early peri-menopause: monthly bleeding with a perceived change in cycle interval, but at least one menstrual period within the past 3 months, 3) Late peri-menopause: amenorrhea in the previous 3 months but menses in the previous 11 months, 4) Postmenopause: 12 consecutive months of amenorrhea.

The cardiometabolic profile included measurement of High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), the HDL-C/LDL-C ratio, triglycerides, glucose, Homeostasis Model Assessment (HOMA) ¹⁴, C-reactive protein (CRP) and fibrinogen. Lipids, lipoproteins, inflammatory, hemostatic, and metabolic markers were measured as previously published ¹⁵. Cardiometabolic markers were obtained from the annual SWAN main study visit corresponding to each DHS visit as indicated by the data coordinating center; DHS visits (from which we determined ovulatory status) were not simultaneous with the annual visit (during which cardiometabolic markers were measured).

Plasminogen activator inhibitor-1 (PAI-1) was measured with a sandwich procedure using a solid phase monoclonal antibody and an enzyme labeled goat second antiserum for detection (IMUBIND plasma PAI-1 ELISA, American Diagnostica, Greenwich, CT).

Standardized protocols were used to measure blood pressure and waist circumference. Briefly, blood pressure was recorded using a standard mercury sphygmomanometer, with appropriate cuff size determined based on arm circumference, following a 5-min rest, in a flat-footed seated position. Two sequential readings were taken on the right arm, with a 2-min intervening rest; these measures were averaged for each participant. Waist circumference at the umbilicus was measured with participants in nonrestrictive undergarments. Based on National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines for women ¹⁶, the *metabolic syndrome* was defined as the presence of 3 of the following criteria: (1) waist circumference ≥ 88 cm for White and African American participants and ≥ 80 cm for Chinese participants; (2) blood pressure ≥ 130 mm Hg systolic, ≥ 85 mm Hg diastolic, or use of antihypertensive medication; (3) fasting serum glucose ≥ 100 mg/dL (or having ever been classified as diabetic); (4) serum triglycerides ≥ 150 mg/dL or medication for hypertriglyceridemia; and (5) HDL cholesterol < 50 mg/dL or use of medication for low HDL cholesterol.

Population for Analysis

Of the 3302 women enrolled into the SWAN longitudinal cohort, 953 consented to be included in the baseline DHS visit. Across the 4 DHS years used in this analysis, 2737 cycles had sufficient information for classification according to the ovulatory algorithm, this corresponds to 81% of samples. DHS participants were excluded from all analyses if available visits were insufficient to classify a woman as either COA (all annual cycles observed as ovulatory prior to postmenopausal status), or nCOA (at least 1 non-ovulatory cycle observed among H1–H4). More *potentially* COA women were excluded from the analysis because of a missing year of data, as we did not assume that an unobserved year mid-study was ovulatory like the years around it, as other research has demonstrated that status varies from year to year¹⁷. The same pattern of missing data would not have led to the exclusion of a record from the nCOA group. Sub analyses centered at time to menopause included women with FMP date in the database.

Statistical Analysis

Women were compared by COA status. Cross-sectional comparisons at baseline used t-test for continuous, and chi-square for categorical measures. Time to FMP was estimated using

the Kaplan Meier method, and compared between COA/nCOA groups using the log-rank test. Adjusted differences between COA and nCOA groups of time-to-FMP were estimated using Cox proportional hazards model, adjusted for baseline age and BMI.

Cross-sectional comparisons of cardiovascular risks were made between groups at the baseline as well as at the 4th annual visit (or last available prior to menopause). Cross sectional adjusted analyses used logistic or linear regression, with results presented as estimated means (95% CI) or proportions from these models.

For longitudinal comparisons of patterns of continuous cardiometabolic measures (e.g. HDL-C, LDL-C, Triglycerides, etc.), time was centered at FMP and a linear mixed effects regression model was estimated including longitudinal BMI and age as covariates, and adjustment for within-person variability over time. Sensitivity analysis included repeating the longitudinal modeling on a subset of the population reaching FMP earlier in SWAN follow-up. Analyses conducted on the log scale and back transformed for presentation as geometric mean. Statistical analysis was conducted in SAS 9.3 TS, some results presented graphically via GraphPad Prism 6.3.

RESULTS

Based on observations across H1–H4, 636 women were included in this analysis, with 232 (36%) classified as consistently ovulatory, and 404 (64%) not consistently ovulatory. At baseline, the consistently ovulatory women were 2.3 years younger ($p<0.001$) and had a BMI 1.3 kg/m^2 lower ($p=0.02$) than those who were not consistently ovulatory, and differences between ethnic groups were not significant, (Table 1). Consistently ovulatory women were more likely to have education beyond high school and half as likely to report financial strain. Differences by COA status in rates of current smoking and High CES-D score (>16)¹⁸ were not significantly different.

Date of FMP was available during all accessible years of SWAN follow-up for 63% of COA women and 69% of nCOA women. Time to FMP was estimated for each group, with time censored at the last reported menstrual period (LMP) date. If a woman was classified as “post-menopausal” without a FMP date, her time to FMP was censored at the LMP date prior to being categorized as post-menopausal. Time to menopause was longer for consistently ovulatory women, with difference at the median survival time of 4 years (COA median: 7.9, 95%CI: 7.6–8.1 years nCOA: 3.9, 95%CI: 3.5–4.4 years) (Figure 1). Time to FMP was estimated in a cox regression model with covariates: baseline age, BMI, tobacco use. Consistent ovulation remained a significant predictor, with nCOA women more likely to reach FMP at any moment compared to COA women (Hazard Ratio 3.1 (2.5–3.9)).

DHS-H1 and DHS-H4 Cross-sectional comparisons of the cardiometabolic profile differences by COA status were adjusted for current BMI and age. Lower HDL –C levels were observed among consistently ovulatory women both at DHS-baseline and the last available DHS visit prior to menopause. This difference was significant for percentage of women with low HDL-C, with higher rates of low HDL-C observed among the consistently ovulatory women (Table 2).

To adjust for potential differences in this cohort due to proximity to menopause, differences in continuous measures of cardiometabolic health were estimated in a mixed-effects linear regression model, adjusted for time in years centered at menopause (including only women with known FMP), and current BMI and age at each visit.

Among women with an FMP (n=460) on record, 39% (n=180) were COA, 61% (n=280) were nCOA. At the time of FMP, nCOA women were younger by half a year, and had a slightly higher BMI. In a mixed-effects longitudinal model adjusted for age and BMI and time centered at FMP date, nCOA women did not have a metabolic profile that was significantly different from COA women in general; the only two instances where between-group differences were statistically significant are indicated on Figure 2 with an asterisk and p-value.

As the definition of COA and nCOA could not be extended beyond the first 4 years of the DHS (data are not available at this time), all longitudinal models were repeated on a smaller subset that reached menopause no later than 2 years after H4. This limited sample allows us to more directly compare women who are in similar stages of perimenopause by their consistency of ovulation in the years prior to menopause. Among women with an FMP who reached menopause no later than 2 years after H4 (n=247) 12% (n=30) were consistently ovulatory during DHS H1–H4, 88% (n=217) were not. At each time point and for every measure, differences by COA status were not statistically significant (all $p>0.05$). In particular, when compared annually over the course of menopause, HDL geometric means were closer together and confidence intervals slightly wider given the smaller sample size; differences were no longer statistically significant (Figure 3).

DISCUSSION

Our data do not support the hypothesis that persistent anovulation is associated with inferior cardiometabolic health during menopausal transition. Contrary to our hypothesis, inconsistently ovulatory women demonstrated higher HDL cholesterol, believed to be a sign of superior cardiometabolic health. When the data were examined in alignment with the FMP, the HDL trends remained but were no longer significant. Although we observe widening of confidence intervals as

There are several potential explanations for our findings. First, it is possible that ovulatory status does not relate to cardiometabolic profile in perimenopausal women. This would imply that ovarian aging is separate from chronological aging. Chronological aging is clearly associated with reduced insulin sensitivity and worsening lipids and lipoproteins. Based on prior data from reproductive-aged women, premature loss of female hormones appears to have consequences on cardiometabolic parameters and to be associated with adverse health outcomes^{6–8}. It is possible that the duration of menstrual cycle perturbations was too short to allow us to measure any adverse effect of anovulation. It is also possible that anovulatory cycles in the DHS are primarily composed of normo-estrogenemic cycles, and thus any association between a lack of estrogen exposure would not be identifiable. However, a substantial proportion of DHS participants experienced their FMP by the H4 collection year, which would be expected to have been preceded by a number of

anovulatory, hypoestrogenic cycles. Finally, it may be that a single, well-characterized menstrual cycle once per year is insufficient evidence for the consistency of ovulatory status. Prior cross sectional study of the SWAN DHS sample found only minimal associations with cardiovascular risk factors and hormone patterns (ovulatory versus anovulatory), although a positive relationship between HDL and both E1c and PdG was observed¹⁹.

Our finding of an elevated HDL cholesterol in the non-consistently ovulatory group of women is consistent with other SWAN data, indicating that the late menopausal transition is associated with a transient increase in HDL cholesterol^{20–22}. It is unclear whether this transient increase reflects a response to a transient increase in hormones. Estrogen is, on average decreasing at this stage of the transition by all measures^{10, 23, 24}. However, some women—particularly those who are overweight--demonstrate a brief rise in estradiol just before their FMP²⁵. However, DHEAS has demonstrated a notable, significant rise in a majority of women in the late transition, and it is possible that this hormone rise is related to the transient increase in HDL²⁶. As it has been shown that LDL particle size gets smaller in menopause²⁷, it is possible that the observed increase in HDL does not reflect an increase in large particle HDL, but may reflect an increase in small, dense lipoprotein particles which are known to be relatively more atherogenic.

Other recent work has linked reduced ovarian reserve to cardiometabolic risk during pre-menopause,⁹ however these patients were younger, and ovarian function was assessed differently, by using AMH and not menstrual cycle characteristics. It is possible that there are other reasons for anovulatory menstrual cycles in proximity to menopause, other than decreased ovarian reserve. Strengths of our study include the large number of women in the SWAN DHS and the overall good retention of this subcohort throughout the 4 years of the DHS covered by this study. The multi-ethnic and community based nature of the SWAN cohort also makes our data reasonably widely applicable to women in the age range of SWAN. The daily sampling paradigm of the DHS protocol also provides much more information than a single, annual serum sampling taken at random points in the cycle and allows us to assess patterns and dynamics of hormone interactions as well as features such as ovulation and anovulation.

Our study is limited by the fact that DHS participants were volunteers from the larger cohort, and may thus be less broadly representative of SWAN, although few demographic differences were present²⁸. The width of confidence intervals among the COA group approaching menopause in Figures 2 and across all time points in Figure 3, as well as the trend for higher HTN among the nCOA women highlight that variability and sample size could be driving non-significance of results.

As no adjustments were made for multiple comparisons, the originally significant difference observed for HDL could be attributed to chance, however note that in Table 2 3/21 comparisons (14%) are significantly different, vs 5% which would be expected by chance alone. A single cycle studied once a year may not be an adequate reflection of hormone performance throughout the rest of the year. Finally, attrition of the cohort may have led to

the introduction of bias, as unhealthier women could have been more likely to drop out, making both groups look healthier and more similar.

CONCLUSIONS

In summary we have not shown that consistent ovulation across the menopausal transition reflects superior cardiometabolic health. The ovary may age apart from the circulatory system during the menopausal transition. Aligning observations by time to menopause may be a more appropriate way to analyze this population, however back-calculating time as “time before menopause” can only be done retrospectively, and is thus less helpful as a tool in characterizing health risk prospectively.

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Figure 1.
Time from SWAN baseline visit to Final Menstrual Period (FMP)

Figure 2.
Estimated group geometric mean and 95% confidence interval in measures of metabolic health across menopause (n=460)

Figure 3. Estimated group geometric mean and 95% confidence interval in measures of metabolic health across menopause, among the subset of women who reached menopause within 2 years of DHS visit 4 (n=247)

Table 1

Baseline study population characteristics

Characteristic ^a	All Women N=636	Consistently Ovulatory n=232	Not Consistently Ovulatory n=404	p-value
Age at start of evaluation	47.3± 2.49	45.9 (45.7, 46.2)	48.2 (47.9, 48.4)	<.001
BMI at start of evaluation	27.4± 7.11	26.6 (25.7, 27.4)	27.9 (27.2, 28.7)	0.02
Ethnicity:				
Black	20.0 (127)	16.8(39)	21.8(88)	0.08
White	30.3 (193)	30.6(71)	30.2(122)	
Chinese	20.3 (129)	23.3(54)	18.6(75)	
Hispanic	8.5 (54)	5.6(13)	10.1(41)	
Japanese	20.9 (133)	23.7(55)	19.3(78)	
Beyond HS	75.4 (479)	81.9(190)	71.7(289)	0.004
Study Site:				
Detroit	11.8 (75)	9.1(21)	13.4(54)	0.2
Boston	8.3 (53)	8.2(19)	8.4(34)	
Chicago	11.0 (70)	10.8(25)	11.2(45)	
Oakland	29.0 (184)	32.3(75)	27.0(109)	
Los Angeles	20.9 (133)	23.7(55)	19.4(78)	
Newark	8.5 (54)	5.6(13)	10.2(41)	
Pittsburgh	10.4 (66)	10.3(24)	10.4(42)	
Currently Smoke	9.4 (59)	7.8(18)	10.3(41)	0.3
Financial strain ^b	7.7 (49)	4.3(10)	9.7(39)	0.01
CESD: depressed mood	17.5 (111)	15.9(37)	18.4(74)	0.4
Menopausal Status:				
Early perimenopausal	71.0 (450)	61.9(143)	76.2(307)	<.001
Premenopausal	27.0 (171)	38.1(88)	20.6(83)	
Unknown due to HT use	2.1 (13)	0.0(0)	3.2(13)	
Ovulatory	77.9 (484)	100.0(232)	64.8(252)	-x-
Cycle length (if ovulatory at baseline)	27.2± 5.27	26.8 (26.4, 27.2)	27.6 (26.8, 28.4)	0.09
age at FMP (if known)	52.2± 2.47	53.2 (52.8, 53.6)	51.7 (51.4, 52.0)	<.001
age at Menarche	12.6± 1.68	12.5 (12.3, 12.7)	12.6 (12.4, 12.8)	0.5
Years between Menarche and FMP	39.7± 2.90	40.7 (40.2, 41.1)	39.1 (38.8, 39.5)	<.001
#pregnancies	2.96± 1.89	2.8 (2.6, 3.0)	3.0 (2.9, 3.2)	0.1
#children	2.05± 1.35	1.9 (1.8, 2.1)	2.1 (2.0, 2.3)	0.04
Pregnancies: Nulligravidity	9.6 (61)	11.6(27)	8.4(34)	0.2
Children: Nulliparity	15.0 (95)	17.2(40)	13.7(55)	0.2

^a values presented are % (n) for categorical measures, Mean±SD for continuous measures overall, and Mean (95% CI) for group-specific results.

^b “Very hard” to pay for the very basics like food, housing, medical care, and heating.

Table 2

Group differences in CV Characteristics

Measure	DHS H1			DHS H4 ^a		
	COA	nCOA	p-value	COA	nCOA	p-value
Waist (cm)	83.28 (81.13, 85.43)	86.60 (84.95, 88.25)	0.07	84.83 (82.63, 87.02)	88.23 (86.55, 89.91)	0.4
SBP (mm Hg)	111.5 (109.5, 113.5)	117.5 (116.0, 119.0)	0.1	112.9 (110.8, 115.1)	118.4 (116.7, 120.0)	0.1
DBP (mm Hg)	72.42 (71.03, 73.81)	75.01 (73.96, 76.06)	0.7	73.20 (71.84, 74.56)	75.71 (74.67, 76.75)	0.2
LDL (mg/dL)	111.0 (106.8, 115.1)	113.8 (110.5, 117.1)	0.9	110.3 (106.2, 114.5)	117.5 (114.3, 120.8)	0.09
HDL (mg/dL)	56.70 (54.63, 58.77)	60.12 (58.49, 61.74)	0.003	55.77 (53.90, 57.63)	59.46 (58.02, 60.89)	<.001
Trig (mg/dL)	114.2 (102.2, 126.1)	126.0 (116.4, 135.5)	0.6	122.6 (111.0, 134.2)	126.4 (117.3, 135.5)	0.98
Glucose (mg/dL)	94.11 (90.30, 97.92)	96.79 (93.74, 99.84)	0.6	93.00 (89.56, 96.44)	95.31 (92.61, 98.01)	0.9
HOMA	2.63 (1.93, 3.33)	3.15 (2.58, 3.71)	0.7	2.77 (1.72, 3.81)	3.73 (2.91, 4.55)	0.4
Fibrinogen (mg/dL)	266.5 (258.3, 274.6)	280.1 (273.7, 286.5)	0.2	259.9 (238.9, 281.0)	280.2 (266.9, 293.5)	0.2
PAI-1 (ng/ml)	28.27 (21.47, 35.06)	36.24 (30.83, 41.65)	0.02	23.02 (17.52, 28.51)	27.22 (22.95, 31.50)	0.4
E1c (ng/mgCr)	1354 (1260, 1448)	1396 (1303, 1489)	0.6	1371 (1292, 1450)	1499 (1298, 1700)	0.3
PDG (mcg/mgCr)	65.16 (60.62, 69.70)	55.55 (51.08, 60.03)	0.06	55.81 (51.65, 59.97)	51.31 (40.76, 61.86)	0.7
FSH (mIU/mgCr)	417.1 (350.6, 483.5)	640.3 (574.7, 705.9)	<.001	554.1 (466.2, 642.0)	1173 (947.1, 1398)	<.001
LH (mIU/mgCr)	73.75 (56.28, 91.22)	93.24 (76.00, 110.5)	0.08	78.49 (66.27, 90.72)	136.4 (105.0, 167.8)	0.001
CRP (mg/dL)	2.49 (1.48, 3.50)	4.01 (3.21, 4.81)	0.3	2.47 (1.80, 3.14)	3.69 (3.17, 4.21)	0.4
% Metabolic Syndrome	22.4 (52)	25.7 (103)	0.4	32.2 (74)	37.9 (148)	0.5
% HTN	19.9 (46)	33.7 (136)	0.2	23.5 (54)	39.5 (156)	0.09
% ↑ Glucose ₁₀₀	17.3 (34)	21.9 (68)	0.6	19.5 (43)	24.3 (88)	0.8
% Obese	38.4 (88)	44.1 (172)	0.09	44.8 (103)	48.7 (191)	0.04
% ↓HDL	33.8 (67)	28.0 (90)	0.07	35.1 (78)	27.8 (104)	0.03
% ↑Triglycerides	20.4 (40)	21.5 (66)	0.4	24.8 (54)	24.0 (86)	0.6

Comparisons are adjusted for current BMI and current age at the indicated visit.

^aThe last available CV visit used prior to menopause for women who reached menopause on or before DHS-H4.