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Changes in adiposity and other factors in relation to age at natural menopause: analyses from the coronary artery risk development (CARDIA) study

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Abstract

Objective: The age at natural menopause has subsequent health implications. Earlier age at natural menopause is a risk factor for cardiovascular disease, atherosclerosis, and stroke. Despite extensive study, no clear and conclusive association between anthropometric measures and age at natural menopause has emerged. This study aims to assess whether baseline and/or longitudinal changes in adiposity are associated with age at natural menopause.

Methods: In all, 2,030 premenopausal women from the Coronary Artery Risk Development in Young Adults study—a prospective study with 25 years follow-up—were included for analysis from 1985 to 1986 until menopause was attained. Anthropometry included body mass index and waist circumference. Discrete-time survival analysis was then used to determine the association between anthropometric measures at baseline, and also their changes with age at natural menopause, while adjusting for various time-varying and invariant covariates in separate models for body mass index and waist circumference.

Results: Multivariate Cox regression analysis showed that baseline body mass index (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.94-0.98) and baseline waist circumference (HR 0.98, 95% CI 0.97-0.99) significantly increased the risk of later age at natural menopause. Neither time-varying body mass index nor waist circumference indicating change across time associated with age at natural menopause. Premenopausal hypertension was strongly associated with an earlier age at natural menopause.

Conclusion: These findings show that age at natural menopause is partly determined by modifiable factors such as premenopausal hypertension and baseline adiposity. These results highlight the importance of both control and prevention of cardiovascular risk factors such as excess weight in early to mid-adulthood before menopause onset.

Key Words: Age at menopause – Body mass index – Risk factors – Waist circumference.

Age at natural menopause (ANM) is of clinical and public health importance as it represents a marker of general health and aging, given that early menopause is associated with higher risk of cardiovascular disease (CVD), cognitive decline, osteoporosis, and premature mortality.[1-12] Despite extensive study, no clear and conclusive association between adiposity (weight and/or body mass index [BMI]) and menopausal age has emerged from the literature. Paramsothy et al,[1] using data from the Study of Women's Health Across the Nation (SWAN), found that women with obesity had longer menstrual cycle lengths than women with normal weight during the menopausal transition. Women with longer menstrual cycles during their reproductive years have been shown to have a later age at menopause.[13] In fact, research has suggested, but not consistently,[2,3] that a higher BMI might increase the risk of a later menopause.[4-6] A recent meta-analysis found that increased BMI is moderately associated with a later ANM[7]; however, the studies included were heterogeneous in terms of their study designs and measures of weight. Therefore, the pooled result requires further confirmation. It is hypothesized that increased production of estrone (a precursor of estrogen) in the adipose tissue of women with obesity might contribute to a delay in their menopause,[14] as estrone may supplement estradiol levels. Estrone is formed by the peripheral aromatization of androgens, namely androstenedione, secreted by the ovaries and/or adrenal glands.[8] Obesity has been linked to more androgens being converted into estrone.[9] Therefore, increased peripheral production of estrone in women with obesity may contribute to the delay in age at menopause.

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It is also suggested that hormonal imbalances occurring as a result of weight change across life increase the rate of follicular atresia,[10] thereby influencing the timing of menopause. Therefore, it may be weight change rather than absolute weight per se that influences ANM. However, few studies have examined the relationship between weight change across time and ANM. In fact, previous findings on weight gain or loss and menopausal age were also inconsistent, possibly because of differing methodologies, with studies across various settings, showing either no association,[11,12] a positive association,[7,15,16] or an inverse association.[3,12] Aydin[15] found that premenopausal BMI gain rate and premenopausal weight loss of more than 5 kg were both associated with later ANM. Similarly, Dorjgochoo et al[7] found a dose-response relationship between midlife weight gain and later ANM. This is in contrast to Kok et al,[17] who reported both increasing and decreasing premenopausal relative weight as risk factors for earlier ANM. In a further study, Hardy et al[11] did not find an association between both underweight or overweight BMI trajectories and ANM; however, BMI and age at menopause were self-reported, and BMI was measured from age 18 until 43 years. On the contrary, using data from SWAN, Gold et al[18] found that an increased concurrent BMI and waist circumference (WC) were significantly associated with incident vasomotor symptoms (VMS), occurring in early menopause, but a lower VMS risk in late menopause. However, no association was observed between changes in BMI or WC and incident VMS. Moreover, recent analysis from the Nurses' Health Study II by Szegda et al[19] showed that substantial weight loss may increase risk for early natural menopause. Women who lost $\geq$20 pounds from age 18 to 35 years had increased odds of early menopause compared with women who gained 5 to 15 pounds. In addition, weight cycling between ages 18 and 30 was also associated with higher risk of early ANM. Ethnicity, in relation to adiposity and age at menopause, was not assessed due to the majority of the study population being White.

To understand the postmenopausal health implications for both underweight and overweight women, further studies are needed to assess whether absolute weight and weight change play a role on menopausal age. Using a life course approach, determining the effect of changes in adiposity on the timing of menopause is important to understand the potential mechanisms by which these changes may act to affect age at menopause, which has been associated with increased risk for various health conditions. Most studies conducted on the effect of the change in adiposity on ANM have, on the whole, relied on recall of early adult weight, and not on objectively and prospectively assessed measures. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we examine the association between baseline, and longitudinal changes in premenopausal adiposity (BMI and WC) and ANM.

METHODS

Study design, sample, and data collection

The CARDIA study is a multicenter longitudinal study of 5,114 (including 2,786 women; one person revoked consent over the course of the study) adults aged 18 to 30 years, who were recruited at baseline (YEAR 0) in 1985 to 1986 from four US urban centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) to examine cardiovascular risk factor trends in young adults. The response rate among individuals invited to participate was 50%. This sample has been followed for the past 25 years, with follow-up examinations occurring during 1987 to 1988 (year 2), 1990 to 1991 (year 5), 1992 to 1993 (year 7), 1995 to 1996 (year 10), 2000 to 2001 (year 15), 2005 to 2006 (year 20), and 2010 to 2011 (year 25). A majority of the group has been examined at each of the follow-up examinations (91%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively). Approximately 88% of participants have attended $\geq$4 CARDIA examinations. For the current investigation, data from all examination cycles (ie, years 0, 2, 5, 7, 10, 15, 20, and 25) were included in the analyses. The sample was recruited to be balanced on sex, race (White or Black), age (18-24 or 25-30 years), and education ($\leq$12, $>$12 years). Data collection and follow-up protocols were approved by the institutional review boards of each field center, with all participants providing written informed consent. Details of the study design and methods are described elsewhere.[20] Women who did not attend the year 25 visit were more likely to be Black, younger, and current smokers, and to have fewer years of education at baseline.[20] At every CARDIA examination, standardized protocols were used to collect information on demographics, anthropometrics, lifestyle and behavioral factors, medical history, biomarkers, and medication use from participants. The study was approved by the institutional review boards from each field center and the coordinating center. Access to the CARDIA database with information from baseline to year 25 was obtained from the National Heart, Lung and Blood Institute (NHLBI) for this analysis. Ethics approval was obtained for secondary data analysis for the present study from the York University Research Ethics Board.

Sample selection criteria

A woman's anthropometric data from a particular examination were excluded if she was pregnant at that exam, although her other examination data were retained in the analyses. Women who had undergone menopause before 40 years of age (n = 17) were excluded from this study, and this was done to exclude women with premature ovarian insufficiency, which is of a different etiology than natural menopause. Women diagnosed with breast, ovarian, or endometrial cancers (n = 19) were also excluded since treatment for these cancers includes hormone use which might mask the true age of menopause.[3] Also excluded were women who were missing data at follow-up by year 15, when menopause was first ascertained (n = 720). Therefore, this analytic sample included 2,030 unique women with complete information on the outcome and exposure variables (Fig. 1**).** Participants excluded from the analytic sample were more likely to be Black, and younger (by design).[20] Missing data on either weight, BMI, or WC among women who completed the

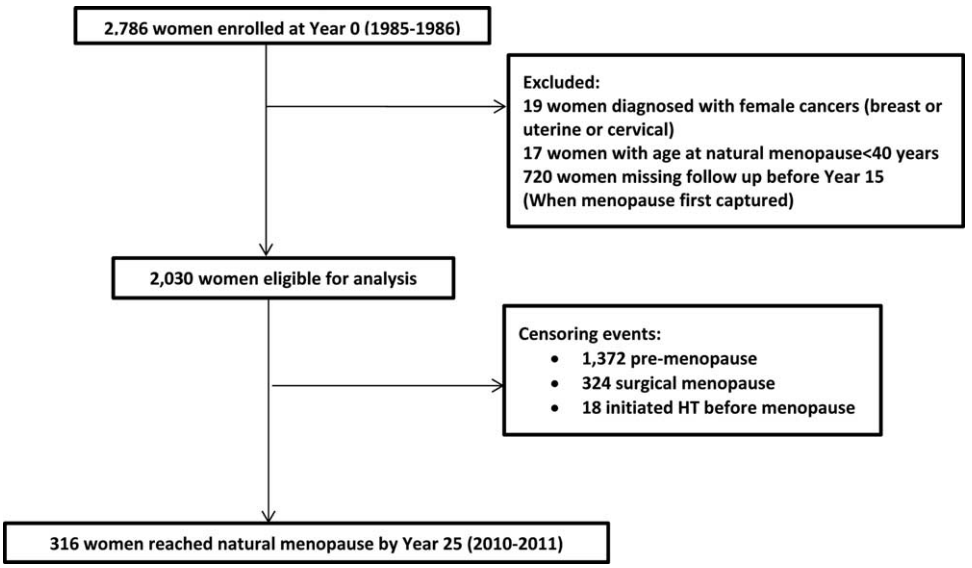

FIG. 1. Flowchart of participants in the CARDIA study (1985-2011).

different cycles ranged between 1% and 7%. Those with missing information on exposure variables at each cycle differed with respect to age, race, and education, and parity, presence of diabetes, hypertension, high cholesterol, and menopause status than those with complete information on those variables.

Outcome variable

Age at natural menopause was the outcome for this analysis. ANM is defined as the age of last menses, occurring after at least 12 months of amenorrhea as per the World Health Organization's (WHO's) definition.[21] Menopausal status, captured at year 15 (women were 33-45 years old), at year 20 (women were 38-50 years old), and at year 25 (women were 43-55 years old) examinations, was assessed with the question ''Have you gone through menopause or the change of life?'' followed by ''If yes, how did your periods stop?'' with the options of ''naturally'', ''surgically'' or ''other.'' Participants were then asked ''How old were you when this occurred?'' which was used in this analysis as age at menopause. Among postmenopausal women, those who reported cessation of menstrual bleeding not preceded by hysterectomy, radiation, or chemotherapy were classified as having a natural menopause, whereas those who reported menstrual cessation due to hysterectomy and/or bilateral oophorectomy were classified as having surgical menopause. Age at menopause was defined as self-reported age at natural cessation of menstrual flow or age at surgery to remove the uterus and/or ovaries. Women were additionally asked about ever use of oral contraceptives (OCs) or current hormone therapy (HT). The definition of natural menopause (our event variable) in the CARDIA study was validated by Nair et al[22] against a question regarding the date of last menstrual period. Ninety-four per cent reported a date within ± 1 year of their reported age at menopause. Moreover, the definition of menopause from the 2000 to 2001 CARDIA examination was validated against follicle stimulating hormone (FSH) levels available in the subset of women who also participated in an ancillary study of the CARDIA, the CARDIA's Women's Study (CWS), in 2002 to 2003. An FSH level >40 mIU/mL at the CWS examination was used as a validation of hypogonadotropic amenorrhea/menopause. At the 2000 to 2001 examination (age 33-45), 18 women reported ''yes'' to ''Have you gone through menopause or the change of life?'' and ''naturally'' to ''If yes, how did your periods stop?'' Of these women, 14/18 (78%) had menopausal FSH levels >40 mIU/mL (FSH range 16-137 mIU/mL) at the 2002 to 2003 CWS examination.[23]

Independent variables

Anthropometric variables which comprise baseline BMI, and WC, and also time-varying BMI and WC, were the primary independent variables. Anthropometrics were measured at each examination. BMI was calculated by dividing weight in kilograms by height in meters squared. Body weight was measured on a calibrated balance scale, whereas participants were dressed in light clothing and without shoes by trained and certified technicians using a calibrated scale. Height (without shoes) was assessed by using a vertical ruler and recorded to the nearest 0.5 cm. WC was measured at the minimum abdominal girth (to the nearest 0.5 cm). Due to its stronger correlation with visceral and abdominal obesity than waist-to-hip ratio (WHR),[18] WC was considered in the analysis rather than WHR. BMI categories include underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2).[24] It should be noted that from this point on, to distinguish between ''change'' which can commonly be interpreted as a change score and ''longitudinal changes'' or ''time-varying changes,'' ''changes'' will be employed to denote longitudinal changes or time-varying changes, whereas ''change'' will

be used to denote change scores or percentages. Both ''change'' and ''changes'' in these senses deal with changes over time in a variable but are characterized differently.

Covariates

Time-varying covariates, measured at each examination, included sociodemographic factors, such as education (high school or less, more than high school), current employment (yes/no), and household income in USD (<25,000, 25,000-49,999, 50,000-99,999, ≥100,000); Health behavior variables included smoking status (never, former, or current), alcohol consumption in the past year (yes/no), ever OC use (yes/no), and self-reported physical activity intensity (vigorous/ moderate/ low). Cigarette smoking was assessed by means of an interviewer-administered tobacco questionnaire. Physical activity level was assessed using a modified version of the Minnesota Leisure Time Physical Activity Questionnaire, with total scores representing self-reported participation in 13 different categories of exercise over the past year, expressed in exercise units.[25] As a useful reference, 200 exercise units (EUs) are roughly equivalent to regularly engaging in exercise at 6 METS (moderate intensity), such as stationary bicycling or swimming 2 hours a week for 11 months per year. Vigorous physical activity intensity was defined as >200 EUs, 100 to 200 EUs corresponded to moderate-intensity physical activity, whereas low-intensity physical activity was defined as <100 EUs. Alcohol intake was defined as consumption of any alcoholic beverages in the past year. Clinical factors that included parity (none vs 1 or more) were also considered as time-varying covariates. At baseline, blood pressure was measured using a random-zero sphygmomanometer with participants seated and after 5 minutes of rest. At the 20-year follow-up examination, three measurements of seated blood pressure were taken from the right arm of each participant after resting for 5 minutes using an Omron HEM907XL automated BP monitor using an appropriately sized cuff and calibrated to the random-zero measures.[26] The average of the second and third consecutive measurements was used for analysis. Hypertension was defined as self-reported diagnosis of hypertension, or SBP >140 mm Hg or DBP >90 mm Hg or use of antihypertensive medications. Before each CARDIA examination, participants fasted for ≥8 hours and were asked to avoid smoking and heavy physical activity for the final 2 hours. Blood was drawn at each examination center by venipuncture according to a standard protocol.[20] Fasting glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase at a collaborative studies clinical laboratory (Minneapolis, MN).[27] Type 2 diabetes was defined as a self-reported diagnosis of diabetes after age 25, a fasting glucose level of at least 126 mg/dL (to convert to mmol/L, multiply by 0.0555), or reported use of diabetes medications. Fasting plasma total cholesterol, triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically by Northwest Lipid Research Laboratories (Seattle, WA).[28] Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation.[28] Hyperlipidemia was defined as self-reported diagnosis of high cholesterol, a total cholesterol level of 240 mg/dL or greater (to convert to mmol/L, multiply by 0.0259), or use of lipid-lowering medications. Details of quality control activities that were conducted at CARDIA field centers, coordinating centers, laboratories, and reading centers are available on the CARDIA web site at www.cardia.dopm.uab.edu. For covariates with missing data (all <5%), missing values were assigned to a missing indicator category, and analyses using missing indicator categories were conducted to maximize statistical power.[29] Results between analyses restricted to women with complete covariate data and analyses using missing indicator categories were comparable (data not shown). For the purpose of this analysis, time-invariant covariates, include race measured at baseline, parity measured at year 10 (in 1995, when participants were 28-40 years old), and intake of protein, fat, and carbohydrates (CHO). A quantitative food frequency (CARDIA Dietary History) was administered by a trained interviewer to assess intake of protein, fats, and CHO, at baseline and year 7. Intake of each food group was calculated as the sum of the number of times a food in each food group was eaten per day (g/d). The CARDIA dietary history is a reasonably reliable and valid ($r = 0.5$-0.7; the CARDIA food questionnaire vs food diaries obtained from a subsample) dietary survey method for obtaining information about habitual intakes in both races.[24-27] The analyses were conducted using year 7 dietary data, because the data were based on an updated and more extensive version of the food database.[24-27] The natural log of fasting insulin and dietary intake variables was taken because these transformations helped improve model fit.

Statistical analysis

Baseline characteristics of the women were compared by menopausal status using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Due to the inter-relationship between baseline BMI and WC, their changes were examined in separate models. Next, discrete-time survival analysis was used to determine the association between anthropometric measures at baseline, their changes as indicated by time-varying variables and ANM while adjusting for all covariates listed above. Hazard ratios (HRs) and their 95% confidence intervals (CIs) for earlier or later ANM were then estimated by a series of separate Cox proportional-hazards models. Women who did not experience menopause were considered as censored observations. Age, rather than time until incident menopause, was used as the time scale for survival analysis. The endpoint age was defined as one of the following: ANM for postmenopausal women (n = 316); age at last follow-up examination if a woman is premenopausal (n = 1,372); age at hysterectomy or bilateral oophorectomy before having ≥12 consecutive months of untreated amenorrhea (n = 324); and age at HT initiation (among women who had used HT before menopause) (n = 18). Criteria for censored observations are

similar to that used by Gold et al.[14] To assess for other potential confounders, nonintentional weight change due to nongynecological cancers or endocrine disrupting conditions, ulcerative colitis, Crohn's disease, rheumatoid arthritis, or systemic lupus throughout the study duration was determined. None of the women included in this analysis had developed these conditions. Women who underwent a hysterectomy after menopause were not censored. Multivariate regression models included covariates selected a priori as factors associated with age at natural menopause and/or body size in the literature. The adjusted model controlled for the following variables: education level, current employment, household income, OC use, smoking status, alcohol intake in the last year, physical activity intensity, and presence of type 2 diabetes, hypertension, and hyperlipidemia, dietary fat, CHO and protein intake, and parity. The assumption of proportional hazards was checked both by inspection plots and Schoenfeld residuals, which did not indicate violation of the assumption. Goodness of fit of the multivariate Cox models was assessed using the likelihood ratio test and Cox-Snell residuals, which indicated a good overall fit. Interaction between smoking status and baseline and time-varying measures of adiposity was assessed by including an interaction term between the exposures in each model and analyzed their combined effects. Furthermore, interaction between hypertension, diabetes and hyperlipidemia, and ANM was also tested to determine whether they had an additive or synergistic effect. Statistical analysis was performed using STATA software (StataCorp LLC, TX, version 13.0). Statistical significance was set at $\alpha = 0.05$. To minimize multiple comparison bias, a post hoc Bonferroni correction was applied, with the uncorrected CIs presented here being similar to those with correction.

RESULTS

Table 1 shows the baseline characteristics by menstrual status. The majority of women were still premenopausal (67.3%), whereas 16.5% were naturally menopausal. The median ANM among women in the CARDIA study was 52 years (interquartile range 50-54). Blacks were more likely to be premenopausal or were more likely to use HT before menopause than White women. Women who had a higher

TABLE 1. *Baseline characteristics of the 2,030 women in the analytic sample by menstrual status during follow-up (CARDIA study, 1985-2011)*

Characteristics	Total	Premenopause (n = 1,372)	Natural menopause (n = 316)	Surgical menopause (n = 324)	Hormone therapy (HT) use before natural menopause (n = 18)
Age, y (mean, SD)	24.8 (3.65)	24.0 (3.59)	27.9 (2.28)	26.25 (3.12)	28.5 (1.92)
Race (n, %)					
White	1,204 (47.0)	709 (70.7)	205 (20.4)	89 (8.9)	3 (6.82)
Black	1,357 (53.0)	663 (65.7)	111 (11.0)	235 (23.3)	14 (25.5)
Educational level (n, %)					
High school graduate or less	966 (35.2)	480 (67.6)	84 (11.8)	146 (20.6)	3 (10.3)
More than high school	1,780 (64.8)	892 (68.5)	232 (17.8)	178 (13.7)	14 (20.0)
Income, USD[a] (n, %)					
<25,000	748 (38.9)	427 (67.7)	95 (15.1)	109 (17.3)	4 (16.0)
25,000-49,999	704 (36.7)	430 (71.3)	81 (13.4)	92 (15.3)	4 (14.3)
50,000-99,999	273 (14.2)	161 (66.3)	52 (21.4)	30 (12.4)	7 (30.4)
≥100,000	—	—	—	—	—
Currently Employed (n, %)	1,666 (65.1)	888 (66.5)	236 (17.7)	212 (15.9)	16 (20.5)
Smoking status					
Never	1,468 (57.5)	846 (71.0)	161 (13.5)	184 (15.5)	8 (15.1)
Past	349 (13.7)	196 (67.4)	55 (18.9)	40 (13.8)	4 (25.0)
Current	736 (28.8)	327 (62.5)	97 (18.6)	99 (18.9)	4 (13.8)
Alcohol intake in the past year (n, %)	2,145 (83.6)	1,161 (68.5)	277 (16.3)	257 (15.2)	16 (18.4)
Oral contraceptive use (n, %)	814 (41.7)	473 (74.5)	75 (11.8)	87 (13.7)	5 (18.5)
Physical activity intensity, exercise units, (mean, SD)	335 (249.7)	354 (260)	362 (240)	284 (241)	459.3 (296)
Parity (n, %)					
None	169 (6.15)	100 (65.8)	24 (15.8)	28 (18.4)	15 (1.3)
1 or more	2,577 (93.9)	1,272 (68.4)	292 (15.7)	296 (15.9)	16 (1.5)
Waist circumference (WC), cm (mean, SD)	74.0 (11.0)	73.70 (11.00)	73.2 (10.2)	76.1 (10.9)	70.2 (7.30)
Body mass index (BMI), kg/m^2 (mean, SD)	24.5 (5.52)	24.3 (5.38)	23.9 (5.15)	25.5 (5.64)	22.9 (3.64)
Dietary fat, g/d (mean, SD)[b]	98.9 (71.5)	95.93 (70.8)	94.5 (61.4)	102 (56.9)	67.7 (21.4)
Dietary CHO, g/d (mean, SD)[b]	216 (131.6)	214 (129.5)	205 (115.6)	217 (119.6)	166.9 (70.8)
Dietary protein, g/d (mean, SD)[b]	76.6 (53.6)	75.0 (50.12)	77.4 (55.8)	74.5 (38.2)	62.8 (19.0)
Current diabetes (n, %)	261 (9.50)	29 (51.8)	6 (10.7)	21 (37.5)	0
Current hypertension (n, %)	403 (14.7)	108 (65.5)	19 (11.5)	38 (23.0)	0
Current hyperlipidemia (n, %)	355 (12.9)	83 (65.4)	23 (18.1)	21 (16.5)	0

Percentages in the last four columns are row %; however, only the percentages within the first three of those columns add to a 100%, because HT use before menopause was a variable on its own (yes/no).

[a]Chi-square test for categorical variables; Kruskal-Wallis test for continuous variables; majority had P values of <0.001.

[b]Information not available at year 0; year at which characteristic was first assessed was taken as baseline.

TABLE 2. *Unadjusted and adjusted hazard ratios (HRs) for the association between adiposity, its changes and ANM in the CARDIA study (1985-2011)*

	Unadjusted HR	95% CI	Adjusted HR[a]	95% CI	Adjusted HR[a]	95% CI
Baseline BMI, kg/m^2	0.99	0.98-0.99[b]	0.96	0.94-0.98[b]	—	—
Time-varying BMI	0.99	0.98 1.00	1.01	0.99-1.03	—	—
Baseline WC, cm	0.99	0.98-0.99[c]	—	—	0.98	0.97-0.99[b]
Time-varying WC	0.99	0.99-1.00	—	—	1.01	1.00-1.01
Race						
White	Ref		Ref		Ref	
Black	0.97	0.90-1.06	0.85	0.73-1.00	0.83	0.71-0.97[b]
Educational level						
High school graduate or less	Ref		Ref		Ref	
More than High school	0.82	0.74-0.91	0.85	0.72-1.00	0.84	0.71-0.99[b]
Household income, USD						
<25,000	Ref		Ref		Ref	
25,000-49,999	0.88	0.76-1.02	0.82	0.68-0.99[b]	0.82	0.68-0.99[b]
50,000-99,999	0.90	0.78-1.05	0.87	0.72-1.06	0.87	0.72-1.06
≥100,000	0.87	0.73-1.03	0.85	0.68-1.07	0.84	0.67-1.05
Currently employed	0.87	0.80-0.95[b]	1.01	0.88-1.15	0.98	0.86-1.13
Smoking status						
Never	Ref		Ref		Ref	
Past	1.12	1.01-1.25[b]	1.23	1.05-1.43[b]	1.21	1.04-1.41[b]
Current	1.90	1.70-2.11[c]	1.83	1.53-2.19[c]	1.79	1.50-2.15[c]
Alcohol intake in the past year	1.13	1.01-1.27[b]	1.20	0.99-1.45	1.22	1.00-1.47
Oral contraceptive use	0.93	0.84-1.04	0.79	0.67-0.94[b]	0.79	0.67-0.94[b]
Physical activity						
Low intensity	Ref		Ref		Ref	
Moderate intensity	0.98	0.85-1.14	1.04	0.85-1.29	1.02	0.83-1.26
High intensity	0.99	0.88-1.12	1.05	0.88-1.26	1.06	0.88-1.27
Parity						
None	Ref		Ref		Ref	
1 or more	1.09	0.95-1.25	1.18	0.94-1.49	1.19	0.94-1.50
Diabetes	0.94	0.83-1.05	0.73	0.53-1.01	0.73	0.53-1.01
Hypertension	1.05	0.96-1.15	1.31	1.10-1.55[b]	1.29	1.08-1.53[b]
Hyperlipidemia	1.02	0.93-1.12	1.11	0.93-1.31	1.11	0.94-1.31
Log dietary fat, g/d	1.23	1.14-1.32[c]	1.35	1.08-1.69[b]	1.34	1.07-1.67[b]
Log dietary CHO, g/d	1.02	0.93-1.11	0.86	0.68-1.08	0.85	0.68-1.07
Log dietary protein, g/d	1.21	1.11-1.32[c]	0.98	0.73-1.32	0.98	0.73-1.32

ANM, age at natural menopause; BMI, body mass index; CHO, carbohydrates; CI, confidence interval; WC, waist circumference.
[a]Adjusted for the following covariates in addition to baseline values for BMI: time-varying covariates include BMI, education, current employment, household income, oral contraceptive use, current smoking, and alcohol intake in the past year, physical activity intensity, and presence of diabetes, hypertension and hyperlipidemia. Time-invariant covariates include race, dietary fat, CHO, and protein intake and parity.
[b]$P < 0.05$.
[c]$P < 0.0001$.

household income (50,000-99,999 USD), who were employed, or who were current smokers were more likely to be premenopausal or to be using HT before menopause. Women who were diagnosed with diabetes, hypertension, or hyperlipidemia were more likely to be premenopausal.

Results of the unadjusted and adjusted Cox regression models with BMI and WC as time-varying variables are outlined in Table 2. Changes in either BMI or WC as indicated by time-varying variables were not associated with ANM. Both baseline BMI (HR 0.96, 95% CI 0.94-0.98), and baseline WC (HR 0.98, 95% CI 0.97-0.99) were significantly associated with a later ANM. Premenopausal hypertension at follow-up was strongly associated with an earlier ANM in the model for BMI (HR 1.31, 95% CI 1.10-1.55) and WC (HR 1.29, 95% CI 1.08-1.53), respectively. In contrast, higher dietary fat intake at follow-up was related to an earlier ANM in the model for BMI (HR 1.35, 95% CI 1.08-1.69) and WC (HR 1.34, 95% CI 1.07-1.67), respectively. The multivariate model for both BMI and WC showed that women whose household income was 25,000 to 49,999 USD at follow-up had a significantly increased hazard of a later ANM versus women with a household income lower than 25,000 USD. Women who ever used OCs were more likely to have a later ANM compared with women who had never taken OCs. Current and past smokers, on the contrary, had a greater hazard of having an earlier natural menopause than never smokers. In the model with only WC (Table 2), women who were Black were significantly more likely to have a later ANM (HR 0.83, 95% CI 0.71-0.97) than White women. A higher education level at follow-up (HR 0.84, 95% CI 0.71-0.99) was also associated with a later ANM compared with high school or less education in the model with WC (Table 2). No significant interaction was noted between baseline and time-varying measures of adiposity, smoking status, cardiovascular risk factors, and ANM.

DISCUSSION

The main aim of this study was to assess whether baseline and longitudinal changes in adiposity are associated with ANM. No association between changes in anthropometrics

across time and onset of menopause was observed, but baseline BMI and WC were negatively associated with ANM. Moreover, the presence of hypertension before menopause and higher fat consumption were also associated with an earlier ANM. In addition, factors consistently related with age at menopause such as higher education levels, OC use, and current smoking status were significantly associated with ANM as indicated in other studies.[2-6,12] Findings might inform prevention strategies that benefit many women going through the menopausal transition, highlighting the importance of both control and prevention of cardiovascular risk factors, especially blood pressure, in adulthood before menopause when cardiovascular risk factors are prone to change.

Although several studies indicate that overweight decelerates menopause, others note no effect of body weight on menopause onset.[2,3,11,12,30-33] The lack of association found between any changes in adiposity throughout the study period was similar to Hardy et al,[30] who, using a nationally representative British cohort of 1,583 women born in March, 1946, reported no relationship between a BMI trajectory from 20 to 36 years and ANM. Similarly, Gold et al,[18] using data from the SWAN study, showed that percentage weight change since baseline and since prior visit was unrelated to any incident VMS, a proxy to menopause onset. This is also in concordance with Gallicchio et al,[33] who, in a longitudinal study of midlife women, demonstrated that change in BMI and weight over 1 to 5 years of follow-up was not linked to hot flashes. A possible explanation for this result might lie in the fact that aging results in a decrease in lean body mass, which decreases resting metabolic rate.[34] Estrogen deprivation after menopause leads to an increase in total body fat,[35] yet it also results in a decrease in lean body mass, such that there is little net effect on weight related to menopause alone.[36,37] In contrast, women who reported severe weight cycling, that is, women who lost $\geq$20 pounds three or more times between age 18 and 35, had higher odds (odds ratio [OR] 1.48, 95% CI 1.04, 2.10) of early natural menopause compared with normal-weight women, as data from the Nurses' Health Study 2 (NHS2), revealed.[19] Weight change in that study was calculated by subtracting weight at age 18 from that at age 35. The study assessment of longitudinal changes of adiposity measures was limited to premenopausal women until age 35, with weight loss or gain being self-reported. Morris et al[16] observed that a greater weight gain from 20 to 40 years of age was associated with a later menopause (HR 0.93, 95% CI 0.87, 0.98) after adjustment for BMI at age 40 years and other factors. These contradictory findings raise the possibility that weight fluctuations may indeed not be related to ANM.

Baseline BMI and WC were consistent yet modest predictors of later ANM in both models as per the results of the multivariate Cox regression. This is in concordance with Zhu et al,[38] who, using data from 11 prospective studies with a sample of 24,196 women, showed that women with an overweight (relative risk ratio 1.52, 95% CI 1.31-1.77) and obese (relative risk ratio 1.54, 95% CI 1.18-2.01) BMI at baseline were at increased risk of late menopause. Their results were strengthened when an obese BMI was reported at least five or more years before the onset of menopause. Baseline measures of adiposity have been shown to be highly correlated with current body size[39,40]; therefore, our result might be in line with the notion that premenopausal obesity delays menopause. Our results were also similar to Gold et al[18] who noted that higher WC was significantly associated with lower VMS risk in late menopause. The relationship between overweight or obesity and late age at menopause may be explained by the complex functions of adipose tissue. Adipose tissue is now recognized as an active metabolic and endocrine organ that regulates various metabolic functions. The production of estrone in the adipose tissue, which is greater in women with obesity, may result in higher levels of circulating estrogens that may result in a longer reproductive function.[8,9] Another explanation might lie in the role of the hormone leptin. Leptin is an adipokine secreted by adipose tissue that inhibits hunger. It communicates information about body energy reserves, nutritional state, and metabolic shifts to the reproductive axis.[41] Leptin can act peripherally at the ovary or centrally at the hypothalamus to augment female reproductive function.[41,42] In fact, Sowers et al[43] found that the levels of adipocyte-derived hormones varied by menopausal stages and were possibly influenced by sex hormones. Moreover, early menopause has been associated with low leptin levels.[44] Therefore, interplay between sex hormones, other endocrine hormones, and also baseline body size might influence ANM. Although the effect sizes obtained for baseline adiposity measures in relation to ANM are modest, they are of clinical significance. When extrapolated, an increase of 5 cm in baseline WC, for example, portends a 9.6% decrease in the hazard of an earlier ANM, which roughly accounts for a year's worth of delay in ANM.

Consistent with previous research,[17,45] another finding from our analysis was that premenopausal hypertension was associated with an earlier menopause. In fact, middle-aged women require careful blood pressure monitoring during the menopausal transition. For example, a study also using the CARDIA by Ebong et al[46] documented an association between high-sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker, and hypertension among premenopausal women, independent of BMI. Estrogen is thought to protect against CVD in premenopausal women via both systemic and local vascular effects. These vasoprotective effects are mediated, in part, through the binding of estrogen to vascular endothelial cells and smooth muscle cells, affecting their function and resulting in decreased vasoconstriction and blood pressure.[47,48] Data from the study by Janssen et al[49] also found that progression through menopause was associated with an increase in the incidence of the metabolic syndrome (MetS) where the odds of developing MetS were 1.45 (95% CI 1.35-1.56) per year during the perimenopause and 1.24 (95% CI 1.18-1.30) per year in the postmenopausal years. Weight, cholesterol level, diabetes mellitus, blood pressure, and smoking have negative vascular effects, but

may also affect hormone production, which, in turn, could have an impact on menopausal age by altering estrogen levels.[50,51] Therefore, the interplay and overlap between the effects of inflammation, obesity, and estrogen loss may contribute to the development of hypertension in the postmenopausal period.

Higher dietary fat intake per day during follow-up was associated with an earlier ANM in our study. The few prospective cohort and cross-sectional studies that have investigated the effect of dietary fat on menopause timing have had inconsistent results.[6,52-57] Findings from the UK Women's Cohort Study showed a 3-year delay in ANM among women who consumed an additional portion/d of oily fish, but found no association between other fats and age at menopause.[52] A German cohort study reported that higher total intakes of fat, meat, and protein were all correlated with later onset of menopause.[53] Another study showing high intakes of fat and cholesterol were associated with earlier menopause.[54] On the contrary, another study using NHS2 data[57] found that only a daily intake of vegetable-based protein was associated with a later ANM. Further longitudinal research is needed to elucidate the relation of dietary factors with ANM.

Interestingly, we found that Black women were significantly more likely to have a later ANM than their White counterparts. The literature on the link between ethnicity and age at menopause remains equivocal. Gold et al[3,12] reported no difference between the races. However, Bromberger et al[2] observed an earlier age at menopause onset for Black women (n = 185). One explanation for our finding might be that estrogen levels may be higher in African American women compared with White women, thus, delaying menopause onset. Among reproductive-aged women, estradiol levels are higher across the menstrual cycle in African American women compared with White women as Marsh et al[58] reported. Nonetheless, studies have found that obesity impairs ovarian function,[59-61] as captured by anti-Mullerian hormone (AMH) concentrations that indicate ovarian reserve. Bernardi et al[61] using data from a prospective cohort on over 1,000 reproductive-aged Black women demonstrated that AMH concentrations declined as current BMI increased, and AMH was significantly lower in females with obesity compared with those who were underweight or normal weight. More research is needed on how race and menopause are related, and specifically how obesity may factor into this overall relationship.

Strengths and limitations

The strengths of the present study include the detailed exposure and outcome information available. This is the first study to evaluate associations of dynamic body size indicators as risk factors of ANM. CARDIA study's design provides a clear temporality between exposure and outcome, and thus builds upon previous literature. Furthermore, the adjustment of multiple established risk factors and censoring at age of initiation of HT and age at surgical menopause limits the potential for confounding bias. All anthropometrics were objectively assessed and obtained across all cycles, therefore allowing examination of body size before menopause and avoiding the potential for recall or reporting bias observed in previous studies. Indeed, few previous studies have considered adiposity in earlier adult life or its changes, and most of those that have were limited by recall bias resulting from the use of retrospective self-reported measures of earlier weight.[2,10,11,16,19] The bi-racial nature of the cohort also enabled examining associations across racial groups. Nonetheless, a few caveats should be mentioned. First, generalizability might be limited due to the self-selected nature of the sample. Yet, it seems unlikely that participants would have self-selected on the basis of relationships between menopausal age and any other variables since they were young at baseline. Moreover, the purpose of the CARDIA study was to examine coronary risk and not menopause per se, with the association of menopause as a risk factor of CVD being still unknown at the time of data collection. Recall bias due to self-report of ANM might be another limitation; however, reporting of menopause has been found to be highly reproducible.[12,62] The data were subject to right censoring because participants had ''survived'' (not yet postmenopausal). A large proportion of women in the youngest age groups had not yet reached menopause, but the analysis methods, which are standard for this type of study,[3,12] allowed their inclusion. Our data were also left-truncated because women with a reported age at menopause below age 40 were not present in the sample. However, our analyses accounted for entry at age 40 years and above. Lastly, some of our results might be due to chance given the number of multiple comparisons; however, this has been minimized after performing a post hoc Bonferroni correction and comparing the corrected and uncorrected CIs, which were similar.

CONCLUSIONS

This study is one of the few prospective studies of objectively assessed anthropometric measures and ANM. Taken together, these findings suggest that baseline BMI and WC are predictors of ANM in middle-aged women. Premenopausal hypertension and also dietary fat intake were also significantly related to an earlier ANM, highlighting that menopausal age is at least, in part, determined by modifiable factors. Further research is warranted on the role of longitudinal changes in adiposity and ANM as this may help inform women and their healthcare providers of ways to modify their risk of an earlier menopause and the health conditions associated with it.

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