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ORIGINAL RESEARCH

Relationship Between Age at Menopause, Obesity, and Incident Heart Failure: The Atherosclerosis Risk in Communities Study

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BACKGROUND: The mechanisms linking menopausal age and heart failure (HF) incidence are controversial. We investigated for heterogeneity by obesity on the relationship between menopausal age and HF incidence.

METHODS AND RESULTS: Using postmenopausal women who attended the Atherosclerosis Risk in Communities Study Visit 4, we estimated hazard ratios of incident HF associated with menopausal age using Cox proportional hazards models, testing for effect modification by obesity and adjusting for HF risk factors. Women were categorized by menopausal age: <45 years, 45 to 49 years, 50 to 54 years, and ≥55 years. Among 4441 postmenopausal women, aged 63.5±5.5 years, there were 903 incident HF events over a mean follow-up of 16.5 years. The attributable risk of generalized and central obesity for HF incidence was greatest among women who experienced menopause at age ≥55 years: 11.09/1000 person-years and 7.38/1000 person-years, respectively. There were significant interactions of menopausal age with body mass index and waist circumference for HF incidence, $P_{interaction}$ 0.02 and 0.001, respectively. The hazard ratios of incident HF for a SD increase in body mass index was elevated in women with menopausal age <45 years [1.39 (1.05–1.84)]; 45–49 years [1.33, (1.06–1.67)]; and ≥55 years [2.02, (1.41–2.89)]. The hazard ratio of incident HF for a SD increase in waist circumference was elevated only in women with menopausal age ≥55 years [2.93, (1.85–4.65)].

CONCLUSIONS: As obesity worsened, the risk of developing HF became significantly greater when compared with women with lower body mass index and waist circumference, particularly among those who had experienced menopause at age ≥55 years.

Key Words: heart failure ■ menopause ■ obesity

Menopause has emerged as a female-specific risk factor for cardiovascular diseases[1] such as heart failure (HF). Although early menopause (the occurrence of menopause at <45 years of age) has been associated with HF in prior studies,[2–4] there is a gap in knowledge regarding the influence of late menopause, the occurrence of menopause at ≥55 years, on HF incidence. The influence of obesity on the association between menopausal age and HF incidence has not been previously investigated. HF affects ≈3.2 million American women.[5] Approximately 10% of women experience natural menopause before 45 years of age.[3] It is important to understand the associations between menopausal age and HF incidence to better target high-risk women for risk factor modification and close surveillance.

Menopause is also associated with obesity.[6] Underweight women have an increased risk of experiencing early menopause, while overweight and obese women are more likely to experience menopause at

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CLINICAL PERSPECTIVE

What Is New?

- As obesity worsens in women, the risk of developing heart failure significantly increases when compared with women with lower body mass index and waist circumference, particularly in those with menopausal age ≥55 years.

What Are the Clinical Implications?

- Maintenance of a healthy body weight and waist circumference may be protective against developing HF, particularly among women who experience menopause at ≥55 years.
- A public heath campaign advocating weight management may be useful for heart failure prevention in postmenopausal women.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities Study
ELITE	Early versus Late Intervention Trial with Estradiol
SWAN	Study of Women's Health across the Nation
WC	waist circumference

later ages.[6] This association is complicated because body fat deposition increases during the menopausal transition and postmenopausal period.[7–9] Adipose tissue is a major source of estrogenic and androgenic steroids,[10] and the changes in sex hormone concentrations that occur after the menopausal transition could also influence the regulation of body fat deposition.[11]

Generalized and central obesity have been associated with HF incidence in multiple studies[12–16] and account for 14% of HF cases in women.[5] The relationship between obesity and incident HF is related to hemodynamic and anatomic cardiac changes, hormonal and metabolic changes, inflammation, and comorbidities resulting from excess body fat.[17–19] In this study, we investigated for the presence of heterogeneity by obesity on the relationship between menopausal age and HF incidence in postmenopausal women of the ARIC study (Atherosclerosis Risk in Communities) at Visit 4. We hypothesized that (1) generalized obesity, indicated by body mass index (BMI), and (2) central obesity, indicated by waist circumference (WC), will moderate the association between menopausal age and HF incidence with greater HF risks in obese women who experienced menopause before 45 years of age. Our conceptual model is depicted in Figure 1.

METHODS

Study Population and Sample

Instructions on how to obtain the data set used for this study can be obtained directly from the ARIC study at https://sites.cscc.unc.edu/aric. The ARIC study prospectively enrolled 15 792 participants including 8710 women, from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland between 1987 and 1989. Six follow-up Visits have been completed; Visit 2 (1990–1992), Visit 3 (1993–1995), Visit 4 (1996–1998), Visit 5 (2011–2013), Visit 6 (2016–2017), and Visit 7 (2018–2019). The ARIC study design and methods have been published.[20] ARIC participants were contacted annually before 2012 and semi-annually afterwards through telephone calls. The ARIC study protocol was approved by Institutional Review Boards at participating institutions and informed consent was obtained from participants.

ARIC Visit 4 serves as baseline for our analysis. Women were considered initially ineligible if they reported having menstrual periods in the preceding 2 years before the Visit 4 examination. We included women with natural or surgical menopause at ARIC Visit 4 (n=5539). In keeping with prior ARIC study analyses, we sequentially excluded Black women from the Minnesota or Maryland centers (n=15) because of their small numbers. We also excluded women who were not of Black or White race (n=26). Next, we excluded women who were missing information on menopausal age (n=626), those who had undergone hysterectomy without bilateral oophorectomy before 55 years of age (n=23) because of inability to accurately define their menopause age, those with missing information on BMI or WC (n=10), women who were underweight, BMI <18.5 kg/m^2 (n=53), those missing information on HF incidence (n=279), and those with prevalent HF at Visit 4 (n=66). Our final sample size of 4441 postmenopausal women included 3636 women with natural menopause and 808 with surgical menopause. Our sample size flow diagram is shown in Figure S1.

Baseline Measurements at Visit 4

Standardized protocols were used to collect data on participant characteristics and known HF risk factors[21,22] such as diabetes, hypertension, kidney function, inflammation, left ventricular hypertrophy, and myocardial infarction (MI) at all follow-up visits. Chronological age, menopausal status, menopausal age, annual income (an indicator of socioeconomic status), smoking, alcohol use, and medication use were obtained using self-report.

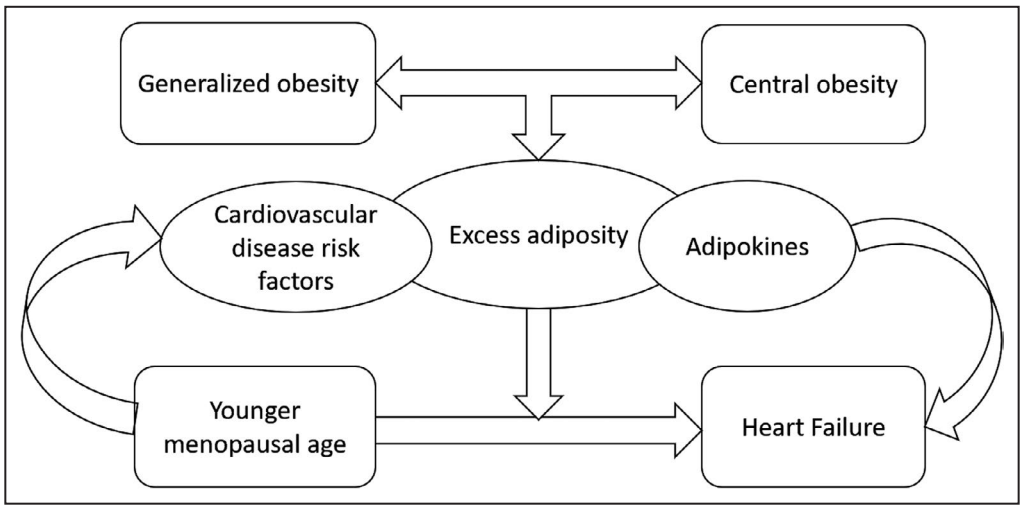

Figure 1. Conceptual model depicting the influence of obesity on the relationship between menopausal age and heart failure.

BMI was calculated by dividing weight by the square of height. Women were classified as normal weight if BMI was between 18.5 and 24.9 kg/m^2, overweight if BMI was between 25.0 and 29.9 kg/m^2, and obese if BMI was ≥30.0 kg/m^2. WC was measured at the umbilicus in light clothing. Women were classified as having central obesity if waist circumference was >88 cm. Two measurements of resting blood pressure were obtained and the average value was used. Diabetes was defined as fasting blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, or self-reported physician diagnosis of/or treatment for diabetes. Glucose was measured using the hexokinase method.[23] Fasting plasma total cholesterol and high-density lipoprotein cholesterol were measured by enzymatic methods.[24] Glomerular filtration rate was estimated using the chronic kidney disease epidemiology collaboration equation.[3] High-sensitivity C-reactive protein was measured with an immunonephelometric assay on a BNII autoanalyzer (Siemens Healthcare Diagnostics, Deerfield, Illinois) with a coefficient of reliability of 0.99.[25] Left ventricular hypertrophy was defined by Cornell criteria using an ECG. Prevalent coronary heart disease was based on information from annual telephone calls, review of hospital discharge diagnoses, and death certificates, and defined as definite or probable MI, definite fatal coronary heart disease, or cardiac procedure on or before Visit 4.[26] After the baseline visit, all MI events in the ARIC study have been adjudicated.[27] Prevalent MI at Visit 4 is a combination of self-report (and MI detected on ECG) at Visit 1 and adjudicated events before Visit 4. Prevalent HF at Visit 4 was determined from hospital discharge lists or death certificates as *International Classification of Diseases (ICD), Ninth Revision* code 428 or *ICD, Tenth Revision* code I50.[26]

Incident HF Definition

Incident HF was defined as the first hospitalization or death from HF. Hospital records of ARIC participants were reviewed to obtain information on HF hospitalizations, and death certificates were examined to identify HF-related deaths.[28] ARIC participants were contacted annually before 2012 and semi-annually afterwards to obtain information on HF events. Before 2005, HF events were determined from hospital discharge lists or death certificates that included *ICD Ninth Revision* code 428 or *ICD Tenth Revision* code I50 as a primary or secondary diagnosis or among the listed causes of death.[26] HF events after January 1, 2005 have been adjudicated by an expert panel.[29] This study utilized HF information based on *ICD* codes and those available until December 31, 2017.

Statistical Analysis

In keeping with prior studies,[3,4] participants were categorized according to menopausal age: <45, 45–49, 50–54, and ≥55 years. Highly skewed variables were log-transformed. Data are presented according to categories of menopausal age using means (SD) or median (interquartile range) for continuous variables and percentage for categorical variables, and comparisons were made between the groups using χ^2 tests for categorical variables and analysis of variance for continuous variables. Kaplan–Meier plots for incident HF are displayed according to menopausal age categories using chronological age at time of event or censoring on the time scale, and compared using the log-rank test. We calculated incidence rates of HF according to obesity and menopausal age categories. Participants were censored if they were lost to follow-up or failed

Table 1. Characteristics of Study Participants at ARIC Visit 4 According to Menopausal Age Categories; The ARIC Study, 1996 to 1998

Characteristics	Menopausal age category, y				*P* value
	<45	46–49	50–54	≥55	
Number of participants	1200	1515	1468	258	
Chronological age, y	63.5 (5.7)	63.0 (5.4)	63.6 (5.4)	65.7 (4.8)	<0.0001
Menopausal age, y	39.5 (3.3)	46.9 (1.5)	51.3 (1.4)	55.7 (1.1)	<0.0001
White race, %	65.7	76.8	83.7	79.1	<0.0001
Visit 4 center					<0.0001
Forsyth county, NC, %	25.1	23.8	23.2	24.8	
Jackson, MS, %	30.9	21.7	14.8	18.2	
Minneapolis, MN, %	18.8	26.3	33.3	26.0	
26.0	25.3	28.2	28.8	31.0	
Current cigarette smoking, %	15.5	14.4	11.1	6.6	<0.0001
Current alcohol use, %	34.6	45.6	47.6	41.9	<0.0001
Hormone therapy use					<0.0001
Never, %	32.8	39.8	46.1	50.0	
Past, %	62.8	56.4	49.1	45.0	
Current, %	4.5	3.8	4.8	5.0	
Annual income					<0.0001
<$25 000, %	47.1	38.5	36.9	39.6	
≥$25 000 to <$50 000, %	32.0	35.6	35.8	35.3	
≥$50 000 to <$100 000, %	17.3	20.8	21.5	20.4	
≥$100 000, %	3.7	5.1	5.7	4.7	
Body mass index, kg/m^2	28.9 (5.7)	28.7 (6.1)	28.8 (6.1)	28.8 (5.7)	0.91
Waist circumference, cm	101.4 (15.5)	100.7 (15.9)	100.5 (15.7)	100.8 (15.0)	0.58
Diabetes, %	17.8	15.2	12.8	15.6	0.006
Hypertension, %	55.4	47.5	45.2	47.3	<0.0001
Total cholesterol, mg/dL	207.8 (36.6)	209.3 (36.4)	208.3 (35.8)	210.6 (37.3)	0.56
High-density lipoprotein cholesterol, mg/dL	55.7 (16.3)	55.8 (17.3)	54.7 (15.7)	54.0 (15.2)	0.14
Statin therapy, %	10.5	9.8	10.5	9.0	0.79
Glomerular filtration rate, mL/min per 1.73 m^2	86.6 (17.3)	86.4 (16.4)	86.2 (15.1)	82.7 (15.9)	0.005
High-sensitivity C-reactive protein, mg/L	3.5 (1.5, 7.0)	3.2 (1.3, 6.6)	2.7 (1.2, 5.5)	2.8 (1.0, 6.1)	<0.0001
Left ventricular hypertrophy, %	4.8	3.3	4.3	5.1	0.36
Coronary heart disease, %	4.0	3.4	3.3	3.5	0.83

Values are means (SD) or median (interquartile range) unless otherwise stated. High-sensitivity C-reactive protein was log transformed because of skewness. *P* values were determined using χ^2 tests for categorical variables and Analysis of Variance for continuous variables. Missing values were <3% for all variables.
ARIC indicates Atherosclerosis Risk in Communities Study; MN, Minnesota; MS, Mississippi; and NC, North Carolina.

to experience HF before administrative censoring on December 31, 2017.

Cox proportional hazards models were used to examine the associations between menopausal age categories and HF incidence, testing for effect modification by obesity and sequentially adjusting for patient characteristics and known HF risk factors. There was a significant interaction between menopausal age category and BMI for HF incidence ($P_{interaction}$ 0.02). We calculated unadjusted and adjusted hazard ratios of incident HF associated with a SD increase in BMI for each menopausal age category. Model 1 was our unadjusted analysis. In model 2, we adjusted for demographic variables; Visit 4 we adjusted for age, and race/center groups. In model 3, we incorporated lifestyle variables and known HF risk factors, annual income, hormone therapy, cigarette smoking, alcohol use, diabetes, hypertension, estimated glomerular filtration rate, high-sensitivity C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, statin

Table 2. Incidence Rates* of Heart Failure According to Obesity and Menopausal Age Categories: The ARIC Study, 1996 to 2017

Category	Menopausal age, y			
	<45	45–49	50–54	≥55
Generalized obesity				
Normal weight	11.89	7.8	8.15	5.1
Overweight	12.91	12.04	8.79	9.66
Obese	21.3	16.05	13.92	16.19
Attributable risk because of overweight	1.02	4.24	0.64	4.56
Attributable risk because of obesity	9.41	8.25	5.77	11.09
Central obesity				
Absent	12.32	7.49	6.85	4.77
Present	16.54	13.58	11.34	12.15
Attributable risk because of central obesity	4.22	6.09	4.49	7.38

ARIC indicates Atherosclerosis Risk in Communities.
*Incidence rates of heart failure were calculated per thousand person-years.

therapy, left ventricular hypertrophy, and prevalent coronary heart disease. MI is a strong HF risk factor[21]; therefore, we included MI during follow-up in model 4 as a time-varying covariate.

There was a significant interaction between menopausal age category and WC ($P_{interaction}$ 0.001). We calculated unadjusted and adjusted hazard ratios of incident HF associated with a SD increase in WC for each menopausal age category using a similar adjustment process. The average age of menopause in the United States is 50 to 52 years.[30] Using the 50 to 54 menopausal age as reference, we plotted the hazard ratios of incident HF for the other menopausal age categories separately at rising values of BMI and WC. The proportional hazards

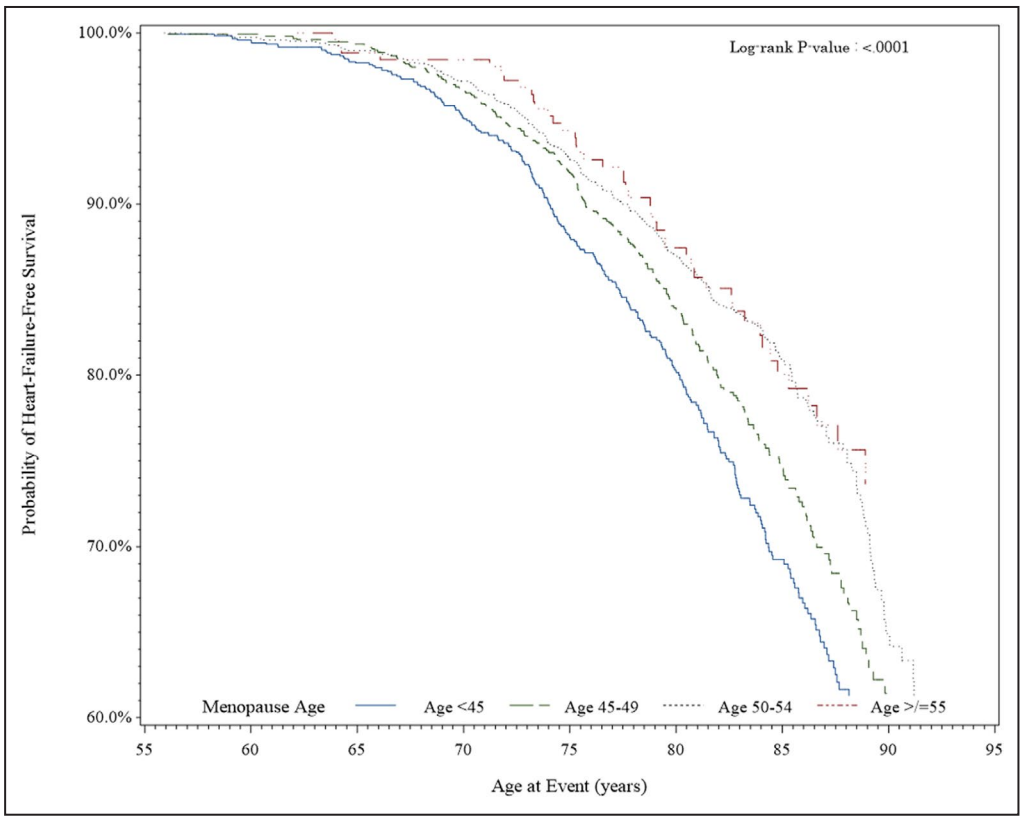

Figure 2. Survival probabilities for incident heart failure according to menopausal age categories at ARIC Visit 4.
ARIC indicates Atherosclerosis Risk in Communities.

Table 3. Hazard Ratios of Incident Heart Failure According to Menopausal Age Categories Associated With a SD Increase in Body Mass Index and Waist Circumference: The ARIC Study, 1996 to 2017

	Menopausal age category, y				
	<45	45–49	50–54	≥55	
	1200	1515	1468	258	
Number of participants*	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	$P_{interaction}$
Body mass index					
Model 1	1.41 (1.26–1.57)	1.35 (1.22–1.49)	1.32 (1.19–1.47)	1.63 (1.27–2.09)	0.45
Model 2	1.43 (1.27–1.60)	1.39 (1.25–1.54)	1.33 (1.20–1.48)	1.76 (1.37–2.26)	0.25
Model 3	1.35 (1.02–1.78)	1.31 (1.04–1.65)	1.01 (0.75–1.34)	1.91 (1.32–2.77)	0.05
Model 4	1.39 (1.05–1.84)	1.33 (1.06–1.67)	0.98 (0.73–1.31)	2.02 (1.41–2.89)	0.012
Waist circumference					
Model 1	1.51 (1.34–1.70)	1.50 (1.32–1.62)	1.39 (1.24–1.55)	1.87 (1.41–2.47)	0.26
Model 2	1.46 (1.29–1.64)	1.44 (1.29–1.61)	1.35 (1.21–1.53)	1.93 (1.45–2.57)	0.18
Model 3	1.26 (0.95–1.68)	1.19 (0.93–1.52)	1.02 (0.77–1.35)	2.70 (1.69–4.31)	0.004
Model 4	1.31 (0.98–1.75)	1.18 (0.92–1.52)	1.00 (0.75–1.32)	2.93 (1.85–4.65)	0.001

SD was 6.0 kg/m^2 for body mass index and 15.7 cm for waist circumference in the study sample.
Model 1, unadjusted.
Model 2, adjusted for Visit 4 age and race/center groups.
Model 3, model 2 adjusted for annual income, hormone replacement therapy use, cigarette smoking, alcohol drinking, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin medication use, left ventricular hypertrophy, high-sensitivity C-reactive protein, glomerular filtration rate, and prevalent coronary disease.
Model 4, model 3 adjusted for myocardial infarction during follow-up.
ARIC indicates Atherosclerosis Risk in Communities; and HR, hazard ratio.
*The number of participants refers to the number of women in each of the menopausal age categories.

assumption was tested by visual examination of the log-log plots. *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

The mean±SD was 63.5±5.5 years for chronological age and 46.9±5.5 years for menopausal age at ARIC Visit 4. The mean±SD was 47.6±5.1 years for age at natural menopause and 43.5±5.9 years for age at surgical menopause. The mean±SD was 28.8±6.0 kg/m^2 for BMI and 100.8±15.7 cm for WC at ARIC Visit 4. Characteristics of our study participants at Visit 4 are shown according to menopausal age categories in Table 1. White women were more likely to experience menopause between 50 and 54 years, while Black women were more likely to experience menopause at <45 years of age. Cigarette smoking, diabetes, hypertension, coronary heart disease, and elevated inflammatory markers were more common and annual income was least among women who experienced early menopause. Alcohol use was most common in the 50 and 54 years menopausal age category.

Over a mean follow-up period of 16.5±5.6 years, we observed 903 incident HF events. The incidence rates of HF were 15.6/1000, 12.1/1000, 10.3/1000, and 10.7/1000 person-years for women who experienced menopause at <45 years, 45 to 49 years, 50 to 54 years, and ≥55 years of age, respectively. The incidence rates of HF were greatest among women with generalized or central obesity who had also experienced menopause at <45 years of age, 21.3/1000 and 16.3/1000 person-years, respectively (Table 2). However, the attributable risk of generalized obesity, overweight, and central obesity for HF incidence was greatest among women who experienced menopause at ≥55 years, 11.09/1000, 4.56/1000, and 7.38/1000 person-years, respectively. The probability of a HF-free survival during follow-up was lowest in women with early menopause (Figure 2). There was a significant interaction between menopausal age and BMI for HF incidence ($P_{interaction}$ 0.02), justifying the presentation of our results according to menopausal age categories. The adjusted hazard ratios of incident HF associated with a SD increase in BMI were 1.39 (1.05–1.84), 1.33 (1.06–1.67), 0.98 (0.73–1.31), and 2.02 (1.41–2.89) for women with menopausal age <45 years, 45 to 49 years, 50 to 54, and ≥55 years, respectively. (Table 3).

There was also a significant interaction between menopausal age and WC for HF incidence ($P_{interaction}$ 0.001). The adjusted hazard ratios of incident HF associated with a SD increase in WC were 1.31 (0.98–1.75), 1.18 (0.92–1.52), 1.00 (0.75–1.32), and 2.93 (1.85–4.65) for women with menopausal age <45, 45 to 49, 50 to 54, and ≥55 years, respectively. (Table 3). As BMI and WC increased, the adjusted hazard ratios of incident HF became greater in women who experienced

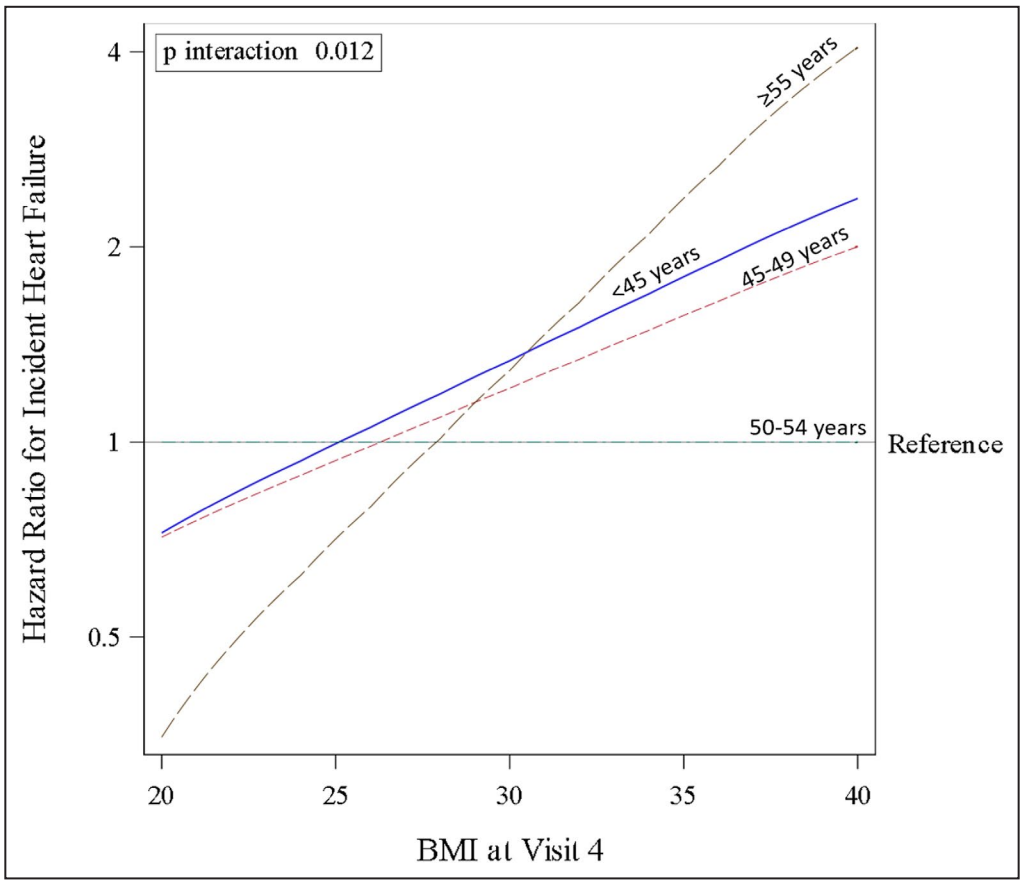

Figure 3. Hazard ratios of incident heart failure according to menopausal age categories at increasing values of body mass index.
Hazard ratios are adjusted for Visit 4 age, race/center groups, annual income, hormone therapy use, cigarette smoking, alcohol drinking, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, left ventricular hypertrophy, high-sensitivity C-reactive protein, glomerular filtration rate, prevalent coronary disease, and myocardial infarction during follow-up. The 50 to 54 years menopausal age category was used as reference. BMI indicates body mass index.

menopause at ≥55 years, when compared with the other menopausal age categories (Figures 3 and 4).

DISCUSSION

In our study involving postmenopausal women at ARIC Visit 4, obesity modified the association between menopausal age category and HF incidence. Although HF incidence was greatest among women with early menopause, the attributable risk of both generalized and central obesity for HF incidence was higher among those who had experienced late menopause. As obesity worsened, the risk of developing HF became significantly greater when compared with women with lower BMI and WC, particularly for those who had experienced late menopause. Maintenance of a healthy body weight and WC may be protective against developing future HF, especially for women with late menopause. This novel finding offers insight into a possible mechanistic basis for HF after menopause and agrees with reports that obese women have greater cardiovascular disease risk.[31]

Obesity affects women of all racial and ethnic groups.[31,32] Generalized obesity is a known risk factor for incident HF.[12] The influence of generalized obesity on the relationship between menopausal age category and HF incidence was independent of established HF risk factors but varied according to the reproductive life span, with the greatest influence on women who experienced late menopause. Obesity causes enlargement of adipocytes, resulting in adipocyte dysfunction that is characterized by increased secretion of proinflammatory adipokines and decreased secretion of anti-inflammatory adipokines.[10] Levels of adipokines such as adiponectin are decreased in obese individuals while leptin increases with adiposity.[33] Elevated leptin and decreased adiponectin levels are associated with inflammation and insulin resistance,[10] which are

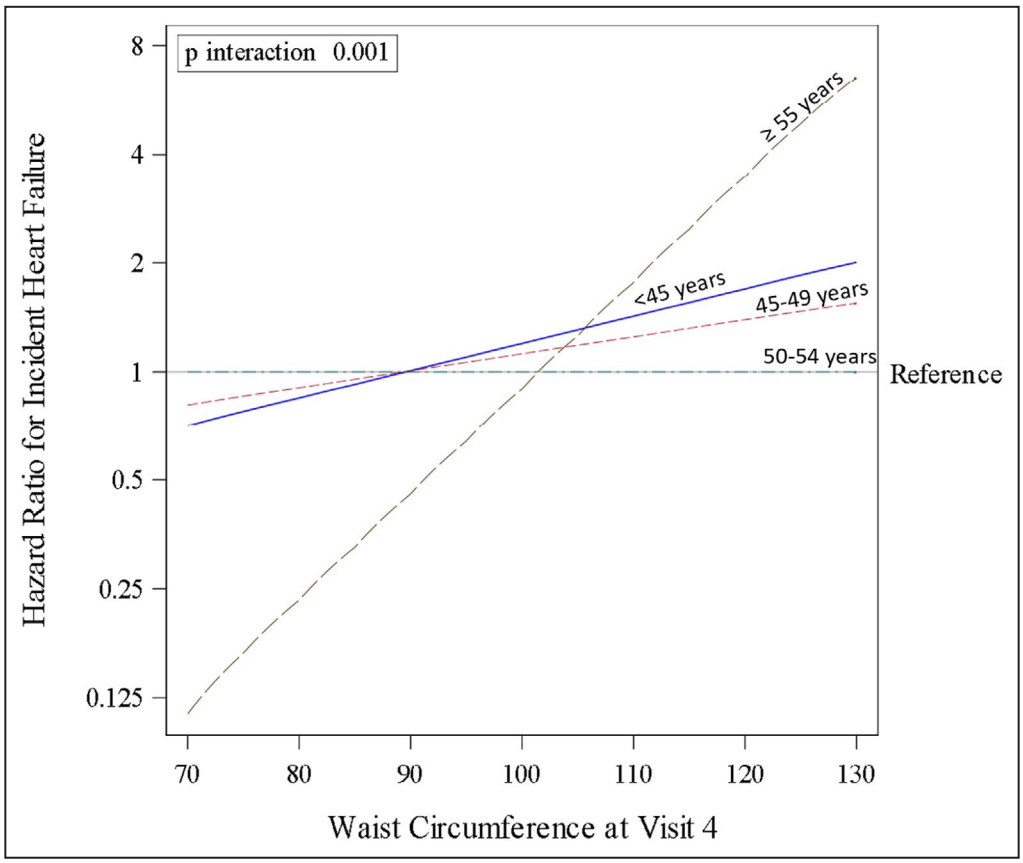

Figure 4. Hazard ratios of incident heart failure according to menopausal age categories at increasing values of waist circumference.
Hazard ratios are adjusted for age, race/center groups, annual income, hormone therapy use, cigarette smoking, alcohol drinking, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, left ventricular hypertrophy, high-sensitivity C-reactive protein, glomerular filtration rate, prevalent coronary disease, and myocardial infarction during follow-up. The 50 to 54 years menopausal age category was used as reference.

known HF risk factors. Ovarian estrogen production decreases after menopause, causing relative androgen predominance,[34] and adipose tissue becomes the major source of estrogens and androgens.[10] The temporal sequence between obesity and sex hormonal changes has previously been established in women at midlife.[35] The postmenopausal hormonal state is characterized by estrogen deficiency and an androgenic milieu that has been associated with adverse left ventricular remodeling in the Multiethnic Study of Atherosclerosis.[36] Menopause is also associated with an unfavorable cardiovascular disease risk profile that comprises known HF risk factors such as metabolic derangements, inflammation, and lipid abnormalities.[2,37]

Adipokines also influence androgenicity because leptin has been associated with increased testosterone and decreased sex hormone binding globulin levels, while adiponectin has been linked with decreased testosterone and increased sex hormone binding globulin levels among postmenopausal women of the ELITE study (Early versus Late Intervention Trial with Estradiol).[10] This is in congruence with reports from SWAN (Study of Women's Health Across the Nation) study where greater body weight and WC predicted an androgenic profile characterized by lower sex hormone binding globulin and higher testosterone levels during follow-up across the menopausal transition.[35] We surmised that the influence of obesity on androgenicity and subsequently HF development becomes greater as BMI increases, with the most robust influence among women with late menopause where excess adiposity possibly counteracts the benefits of a delay in sex hormonal changes that occur with the menopausal transition, and the absence of excessive adiposity of any degree may confer a protective effect against HF development.

Central obesity is common after menopause[2,34] and also predicts HF incidence.[12] Central obesity similarly modified the relationship between menopausal age category and HF incidence. This finding is not surprising because BMI is highly correlated with WC.[13] Consequently, HF prevention in women with late

menopause should involve monitoring both BMI and WC, with utilization of weight loss or weight control strategies to mitigate the adverse effects of excess adiposity.

Our study has multiple strengths. ARIC is a prospective study with a biracial cohort and large number of participants from 4 geographic regions in the United States. Data collection procedures and HF events were highly standardized. We are the first to investigate the effects of obesity on the association between menopausal age and HF. There are also limitations. Six hundred twenty-six postmenopausal women were missing information on menopausal age at ARIC Visit 4 and were excluded from this analysis. Menopausal age was based on self-report, but women recall their menopausal transition with moderate accuracy.[38] Because measurements of BMI and WC were obtained at ARIC Visit 4 and not at the exact time of menopause, weight changes may have occurred in the interval between the onset of menopause and ARIC Visit 4, which was our study baseline. However, the causes of weight changes in postmenopausal women are a subject of controversy. Evidence from the SWAN study by Wildman et al[35] offers credence to other studies that have reported that weight gain after menopause is more likely a consequence of aging rather than the menopausal transition itself. Consequently, we adjusted for chronological age in our analysis. The mean menopausal age of our study participants was 46.9 years, which is less than the average range of 50 to 52 years reported in the US population. Therefore, our findings may not be generalizable to other cohorts but are a reflection of our study sample, which comprised 6% of women with menopausal age ≥55 years. Our definition of incident HF in ARIC was based on *ICD* codes and included events that listed HF as either the primary or secondary diagnosis or causes of death. Irrespective, the ARIC HF *ICD* classification protocol has been evaluated previously, and performed similarly to other HF classification criteria, by exhibiting a high specificity and poor sensitivity in identifying any HF (decompensated or chronic).[29] Risk factors such as sex hormones and adipokines were not included in this analysis. Information on HF subtype was available for 500 (55.4%) HF events (those that occurred after January 1, 2005). This included 270 (54%), 207 (41.4%), and 23 (4.6%) cases with preserved, reduced, or recovered left ventricular ejection fraction, respectively. Because of insufficient power, we did not perform our analysis according to HF subtype.

CONCLUSIONS

Obesity modified the association of menopausal age category and HF incidence. As obesity worsened, the risk of developing HF became significantly greater when compared with women with lower BMI and WC, particularly among those who had experienced menopause at ≥55 years of age. Maintenance of a healthy body weight and waist circumference may be protective against developing HF, particularly among women who have experienced late menopause. These findings support a public health campaign advocating weight management in postmenopausal women, particularly among those with late menopause. Our findings should be replicated in other cohorts.

ARTICLE INFORMATION

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Disclosures

The authors have no conflicts of interests to disclose.

Supplemental Material

Figure S1

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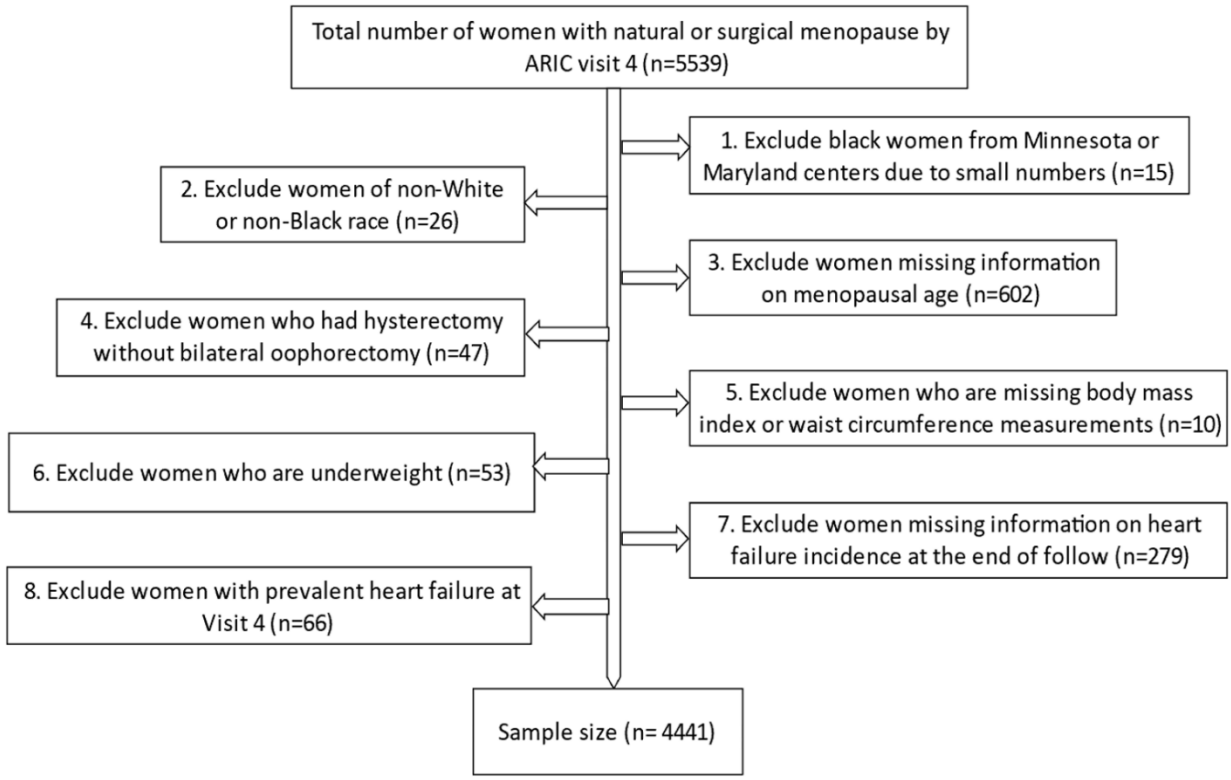
Supplemental Material

Figure S1. Sample size flow diagram at ARIC Visit 4.



ARIC, Atherosclerosis Risk in Communities