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Authors

Cordola Hsu, Amber R
Xie, Bin
Peterson, Darleen V
et al.

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ORIGINAL ARTICLE

Metabolically Healthy/Unhealthy Overweight/Obesity Associations With Incident Heart Failure in Postmenopausal Women

The Women's Health Initiative

Amber R. Cordola Hsu, PhD, MPH; Bin Xie, PhD, MS; Darleen V. Peterson, PhD, MPH, MA; Michael J. LaMonte, PhD, MPH; Lorena Garcia, DrPH, MPH; Charles B. Eaton, MD, MS; Scott B. Going, PhD; Lawrence S. Phillips, MD; JoAnn E. Manson, MD, DrPH; Hoda Anton-Culver, PhD*; Nathan D. Wong, PhD, MPH*

BACKGROUND: Obesity is associated with an increased risk of heart failure (HF); however, how metabolic weight groups relate to HF risk, especially in postmenopausal women, has not been demonstrated.

METHODS: We included 19 412 postmenopausal women ages 50 to 79 without cardiovascular disease from the Women's Health Initiative. Normal weight was defined as a body mass index ≥18.5 and <25 kg/m^2 and waist circumference <88 cm and overweight/obesity as a body mass index ≥25 kg/m^2 or waist circumference ≥88 cm. Metabolically healthy was based on <2 and unhealthy ≥2 cardiometabolic traits: triglycerides ≥150 mg/dL, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or blood pressure medication, fasting glucose ≥100 mg/dL or diabetes medication, and HDL-C (high-density lipoprotein cholesterol) <50 mg/dL. Risk factor-adjusted Cox regression examined the hazard ratios (HRs) for incident hospitalized HF among metabolically healthy normal weight (reference), metabolically unhealthy normal weight, metabolically healthy overweight/obese, and metabolically unhealthy overweight/obese.

RESULTS: Among our sample, 455 (2.34%) participants experienced HF hospitalizations over a mean follow-up time of 11.3±1.1 years. Compared with metabolically healthy normal weight individuals, HF risk was greater in metabolically unhealthy normal weight (HR, 1.66 [95% CI, 1.01–2.72], *P*=0.045) and metabolically unhealthy overweight/obese individuals (HR, 1.95 [95% CI, 1.35–2.80], *P*=0.0004), but not metabolically healthy overweight/obese individuals (HR, 1.15 [95% CI, 0.78–1.71], *P*=0.48). Subdividing the overweight/obese into separate groups showed HRs for metabolically unhealthy obese of 2.62 (95% CI, 1.80–3.83; *P*<0.0001) and metabolically healthy obese of 1.52 (95% CI, 0.98–2.35; *P*=0.06).

CONCLUSIONS: Metabolically unhealthy overweight/obese and metabolically unhealthy normal weight are associated with an increased risk of HF in postmenopausal women.

Key Words: diabetes ■ heart failure ■ postmenopause ■ obesity ■ women

Heart failure (HF) affects over 6 million US adults.[1] Diabetes mellitus (DM), coronary heart disease, and hypertension greatly increase the risk of developing HF.[2] Obesity is a key risk factor for HF.[3–6] Abdominal obesity is also associated with an increased risk of HF.[7] The Physicians' Health Study described that overweight and obesity were associated with a greater risk of HF,[6] and the Framingham Heart Study showed an increased incidence of HF across the entire spectrum of body mass index (BMI), with a 7% increase in HF incidence

Correspondence to: Nathan D. Wong, Division of Cardiology, University of California, Irvine, C240, Medical Sciences, Irvine, CA 92697. Email ndwong@uci.edu
*N.D. Wong and H. Anton-Culver contributed equally.
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WHAT IS NEW

- Although obesity is common among postmenopausal women and is a known risk factor for heart failure, our investigation shows increases in risk for heart failure among those who are metabolically unhealthy normal weight or overweight/obese, but not when one is metabolically healthy even if overweight/obese.
- Heart failure risk is also further complicated by the presence of diabetes and directly related to the number of abnormal metabolic factors.

WHAT ARE THE CLINICAL IMPLICATIONS

- Metabolic risk factors predisposed to increases in heart failure risk even in those of normal weight, and should thus be monitored and controlled according to guidelines. Moreover, those who are metabolically unhealthy and overweight/obese are at even higher risk and warrant close clinical supervision.
- Future therapies might address whether these heart failure risks due to metabolic abnormalities, even in those of normal weight, can be reduced.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
BP	blood pressure
CHS	Cardiovascular Health Study
CVD	cardiovascular disease
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HRs	hazard ratios
MHNW	metabolically healthy normal weight
MHO	metabolically healthy overweight/obese
MUHNW	metabolically unhealthy normal weight
MUHO	metabolically unhealthy overweight/obese
WHI	Women's Health Initiative

in women for every 1 kg/m^2 increase in BMI.[4] Asian/Pacific Islander and Hispanic postmenopausal women have been found to have decreased incident HF rates, whereas Black women had increased rates of HF.[8] Lastly, Black postmenopausal women with obesity have been found to be at a greater risk for HF with preserved ejection fraction.[9]

Of more recent interest, however, is whether the presence of metabolic risk factors might affect the relation of obesity or even normal weight with the risk for developing HF. A recent study found a greater risk of HF in those who were metabolically healthy and unhealthy obese, as compared to those who were normal weight.[10] Others find the risk of HF is increased in patients with obesity regardless of cardiometabolic status.[11] It is not established if metabolic status might affect HF risk according to obesity status in older postmenopausal women.

The purpose of this study was to evaluate the relationship between metabolically healthy and unhealthy weight categories and the incidence of HF hospitalizations in US postmenopausal women. Our hypothesis was that the risk of incident HF hospitalizations among postmenopausal women would be greater among those who were of metabolically unhealthy normal weight (MUHNW), metabolically unhealthy overweight/obese (MUHO), and metabolically healthy overweight/obese (MHO) as compared to those metabolically healthy normal weight (MHNW).

METHODS

Study Population

The Women's Health Initiative (WHI) consisted of randomized clinical trials (N=68 132) and an observational cohort study (N=93 676).[12] The WHI makes specific datasets available to the public from the National Institutes of Health Biospecimen and Data Repository Coordinating Center. The clinical trial comprised 3 concurrent, randomized controlled trials among postmenopausal women aged 50 to 79 years: Hormone Therapy trials, the Dietary Modification trial, and the Calcium and Vitamin D trial.[13] The WHI established a Data and Safety Monitoring Board, which was accountable for supervising the trial and safety of their participants.[12] WHI recruitment was conducted from 1993 to 1998 at 40 Clinical Centers in 24 states and the District of Columbia.[13] Recruitment took place locally, at Clinical Centers, and nationally at the National Institutes of Health, the WHI Clinical Coordinating Center in Seattle, WA, and various study-wide committees.[13]

All participants provided informed consent to participate at their local clinical center which obtained their own institutional review board approval to participate in the WHI.[13] Recruitment strategies included mass mailings, community presentations, local newspaper ads, public service announcements (television and radio), and health fairs.[13] All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Because of the sensitive nature of the data collected for this study, requests to access the datasets from qualified researchers may be sent to the Women's Health Initiative at whi.org.

A baseline cardiovascular disease (CVD) risk factor and biomarker subset sample of ≈25 000 participants was derived from specific samples of the WHI cohort, as previously described.[13] This included fasting serum glucose, total cholesterol, HDL-C (high-density lipoprotein cholesterol), and triglycerides[13] and are described in detail below.

Persons with prevalent CVD were excluded from our analysis since our hypothesis focused on examining the development of HF as a result of our metabolic obesity groups in the

primary prevention setting. This included those with a history of myocardial infarction, stroke, percutaneous intervention, HF, or peripheral arterial disease at baseline.

Measures and Outcomes

Overweight/obesity was defined by a BMI ≥25 kg/m^2 or elevated waist circumference (≥88 cm) and were measured by trained staff during clinic visits.[14–16] Metabolically unhealthy overweight/obesity (MUHO) was defined by having at least 2 of 4 cardiometabolic traits, including high triglycerides (≥150 mg/dL), elevated systolic blood pressure (BP; ≥130 mm Hg), or diastolic BP (≥85 mm Hg; based on averaging 2 baseline measurements and if only one BP measurement was known, the single value was used)[13] or antihypertensive drug use (including diuretics); high fasting glucose (≥100 mg/dL) or use of medications for DM (insulin and oral antidiabetics); and low HDL-C (<50 mg/dL).[14–16] Metabolically healthy overweight/obesity (MHO) was defined by having <2 of the above metabolic traits[14–16] in addition to being overweight/obese as defined above.

Normal body weight was defined as a BMI ≥18.5 and <25 kg/m^2 and without elevated waist circumference (<88 cm).[14–16] Metabolically unhealthy normal (MUHNW) was defined by having at least 2 of the 4 above metabolic traits.[14–16] Metabolically healthy normal (MHNW) was defined by having <2 of the above metabolic traits while being of normal body weight.[14–16]

Prevalent DM included those with known DM at baseline (self-report, fasting glucose ≥126 mg/dL or current insulin or oral medications for DM). Estimated glomerular filtration rate (eGFR) in ml/min/1.73m^2 was defined=([186.3×creatinine (mg/dL)^−1.154×age (years)^−0.203×0.742 (if female)×1.210 (if Black)]) based on the Modification of Diet in Renal Disease equation.[17] Alcohol intake was categorized as nondrinker, past drinker, <1 drink per month, <1 drink per week, 1 to <7 drinks per week, or 7+ drinks per week.[13] Total Healthy Eating Index Score was calculated from baseline food-frequency questionnaires providing a score from 0 to 100 based on sum of 12 components of healthy eating with higher scores indicating conformance to the 2005 United States Department of Agriculture dietary guidelines.[13]

Self-reported measures included age, race/ethnicity, income, smoking (current, past, or never), healthy eating index score, and total energy expenditure from recreational physical activity (metabolic equivalent-hours/wk).

Laboratory variables consisted of glucose, total cholesterol, HDL-C, and triglycerides were measured at Medical Research Laboratories/PPD and University of Minnesota labs.[13] Glucose was measured in serum via the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics, Indianapolis, Indiana) and the Gluco-quant Glucose/hexokinase reagent (Roche Diagnostics, Indianapolis, IN 46250) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation).[13] Total cholesterol was analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN).[13] HDL-C was isolated using heparin manganese chloride with the supernate measured enzymatically on the Hitachi 747.[13] Triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) and in serum using Triglyceride GB reagent (Roche Diagnostics, Indianapolis, IN 46250) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation).[13] Glucose and total cholesterol measures were obtained by multiple labs utilizing different techniques and various instruments (see CVD risk factor and biomarker assays section above).[13] The glucose and total cholesterol biomarkers were collected as a blood sample with participants fasting for at least 12 hours before draws.[13] The residual blood samples were stored at 4 °C for up to 1 hour until plasma or serum was separated from the cells.[13]

Incident HF hospitalizations, as previously defined by WHI, included diagnoses by a physician and receipt of medical treatment for HF during admission, including diuretics, digitalis, vasodilators, and angiotensin-converting enzyme inhibitors; or HF diagnosed by a physician and receipt of medical treatment for HF during admission plus documented impaired systolic or diastolic left ventricular function; or pulmonary edema or congestion by chest X-ray on admission; or dilated ventricles or poor left- or right-side ventricular function (eg, wall motion abnormalities) by echocardiography, radionuclide ventriculogram/multigated acquisition, or other contrast ventriculography or evidence of left ventricular diastolic dysfunction.[18] All incident HF hospitalizations were adjudicated using a standardized protocol by trained physicians locally for quality control for the WHI core study group to the end of the study.[18]

Data Analysis

The demographic, health, and metabolic characteristics of participants at baseline according to incident HF hospitalizations were compared using Pearson χ^2 test for categorical dependent variables and an independent *t* test for continuous variables. Measures were log-transformed if skewed to normalize outliers. HF rates per 1000 person-years were displayed across the disease groups. Among the 4 groups (MHO, MUHO, MHNW, MUHNW), the risk of incident HF hospitalizations using Cox regression analyses was evaluated, unadjusted, and adjusted for key covariates hypothesized to be potential confounders. Time to development of incident HF hospitalizations was defined as the number of days from enrollment to HF hospital admission (days were converted to years in the analysis). A sensitivity analysis was performed separating those classified as overweight/obese separately into overweight and obese in addition to normal weight which were then further stratified according to whether metabolically or unhealthy (6 groups total). The cumulative HF-free event rates by group across follow-up time were plotted using Kaplan-Meier curves along with the adjusted restricted cubic spline of metabolic health status versus BMI. The restricted cubic spline results of BMI adjusted for metabolic health status, prevalent diabetes, age, race/ethnicity, income, smoked ever, total healthy eating index, total energy expenditure from recreational physical activity (MET-hours/wk), and total cholesterol. We also examined using adjusted Cox regressions the contribution of each of the individual metabolic and obesity variables measured categorically and continuously (per SD) with incident HF, as well as tested whether there was a dose-response relationship of the number of obesity/cardiometabolic traits with HF risk.

Although our main analysis focused on the development of HF in those without CVD at baseline, we also did sensitivity analyses using additional Cox regression models where we additionally adjusted for prior CVD, as well as eGFR and alcohol

intake (eGFR in particular would have substantially reduced our sample size in our original model but including those with prior CVD compensated for this). Additional sensitivity analyses examined the impact of metabolically unhealthy status separated from overweight/obesity, as well as assigning all persons with DM to the metabolically unhealthy group.

All of the statistical tests were 2-sided, and all of the statistical analyses were performed using SAS Software Version 9.4.[19]

RESULTS

Table 1 compares general characteristics according to the presence of MHNW (reference group; 16.8%), MUHNW (5.9%), MHO (35.4%), and MUHO (41.9%). Those with MHNW had the lowest prevalence of DM, were predominately White (not of Hispanic origin), had a baccalaureate degree or higher, and had higher levels of alcohol consumption, physical activity, and HDL-C as compared to the other 3 groups. Those with MUHNW had the highest mean age, were mainly White, had some college, vocational training, or an associate's degree, reported lower income, and had higher prevalences of current smoking and total cholesterol levels as compared to the MHNW. The MHO group had the lowest mean age, were mostly Black, had some college, vocational training, or an associate's degree, reported a low to moderate income, and a lower prevalence of current smoking as compared to the MHNW. The MUHO group had the highest prevalence of DM, the majority were White (not of Hispanic origin), had some college, vocational training, or an associates degree, reported lower income, but had a higher prevalence of ever or current smoking, family history of heart attack, and higher waist circumferences, BMIs, glucose, and triglycerides as compared to the MHNW. The MUHNW and MUHO groups had the highest levels of both systolic and diastolic BP.

The mean follow-up time to incident HF hospitalization was 11.28±1.09 years, during which 455 cases were identified. The MHNW had the lowest incidence of HF, and the MUHO group had the highest incidence of HF. Those with MUHO had the highest incident HF hospitalizations rates per 1000 person-years (3.07) followed by those with MUHNW (2.86). Conversely, those with MHNW had the lowest incident HF hospitalization rate per 1000 person-years (1.03), and those with MHO were not much higher (1.28). Moreover, unadjusted hazard ratios were 2.78 (95% CI, 1.77–4.37) for MUHNW, 1.25 (0.86–1.81) for MHO, and 2.98 (2.12–4.18) for MUHO with fully adjusted hazard ratios (HRs) being 1.66 (1.01–2.72), 1.15 (0.78–1.71), and 1.95 (1.35–2.80), respectively (Table 2).

Kaplan-Meier curves for HF hospitalization-free probability in the 4 metabolic groups ($P<0.0001$ across groups) are displayed in the Figure. The MUHNW and MUHO groups are more likely to experience incident HF as compared to the MHNW and MHO groups. Figure I in the Data Supplement displays the adjusted restricted cubic spline of metabolic health status versus BMI. Metabolic unhealthy was significant (odds ratio, 1.54 [95% CI, 1.21–1.96], $P=0.0004$) as compared to metabolic healthy. BMI only spline knot 4 (31.19) was significant ($P=0.02$).

Table 3 shows results from the full Cox proportional hazards regression model demonstrating those with MUHO had the highest risk of HF (HR, 1.95 [95% CI, 1.35–2.80], $P=0.0004$) compared with MHNW (reference group) after adjusting for covariates. Moreover, those with MUHNW had an increased risk of HF (HR, 1.66 [95% CI, 1.01–2.72], $P=0.045$) but not those with MHO (HR, 1.15 [95% CI, 0.78–1.71], $P=0.48$). Other covariates, including prevalent DM, age, Hispanic/Latino ethnicity, moderate income, current cigarette smoking, and decreased physical activity were significantly associated with an increased risk of incident HF. From sensitivity analyses subdividing overweight/obese separately into overweight and obese in addition to normal weight stratified by metabolically healthy versus unhealthy (6 groups total), adjusted HRs for the MUHNW (HR, 1.66 [95% CI, 1.01–2.72], $P=0.044$) and metabolically unhealthy obese (HR, 2.62 [95% CI, 1.80–3.83], $P<0.0001$) were statistically significant as compared with MHNW (reference group). The metabolically healthy overweight (HR, 0.94 [95% CI, 0.59–1.48], $P=0.78$), metabolically unhealthy overweight (HR, 1.20 [95% CI, 0.79–1.84], $P=0.39$), and the metabolically healthy obese (HR, 1.52 [95% CI, 0.98–2.35], $P=0.06$) were not statistically significant as compared with MHNW (reference group) after adjusting for covariates.

From additional analyses examining the independent associations of our obesity (BMI and waist circumference) and cardiometabolic (systolic BP, diastolic BP, triglyceride, glucose, and HDL-C) measures with HF risk, each classified according to their cut points as previously defined, high waist circumference (HR, 1.63 [95% CI, 1.23–2.16], $P=0.0006$), elevated systolic BP (HR, 1.65 [95% CI, 1.31–2.07], $P<0.0001$), and elevated diastolic BP (HR, 1.33 [95% CI, 1.04–1.70], $P=0.02$) were statistically significant after adjusting for covariates (Table 4). When stratified by our metabolic weight groups, for the MHO group, systolic BP (HR, 3.58 [95% CI, 1.93–6.65], $P<0.0001$) and for the MUHO group, diastolic BP (HR, 1.44 [95% CI, 1.07–1.92], $P=0.01$) and glucose (HR, 1.49 [95% CI, 1.06–2.11], $P=0.02$) significantly predicted incident HF after adjusting for covariates. Table 5 shows the relation of the obesity and metabolic variables, each measured continuously (per SD), with HF risk. BMI (HR, 1.19 [95% CI, 1.03–1.38], $P=0.02$), waist circumference (HR, 1.20 [95% CI, 1.02–1.41], $P=0.03$), systolic BP (HR, 1.47 [95% CI, 1.32–1.64], $P<0.0001$), and glucose (HR, 1.26 [95% CI, 1.16–1.37], $P<0.0001$) were significantly associated with incident HF after adjusting for covariates.

Table 6 shows results from the adjusted Cox proportional hazards regression demonstrating a

Table 1. Baseline Sociodemographic and Other Metabolic Risk Factor Characteristics According to Metabolic Weight Categories in WHI Postmenopausal Women

	MHNW (n=3254) (reference)	MUHNW (n=1154)	MHO (n=6867)	MUHO (n=8137)	
	(16.8%)	(5.9%)	(35.4%)	(41.9%)	*P* value
Age, y (n=19412)	63.8±7.7	65.9±7.1	62.4±7.3	63.5±7.1	<0.0001
Prevalent diabetes (n=2369)	51 (1.6)	144 (12.5)	264 (3.8)	1910 (23.5)	<0.0001
Race/ethnicity (n=19412)					<0.0001
Asian or Pacific Islander	89 (2.7)	53 (4.6)	52 (0.8)	100 (1.2)	
Black	809 (24.9)	217 (18.8)	3031 (44.1)	2585 (31.8)	
Hispanic/Latino	568 (17.5)	215 (18.6)	1039 (15.1)	1367 (16.8)	
White (not of Hispanic origin)	1763 (54.2)	662 (57.4)	2684 (39.1)	4011 (49.3)	
Other	25 (0.8)	7 (0.6)	61 (0.9)	74 (0.9)	
Education (n=19251)					<0.0001
<12th grade	180 (5.6)	113 (9.9)	563 (8.3)	920 (11.4)	
High school diploma/GED	487 (15.0)	246 (21.5)	1155 (17.0)	1600 (19.9)	
Some college/associate degree/vocational training	1219 (37.6)	441 (38.6)	2609 (38.3)	3322 (41.2)	
Baccalaureate degree/higher	1353 (41.8)	342 (30.0)	2483 (36.5)	2218 (27.5)	
Income (n=18715)					<0.0001
Less than $19999	521 (16.6)	305 (27.3)	1450 (21.9)	2169 (27.7)	
$20000–$34999	735 (23.4)	291 (26.1)	1702 (25.7)	2125 (27.2)	
$35000–$49999	654 (20.8)	207 (18.6)	1300 (19.6)	1481 (18.9)	
$50000–$74999	626 (19.9)	166 (14.9)	1167 (17.6)	1164 (14.9)	
≥$75000	522 (16.6)	112 (10.0)	847 (12.8)	650 (8.3)	
Do not know	82 (2.6)	35 (3.1)	165 (2.5)	239 (3.0)	
Smoking (n=19133)					<0.0001
Never smoked	1724 (53.7)	626 (55.2)	3601 (53.2)	4249 (53.0)	
Current smoker	346 (10.8)	164 (14.5)	492 (7.3)	719 (9.0)	
Past smoker	1140 (35.5)	345 (30.4)	2674 (39.5)	3053 (38.1)	
Alcohol (n=19185)					<0.0001
Nondrinker	375 (11.6)	174 (15.3)	879 (13.0)	1289 (16.0)	
Past drinker	522 (16.2)	234 (20.5)	1504 (22.2)	2102 (26.2)	
<1 drink per month	379 (11.8)	133 (11.7)	940 (13.9)	1238 (15.4)	
<1 drink per week	618 (19.2)	219 (19.2)	1466 (21.6)	1588 (19.8)	
1–<7 drinks per week	865 (26.8)	247 (21.7)	1441 (21.2)	1317 (16.4)	
7+ drinks per week	464 (14.4)	133 (11.7)	557 (8.2)	501 (6.2)	
Family history of MI (n=18111)	1303 (42.8)	547 (50.9)	2909 (45.5)	3886 (51.1)	<0.0001
Total Healthy Eating Index Score (n=19368)	67.4±11.0	67.1±11.0	67.6±11.2	67.5±11.0	<0.0001
Total energy expend (MET-hrs/wk; n=18341)	14.6±15.5	12.7±14.1	10.9±13.4	8.9±11.7	<0.0001
Waist, cm (n=19363)	74.0±5.5	76.8±5.7	90.4±11.4	96.5±12.1	<0.0001
BMI, kg/m^2 (n=19412)	22.6±1.6	23.1±1.5	30.6±5.0	32.3±5.6	<0.0001
Systolic BP, mm Hg (n=19412)	122.1±16.8	135.5±18.1	125.0±16.0	135.5±16.8	<0.0001
Diastolic BP, mm Hg (n=19412)	73.0±8.8	76.7±9.5	75.4±8.7	78.6±9.2	<0.0001
Biomarkers					
Glucose, mg/dL (n=19403)	89.6±13.4	103.5±32.5	93.0±18.2	115.9±42.6	<0.0001
Total cholesterol, mg/dL (n=19412)	224.2±36.2	238.6±46.0	226.2±38.5	235.1±43.7	<0.0001
HDL cholesterol, mg/dL (n=19412)	64.3±13.3	50.1±13.0	59.5±11.6	46.2±10.2	<0.0001
Triglycerides, mg/dL (n=19412)	93.3±36.6	169.2±112.8	100.6±36.6	177.2±94.8	<0.0001
MDRD eGFR, ml/min/1.73m^2 (n=17614)	91.9±19.1	90.7±21.5	93.5±20.3	92.1±22.4	<0.0001

N (percentage) are reported for categorical variables. Mean±SD are reported for continuous variables. Total energy expend (MET-hrs/wk)=total energy expenditure from recreational physical activity (MET-hours/wk), MDRD eGFR in ml/min/1.73m^2=([186.3×creatinine (mg/dL)^−1.154×age (years)^−0.203×0.742 (if female)×1.210 (if Black)]). Information for alcohol use was missing in 227, eGFR in 1798, education in 161, income in 697, smoking status in 279, family history of MI in 1301, total healthy eating index score in 44, total energy expenditure in 1071, waist in 49, and glucose in 9. BMI indicates body mass index; BP, blood pressure; Coll, college; eGFR, estimated glomerular filtration rate; GED, general education development; HDL, high-density lipoprotein; MET, metabolic equivalent; MDRD, Modification of Diet in Renal Disease; MHNW, metabolically healthy normal weight; MHO, metabolically healthy overweight/obese; MI, myocardial infarction; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy overweight/obese; and WHI, Women's Health Initiative.

Table 2. HF Incidence According to Metabolic Weight Categories in WHI Postmenopausal Women

	MHNW (n=3254) (reference)	MUHNW (n=1154)	MHO (n=6867)	MUHO (n=8137)	
	(16.8%)	(5.9%)	(35.4%)	(41.9%)	*P* value
HF incidence, n (%)	38 (1.2)	37 (3.2)	100 (1.5)	280 (3.4)	<0.0001
Incident HF hospitalization event rates per 1000 person-years	1.03	2.86	1.28	3.07	
Unadjusted HR (95% CI) for incident HF	1.00	2.78 (1.77–4.37)*	1.25 (0.86–1.81)	2.98 (2.12–4.18)*	
Fully adjusted HR (95% CI) for incident HF	1.00	1.66 (1.01–2.72)†	1.15 (0.78–1.71)	1.95 (1.35–2.80)†	

Pearson χ^2 test for categorical variables and ANOVA for continuous dependent variables. Fully adjusted HRs adjusts for age, race/ethnicity, income, prevalent diabetes, ever smoking, total healthy eating index score, total energy expenditure from recreational physical activity (metabolic equivalent-hours/wk), and total cholesterol. Unadjusted total sample size=19 412; adjusted sample size=17 427 due to missing covariates. HF indicates heart failure; HR, hazard ratio; MHNW, metabolically healthy normal weight; MHO, metabolically healthy overweight/obese; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy overweight/obese; and WHI, Women's Health Initiative.

*P<0.0001.

†P<0.05.

dose-response relationship of the number of obesity/cardiometabolic traits with HF risk. Compared with zero cardiometabolic traits, 4 cardiometabolic traits had the highest risk of incident HF (HR, 3.68 [95% CI, 2.26–5.99], P<0.0001), followed by 3 (HR, 2.90 [95% CI, 1.86–4.52], P<0.0001), 2 (HR, 2.58 [95% CI, 1.68–3.97], P<0.0001), and 1 cardiometabolic trait (HR, 1.89 [95% CI, 1.22–2.91], P=0.0004).

When conducting a sensitivity analysis additionally adjusting for prior CVD, eGFR, and alcohol intake, the adjusted HRs for the MUHNW (HR, 1.59 [95% CI, 1.06–2.39], P=0.03) and MUHO (HR, 1.95 [95% CI, 1.43–2.65], P<0.0001) compared with MHNW (reference group) were essentially unchanged from the original model. Not surprisingly, however, prior CVD was strongly related to incident HF (HR, 2.60 [95% CI, 2.22–3.04], P<0.0001) as was eGFR (HR, 0.87 [95% CI, 0.81–0.94], P=0.0003) and past drinking (HR, 1.29 [95% CI, 1.01–1.65], P=0.04; see Table I in the Data Supplement).

Furthermore, we examined metabolically unhealthy status (as previously defined) separate from overweight/obesity, showing metabolic unhealthy compared with healthy to be significantly associated with incident HF (adjusted HR, 1.66 [95% CI, 1.01–2.72], P=0.045). Overweight/obese status was not significant (adjusted HR, 1.15 [95% CI, 0.78–1.71], P=0.48) as compared to normal weight

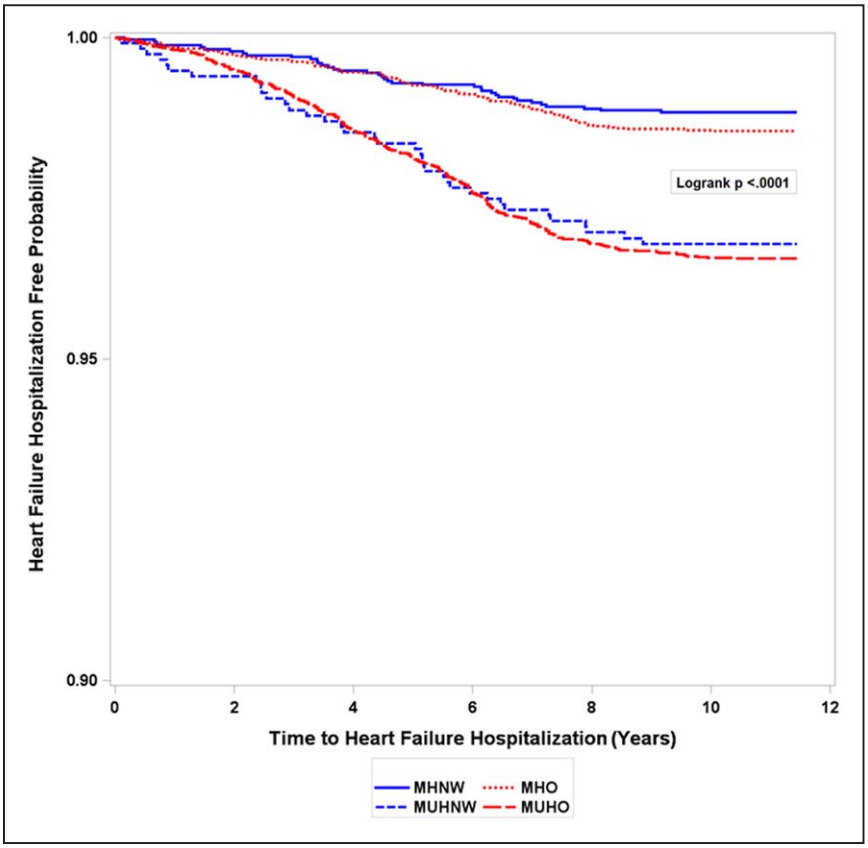

Figure. Heart failure hospitalization-free probability by metabolic weight group.
MHNW indicates metabolically healthy normal weight; MHO, metabolically healthy overweight/obese; MUHNW, metabolically unhealthy normal weight; and MUHO, metabolically unhealthy overweight/obese.

Table 3. Cox Proportional Hazards Regression of Incident Heart Failure Hospitalizations According to Metabolic Weight Categories, Other Risk Factors and Prevalent Diabetes in WHI Postmenopausal Women at Baseline (n=17 427)

Risk factor	HR (95% CI)	*P* value
MUHNW vs MHNW	1.66 (1.01–2.72)	0.045
MHO vs MHNW	1.15 (0.78–1.71)	0.48
MUHO vs MHNW	1.95 (1.35–2.80)	0.0004
Prevalent diabetes, yes vs no	2.72 (2.17–3.42)	<0.0001
Age, y	1.06 (1.05–1.08)	<0.0001
Race/ethnicity		
Asian or Pacific Islander vs White	0.54 (0.17–1.68)	0.28
Black vs White	0.86 (0.69–1.09)	0.21
Hispanic/Latino vs White	0.53 (0.36–0.78)	0.001
Other vs White	0.26 (0.04–1.83)	0.17
Income		
<$19 999 vs $20 000–$34 999	1.00 (0.78–1.27)	0.98
$35 000–$49 999 vs $20 000–$34 999	0.72 (0.53–0.96)	0.03
$50 000–$74 999 vs $20 000–$34 999	0.48 (0.32–0.69)	0.0001
≥$75 000 vs $20 000–$34 999	0.72 (0.48–1.09)	0.12
Do not know vs $20 000–$34 999	0.84 (0.46–1.56)	0.58
Smoking		
Current smoker vs never smoked	1.54 (1.10–2.14)	0.01
Past smoker vs never smoked	1.21 (0.98–1.49)	0.07
Total Healthy Eating Index Score	0.99 (0.98–1.00)	0.13
Total energy expenditure from recreational physical activity (MET-hrs/wk)	0.99 (0.98–1.00)	0.04
Biomarker		
Total cholesterol (mg/dL)	1.00 (1.00–1.00)	0.64

Variables included in the adjusted model: metabolic groups, prevalent diabetes, age, race/ethnicity, income, smoked ever, total energy expenditure from recreational physical activity (MET-hours/wk), and total cholesterol. HR indicates hazard ratio; MET, metabolic equivalent; MHNW, metabolically healthy normal weight; MHO, metabolically healthy overweight/obese; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy overweight/obese; and WHI, Women's Health Initiative.

Table 4. Cox Proportional Hazards Regression of Incident Heart Failure Hospitalizations According to Separate Obesity and Metabolic Risk Factors in WHI Postmenopausal Women at Baseline Using Categorical Cut Points (n=19 412)

Risk factor	HR (95% CI)	*P* value
BMI (≥25 vs 18.5≤ BMI <25 kg/m²)	0.87 (0.63–1.22)	0.43
Waist circumference (≥88 vs <88 cm)	1.63 (1.23–2.16)	0.0006
Systolic BP (≥130 vs <130 mm Hg)	1.65 (1.31–2.07)	<0.0001
Diastolic BP (≥85 vs <85 mm Hg)	1.33 (1.04–1.70)	0.02
Triglyceride (≥150 vs <150 mg/dL)	0.88 (0.70–1.12)	0.30
Glucose (≥100 vs <100 mg/dL)	1.26 (0.98–1.61)	0.07
HDL cholesterol (<50 vs ≥50 mg/dL)	1.24 (0.99–1.56)	0.06

Presented measures were included as categorical variables: BMI ≥25 or (18.5≤ BMI <25); waist circumference ≥88 or waist circumference <88; systolic BP ≥130 or systolic BP <130; diastolic BP ≥85 or diastolic BP <85; triglyceride ≥150 or triglyceride <150; glucose ≥100 or glucose <100; HDL cholesterol <50 or HDL cholesterol ≥50. Models were adjusted for prevalent diabetes, age, race/ethnicity, income, smoked ever, total healthy eating index score, total energy expenditure from recreational physical activity (MET-hours/wk), and total cholesterol. BMI indicates body mass index; BP, blood pressure; HDL, high-density lipoprotein; HR, hazard ratio; and WHI, Women's Health Initiative.

status for increased risk of HF. The interaction term of metabolic health with overweight/obese status was also not significant (HR, 1.02 [95% CI, 0.59–1.76], *P*=0.95).

Lastly, we have included analyses classifying those with prevalent diabetes within those classified as metabolically unhealthy (see Table II in the Data Supplement). The adjusted HRs for the MUHNW (HR, 2.07 [95% CI, 1.27–3.38], *P*=0.004) and MUHO (HR, 2.67 [95% CI, 1.86–3.84], *P*<0.0001), not surprisingly, are larger than in our original analyses because of the inclusion of diabetes in these groups.

DISCUSSION

Our study shows postmenopausal women with MUHO have double the risk and those with MUHNW an approximate two-thirds greater risk of developing HF compared to those with MHNW. However, those with MHO did not have greater HF risk, suggesting metabolic factors may drive HF risk more than obesity alone in postmenopausal women. When patients with obesity and overweight were examined as separate groups, there was a 2.6-fold greater risk in patients who were metabolically unhealthy and obese, but no significant increase in risk for those who were metabolically healthy and obese. We showed independent of our metabolic weight categories prevalent DM to be associated with nearly a 3-fold increased risk of HF hospitalization, consistent with prior literature.[2]

Obesity aggravates conditions, such as DM, hypertension, and hyperlipidemia.[2,20,21] In addition, DM exacerbates HF among patients who are overweight/obese or with other metabolic factors. We found when persons with DM were classified as metabolically unhealthy in sensitivity analyses, relationships of MUHNW and MUHO with HF risk were strengthened even further. In addition, elevated systolic BP and waist circumference were the most consistent individual cardiometabolic / obesity predictors of HF risk and there was a graded relation of the number of metabolically unhealthy parameters present and HF risk.

Previously, in a more general patient sample, the risk of HF was shown to be increased in the metabolically healthy and unhealthy obese as compared to normal weight[10] and in patients with obesity regardless of cardiometabolic status.[11] Furthermore, the Health Improvement Network cohort of 3.5 million men and women, those with MHO had a reported 96% higher risk of HF than MHNW,[22] which contrasts from our study not showing an increased risk of MHO in postmenopausal women. In the Nord-Trøndelag health study of adults free of CVD at baseline, there was a 70% increased risk of HF for both MHO and MUHO.[10] Voulgari et al[23] described that

Table 5. Cox Proportional Hazards Regression of Incident Heart Failure Hospitalizations According to Separate Obesity and Metabolic Risk Factors in WHI Postmenopausal Women at Baseline Measured Continuously (per SD; n=17 378)

Risk factor	HR (95% CI)	*P* value
BMI, kg/m^2	1.19 (1.03–1.38)	0.02
Waist circumference, cm	1.20 (1.02–1.41)	0.03
Systolic BP, mm Hg	1.47 (1.32–1.64)	<0.0001
Diastolic BP, mm Hg	0.94 (0.84–1.05)	0.27
Triglyceride, mg/dL	1.02 (0.93–1.13)	0.64
Glucose, mg/dL	1.26 (1.16–1.37)	<0.0001
HDL cholesterol, mg/dL	0.91 (0.80–1.04)	0.16

Presented measures were included as continuous variables (per SD): BMI SD=6.06; waist circumference SD=13.61; systolic BP SD=17.58; diastolic BP SD=9.25; triglyceride SD=82.14; glucose SD=33.28; HDL cholesterol SD=13.63. Models were adjusted for prevalent diabetes, age, race/ethnicity, income, smoked ever, total healthy eating index score, total energy expenditure from recreational physical activity (MET-hours/wk), and total cholesterol. BMI indicates body mass index; BP, blood pressure; MET, metabolic equivalent; HDL, high-density lipoprotein; HR, hazard ratio; and WHI, Women's Health Initiative.

Table 6. Cox Proportional Hazards Regression of Incident Heart Failure Hospitalizations According to Number of Cardiometabolic Traits and Other Risk Factors in WHI Postmenopausal Women at Baseline (n=17 385)

Risk factor	HR (95% CI)	*P* value
1 cardiometabolic trait vs 0 cardiometabolic traits	1.89 (1.22–2.91)	0.0004
2 cardiometabolic traits vs 0 cardiometabolic traits	2.58 (1.68–3.97)	<0.0001
3 cardiometabolic traits vs 0 cardiometabolic traits	2.90 (1.86–4.52)	<0.0001
4 cardiometabolic traits vs 0 cardiometabolic traits	3.68 (2.26–5.99)	<0.0001

Variables included in the adjusted model: cardiometabolic traits, age, race/ethnicity, income, smoked ever, total healthy eating index score, total energy expenditure from recreational physical activity (MET-hours/wk), body mass index (kg/m^2), waist circumference (cm), and total cholesterol. Cardiometabolic traits based on triglycerides ≥150 mg/dL, systolic blood pressure (BP) ≥130 mm Hg or diastolic BP ≥85 mm Hg or BP medication, fasting glucose ≥100 mg/dL or diabetes medication, and HDL-C <50 mg/dL. BP indicates blood pressure; MET, metabolic equivalent; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; and WHI, Women's Health Initiative.

MHO without metabolic syndrome actually showed a decreased 6-year HF risk as compared to MHNW with metabolic syndrome. Additionally, Pandey et al[24] showed strong evidence that leisure physical activity and BMI were independently associated with the decreased risk of HF in postmenopausal women enrolled in WHI. Another meta-analysis[25] showed overweight, obesity, and abdominal adiposity were associated with an increased risk of HF. Agha et al[26] showed that a healthy lifestyle was correlated with a lower risk of incident HF among postmenopausal women in WHI, despite the nonexistence of coronary heart disease, hypertension, or DM. Our study shows among lifestyle factors, after adjustment for metabolic weight categories, current cigarette smoking remained strongly related to increased risk, physical activity to have a modest inverse association, but the healthy eating index was not independently associated with HF risk.

Of note, our incidence of HF is relatively low (2.3%) in our sample of postmenopausal women compared to what other studies have previously reported. For example, the CHS (Cardiovascular Health Study)[27] previously showed a 7.5% rate of incident HF at 5 years of follow-up and the ARIC (Atherosclerosis Risk in Communities)[28] cohort at an 11% rate of incident HF at 15.5 years to develop HF; however, these studies included both men and women in their studies. The overall CHS sample had a higher SBP and a higher mean age. In addition, ARIC had a larger Black HF study population, included prevalent coronary heart disease, had a higher fasting glucose, and a higher current smoking prevalence. Our sample was all-female, largely white, and with a lower mean SBP, age, fasting glucose, smoking rate, and exclusion of prevalent CVD, which may in part explain our lower reported HF incidences.

A strength in our study was the standardized measurement of risk factors across all clinical sites and centrally adjudicated HF hospitalizations. A limitation is that our study participants, being mostly white with an interest in health motivating them to participate in WHI, may not be truly representative of a population-based sample. Also, we studied only postmenopausal women, and therefore, our study may not be generalizable to younger women and men. In addition, as a secondary data analysis, not all potential variables of interest may have been collected during the original study sample data collection to address all possible confounders. The type of incident HF (reduced versus preserved ejection fraction HF) could not be characterized given the absence of data for left ventricular ejection fraction in individuals with incident HF. Lastly, classification of metabolic weight groups only at baseline may be a potential limitation as we did not have sufficient repeated measures to look at effects of changes in weight or metabolic risk factors on outcomes (eg, as time-dependent covariates).

Our findings may have implications for refining how we assess HF risk and the management of cardiometabolic risks in women who are overweight or obese. For example, intensive control of hypertension in older individuals substantially reduces HF risk,[29] warranting the need for improved awareness of the importance of its control.[30] Although postmenopausal hormone replacement therapy is not recommended for cardioprotection, Liu et al[31] reported that postmenopausal hormone therapy did not change the risk of HF hospitalizations throughout the WHI intervention phase nor the follow-up period. Future research should also examine whether newer DM therapies such as sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists might mitigate the increased risk of HF, particularly in patients who are metabolically unhealthy and overweight/obese. Finally, additional research should establish whether intentional

weight loss in patients who are overweight and obese with improved physical activity will decrease the incidence of HF among postmenopausal women.[6]

In summary, we observed among WHI postmenopausal women that metabolically unhealthy overweight/obese was associated with the greatest increased risk of HF, with a moderately greater risk of HF seen with those who were metabolically unhealthy but normal weight, whereas patients who were overweight or obese but metabolically healthy did not have an increased risk of HF. This underscores the importance of metabolic health as a key determinant of HF risk.

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Affiliations

Heart Disease Prevention Program, Division of Cardiology, Department of Medicine (A.R.C.H., N.D.W.) and Department of Medicine (H.A.-C.), UC Irvine School of Medicine, University of California. School of Community and Global Health, Claremont Graduate University, The Claremont Colleges, CA (A.R.C.H., B.X., D.V.P.). School of Public Health and Health Professions, University of Buffalo, NY (M.J.L.). Division of Epidemiology, Department of Public Health Sciences, UC Davis School of Medicine, CA (L.G.). Departments of Family Medicine and Epidemiology, Alpert Medical School and School of Public Health, Brown University, Pawtucket, RI (C.B.E.). Department of Nutritional Sciences, College of Agriculture and Life Sciences, University of Arizona, Tucson (S.B.G.). Atlanta VA Medical Center and Division of Endocrinology, Department of Medicine, Emory University, GA (L.S.P.). Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (J.E.M.).

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Drs Cordola Hsu, Anton-Culver, and Wong contributed to study concept and design. Drs Cordola Hsu, Xie, Peterson, Manson, Anton-Culver, and Wong contributed to acquisition, analysis, or interpretation of data. All authors participated in drafting of the article. All authors participated in critical revision of the article for important intellectual content. Drs Cordola Hsu, Xie, Wong participated in statistical analysis. Drs Cordola Hsu, Xie, Peterson, Anton-Culver, Wong provided administrative, technical, or material support. Drs Xie, Peterson, Manson, Anton-Culver, and Wong participated in study supervision.

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Supplemental Materials

Figure I
Tables I–II

APPENDIX

Short List of WHI Investigators

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner. Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland.

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