JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 17, 2018

PUBLISHED BY ELSEVIER

Metabolically Healthy Obesity, Transition to Metabolic Syndrome, and Cardiovascular Risk

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ABSTRACT

BACKGROUND Debate over the cardiometabolic risk associated with metabolically healthy obesity (MHO) continues. Many studies have investigated this relationship by examining MHO at baseline with longitudinal follow-up, with inconsistent results.

OBJECTIVES The authors hypothesized that MHO at baseline is transient and that transition to metabolic syndrome (MetS) and duration of MetS explains heterogeneity in incident cardiovascular disease (CVD) and all-cause mortality.

METHODS Among 6,809 participants of the MESA (Multi-Ethnic Study of Atherosclerosis) the authors used Cox proportional hazards and logistic regression models to investigate the joint association of obesity (≥30 kg/m^2) and MetS (International Diabetes Federation consensus definition) with CVD and mortality across a median of 12.2 years. We tested for interaction and conducted sensitivity analyses for a number of conditions.

RESULTS Compared with metabolically healthy normal weight, baseline MHO was not significantly associated with incident CVD; however, almost one-half of those participants developed MetS during follow-up (unstable MHO). Those who had unstable MHO had increased odds of CVD (odds ratio [OR]: 1.60; 95% confidence interval [CI]: 1.14 to 2.25), compared with those with stable MHO or healthy normal weight. Dose response for duration of MetS was significantly and linearly associated with CVD (1 visit with MetS OR: 1.62; 95% CI: 1.27 to 2.07; 2 visits, OR: 1.92; 95% CI: 1.48 to 2.49; 3+ visits, OR: 2.33; 95% CI: 1.89 to 2.87; p value for trend <0.001) and MetS mediated approximately 62% (44% to 100%) of the relationship between obesity at any point during follow-up and CVD.

CONCLUSIONS Metabolically healthy obesity is not a stable or reliable indicator of future risk for CVD. Weight loss and lifestyle management for CVD risk factors should be recommended to all individuals with obesity.
(J Am Coll Cardiol 2018;71:1857–65) © 2018 by the American College of Cardiology Foundation.

The high prevalence of obesity is a costly burden on the U.S. health care system (1). Finding a subset of the population that is resilient to the effects of obesity on cardiovascular outcomes is of great interest to focus limited resources on those most at risk and to develop novel treatments that might target these resiliencies. This condition of having obesity without metabolic syndrome (MetS) is referred to as metabolically healthy obesity (MHO). Individuals with MHO display a relatively favorable

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Manuscript received November 8, 2017; revised manuscript received February 8, 2018, accepted February 9, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.02.055

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

MESA = Multi-Ethnic Study of Atherosclerosis

MetS = metabolic syndrome

MHN = metabolically healthy normal weight

MUN = metabolically unhealthy normal weight

MHO = metabolically healthy obesity

MUO = metabolically unhealthy obesity

metabolic profile compared with the group that has already developed the health consequences of obesity referred to as metabolically unhealthy obesity (MUO), despite having comparable levels of total excess body fat (2–4). MHO has also been associated with intermediate levels of visceral adiposity and cardiovascular risk (5,6) between metabolically healthy normal weight (MHN) and MUO (7–10). MHO is not a stable state (11–15), with our prior work showing that a large proportion of individuals with MHO will transition to MUO, at a rate associated with their cumulative exposure to obesity (16). The level of risk remains contentious, especially for mortality, with MHO seen as either a marker of true resilience or as a transient state on the pathway to risk.

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Although the accumulating evidence is leaning toward the consensus that MHO is not a low risk state compared with MHN (7–10,17), many questions remain about the risk stratification for this group and what causes the heterogeneity seen in the literature (18). To answer those questions, we posed 3 a priori hypotheses in the Multi-Ethnic Study of Atherosclerosis (MESA):

1. Those with MHO at baseline will be at intermediate risk for CVD events and all-cause mortality between estimates for those with MHN and MUO.
2. Transition to MetS will explain a significant portion of the variance in CVD risk for those with MHO at baseline, and there will be a significant dose-response relationship between duration of MetS and CVD.
3. The relationship between obesity and CVD will be substantially mediated by MetS, explaining a lack of an independent association of obesity with CVD when adjusted for MetS.

METHODS

STUDY POPULATION. MESA is a population-based longitudinal cohort study started in 2000 with 6,814 participants recruited from 6 sites in the United States (19). Clinical evaluation was repeated every 2 years, for a total of 5 study visits included in this analysis. We excluded participants with CVD events before baseline (n = 5). Other exclusions are described in the following sections. All participants provided written informed consent and data collection was overseen by institutional review boards at all MESA sites.

MEASUREMENT OF METABOLIC STATUS. We divided the MESA participants into 4 groups, based on their obesity and MetS status at baseline. We defined obesity as a body mass index (BMI) ≥30 kg/m^2 and used the harmonized International Diabetes Federation criteria for MetS (**Table 1**) (20). All MetS components were measured using a standardized protocol at all study visits (19). We used this definition to characterize MetS as present or absent at baseline; ever as having MetS at any time during follow-up; intermittent as having MetS at any visit followed by not having MetS at the subsequent visit and consistent as having MetS at any visit followed only by visits with MetS; and MetS duration as the cumulative number of visits with MetS. Combining obesity status with MetS, we categorized 4 metabolic status groups as shown in **Table 1**. We generated these categories separately for every visit in MESA and used them to define metabolic status groups at baseline, as well as transition from MHO to MUO during follow-up. For our primary analysis of transition from MHO to MUO, we excluded 968 participants with metabolically unhealthy normal weight at baseline (MUN) and 836 participants who transitioned from MHN to MUN during follow-up, for a final sample size of 5,005. Of the 5,005 participants included in the primary analysis, 2,254 had obesity at baseline.

CARDIOVASCULAR DISEASE EVENTS AND ALL-CAUSE MORTALITY. Primary outcomes for this analysis included incident coronary heart disease (fatal and nonfatal), stroke (fatal and nonfatal), heart failure, combined cardiovascular disease (CVD; coronary heart disease, stroke, and heart failure), and all-cause mortality. Systematic attainment and adjudication of events in MESA has been described in detail elsewhere (21).

COVARIATES. Age, sex, race/ethnicity, education and income, and smoking status, were self-reported at baseline. Physical activity was also self-reported at baseline as total intentional exercise in metabolic

TABLE 1 Definition of Metabolic Syndrome and Metabolically Healthy Obesity

Harmonized International Diabetes Federation criteria for MetS: ≥3 of the following components:
Triglyceride level ≥150 mg/dl
HDL cholesterol <40 mg/dl in men and <50 mg/dl in women
SBP ≥130 mm Hg or DBP ≥85 mm Hg or BP medications
Fasting glucose ≥100 mg/dl or medications for diabetes
Waist circumference >102 cm in men and >88 cm in women
Metabolic status groups
MHN: BMI <30 kg/m^2 without MetS
MUN: BMI <30 kg/m^2 with MetS
MHO: BMI ≥30 kg/m^2 without MetS
MUO: BMI ≥30 kg/m^2 with MetS

BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; MetS = metabolic syndrome; MHN = metabolically healthy normal weight; MHO = metabolically healthy obesity; MUN = metabolically unhealthy normal weight; MUO = metabolically unhealthy obesity; SBP = systolic blood pressure.

TABLE 2 Characteristics of 5,005 MESA Participants by Obesity and MetS Status Across Follow-Up

	MHN (n = 2,751)	MHO (n = 550)	MHO to MUO (n = 501)	MUO (n = 1,203)	p Value*
Baseline					
Age, yrs	62.0 ± 0.20	58.0 ± 0.41	59.5 ± 0.41	61.0 ± 0.27	0.001
Sex (% female)	45.9 ± 1.00	60.7 ± 2.08	54.5 ± 2.23	59.9 ± 1.41	<0.001
Race					<0.001
Caucasian	44.8 ± 0.95	35.6 ± 2.04	37.9 ± 2.17	20.7 ± 1.33	
Asian	16.2 ± 0.70	1.09 ± 0.44	1.60 ± 0.56	2.49 ± 0.45	
African American	23.0 ± 0.80	41.3 ± 2.10	36.5 ± 2.15	26.7 ± 1.39	
Hispanic	15.9 ± 0.70	22.0 ± 1.77	24.0 ± 1.91	30.2 ± 1.32	
Education (% ≥high school)	96.6 ± 0.65	87.8 ± 1.40	83.8 ± 1.65	77.2 ± 1.21	<0.001
Income (% ≥$35,000)	61.4 ± 0.93	60.4 ± 2.11	59.8 ± 2.20	49.8 ± 1.46	<0.001
Current smoking, %	13.0 ± 0.64	12.0 ± 1.39	11.6 ± 1.43	14.1 ± 1.00	0.52
Physical activity (METS)	1,767 ± 48.5	1,658 ± 112.0	1,479 ± 90.7	1,226 ± 57.1	<0.001
Total cholesterol, mg/dl	193.3 ± 0.64	195.8 ± 1.42	195.6 ± 1.6	192.4 ± 1.09	0.67
LDL cholesterol, mg/dl	116.8 ± 0.59	120.2 ± 1.20	120.9 ± 1.44	115.9 ± 0.97	0.97
Statin use, %	11.6 ± 0.61	10.5 ± 1.31	17.2 ± 1.69	21.9 ± 1.19	<0.001
BMI, kg/m^2	24.6 ± 0.06	32.7 ± 0.19	34.0 ± 0.20	34.5 ± 0.14	<0.001
Waist circumference, cm	88.6 ± 0.19	106.0 ± 0.53	111.2 ± 0.52	112.9 ± 0.3	<0.001
HDL cholesterol, mg/dl	56.8 ± 0.30	55.3 ± 0.58	47.8 ± 0.54	44.6 ± 0.32	<0.001
Triglycerides, mg/dl	98.4 ± 0.95	99.0 ± 2.02	136.3 ± 3.52	163.1 ± 2.93	<0.001
Hypertension, %	27.4 ± 0.85	23.5 ± 1.81	53.7 ± 2.23	65.8 ± 1.37	<0.001
SBP, mm Hg	120.6 ± 0.39	121.0 ± 0.76	128.2 ± 0.92	132.8 ± 0.58	<0.001
Type 2 diabetes, %	3.72 ± 0.36	2.74 ± 0.70	5.04 ± 0.98	31.1 ± 1.34	<0.001
Fasting glucose, mg/dl	88.7 ± 0.37	87.6 ± 0.57	94.5 ± 0.93	112.5 ± 1.18	<0.001
Across follow-up					
CHD, %	5.74 ± 0.44	3.64 ± 0.80	6.59 ± 1.1	11.3 ± 0.91	<0.001
Stroke, %	2.33 ± 0.29	2.18 ± 0.62	3.19 ± 0.79	5.15 ± 0.64	<0.001
HF, %	2.69 ± 0.31	2.55 ± 0.67	3.79 ± 0.8	6.57 ± 0.71	<0.001
Combined CVD, %	8.43 ± 0.52	6.00 ± 1.01	10.2 ± 1.35	16.5 ± 1.07	<0.001
Mortality, %	14.1 ± 0.66	8.55 ± 1.19	7.19 ± 1.15	15.8 ± 1.05	0.81

Values are mean ± SD. *p value from Cizick nonparametric test for trend.

CHD = coronary heart disease; CVD = cardiovascular heart disease; HF = heart failure; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis; METS = metabolic equivalent units; other abbreviations as in Table 1.

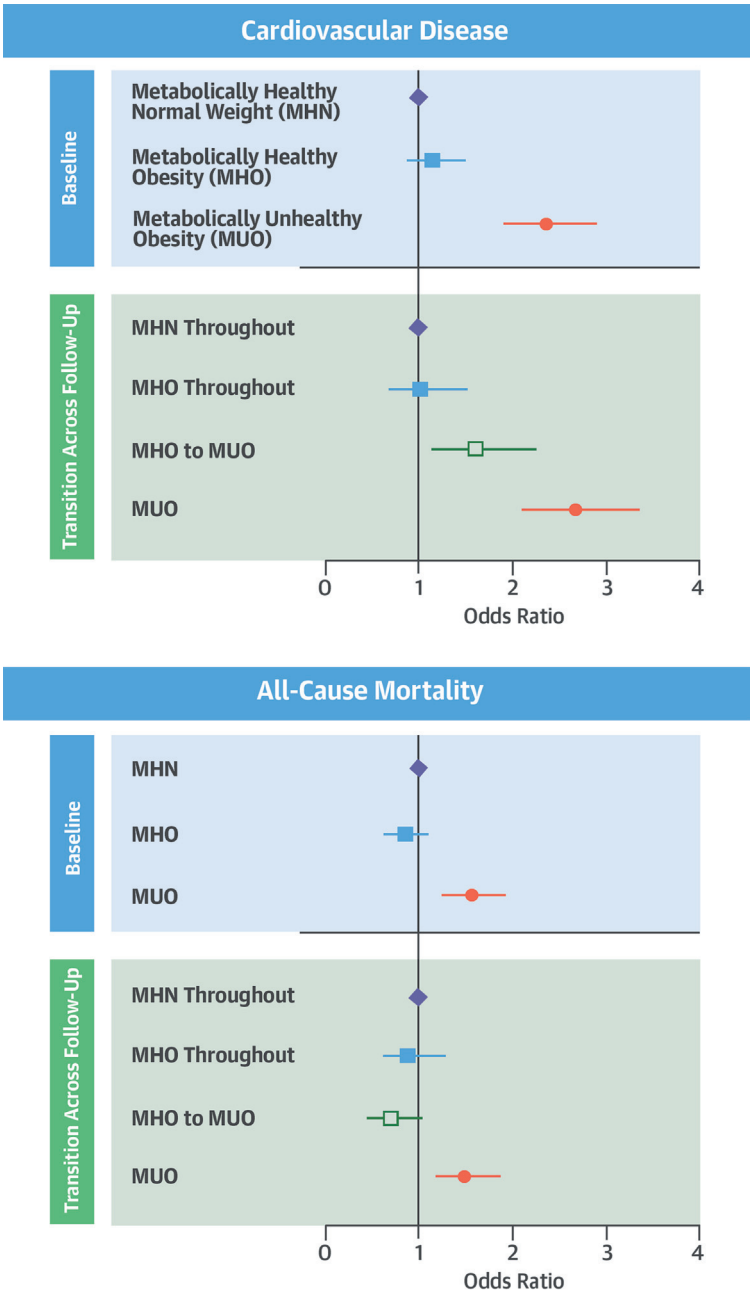
TABLE 3 Characteristics of 2,254 MESA Participants With Obesity by MetS Duration Across Follow-Up

	No MetS (n = 550)	1 Visit (n = 382)	2 Visits (n = 302)	3+ Visits (n = 1,020)	p Value*
Baseline					
Age, yrs	58.0 ± 0.41	60.9 ± 0.51	60.8 ± 0.55	60.3 ± 0.29	<0.001
Current smoking, %	12.0 ± 1.39	13.1 ± 1.73	17.2 ± 2.18	12.4 ± 1.03	0.84
Total cholesterol, mg/dl	196 ± 1.42	193 ± 1.71	192 ± 2.27	194 ± 1.19	0.27
LDL cholesterol, mg/dl	120 ± 1.20	119 ± 1.53	117 ± 2.10	117 ± 1.06	0.008
Statin use, %	10.5 ± 1.31	16.2 ± 1.89	19.2 ± 2.27	22.5 ± 1.31	<0.001
BMI, kg/m^2	32.7 ± 0.19	34.0 ± 0.23	33.9 ± 0.28	34.6 ± 0.15	<0.001
Waist circumference, cm	106 ± 0.53	111 ± 0.60	111 ± 0.80	113 ± 0.37	<0.001
HDL cholesterol, mg/dl	55.3 ± 0.58	48.9 ± 0.66	46.5 ± 0.64	44.1 ± 0.34	<0.001
Triglycerides, mg/dl	99.0 ± 2.02	130 ± 5.70	141 ± 4.57	169 ± 2.88	<0.001
Hypertension, %	23.5 ± 1.81	49.7 ± 2.56	57.9 ± 2.85	68.1 ± 1.56	<0.001
SBP, mm Hg	121 ± 0.76	129 ± 1.05	130 ± 1.19	133 ± 0.63	<0.001
Type 2 diabetes, %	2.74 ± 0.70	12.4 ± 1.70	15.4 ± 2.10	29.9 ± 1.4	<0.001
Fasting glucose, mg/dl	87.6 ± 0.57	98.8 ± 1.65	101 ± 1.68	112 ± 1.25	<0.001
Across follow-up					
Combined CVD, %	6.0 ± 1.01	12.0 ± 1.67	12.6 ± 1.91	16.2 ± 1.15	<0.001
Mortality, %	8.5 ± 1.19	19.1 ± 2.01	14.9 ± 2.05	10.6 ± 0.96	0.88

Values are mean ± SD. *p value for Cizick nonparametric test for trend.

Abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Metabolically Healthy Obesity With Cardiovascular Disease**



Mongraw-Chaffin, M. et al. J Am Coll Cardiol. 2018;71(17):1857-65.

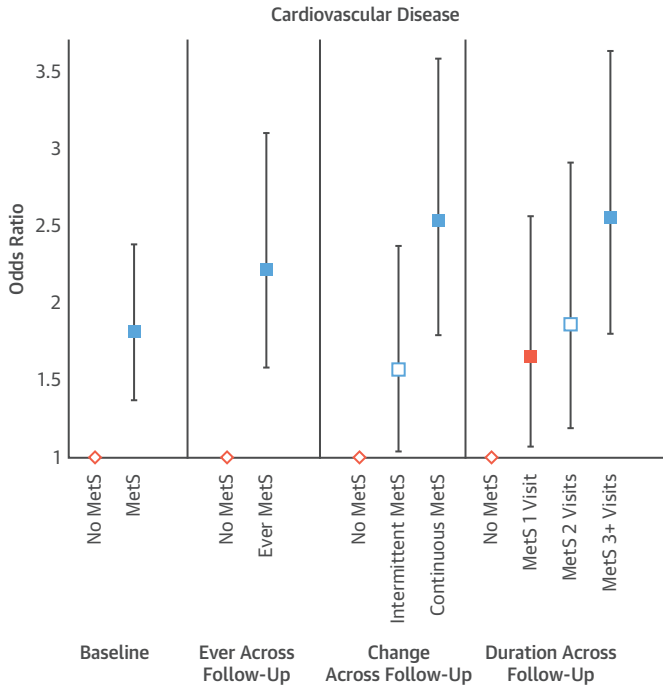
Association of metabolically healthy obesity with cardiovascular disease and all-cause mortality (odds ratios and 95% confidence intervals) in 5,841 MESA participants. Metabolically healthy indicates <3 metabolic syndrome components. Unhealthy indicates ≥3 metabolic syndrome components. All models adjusted for age, sex, race/ethnicity, education, income, smoking status, low-density lipoprotein cholesterol, and statin use. Sample sizes: at baseline, n = 3,587 for MHN; n = 1,051 for MHO; and n = 1,203 for MUO. For transition across follow-up, n = 2,751 for MHN; n = 550 for MHO throughout; n = 501 for MHO to MUO; and n = 1,203 for MUO.

equivalent units. Because CVD risk factors are included in the MetS definition, most were not included in statistical models as potential confounders. Low-density lipoprotein (LDL) cholesterol and statin use were measured at clinic visits similar to MetS components.

STATISTICAL ANALYSIS. We characterized the metabolic status groups at baseline using means and standard deviations and Cuzick nonparametric test for trend. We similarly described baseline characteristics by groups with different MetS duration across follow-up. We used Cox proportional hazards models to estimate the associations for metabolic status groups at baseline with MHN as the reference. We used nested models to adjust for confounding that included: model 1, no adjustment; model 2, age; model 3, age, sex, race/ethnicity, education, and income; model 4, model 3 with the addition of smoking, LDL cholesterol, and statin use. We then used logistic regression with the final adjustment model instead of Cox proportional hazards models for the rest of the analyses because variables that accounted for cumulative exposure did not allow for a calculation of person-time. As such, we assessed whether transitioning from MHO at baseline to MUO during follow-up was associated with higher odds of CVD and mortality compared with remaining MHO. We also determined the association for never versus ever having MetS during follow-up, and duration of MetS adjusted for concurrent obesity status to assess dose response to cumulative exposure. We estimated the association of having intermittent compared with consistent MetS. We also formally tested for mediation of the relationship between obesity and CVD by MetS using the Hicks and Tingley method (22). All analyses were conducted using Stata 14 (StataCorp., College Station, Texas) (23).

SENSITIVITY ANALYSIS. We assessed the sensitivity of our results to the use of hard CVD events (myocardial infarction, resuscitated cardiac arrest, congenital heart disease death, stroke, and stroke death) compared with all CVD events and to adjustment for physical activity. We formally tested for effect modification by age, sex, and race/ethnicity using interaction terms. We also determined whether results were similar for different definitions of MetS, including: 1) harmonized International Diabetes Federation definition that does not include waist circumference as a component; and 2) a definition with a "super healthy" reference group that has no components of MetS. Finally, we estimated the association with CVD for a certain specific subgroup of interest with resilience to long-term exposure to obesity, defined by participants with obesity at every visit but no MetS. All sensitivity analyses were conducted using the final adjustment model (model 4).

FIGURE 1 Association of Metabolic Syndrome With Cardiovascular Disease (Odds Ratios and 95% Confidence Intervals) in 2,744 MESA Participants With Obesity



Estimates for baseline, ever across follow-Up, and change across follow-up are significantly different at the $p < 0.05$ level. For duration of MetS, p value for trend was $p < 0.001$. All models adjusted for age, sex, race/ethnicity, education, income, smoking status, low-density lipoprotein cholesterol, and statin use. Sample sizes: at baseline, n = 1,033 for no MetS; n = 1,159 for MetS. Ever across follow-up, n = 685 for no MetS and n = 2,059 for ever MetS. Change across follow-up, n = 685 for no MetS; n = 1,434 for intermittent MetS; n = 625 for continuous MetS. Duration across follow-up, n = 685 for no MetS; n = 448 for MetS 1 visit; n = 371 for MetS 2 visits; n = 1,240 for MetS 3+ visits. MetS = metabolic syndrome.

RESULTS

Baseline demographic and socioeconomic factors differed significantly between the metabolic status groups, as did statin use, but not total or LDL cholesterol or current smoking status (Table 2). Baseline risk factor prevalence, including BMI, for those who transitioned from MHO to MUO were generally between estimates of those who were consistently MHO or MUO across the study period. Estimates for events exhibited a similar pattern, with the exception of mortality. Baseline risk factors and CVD and mortality prevalence at follow-up also showed a significant increasing trend across MetS duration (Table 3).

With a median follow-up time of 12.2 years, 791 CVD events and 975 deaths were recorded. Cox proportional hazards models for each event type produced estimates of significantly increased risk for the

TABLE 4 Sensitivity Analyses for Combined CVD and All-Cause Mortality by MetS and MetS Transition

	Metabolic Status	CVD		Mortality	
		OR	95% CI	OR	95% CI
Primary analysis (n = 4,859)					
	MHN	1.00	Ref	1.00	Ref
	MHO	1.03	0.69–1.52	0.91	0.64–1.30
	MHO to MUO	**1.60**	**1.14–2.25**	0.70	0.48–1.03
	MUO	**2.67**	**2.12–3.37**	**1.51**	**1.20–1.89**
Adjustment for physical activity (n = 4,857)					
	MHN	1.00	Ref	1.00	Ref
	MHO	1.01	0.68–1.50	0.74	0.53–1.02
	MHO to MUO	**1.57**	**1.12–2.21**	0.81	0.60–1.10
	MUO	**2.60**	**2.06–3.28**	**1.69**	**1.31–2.18**
Hard events (n = 4,859)					
	MHN	1.00	Ref	NA	
	MHO	1.16	0.75–1.81		
	MHO to MUO	**1.64**	**1.10–2.42**		
	MUO	**2.53**	**1.94–3.30**		
Sex					
Women (n = 2,516)	MHN	1.00	Ref	1.00	Ref
	MHO	1.46	0.81–2.62	1.13	0.68–1.88
	MHO to MUO	**2.00**	**1.17–3.42**	0.69	0.38–1.25
	MUO	**3.18**	**2.17–4.65**	**1.83**	**1.30–2.57**
Men (n = 2,343)	MHN	1.00	Ref	1.00	Ref
	MHO	0.80	0.46–1.39	0.79	0.47–1.32
	MHO to MUO	1.40	0.90–2.19	0.71	0.43–1.18
	MUO	**2.46**	**1.83–3.31**	1.33	0.97–1.82
p value for difference		0.19		0.33	
Age					
<70 yrs (n = 3,721)	MHN	1.00	Ref	1.00	Ref
	MHO	0.83	0.49–1.41	0.70	0.43–1.14
	MHO to MUO	**1.95**	**1.30–2.90**	0.61	0.37–1.03
	MUO	**3.39**	**2.52–4.55**	**1.53**	**1.13–2.06**
≥70 yrs (n = 1,138)	MHN	1.00	Ref	1.00	Ref
	MHO	1.18	0.64–2.17	0.89	0.53–1.50
	MHO to MUO	0.89	0.45–1.76	0.75	0.42–1.33
	MUO	1.46	0.99–2.13	1.28	0.92–1.78
p value for difference		**<0.001**		0.44	
Race/ethnicity					
Caucasian (n = 1,938)	MHN	1.00	Ref	1.00	Ref
	MHO	1.32	0.76–2.29	1.01	0.58–1.76
	MHO to MUO	1.07	0.59–1.93	0.56	0.28–1.12
	MUO	**2.65**	**1.86–3.79**	**1.87**	**1.30–2.69**
African American (n = 1,416)	MHN	1.00	Ref	1.00	Ref
	MHO	0.64	0.29–1.40	0.81	0.46–1.46
	MHO to MUO	1.48	0.82–2.68	0.65	0.35–1.20
	MUO	**2.60**	**1.71–3.93**	1.34	0.92–1.96
Hispanic (n = 1,020)	MHN	1.00	Ref	1.00	Ref
	MHO	1.00	0.40–2.51	0.86	0.37–1.98
	MHO to MUO	**2.98**	**1.55–5.74**	0.89	0.41–1.90
	MUO	**2.80**	**1.69–4.65**	1.25	0.77–2.04
p value for difference		0.079		0.50	

Continued on the next page

groups with MetS (MUN and MUO), but not for MHO compared with MHN at baseline (Online Table 1). Survival estimates for MHO at baseline were predominantly nonsignificant and even close to null, with the exception of positive estimates for heart failure and inverse for the unadjusted model for mortality. There was no evidence of deviation from the proportional hazards assumption using scaled Schoenfeld residuals. Models investigating transition in metabolic status groups across follow-up are similar to Cox proportional hazards results, but indicate significant heterogeneity in the group with MHO at baseline (**Central Illustration**). Of those with MHO at baseline, 48% (501 of 1,051) developed MetS during follow-up and then had an increased odds of CVD compared with those who stayed MHO, and to the MHN reference group. Results for coronary heart disease, stroke, and heart failure were similar to combined CVD results (Online Figure 1).

Among participants with obesity, CVD estimates for the group that had ever had MetS were similar to baseline estimates, and the estimates for intermittent MetS fell between those with no MetS and those with consistent MetS (**Figure 1**). Duration of MetS was significantly associated with higher odds of CVD in a graded and linear fashion (p value for trend <0.001), with an odds ratio (OR) of 1.42 (95% CI: 1.07 to 1.89) for every additional visit of MetS specifically after transition from MHO at baseline. Results were similar for participants who were normal weight (Online Table 2).

CVD OR for obesity compared with normal weight, unadjusted for MetS, displayed a similar pattern to those of MetS with a significant estimate for baseline obesity (OR: 1.49; 95% CI: 1.26 to 1.78); an intermediate estimate for intermittent (OR: 1.12; 95% CI: 0.83 to 1.52) compared with consistent obesity (OR: 1.52; 95% CI: 1.27 to 1.81); and a significant linear trend for higher obesity duration (p < 0.001). Estimates for obesity are strongly attenuated and nonsignificant when adjusted for MetS (not shown). Mediation analysis indicated that 62% (44% to 100%) of the ever obesity effect was mediated by ever MetS.

SENSITIVITY ANALYSES. Formal analysis of interaction produced little evidence of significant heterogeneity (p > 0.10), except for CVD by age (p < 0.001) and race/ethnicity (p = 0.079), with stronger associations for younger participants and Hispanics (**Table 4**). Estimates for Asian participants were omitted because of instability from small sample sizes. We found some mild attenuation for smoking status subgroup analysis, adjustment for physical activity, including only hard CVD events, excluding waist circumference from the MetS definition, and excluding overweight from the reference group. Using a definition of healthy with only 1 MetS component produced attenuated results for MHO; however, with only 0.4% (27 of 6,890) of participants categorized as MHO at baseline, there were few participants left to transition to the

unhealthy state. Compared with participants who were MHN at all visits, those who had obesity at all 5 visits but did not have MetS had an OR for CVD of 0.41 (95% CI: 0.15 to 1.13); obesity and 1 visit with MetS (OR: 1.06; 95% CI: 0.52 to 2.16); obesity and 2 or 3 visits with MetS (OR: 2.19; 95% CI: 1.37 to 3.51); and obesity and 4 to 5 visits with MetS (OR: 2.50; 95% CI: 1.79 to 3.49).

TABLE 4 Continued

	Metabolic Status	CVD		Mortality	
		OR	95% CI	OR	95% CI
Smoking					
No (4,235)	MHN	1.00	Ref	1.00	Ref
	MHO	1.08	0.71–1.65	1.06	0.73–1.56
	MHO to MUO	**1.66**	**1.16–2.39**	0.79	0.53–1.18
	MUO	**2.70**	**2.10–3.46**	**1.63**	**1.27–2.09**
Yes (624)	MHN	1.00	Ref	1.00	Ref
	MHO	0.73	0.24–2.21	0.37	1.13–1.03
	MHO to MUO	1.28	0.45–3.61	0.31	0.09–1.12
	MUO	**2.45**	**1.34–4.47**	1.02	0.58–1.78
p value for difference		0.51		0.13	
MetS without waist circumference (n = 4,273)					
	MHN	1.00	Ref	1.00	Ref
	MHO	1.09	0.72–1.65	0.96	0.67–1.39
	MHO to MUO	**1.57**	**1.10–2.25**	0.65	0.43–0.96
	MUO	**2.83**	**2.20–3.64**	**1.48**	**1.16–1.88**
MetS as ≥1 component (n = 2,668)					
	MHN	1.00	Ref	1.00	Ref
	MHO	No obs		No obs	
	MHO to MUO	0.92	0.11–7.80	1.08	0.26–4.52
	MUO	3.69	2.12–6.41	0.85	0.58–1.25
Ref group excludes overweight (n = 3,621)					
	MHN	1.00	Ref	1.00	Ref
	MHO	1.05	0.69–1.61	0.84	0.58–1.22
	MHO to MUO	**1.63**	**1.12–2.38**	**0.65**	**0.43–0.97**
	MUO	**2.74**	**2.07–3.62**	**1.39**	**1.07–1.80**

All models are adjusted for age, sex, race/ethnicity, education, income, smoking, LDL, and statin use. Asian participants are excluded only from the race-specific interaction analysis. Hard CVD events include myocardial infarction, resuscitated cardiac arrest, CHD death, stroke, and stroke death only. **Bold** Indicates estimates that are significantly different from the reference at the $p < 0.05$ level.

CI = confidence interval; obs = observations; OR = odds ratio; Ref = reference; other abbreviations as in Tables 1 and 2.

DISCUSSION

Among MESA participants, having MHO at baseline was not associated with risk for incident CVD or all-cause mortality; however, this association obscured the heterogeneity in this group. Supporting our hypothesis, almost one-half of those with MHO at baseline developed MetS during follow-up and then had significantly higher odds of CVD, although lower than for those with MUO from baseline. Higher MetS duration was also significantly associated with CVD, adding dose-response evidence to the theory that risk resulting from obesity is cumulative. The association between obesity and CVD was strongly mediated by MetS, reinforcing the premise that obesity is an originating cause of cardiometabolic risk.

A growing body of work has sought to end the controversy about MHO, but confusion about appropriate clinical recommendations and public health messaging lingers, and many questions remain unanswered regarding appropriate advice for individuals. Although 4 main meta-analyses came to the similar conclusion that MHO is not necessarily a low-risk condition (7-9,17), they also found high levels of heterogeneity for MHO and MUO and suggest that the literature provides few answers about risk resulting from longitudinal changes between categories, differences in length of follow-up, adjustment for differing MetS definitions and cardiometabolic fitness, and a lack of diversity in study populations.

Our results support and build on this foundation in several key areas. First, our results provide an explanation at the individual level for why the meta-analyses found an increased risk for MHO only with longer duration of follow-up. Both transition to MetS and longer duration of MetS were associated with CVD, indicating that those with MHO may experience a lag in risk while they progress to MetS and develop the resultant cardiometabolic risk. Similarly, it may be that MHO estimates for mortality are not increased because the lag time is longer for mortality than for CVD and therefore cannot be observed during the follow-up of most studies. There has been special interest in those who appear to have long-term resistance to the consequences of obesity. In MESA, participants with obesity at all 5 visits and no MetS were not at increased risk compared with MHN; however, as reported previously, that group differs from the rest of the MESA participants in highly specific ways and makes up only 3% of the cohort (16). These results and our prior work in MESA suggest that very few individuals can truly maintain long-term metabolic health when exposed to continued obesity (16).

Second, we found that being MHO at baseline does not confer low odds of CVD for individuals who transition to MetS later. The likelihood of underestimating risk based on MHO at a single time point has clear implications for clinical practice and resource management. These results are not entirely consistent with the few prior studies that assessed risk associated with the persistence of MHO (11-15). Although all 4 conclude that MHO is not a stable condition, their analyses and resulting conclusions differ, from no significant association with MHO (13) to increased CVD risk from persistent MHO compared with persistent MHN (12,14). As the only group that addressed the question

of transition to MetS directly, Appleton et al. (11) found nonsignificant associations for MHO at baseline and for transition to MetS. These differences are likely explained by small numbers of events, wide variation in definitions for obesity and MetS, and diverging analytical choices.

Finally, our results fully support the concept that cardiometabolic risk is due to cumulative exposure from obesity, and that prevention of obesity will be central to the prevention of CVD. Although the full mechanisms for the pathway from obesity to MetS to CVD remain unknown, evidence such as the findings from this study increasingly explain variation in the MetS/CVD relationship through differences in exposure to obesity. MetS prevalence is consistently graded by BMI category (9), and obesity has been repeatedly shown to be 1 of the strongest risk factors for the development of MetS and its CVD risk factor components (16,24–26). In this respect, MetS may be a marker of the threshold of cumulative obesity exposure that translates to measurable CVD risk. Consistent with our results, a growing consensus indicates that when obesity and MetS are considered together for CVD and mortality, obesity is not an independent risk factor (8). In contrast to the conclusion that obesity is less important for the development of CVD, multiple mediation analyses, including this one, indicate that obesity is likely a major primary cause of both MetS and the resulting CVD risk (27,28).

STUDY LIMITATIONS. First, this study may not be powered to fully assess interaction and has small numbers of events, which may limit the interpretation of results for certain subgroups. Second, there may be differential loss to follow-up for later visits, which would likely underestimate the associations for CVD. Third, additional considerations for mortality separate from CVD may be necessary to understand why the estimates differ between these 2 outcomes. Last, limited measurement of physical activity and cardiorespiratory fitness in MESA restricted our ability to address issues relating to fitness as a determinant and confounder of MHO (29–32).

These limitations are compensated for by numerous strengths and a novel approach. Primarily, this is 1 of the only studies that directly tests whether those with MHO at baseline maintain this status over time and are at increased risk for incident CVD. This approach provides answers to several unresolved questions by providing the following evidence: 1) shows that MHO at baseline may mischaracterize the CVD risk for half the group; 2) explains why studies with longer follow-up report higher risks for MHO on the individual level; 3) demonstrates a dose response between cumulative exposure to MetS and CVD; and 4) provides additional evidence that obesity is an originator of metabolic dysfunction and CVD risk through mediation analysis. Finally, this study presents exceptional consideration of concerns about prior work through extensive sensitivity analyses, including removing overweight from the reference group; assessing different definitions of MetS; restricting analysis to hard CVD events; investigating interaction by age, sex, and race/ethnicity; and adjusting for physical activity.

CONCLUSIONS

Transition to MetS from MHO at baseline and higher duration of MetS were significantly associated with incident CVD in MESA. Our prior work showed that MHO is an unstable condition for many individuals in MESA (16). Combined, these results imply that, although stable MHO may be a lower risk state, the lack of reliable predictors for MHO stability and the increased risk of transitioning to MUO from continuing obesity itself severely limit the use of MHO to predict future risk in the clinical setting. Further supporting this premise, the higher index of suspicion for all CVD risk factors resulting from obesity, even in the MHO group, indicates that constant vigilance is necessary to avoid transitioning to MetS and the associated increased likelihood of incident CVD.

These results implicate MHO as an opportunity for primary prevention of CVD, whereas MUO offers the opportunity only for secondary prevention through treatment of already existing risk factors. Given the strong mediation of the obesity/CVD relationship by MetS, prevention of incident MetS and resulting CVD at the population level will necessitate the prevention of obesity. This study provides new evidence that MHO alone is not a stable or reliable characterization of lower clinical risk. Instead, MHO signals an opportunity for weight reduction, and prevention and management of existing MetS components should be prioritized.

ACKNOWLEDGMENTS The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. The information contained herein was derived in part from data provided by the Bureau of Vital Statistics, New York City Department of Health and Mental Hygiene.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Individuals with metabolically healthy obesity are likely to transition to metabolic syndrome over time. This group should not be considered low risk for cardiometabolic disease and may benefit from weight management and risk factor intervention.

TRANSLATIONAL OUTLOOK: Clinical trials of weight loss in patients with metabolically healthy obesity are needed to confirm the benefit of earlier intervention to prevent ischemic events.

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KEY WORDS cardiovascular disease, epidemiology, metabolic syndrome, metabolically healthy obesity, mortality, obesity

APPENDIX For supplemental tables and a figure, please see the online version of this paper.