Heterogeneity in transition from metabolically healthy obesity at baseline to metabolic syndrome obscures the cardiovascular disease and mortality risk: The Multi-Ethnic Study of Atherosclerosis

Short title: Metabolically healthy obesity with CVD and mortality

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ABSTRACT

Background: Debate over the cardiometabolic risk associated with metabolically healthy obesity continues. Many studies have investigated this relationship by examining metabolically healthy obesity at baseline with longitudinal follow-up, with inconsistent results. We hypothesized that metabolic health in obesity at baseline is transient and that transition to metabolic syndrome (MetS) and duration of metabolic syndrome would explain heterogeneity in incident cardiovascular disease (CVD) and all-cause mortality.

Methods: Among 6809 participants of the Multi-Ethnic Study of Atherosclerosis with non-missing MetS components and incident event follow-up, we used Cox proportional hazards and logistic regression models to investigate the joint association of obesity ($\geq$30kg/m^2) and MetS (IDF consensus definition) with CVD and mortality in a variety of ways. We formally tested for interaction and conducted sensitivity analyses for a number of conditions.

Results: Compared to metabolically healthy normal weight, baseline metabolically healthy obesity was not significantly associated with CVD; however, almost half of those participants developed MetS and were at increased risk for CVD (OR=1.60 (1.14-2.25)). Dose response for duration of MetS was significantly and linearly associated with higher CVD (1 visit OR=1.62 (1.27-2.07); 2 visits OR=1.92 (1.48-2.49); 3+ visits OR=2.33 (1.89-2.87); p-value for trend <0.001) and the relationship between obesity at any point during follow-up and CVD was 62% (44-100%) mediated by MetS.

Conclusion: Metabolically healthy obesity is not a stable or accurate indicator of future risk for CVD. Weight loss and lifestyle management for CVD risk factors should be recommended to all individuals with obesity.

INTRODUCTION

The high prevalence of obesity is a costly burden on the US healthcare system. Healthcare workers are eager to find a subset of the population that is resilient to the effects of obesity both in order to preserve limited resources for those most at risk, as well as for opportunities 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 metabolic profile compared to the group that has already developed the healthy consequences of obesity referred to as metabolically unhealthy obesity (MUO), despite having comparable levels of total excess body fat.[1-3] MHO has similarly been associated with intermediate levels of visceral adiposity and cardiovascular risk,[4, 5] between metabolically healthy normal weight (MHN) and MUO.[6-8] Troublingly, MHO has been shown not to be a stable state,[9-13] with our prior work showing that a large proportion of individuals with obesity will transition to MUO, graded by their cumulative exposure to obesity.[14] The level of risk remains contentious, especially for mortality, with MHO as a marker of true resilience on the low end and MHO as a transient state on the pathway to risk on the other.

Complicating this issue are differences in MHO prevalence by age, sex, and race/ethnicity.[15] MHO prevalence has been shown to decrease with aging and is higher in women than men, most likely due to known differences in regional fat distributions.[16] It remains unknown whether cardiovascular risk associated with this condition is similarly heterogeneous, with questions about racial/ethnic differences hindered by the small number of data sets (i.e., diverse cohorts) available to explore these questions.

While the accumulating evidence is leaning towards the consensus that MHO is not a low risk state compared to MHN,[6-8, 17] many questions remain about the risk stratification for this group and what causes the heterogeneity between the levels.[18] To answer those questions, we posed four *a priori* hypotheses in the Multi-Ethnic Study of Atherosclerosis:

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, with MetS duration as a significant positive marker of dose response.
3. Relationships between MHO and risk will differ by age, sex, and race/ethnicity, with stronger associations for younger, female, and African American individuals.
4. The relationship between obesity and CVD will be substantially mediated by MetS, explaining a lack of independent association for obesity.

METHODS

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based longitudinal cohort study started in 2000 with 6814 participants recruited from six sites in the US. [19] Baseline clinical evaluation was followed every two years for a total of five study visits included in this analysis. Follow-up is ongoing. We excluded participants with CVD events before baseline (n=5). 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 four groups, based on their obesity and MetS status at baseline. We defined obesity as a BMI ≥30kg/m^2 and used the harmonized International Diabetes Federation criteria for MetS,[20] defined as three or more of the following components:

- Triglyceride level ≥150mg/dL
- HDL cholesterol <40mg/dL in men and <50mg/dL in women
- Systolic blood pressure ≥130mmHG or diastolic blood pressure ≥85mmHG or blood pressure medications
- Fasting glucose ≥100mg/dL or medications for diabetes
- Waist circumference of >102 cm in men and >88 cm in women

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 at any time during follow-up; inconsistent 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 four metabolic status groups as follows:

1. Metabolically healthy normal weight (MHN): BMI<30kg/m^2 without MetS.
2. Metabolically unhealthy normal weight (MUN): BMI<30kg/m^2 with MetS.
3. Metabolically healthy obesity (MHO): BMI ≥30kg/m^2 without MetS.
4. Metabolically unhealthy obesity (MUO): BMI ≥30kg/m^2 with MetS.

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.

Cardiovascular Disease Events and All-Cause Mortality

Primary outcomes for this analysis included incident coronary heart disease (fatal and non-fatal), stroke (fatal and non-fatal), heart failure, combined cardiovascular disease, 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, smoking status, and physical activity were self-reported at baseline. Since CVD risk factors are included in the MetS definition most were not included in statistical models as potential confounders, with the exception of LDL cholesterol and statin use which 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 non-parametric test for trend. We similarly characterized MetS duration groups at baseline. 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 to assess whether transitioning from MHO at baseline to MUO during follow-up was associated

with higher odds of CVD and mortality compared to remaining MHO. We also determined the association for never vs. 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 to consistent MetS. We formally tested for effect modification by age, sex, and race/ethnicity using interaction terms. We also formally tested for mediation of the relationship between obesity and CVD by MetS using the Hicks and Tingley method.[22] All analysis was conducted using Stata 14.[23]

Sensitivity Analysis

We assessed the sensitivity of our results to the use of hard CVD events (myocardial infarction, resuscitated cardiac arrest, CHD death, stroke, and stroke death) compared to all CVD events and to adjustment for physical activity. We also determined whether results were similar for different definitions of MetS including 1. Harmonized IDF definition but 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 defined by participants with obesity at every visit but no MetS.

RESULTS

Demographic and socioeconomic factors differed significantly between the metabolic status groups, as did statin use, but not total or LDL cholesterol (Table 1). Risk factor estimates, including BMI, for those who transitioned from MHO to MUO were generally in between estimates of those who were consistently MHO or MUO across the study period. Prevalence of

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 (Supplemental Table 2).

With a mean follow-up time of 11.7 years, Cox proportional hazards models for each event type produced estimates of significantly increased risk for the groups with MetS (MUN and MUO), but not for MHO compared to MHN at baseline (Supplemental Table 2). Estimates for MHO were predominantly non-significant and even close to null, with the exception of positive estimates for heart failure and inverse for the unadjusted model for mortality. Models investigating metabolic status groups across follow-up indicate significant heterogeneity in the group with MHO at baseline (Figure 1). Of those with MHO at baseline, 48% (501/1051) developed MetS during follow-up and then had an increased risk for CVD compared to 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 (Supplemental Figure 1). There was no evidence of deviation from the proportionality assumption.

Logistic estimates for the group that had ever had MetS were similar to baseline estimates, and the group with intermittent MetS had a risk estimate that fell between those without MetS and those with consistent MetS (Figure 2). 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 of 1.42 (1.07-1.89) for every additional visit of MetS specifically after transition from MHO at baseline. Results were similar for participants who were normal weight (Supplemental Table 3). Estimates for obesity from the models shown in Figure 2 were non-significant, and close to null (ever MetS model: obesity OR=1.10 (0.92-1.32); and duration MetS model: obesity OR=1.05 (0.88-1.26).

CVD odds ratios for obesity, unadjusted for MetS, displayed a similar pattern to those of MetS with a significant estimate for baseline obesity (OR=1.49 (1.26-1.78)); an intermediate estimate for intermittent (OR=1.12 (0.83-1.52) compared to consistent obesity (1.52 (1.27-1.81); and a significant linear trend for higher obesity duration ($p<0.001$). Mediation analysis indicated that 31% (22-51%) of the total baseline obesity effect was mediated by baseline MetS and that 62% (44-100%) of the ever obesity effect was mediated by ever MetS.

Sensitivity Analyses

Formal analysis of interaction produced little evidence of significant heterogeneity, except for CVD by age and race/ethnicity (Table 2), with stronger associations for younger participants and qualitative differences by race/ethnicity. 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 one MetS component produced attenuated results for MHO; however, with only 0.4% (27/6890) participants categorized as MHO at baseline there were few participants left to transition to the unhealthy state. Compared to participants who were MHN at all visits, those who had obesity at all 5 visits but did not have MetS had an odds ratio for CVD of 0.41 (0.15-1.13); obesity and one visit with MetS (OR=1.06 (0.52-2.16)); obesity and two or three visits with MetS (OR=2.19 (1.37-3.51)); and obesity and four or five visits with MetS (OR=2.50(1.79-3.49)).

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 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 due to 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. While four main meta-analyses came to the similar conclusion that MHO is not necessarily a low risk condition,[6-8, 17] they also found high levels of heterogeneity for MHO and MUO and suggest that the literature provides few answers about risk due to 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 to 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.[14] These results and our prior work in MESA suggest that very few individuals can truly maintain long-term metabolic health when exposed to obesity.[14]

Second, we found that being MHO at baseline does not confer low risk 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.[9-13] While all four conclude that MHO is not a stable condition, their analyses and resulting conclusions differ, from no significant association with MHO,[11] to increased CVD risk from persistent MHO compared to persistent MHN.[10, 12] As the only one who addressed the question of transition to MetS directly, Appleton et al. found non-significant associations for MHO at baseline and for transition to MetS.[9] 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. While the full mechanisms for the pathway from obesity to MetS to CVD remain unknown, evidence like 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,[8] and obesity has been repeatedly shown to be one of the

strongest risk factors for the development of MetS and its CVD risk factor components.[14, 24-26] In this respect, MetS may be a marker of the threshold of cumulative obesity exposure that translates to measureable 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.[7] 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]

This study has several limitations. First, this study may not be powered to fully assess interaction and 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 two outcomes. Lastly, 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]

These limitations are compensated for by numerous strengths and a novel approach. Primarily, this is one 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 the following unresolved questions: 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 and 3. Demonstrates a dose response between cumulative exposure to MetS and CVD 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.

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.[14] Combined, these results imply that while 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 in the clinical setting. Further supporting this premise, the higher index of suspicion for all CVD risk factors due to 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, while 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 for predicting clinical risk. Instead, MHO signals an opportunity for weight reduction, and prevention and management of existing MetS components should be prioritized.

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Conflict of Interest: The authors have nothing to disclose.

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Figure 1. Association of metabolically healthy obesity with cardiovascular disease and all-cause mortality (Odds ratios and 95% confidence intervals) in 6573 MESA participants.

Metabolically healthy indicates <3 metabolic syndrome components. Unhealthy indicates 3 or more metabolic syndrome components. Categories are mutually exclusive. MHN=Metabolically heathy normal weight; MHO=Metabolically healthy obesity; MUO=Metabolically unhealthy obesity

All models adjusted for age, sex, race/ethnicity, education, income, smoking status, LDL cholesterol, and statin use.

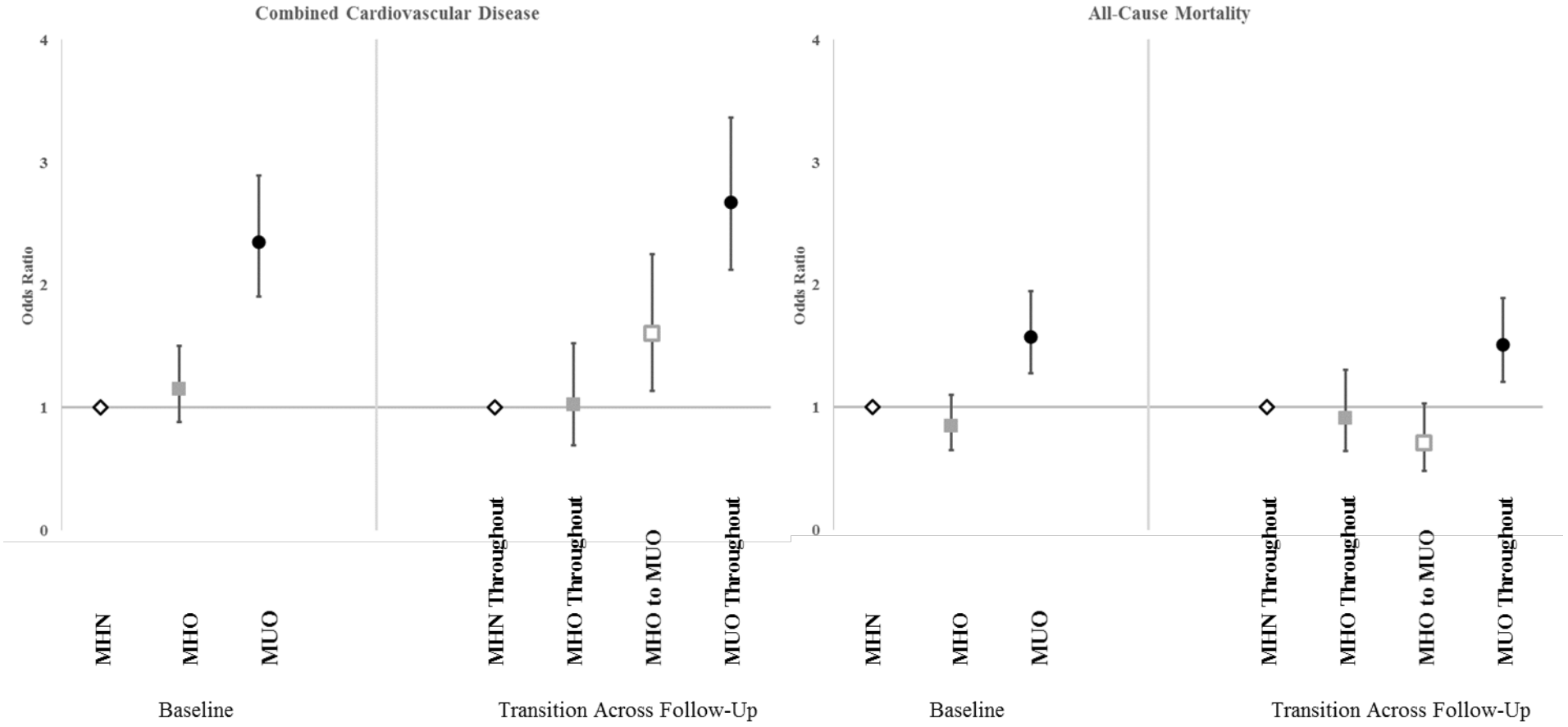

Figure 2. Association of metabolic syndrome with cardiovascular disease (Odds ratios and 95% confidence intervals) in 6573 MESA participants.

MetS=Metabolic syndrome

All models adjusted for age, sex, race/ethnicity, education, income, smoking status, LDL cholesterol, statin use, and obesity.

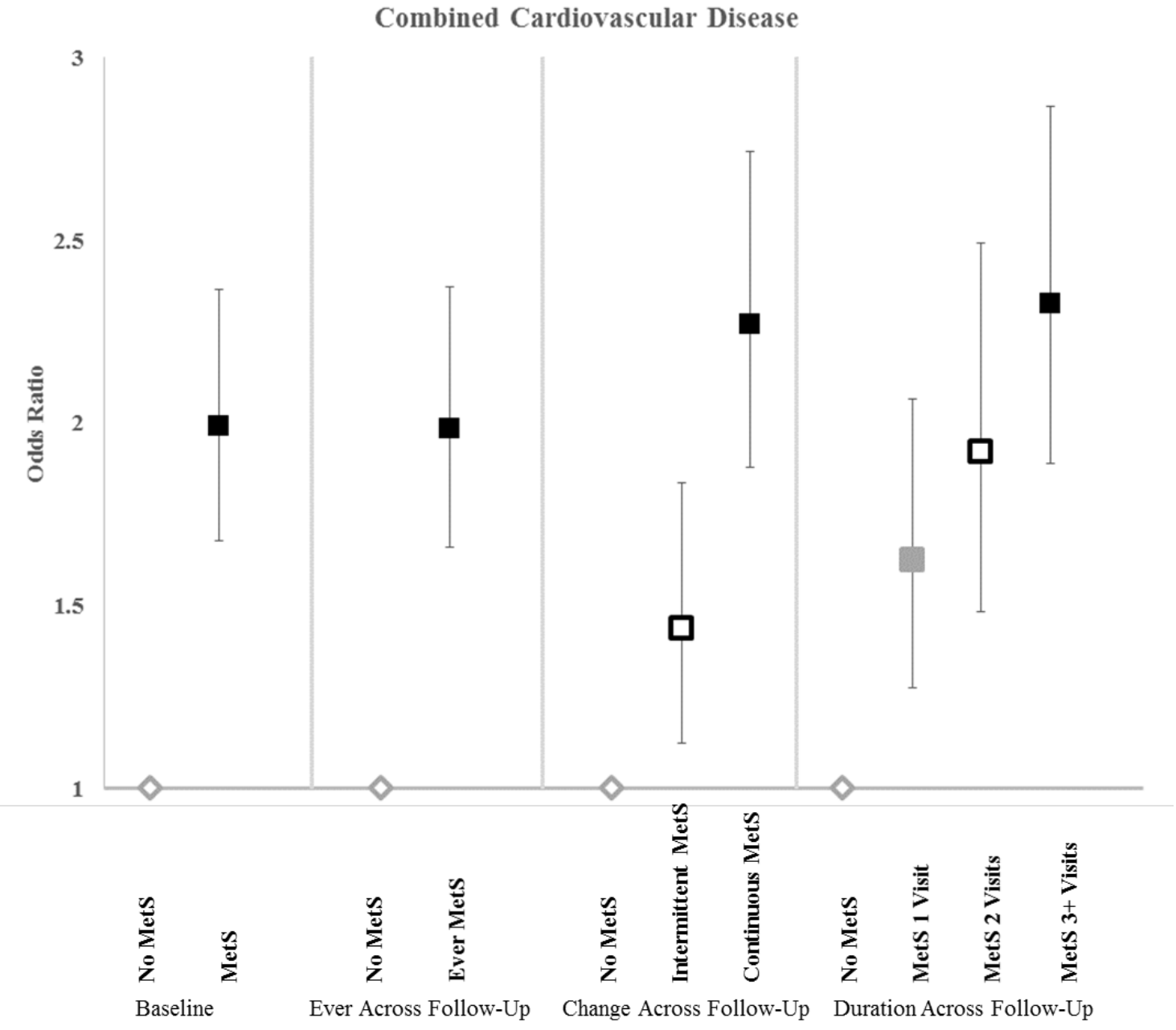

Table 1. Baseline Characteristics (Mean (SD)) of 5,005 MESA participants by obesity and metabolic syndrome status across follow-up

MHN = Metabolically healthy normal weight throughout; MHO = Metabolically healthy obesity throughout; MHO to MUO = Transition from metabolically healthy obesity at baseline to metabolically unhealthy obesity; MUO = Metabolically unhealthy obesity throughout

Characteristic	MHN	MHO	MHO to MUO	MUO	p-value *
N	2751	550	501	1203	
Age (years)	62.1 (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					
Caucasian	44.8 (0.955)	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)	<0.001
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
Total Cholesterol (mg/dL)	193.3 (0.64)	195.8 (1.42)	195.6 (1.61)	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 (0.36)	<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
Systolic BP (mmHg)	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					
Coronary Heart Disease (%)	5.74 (0.44)	3.64 (0.80)	6.59 (1.11)	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
Heart Failure (%)	2.69 (0.31)	2.55 (0.67)	3.79 (0.85)	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

* p-value for Cizick non-parametric test for trend

Table 2. Sensitivity analyses for combined cardiovascular disease and all-cause mortality (odds ratios and 95% confidence intervals) by metabolic status and metabolic syndrome transition

		Cardiovascular Disease		Mortality	
Model (n)	**Metabolic Status***	**OR**	**95% CI**	**OR**	**95% CI**
Primary Analysis					
(4859)	MHN	1.0	Ref	1.0	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					
(4857)	MHN	1.0	Ref	1.0	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					
(4859)	MHN	1.0	Ref		
	MHO	1.16	0.75-1.81		NA
	MHO to MUO	**1.64**	**1.10-2.42**		
	MUO	**2.53**	**1.94-3.30**		
Sex					
Women	MHN	1.0	Ref	1.0	Ref
(2516)	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	MHN	1.0	Ref	1.0	Ref
(2343)	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
Age					
<70 years	MHN	1.0	Ref	1.0	Ref
(3721)	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 years	MHN	1.0	Ref	1.0	Ref
(1138)	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
Race/Ethnicity					
Caucasian	MHN	1.0	Ref	1.0	Ref
(1938)	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**

Asian	MHN	1.0	Ref	1.0	Ref
(479)	MHO	**2.92**	**0.30-28.0**	No obs	
	MHO to MUO	No obs		2.43	0.25-23.8
	MUO	1.60	0.42-6.18	1.76	0.52-5.93
African American	MHN	1.0	Ref	1.0	Ref
(1416)	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	MHN	1.0	Ref	1.0	Ref
(1020)	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
Smoking					
No	MHN	1.0	Ref	1.0	Ref
(4235)	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	MHN	1.0	Ref	1.0	Ref
(624)	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
Metabolic syndrome without waist circumference					
(4273)	MHN	1.0	Ref	1.0	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**
Metabolic syndrome as ≥ 1 component					
(2668)	MHN	1.0	Ref	1.0	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
Reference group excludes overweight					
(3621)	MHN	1.0	Ref	1.0	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.
BOLD Indicates estimates that are significantly different from the reference at the $p<0.05$ level.
*MHN = Metabolically healthy normal weight throughout follow-up
MHO = Metabolically healthy obesity throughout follow-up
MHO to MUO=Transition from metabolically healthy obesity at baseline to metabolically unhealthy obesity during follow-up
MUO = Metabolically unhealthy obesity throughout follow-up