Metabolically Healthy Obesity, Metabolic Syndrome, and Cardiovascular Risk

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Abstract

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Clinical 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.

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

Methods—Among 6,809 participants of the Multi-Ethnic Study of Atherosclerosis we used Cox proportional hazards and logistic regression models to investigate the joint association of obesity (30kg/m^2) and MetS (IDF 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 to metabolically healthy normal weight, baseline MHO was not significantly associated with incident CVD; however, almost half of those participants developed MetS during follow-up (unstable MHO). Those who had unstable MHO had increased odds of CVD (OR=1.60 (1.14-2.25)), compared to those with stable MHO and healthy normal weight. Dose response for duration of MetS was significantly and linearly associated with CVD (1 visit with MetS 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 MetS mediated approximately 62% (44-100%) 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.

Introduction

The high prevalence of obesity is a costly burden on the US healthcare system.(1) Finding a subset of the population that is resilient to the effects of obesity on cardiovascular outcomes is of great interest in order 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 metabolic profile compared to 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.

While the accumulating evidence is leaning towards the consensus that MHO is not a low risk state compared to 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:

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

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based longitudinal cohort study started in 2000 with 6,814 participants recruited from six 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 below. 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 BMI $\geq$ 30kg/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 5005. Of the 5005 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 non-fatal), stroke (fatal and non-fatal), heart failure, combined cardiovascular disease (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 equivalent units. Since CVD risk factors are included in the MetS definition, most were not included in statistical models as potential confounders. 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's non-parametric 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 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 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.(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 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 IDF 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).

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 in 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 groups with MetS (MUN and MUO), but not for MHO compared to MHN at baseline (Online Table 1). Survival estimates for MHO at baseline 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. 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% (501/1051) 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 (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 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 (Online Table 2).

CVD odds ratios for obesity compared to normal weight, 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). Estimates for obesity are strongly attenuated and non-significant when adjusted for MetS (not shown). Mediation analysis indicated 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 (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 due to 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 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 2 or 3 visits with MetS (OR=2.19 (1.37-3.51)); and obesity and 4-5 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 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 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.(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 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.(11-15) While all four 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 to persistent MHN.(12,14) 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.(11) 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 (9), 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 (16,24-26). 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 (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

This study has several 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. 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 (29-32).

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 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 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.(16) 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 to predict future risk 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.

Conclusions

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 of lower clinical risk. Instead, MHO signals an opportunity for weight reduction, and prevention and management of existing MetS components should be prioritized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

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
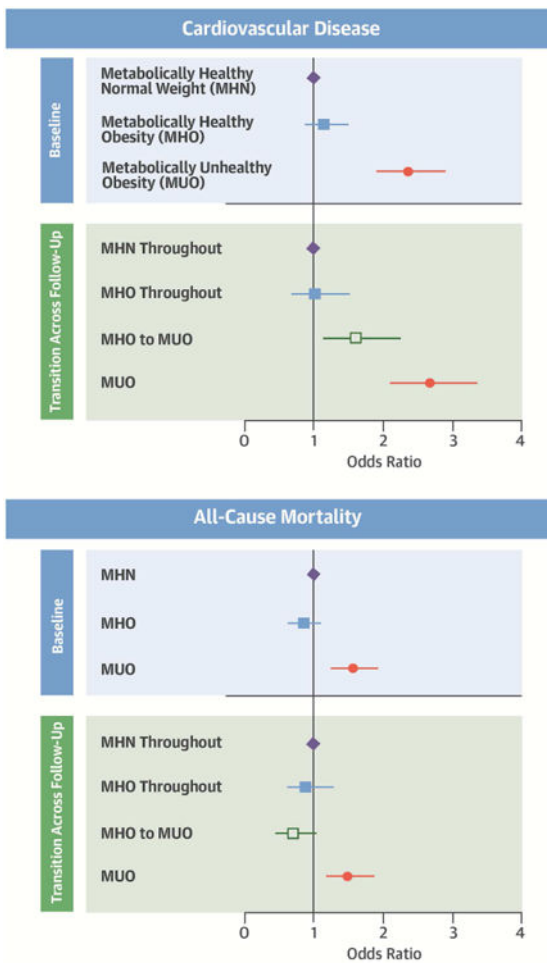
Figure 1. Association of metabolic syndrome with cardiovascular disease (Odds ratios and 95% confidence intervals) in 2744 MESA participants with obesity

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. MetS=Metabolic syndrome. All models adjusted for age, sex, race/ethnicity, education, income, smoking status, LDL cholesterol, and statin use. Sample sizes: At baseline n=1033 for No MetS; n=1159 for MetS. Ever across follow-up n=685 for No MetS and n=2059 for Ever MetS. Change across follow-up n=685 for No MetS; n=1434 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=1240 for MetS 3+ Visits.
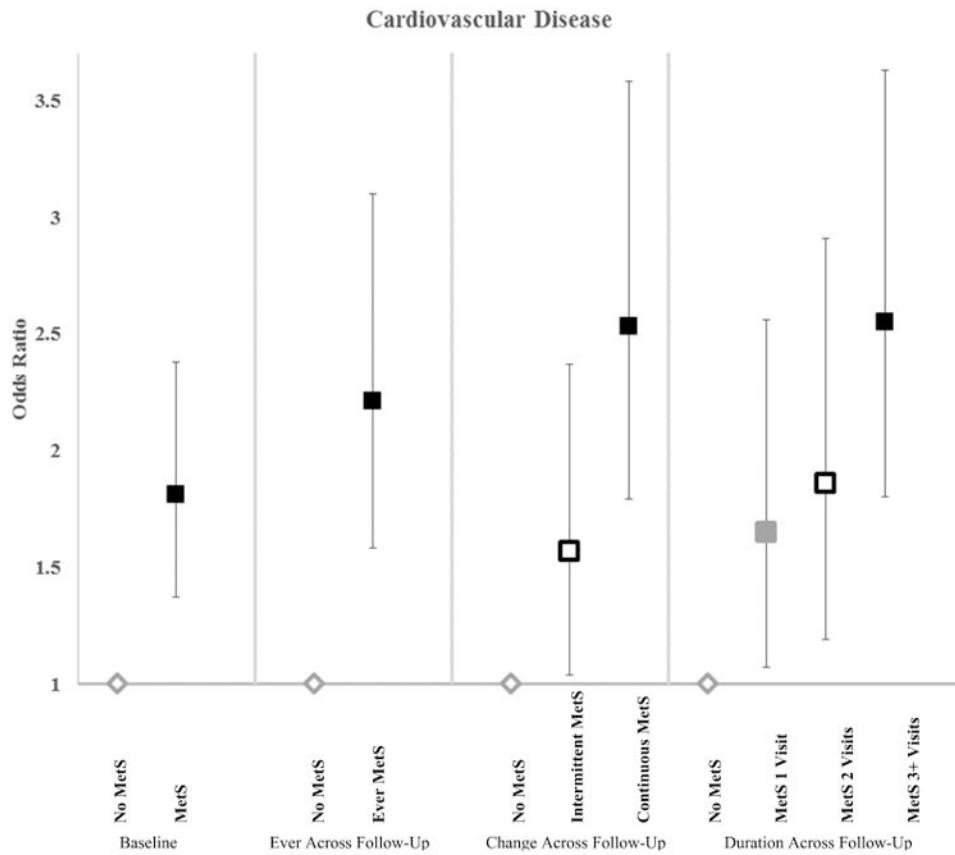
Central Illustration. Metabolically Healthy Oobesity with Cardiovascular Disease
Association of metabolically healthy obesity with cardiovascular disease and all-cause mortality (Odds ratios and 95% confidence intervals) in 5841 MESA participants. MHN=Metabolically heathy normal weight; MHO=Metabolically healthy obesity; MUO=Metabolically unhealthy obesity (categories are mutually exclusive). Metabolically healthy indicates <3 metabolic syndrome components. Unhealthy indicates 3 or more metabolic syndrome components. All models adjusted for age, sex, race/ethnicity, education, income, smoking status, LDL cholesterol, and statin use. Sample sizes: At baseline n=3587 for MHN; n=1051 for MHO; 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.

Table 1

Definition of metabolic syndrome and metabolically healthy obesity

Harmonized International Diabetes Federation criteria for metabolic syndrome (MetS): 3 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

Metabolic Status Groups:	
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.

Table 2

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

Characteristic	MHN (n=2751)	MHO (n=550)	MHO to MUO (n=501)	MUO (n=1203)	p-value*
Baseline					
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 (0.95)	35.6 (2.04)	37.9 (2.17)	20.7 (1.33)	<0.001
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)	1767 (48.5)	1658 (112.0)	1479 (90.7)	1226 (57.1)	<0.001
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

Characteristic	MHN (n=2751)	MHO (n=550)	MHO to MUO (n=501)	MUO (n=1203)	p-value [*]
Mortality (%)	14.1 (0.66)	8.55 (1.19)	7.19 (1.15)	15.8 (1.05)	0.81

[*]
p-value from Cizick's non-parametric test for trend.

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

Table 3

Characteristics (Mean (SD)) of 2,254 MESA participants with obesity by metabolic syndrome duration across follow-up

Characteristic	No MetS (n=550)	1 Visit (n=382)	2 Visits (n=302)	3+ Visits (n=1020)	p-value [*]
Baseline					
Age (years)	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 (1.200)	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 (0.340)	<0.001
Triglycerides (mg/dL)	99.0 (2.02)	130 (5.700)	141 (4.57)	169 (2.88)	<0.001
Hypertension (%)	23.5 (1.81)	49.7 (2.560)	57.9 (2.85)	68.1 (1.56)	<0.001
Systolic BP (mmHg)	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 (1.44)	<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 (1.150)	<0.001
Mortality (%)	8.5 (1.19)	19.1 (2.01)	14.9 (2.05)	10.6 (0.96)	0.88

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

MetS=Metabolic syndrome

Table 4

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

Model (n)	Metabolic Status*	Cardiovascular Disease		Mortality	
		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	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					
(2516)	MHN	1.0	Ref	1.0	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					
(2343)	MHN	1.0	Ref	1.0	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	

Model (n)	Metabolic Status*	Cardiovascular Disease		Mortality	
		OR	95% CI	OR	95% CI
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
p-value for difference		**<0.001**		0.44	
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**
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
p-value for difference		0.079		0.50	
Smoking					
No	MHN	1.0	Ref	1.0	Ref
(4235)	MHO	1.08	0.71-1.65	1.06	0.73-1.56

Model (n)	Metabolic Status*	Cardiovascular Disease		Mortality	
		OR	95% CI	OR	95% CI
	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	1.0	Ref	1.0	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	
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**

*
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

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 only myocardial infarction, resuscitated cardiac arrest, coronary heart disease death, stroke, and stroke death. **BOLD** Indicates estimates that are significantly different from the reference at the p<0.05 level.