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The Association Between Metabolically Healthy Obesity and Coronary Heart Disease Among Regards Study Participants

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THE ASSOCIATION BETWEEN METABOLICALLY HEALTHY OBESITY AND CORONARY HEART DISEASE AMONG REGARDS STUDY PARTICIPANTS

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MASTER OF SCIENCE: APPLIED EPIDEMIOLOGY

ABSTRACT

A major obstacle to the advancement of our understanding of the metabolically healthy obesity (MHO) phenotype is the inconsistent definition of metabolic health and obesity among studies. A harmonized definition of MHO in adults has been proposed based on the diagnosis of obesity (BMI $\geq$ 30 k/m^2) and meeting the cardio-metabolic criteria for triglycerides, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), no antihypertensive treatment, fasting blood glucose, and no drug treatment with glucose-lowering agents. In addition, waist circumference can be associated with increased disease risk when WC is $\geq$94 cm in men and $\geq$80 cm in women. Individuals with MHO have been shown to have a lower risk of cardiovascular disease (CVD) and mortality compared to those with metabolically unhealthy obesity (MUHO). MUHO has been defined as being obese with the presence of metabolic risk factors. However, a person can transition from MHO to metabolically unhealthy obesity (MUHO), potentially developing a greater risk for CVD. Data were collected as part of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. The association between MHO (compared to MUHO and compared to other healthy and unhealthy phenotypes) and coronary heart disease (CHD) was tested

using Cox proportional hazards models. To define MHO and other phenotypes, we included WC as one of the criteria.

The analysis included 20,142 participants who were free of CHD at baseline. Among those in the obese group, MHO represented 0.8% (N=61). BMI (35.5 $\pm$ 4.9) and waist circumference (WC) (107.5 $\pm$ 12.9) were highest in the MUHO group. Black adults represented 53.0% of the obese category (N=4,054). The MUHO group showed a 2.7 times higher risk (hazard ratio [HR]: 2.66; 95% CI: 2.08-3.40) with metabolically healthy without obesity (MHWO) as a reference.

Primary analyses showed that the unadjusted model for the MHO group showed no difference: HR: 1.002 [95% CI: 0.25-4.09] with MHWO as the reference group. When adjusted for covariates of interest, the MHO group showed a 21% increased risk, with a HR of 1.21 [95% CI: 0.30, 4.93]. By the second in-home visit, approximately 10 years after study entry, only 16% (N=4) of participants who were MHO at baseline remained MHO.

Our results indicate that further analysis is needed when describing the various metabolic phenotypes and utilizing WC as a method of categorizing people as unhealthy or healthy. WC, in addition to BMI, could help determine fat distribution, which, in turn, helps to better define “obesity” and those who are truly healthy.

Keywords: metabolically healthy obesity, coronary heart disease, obesity, metabolic syndrome

DEDICATION

This thesis is dedicated to my late grandmother, Earnestine Aaron.

ACKNOWLEDGMENTS

I would like to express much gratitude to my mom for supporting me in all aspects of my graduate education while being employed full-time. To my chair, Dr. Emily Levitan, committee members, Dr. Suzanne Judd, Dr. Bertha Hidalgo, and co-authors, I appreciate the guidance, suggestions, and insight during this process. You all have helped me to understand this complex topic more, including the ins and outs of conducting epidemiologic research. I would also like to thank the REGARDS committee and study participants for making this project possible.

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LIST OF ABBREVIATIONS

BMI	body mass index
CHD	coronary heart disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
ECG	electrocardiogram
HDL	high-density lipoprotein
HR	hazard ratio
MHO	metabolically healthy obesity
MHWO	metabolically healthy without obesity
MI	myocardial infarction
MUHO	metabolically unhealthy obesity
MUHWO	metabolically unhealthy without obesity
NIH	National Institute of Health
REGARDS	Reasons for Geographic and Racial Differences in Stroke
SBP	systolic blood pressure
SD	standard deviation
WHO	World Health Organization

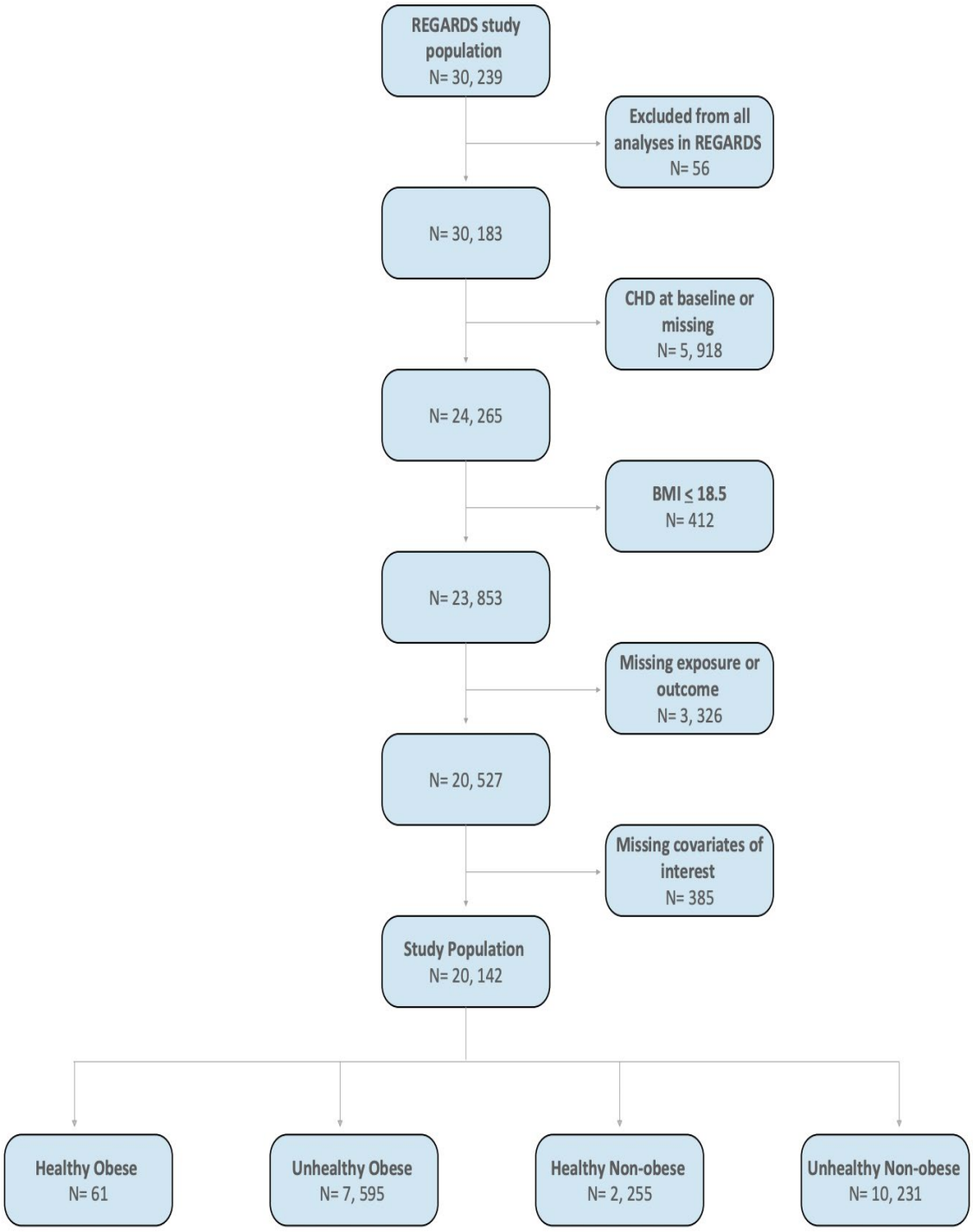
INTRODUCTION

Obesity prevalence has been increasing for over 50 years and has been associated with an increase in comorbidities such as coronary heart disease (CHD) [1]. CHD is the most common type of heart disease, resulting in 319,000 deaths in the United States by 2019 [3]. Metabolically healthy obesity (MHO) has been classified based on elevated body mass index (BMI) and the absence metabolic abnormalities. In contrast, metabolically unhealthy obesity (MUHO) is described as those who present with metabolic risk factors. MHO has been a complex topic due to differences in study design and methods of defining the phenotype, resulting in difficulty comparing results between study populations [4]. The value of the MHO phenotype has been debated because it may be a transient state towards being metabolically unhealthy, increasing the risk of cardiovascular disease (CVD) and death [5]. More recently, a harmonized definition of MHO in adults has been proposed based on the diagnosis of obesity (BMI $\geq$ 30 k/m^2) and meeting the cardio-metabolic criteria for triglycerides, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), diastolic blood pressure, (DBP), no antihypertensive treatment, fasting blood glucose, and no drug treatment with glucose-lowering agents [3]. In addition, the World Health Organization (WHO) stated that WC $\geq$ 94 cm in men and $\geq$ 80 cm in women indicates a risk of developing metabolic conditions [6]. When utilizing BMI to determine obesity, it does not capture the full span of body fat distribution, which may increase the risk of cardiovascular disease (CVD) [7].

In 1947, Jean Vague introduced the WC measurement to differentiate between abdominal and peripheral obesity, assessing for excess adiposity which appears mostly in the upper region of the body [8]. WC is typically correlated with abdominal fat mass and is therefore used as the primary marker for abdominal fat [9].

The aims of the current study were to (1) determine the association between MHO and incident CHD disease compared to the MUHO phenotype; (2) describe the transition between MHO and MUHO over time.

Figure 1. Flow Diagram of Study Population



METHODS

Study Participants

We conducted a secondary data analysis involving Black and White adults 45 years and older. Data was collected as part of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, sponsored by the National Institute of Health (NIH), which enrolled 30,239 participants between 2003-2007 in the United States [12]. This included phone interviews and conducting in-home physical examinations. Measurements of traditional risk factors were also collected. Participants who had data on triglycerides, HDL, glucose, BMI, WC, SBP, DBP, information on antihypertensive treatment, treatment with glucose-lowering agents, and complete data for covariates of interest. Those who were underweight (BMI <18.5 kg/m^2), had history of CHD at baseline or missing data on history of CHD, and missing covariates of interest, were excluded from the study. The final study sample included 20,142 participants (Figure 1). Approval to assess REGARDS data was reviewed and approved by the REGARDS committee and The University of Alabama at Birmingham's Institutional Review Board. REGARDS participants provided written informed consent for research.

Data Collection

Information on BMI, metabolic conditions, and covariates of interest was collected during the baseline visit (2003-2007), then again at the second in-home visit

(2013-2016). Information regarding CHD events was collected between baseline and 12/31/2018. Further details on the collection of data within the REGARDS study have been provided in prior publications [12-14].

CHD and CHD Events

The outcome of interest was incident CHD, defined as myocardial infarction (MI) or death from CHD. Potential CHD events were detected based on participant or proxy self-report of hospitalizations during twice annual telephone calls or deaths detected using proxy reports, the National Death Index, and other sources. CHD events were adjudicated by a team of experts and disagreements were then adjudicated by the committee. Adjudicators reviewed hospitalization records for diagnostic enzymes, electrocardiogram (ECG), and signs or symptoms indicative of ischemia [15]. Increase (greater than twice the upper limit of normal) or decline in cardiac level over six or more hours is classified as diagnostic cardiac enzymes [15]. For adjudication of cause of death, adjudicators reviewed information from hospitalizations shortly prior to death, death certificates, interviews with participant proxies, and, when available, autopsy reports. Further details are described elsewhere [16].

Metabolic Phenotypes

BMI was calculated as weight, in kilograms, divided by height in meters squared. Using a measuring tape, WC was measured over the skin at the midpoint between the lowest rib to the top of the iliac crest. BMI was used to categorize participants into two categories: obese (BMI $\geq$30 kg/m^2 or non-obese (BMI >18.5- <30 kg/m^2. Metabolic abnormalities were categorized as elevated serum triglycerides (> 150 mg/dl); low HDL (<40 mg/dl in men and (<50 mg/dl in women); elevated SBP (>130 mmHg); elevated DBP (>85 mmHg); elevated fasting glucose (>100 mg/dl); use of antihypertensive treatment and/or treatment with glucose-lowering agents; WC of $\geq$80 in women and $\geq$94in men.

Participants were defined as metabolically healthy if $\leq$1 metabolic abnormality was present and metabolically unhealthy if $\geq$2 metabolic abnormalities were present.

According to previous studies, there may be significant covariates in the study [10]. Thus, we adjusted for age, gender, and race, personal behaviors such as physical activity and smoking, and socioeconomic status (education and income).

Confounders of Interest

Socioeconomic status: Income and Education have been shown to have a significant impact on obesity and could be beneficial to reduce the high prevalence of obesity and other obesity-associated diseases [17-18]. REGARDS categorized income into five categories: <$20k, $20-$35k, $35-$75k, $75k or more, and declined to report. Education was also split into four categories: less than high school, high school graduate, some

college, and college graduate and above. Models were adjusted for income and education as confounders.

Alcohol Consumption

Several studies have shown that alcohol consumption is associated with obesity-related comorbidities such as CHD. We determined alcohol consumption to be a confounder. Alcohol use was categorized into three categories in REGARDS: None/light, moderate, and heavy. Models were adjusted accordingly to determine the risk level between phenotypes in association with CHD.

Smoking Status

Smoking status is considered an important factor because those that have a history of smoking may be at an increased risk of being obese and developing chronic illness. Smoking status was split into three categories in REGARDS: Past, never, or current smoker.

Physical Activity

In addition, higher physical activity levels may prevent the development of cardio-metabolic conditions. Physical activity was categorized into three levels in REGARDS: 1 to 3 times per week, 4 or more times per week, or none.

Statistical Methods

We calculated means and standard deviation (SD) or sample size (N) and percentage by obesity and metabolic phenotypes. The association between MHO and CHD was tested using cox proportional hazard models compared to MUHWO and MUHO. To assess the risk of CHD between non-obese and obese groups, we applied the following three models: the unadjusted baseline model 1, model 2 adjusted for age, gender, race, and smoking status, and model 3 adjusted for age, gender, race, smoking status, socioeconomic status (income and education), physical activity, and alcohol consumption. Among individuals with MHO who participated in the second in-home visit (n =25), we examined the risk of becoming MUHO.

A P-value of <0.05 was considered statistically significant. All statistical analyses were performed in SAS, version 9.4.

RESULTS

A total of 20,142 participants were included in this analysis. Table 1 shows the baseline characteristics of healthy and unhealthy (non-obese and obese) adults. Among the 7,656 obese individuals, 0.80% were categorized as MHO (61/7,656). Most of the obese category was comprised of MUHO individuals (7,595/7,656), who accounted for 99.2% of the obese population. There were more females in the non-obese category, representing 53.4% (n=6,667) with the mean BMI being highest among those categorized under the unhealthy non-obese group (26.0 $\pm$ 2.6). WC was highest among those who were unhealthy obese (107.5 $\pm$ 12.9) and lowest among healthy non-obese individuals (77.6 $\pm$ 8.5). In the obese group, females represented 64.5% (n= 4,940). Those categorized as MUHO had the highest BMI (35.5 $\pm$ 4.9) with the lowest BMI being in those who are metabolically healthy without obesity (MHWO) (23.5 $\pm$ 2.4). The MUHO group included mostly Black adults, which resulted in 64.0% (n=4,892) of the obese population, while the metabolically unhealthy without obesity (MUHWO) group consisted mainly of White adults; 51.7% (n=6,456). The MHO phenotype consisted of mostly Black adults; 52.5% (n=32).

Table 1. Baseline Characteristics of Obese and Non-obese adults
N= 20, 142

	Obese (N= 7, 656)		**Non-obese (N= 12, 486)**	
Baseline Characteristics	**Metabolically Healthy Obese** N= 61	**Metabolically Unhealthy Obese** N=7, 595	**Metabolically Healthy Non obese** N= 2, 255	**Metabolically Unhealthy Non-obese** N= 10, 231
Age, N (%)				
45-65 Years of age	50 (82.0)	4,639 (61.1)	1,470 (65.2)	4,741 (46.3)
65-85 Years of age	11 (18.0)	2,956 (38.9)	785 (34.8)	5,490 (53.7)
Gender, N (%)				
Female	48 (78.7)	4,892 (64.4)	1,486 (65.9)	5,181 (50.6)
Male	13 (21.3)	2,703 (35.6)	769 (34.1)	5,050 (49.4)
Race/ethnicity, N (%)				
Black/African American	32 (52.5)	4,022 (53.0)	556 (24.7)	3,775 (36.9)
White/Caucasian	29 (47.5)	3,573 (47.0)	1,699 (75.3)	6,456 (63.1)
Smoking Status, N (%)				
Current	5 (8.2)	867 (11.4)	298 (13.2)	1,622 (15.8)
Never	35 (57.4)	3,719 (49.0)	1,201 (53.3)	4,623 (45.2)
Previous	21 (34.3)	3,009 (39.6)	756 (33.5)	3,986 (39.0)
BMI (kg/m2); mean (SD)	33.0 (3.9)	35.5 (4.9)	23.5 (2.4)	26.0 (2.6)
WC (CM); mean (SD)	90.6 (13.8)	107.5 (12.9)	77.6 (8.5)	90.5 (9.7)
Weight (kg); mean (SD)	89.4 (15.2)	100.4 (16.5)	66.2 (10.3)	76.1 (11.8)

SBP; mean (SD)	116.0 (10.2)	130.1 (16.0)	114.0 (11.1)	127.2 (16.2)
DBP; mean (SD)	73.9 (7.3)	78.8 (9.7)	71.1 (7.6)	76.1 (9.2)
HDL; mean (SD)	65.4 (12.6)	49.3 (14.4)	66.2 (15.1)	52.2 (16.1)
Serum triglycerides; mean (SD)	71.8 (48.3)	141.4 (87.1)	88.7 (44.3)	130.9 (85.4)

BMI categories: Obese group >30 kg/m2; non-obese group: <30 kg/m2

In primary analyses, the reference group was MHWO. The unadjusted model for MHO showed no meaningful difference, resulting in an (HR of 1.002; 95% CI: 0.25-4.09) as compared to MHWO as the reference group. Model 2 was adjusted for age, gender, race, and smoking status, resulting in MHO having an (HR of 1.25; 95% CI: 0.31-5.08); indicating a 25% increased risk of CHD. Model 3 was adjusted for age, gender, race, smoking status, socioeconomic status (income and education), and alcohol consumption. The model showed a 21% increased risk presenting with an HR of 1.21 (95% CI: 0.30-4.93). The MUHO group was associated with a 2.28 times higher risk. (Adjusted HR: 2.28; 95% CI: 1.78-2.93).

Table 2: Primary analyses of the risk of Coronary Heart Disease in Metabolically Healthy Obese Participants

	Obese		Non-obese	
	Metabolically Healthy Obese N= 61	**Metabolically Unhealthy Obese** N=7, 595	**Metabolically Healthy Non-Obese** N= 2, 255	**Metabolically Unhealthy Non-Obese** N= 10, 231
Model 1 (HR 95% CI)	1.002 (0.25, 4.09)	2.66 (2.08, 3.40)	1 (reference)	2.64 (2.07, 3.37)
Model 2 (HR 95% CI)	1.25 (0.31, 5.08)	2.60 (2.00, 3.28)	1 (reference)	2.09 (1.64, 2.67)
Model 3 (HR 95% CI)	1.21 (0.30, 4.93)	2.28 (1.78, 2.93)	1 (reference)	1.95 (1.52, 2.49)

Model 1: unadjusted model
Model 2: adjusted for age, gender, race, smoking status
Model 3: adjusted for age, gender, race, smoking status, socioeconomic status, alcohol consumption, and physical activity

Secondary analyses to describe the association between MHO and coronary heart disease risk with MUHO as a reference group are described in table 3. As compared to MUHO, MHO was at a decreased risk and presented with an (HR of 0.38; 95% CI: 0.09-1.51) in the unadjusted model. Model 2, adjusted for age, smoking status, gender, and race were also associated with a decreased risk, with (HR: 0.49; 95% CI: 0.12-1.95].

Model 3 was adjusted for covariates of interest and was at a decreased risk, (HR: 0.53; 95% CI: 0.13-2.12).

Furthermore, upon examining the transition of those who are MHO, 16% (N=4) remained metabolically healthy while 84% (N=21) of participants became metabolically unhealthy.

Table 3. Subgroup analyses of the risk of Coronary Heart Disease in Obese and Non-obese Participants

	Obese		**Non-obese**	
	Metabolically Healthy Obese N= 61	**Metabolically Unhealthy Obese** N=7, 595	**Metabolically Healthy Non-obese** N= 2, 255	**Metabolically Unhealthy Non-obese** N= 10, 231
Model 1 (HR 95% CI)	0.38 (0.09-1.51)	1 (reference)	0.38 (0.29-0.48)	0.99 (0.89-1.11)
Model 2 (HR 95% CI)	0.49 (0.12-1.95)	1 (reference)	0.39 (0.31-0.50)	0.82 (0.73-0.91)
Model 3 (HR 95% CI)	0.53 (0.13-2.12)	1 (reference)	0.44 (0.34-0.56)	0.85 (0.76-0.95)

Model 1: unadjusted model
Model 2: adjusted for age group, gender, race, smoking status
Model 3: adjusted for age group, gender, race, smoking status, socioeconomic status, alcohol consumption, and physical activity

DISCUSSION

In this study, we examined the association between MHO and CHD as compared to non-obese and obese phenotypes in adults aged 45 years and older. Overall, those who were MHO showed no difference in developing CHD (HR: 1.002; 95% CI: (0.25, 4.09) with MHWO as the reference group. Based on worldwide findings with MHWO as a reference group, MHO represented with a 1.52 (HR) [19, 20]. However, when adjusted for covariates of interest in our study, MHO showed a 21% increased risk presenting with an HR of 1.21 (95% CI: 0.30-4.93). Our results are compatible with those of previous meta-analyses that have demonstrated that individuals with MHO present with a risk of CVD as compared to the MHWO phenotype [19]. Of note, a very small percentage of obese individuals in this population were MHO. Upon examining the transition from MHO to MUHO, 84% (N=21) of participants became metabolically unhealthy at the second in-home visit, resulting in 16% (N=4) of participants remaining metabolically healthy.

Results from this study should be interpreted in light of several strengths and limitations. One strength was that we used data from a cohort of people with a long follow-up period to reduce potential selection bias. Another strength was that we considered waist circumference, as BMI has several limitations, such as the inability to determine fat distribution when categorizing individuals into non-obese and obese phenotypes. The combination of BMI and waist circumference better identifies the

obesity phenotype, rather than either measure alone [21]. WC can be a powerful predictor of determining long-term CVD outcomes [22]. Questions on how reliable BMI is concerning obesity and health risk remains a constant debate, specifically in non-Hispanic Black individuals. However, most clinicians continue to utilize BMI to determine those health risks [22]. Some limitations of our study included 1) the study population was limited to Black and White individuals and 2) the MHO sample size was small compared to the other metabolic phenotypes. Because REGARDS did not include people who identified as race and ethnicity other than non-Hispanic/Latino Black and White, external validity may be limited and/or generalizability of findings to other race/ethnic groups. Effect modification was not tested due to the small sample size in the MHO group. In this analysis, we did not control measurement errors around those who are MHO and MUHO that may arise from a single measurement of the metabolic conditions.

In addition, there is limited information on the MHO phenotype in Black individuals compared to White individuals. However, some studies have shown that Black individuals have less visceral fat when presented with a similar BMI [23-26]. Most MHO definitions has been defined as an individual presenting with one or no metabolic conditions. Although studies indicated conflicting relationships between visceral fat and body composition in Black individuals, the duration of remaining metabolically healthy obese has been longer compared to White individuals; hence, the presence of more visceral fat is a great predictor in determining metabolic syndrome in several populations [27-29]. Vague considered people to be unhealthy based on an “apple shape” that

indicates more visceral fat. This fat lies within the abdomen and waistline region. Those who were healthy were considered to have a “pear shape”, indicating subcutaneous fat that lies in the thighs and hips [30-31]. Despite the increase of information regarding body composition differences in race/ethnic groups, there remains a lack of representation in clinical cohorts for minorities. Therefore, there is insufficient information on the impact and correlation of anthropometric measures of visceral fat and body composition.

CONCLUSION

In conclusion, our study suggests that MHO individuals show similar risk of developing CHD as compared to other phenotypes. Therefore, even with the absence of metabolic abnormalities, and those who are not currently taking medication for diabetes and hypertension, obesity remains a concern in developing CHD. In addition, our findings also suggest that MHO is a transient state to MUHO**.**

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APPENDIX

APPROVAL TO ANALYZE REGARDS DATA

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

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APPROVAL LETTER

TO: Levitan, Emily Bess

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 17-Mar-2022

RE: IRB-060217017
Reasons for Geographic And Racial Differences in Stroke (REGARDS) - Myocardial Infarction (MI3)

The IRB reviewed and approved the Personnel Amendment submitted on 15-Mar-2022 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: 4,
Determination: Approved