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Is Muscle Density an Effect Modifier in the BMI-Mortality Relationship?

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by

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The thesis of Emily Ava Eshraghian is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

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DEDICATION

For my family

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ABSTRACT OF THE THESIS

Is Muscle Density an Effect Modifier in the BMI-Mortality Relationship?

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Professor Britta Larsen, Chair

The obesity paradox is characterized by a U- or J-shaped curve, suggesting that overweight individuals have a lower risk of mortality compared to their normal weight counterparts. It is largely unknown whether muscle density plays a role in the relationship between BMI and mortality. We use data from the Multi-Ethnic Study of Atherosclerosis, an ethnically diverse longitudinal study of males and females, to examine whether muscle density or sex modify the BMI-mortality relationship. Results indicate that obese males with high muscle density have a lower risk of mortality (HR:

0.59, 95% CI: (0.23, 1.50)) compared to their normal weight counterparts, while obese females with high muscle density have a higher risk of mortality (HR: 1.37, 95% CI: 0.63, 3.00)) compared to their normal weight counterparts. Our results show that muscle density is a mediator, but not an effect modifier, in the association between BMI and mortality. Sex is an effect modifier in this association, with attenuated risk of mortality among obese men (HR: 0.50, 95% CI: (0.36, 0.69)), but not obese women (HR: 0.95, 95% CI: (0.65, 1.39)). Overall, our data are consistent with the survival advantage seen in obese populations.

Chapter 1: INTRODUCTION

1.1 The Obesity Epidemic

The obesity epidemic is a complex public health issue that impacts more than one third of the current global population.[1] Prediction models suggest that by 2030, 58% of the world population will be classified as overweight or obese.[2] Data from the 2013-2014 NHANES indicates that 32.5% of adult Americans are overweight and 37.7% of adult Americans are obese.[3] Such predictions are vital in design and implementation of current public health policies and clinical recommendations and will have a profound burden on individual and population health. As the obesity epidemic continues to spread throughout developed and developing regions of the globe, assessing prominent risk factors and plausible interventions will allow public health professionals to mitigate associated health impacts.

1.2 The Obesity Paradox

Though numerous studies indicate excess adiposity as a known risk factor for premature mortality, some studies suggest that obesity may have a protective effect against mortality. The evidence suggests that those who are overweight (BMI = 25 to <30 kg/m^2) may have better health outcomes compared to their normal weight (BMI = 18.5 to <25 kg/m^2) counterparts.[4] This phenomenon is known as the obesity paradox.

The obesity paradox is characterized by a U- or J-shaped curve describing the association between the risk of all-cause mortality (ACM) and BMI, such that a higher risk of mortality is observed among individuals with normal weight BMI.[5–7] Epidemiological studies indicate that this upper limit of adiposity may be suggestive of

better outcomes among patients with various conditions, such as cardiac dysfunction, renal disease, colorectal center, patients undergoing surgical procedures, and patients presenting in inpatient settings with critical illnesses.[8–12] This implies that overweight individuals are likely to have better prognoses, which is in disagreement with the common consensus that obesity is a major risk factor for premature morbidity or mortality.

It is unclear why overweight individuals have better outcomes than normal weight individuals. This may be, in part, due to the limitations of BMI, as this measurement lacks the ability to differentiate between adipose and muscle tissues. One study predicts misclassification of cardiometabolic health status when assessed based on BMI.[13] Other studies have shown that muscle mass changes across BMI categories.[14] A plausible explanation is that muscle density may change across BMI categories. For example, those that are classified as obese may have denser muscle, which further increases their BMI. However, little is known about how muscle density changes across BMI categories.

One hypothesis suggests that the obesity paradox may result from the inability of BMI to account for the discrepancies in muscle mass among BMI categories. Low muscle mass is associated with several negative health outcomes.[15] Among those classified as overweight by BMI status, protective effects have been limited to those with normal or high muscle mass.[16] There is evidence that skeletal muscle mass is inversely associated with the risk of death. A secondary analysis of NHANES data (n = 11,687) indicates that when adjusting for muscle mass, greater survival shifts are seen among individuals with normal BMI.[14] This suggests that muscle mass may modify the

BMI-mortality relationship, and that greater mortality in normal weight individuals may partially be due to low muscle mass.

Another hypothesis suggests the potential role of muscle quality, rather than muscle quantity, in health outcomes. Maintenance of muscle mass does not prevent changes in muscle quality, including declines in muscle strength. Results from a longitudinal cohort study among older adults indicate that even in the presence of preserved muscle mass, changes in muscle strength are not prevented.[17] Muscle quality is often measured quantitatively, by assessment of skeletal muscle fat infiltration (or myosteatosis) via computed tomography (CT) or bone density (DEXA) scans. Myosteatosis is associated with poorer health outcomes, including higher cardiovascular-related and all-cause mortalities.[19] After adjustment for BMI, the association between abdominal myosteatosis and cardiometabolic risk is attenuated.[20] Though muscle quality is a determinant in estimation of mortality risk,[18] it is unclear whether muscle density modifies the association between BMI and risk of mortality.

Further, there are sex-based differences in body composition. In general, women have more fat mass and males have more muscle mass.[21,22] Men are shown to have better muscle quality compared to women.[23] One study shows that BMI is a strong predictor of hypertension in males, but not in females. This may indicate that BMI is a less robust predictor across genders, depending on the outcome. Due to the sex-based differences seen in body composition and BMI as a predictor, further examining these associations by sex can provide valuable allocation of resources for sex-specific interventions.

Our study aims to examine: 1) whether muscle density modifies the association between BMI and ACM and 2) whether sex modifies the association between BMI and ACM. To analyze these relationships, we used data from the Multi-Ethnic Study of Atherosclerosis (MESA).

Chapter 2: METHODS

2.1 Study Design

Our study is a secondary analysis of data from the Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter prospective cohort study of ethnically diverse adults. The overall design of MESA has been previously published.[24] Briefly, this cohort includes 6,814 adults aged 45 to 84 years who were free from clinical evidence of cardiovascular disease at their time of enrollment. Written consent was provided by all participants and approval by the Institutional Review Board was given at each study site. Racial/ethnic groups of participants were African American, Chinese American, Hispanic, and Non-Hispanic White. Follow up visits occurred at 2, 4, 6, and 10 years after the baseline clinic visit, which took place between years 2000 and 2002.

2.2 Study Population

The individuals included in our analysis were enrolled in the Abdominal Body Composition, Inflammation and Cardiovascular Disease cohort, which is an ancillary study of MESA. At clinic visit 2 or 3, a random subset of participants were enrolled in this ancillary study (n = 1,970). During this visit, individuals received abdominal CT scans, which were later used to quantify abdominal muscle area, muscle radiodensity, visceral adipose tissue, and subcutaneous adipose tissue (see Measures). Approximately half of the participants in this ancillary study completed CT scans at visit 2; the remainder completed CT scans at visit 3. Participants with complete data on muscle radiodensity, BMI, ACM, and potential covariates are included in our study (n = 1,879).

2.3 All-Cause Mortality Measurement

Telephone interviews were conducted by trained staff every 9 to 12 months after the initial baseline visit to ask individuals or next of kin about hospital admissions, cardiovascular events, and deaths. If the participant died, the next of kin gave information on the date and cause of death. Trained MESA staff reviewed death certificates, which were coded for the cause of death, and verified death with the National Death Index.

2.4 BMI Measurement

Data on weight and height were collected by trained staff at each visit using a balance-beam scale and stadiometer, respectively. These data were collected at the baseline visit (between year 2000 and 2002). BMI was calculated as weight in kilograms divided by height in meters squared.

2.5 Muscle Density Measurement

Muscle density was measured via CT scan of the abdominal region. At visits 2 or 3, abdominal CT scans were performed using a single CT slice at lumbar vertebrae 4 (L4) to 5 (L5). The Medical Imaging Processing Analysis and Visualization software version 4.1.2 was utilized (NIA/NIH, Bethesda, MD). Tissue was categorized as lean muscle (0 to 100 HU), fat (-190 to -30 HU), and mixed connective tissue (intervening range: -29 to -1 HU) based on the Hounsfield units (HU) observed. Muscles were grouped into muscles of stabilization (oblique, rectus abdominis, and paraspinal

muscles) or locomotion (psoas muscle). Area was determined for each muscle by summing the number of pixels of 0 to 100 HU within that muscle's corresponding fascial plane. Abdominal muscle density was calculated as the average HU measurement within the muscle's distinct fascial plane for those with an HU value within the appropriate range. A similar process was completed for visceral and subcutaneous fat.

2.6 Potential Covariates

Potential covariates included in our analyses are: age (years), race/ethnicity, diabetes, systolic blood pressure (mmHg), antihypertensive medication, total cholesterol (mg/dL), HDL cholesterol (mg/dL), statin use, cigarette smoking, cancer history, kidney function (mL/min/1.73m^2), and total weekly moderate to vigorous physical activity (MET-HOURS/WK M-SU). All covariates included in our analyses were assessed at baseline visit, between year 2000 and 2002. Diabetes was defined as a fasting blood glucose ≥ 126 mg/dL or use of hypoglycemic medications. Resting blood pressure was measured using a DinaDinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida) while individuals were in the seated position; three measurements were taken and an average of the last two were included in the analyses. Blood draws allowed assessment of lipids and lipoproteins (e.g. cholesterol); aliquots of blood (approximately 65 aliquots per participant) were prepared for analysis at the University of Vermont and the University of Minnesota. A random urine sample was collected to quantify kidney function. Physical activity was measured by utilization of a questionnaire adapted from Cross-Cultural Activity Participation study. The

remaining potential covariates (age, race/ethnicity, antihypertensive medication, cigarette smoking, and cancer history) were assessed by questionnaire.

2.7 Statistical Analyses

Participant characteristics were examined by BMI groups (normal, overweight, obese) and by muscle density groups (low, high). BMI was categorized according to current criteria by the World Health Organization[25] as follows: normal weight (BMI = 18.5 to <25 kg/m^2), overweight (BMI = 25 to <30 kg/m^2), and obese (BMI ≥30 kg/m^2). Underweight participants (BMI = <18.5 kg/m^2, n = 9) were omitted from our analyses. Muscle density groups were created by median split, as there is no current consensus in literature for quantitative characterization of low versus high muscle density. Sex-stratified models used gender-specific median splits. Unadjusted differences between participants at baseline were examined by t-test, chi-squared tests, and analysis of variance (ANOVA) tests, as appropriate.

Cox proportionate hazards models were used to examine the hypothesis that muscle density modifies the relationship between BMI and ACM. First, we ran univariable and multivariable Cox regression analyses to assess the relationship of 1) ACM by BMI status and 2) ACM by muscle density. To select potential covariates for the multivariable model, we used univariable Cox regression to assess the association between each covariate and ACM. Variables that were significantly associated with the ACM in the univariable analysis ($p<0.20$) were included in the multivariable model. Then, backward variable elimination was performed by removing the covariate with the

largest p-value from the model at each step. Final models were adjusted for age, race, diabetes, total cholesterol, HDL cholesterol, cigarette smoking, and physical activity.

To examine the effect of muscle density on the BMI-mortality relationship, muscle density was forced into the final model and the interaction between BMI and muscle density was examined using a multiplicative approach with similarly staged models. A similar analysis was performed to examine whether sex modifies the BMI-mortality relationship.

Chapter 3: RESULTS

3.1 Participant Characteristics

Table 1 shows participant characteristics by muscle density status and BMI category. Participants were between 46 and 88 years old, with a mean age of 64.6 years. Non-Hispanic White participants comprised 40.4% of the total sample. Mean BMI in the total sample was 28.1 kg/m^2. Compared to participants in low muscle density groups, those in high muscle density groups were younger, more likely to be male, had lower mean systolic blood pressure, lower mean HDL cholesterol levels, and were less likely to use statins (for all $p<0.05$). On average, those with normal BMI were older than those with overweight BMI; those with overweight BMI were older than those with obese BMI. Overweight participants were more like to have a history of cancer than normal weight or obese participants (for $p<0.05$). For the total sample, a median split resulted in low muscle density defined as less than 42.7 HU. In females, the median was 40.3 HU; in males, the median split was 45.0 HU.

Table 1. Participants characteristics in subsample of MESA cohort (n=1870).

		Muscle density			BMI			
	Total sample (n=1870)	**Low (n=935)**	**High (n=935)**	**p-value**	**Normal (n=541)**	**Over-weight (n=772)**	**Obese (n=557)**	**p-value**
Categorical variables, n (%)								
Women	936 (50.1)	629 (67.0)	313 (33.2)	<0.001	282 (52.1)	339 (43.9)	315 (53.6)	<0.001
Race/Eth *White/Cauc.* *Chinese Am.* *Black/AA* *Hispanic*	 755 (40.4) 241 (12.9) 392 (21.0) 482 (25.8)	 419 (44.8) 105 (11.2) 149 (15.9) 262 (28.0)	 336 (35.9) 136 (14.5) 243 (26.0) 220 (23.5)	 <0.001	 235 (43.4) 146 (27.0) 75 (13.9) 85 (15.7)	 317 (41.1) 85 (11.0) 164 (21.2) 206 (26.7)	 203 (36.4) 10 (1.8) 153 (27.5) 191 (34.3)	 <0.001
Smoking *Never* *Former, quit >1 yr* *Former, quit <1 yr*	 895 (47.9) 752 (40.2) 223 (11.9)	 468 (50.1) 372 (39.8) 95 (10.2)	 427 (45.7) 380 (40.6) 128 (13.7)	 <0.001	 279 (51.6) 208 (38.4) 54 (10.0)	 379 (49.1) 295 (38.2) 98 (12.7)	 237 (42.5) 249 (44.7) 71 (12.7)	 <0.001
Diabetes *Normal* *Impaired Fasting BG* *Untreated*	 1357 (72.6) 253 (13.5) 260 (13.9)	 649 (69.4) 134 (14.3) 152 (16.3)	 708 (75.7) 119 (12.7) 108 (11.6)	 <0.001	 451 (24.1) 46 (2.5) 44 (2.4)	 553 (71.6) 123 (15.9) 96 (21.5)	 353 (63.4) 84 (15.1) 120 (21.5)	 <0.001
Antihypertensive medication usage	767 (41.0)	454 (48.6)	313 (33.5)	<0.001	156 (28.8)	326 (51.2)	285 (42.2)	<0.001
Statin usage	376 (20.1)	229 (24.5)	147 (15.7)	<0.001	83 (15.3)	172 (21.7)	121 (22.3)	<0.001
Cancer history	151 (8.1)	93 (9.9)	58 (6.2)	<0.001	43 (7.9)	60 (8.6)	48 (7.7)	0.8487
Continuous variables, mean (SD)								
Age (years)	64.6 (9.6)	68.4 (9.1)	60.8 (8.6)	<0.001	65.2 (10.0)	64.8 (9.8)	63.7 (8.9)	0.0302
Systolic BP (mmHg)	124.9 (21.1)	127.8 (22.2)	121.9 (19.5)	<0.001	120.8 (21.2)	124.8 (20.9)	129.0 (20.4)	<0.001
BMI (kg/m^2)	28.1 (5.0)	29.0 (5.6)	27.1 (4.2)	<0.001	22.8 (1.6)	27.4 (1.4)	34.1 (3.9)	<0.001
Total chol (mg/dL)	190.9 (35.3)	190.9 (35.7)	190.9 (34.9)	0.9875	193 (34.0)	190.0 (34.0)	190.0 (38.1)	0.239
HDL chol (mg/dL)	51.0 (15.0)	52.4 (15.5)	49.6 (14.3)	<0.001	57.0 (17.2)	49.5 (13.6)	47.2 (12.7)	<0.001
Kidney function (mL/min/1.73m^2)	79.1 (17.3)	76.5 (17.9)	81.8 (16.3)	<0.001	80.4 (16.5)	77.7 (17.6)	80.0 (17.6)	0.0079
Total physical activity (MET-HOURS/WK M-SU)	83.0 (79.6)	70 (68.3)	95.9 (87.6)	<0.001	78.7 (73.3)	86.4 (80.8)	82.4 (83.5)	0.214

3.2 Relationship Between BMI, Muscle Density, and ACM in Total Population

Adjusted HRs of ACM by BMI category are shown in Table 2. Our analyses indicate that there is no difference in risk of mortality among those who are overweight

(HR: 0.99, 95% CI: (0.77, 1.28)) compared to those who are normal weight. There is a slight, non-significant decrease in risk of mortality among those who are obese (HR: 0.92, 95% CI: (0.69, 1.22)) compared to those with normal BMI. Though not statistically significant, adjustment for muscle density lowers the risk of mortality in individuals who are obese (HR: 0.81, 95% CI: (0.61, 1.09)) compared to normal weight.

Table 2. Adjusted HR of ACM by BMI category dependent on muscle density (Model 1) and independent of muscle density (Model 2). Values reported as HR (95% CI).

BMI category	**Hazard of ACM**	
	Model 1	Model 2
Normal (n=541)	Reference	Reference
Overweight (n=772)	0.99 (0.77, 1.28)	0.97 (0.76, 1.25)
Obese (n=557)	0.91 (0.69, 1.22)	0.81 (0.61, 1.09)

*indicates p<0.05
Model 1: Adjusted for covariates (age, race, diabetes, total cholesterol, HDL cholesterol, cigarette smoking, physical activity)
Model 2: Adjusted for all covariates + muscle density category

Table 3 shows HRs of ACM by muscle density category. Those with high muscle density have a significantly lower risk of mortality (HR: 0.67, 95% CI: (0.53, 0.84)) compared to those with low muscle density. Results are similar and remain significant regardless of adjustment for BMI category.

Table 3. Adjusted HR of ACM by muscle density dependent on BMI (Model 1) and independent of BMI (Model 2). Values reported as HR (95% CI).

Muscle density	**Hazard of ACM**	
	Model 1	Model 2
Low (n=935)	Reference	Reference
High (n=935)	0.67 (0.53, 0.84) *	0.64 (0.50, 0.81) *

*indicates p<0.05
Model 1: Adjusted for covariates (age, race, diabetes, total cholesterol, HDL cholesterol, cigarette smoking, physical activity)
Model 2: Adjusted for all covariates + BMI category

To assess whether muscle density modifies the association of BMI with ACM, BMI categories were further stratified by muscle density categories to allow for within-group comparisons (Table 4). For both high and low muscle density, obese individuals had a lower risk of mortality than normal weight individuals. However, the difference was greater for obese individuals with low muscle density (HR: 0.75, 95% CI: (0.54, 1.06)) than obese individuals with high muscle density (HR: 0.86, 95% CI: (0.48, 1.55)). There is no difference in risk of mortality between overweight and normal weight persons with high muscle densities (HR: 1.03, 95% CI: (0.67, 1.58)). The interaction was not statistically significant ($p>0.20$).

Table 4. HR of ACM by BMI category and muscle density in 1879 participants. Reported as HR (95% CI). Adjusted for all covariates.

BMI category	Hazard of ACM	
	Low muscle density (n=935)	High muscle density (n=935)
Normal (n=541)	Reference	Reference
Overweight (n=722)	0.92 (0.67, 1.26)	1.03 (0.67, 1.58)
Obese (n=557)	0.75 (0.54, 1.06)	0.86 (0.48, 1.55)

*indicates $p<0.05$

3.3 Relationship Between BMI, Muscle Density, and ACM in Sex-Stratified Population

Adjusted HRs of ACM by BMI category stratified by sex are shown in Table 5. There was no difference in mortality risk between obese and normal weight females (HR: 0.98, 95% CI: (0.63, 1.54)); adjustment for muscle density did not have a significant impact on this risk. There was a non-significant reduction in mortality risk among obese males when adjusting for muscle density, such that obese males have a lower risk of mortality (HR: 0.84, 95%CI: (0.56, 1.26)) compared to their normal weight

counterparts. The protective effect of obesity is only found in males after adjusting for muscle density.

Table 5. Sex-stratified adjusted HR of ACM by BMI category dependent on muscle density (Model 1) and independent of muscle density (Model 2). Values reported as HR (95% CI).

BMI category	Hazard of ACM			
	Female (n=936)		Male (n=934)	
	Model 1	Model 2	Model 1	Model 2
Normal	Reference	Reference	Reference	Reference
Overweight	1.02 (0.68, 1.53)	1.02 (0.68, 1.54)	1.01 (0.73, 1.40)	0.98 (0.71, 1.36)
Obese	0.99 (0.64, 1.54)	0.98 (0.63, 1.54)	1.00 (0.68, 1.48)	0.84 (0.56, 1.26)

*indicates p<0.05
Model 1: Adjusted for covariates (age, race, diabetes, total cholesterol, HDL cholesterol, cigarette smoking, physical activity)
Model 2: Adjusted for all covariates + muscle density category

Table 6 shows the relationship between muscle density and risk of mortality. This did not significantly change when adjusting for BMI category. Sex-stratified results showed variations in the muscle density-mortality relationship. There was a significant decrease in risk of mortality among males with high muscle density compared to males with low muscle density (HR: 0.50, 95% CI: (0.36, 0.69)). Although results are not significant, females with high muscle density had a slightly lower risk of mortality (HR: 0.95, 95% CI: (0.65, 1.39)) compared to females with low muscle density.

Table 6. Sex-stratified adjusted HR of ACM by muscle density dependent on BMI (Model 1) and independent of BMI (Model 2). Values reported as HR (95% CI).

Muscle density	Hazard of ACM			
	Female (n=936)		Male (n=934)	
	Model 1	Model 2	Model 1	Model 2
Low	Reference	Reference	Reference	Reference
High	0.96 (0.66, 1.38)	0.95 (0.65, 1.39)	0.51 (0.37, 0.71) *	0.50 (0.36, 0.69) *

*indicates p<0.05
Model 1: Adjusted for covariates (age, race, diabetes, total cholesterol, HDL cholesterol, cigarette smoking, physical activity)
Model 2: Adjusted for all covariates + BMI category

Table 7 presents risk of mortality by sex and muscle density as predicted by BMI status. Among females with low muscle density, obese females have a lower risk of mortality (HR: 0.86, 95%CI: (0.49, 1.50)) compared to their normal weight counterparts. Among females with high muscle density, obese females have a higher risk of mortality (HR: 1.37, 95%CI: (0.63, 3.00)) compared to their normal weight counterparts. Among males with high muscle density, there was a lower risk of mortality among overweight (HR: 0.66, 95% CI: (0.35, 1.21)) and obese males (HR: 0.59, 95% CI: (0.23, 1.50)) compared to their normal weight counterparts.

Table 7. Sex-stratified HR of ACM by BMI category and muscle density in 1879 participants. Reported as HR (95% CI). Adjusted for all covariates.

BMI category	Hazard of ACM			
	Female		Male	
	Low muscle density (n=468)	High muscle density (n=468)	Low muscle density (n=467)	High muscle density (n=467)
Normal	Reference	Reference	Reference	Reference
Overweight	1.04 (0.61, 1.77)	0.86 (0.44, 1.69)	1.13 (0.77, 1.67)	0.66 (0.35, 1.21)
Obese	0.86 (0.50, 1.50)	1.37 (0.63, 3.00)	0.92 (0.58, 1.46)	0.59 (0.23, 1.50)

*indicates $p<0.05$

Chapter 4: DISCUSSION

Our results from an ethnically diverse cohort of males and females show that muscle density is a mediator, but not an effect modifier, in the BMI-mortality relationship. Among different groups of BMI, there are no differences in the risk of mortality regardless of muscle density. Further, our results indicate effect modification by sex. Sex-stratified results show an increased protective effect from obesity in males, but not in females.

Our data are consistent with the survival advantage seen in obese populations. Adjustment for muscle density as a categorical variable attenuated the risk of mortality associated with high BMI, suggesting muscle density's role as a mediator in the BMI-mortality relationship. Some have hypothesized that excess adiposity may be beneficial for counteracting episodes of catabolic stress. As populations age, there is a decrease or plateau in weight gain, which may be a result of increased fat mass and losses in lean body mass, such as decreases in muscle tissue.[34] However, it is possible that the data in our study show a protective effect of mortality due to a prevalence of lower muscle density in obese people in general. In such a case, adjustment for muscle density would cause an increased attenuation in risk of mortality. There is evidence that obese persons have poorer muscle quality compared to normal weight persons.[35]

Examination of muscle density as a potential risk factor for mortality is a novel avenue of research and may provide implications regarding metabolic health and aging. Age-related decline of muscle function, as characterized by muscle strength, is associated with mortality in older adults.[18] However, few studies have examined the association between muscle density and mortality. Existing studies have focused largely

on elderly populations[19,26] or select individuals.[27,28] Similarly to our findings, results from the Tobago Health study, a prospective longitudinal study, show an independent and inverse association between muscle density and all-cause mortality.[28] The Health, Aging, and Body Composition (Health ABC) Study also shows a strong association between muscle strength and mortality; their findings indicate that muscle quality is a more important marker of mortality compared to muscle mass.[18]

Further, our results show that sex modifies the relationship between muscle density and mortality. This may be, in part, due to sex-based differences in skeletal muscle fiber characteristics.[29] Results from the Framingham study indicate a greater proportion of mobility impairments, in part due to higher levels of myosteatosis, among women compared to men.[30] Obese females with high muscle density may have a higher risk of mortality as a result of functional changes in skeletal muscle, which alter homeostasis of the body as a whole.[31] Sex hormone treatment has been shown to cause changes in skeletal muscle strength in transgender individuals, indicating that modification by sex may be a result of underlying endocrinological functions.[32] Differences in physiology between sexes may describe this. One study indicates that variations in female physiology may be explained by varying capabilities in female skeletal muscle fibers.[33] Our findings are consistent with other studies, which report independent associations between myosteatosis and ACM among men.[19,28]

4.1 Limitations

Limitations of the current study should be acknowledged. First, assessment of variables as categorical (i.e. muscle density, BMI), rather than continuous, may have

resulted in residual error in results, thus lowering the power of the study. However, to remain consistent, we determined that use of categorical variables would allow better comparability. Second, slack of access to certain data variables may have resulted in errors in results. Several other variables may have impacted the relationship seen in our results, such as visceral adipose tissue, hormone therapy, and muscle area. Our models did not include all potential confounders in the BMI-mortality relationship. Third, our study does not account for changes in BMI over follow-up. Given that BMI was calculated at baseline and muscle density was assessed at follow-up visit 2 (2 years after baseline) or 3 (4 years after baseline), significant changes in BMI may have occurred between these time points. Given that individuals were enrolled in a longitudinal cohort for assessment of cardiovascular disease, individuals may have been more motivated to change health behaviors, such as increase physical activity or partake in better nutritional habits. Differential changes in BMI or muscle density changes as a result of health behavior changes are not accounted for in our analyses; such behaviors would likely cause changes in BMI which were not captured at follow-up visits. Lastly, our results are not significant and have a large spread, which makes it difficult to detect effects. We suggest future studies include larger sample sizes to increase study power and increase the ability to detect possible effect modification by muscle density.

Chapter 5: CONCLUSION

Muscle density is a mediator, but not an effect modifier, in the association of BMI with mortality. When adjusting for muscle density, the risk of mortality is attenuated in obese populations. This evidence corroborates with previous studies that indicate presence of an obesity paradox, such that overweight and obese persons have a lower risk of mortality compared to their normal weight counterparts. Further, our analyses indicate that sex modifies the BMI-mortality relationship, such that a protective effect of obesity is seen in men, but not in women. Further analyses that account for greater potential covariates and are more powered to detect such differences are necessary to better understand the roles of muscle density and sex in the BMI-mortality relationship.

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