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Relation of Anthropometric Obesity and Computed Tomography measured Non-alcoholic Fatty Liver Disease (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

We hypothesized that anthropometric measures of abdominal obesity would have a stronger positive association with non-alcoholic fatty liver disease (NAFLD) measured by non-contrast computed tomography versus general measures of obesity. The Multi-Ethnic Study of Atherosclerosis (MESA) is comprised of participants aged 45–84 years free of known cardiovascular disease. We studied 4,088 participants with adequate liver and spleen CT-imaging and no prior use of oral steroids, class 3 anti-arrhythmics, moderately-heavy alcohol use, or cirrhosis. Prevalent NAFLD was defined as a liver:spleen Hounsfield attenuation ratio of <1. Multivariable log-linear regression modeled the association of 4 obesity measures—weight, body mass index, waist circumference and waist-to-hip ratio—with prevalent NAFLD. Receiver operator curve analysis compared NAFLD discrimination. Median age was 63 years, and 55% were female. For each obesity measure, adjusted prevalence ratios for NAFLD were 4–5 fold greater in the highest versus the lowest quartile ($p<0.001$). Waist circumference and body mass index had the highest prevalence ratios, and waist circumference had the best discrimination, for NAFLD in the total population; although an abnormal body mass index categorized individuals with NAFLD as well if not better than waist circumference. In ethnic-specific analysis, Whites and Chinese had the strongest association of obesity and NAFLD compared to other ethnicities. In

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conclusion, though waist circumference provided the best discrimination for NAFLD, body mass index may perform similarly well in clinical settings to screen for NAFLD.

Keywords

Obesity; Abdominal Obesity; Liver Disease; Epidemiology

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States[1] affecting 30% of the general population[2] and up to 80% of those with obesity or diabetes[3]. NAFLD is strongly linked to metabolic risk factors, including diabetes, insulin resistance and inflammation[4], and cardiovascular disease is a more common cause of death in patients with NAFLD than liver disease[5]. Some studies have suggested that, similar to the metabolic syndrome, NAFLD is more strongly associated with visceral fat accumulation than other fat distributions [6,7]. However, this has not been seen in all populations [8,9], and many of these studies had limitations such as enrolling relatively small sample sizes, comparing only 2 anthropometric obesity measures, or utilizing less sensitive estimates of NAFLD such as elevated liver enzymes [10]. The aim of this present study was to use the multi-center Multi-Ethnic Study of Atherosclerosis (MESA) cohort to examine the association of 4 anthropometric measures of obesity with NAFLD measured by CT. We hypothesized that measures of abdominal obesity, such as waist circumference or WHR, would be more strongly associated with NAFLD than more general measures of obesity.

METHODS

The Multi-Ethnic Study of Atherosclerosis (MESA) is a cohort study aiming at investigating the prevalence, correlates and progression of subclinical cardiovascular disease. Details of its design have been reported[11]. MESA includes 6,814 men and women aged 45–84 years, free of clinical cardiovascular disease at baseline (2000–2002), recruited from 6 US field centers. Approximately 53% of the cohort is female, 38% White, 12% Chinese, 28% Black and 22% Hispanic.

We excluded all participants with computed tomography (CT) imaging that did not extend inferiorly enough to measure attenuation of both the liver and the spleen (n=2,430). We also excluded participants with a history of moderately-heavy alcohol use (>7 drinks per week in women and >14 drinks per week in men, n=219), self-reported cirrhosis (n=5), and those using oral steroids (n=70) and class 3 anti-arrhythmics (n=2), as use of these agents can cause macrovesicular steatosis. Our final study population was 4,088.

Participants completed a self-administered questionnaire on demographics, and medical and family histories. Anthropometric measures were performed in light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Waist circumference was measured horizontally at the level of the umbilicus. Hip girth was measured at the maximum circumference of the buttocks. The ratio of waist circumference

to hip girth defined waist-to-hip ratio (WHR). Systolic blood pressure was measured in a seated position 3 times with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Wipro GE Healthcare, Waukesha, Wisconsin); the final 2 measurements' average was used for analysis. Hypertension was defined by the stages of Joint National Commission on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure VII criteria [12]. Diabetes was defined as either a fasting glucose ≥126 mg/dl, self-reported prior diagnosis or use of diabetes medication. Blood samples were obtained after a 12 hour fast and were used to measure glucose, lipid profile, C-reactive protein and interleukin-6.

After providing informed consent, all participants underwent 2 consecutive baseline non-contrast cardiac CT scans, as previously described[13]. Three sites used the Imatron C-150XL CT scanner (GE-Imatron, San Francisco, California), and 3 sites used multi-detector CT scanners (4 slices). Each scan was performed from the carina to below the apex of the heart during a breath hold, which in the majority of cases, contains images of the liver and spleen. Scans were read independently by 2 experienced readers, blinded to demographic data. The liver to spleen attenuation ratio was selected as the most stable measure of hepatic fat content, and a liver to spleen ratio (LSR) of <1.0 was defined *a priori* as the cut-point for NAFLD[14–17]. The largest scan span was selected for measurement of liver fat. Hepatic and splenic Hounsfield unit attenuation values were measured using regions of interest > 100 mm^2. There were 2 regions of interest in the right liver lobe anteroposteriorly, 1 in the left lobe and 1 in the spleen. Regions of interest with larger areas were used whenever possible. LSR was calculated by taking the mean Hounsfield unit measurement of both right liver lobe regions of interest and dividing it by the spleen Hounsfield unit measurement. MESA reproducibility and variability levels for LSR have been published[14].

Differences in baseline characteristics between those with and without NAFLD were compared using ANOVA for continuous variables and χ^2 tests for categorical variables. The Mann-Whitney-Wilcoxon rank sum was used to compare C-reactive protein and triglycerides. Since the prevalence of NAFLD was >10%, prevalence ratios, rather than odds ratios, were calculated from the regression model $y=\exp(X^T\beta)$, assuming Gaussian error and using robust standard error estimates; the exponentiated parameter β is interpreted as the prevalence ratio. The 4 primary predictor variables were the anthropometric obesity measures of weight (lbs), BMI (kg/m^2), waist circumference (cm), and WHR; each obesity measure was modeled in a separate regression model. Linear assumptions between predictor and outcome variables were checked. Prevalence ratios were calculated for the highest versus lowest quartile of each obesity measure. An unadjusted model and a model adjusted for age, gender, race/ethnicity and MESA site were fitted. Receiver operator curve (ROC) analysis yielded areas under the curve (AUC) to assess the discrimination of LSR<1.0 for each obesity measure. Tests of equality compared the AUCs from models of each obesity measure and Chi-squared and Bonferroni corrected p-values were calculated.

For regressions that used the highest vs. lowest quartile of obesity measure, a p-value for linear trend across all quartiles is reported. In race/ethnic strata where highest vs. lowest quartile analysis was used, race/ethnicity-specific quartiles of each obesity measure were re-calculated. To perform a "discordance" analysis, we used World Health Organization and

Adult Treatment Panel III cutoffs to dichotomize BMI and waist circumference, respectively, as either “abnormal” or “normal” for every individual in the cohort: “abnormal" BMI is defined as BMI≥30 in both genders, "normal" is BMI<30; "abnormal" waist circumference is defined as >102cm for male and >88cm female; "normal" waist circumference is ≤102cm in males and ≤88cm in females. We then fitted a regression model comparing groups of individuals with each combination of BMI and waist circumference “normality” for the outcome of LSR<1. A p-value ≤ 0.05 was considered statistically significant for all analyses. All analyses were performed using STATA 10.0 (Stata Co., College Station, TX).

RESULTS

The prevalence of NAFLD in our sample was 17.3%, and was similar in females and males; in Whites, Chinese, Blacks and Hispanics it was, respectively, 15.2%, 20.2%, 11.2% and 27.1%. The range of each obesity measure was: weight (85.8–314.4), BMI (15.9–54.5), waist circumference (61–156) and WHR (0.6–1.3). NAFLD participants were younger and had higher obesity measures, diabetes, fasting glucose, hypertension and mean systolic blood pressure, triglycerides, CRP and IL-6, and had lower education level and mean HDL (Table 1).

For each obesity measure, the NAFLD prevalence-ratio ranged from 4- to 5-fold greater in the highest versus the lowest quartile, after adjustment for age, gender, race and MESA site (Table 2A), with waist circumference and BMI demonstrating the strongest prevalence ratios. A significant and graded relationship was observed between each increasing quartile of all baseline obesity measures and NAFLD ($p<0.001$ for linear trend, data not shown). In sensitivity analyses to confirm the overall direction of association, absolute change in continuous LSR was calculated for 1 standard deviation increase in each baseline obesity measure: correlating with a decrease of approximately 0.05 in LSR, for all measures ($p<0.001$ for all measures). Waist circumference demonstrated the largest decrease in LSR, consistent with the strongest association with NAFLD (data not shown).

Race/ethnicity-stratified analysis was performed since heterogeneity between obesity measures and race/ethnicity was tested and found to be significant for obesity-measure/ethnicity combinations. In each race/ethnicity stratum, the highest vs. lowest quartile of each obesity measure was strongly positively associated with NAFLD (Table 2B). In MESA, Whites and Chinese demonstrated higher prevalence ratios for NAFLD for nearly every obesity measure (with the exception of Chinese-weight) compared to those for Blacks and Hispanics.

Receiver operator curve analysis provided AUC estimates for the ability of each obesity measure to discriminate NAFLD using an adjusted regression-model (Table 3A). Waist circumference had the highest AUC compared to BMI, WHR and weight. This difference persisted in male and female strata. A significance test for equality demonstrated that the waist circumference AUC was significantly higher than that of all other obesity measures in the total population and in both gender strata (Table 3A, Table 3B); BMI had the second highest AUC in each of these strata. Among ethnic strata, waist circumference demonstrated

the highest AUC in all ethnicities except Hispanics where BMI had a marginally higher AUC (data not shown). Within ethnic strata, however, the AUC of waist circumference and BMI were not statistically different. Waist circumference AUCs were tested for equality between ethnicities, and that of whites (0.6979) was significantly higher than that of the other ethnicities; the waist circumference AUC of Chinese was the second highest (0.6868) and was significantly higher than that of Blacks (0.6715), but not of Hispanics (0.6803).

To further explore the clinical relevance of the higher AUC of waist circumference to predict NAFLD, we performed a concordance/discordance analysis for waist circumference and BMI, comparing individuals who had combinations of abnormal WC or BMI against those that were normal for both measures (Table 4). Those who had both BMI and WC abnormal had the highest prevalence ratio for NAFLD, while those having BMI abnormal and WC normal had a higher prevalence ratio than those who had WC abnormal and BMI normal. In light of the continuing debate about ethnic-specific cut-offs to define obesity, we performed a sensitivity analysis adopting lower cut-offs to define abnormal BMI and waist circumference among Asians, the ethnic group with arguably the most robust data to suggest alternate thresholds[18]; point estimates using these cut-offs were not materially changed from those in Table 4.

DISCUSSION

Our findings suggest that waist circumference and body mass index had the highest prevalence ratios, and waist circumference had the best discrimination, for NAFLD. However, in discordance analysis, those with an abnormal body mass index categorized individuals with NAFLD as well if not better than those with abnormal waist circumference. There was some variation observed by ethnicity. The superior discrimination of waist circumference seems corroborate a growing literature suggesting that visceral adiposity may contribute to the etiology of NAFLD[7,10], perhaps by releasing free fatty acids and adipocytokines such as leptin, adiponectin, resistin and TNF-alpha[1,19].

The location of visceral fat results in a high flux of free fatty acids and adipocytokines through the liver via the portal vein, which causes hepatic steatosis, increased inflammation and insulin resistance [5,20]. Studies that have utilized imaging modalities such as CT to measure visceral fat have shown a positive association with NAFLD[8,21]. Similarly, van der Poorten et al. used MRI to demonstrate that visceral fat is independently associated with the presence and severity of hepatic inflammation and fibrosis diagnosed by liver biopsy[6]. Interestingly, a study in 400 Korean patients demonstrated that waist circumference performed similarly to multiple other measures to predict NAFLD including visceral fat area measured by CT, trunk fat mass measured by dual-energy X-ray absorpitometry and WHR[22].

Gender differences in body fat distribution have long been recognized, and have been posited to underlie gender differences in the metabolic syndrome and cardiovascular disease[23,24]. Several studies have reported gender differences with specific regard to NAFLD, though directions of association have not always been consistent between reports[7,25,26]. In a small study of Japanese patients, Ishibashi et al. reported a significant

negative association of waist circumference with LSR in men but not in women[8]. In our study, we found no variation in the relation of abdominal obesity and NAFLD by gender.

Ethnic specific data on NAFLD is relatively limited, making findings in our ethnic sub-strata of particular importance. In our study, the high prevalence of NAFLD in Hispanics and the low prevalence in Blacks mirror prevalence trends by ethnicity that have been published in previous reports[2,26,27]. In studies utilizing biopsy data, Blacks have been shown to have lower rates of hepatic steatosis and steatohepatitis than Whites or Hispanics[27], despite Blacks having among the highest prevalence of relevant risk factors such as insulin resistance and obesity. These findings emphasize that risk factor differences alone do not fully explain the ethnic differences observed in NAFLD and suggest that there may be a differential response by ethnicity to certain risk factors[2,7].

The stronger association of obesity and NAFLD among Whites and Chinese, and Whites having a significantly higher AUC for waist circumference compared to other race/ethnic strata, are 2 of the novel ethnic-specific findings of our study. This suggests that obesity itself may differentially predispose to NAFLD by ethnicity. In MESA, though Hispanics had the highest overall prevalence of NAFLD at 27.1%, Hispanics had the lowest strength of association of obesity with NAFLD, and among the lowest waist circumference AUC for NAFLD. Only in Hispanics was the AUC for BMI marginally higher than that for waist circumference. As a risk factor, obesity overall may play less strong of a role in NAFLD development in Hispanics, and abdominal obesity similarly may be less important.

Despite the significantly higher AUC of WC for NAFLD, our discordance analysis suggests that individuals with “abnormal” BMI seem to have a stronger association with NAFLD than those with abnormal WC. This analysis is distinct from our other analyses since it groups individuals into categories of “abnormal” BMI or WC by a defined cut-off value, and reports the prevalence ratio of that group of individuals for having NAFLD. The improved ability of BMI to categorize individuals with NAFLD in this analysis may largely be a reflection to the cut-off values chosen to define “abnormal” values—we utilized WHO standard cut-offs, although we did incorporate a lower cut-off for Asians in our sensitivity analysis, which did not change inferences. These findings may also question the clinical relevance of the higher AUC for WC. BMI may perform just as well if not better in clinical settings to screen for NAFLD when using accepted cut-offs. Notably, in our population waist circumference classified more individuals as obese than did BMI, which may have diluted its association with NAFLD. In addition, most individuals who had abnormal BMI also had abnormal waist circumference (96%).

One limitation of this study is the cross-sectional design, limiting conclusions regarding risk of developing NAFLD. In addition, though CT measurement of LSR<1.0 is a well validated method to diagnose NAFLD[14–16,28], there will be classification error compared to the gold standard of liver histology which is not available in MESA. This would likely cause nondifferential misclassification, underestimating associations in our study. The aim of this study was to compare anthropometric measures of obesity; however, abdominal obesity measures such as waist circumference are only surrogates for visceral adiposity. The future availability of CT-measured regional fat distribution data in MESA may permit closer

examination of the association of fat distribution and NAFLD. Another limitation is the possibility that the 2,430 MESA participants with insufficient CT data to measure LSR may have been systematically different from those with adequate CT data. An examination of both groups demonstrated that those missing CT data tended differ slightly, but significantly, in having less of some metabolic risk factors—such as diabetes or hypertension. To examine the possible influence of this on selection bias, we performed a stratified sensitivity analysis by both diabetes and hypertension and found that the associations between obesity and NAFLD were homogenous. The fact that the associations were not affected by these variables suggests that selection bias by availability of CT data is less likely. Strengths of our study include our large population-based cohort from 6 geographically distinct centers, which increases the generalizability of our findings compared to the relatively large number of studies using convenience samples in the NAFLD literature, as well as the ethnic diversity of our population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Comparison of characteristics by presence of Non-alcoholic Fatty Liver Disease

	Non-Alcoholic Fatty Liver Disease		
Variable	**NO (n=3,382)**	**YES (n=706)**	**p-value**
Male	1,519 (44.9%)	326 (46.2%)	0.54
Age (year) mean ± SD	63.3 ± 10.5	61.0 ± 9.6	**<0.01**
White	1,274 (84.8%)	229 (15.2%)	**<0.01**
Chinese	317 (79.9%)	80 (20.2%)	
Black	1,095 (88.8%)	138 (11.2%)	
Hispanic	696 (72.8%)	259 (27.1%)	
Education >High School	2,775 (82.4%)	525 (74.7%)	**<0.01**
Weight (lbs), mean ± SD	170.1 ± 36.6	187.3 ± 37.8	**<0.01**
BMI (kg/m^2), mean ± SD	28.1 ± 5.2	31.1 ± 5.4	**<0.01**
Waist Circ. (cm), mean ± SD	97.3 ± 13.6	105.7 ± 13.4	**<0.01**
Waist to Hip Ratio, mean ± SD	0.925 ± 0.078	0.965 ± 0.063	**<0.01**
Diabetes Mellitus			
Normal	77.9 (2,624)	55.6 (392)	**<0.01**
Impaired Fasting Glucose	10.7 (361)	21.8 (154)	
Untreated Diabetes	2.2 (75)	7.1 (50)	
Treated Diabetes	9.1 (308)	15.5 (109)	
Fasting Glucose (mg/dl), mean ± SD	95.6 ± 28.3	108.5 ± 39.0	**<0.01**
Hypertension			
Normal	1,471 (43.5%)	24 (34.3%)	**<0.01**
Prehypertension	1,035 (30.6%)	267 (37.8%)	
Hypertension Stage 1	630 (18.6%)	130 (18.4%)	
Hypertension Stage 2	243 (7.2%)	67 (9.5%)	
Smoking			
Never Smoker	1,744 (51.8%)	393 (55.9%)	0.14
Former Smoker	1,230 (36.5%)	235 (33.4%)	
Current Smoker	395 (11.7%)	75 (10.7%)	
Systolic blood pressure (mmHg), mean ± SD	126.7 ± 21.6	130.1 ± 20.7	**<0.01**
Total Cholesterol (mg/dl), mean ± SD	193.9 ± 34.9	194.5 ± 39.0	0.64
LDL Cholesterol (mg/dl), mean ± SD	117.9 ± 31.2	115.9 ± 31.1	0.12
HDL Cholesterol (mg/dl), mean ± SD	51.6 ± 14.8	44.5 ± 11.9	**<0.01**
Triglycerides median (mg/dl), median (IQR)	104 (74–151)	154 (105–211)	**<0.01**
C-Reactive Protein (mg/L), median (IQR)	1.8 (0.8–4.1)	3.0 (1.4–6.5)	**<0.01**
Interleukin-6 (pg/mL), mean ± SD	1.53 ± 1.18	1.88 ± 1.31	**<0.01**

Table 2

A: Prevalence ratio for Non-alcoholic Fatty Liver Disease for the highest vs lowest quartile of each obesity measure

	Prevalence Ratio (95% CI)							
	Weight (lbs)	**p-value**	**BMI**	**p-value**	**Waist Circ (cm)**	**p-value**	**WHR**	**p-value**
Model 1	2.81 (2.27–3.49)	<0.001	4.62 (3.54–6.03)	<0.001	4.43 (3.42–5.74)	<0.001	3.79 (2.96–4.86)	<0.001
Model 2	4.36 (3.29–5.79)	<0.001	5.69 (4.19–7.73)	<0.001	5.82 (4.30–7.88)	<0.001	4.41 (3.30–5.88)	<0.001

B: Prevalence ratio for Non-alcoholic Fatty Liver Disease for the highest vs lowest quartile of each baseline obesity measure, stratified by race/ethnicity

	Weight (lbs)	**p-value**	**BMI (kg/m^2)**	**p - value**	**Waist Circ (cm)**	**p-value**	**WHR**	**p-value**
White	6.89 (4.16–11.40)	<0.001	6.74 (4.11–11.06)	<0.001	7.93 (4.72–13.33)	<0.001	9.50 (5.50–16.41)	<0.001
Chinese	4.23 (1.95–9.18)	<0.001	6.09 (2.63–14.12)	<0.001	4.79 (2.23–10.28)	<0.001	5.22 (2.29–11.88)	<0.001
Black	5.76 (3.08–10.77)	<0.001	4.43 (2.45–8.01)	<0.001	4.27 (2.42–7.53)	<0.001	3.36 (2.01–5.62)	<0.001
Hispanic	2.52 (1.77–3.57)	<0.001	3.42 (2.29–5.11)	<0.001	3.44 (2.31–5.11)	<0.001	2.34 (1.56–3.21)	<0.001

Model 1 is unadjusted

Model 2 is adjusted for age, gender, race and MESA site

p-values are for linear trend across the entire range of each obesity measure

Model is adjusted for age, gender, race and MESA site

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Table 3

A: Receiver Operator Curve analysis in the total population for association with prevalent Non-alcoholic Fatty Liver Disease

	n	AUC	95% CI
Weight	4088	0.7124	(0.691–0.733)
BMI	4088	0.7196	(0.699–0.740)
Waist Circumference*	4088	0.7310	(0.711–0.751)
WHR	4088	0.7130	(0.693–0.733)

B: Receiver Operator Curve analysis stratified by gender for association with prevalent Non-alcoholic Fatty Liver Disease

Male:

	n	AUC	95% CI
Weight	1845	0.7013	(0.680–0.723)
BMI	1845	0.7183	(0.698–0.739)
Waist Circumference*	1845	0.7268	(0.707–0.747)
WHR	1845	0.6985	(0.678–0.719)

Female:

	n	AUC	95% CI
Weight	2243	0.7027	(0.682–0.724)
BMI	2243	0.7139	(0.693–0.735)
Waist Circumference*	2243	0.7286	(0.709–0.749)
WHR	2243	0.7046	(0.674–0.725)

ROC analyses adjusted for age, gender, race and MESA site

*Waist circumference AUC is statistically significant higher than that of other obesity measures

ROC analyses adjusted for age, gender, race and MESA site

*Waist circumference AUC is statistically significant higher than that of other obesity measures

Table 4

Prevalence ratios of Non-alcoholic Fatty Liver Disease among patients with concordant and discordant waist circumference and body mass index

	Prevalence ratio (95% CI)	p-value
BMI normal and WC normal	1 (referent group)	
BMI abnormal and WC abnormal	3.04 (2.52–3.66)	<0.001
BMI normal and WC abnormal	1.91 (1.55–2.35)	<0.001
BMI abnormal and WC normal	2.78 (1.83–4.22)	<0.001

* Model is adjusted for age, gender, race and MESA site

** "Abnormal" body mass index (BMI) is defined as BMI ≥ 30 in both genders; "Normal" is BMI < 30

*** "Abnormal" waist circumference (WC) is defined as WC >102cm for male and WC > 88cm female; "Normal" is WC ≤102cm in males and ≤ 88cm in females