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Metabolic abnormalities, liver and body fat in American versus Chinese patients with non-alcoholic fatty liver disease

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jgh3.12756

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Statements

Availability of data

The data that support the findings of this study are available from the corresponding author on reasonable request.

Funding

This study was supported by University of Michigan – Peking University Health Sciences Center Joint Institute for Clinical and Translational Research (BMU20160543). WZ was supported in part by the Thomas HC Cheung Foundation (to ASL).

Conflicts of interest disclosure

ASL has received research grants from Bristol-Myers Squibb, Gilead, and TARGET PharmaSolutions, and served as advisor for Bristol-Myers Squibb and TARGET PharmaSolutions, and on DSMB for Novo Nordisk.

GLS has received research fundings from the United States Department of Veterans Affairs Health Services (IIR 17-269), R&D (HSRD) Service and the National Institute of Health (U01 CA230669).

LW has received research grants from Abbvie, Bristol-Myers Squibb and Gilead, served as a consultant for Gilead, Huahui, MSD, Pfizer, and received a speaker honorarium from Ascletis Pharma, Bristol-Myers Squibb, Gilead and Kaiyin.

HYR has received a speaker honorarium from Bristol-Myers Squibb, Gilead and AbbVie.

WZ has received research fundings from the Peking University Medicine Seed Fund for Interdisciplinary Research and the Fundamental Research Funds for the Central Universities in P. R. China (BMU2020MX006).

Sravanthi Kaza, Rui Huang and Yi Wang declare that they have no conflict of interest.

Ethics approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Peking University and the University of Michigan).

Consent to Participate

Informed consent was obtained from all patients for being included in the study.

Clinical Trials Registration

Not applicable**.**

Consent to Publication

All authors give final approval of the version to be published and agree to be accountable for all aspects of the work.

Authors' contributions

WZ enrolled patients, analyzed data and wrote the draft of the manuscript. SK, RH and HYR enrolled patients and collected data. YW and HYR contributed to the study design. GLS and LW contributed to the study design and provided data interpretation and critically reviewed the draft manuscript. ASL conceptualized the study, provided oversight of the conduct of the study and data interpretation, critically reviewed the draft manuscript, and serve as the submission guarantor. All authors reviewed and approved the final manuscript.

Acknowledgement

The authors would like to express our appreciation to Brian Ross and Brian Derstine (Morphomics Analysis Group (MAG), Department of Surgery, University of Michigan) for their assistance with processing analytic morphomics data; Elizabeth Wu (University of Michigan, Division of Gastroenterology and Hepatology)

for her assistance with editing the protocol and manual of operations; Ran Fei (Peking University Health Sciences Center, Peking University People's Hospital) for her assistance with processing specimens; and Chao Sun, Anqi Li and Xinyu Zhang (Peking University Health Sciences Center, Peking University People's Hospital) for their assistance with uploading CT scans and quality assurance of CT images.

Abstract

Background and Aims

Non-alcoholic fatty liver disease (NAFLD) is common in the U.S. and China. We compared prevalence of metabolic syndrome (MS), hepatic steatosis and fibrosis, and quantity and quality of body fat between American vs. Chinese patients with NAFLD.

Methods

NAFLD patients were prospectively recruited from the University of Michigan Health System (UMHS) in U.S. and Peking University Health Sciences Center (PUHSC) in China. All patients had baseline computed tomography (CT), laboratory tests and Fibroscan® controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Comparisons were made for overall cohorts and matched cohorts (matched for sex, age and BMI category). Logistic regression was performed to identify independent predictors of moderate/severe steatosis and lack of advanced fibrosis.

Results

101 American and 160 Chinese patients were included. UMHS patients were older, with higher prevalence of MS, had higher LSM and CAP score, and more fat in liver, visceral, subcutaneous and muscle compartments than PUHSC patients. Differences in LSM, visceral fat Hounsfield unit and subcutaneous fat area persisted in the matched cohort. NAFLD patients with MS had significantly higher LSM, and more fat in liver, visceral, subcutaneous and muscle compartments than those without. Moderate/severe steatosis was independently associated with MS, visceral fat quality and subcutaneous fat area while absence of advanced fibrosis was associated with Asian race and not having MS.

Conclusions

American patients with NAFLD had more liver fibrosis than Chinese patients despite having better quality visceral fat and after matching for age, sex, and BMI category.

Keywords*:* fatty liver disease, metabolic syndrome, hepatic steatosis, hepatic fibrosis, visceral adiposity

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. Global prevalence of NAFLD in 2016 based on imaging is estimated at 25%, 24% in the United States (U.S.) and 27% in Asia.[1] A meta-analysis of studies conducted between 2008 and 2018 revealed the prevalence of NAFLD in China was 29%.[2]

NAFLD is defined as the presence of fat in the liver (≥5%) but it is also associated with excess fat deposition in the subcutaneous tissue, visceral compartment, and ectopic areas (e.g., muscles). Many studies have shown that fat deposition in viscera and muscles play a more prominent role in the development of metabolic abnormalities than fat deposition in subcutaneous tissues.[3, 4] Increased visceral fat have been attributed to be an important contributor to diabetes and NAFLD in patients with normal body mass index (BMI) – a condition known as "lean NAFLD".[5] Some studies found that "lean NAFLD" is associated with a lower prevalence of metabolic diseases and advanced liver disease than obese NAFLD but other studies showed opposite results.[6, 7] Genetic variants such as *PNPLA3*, contribute not only to risk of hepatic steatosis but also risk of cirrhosis and metabolic abnormalities in NAFLD patients. The *PNPLA3* I148M (rs738409) variant is more common among Hispanics and Asians, and less common among Whites and Blacks.[8] Thus, while NAFLD is prevalent worldwide, patient and disease characteristics of NAFLD in Asia and in the U.S. may be different.

We designed this study with the aims: 1) to compare prevalence of metabolic abnormalities, degree of hepatic steatosis and fibrosis, and quantity and quality of fat depot in subcutaneous, visceral and musde compartments between American vs. Chinese patients with NAFLD, 2) to compare fat depot in patients with and those without metabolic syndrome (MS), and 3) to explore the association of liver fibrosis and liver steatosis, with MS, and fat in subcutaneous, visceral, and muscle compartments.

Patients and Methods

Study population and design

NAFLD patients were prospectively recruited from the University of Michigan Health System (UMHS) in Ann Arbor, Michigan, in the U.S. and Peking University Health Sciences Center (PUHSC) in Beijing, China. The study design was previously described (Supporting Information).[9]

Definition of metabolic abnormalities

For non-Asian Americans, lean was defined as BMI <25, overweight as BMI 25 to <30, obesity class 1 as BMI 30 to <35, and obesity class 2/3 as BMI ≥35 kg/m^2. For Asian Americans and Chinese patients, lean was defined as BMI <24, overweight as BMI 24 to <28, obesity class 1 as BMI 28 to 35, and obesity class 2/3 as BMI ≥35 kg/m^2. Ethnic cutoffs of waist circumference were also used to define truncal obesity: ≥102 cm in males and ≥88 cm in females for non- Asian Americans; and ≥90 cm in males and ≥80 cm in females for Asian Americans and Chinese. [10, 11]

Diagnosis of diabetes mellitus was based on fasting plasma glucose ≥7.0 mmol/L or HbA1c ≥6.5%, previously diagnosed type 2 diabetes or currently on medications for elevated glucose.[12] MS was defined based on 3 of 5 criteria: truncal obesity, hypertension, diabetes or hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein.[11]

Measurements of hepatic steatosis and liver stiffness

Hepatic steatosis was assessed by CT liver attenuation in Hounsfield unit (HU), controlled attenuation parameter (CAP), and NAFLD liver fat score (LFS). Liver fibrosis was assessed by liver stiffness measurement (LSM), NAFLD-fibrosis score (NAFLD-FS) and Fibrosis-4 markers (FIB-4). CAP and LSM were assessed using vibration controlled transient elastography (VCTE, Fibroscan®) (Echosens, Paris, France) in fasting state and XL probe was used for obese patients.

Measurements of subcutaneous, visceral and intermuscular fat

Analytic Morphomics, a platform for semi-automated image analysis developed at the University of Michigan was applied to CT scans to measure fat and muscle area and quality.[13, 14] This method had been shown to be consistent with multiple published methods for measuring fat and muscles in a recent systematic review.[15] While body types varied significantly with race, we have not noticed any difference in performance of the algorithms based on race or body type in previous studies. Mean of measurements at the bottom of T12, L1, and L2 were reported. Fat measurements included both areas (visceral fat area (VFA) and subcutaneous fat area (SFA)) as well as density (visceral fat HU (VFHU) and subcutaneous fat HU (SFHU)). For muscles, we focused on the dorsal muscle group because this constitutes a consistent area for measurement across these spinal levels.[14] Total and low-density muscle areas were reported with the latter reflecting a lower quality of muscle with higher intra/intermuscular fat content. Muscle density was also measured in HU.

Data Analyses

Statistical analyses were performed using SPSS version 25 (Chicago, IL) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, the U.S.).

Because of the marked differences in age and BMI between the UMHS and PUHSC cohorts, we performed two comparisons: (i) entire cohort in the two sites, and (ii) matched cohort with matching for age (within 5 years), BMI category (lean, overweight, obesity class 1, obesity class 2/3) and sex. For the matched cohort, paired *t* test or Wilcoxon matched-pair signed-rank test was used for comparison of continuous data, and McNemar test and Kappa test for categorical data. For the entire cohort, comparisons were made using Mann-Whitney U test if continuous variables were not normally distributed and chi square test for categorical data. *P* values < 0.05 were considered statistically significant.

For analysis of association of liver steatosis and liver fibrosis, with MS and fat in subcutaneous, visceral, and muscle compartments, we used two measurements for moderate/severe steatosis: CAP (≥300 vs. <300 dB/m) and CT HU (≤40 vs. >40), and two measurements to exclude advanced fibrosis (>F2): VCTE LSM (<7.1 vs. ≥7.1 kPa) and FIB-4 (<1.3 vs. ≥1.3).[16, 17] Association with exclusion of advanced fibrosis was chosen because few PUHSC patients had advanced fibrosis or cirrhosis. To identify analytic morphomics features predictive of presence of MS, moderate/severe hepatic steatosis or advanced fibrosis, multivariate analyses were performed. Details of these analyses are provided in the Supporting Information.

Results

Characteristics of the patients

From May 2016 to July 2019, 116 American patients with NAFLD were recruited in UMHS and 169 in PUHSC. Of these, 101 UMHS and 160 PUHSC patients completed CT scans and were included in this analysis. Among the UMHS patients, 88.1% were Caucasian and 5.9% were Asian. Diagnosis of NAFLD was made mainly based on clinical assessment and confirmed with imaging as only 34 (34%) UMHS and 5 (3.1%) PUHSC patients had liver biopsies. Of the latter, 32 (94.1%) UMHS and 4 (80%) PUHSC patients had nonalcoholic steatohepatitis.

UMHS patients were older (54 vs. 46.5 years) than PUHSC patients. They also had higher BMI (32.9 vs. 26 kg/m^2) and wider waist circumference (106.7 vs. 87 cm) and were more likely to be obese (77.2% vs. 50%), and to have truncal obesity (84.2% vs. 60.6%) even with using ethnic cutoffs for BMI and waist circumference (P<0.001) (Table 1). The matched cohort (matched for age, BMI category and sex) included 64 patients at each site.

Diet and Physical activity

UMHS patients had significantly higher daily calorie intake (median 1671 vs. 1527 kcal) than PUHSC patients (Table 1). A similar percentage of UMHS and PUHSC (65% vs. 61%) patients met WHO recommendations for physical activity; with more UMHS patients engaged in vigorous work or recreational activities while more PUHSC patients were engaged in transport activities (Table 1). Results were similar in the matched cohort.

Metabolic abnormalities

A higher percentage of UMHS patients had diabetes (51.5% vs. 23.8%), cardiovascular disease (12.9% vs. 5.6%), and MS (77.2% vs. 56.3%) than PUHSC patients. None of these differences persisted in the matched cohort (Table 1, Figure.1).

Hepatic steatosis and liver fibrosis in NAFLD patients

UMHS patients had significantly more fat in liver as measured by CT scan liver HU (40.7 vs. 47.3), CAP (335 vs. 298 dB/m), and NAFLD liver fat score than PUHSC patients (Table 2, Figure. 2A). They also had significantly more advanced liver fibrosis as reflected by higher LSM (6.8 vs. 4.5 kPa), FIB-4 (1.3 vs. 0.92) and NAFLD-FS. Furthermore, UMHS patients had higher aspartate and alanine aminotransferase (AST, ALT) levels than PUHSC patients. The differences in hepatic steatosis and NAFLD-FS were no longer observed in the matched cohort but differences in LSM (6.3 vs. 4.8 kPa), FIB-4 (1.19 vs. 1.01), AST and ALT persisted (Table 2).

Fat depot in visceral, subcutaneous and muscle compartments

Compared to PUHSC patients, UMHS patients had significantly larger fat areas in the visceral, subcutaneous and muscle compartments. In addition, muscle density was lower suggestive of higher fat content. Visceral and subcutaneous fat density were higher in the UMHS patients (Table 2, Figure. 2B-F). Higher VFHU and larger SFA in UMHS than PUHSC patients persisted in the matched cohort.

Liver steatosis/fibrosis and fat depot in patients with vs. without metabolic syndrome

Seventy-eight (77.2%) UMHS and 90 (56.3%) PUHSC patients met criteria for MS. Both UMHS and PUHSC patients with MS were older and more likely to be obese than those without. Analysis of the entire cohort showed that NAFLD patients with MS had more severe hepatic steatosis (42.1 vs. 50.4 HU) and higher LSM (5.6 vs. 4.4 kPa) than those without MS. In addition, they had significantly larger fat areas in the visceral, subcutaneous and muscle compartments, and lower muscle density and VFHU. Multivariate analysis showed that female sex, older age, obesity, and larger VFA were independently associated with presence of MS (Table 3 and Table S1).

Significantly higher LSM as well as larger fat areas in the visceral, subcutaneous and muscle compartments and lower muscle density in patients with MS compared to those without, were also observed in each cohort when PUHSC and UMHS patients were separately analyzed. While patients with MS in each cohort had higher LSM, a difference in hepatic steatosis was observed only in the PUHSC cohort (Table S1).

Association between liver steatosis and liver fibrosis with MS and fat depot

Univariate analysis showed that factors significantly associated with moderate/severe steatosis (based on liver HU) in the entire cohort included BMI category, MS, VFA and VFHU, SFA (but not HU), and low-density muscle area and muscle density; and race showed a trend. Multivariate analysis showed that MS, VFHU and SFA were independently associated with moderate/severe steatosis (Table 4A, Model A). When MS was substituted for its individual components, hypertriglyceridemia remained in the model along with VFA and SFA (Table 4A, Model B). Results were similar when CAP measurement was used to define moderate/severe steatosis.

Univariate analysis of factors associated with absence of advanced fibrosis (based on LSM) showed significant associations with race, age and BMI category, MS, hepatic steatosis (liver HU), VFA, SFA, low density muscle area and muscle density; and sex and VFHU showed a trend. Multivariate analysis showed that race, MS and hepatic steatosis (liver HU) were the only independent factors associated with absence of advanced fibrosis (Table 4B, Model A). When MS was substituted for its individual components, hypertension, diabetes/hyperglycemia, and hypertriglyceridemia) remained in the model (Table 4B, Model B). Results were similar when FIB-4 was used to rule out advanced fibrosis.

Multivariate analyses of factors associated with moderate/severe steatosis and absence of advanced fibrosis in each cohort showed similar findings (Table S2 and S3) but are limited by smaller sample size.

Discussion

NAFLD is a major global health problem. Several systematic reviews compared severity of hepatic steatosis and fibrosis and metabolic abnormalities between patients in Asia and western countries.[1,18] One study found that metabolic abnormalities were more common among patients in North America than those in Asia[1] while another study showed that association between "severe" NAFLD and incident diabetes was stronger in Japan and China than in the U.S.[18] Very few original studies comparing metabolic abnormalities and liver disease severity in NAFLD patients from different parts of the world have been performed despite obvious differences in genetics and lifestyle. In this study, we compared the prevalence of metabolic abnormalities, degree of hepatic steatosis and liver fibrosis between American and Chinese patients with NAFLD. Recognizing that visceral and ectopic fat play a more important role in NAFLD than BMI, we also analyzed quantity and quality of fat in visceral, subcutaneous, and muscle compartments using non-contrast CT scans. As expected, UMHS patients had higher BMI and were more likely to have MS than PUHSC patients. They also had more marked hepatic steatosis and liver fibrosis, and larger quantities of fat in visceral, subcutaneous as well as muscle compartments.

Due to marked differences in BMI category and age in the two cohorts and inherent sex-differences in quantity and distribution of body fat, we focused our comparisons on the matched cohort of 128 patients. In this matched cohort, prevalence of MS and its individual components, daily calorie intake and sum of all physical activities per week were similar in the UMHS and PUHSC patients. However, UMHS patients had a higher proportion of their time spent on physical activities attributed to work or recreational activities compared to PUHSC patients who had a higher proportion of their physical activities attributed to transportation. The differences in type of physical activities were not surprising given that cycling and public transport remain the most common mode of transportation in Beijing versus self-driving in Michigan.

There are known differences in body fat distribution across racial/ethnic groups independent of obesity. The Multicultural Community Health Assessment Trial conducted in Canada found Chinese and South Asians had more visceral and subcutaneous abdominal fat than Europeans.[19] Another study found East Asians had more visceral fat than Southeast Asians, Europeans and African blacks.[20] Among the matched

cohort in this study, VFA and ratio of VFA to SFA was similar in the two cohorts but the PUHSC patients had lower HU in the visceral fat compartment, indicating they had more fat and less vascularity and extracellular matrix,[21] in line with other studies.[19, 20]

Increased visceral fat relative to BMI or subcutaneous fat, has been postulated to explain the high prevalence of metabolic abnormalities in Asians, particularly among those with normal BMI.[20, 22] In our study, while NAFLD patients with MS had larger areas of fat in visceral, subcutaneous and muscle compartments compared to those without MS, only VFA remained significantly different on multivariate analysis.

In this study, we found that VFHU and SFA were associated with moderate/severe steatosis. Similar associations had been reported in an international study.[20] We found an association between hepatic fibrosis and fat in liver but not in visceral, subcutaneous or muscle compartments but only a small percentage of patients in our study had advanced fibrosis. Two meta-analyses found that diabetes, dyslipidemia and hypertension were also independently associated with adverse liver disease outcomes.[23, 24] We found that MS as well as its individual components were associated with hepatic fibrosis.

Comparison of liver disease between UMHS and PUHSC patients showed no differences in hepatic steatosis in the matched cohort; however, UMHS patients had higher AST and ALT levels and worse hepatic fibrosis than PUHSC patients. Multivariable analysis indicated that the PUHSC patients were 6-fold less likely to have advanced fibrosis and showed a trend toward having less severe steatosis, compared to the UMHS patients. The reasons for the differences are unclear and may be related to a higher prevalence of MS among the UMHS patients but it is also possible that the UMHS patients have had a longer duration of NAFLD given the earlier onset of the obesity epidemic in the United States. The prevalence of obesity in 2004 in China was reported to be only 3.1% while that in the United States was 32.2%.[25, 26] Indeed, many of the UMHS patients had been aware of their NAFLD diagnosis for years and sometimes decades while the diagnosis is more recent among most PUHSC patients.

This study has several unique strengths including the use of a common protocol with prospective data collection at both sites, detailed analyses of the quantity and quality of fat in visceral, subcutaneous and muscle compartments, and in-depth comparisons between patients in the matched cohort minimizing invariable confounders. However, there are some limitations. First, the number of patients studied was

small and all patients were enrolled from one site in each country limiting generalizability of results. Second, this was a cross-sectional study; thus, neither temporal nor causal associations can be inferred, particularly regarding fibrosis progression. Third, histology was lacking in most patients, and both steatosis and fibrosis were assessed using CT scans and VCTE, but these methods have been widely used in other studies and shown to have good correlation with histology. Fourth, information on diet and physical activity was based on self-reporting and may not be accurate.

In summary, we found that NAFLD patients in Michigan, U.S. had more advanced liver fibrosis and more subcutaneous fat but less visceral fat tissue compared with those in Beijing, China after matching for age, BMI category and sex. Among patients with NAFLD, presence of MS was independently predictive of moderate/severe steatosis and advanced fibrosis; and visceral fat quality and subcutaneous fat area were associated with moderate/severe steatosis but not with advanced liver fibrosis. Further studies involving larger cohorts of patients enrolled from multiple sites in each country are needed to confirm our findings and to determine whether outcomes and response to treatments in Americans versus Chinese with NAFLD are different.

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Tables

Table 1. Demographics, anthropometrics, diet, physical activity, and metabolic abnormalities in UMHS and PUHSC patients

	Entire Cohort			Matched Cohort		
	UMHS	PUHSC	*P* value	UMHS	PUHSC	*P* value
N	101	160		64	64	
Sex, male	42 (41.6%)	73 (45.6%)	0.522	29 (45.3%)	27 (42.2%)	0.804
Age (years)	54 (44, 61)	46.5 (35.3, 58)	0.004	52.5 (42.5, 61.8)	49.5 (37.8, 60)	0.347
Race						
Asian	6 (5.9%)	160 (100%)	<0.001	5 (7.8%)	64 (100%)	<0.001
White or Caucasian	89 (88.1%)	NA	NA	54 (84.4%)	NA	NA
Black or African American	2 (2%)	NA	NA	2 (3.1%)	NA	NA
Other	2 (2%)	NA	NA	1 (1.6%)	NA	NA
BMI (kg/m^2)	32.9 (30, 37.9)	26 (23.1, 30.4)	<0.001	31.2 (27.4, 33.7)	30.3 (28.3, 32.7)	0.026
BMI category			<0.001			0.230
Lean	9 (8.9%)	80 (50%)		9 (14.1%)	11 (17.2%)	
Overweight	14 (13.9%)	0		14 (21.9%)	0	
Obesity class 1	38 (37.6%)	74 (46.3%)		33 (51.6%)	47 (73.4%)	
Obesity class 2/3	40 (39.6%)	6 (3.8%)		8 (12.5%)	6 (9.4%)	
Diet						
Total calorie intake (kcal/day)	1671 (1392, 2154)	1527 (1237, 1911)	0.021	1744 (1424, 2227)	1567 (1395, 2051)	0.261
% of calories from carbohydrate	0.63 (0.53, 0.73)	0.55 (0.5, 0.61)	<0.001	0.64 (0.55, 0.75)	0.55 (0.5, 0.62)	<0.001
% of calories from fat	0.36 (0.3, 0.4)	0.31 (0.25, 0.36)	<0.001	0.35 (0.31, 0.41)	0.31 (0.22, 0.35)	<0.001
% of calories from protein	0.16 (0.14, 0.19)	0.16 (0.14, 0.18)	0.070	0.16 (0.14, 0.19)	0.16 (0.14, 0.18)	0.888
Physical activity						
Engaged in vigorous work activity	14 (13.9%)	0	<0.001	8 (12.5%)	0	0.008

Engaged in transport activity	39 (38.6%)	110 (68.8%)	<0.001	27 (42.2%)	47 (73.4%)	0.001
Engaged in vigorous recreational activity	35 (34.7%)	20 (12.5%)	<0.001	24 (37.5%)	6 (9.4%)	<0.001
Sum of all activity, minutes/week†	280 (60, 720)	210 (60, 443)	0.099	275 (60, 720)	300 (90, 561)	0.127
Medical history						
Diabetes	52 (51.5%)	38 (23.8%)	<0.001	26 (40.6%)	20 (31.3%)	0.361
Cardiovascular disease	13 (12.9%)	9 (5.6%)	0.035	8 (12.5%)	7 (10.9%)	1.000
Metabolic syndrome	78 (77.2%)	90 (56.3%)	0.001	44 (68.8%)	47 (73.4%)	0.648
Truncal obesity	85 (84.2%)	97 (60.6%)	<0.001	48 (75%)	55 (85.9%)	0.118
Hypertriglyceridemia	63 (62.4%)	108 (67.5%)	0.396	38 (59.4%)	47 (73.4%)	0.151
Low HDL	67 (66.3%)	94 (58.8%)	0.219	41 (64.1%)	36 (56.3%)	0.458
Hypertension	68 (67.3%)	70 (43.8%)	<0.001	40 (62.5%)	40 (62.5%)	1.000
Hyperglycemia/ diabetes	58 (57.4%)	66 (41.3%)	0.011	32 (50%)	34 (53.1%)	0.850

Data expressed as median (IQR) or n (%).

† Including all participants

UMHS, University of Michigan Health System; *PUHSC*, Peking University Health Sciences Center; *NA*, not applicable; *BMI*, body mass index; *HDL*, high density lipoprotein.

Table 2. Hepatic steatosis and fibrosis and body fat in UMHS and PUHSC patients

	Entire Cohort			Matched Cohort		
Characteristics	UMHS	PUHSC	*P* value	UMHS	PUHSC	*P* value
N	101	160		64	64	
Hepatic steatosis						
Liver HU	40.7 (29.3, 50.6)	47.3 (36.4, 54.4)	0.005	44.6 (31.2, 51.5)	43.2 (36.5, 51.2)	0.494
Liver HU ≤ 40	48 (47.5%)	53 (33.1%)	0.020	26 (40.6%)	23 (35.9%)	0.585
CAP (dB/m)	335 (289. 369.3)	297.5 (250.5, 332.8)	<0.001	317.5 (284, 355.5)	326.5 (260.8, 356.3)	0.464
CAP ≥ 300 dB/m	68/98 (69.4%)	79/160 (49.4%)	0.001	39/62 (62.9%)	41/64 (64.1%)	0.572
NAFLD liver fat score	3.3 (0.9, 5)	0.7 (-0.9, 2.3)	<0.001	2.2 (0.2, 4.3)	1.3 (0.2, 3.4)	0.051
Liver fibrosis						
LSM (kPa)	6.8 (5.1, 12.8)	4.5 (3.7, 5.3)	<0.001	6.3 (4.9, 9.7)	4.8 (3.8, 5.6)	<0.001
LSM < 7.1 kPa	52/99 (52.5%)	141/155 (91%)	<0.001	38/63 (60.3%)	53/60 (88.3%)	<0.001
FIB-4	1.3 (0.8, 1.8)	0.9 (0.7, 1.3)	<0.001	1.2 (0.8, 1.7)	1 (0.8, 1.4)	0.010
FIB-4 < 1.3	50/99 (50.5%)	119/159 (74.8%)	<0.001	35/63 (55.6%)	45/64 (70.3%)	0.085
NAFLD-FS	(-0.9) (-2.6, 0.02)	(-2.4) (-3.3, -1.5)	<0.001	(-1.4) (-2.7, -0.2)	(-1.9) (-2.9, -0.9)	0.065
Lab						
ALT (U/L)	48 (36, 74)	33 (22.3, 47.8)	<0.001	48 (36, 74)	34 (20.5, 51.3)	0.002
Triglyceride (mmol/L)	1.7 (1.3, 2.4)	2.1 (1.5, 2.6)	0.013	1.6 (1.2, 2.2)	2.2 (1.5, 2.6)	0.005
HDL (mmol/L)	1.2 (1, 1.4)	1.2 (1, 1.3)	0.586	1.2 (1, 1.5)	1.2 (1, 1.3)	0.565
LDL (mmol/L)	2.7 (2, 3.2)	3.5 (3, 3.9)	<0.001	2.7 (2.1, 3.2)	3.5 (2.9, 4)	<0.001
HbA1c	5.8 (5.4, 6.6)	5.8 (5.6, 6.3)	0.804	5.8 (5.4, 6.5)	6 (5.7, 6.6)	0.099
HOMA-IR	6.2 (3.2, 9.5)	3.8 (2.6, 5.6)	<0.001	4.7 (2.9, 7.8)	5 (3.1, 7.7)	0.789
Body composition						

VFA (cm^2)	209.8 (106.8, 280.1)	136.1 (102.8, 191.9)	<0.001	187.3 (149, 239.8)	173.8 (118.2, 227.6)	0.224
VFHU	(-104.7) (-107, -101.7)	(-106.8) (-108.7, -104.9)	<0.001	(-104.7) (-107.3, -101)	(-107.5) (-109.7, -105.3)	<0.001
SFA (cm^2)	231.2 (162.8, 369.3)	120.6 (87.1, 185.3)	<0.001	196.4 (147.4, 296.9)	176 (122.3, 206.4)	0.001
SFHU	(-109.7) (-112, -107)	(-111) (-114, -108.7)	0.012	(-110.3) (-112.3, -108)	(-110.3) (-112.3, -108.3)	0.552
Ratio of VFA to SFA	0.79 (0.59, 1.25)	1.06 (0.77, 1.49)	<0.001	0.84 (0.63, 1.38)	1.02 (0.74, 1.48)	0.117
Total muscle area (cm^2)	48.6 (40.3, 57.2)	43.8 (35.7, 55.6)	0.026	47.9 (38.9, 58)	45 (36.8, 60.1)	0.886
Low density muscle area (cm^2)	12.7 (9.3, 14.8)	9.5 (7.5, 11.4）	<0.001	10.9 (8.4, 13.7)	10.6 (9, 13.4)	0.702
Muscle density (HU)	40.7 (34.3, 46.5)	47 (41.6, 51)	<0.001	42.8 (37.5, 48)	45.4 (39.9, 47.7)	0.096
Ratio of low density to total muscle area	0.25 (0.2, 0.32)	0.21 (0.18, 0.25)	<0.001	0.23 (0.18, 0.3)	0.23 (0.2, 0.26)	0.912

Data expressed as median (IQR) or n (%).

UMHS, University of Michigan Health System; *PUHSC*, Peking University Health Sciences Center; *HU*, Hounsfield unit; *CAP*, controlled attenuation parameter; *LSM*, liver stiffness measurement; *FIB-4*, fibrosis-4 markers; *NAFLD-FS*, NAFLD-fibrosis score; *ALT*, alanine aminotransferase; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *HOMA-IR*, the homeostasis model assessment of insulin resistance; *VFA*, visceral fat area; *VFHU*, visceral fat HU; *SFA*, subcutaneous fat area; *SFHU*, subcutaneous fat HU.

Table 3. Hepatic steatosis and fibrosis and body fat in patients with and without metabolic syndrome

	Entire Cohort			
	Total with MS	Total without MS	*P* value (with vs. without MS)	*P* value (UMHS vs. PUHSC with MS)
N	168	93	168 vs. 93	78 vs. 90
Sex, male	66 (39.3%)	49 (52.7%)	0.037	0.839
Age (years)	54.5 (44, 61)	44 (33.5, 53)	<0.001	0.142
BMI (kg/m^2)	31.2 (28.4, 35)	23.9 (22.5, 30)	<0.001	<0.001
BMI category			<0.001	<0.001
Lean or Overweight	40 (23.8%)	62 (66.7%)		
Obesity class 1/2/3	128 (76.2%)	31 (33.3%)		
Components of MS				
Truncal obesity	146 (86.9%)	36 (38.7%)	<0.001	<0.001
Hypertriglyceridemia	141 (83.9%)	30 (32.3%)	<0.001	0.006
Low HDL	132 (78.6%)	29 (31.2%)	<0.001	0.914
Hypertension	117 (69.6%)	21 (22.6%)	<0.001	0.216
Hyperglycemia/ diabetes	107 (63.7%)	17 (18.3%)	<0.001	0.285
Liver HU	42.1 (31.3, 50)	50.4 (39.6, 56.7)	<0.001	0.387
CAP (dB/m)	329 (286, 364)	288 (242.5, 315.5)	<0.001	0.040
LSM (kPa)	5.6 (4.6, 9)	4.4 (3.7, 5.1)	<0.001	<0.001
Body composition				
VFA (cm^2)	190.7 (143.9, 258.5)	122.5 (84, 165.4)	0.001	<0.001
VFHU	(-106.7) (-108.8, -104)	(-105.7) (-107.3, -103.7)	0.030	<0.001
SFA (cm^2)	195 (120.6, 266)	115.8 (76, 177)	<0.001	<0.001
SFHU	(-110.3) (-113, -108)	(-111) (-113.7, -108.5)	0.830	0.016

Total muscle area (cm^2)	45.5 (37.7, 56.7)	44.3 (35.8, 56)	0.282	0.119
Low density muscle area (cm^2)	11.2 (8.9, 14.3)	8.5 (6.4, 11)	<0.001	<0.001
Muscle density (HU)	42.4 (36.6, 47.5)	47.6 (44.4, 52.9)	<0.001	<0.001
Ratio of low density to total muscle area	0.24 (0.2, 0.3)	0.19 (0.16, 0.23)	<0.001	0.003

Data expressed as median (IQR) or n (%).

MS, metabolic syndrome; *UMHS*, University of Michigan Health System; *PUHSC*, Peking University Health Sciences Center; *BMI*, body mass index; *HDL*, high density lipoprotein; *HU*, Hounsfield unit; *CAP*, controlled attenuation parameter; *LSM*, liver stiffness measurement; *VFA*, visceral fat area; *VFHU*, visceral fat HU; *SFA*, subcutaneous fat area; *SFHU*, subcutaneous fat HU.

Table 4A. Comparison of patients with and without moderate/severe hepatic steatosis

	Entire Cohort		Univariate Analysis		Model A		Model B	
Characteristics	Liver HU ≤40	Liver HU ＞40	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
N	101	160						
Asian								
no	44 (43.6%)	51 (31.9%)	1.65 (0.99 - 2.76）	0.057				
yes	57 (56.4%)	109 (68.1%)	1					
Sex								
male	44 (43.6%)	71 (44.4%)	0.97 (0.59 - 1.6）	0.898				
female	57(56.4%)	89 (55.6%)	1					
Age (years)	50 (35.5, 60)	52 (39, 59)	1 (0.98 - 1.02)	0.924				
BMI (kg/m^2)	31.2 (27.8, 35.8)	28.7 (23.3, 32.1)	1.09 (1.05 - 1.14)	<0.001				
BMI Category								
Obesity class 1/2/3	74 (73.3%)	84 (52.5%)	2.48 (1.45 – 4.25)	0.001				
Lean or Overweight	27 (26.7%)	76 (47.5%)	1					
MS								
Yes	78 (77.2%)	90 (56.3%)	2.64 (1.51 - 4.62)	0.001	1.84 (1.01 - 3.37)	0.048		
No	23 (22.8%)	70 (43.7%)	1		1			
Truncal obesity								
yes	82 (81.2%)	100 (62.5%)	2.59 (1.43 - 4.69)	0.002				
no	19 (18.8%)	60 (37.5%)	1					
Hypertriglyceridemia								
yes	74 (73.3%)	97 (60.6%)	1.78 (1.03 - 3.06)	0.037			1.84 (1 - 3.29)	0.039
no	27 (26.7%)	63 (39.4%)	1				1	
Low HDL								

yes	64 (63.4%)	97 (60.6%)	1.12 (0.67 - 1.88)	0.657				
no	37 (36.6%)	63 (39.4%)	1					
Hypertension								
yes	62 (61.4%)	76 (47.5%)	1.76 (1.06 - 2.92)	0.029				
no	39 (38.6%)	84 (52.5%)	1					
Hyperglycemia/ diabetes								
yes	57 (56.4%)	67 (41.9%)	1.8 (1.09 - 2.98)	0.022				
no	44 (43.6%)	93 (58.1%)	1					
Body composition								
VFA (cm^2)	192 (144, 259)	145 (101, 206)	1.006 (1.003 - 1.009)	<0.001			1.004 (1.001 - 1.008)	0.025
VFHU	(-107) (-109, -105)	(-106) (-108, -103)	0.91 (0.85 - 0.97)	0.006	0.91 (0.85 - 0.98)	0.015		
SFA (cm^2)	197 (127, 287)	146 (94, 205)	1.004 (1.002 - 1.007)	<0.001	1.004 (1.001 - 1.006)	0.004	1.003 (1 - 1.006)	0.025
SFHU	(-110) (-113, -108)	(-111) (-113, -108)	1.02 (0.96 - 1.09)	0.453				
Low density muscle area (cm^2)	11.3 (8.9, 14.5)	9.6 (7.6, 12.5)	1.14 (1.06 - 1.22)	<0.001				
Muscle density (HU)	44 (36.8, 48)	45.6 (39.8, 50.8)	0.96 (0.93 - 0.99)	0.015				

Data expressed as median (IQR) or n (%).

Model A includes Asian (yes vs. no), sex (male vs. female), age (<= 50 vs. > 50y), BMI category (obesity1/2/3 vs. lean/overweight), MS (yes vs. no), and continuous data of VFA, VFHU, SFA, Low density muscle area and Muscle density.

Model B includes Asian (yes vs. no), sex (male vs. female), age (<= 50 vs. > 50y), BMI category (obesity1/2/3 vs. lean/overweight), individual components of MS (yes vs. no), and continuous data of VFA, VFHU, SFA, Low density muscle area and Muscle density.

HU, Hounsfield unit; *CI*, confidence interval; *BMI*, body mass index; *MS*, metabolic syndrome; *HDL*, high density lipoprotein; *VFA,* visceral fat area; *VFHU*, visceral fat HU; *SFA*, subcutaneous fat area; *SFHU*, subcutaneous fat HU.

Table 4B. Comparison of patients with and without lack of advanced fibrosis

	Entire Cohort		Univariate Analysis		Model A		Model B	
Characteristics	LSM < 7.1 kPa	LSM ≥ 7.1 kPa	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
N	193	61						
Asian								
yes	143 (74.1%)	18 (29.5%)	6.8 (3.6 - 12.9)	<0.001	5.53 (2.73 - 11.22)	<0.001	5.87 (2.74 -12.57)	<0.001
no	50 (25.9%)	43 (70.5%)	1		1		1	
Sex								
male	90 (46.6%)	21 (34.4%)	1.66 (0.91 - 3.03)	0.096				
female	103 (53.4%)	40 (65.6%)	1					
Age (years)	48 (37, 58)	55 (47.5, 62)	0.96 (0.94 - 0.99)	0.002				
Age category								
<= 50 years	105 (54.4%)	18 (29.5%)	2.85 (1.54 - 5.29)	0.001				
> 50 years	88 (45.6%)	43 (70.5%)	1					
BMI (kg/m^2)	28.8 (23.4, 31.6)	33.4 (29.9, 37.9)	0.86 (0.82 - 0.91)	<0.001				
BMI category								
Lean or Overweight	90 (46.6%)	11 (18%)	3.97 (1.95 -8.09)	<0.001				
Obesity class 1/2/3	103 (53.4%)	50 (82%)	1					
MS								
no	90 (46.6%)	2 (3.3%)	25.78 (6.12 - 108.5)	<0.001	21.68 (4.95 - 94.9)	<0.001		
yes	103 (53.4%)	59 (96.7%)	1		1			
Truncal obesity								
no	72 (37.3%)	5 (8.2%)	6.66 (2.55 - 17.41)	<0.001				
yes	121 (62.7%)	56 (91.8%)	1					
Hypertriglyceridemia								

no	75 (38.9%)	15 (24.6%)	1.95 (1.02 - 3.74)	0.044			2.68 (1.14 - 6.32)	0.024
yes	118 (61.1%)	46 (75.4%)	1				1	
Low HDL								
no	79 (40.9%)	19 (31.1%)	1.53 (0.83 - 2.83)	0.170				
yes	114 (59.1%)	42 (68.9%)	1					
Hypertension								
no	112 (58%)	9 (14.8%)	7.99 (3.72 - 17.14)	<0.001			5.49 (2.31 - 13.1)	<0.001
yes	81 (42%)	52 (85.2%)	1				1	
Hyperglycemia/ diabetes								
no	117 (60.6%)	16 (26.2%)	4.33 (2.28 - 8.21)	<0.001			2.83 (1.33 - 6.02)	0.007
yes	76 (39.4%)	45 (73.8%)	1				1	
Body composition								
Liver HU	47.3 (36.4, 55)	38.7 (26.1, 46.7)	1.04 (1.02 - 1.07)	<0.001	1.03 (1.01 - 1.06)	0.02	1.04 (1.01 - 1.07)	0.008
VFA (cm^2)	148.8 (104.6, 205.1)	215 (161, 285.1)	0.99 (0.99 - 0.99)	<0.001				
VFHU	(-106.7) (-108.3, -104.3)	(-105.3) (-107.3, -102.3)	0.94 (0.87 - 1.0)	0.060				
SFA (cm^2)	144.3 (91, 206.9)	247.2 (169.7, 356.7）	0.99 (0.99 - 0.99)	<0.001				
SFHU	(-111) (-113.7, -108.3)	(-110) (-112.1, -106.9)	0.96 (0.89 - 1.03)	0.240				
Low density muscle area (cm^2)	9.7 (7.7, 12.1)	12.5 (9.6, 14.9)	0.84 (0.78 - 0.92)	<0.001				
Muscle density (HU)	46.4 (40.6, 50.8)	38.9 (32.8, 45.8)	1.1 (1.06 - 1.14)	<0.001				

Data expressed as median (IQR) or n (%).

Model A includes Asian (yes vs. no), sex (male vs. female), age (<= 50 vs. > 50y), BMI category (obesity1/2/3 vs. lean/overweight), MS (yes vs. no), and continuous data of liver HU, VFA, VFHU, SFA, Low density muscle area and Muscle density.

Model B includes Asian (yes vs. no), sex (male vs. female), age (<= 50 vs. > 50y), BMI category (obesity1/2/3 vs. lean/overweight), components of MS (yes vs. no), and continuous data of liver HU, VFA, VFHU, SFA, Low density muscle area and Muscle density.

LSM, liver stiffness measurement; *CI*, confidence interval; *BMI*, body mass index; *MS*, metabolic syndrome; *HDL*, high density lipoprotein; *HU*, Hounsfield unit; *VFA*, visceral fat area; *VFHU*, visceral fat HU; *SFA*, subcutaneous fat area; *SFHU*, subcutaneous fat HU.

Figure legends

Figure.1 Bar diagrams showing prevalence of metabolic syndrome and its individual components in the entire cohorts of UMHS and PUHSC patients (A) and the matched cohort (B). MS= Metabolic Syndrome; UMHS = University of Michigan Health System; PUHSC = Peking University Health Sciences Center; HDL = High density lipoprotein. ** *P* value < 0.01; *** *P* value < 0.001.

Figure.2 Box plots showing CT scan liver HU (hepatic steatosis) (A); fat areas in the subcutaneous (B), visceral (C) and muscle group compartments (Low density muscle area) (D); CT scan HU in the subcutaneous and visceral fat tissue (E) and the muscle group (Muscle density) (F). Boxes show 25th and 75th percentiles, horizontal line shows median and cross (x) shows mean value. UMHS = University of Michigan Health System; PUHSC = Peking University Health Sciences Center; HU = Hounsfield unit. * *P* value < 0.1, ** *P* value < 0.01; *** *P* value < 0.001.

Supporting Information

Supplemental Materials and Methods

Supplementary tables

Supplementary Table 1A. Hepatic steatosis and fibrosis and body fat in UMHS and PUHSC patients with and without metabolic syndrome

Supplementary Table 1B. Multivariate regression analysis for presence of metabolic syndrome in entire and each cohort

Supplementary Table 2. Univariate and multivariate regression analysis for UMHS and PUHSC patients with moderate and severe steatosis (liver HU ≤ 40)

Supplementary Table 3. Univariate and multivariate regression analysis for UMHS and PUHSC patients with lack of advanced fibrosis (LSM < 7.1 kPa)

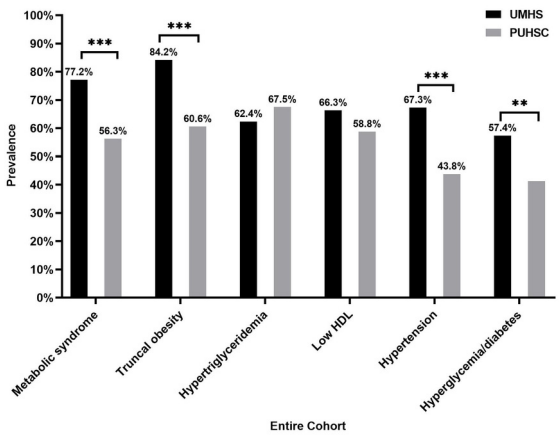


Figure_1A.jpg

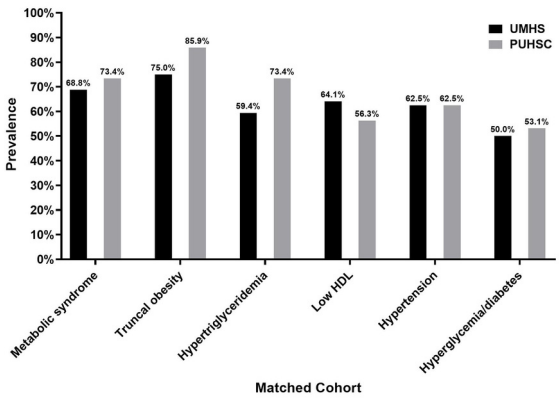
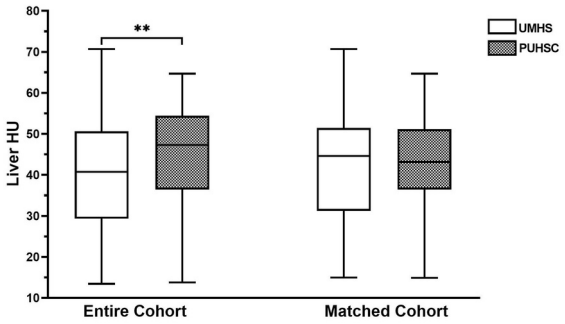


Figure_1B.jpg



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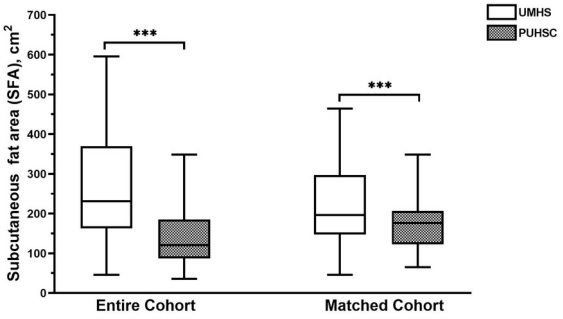

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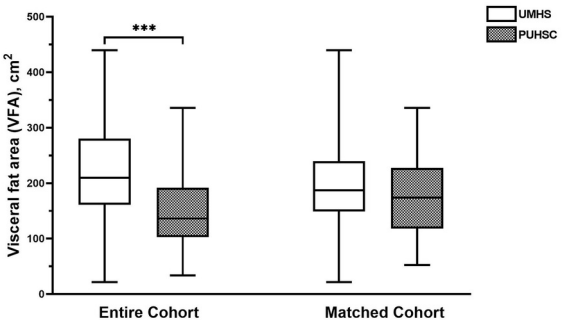

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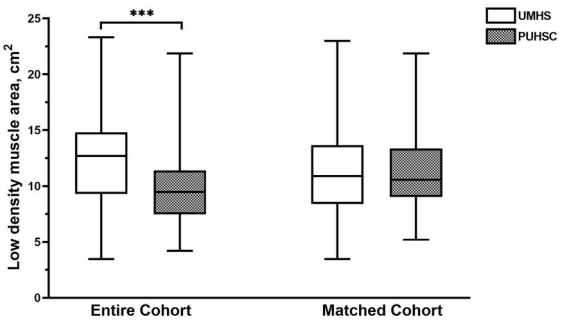
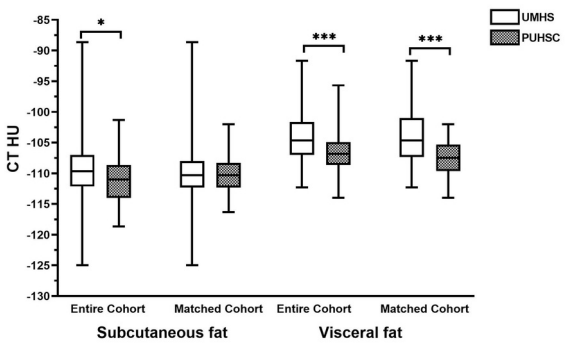


Figure_2D.jpg



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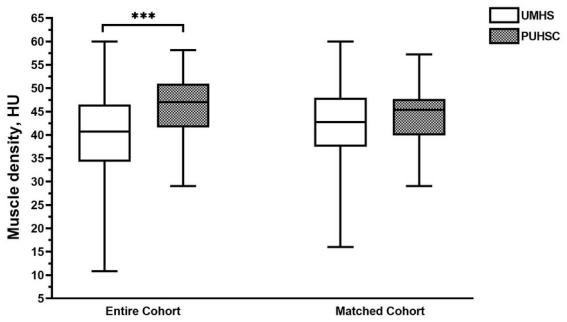
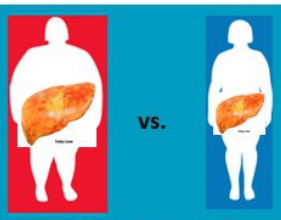


Figure_2F.jpg

Metabolic abnormalities, liver and body fat in American versus Chinese patients with non-alcoholic fatty liver disease

Study Population



vs.

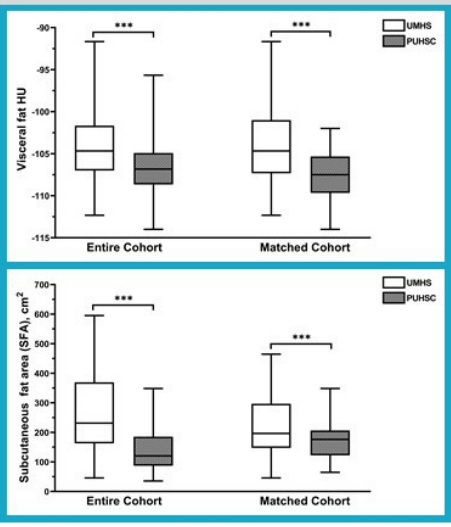
101 American (UMHS) vs. 160 Chinese (PUHSC) patients with NAFLD

64 in each cohort matched for sex, age, and BMI category

Labs, VCTE and CT scan to assess quality and quantity of fat in liver, visceral, subcutaneous and muscle compartments

American patients had larger fat areas in all compartments

Higher visceral fat HU and larger subcutaneous fat area persisted in the matched cohort



Predictors associated with

Metabolic syndrome: visceral fat area & liver stiffness

Moderate/marked steatosis: metabolic syndrome, visceral fat HU and subcutaneous fat area

Lack of advanced fibrosis: metabolic syndrome and liver HU

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Graphical Summary_JI NAFLD Paper3_JGH Open.jpg