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LEADING ARTICLE

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

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Author contribution: Wei Zhang enrolled patients, analyzed data, and wrote the draft of the manuscript. Sravanthi Kaza, Rui Huang, and Huiying Rao enrolled patients and collected data. Yi Wang and Huiying Rao contributed to the study design. Grace L Su and Lai Wei contributed to the study design and provided data interpretation and

Abstract

Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is common in the United States and China. We compared prevalence of metabolic syndrome (MS), hepatic steatosis and fibrosis, and quantity and quality of body fat between American *versus* Chinese patients with NAFLD.
Methods: NAFLD patients were prospectively recruited from the University of Michigan Health System (UMHS) in the United States 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 body mass index [BMI] category). Logistic regression was performed to identify independent predictors of moderate and severe steatosis and lack of advanced fibrosis.
Results: One-hundred and one American and One-hundred and sixty Chinese patients were included. UMHS patients were older, with higher prevalence of MS, had higher LSM and CAP scores, and more fat in liver, visceral, subcutaneous, and muscle compartments than PUHSC patients. Differences in LSM, visceral fat Hounsfield unit, and subcutaneous fat area (SFA) 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 or severe steatosis was independently associated with MS, visceral fat quality, and SFA, while the absence of advanced fibrosis was associated with Asian race and not having MS.
Conclusion: 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.

critically reviewed the draft manuscript. Anna S Lok 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, and agreed to be accountable for all aspects of the work.

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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 and 27% in Asia.[1] A meta-analysis of studies conducted between 2008 and 2018 revealed that 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 plays a more prominent role in the development of metabolic abnormalities than fat deposition in subcutaneous tissues.[3,4] Increased visceral fat is thought 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 have found that lean NAFLD is associated with a lower prevalence of metabolic diseases and advanced liver disease than obese NAFLD, but other studies have found the opposite.[6,7] Genetic variants, such as *PNPLA3*, contribute to the risk of not only hepatic steatosis but also 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, although NAFLD is prevalent worldwide, patient and disease characteristics of NAFLD in Asia and in the United States may be different.

We designed this study with the following aims: (i) to compare prevalence of metabolic abnormalities, degree of hepatic steatosis and fibrosis, and quantity and quality of fat depot in subcutaneous, visceral, and muscle compartments between American *versus* Chinese patients with NAFLD; (ii) to compare fat depot in patients with and without metabolic syndrome (MS); and (iii) to explore the association of liver fibrosis and liver steatosis, with MS, and fat in subcutaneous, visceral, and muscle compartments.

Methods

Study population and design. NAFLD patients were prospectively recruited from the University of Michigan Health System (UMHS) in Ann Arbor, Michigan, USA, and Peking University Health Sciences Center (PUHSC), 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 kg/m^2, overweight as BMI 25 to <30 kg/m^2, obesity class 1 as BMI 30 to <35 kg/m^2, and obesity class 2/3 as BMI ≥35 kg/m^2. For Asian Americans and Chinese patients, lean was defined as BMI <24 kg/m^2, overweight as BMI 24 to <28 kg/m^2, obesity class 1 as BMI 28 to 35 kg/m^2, 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 three of five 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 computed tomography

(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 was shown to be consistent with multiple published methods for measuring fat and muscles in a recent systematic review.[15] Although body types varied significantly with race, we did not notice any difference in performance of the algorithms based on race or body type in previous studies. The 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, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA).

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, the paired *t*-test or the 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 the 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 the 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 a few PUHSC patients had advanced fibrosis or cirrhosis. To identify analytic morphomic features predictive of the presence of MS, moderate/severe hepatic steatosis, or advanced fibrosis, multivariate analyses were performed. Details of these analyses are provided in Supporting information.

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

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 on the basis of 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, Fig. 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 LFS than PUHSC patients (Table 2, Fig. 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 UMHS patients (Table 2, Fig. 2b–f). Higher VFHU and larger SFA in UMHS than PUHSC patients persisted in the matched cohort.

Table 1 Demographics, anthropometrics, diet, physical activity, and metabolic abnormalities in University of Michigan Health System (UMHS) and Peking University Health Sciences Center (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

[†]Including all participants.

Data expressed as median (interquartile range) or *n* (%).

BMI, body mass index; HDL, high-density lipoprotein; NA, not applicable.

Liver steatosis/fibrosis and fat depot in patients with versus without MS. Seventy-eight (77.2%) UMHS and 90 (56.3%) PUHSC patients met the 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 the presence of MS (Tables 3 and S1).

Significantly higher LSM, 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. Although 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-

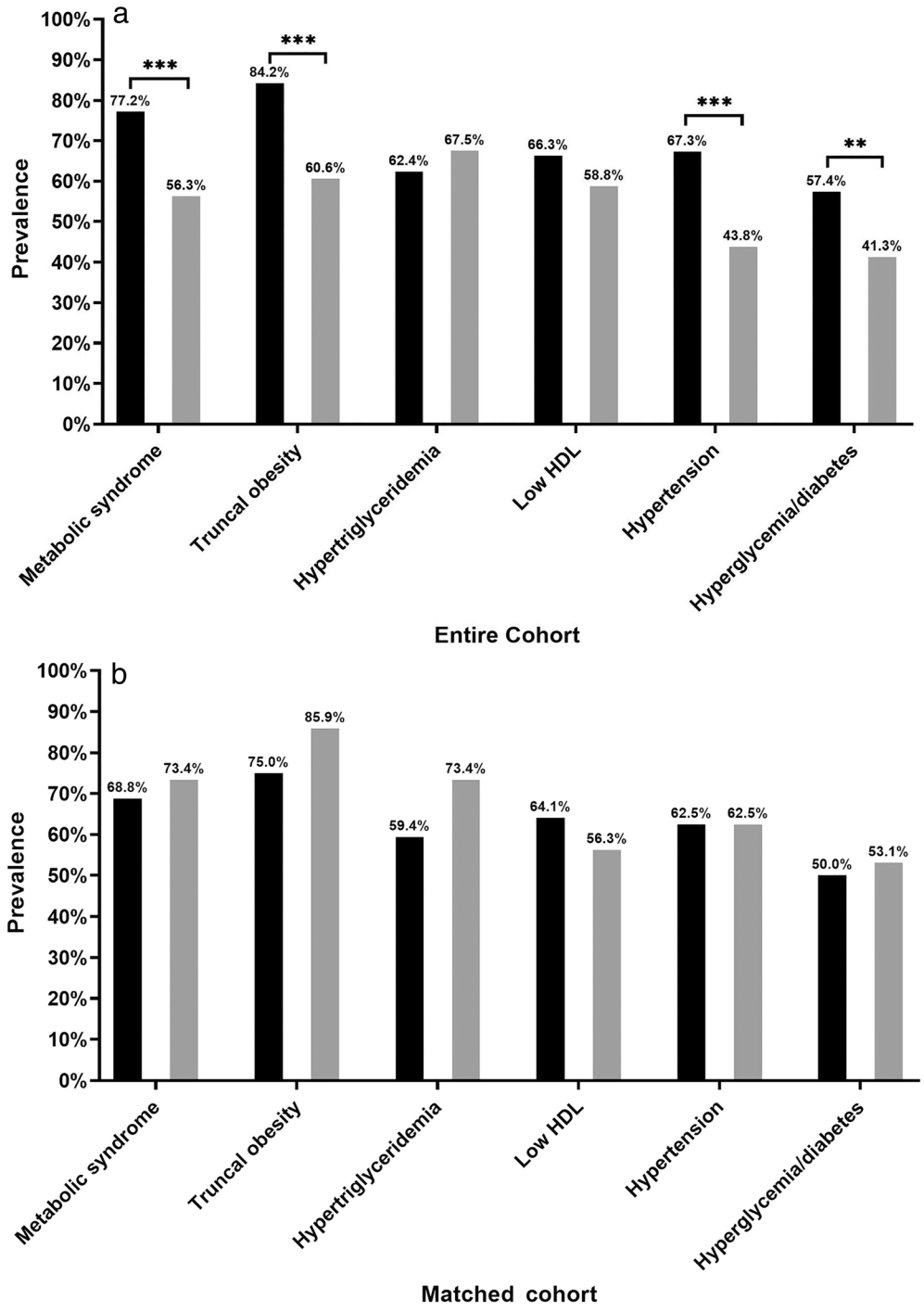

Figure 1 Bar diagrams showing prevalence of metabolic syndrome and its individual components in the entire cohorts of University of Michigan Health System (UMHS) and Peking University Health Sciences Center (PUHSC) patients (a) and the matched cohort (b). ***P*-value <0.01; ****P*-value < 0.001. HDL, high-density lipoprotein. (■), UMHS; (■), PUHSC.

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 4, Model A). When MS was substituted for its individual components, hypertriglyceridemia remained in the model along with VFA and SFA (Table 4, 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

Table 2 Hepatic steatosis and fibrosis and body fat in University of Michigan Health System (UMHS) and Peking University Health Sciences Center (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 (interquartile range) or *n* (%).

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

(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 the absence of advanced fibrosis (Table 5, Model A). When MS was substituted for its individual components, hypertension, diabetes/hyperglycemia, and hypertriglyceridemia remained in the model (Table 5, 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 the absence of advanced fibrosis in each cohort showed similar findings (Tables S2 and S3) but were limited by smaller sample size.

Discussion

NAFLD is a major global health problem. Several systematic reviews have compared the 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] whereas another study found that the association between "severe" NAFLD and incident diabetes was

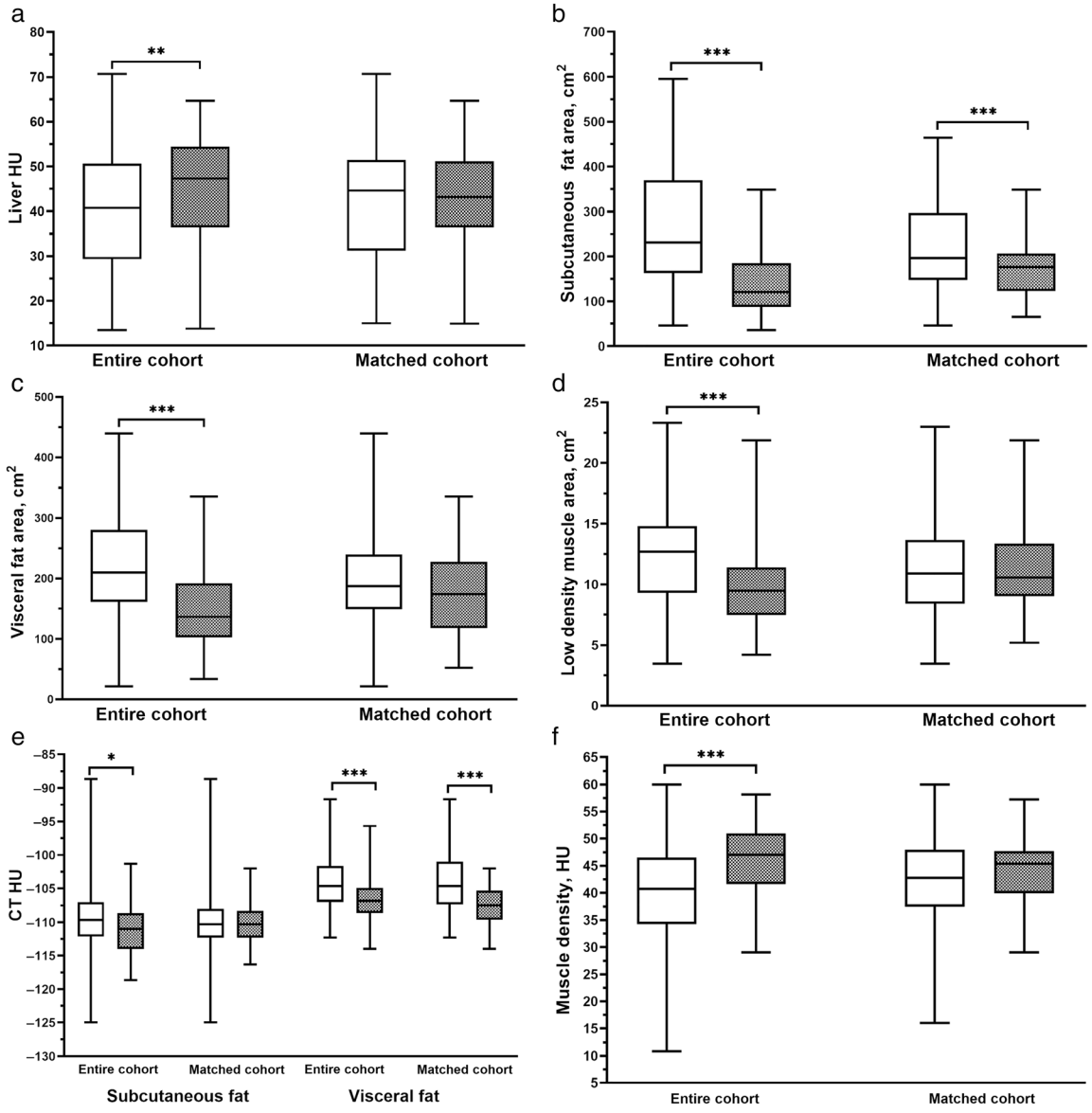

Figure 2 Box plots showing computed tomography (CT) scan liver Hounsfield unit (HU) (hepatic steatosis) (a); fat areas in the subcutaneous (b), visceral (c) and muscle group compartments (low density muscle area) (d); CT scan HU in the subcutaneous and visceral fat tissue (e) and the muscle group (muscle density) (f). Boxes show 25th and 75th percentiles, horizontal line shows median. **P*-value < 0.1, ***P*-value < 0.01; ****P*-value < 0.001. (▭), University of Michigan Health System; (▨), Peking University Health Sciences Center.

stronger in Japan and China than in the United States.[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 the 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 the 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, and muscle compartments.

Because of the marked differences in BMI category and age in the two cohorts and inherent sex differences in the 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

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 (interquartile range) or *n* (%).

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

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 that Chinese and South Asians had more visceral and subcutaneous abdominal fat than Europeans.[19] Another study found that 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 were 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, although 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 earlier 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 and 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 six–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 but may be related to a higher prevalence of MS among the UMHS patients; however,

Table 4 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 (interquartile range) or *n* (%).

Model A includes Asian (yes *vs* no), sex (male *vs* female), age (≤50 *vs* >50 years), BMI category (obesity 1/2/3 *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* >50 years), BMI category (obesity 1/2/3 *vs* lean/overweight), individual components of MS (yes *vs* no), and continuous data of VFA, VFHU, SFA, low-density muscle area, and muscle density.

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

it is also possible that 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%, whereas 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, whereas the diagnosis was more recent among most PUHSC patients.

Table 5 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 (interquartile range) or *n* (%).

Model A includes Asian (yes *vs* no), sex (male *vs* female), age (≤50 *vs* > 50 years), BMI category (obesity 1/2/3 *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* >50 years), BMI category (obesity 1/2/3 *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.

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

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 had more advanced liver fibrosis and more subcutaneous fat but less visceral fat tissue compared with those in Beijing after matching for age, BMI category, and sex. Among the patients with NAFLD, presence of MS was independently predictive of moderate/severe steatosis and advanced fibrosis; and visceral fat quality and SFA 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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Data availability statement. The data that support the findings of this study are available from the corresponding author on reasonable request.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1A. Hepatic steatosis and fibrosis and body fat in UMHS and PUHSC patients with and without metabolic syndrome.
Table S1B. Multivariate regression analysis for the presence of metabolic syndrome in the entire and each cohort.
Table S2. Univariate and multivariate regression analysis for UMHS and PUHSC patients with moderate and severe steatosis (liver HU ≤ 40).
Table S3. Univariate and multivariate regression analysis for UMHS and PUHSC patients with lack of advanced fibrosis (LSM < 7.1 kPa).