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Hepatic Steatosis: CT-based Prevalence in Adults in China and the United States and Associations with Age, Sex, and Body Mass Index

Zhe Guo, MD, Glen M. Blake, PhD, Peter M. Graffy, BA, Veit Sandfort, MD, Ronald M. Summers, MD, PhD, Kai Li, MD, Shaoqi Xu, MD, Yizhong Chen, MD, Jun Zhou, MD, Jiman Shao, MD, Yonghong Jiang, MD, Haibo Qu, MD, Baoqing Li, MD, Xiaoguang Cheng, MD, Perry J. Pickhardt, MD

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Abstract

Background: Calibrated CT fat fraction (FFCT) measurements derived from non-enhanced abdominal CT reliably reflect liver fat content, allowing largescale population-level investigations of steatosis prevalence and associations.

Objective: To compare prevalence of hepatic steatosis, assessed by calibrated CT measurements, between population-based Chinese and U.S. cohorts, and to investigate in these populations the relationship of steatosis with age, sex, and body mass index (BMI).

Methods: This retrospective study included 3176 adults (1985 women, 1191 men) from seven Chinese provinces and 8748 adults (4834 women, 3914 men) from a single U.S. medical center, drawn from earlier studies. All participants were at least 40 years old and underwent unenhanced abdominal CT for the earlier studies. Liver fat content measurements on CT were cross-calibrated to MRI proton density fat fraction measurements using phantoms and expressed as adjusted FFCT. Mild, moderate, and severe steatosis were defined as adjusted FFCT of 5.0%-14.9%, 15.0%-24.9%, and ≥25.0%, respectively. The two cohorts were compared.

Results: Median adjusted FFCT was for women 4.7% and 4.8%, and for men 5.8% and 6.2%, in the Chinese and U.S. cohorts, respectively. Steatosis prevalence was for women 46.3% and 48.7%, and for men 58.9% and 61.9%, in the Chinese and U.S. cohorts, respectively. Severe steatosis prevalence was for women 0.9% and 1.8%, and for

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men, 0.2% and 2.6%, in the Chinese and U.S. cohorts, respectively. Adjusted FFCT did not vary across age decades in women or men in the Chinese cohort, though increased across age decades in women and men in the U.S. cohort. Adjusted FFCT and BMI exhibited weak correlation (r=0.312-0.431). Among participants with normal BMI, 36.8% and 38.5% of those in the Chinese and U.S. cohorts had mild steatosis, and 3.0% and 1.5% had moderate or severe steatosis, respectively. Among U.S. participants with BMI ≥40.0, 17.7% had normal liver content.

Conclusion: Steatosis and severe steatosis had higher prevalence in the U.S. than Chinese cohort in both women and men. BMI did not reliably predict steatosis.

Clinical Impact: The findings provide new information on the dependence of hepatic steatosis on age, sex, and BMI.

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HIGHLIGHTS

Key Finding: Among participants with normal BMI, 36.8% and 38.5% in the Chinese and U.S. cohorts had mild steatosis, and 3.0% and 1.5% in the two cohorts had moderate or severe steatosis, respectively. Among U.S. participants with BMI ≥40.0, 17.7% had normal liver fat.

Importance: Calibrated CT measurements could be useful for population-level screening for hepatic steatosis, particularly given the weak association of liver fat content and BMI.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a range of diseases characterized by excess fat deposition in the liver [1,2]. Risk factors for NAFLD include body mass index (BMI) ≥25, diabetes, hypertension, and hyperlipidemia [1,3]. In many countries, the prevalence of NAFLD is greater than 25% [4]. Although NAFLD has traditionally been considered to be common in middle- and high-income countries such as the United States, its prevalence in low-income regions has risen greatly in the past 20 years given improvements in living conditions and changes in lifestyle and dietary habits [3].

Most studies of the prevalence of NAFLD have used ultrasound to establish the diagnosis of steatosis, as ultrasound is readily available and does not involve ionizing radiation [5]. However, because ultrasound diagnoses steatosis in a semi-quantitative manner, the diagnosis is operator dependent [6]. Further, ultrasound underestimates the prevalence of steatosis in individuals with liver fat content less than 20% [5]. In comparison, quantitative imaging methods could more accurately determine the presence and severity of hepatic steatosis [6-12]. Among quantitative methods, the MRI proton density fat fraction (PDFF), expressed as a percentage from 0% to 100%, is considered the non-invasive reference standard for liver fat measurement [12,13].

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Past work also supports the role of unenhanced CT measurements to quantify liver fat content [11,14-16]. The CT fat fraction (FF_{CT}) measures the unenhanced attenuation of the liver on a scale from 0% to 100% in a manner analogous to MRI PDFF [14]. However, fat-free tissue includes non-aqueous contents, such as protein and minerals, which contribute substantively to CT attenuation measurements, though have minimal or no contribution to the MRI signal. Thus, FF_{CT} and PDFF have a non-linear relationship [14]. CT measurements of liver fat expressed as FF_{CT} may be calibrated to a scale comparable to PDFF using an algorithm developed in a cross-calibration study that compared FF_{CT} with PDFF measurements from chemical-shift encoded MRI (CSE-MRI) in 400 participants [14]. Given the widespread availability and utilization of CT, these PDFF-calibrated CT measurements of liver fat allow for largescale population-level investigations of steatosis prevalence and associations.

The purpose of this study was to compare the prevalence of hepatic steatosis, assessed by calibrated CT measurements, between population-based cohorts in China and the United States, and to investigate in these populations the relationship of steatosis with age, sex, and BMI.

Methods

Study Participants

This study entailed retrospective evaluation of two patient cohorts that were included in earlier studies, [17, 18], hereafter referred to as the Chinese cohort and U.S. cohort.

Chinese cohort—The Chinese cohort was drawn from the China Action on Spine and Hip status (CASH) study of the prevalence of osteoporosis and the association of osteoporotic spinal fracture with bone mineral density in China [17]. The CASH study prospectively enrolled 3,517 participants with age ≥40 years between 2013 and 2017 to undergo unenhanced quantitative CT (QCT) of the abdomen, using a calibration phantom. Participants were recruited at urban and rural sites at 12 centers in 7 Chinese provinces. A total of 3,176 participants with CT scans performed on 8 different scanners were included in the present investigation after excluding those in whom the phantom was poorly positioned and participants with missing height and/or weight information, precluding BMI calculation. The CASH study was approved by the ethics committee of Beijing Jishuitan Hospital, Peking University and conducted in accordance with the Declaration of Helskinki; additional approval was not required for this retrospective analysis. Informed consent was obtained from all participants.

U.S. cohort—The U.S. cohort was drawn from a retrospective study that used a deep learning–based automated liver fat quantification tool for population-based steatosis assessment using nonenhanced CT [18]. The study included 9552 asymptomatic adults who underwent CT colonography at a single academic medical center in Madison Wisconsin between 2004 and 2016. A total of 8,748 patients in the study were included in the present investigation after excluding patients with age <40 years and those with missing height and/or weight data. The earliest available unenhanced abdominal CT in each patient was analyzed. The study was approved by the institutional review board of the University of Wisconsin School of Medicine and was HIPAA-compliant; additional approval was not required for this retrospective analysis. The requirement for written informed consent was waived.

CT Protocol and Measurement of Liver Fat Content

Chinese cohort—Participants in the Chinese cohort underwent QCT using ≥16-row spiral CT scanners with a five-rod calibration phantom placed beneath the spine (Model 3 phantom; Mindways Software, Austin, TX). Except for Sichuan, where urban and rural participants were imaged on different scanners, all participants from a given province were imaged using a single CT scanner. Scan parameters were 120 kVp; 150-200 mAs; FOV, 500 mm; and slice thickness, 1-1.25 mm. The FOV included the entire liver. Images were reconstructed using a standard algorithm with 1-1.25 mm section thickness and interval, and 400 mm display FOV. All CT scanners were calibrated daily for quality control of attenuation measurements.

QCT images from all centers were transferred to Beijing Jishuitan Hospital for analysis. A single musculoskeletal radiologist with 11 years of post-fellowship experience (ZG) reviewed all scans. The radiologist selected a slice of the liver in which the right branch of the portal vein enters the liver. Three ROIs, each with an area of 300 mm^2, were placed on that slice in the periphery of the left lobe, right anterior lobe, and right posterior lobe (Fig. S1A). The ROIs were selected to avoid major blood vessels and bile ducts, calcifications, cysts, artefact from the ribs or gas in the lung or gastrointestinal tract. The mean value of the three ROIs was used for the final measurement of liver fat for the patient.

U.S. cohort—Patients in the U.S. cohort underwent CT using 8–64-section MDCT scanners (GE Healthcare, Waukesha, Wis) by using 120 kVp with low-dose milliampere settings (typically between 30–300 mA). Mean liver attenuation of the entire liver was obtained

using the automated liver fat quantification algorithm described by Graffy et al. (Fig. S1B) [18].

Further details of the methods used for liver fat measurement in the two cohorts were previously described [11,14,18].

Calculation of Adjusted FF_{CT}

Chinese cohort—In the Chinese cohort, liver fat content was initially determined using the Mindways QCT PRO 6.0 Supplementary Tissue Measurements application. This application calculates the percentage of fat in an ROI drawn in the liver parenchyma based on the mean attenuation within the ROI combined with data from the calibration phantom. Specifically, the application calculates FF_{CT} using the equation [14,15]:

$$FF_{CT} = \left(\frac{HU_{lean} - HU_{liver}}{HU_{lean} - HU_{fat}}\right) \quad (1)$$

In this equation, HU_{liver} is the attenuation of the liver ROI, HU_{lean} is the attenuation of fat-free liver tissue, and HU_{fat} is the attenuation of 100% fat. As HU_{liver} varies between HU_{lean} and HU_{fat} the value of FF_{CT} varies from 0 % to 100% (Fig. S2A). Values of HU_{lean} and HU_{fat} were determined from phantom calibration and tissue composition data [15].

CT fat measurements lack a consistent origin for the fat scale due to differences in calibration of Hounsfield units between scanners [19]. A study of FF_{CT} and CSE-MRI PDFF measurements in 400 patients from the Beijing center found an offset of 1.5% between the origins of the FF_{CT} and PDFF scales [14]. However, this offset varies between CT systems. To align the fat scales, histograms of the fat distribution were created for each center by

binning the FF_{CT} measurements in intervals of 1% liver fat. The FF_{CT} measurements at the remaining centers were then aligned with the measurements from the Beijing center [14] by finding the maximum of the cross-correlation function [20] between the two histograms. If N_i is the number of participants in the i^{th} bin of the histogram and M_{i+j} is the number of participants in the $(i+j)^{th}$ bin of the histogram of the comparison center, then the cross-correlation function CC_j is defined by:

$$CC_j = \sum_{i=-\infty}^{\infty} N_i \times M_{i+j} \qquad (2)$$

The optimum match of the two histograms is given by the offset *j* that yields the maximum value of CC_j. To more accurately locate the peak of the cross-correlation function, the 7 or 8 points with CC_j values >50% of the maximum value were fitted with a Gaussian curve to determine the offset of the fat scales that achieves a precision of approximately 0.2%. Based on this process, the following offsets were added to the FF_{CT} measurements from each CT scanner to bring the origins of their fat scales into alignment with the Beijing scanner: Jiangsu: +0.8%; Jiangxi: +1.3%; Shaanxi: -1.7%; Liaoning: +2.2%; Shanxi: -3.6%; Sichuan rural: +1.1%; Sichuan urban: 0.0%. A further adjustment was made by subtracting 1.5% from all measurements to bring the origin of the pooled FF_{CT} data into alignment with the origin of the MRI PDFF measurements from the Beijing center. These zero-point corrected FF_{CT} data with the same origin as the PDFF scale were then transformed into adjusted FF_{CT} values using the following equation, where FF_{CT}' refers to the zero-point corrected FF_{CT} values and the coefficient α equals 0.766 [14]:

$$\text{Adjusted } FF_{CT} = \left(\frac{FF_{CT}'}{FF_{CT}' + \alpha\ (1 - FF_{CT}')} \right) \qquad (3)$$

The final adjustment in equation 3 corrects for the non-linear relationship between FF_{CT} and PDFF measurements and places these measurements on the same scale (Figs. S2B and S2C).

U.S. Cohort—In the U.S. cohort, an empirical evaluation of the origin of the CT fat scale was performed by scanning an in-house developed agar based fat-water phantom containing an iodine contrast agent to simulate lean liver [11]. The zero-point of the fat scale was then set at HU_{lean}= 65.9. The value of ($HU_{lean} - HU_{fat}$) at 120 kV was determined from the mean value for the Chinese cohort and was set at 202.2 (95% CI: ± 2.3). Individual FF_{CT} values were then determined using equation 1. When the FF_{CT} histograms for the Beijing center and the U.S. cohort were compared using the cross-correlation function, the offset was +1.4%, giving a net offset of the U.S. cohort relative to the CSE-MRI PDFF measurements from the Beijing center of -0.1% (95% CI: -0.4 to +0.2%). Since this result was not statistically significantly different from an offset of zero, final adjusted FF_{CT} values for the U.S. cohort were calculated using equation 3 without any offset correction.

Statistical Analysis

The statistical analysis is described in the Supplemental Methods. For purposes of analysis, normal liver fat was defined as adjusted FF_{CT} <5%, mild steatosis as adjusted FF_{CT} of 5% to 15%, moderate steatosis as adjusted FF_{CT} of 15% to 25%, and severe steatosis as adjusted FF_{CT} ≥25% [12,21-23]. BMI was defined as normal when 18.5 to 24.9, overweight when 25.0 to 29.9, obese when 30.0 to 34.9, and severely obese when ≥35.0.

Results

Comparison of Demographic Characteristics Between Chinese and U.S. Cohorts

In the Chinese cohort, 62.5% (1985/3176) of participants were women, and 37.5% (1191/3176) were men. In the U.S. cohort, 55.3% (4834/8748) of participants were women, and 44.7% (3914/8748) were men. Demographic characteristics are compared between the Chinese and U.S. cohorts, separately for women (Table 1) and men (Table 2). The median age was 62 years and 63 years for women and men in the Chinese cohort, respectively, and 55 years and 56 years for women and men in the U.S. cohort, respectively. In the Chinese cohort, women and men had similar BMI [median BMI of 24.5 (IQR, 22.4-26.9) vs. 24.5 (IQR, 22.5-26.8), respectively; P = .93]. In the U.S. cohort, women had lower BMI than men [median BMI of 27.1 (IQR, 23.6-31.8) vs. 28.4 (IQR, 25.7-31.8), respectively; P < .001]. Women and men from the U.S. cohort had higher BMI than women and men from the Chinese cohort (women: median BMI of 27.1 vs. 24.5, respectively, P < .001; men: median BMI of 28.4 vs. 24.5, respectively, P < .001) (Fig. 1A).

Comparison of Adjusted FF_{CT} Between Chinese and U.S. Cohorts

Figure 2 shows histograms of the distribution of adjusted FF_{CT} values, normalized in terms of the number of individuals per 1,000 participants, in the Chinese cohort (Fig. 2A) and the U.S. cohort (Fig. 2B). The histograms peak at an adjusted FF_{CT} of 4% in the Chinese cohort and 5% in the U.S. cohort. In both cohorts, the histograms show a long tail to the right of the peak, corresponding with participants having mild, moderate, or severe steatosis. Both histograms fall sharply to the left of the peak, with extensions into negative values

corresponding with random measurement errors. The histogram in the U.S. cohort shows a heavier rightward tail compared with the histogram in the Chinese cohort, corresponding with a larger percentage of participants in the U.S. cohort with higher adjusted FF_{CT} values.

The median adjusted FF_{CT} for women was not significantly different between the Chinese and U.S. cohorts (4.7% vs. 4.8%, respectively; P = .47), respectively, but for men was significantly higher in the U.S. cohort than in the Chinese cohort (6.2% vs. 5.8%, respectively; P < .001), compared using the Mann-Whitney test (Fig. 1B). In both cohorts, adjusted FF_{CT} was higher (P < .001) for men than for women [Chinese cohort: median of 5.8% (IQR, 3.6%-8.6%) in men vs. 4.7% (IQR, 2.6%-7.7%) in women; U.S. cohort: median of 6.2% (IQR, 3.6%-10.2%) in men vs. 4.8% (IQR, 2.3%-8.2%) in women]. When participants were stratified into four age groups, those in the Chinese cohort showed no significant difference in adjusted FF_{CT} across age groups for women (P = .49) or men (P = .71); in the U.S. cohort, adjusted FF_{CT} in men increased progressively with age from 4.4% for age 40-49 years to 7.2% for age ≥70 years (P < .001), and in women increased to 6.0% for age ≥70 years versus 4.7%-5.0% in younger age groups (Table 3).

Comparison of Steatosis Severities Between Chinese and U.S. Cohorts

Figure 3 compares women and men in the two cohorts in terms of the percentages of participants with normal liver fat (Fig. 3A) and with mild (Fig. 3B), moderate (Fig. 3C), and severe (Fig. 3D) steatosis. The percentages of women with normal liver fat, with mild steatosis, and with moderate steatosis were not significantly different between the pooled Chinese and U.S. cohorts (all P > .05). However, the percentage of women with severe

steatosis was significantly higher for the U.S. cohort than for the Chinese cohort (1.8% vs. 0.9%, P = .003). The percentages of men with normal liver fat and with mild steatosis were not significantly different between the two cohorts (both P > .05). However, the percentage of men with moderate or severe steatosis was significantly higher for the U.S. cohort than for the Chinese cohort [moderate: 8.5% vs. 6.2% (P = .009); severe: 2.6% vs. 0.2% (P <.001)]. In both cohorts, higher percentages of women than men had normal liver fat (Chinese cohort: 53.7% vs. 41.1%; U.S. cohort: 51.3% vs. 38.1%; both P < .001), while higher percentages of men than women had mild steatosis (Chinese cohort: 52.6% vs. 39.7%; U.S. cohort: 50.9% vs. 40.8%; both P < .001).

Comparison of BMI Between Chinese and U.S. Cohorts

Figure S3 compares the Chinese and U.S. cohorts in terms of the percentages of women and men with normal weight (Fig. S3A) and who were overweight (Fig. S3B), obese (Fig. S3C), and very obese (Fig. S3D). The percentage of participants in the Chinese versus U.S. cohorts who were normal weight was, for women 54.3% vs. 34.7% (P < .001), and for men, 52.8% vs. 17.6% (P < .001); who were obese was, for women 6.6% vs. 16.5% (P < .001), and for men 5.7% versus 24.8% (P < .001); and who were very obese was, for women 0.9% vs. 16.1% (P < .001), and for men was 0.3% vs. 12.5% (P < .001). Across age groups, median BMI ranged from 23.9 to 24.8 for women in the Chinese cohort, from 24.2 to 24.8 for men in the Chinese cohort, from 26.2 to 27.3 for women in the U.S. cohort, and from 27.3 to 28.5 for men in the U.S. cohort (Table 3).

Associations Between Adjusted FF_{CT} and BMI in Chinese and U.S. Cohorts

Scatterplots of adjusted FF_{CT} versus BMI showed distributions extending to higher values along both axes for women and men from the U.S. cohort than for women and men from the Chinese cohort (Fig. S4). The Spearman correlation coefficient between adjusted FF_{CT} and BMI in women and men from the two cohorts ranged from 0.312 to 0.431. When stratifying adjusted FF_{CT} by BMI in women and men, in both the Chinese cohort (Table 4) and the U.S. cohort (Table 5), except for BMI <18.5, men had a higher adjusted FF_{CT} than women, with the difference between men and women increasing in higher BMI categories. Figure 4 demonstrates the distribution of steatosis categories among participants stratified by six BMI categories for both cohorts. Visual assessment of the plots indicate that the percentage of participants with moderate and severe liver steatosis increased with increasing BMI category for both cohorts. However, mild steatosis did not exhibit this pattern; in the U.S. cohort, the plots show that approximately 50% participants in the overweight, obese, very obese, and morbidly obese groups had mild steatosis.

In participants with normal BMI, 36.8% of those in the Chinese cohort and 38.5% of those in the U.S. cohort had mild steatosis, while 3.0% of those in the Chinese cohort and 1.5% of those in the U.S cohort had moderate or severe steatosis. In participants who were obese, 16.1% of those in the Chinese cohort and 34.3% of those in the U.S. cohort had normal liver fat content. In participants who were very obese, 15.8% of those in the Chinese cohort and 24.5% of those in the U.S. cohort had normal liver fat content. Only one Chinese participant was morbidly obese. However, among U.S. participants with BMI ≥40.0, 17.7% had normal liver content. A total of 44.5% and 23.1% of participants with mild steatosis in the Chinese and U.S. cohorts, respectively, had normal BMI.

Comparisons Among Chinese Provinces

Figure S5 shows histograms of adjusted FF_{CT} for each of the seven Chinese provinces and for the pooled data from the Chinese cohort. The adjusted FF_{CT} histograms all peaked at approximately 4% and showed similar shapes, with long tails to the right and sharp falls to the left, similar to the shape of the histogram for the pooled Chinese cohort.

Figure S6 shows plots of median and IQR of adjusted FF_{CT} and BMI for women and men from the Chinese provinces and for the pooled Chinese cohort. Differences in adjusted FF_{CT} among centers were not significant for women (P = .50; Fig. S6A), but were significant for men (P < .001; Fig. S6B), based on Kruskal-Wallis tests. For BMI, differences among provinces were statistically significant for both women (P < .001; Fig. S6C) and men (P < .001; Fig. S6D), based on Kruskal-Wallis tests. Visual assessment of the plots indicates greater variation among provinces for both men and women in terms of BMI than in terms of adjusted FF_{CT}.

Figure S7 shows plots of the percentages of women and men with normal liver fat and with mild, moderate, and severe steatosis, based on adjusted FF_{CT} values, from the Chinese provinces and for the pooled Chinese cohort. These percentages were similar across the Chinese provinces, and chi-squared tests showed no statistically significant differences among these. Three of the seven provinces had no participants with severe steatosis. Figure S8 shows plots of the percentages of women and men with normal weight and who were overweight, obese, and very obese, based on BMI, from the Chinese provinces and for the pooled Chinese cohort. The percentages of participants with normal weight and those who were overweight and obese varied significantly across the Chinese provinces, based on chi-

squared tests. The sample size of participants who were very obese was too small for statistical comparisons across the provinces.

Discussion

The overall prevalence of liver steatosis (adjusted FF_{CT} ≥5%) was greater in women and men in the U.S. cohort (48.7% and 61.9%, respectively) than in the Chinese cohort (46.3% and 58.9%, respectively). Further, severe steatosis was present in a higher percentage of men and women, and moderate steatosis in a higher percentage of men, in the U.S. cohort than in the Chinese cohort. BMI and adjusted FF_{CT} were weakly correlated in both cohorts.

The prevalence of steatosis reported in this study is higher than reported in previous studies [6,21,24] that used MRI or MR spectroscopy to establish the diagnosis. The higher frequency of steatosis may in part relate to the threshold of 5% for defining steatosis. A uniform threshold for defining steatosis is lacking, and earlier studies have used a similar threshold as in our study, even if obtaining a lower percentage of patients with steatosis. For example, in a study of 2561 participants from northeast Germany who underwent CSE-MRI, Kühn et al. reported that 42.4% had PDFF >5.1%, including 12.0% with moderate liver fat content (PDFF 14.1-28.0%) and 1.8% with high fat content (PDFF >28.0%) [21]. In a study of 2349 participants from the Dallas Heart Study who underwent MR spectroscopy, Szczepaniak et al. used a threshold of 5.56% for elevated hepatic triglyceride content and reported a prevalence of hepatic steatosis of 33.6% [6]. In a study of 1006 adult patients referred to a tertiary care center, Fraum et al. reported hepatic steatosis (PDF ≥5.5%) in 25% of patients [grade 1 (5.5%-16.2%) in 19%; grade 2 (16.3%-21.6%) in 3%; and grade 3 (≥21.7%)

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in 3%)] [24]. McHenry et al. also used a cut-off of 5.5% for hepatic steatosis [25]. Other authors used a cut-off of 6.4% [26]. While a relatively high percentage of participants in our study had steatosis, most cases of steatosis were mild.

The higher prevalence of liver steatosis in men than in women in both the Chinese and U.S. cohorts in our study is consistent with previous studies [27-31]. This difference has been mainly attributed to sex difference in estrogen levels. Estrogen protects women from NAFLD by regulating the secretion of insulin and growth hormone [32,33]. The decline of estrogen levels leads to weight gain in postmenopausal women.

"Lean NAFLD" (or "non-obese NAFLD") refers to NAFLD in the presence of normal BMI and has a prevalence that ranges from 10%-30% [34,35]. Lean NAFLD is closely related to insulin resistance and excess visceral adiposity. In long-term follow-up, patients with lean NAFLD have a higher risk of developing severe liver diseases compared with patients with NAFLD and increased BMI [35]. Individuals with normal BMI may not be considered for screening and follow-up of NAFLD. It is generally believed that the prevalence of lean NAFLD is higher in Asian individuals than in White individuals [36]. Participants in both cohorts in our study with normal BMI commonly had steatosis, typically mild steatosis. Conversely, a considerable fraction of participants in both cohorts who were obese, very obese, or morbidly obese had normal liver fat. Previous studies have shown challenges in the use of BMI in characterizing the degree of obesity without considering the distribution of adipose tissue in the body, given that individuals with normal BMI may have excess adipose tissue, especially visceral adipose tissue, which plays a critical role in NAFLD development [36,37]. The poor correlation between adjusted FF_{CT} and BMI further indicates that BMI is not a

major determinant of liver steatosis. The stratification of liver fat across BMI categories suggests a relationship of BMI with moderate and severe, but not mild, steatosis.

Previous studies obtained heterogeneous results in terms of how liver fat content varies by age [38-40]. We observed no significant difference in liver fat content across age groups in the Chinese cohort, though an increase in liver fat content in older participants in the U.S. cohort.

Care is necessary when interpreting CT measurements of liver fat to ensure that the origin of the fat scale is set accurately. At 120 kV, a 1% difference in fat content corresponds to a difference in attenuation of approximately 2 HU. Given this study's adjusted FF_{CT} threshold of 5% to differentiate normal liver fat content and mild steatosis, an accuracy of <1 HU in aligning the origins of the fat scale is desired. For both participants from the Beijing center and the U.S. cohort, the zero-point of the FF_{CT} scale was based on cross-calibration with CSE-MRI measurements of liver PDFF [11,14]. For the other Chinese centers, the FF_{CT} scale was cross-correlated to the Beijing center to ensure consistent origins across centers. Cross-correlation analysis was developed as an aid in signal processing to locate identical patterns in streams of noisy data [20]. If two histograms have comparable shapes but different origins, cross-correlation analysis of the histograms provides a reliable method of inferring their offset. In the present study, all histograms had a similar shape, with a prominent peak that corresponded to individuals with normal liver fat and an extended positive tail at higher adjusted FF_{CT}values that corresponded to individuals with steatosis. Given the histograms' similarly shaped peaks, with only slight differences in terms of their tails, the resulting offset was strongly weighted towards ensuring alignment of the peaks, with any errors expected to be small. Other methods exist to align liver fat measurements on different CT systems [41].

Our study has limitations. Our findings depend on the diagnostic thresholds used for the various categories of liver steatosis. This is particularly true for the threshold of mild steatosis, for which our selected threshold of 5% is close to the peak of the liver fat histograms. While participants in the Chinese cohort were drawn from different geographic areas throughout China, patients in the U.S. cohort were from a single center. However, obesity and metabolic syndrome differ in prevalence across different regions of the United States [42]. The Chinese and U.S. cohorts also exhibited technical differences, including scanner settings and the manner in which the mean liver attenuation was obtained from CT images. However, measurements in the two cohorts were independently calibrated against MRI measurements of liver fat. While the cohorts used different phantoms, when assessed by their cross-correlation function, the origins of the histograms for the U.S. cohort and for CSE-MRI PDFF measurements from the Beijing center were within 0.1%. For the Chinese cohort, ROIs were manually placed in three locations in the liver, while for the U.S. cohort, mean attenuation of the entire liver was obtained using an automated algorithm. However, the automated method used showed strong agreement with manual measurement [18]. Finally, although patients from the U.S. cohort were imaged on several different scanners, we were not able to adjust the origins of the fat scale across the scanners as was performed in the Chinese cohort.

In conclusion, the prevalence of severe steatosis was higher in the U.S. cohort than in the Chinese cohort in both women and men. Men had higher prevalence of liver steatosis than women in both the Chinese and U.S. cohorts. The association of age with liver fat content differed between the Chinese and U.S. cohorts. BMI was weakly related to liver steatosis,

particularly mild steatosis. The findings provide new information on the dependence of hepatic steatosis on age, sex, and BMI.

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Tables

Table 1. Characteristics of women from the Chinese and U.S. cohorts

Variable	Chinese Cohort (n = 1985 women)					U.S. Cohort (n = 4834 women)				
	Age (y)	Height (cm)	Weight (kg)	BMI	Adjusted FF_{CT} (%)	Age (y)	Height (cm)	Weight (kg)	BMI	Adjusted FF_{CT} (%)
Median	62	156.0	60.0	24.5	4.7	55	165.1	72.5	27.1	4.8
25^{th} percentile	54	152.0	53.4	22.4	2.6	51	160.0	62.8	23.6	2.3
75^{th} percentile	68	160.0	65.8	26.9	7.7	61	167.6	86.0	31.8	8.2
IQR	13	8.0	12.0	4.5	5.1	10	7.6	23.3	8.2	5.8
Maximum	95	195	104.7	43.0	38.7	95	198.1	204.5	70.6	45.5
Minimum	40	133	33.0	14.5	-10.6	40	124.5	33.5	14.9	-26.5

Adjusted FF_{CT} = adjusted CT fat fraction cross-measurements, cross-calibrated to the scale of MRI proton density fat fraction measurements; BMI = body mass index; IQR = interquartile range

Table 2. Characteristics of men from the Chinese and U.S. cohorts

Measure	Chinese Cohort (n = 1191 men)					U.S. Cohort (n = 3914 men)				
	Age (y)	Height (cm)	Weight (kg)	BMI	Adjusted FF_{CT} (%)	Age (y)	Height (cm)	Weight (kg)	BMI	Adjusted FF_{CT} (%)
Median	63	166.5	67.9	24.5	5.8	56	177.8	90.6	28.4	6.2
25th percentile	56	161.2	60.5	22.5	3.6	51	172.7	81.1	25.7	3.6
75th percentile	69	170.5	75.6	26.8	8.6	61	182.9	102.2	31.8	10.2
IQR	13	9.3	15.1	4.3	5.0	10	10.2	21.1	6.1	6.6
Maximum	83	196	116.0	37.9	28.7	95	213.4	204.2	63.5	49.4
Minimum	40	142	41.0	15.6	-2.9	40	134.6	49.6	15.5	-13.6

Adjusted FF_{CT} = adjusted CT fat fraction measurements, cross-calibrated to the scale of MRI proton density fat fraction measurements; BMI = body mass index; IQR = interquartile range

Table 3. Median adjusted FF_{CT} and BMI, stratified by age, in women and men in the Chinese and U.S. cohorts

Cohort	Sex	Variable	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70+ y	p[a]
Chinese	Women	N	238	569	788	383	-
		Median adjusted FF_{CT} (%)	4.4	4.9	4.4	5.0	.49
		Median BMI	23.9	24.5	24.5	24.8	.006
Chinese	Men	N	119	285	496	285	-
		Median adjusted FF_{CT} (%)	5.2	5.8	5.8	5.8	.71
		Median BMI	24.4	24.8	24.7	24.2	.036
U.S.	Women	N	189	3191	1119	335	-
		Median adjusted FF_{CT} (%)	5.0	4.7	5.0	6.0	<.001
		Median BMI	26.2	26.9	27.3	26.6	.007
U.S.	Men	N	112	2546	957	299	-
		Median adjusted FF_{CT} (%)	4.4	6.1	6.7	7.2	< 001
		Median BMI	28.0	28.4	28.5	27.3	.01

[a]Kruskal-Wallis test

Adjusted FF_{CT} = adjusted CT fat fraction measurements, cross-calibrated to the scale of MRI proton density fat fraction measurements; BMI = body mass index.

Table 4. Comparison of adjusted FF_{CT} between sexes, stratified by BMI, in Chinese cohort

BMI	Women			Men			Difference in Adjusted FF_{CT} between sexes (%)	P (between sexes)
	N	Median BMI	Median Adjusted FF_{CT} (%)	N	Median BMI	Median Adjusted FF_{CT} (%)		
<18.5	40	17.9	2.61	26	17.6	2.45	-0.17	.88
18.5-21.9	380	20.8	3.31	228	20.9	4.10	0.79	<.001
22.0-24.9	697	23.6	4.26	400	23.7	5.38	11.11	<.001
25.0-29.9	720	26.8	5.69	465	26.7	7.20	1.52	<.001
≥30.0	148	31.6	8.81	71	31.5	10.29	1.48	.29

Adjusted FF_{CT} = adjusted CT fat fraction measurements, cross-calibrated to the scale of MRI proton density fat fraction measurements; BMI = body mass index.

Table 5. Comparison of FF_{CT} Between Sexes, Stratified by BMI, in U.S. Cohort

BMI	Women			Men			Difference in Adjusted FF_{CT} Between Sexes (%)	P (between sexes)
	N	Median BMI	Median Adjusted FF_{CT} (%)	N	Median BMI	Median Adjustd FF_{CT} (%)		
18.5-21.9	600	21.0	4.45	123	21.1	4.52	0.07	.25
22.0-24.9	1080	23.6	3.74	567	23.6	4.71	0.98	<.001
25.0-29.9	1526	27.2	4.19	1754	27.2	5.69	1.50	<.001
30.0-34.9	797	32.0	6.31	971	31.8	7.53	1.21	<.001
35.0-39.9	419	36.8	8.08	302	36.7	10.85	2.77	<.001
≥40.0	359	44.5	9.73	188	43.6	12.36	2.64	<.001

Data not reported for BMI <18.5 due to presence of only 9 men with BMI <18.5 in U.S. cohort

Adjusted FF_{CT} = adjusted CT fat fraction measurements, cross-calibrated to the scale of MRI proton density fat fraction measurements; BMI = body mass index.

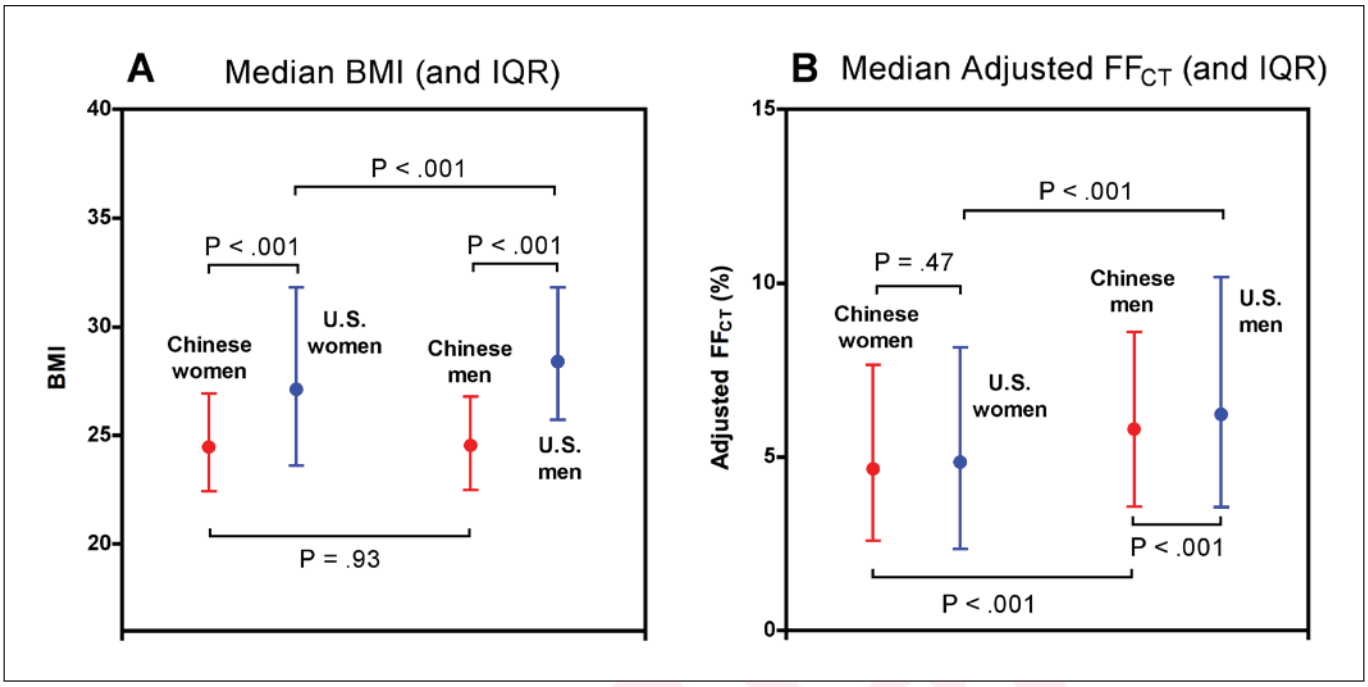

Figure 1. Median adjusted BMI (A) and adjusted FFCT (B), with associated IQRs, for women and men in pooled Chinese cohort and U.S cohort. FFCT = CT fat fraction (liver fat content determined from attenuation measurements using equation 1); adjusted FFCT = FFCT measurements cross-calibrated to the scale of MRI measurements of proton density fat fraction (PDFF); BMI = body mass index; IQR = interquartile range.

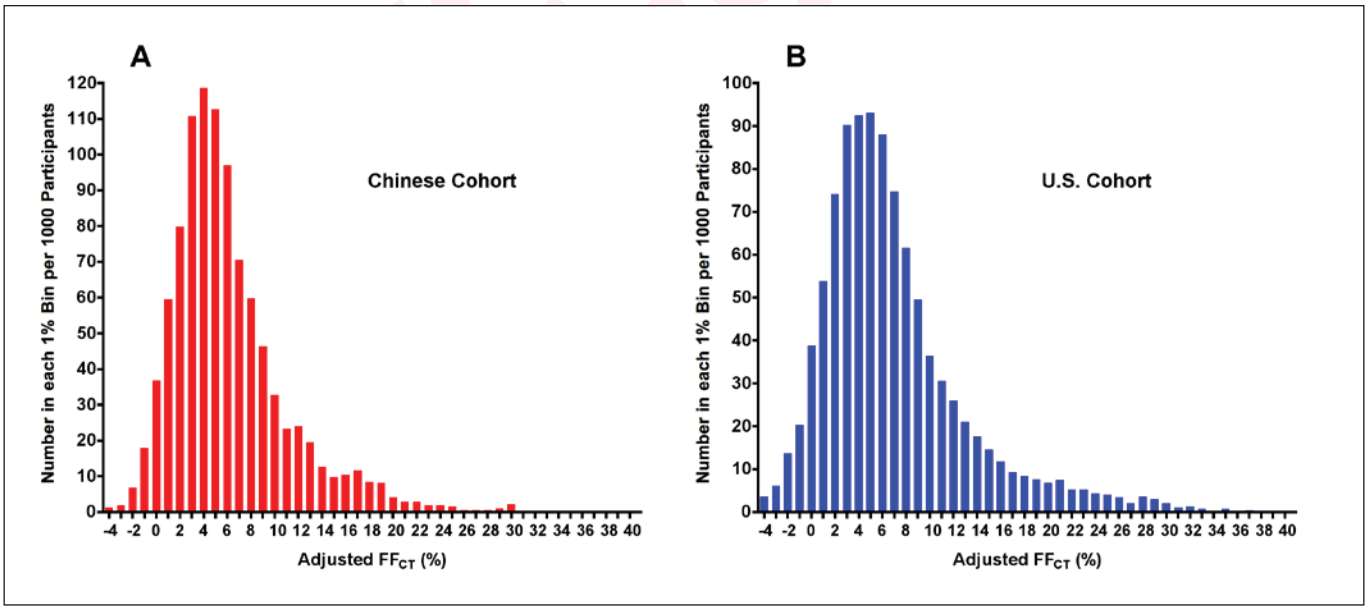

Figure 2. Histograms of adjusted FFCT for (A) Chinese cohort, pooled across seven provinces, of 3176 women and men enrolled in the CASH study, and (B) U.S. cohort of 8748 women and men from retrospective study conducted in Madison, WI. Vertical axis represents the number of participants in each 1% bin of adjusted FFCT per 1000 participants. FFCT = CT fat fraction (liver fat content determined from attenuation measurements using equation 1); adjusted FFCT = FFCT measurements cross-calibrated to the scale of MRI measurements of proton density fat fraction (PDFF); CASH =China Action on Spine and Hip status

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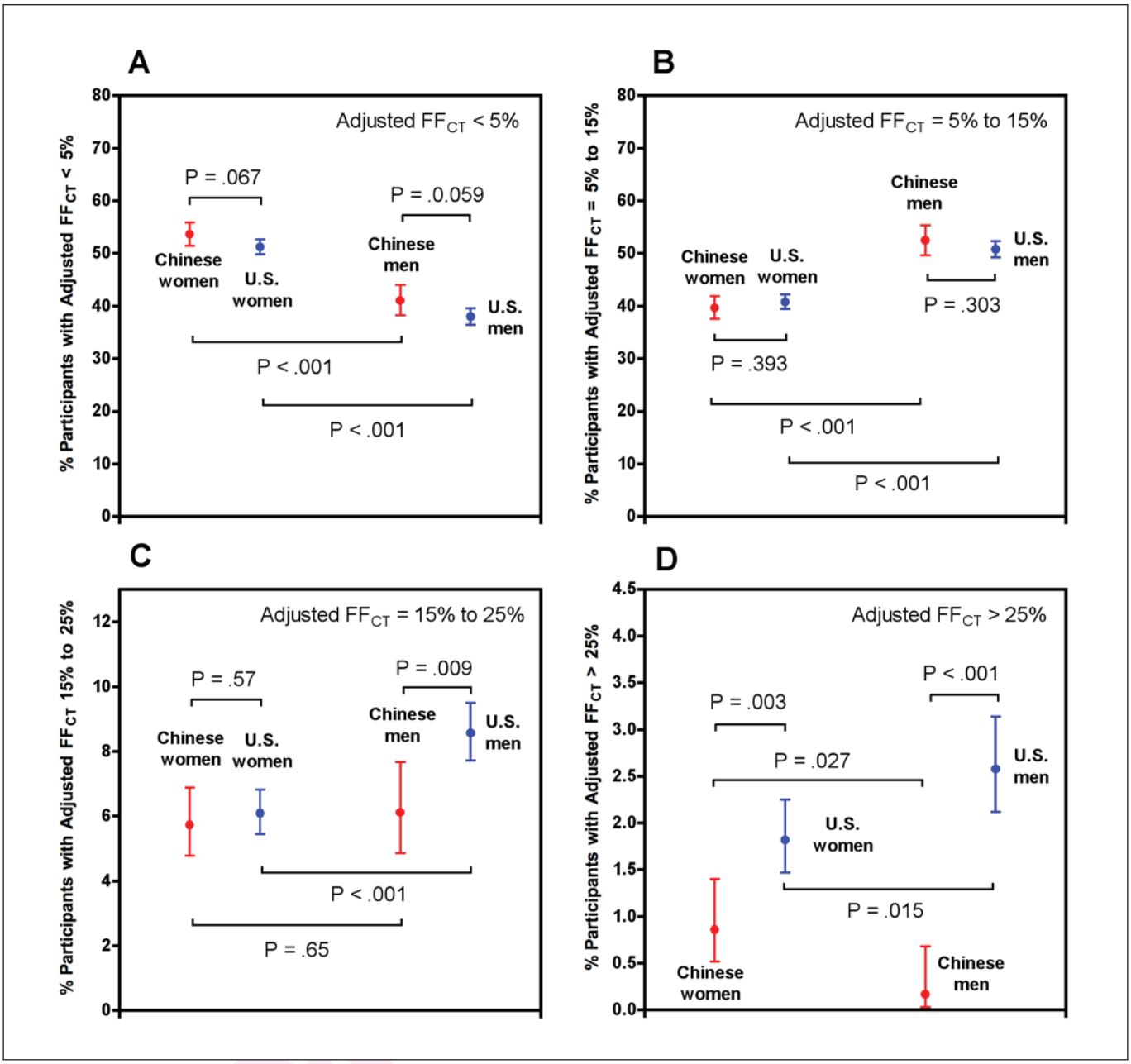

Figure 3. Percentages of participants and 95% CIs for women and men in pooled Chinese cohort and U.S. cohort with: (A): normal liver fat (adjusted FFCT <5%), (B) mild steatosis (adjusted FFCT 5% to 15%), (C) moderate steatosis (adjusted FFCT 15% to 25%), and (D) severe steatosis (adjusted FFCT ≥25%). FFCT = CT fat fraction (liver fat content determined from attenuation measurements using equation 1); adjusted FFCT= FFCT measurements cross-calibrated to the scale of MRI measurements of proton density fat fraction (PDFF)

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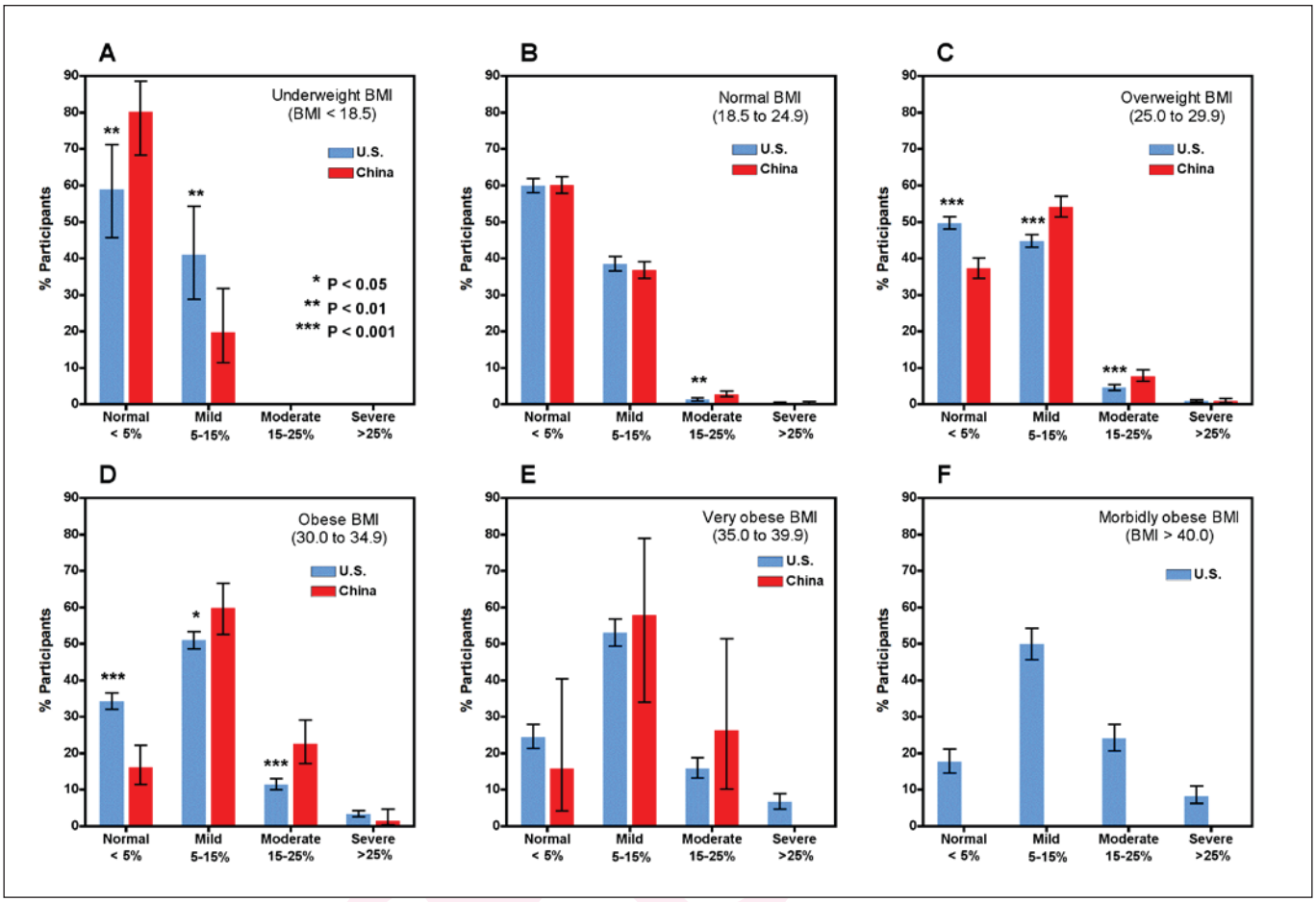

Figure 4. Histograms comparing the percentages of participants in the pooled Chinese and U.S. cohorts with normal liver fat content (adjusted FFCT <5%), mild steatosis (FFCT 5% to 15%), moderate steatosis (FFCT 15% to 25%), and severe steatosis (FFCT ≥25%), stratified by six BMI categories: (A) underweight (BMI <18.5), (B) normal weight (BMI 18.5-24.9), (C) overweight (BMI 25.0-29.9), (D) obese (BMI 30.0-34.9), (E) very obese (35.0-39.9), and morbidly obese (≥40.0). Data for women and men have been pooled. FFCT = CT fat fraction (liver fat content determined from attenuation measurements using equation 1); adjusted FFCT = FFCT measurements cross-calibrated to the scale of MRI measurements of proton density fat fraction (PDFF); BMI = body mass index.

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Hepatic Steatosis: CT-based Prevalence in Adults in China and the United States and Associations with Age, Sex, and Body Mass Index

Original Research

Zhe Guo, MD[1a], Glen M. Blake, PhD[2a], Peter M. Graffy, BA[3a], Veit Sandfort, MD[4], Ronald M. Summers, MD, PhD[5], Kai Li, MD[1], Shaoqi Xu, MD[6], Yizhong Chen, MD[7], Jun Zhou, MD[8], Jiman Shao, MD[9], Yonghong Jiang, MD[10], Haibo Qu, MD[11], Baoqing Li, MD[12], Xiaoguang Cheng, MD[1], Perry J. Pickhardt, MD[3*]

1. Department of Radiology, Beijing Jishuitan Hospital, Beijing, China
2. School of Biomedical Engineering & Imaging Sciences, King's College London, St Thomas' Hospital, London, England
3. Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
4. Department of Radiology, Stanford University School of Medicine, Stanford, CA, USA
5. Imaging Biomarkers and Computer-Aided Diagnosis Laboratory, Department of Radiology and Imaging Sciences, National Institutes of Health Clinical Center, Bethesda, MD, USA
6. Department of Radiology, Wujin Hospital of Traditional Chinese Medicine, Changzhou, China
7. Department of Radiology, Dayi County People's Hospital, Chengdu, China
8. Department of Radiology, Shenyang Fourth People's Hospital, Shenyang, China
9. Department of Radiology, Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Nanchang, China
10. Department of Radiology, Xi'an Honghui Hospital, Xi'an, China
11. Department of Radiology, West China Second Hospital, Sichuan University, Chengdu, China
12. Department of Radiology, Shijingshan Hospital, Beijing, China

[a] These authors contributed equally to this work

[*]Correspondence authors at Perry J. Pickhardt, Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, Wis, USA.
E-mail address: ppickhardt2@uwhealth.org

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