Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Cardiometabolic and Metabolic Profiles of Lean/Normal, Overweight and Obese Patients with Nonalcoholic Fatty Liver Disease

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Purpose: Disagreements about the risk of non-obese, non-alcoholic fatty liver disease for cardiometabolic outcomes occurred widely. This study aims to characterize the cardiometabolic and metabolic profile of lean/normal, overweight and obese patients with nonalcoholic fatty liver disease on a big sample.

Patients and methods: Appeared healthy adults who participated in health examinations during the year of 2019–2022 were screened for fatty liver diagnosis. BMI classified fatty livers as lean, overweight and obese. Eleven cardiometabolic metrics (SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol) and metabolic metrics (GLU: blood glucose; GHB: glycated haemoglobin; UA: uric acid; AST: aspartate aminotransferase; ALT: alanine aminotransferase) were included, described and compared among BMI categories.

Results: There were 56,496 fatty livers diagnosed by ultrasound in this study. In total, the lean fatty liver had lowest mean SBP, DBP, GLU, TG, UA, AST, and ALT but highest TC and HDL among BMI categories (all $p < 0.001$). The number of abnormal metrics in total was 2.5, 2.9 and 3.4 in lean, overweight, and obesity, respectively ($p < 0.001$, $p\_trend < 0.001$). Visualized data showed that lean fatty liver was similar but milder in all metabolic metrics than overweight and obesity at the young ages. However, lean fatty liver had higher coefficients of age and risk of metabolic abnormality regression ($p < 0.001$ for SBP, DBP, GLU, GHB, TC).

Conclusion: The lean type of fatty livers at a younger age has a relatively favourable cardiometabolic and metabolic profile compared to overweight and obese fatty livers. Due to the possible catch-up effect of metabolic dysfunctions in young lean fatty liver, lean fatty liver may have the same health outcomes as overweight/obesity fatty liver in long term. The evaluation and intervention may be critical for young lean fatty liver management to slowdown the rapid progress of metabolic dysfunction.

Keywords: fatty liver, cardiometabolic profile, metabolic profile, body mass index

Introduction

Fatty liver or hepatic steatosis is an abnormal fat accumulation in more than 5% of hepatocytes. From the etiology, hepatic steatosis can occur because of overnutrition, alcoholism, chemotherapy, toxic, and infectious causes. When obvious alcohol consumption (over 20g for women and 30g for men per week) and another secondary hepatic steatosis can be ruled out, it then can be called non-alcoholic fatty liver disease (NAFLD). NAFLD was predominantly the type of hepatic steatosis according to a study based on NHANES data. The prevalence of NAFLD during the year of 2013–2016 was 31.9%, accounting for 91.4% of all types of hepatic steatosis.[1] Hepatic steatosis can further progress to steatohepatitis, cirrhosis and liver cancer. Due to the high prevalence and severe prognosis, NAFLD is now a major public health problem and heavy economic burden around the world.[2]

From epidemiology, fatty liver is highly related to overweight and obesity, which shows a condition of metabolism dysfunction. On the other side, fatty liver itself is a sign of metabolic dysfunction and shared common metabolic changes

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with simple obesity[3] and can increase the risk of cardiometabolic disease alone without obese.[4,5] Because of the fact that NAFLD is deeply rooted in metabolic dysfunction, recently, there is an endeavor to rename NAFLD with metabolic dysfunction associated with fatty liver disease (MAFLD). The proposed diagnostic criteria for MAFLD are fatty liver detected either by imaging techniques, blood biomarkers or liver histology with any of three conditions: overweight or obesity, type 2 diabetes mellitus, or at least two out of seven metabolic risk factors when weight is normal or lean.[6] According to the diagnosis of MAFLD, the causes of hepatic steatosis are no longer taken into account, which is one of the reasons for the heated debate over NAFLD renaming. Now, steatotic liver disease (SLD) has been selected as a universal term to cover diverse causes of hepatic steatosis.[7]

Although fatty liver is highly related to obesity, fatty liver can also be developed without the presence of obesity. A systematic review showed that 40.8% of NAFLD can be classified as non-obese fatty liver and 19.2% as lean fatty liver.[8] It looks reasonable that lean or non-obese fatty liver had a better metabolic profile[9] and lower risks of severe morbidity and mortality than its obese counterpart demonstrated,[10–12] lean or non-obesity fatty liver was therefore recognized as a benign subtype of fatty liver. However, others challenged it for lean or non-obese fatty liver was found more progressive in steatohepatitis and cirrhosis,[8] and more likely to have cardiovascular events and premature mortalities than obese fatty liver. In addition, histologic diagnosed NAFLD showed that lean NALFD has a higher level of inflammation and fibrosis than obese control.[13] Some cohort studies also showed that non-overweight NAFLD had a higher risk of CVD event and mortality than overweight/obese NAFLD.[14,15] A Korean population-based study also found that lean NAFLD (BMI < 25) had higher ASCVD scores than obese NAFLD.[16] To make matters worse, a cohort study about Caucasian reported no significant difference between lean and non-lean fatty liver in prognosis.[17]

Therefore, whether the lean fatty liver is benign or worse than obese counterpart is still controversial and under debate. Many reasons may be involved in those conflicting studies, such as sample selection bias, genetic backgrounds, lifestyles, fatty liver diagnostic methods and criteria and follow-up durations, under-reporting of alcohol intakes, weight losses due to advanced diseases, myosteatosis or sarcopenia.[18] This knowledge gap limits NAFLD management and counselling in practices. Because metabolic profile and cardiometabolic profile are well validated biomarkers or predictors of health outcomes, in this study, we aimed to compare the age-dependent metabolic and cardiometabolic profile and to clarify if lean or non-obese fatty liver is the same on health as obese fatty liver.

Methods

This is a cross-sectional study; historical medical records from subjects taking routine health check-ups in the health care centre of the second affiliated hospital of Chongqing Medical University in Chongqing City were retrieved and analyzed. This study was approved by the second affiliated hospital of Chongqing Medical University ethics committee (no. 2020–252). According to the principles of the Declaration of Helsinki, identification information of subjects was carefully masked when retrieving their medical records, and consents were not required from those de-identified participants.

Subjects

Each year, more than 100,000 appeared healthy people will participate in the routine health examination at this center. In this study, a database about 400,000 electronic medical records generated during the year of 2019 to 2022 was used. Because fatty liver is a multi-factor-caused and progressive disease, the fatty liver screening was further limited to people: 1) born in Chongqing city; 2) born in the year ranged from 1930 to 1999. By applying those limitations, there were 198,466 unique records available. In the present study, 61,326 fatty livers, about 30.9% of the total available subjects, were found. After dropping data on missing subjects, 56,496 (92.1%) were included in the analysis.

Data Collection

Database was inquired to obtain the fatty livers with anthropometric data (weight, height, waist, and hip circumferences), blood pressures, serum biomarkers from fasting blood samples (blood glucose, glycated hemoglobin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, uric acid, aspartate aminotransferase, alanine aminotransferase) and the ultrasound diagnosed steatosis status. The one with the latest checking date was

kept for duplicated records with the same identifications. Data were mainly the healthy check-ups, confounders such as, comorbidity, lifestyles and medication treatments were not available in this study.

Classification of Body Mass Index (BMI)

According to the suggestions of the Working Group on Obesity in China (WGOC),[19] BMI cutoff values for lean/normal, overweight and obesity were 18.5–24, 24–28, and >28, respectively. The fatty liver in this study was then categorized as lean/normal, overweight and obese fatty liver accordingly.

Definition of Abnormal Cardiometabolic Indexes

In this study, 11 cardiometabolic indexes which were widely investigated as the risk factors of cardiometabolic diseases and mostly available in our health check-ups were included. They were systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (GLU), glycated haemoglobin (GHB), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), uric acid (UA), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

According to the consensus and criteria set up by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL)[7] or ATP III guideline[20] or the clinic diagnosis standards in local laboratory: high SBP was defined as ≥130 mmHg; high DBP >85 mmHg; high GLU ≥ 100 mg/dL (≥5.6 mmol/L), high GHB ≥ 5.7%; high TC > 240mg/dl (>6.2 mmol/L); high TG ≥150 mg/dL (≥1.70 mmol/L); low HDL < 40 mg/dL (<1.0 mmol/L); high LDL > 130mg/dl (>3.4 mmol/L); high UA >7mg/dl (>420 μmoL/L); high AST > 40UI/L; and high ALT >40UI/L.

Data Analysis

Category variables were expressed as proportions; continuous variables were expressed as mean and standard deviation (SD). Mean differences between groups were compared using Analysis of Variance (ANOVA), *t*-test and chi-square for category variables. LSD compared means of multiple groups; multivariable logistic regressions were used to explore the relationship between body weight and abnormal cardiometabolic factors. P <0.05 was set as a significant level for all tests. The software for the statistics test was SPSS 19.0 for Windows.

Results

The Characteristics of Subjects by Fatty Liver BMI Categories

There were 56,496 fatty livers diagnosed by ultrasound in this study. Among them, 12,158 (21.5%) belonged to normal weight, 30,896 (54.7%) belonged to overweight, and 13,442 (23.8%) belonged to obese. Lean or overweight fatty livers were for granted to be lighter and slimmer with smaller waist circumferences and hip circumferences in shape when compared to obesity fatter livers. In addition, lean fatty liver tended to be more female, born in urban and older. When stratified fatty livers by age, the peak ages for lean, overweight and obese fatty livers were 55–65, 45–55, and 45–55, respectively; the older people were more prone to be lean fatty liver. All characteristics included among BMI categories were significantly different and had a linear trend (P < 0.001) (Table 1).

The Measurements of Metabolic Metrics by Fatter Liver BMI Categories

For those eleven metabolic metrics included. The lean fatty liver had lower mean SBP (126.52 ± 17.79 vs 130.24 ± 17.65 and 134.72 ± 17.49 mmHg), DBP(75.99±11.03 vs 79.00 ± 11.57 and 82.39 ± 82.39 mmHg), GLU (5.66 ± 1.85 vs 5.72 ± 1.82 and 5.85 ± 1.97 mmol/L), TG (2.24 ± 1.95 vs 2.45 ± 2.18 and 2.60 ± 2.28 mmol/L), UA (368.20 ± 87.76 vs 394.47 ± 91.28 and 413.14 ± 96.67μmol/L), AST (25.08 ± 16.16 vs 27.85 ± 19.06 and 31.92 ± 22.41 UI/L) and ALT (25.27 ± 16.16 vs 28.53 ± 19.06 vs 32.33 ± 22.51 UI/L) but higher TC (5.36 ± 1.07 vs 5.29 ± 1.02 and 5.24 ± 1.01 mmol/L) and HDL(13.2 ±0.30 vs 1.25 ± 0.28 and 1.21 ± 0.26 mmol/L) than overweight and obesity among BMI categories (all p < 0.001). No significant mean differences were found for GHB (6.04 ± 1.12 vs 6.03 ± 1.08 and 6.03 ± 1.05%) and LDL (2.94 ± 0.81 vs 2.92 ± 0.77 and 2.92 ± 0.78 mmol/L) among BMI categories (p > 0.05) (Table 2).

Table 1 The Characteristics of Fatty Liver by BMI Categories

	Lean/normal (n=12,158)	Overweight (n=30,896)	Obesity (n=13,442)	p	P_trend
Gender (%)				<0.001	<0.001
Male	55.0%	71.5%	71.7%		
Female	45.0%	28.5%	28.3%		
Birthplace (%)				<0.001	<0.001
Rural	28.0%	33.7%	36.4%		
Urban	72.0%	66.3%	63.6%		
Age(year)	52.4±11.1	51.3±11.1	49.7±11.4	<0.001	<0.001
Height(cm)	163.49±8.47	164.63±8.20	164.50±8.49	<0.001	<0.001
Weight (Kg)	60.72±7.21	70.52±7.63	81.54±9.87	<0.001	<0.001
BMI(Kg/m^2)	22.64±1.12	25.95±1.11	30.05±1.95	<0.001	<0.001
Waist(cm)	81.32±6.01	88.54±5.81	96.71±7.15	<0.001	<0.001
Hip(cm)	91.72±4.32	96.55±4.33	102.75±9.98	<0.001	<0.001
Waist/hip ratio	0.89±0.06	0.92±0.05	0.94±0.06	<0.001	<0.001
Age group (n, %)				<0.001	<0.001
85–95	113(0.9)	296(1.0)	99(0.7)		
75–85	651(5.4)	1451(4.7)	649(4.8)		
65–75	1896(15.6)	4099(13.3)	1470(10.9)		
55–65	4076(33.5)	9591(31.0)	3565(26.5)		
45–55	3497(28.8)	9950(32.2)	4596(34.2)		
35–45	1646(13.5)	4747(15.4)	2578(19.2)		
25–35	279(2.3)	762(2.5)	485(3.6)		

Notes: P: P value for overall difference among 3 BMI categories. P_trend: P value for the linear trend among BMI categories.
Abbreviations: BMI, Body mass index; Cm, centimeters; Kg, Kilograms; n, number of participants.

Table 2 The Means of Metabolic Metrics by BMI Categories (Mean± SD)

	Lean (n=12,158)	Overweight (n=30,896)	Obesity (n=13,442)	p	P_trend
SBP (mmHg)	126.52 ±17.79	130.24±17.65	134.72±17.49	<0.001	<0.001
DBP (mmHg)	75.99±11.03	79.00±11.57	82.39±12.16	<0.001	<0.001
GLU (mmol/L)	5.66±1.85	5.72±1.82	5.85±1.79	<0.001	<0.001
GHB (%)	6.04±1.12	6.03±1.08	6.03±1.05	0.535	0.638
TC (mmol/L)	5.36±1.07	5.29±1.02	5.24±1.01	<0.001	<0.001
TG (mmol/L)	2.24±1.95	2.45±2.18	2.60±2.28	<0.001	<0.001
HDL (mmol/L)	1.32±0.30	1.25±0.28	1.21±0.26	<0.001	<0.001
LDL (mmol/L)	2.94±0.81	2.92±0.77	2.92±0.78	0.262	0.170
UA (μmoL/L)	368.20±87.76	394.47±91.28	413.14±96.67	<0.001	<0.001
AST (UI/L)	25.08±16.16	27.85±19.06	31.92±22.41	<0.001	<0.001
ALT (UI/L)	25.27±15.11	28.53±20.79	32.33±22.51	<0.001	<0.001

Notes: P: P value for overall difference among 3 BMI categories. P_trend: P value for the linear trend among BMI categories. mmHg: millimetre of mercury. mmol/L: millimoles per litre. UI/L: International Units Per Liter. μmoL/L: Millimole per liter. SD: standard deviation.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; GHB, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

The Prevalence of Abnormal Metabolic Metrics by Fatty Liver BMI Categories

The lean fatty liver had lower prevalence of abnormal SBP (37.8% vs 46.0% and 56.7%), DBP (18.8% vs 27.0% and 37.5%), GLU (28.7% vs 31.9% and 38.1%), TG (53.7% vs 59.8% and 64.0%), HDL (12.3% vs 17.1% vs 21.0%), UA

(25.2% vs 36.3% and 44.8%), AST (8.7% vs 12.6% and 19.3%), and ALT (8.9% vs 13.5% and 20.2%) than overweight and obesity fatter liver (all $p < 0.001$), but not for LDL (26.2% vs 25.3% and 25.0%) and GHB (48.4% vs 48.5% and 49.7%) as both $p > 0.05$. The three most common abnormalities in all three types of fatty liver were the same, ie, TG, GHB and SBP. It was noteworthy that abnormal TC (19.1 vs 16.4 and 15.1, $p < 0.001$) was reversely higher in lean fatty liver than overweight and obesity fatter liver (Table 3).

Fatty Liver BMI Categories and the Risk of Abnormal Metabolic Metrics

According to logistic regression coefficients, SBP, DBP, ALT, AST, and AU had the five highest risks of being abnormal due to fatty liver BMI increasing (all $\beta > 0.3$ and $p < 0.001$), which meant these metrics were the most sensitive indexes to lost balances when BMI increased. On the contrary, LDL(β=−0.028, $p = 0.061$), GHB(β=0.110, $p < 0.001$), and TC(β=−0.101, $p < 0.001$), were influenced by BMI the least based on the regression coefficients (Table 4).

Table 3 The Prevalence of Abnormal Metabolic Indexes in Each BMI Categories (%)

Risk factors	Lean (n=12,158)	Overweight (n=30,896)	Obesity (n=13,442)	p	P_trend
High SBP	37.8	46.0	56.7	<0.001	<0.001
High DBP	18.8	27.0	37.5	<0.001	<0.001
High GLU	28.7	31.9	38.1	<0.001	<0.001
High GHB	48.4	48.5	49.7	0.190	0.122
High TC	19.1	16.4	15.1	<0.001	<0.001
High TG	53.7	59.8	64.0	<0.001	<0.001
Low HDL	12.3	17.1	21.0	<0.001	<0.001
High LDL	26.2	25.3	25.0	0.071	0.034
High UA	25.2	36.3	44.8	<0.001	<0.001
High AST	8.7	12.6	19.3	<0.001	<0.001
High ALT	8.9	13.5	20.2	<0.001	<0.001

Notes: P: P value for overall difference among 3 BMI categories. P_trend: P value for the linear trend among BMI categories.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; GHB, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4 The Logistic Regression of BMI* and Risk of Abnormal Metabolic Metrics

Dependent variable	B#	S.E.	OR	95% CI of OR	P value
High SBP	0.480	0.013	1.616	1.574–1.659	<0.001
High DBP	0.452	0.015	1.572	1.528–1.618	<0.001
High ALT	0.416	0.012	1.516	1.460–1.574	<0.001
High AST	0.402	0.013	1.495	1.438–1.554	<0.001
High UA	0.342	0.015	1.408	1.368–1.450	<0.001
High GLU	0.272	0.015	1.313	1.274–1.353	<0.001
Low HDL	0.231	0.018	1.260	1.216–1.305	<0.001
High TG	0.168	0.014	1.183	1.150–1.217	<0.001
High GHB	0.110	0.018	1.116	1.078–1.156	<0.001
High LDL	−0.028	0.015	0.973	0.945–1.001	0.061
High TC	−0.101	0.017	0.904	0.874–0.935	<0.001

Notes: *BMI was coded as 1, normal; 2, overweight; 3, obese. # regression coefficient, adjusted by gender, birth year, birthplace (urban and rural).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; GHB, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase. CI, Confidence Interval. OR, Odds ratio.

The Age and the Prevalence/Risk of Abnormal Metabolic Metrics

Visualized prevalence of abnormal metabolic metrics showed that lean fatty liver has the similar age-prevalence patterns of metabolic profile as overweight and obesity in both sexes; lean fatty livers were milder than overweight and obesity at the youngest ages but tended to reach the same at older ages (Figure 1).

According to logistic regression coefficients, risk of abnormal SBP, GLU, and GHB were positively related to age, especially higher in lean fatty liver (p_trend < 0.001), which means SBP, GLU, and GHB became worse more quickly in lean fatty liver. In contrast, risk of abnormal HLD, UA, AST, and ALT were negatively related to age, but lower in lean fatty liver (p_trend < 0.001), which means HDL UA, AST, and ALT relieved more slowly in lean fatty liver. LDL was not influenced by age in this analysis (Table 5).

BMI and the Number of Abnormal Cardiometabolic Factors

The number of abnormalities in total was 2.5, 2.9 and 3.4 in lean, overweight, and obesity, respectively ($p < 0.001$, p_trend < 0.001). When stratifying the subjects by age, the lean and overweight fatty liver had fewer abnormal metabolic factors than obesity fatty liver in those subjects younger than 75 ($p < 0.001$, p_trend < 0.001). For those over 75, the abnormality numbers in lean, overweight and obese groups were no significant differences (Table 6).

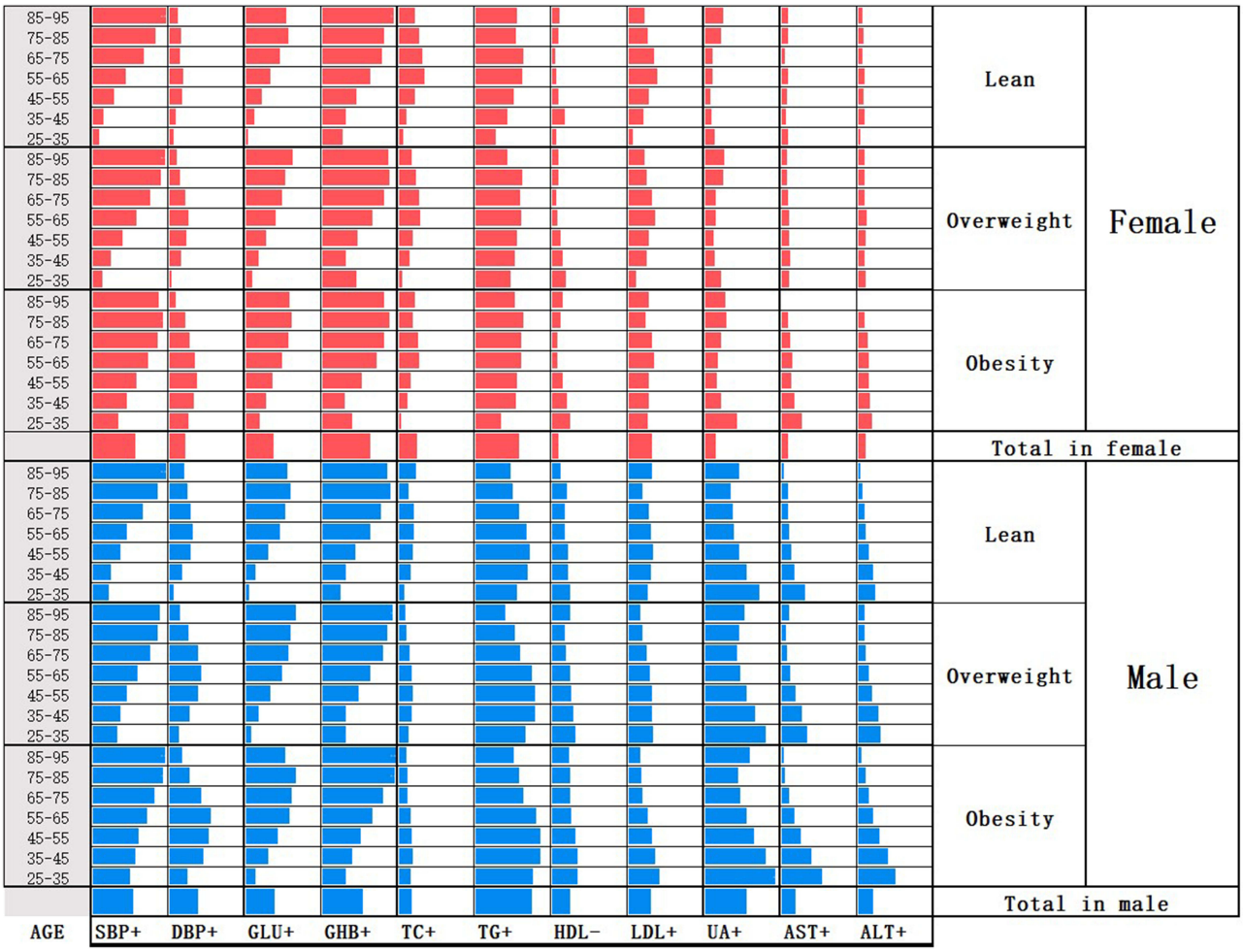

Figure 1 The prevalence of abnormal metabolic metrics by age, BMI categories and gender. The length of the colored bar means the prevalence of abnormal metrics (%) in fatty liver, the whole cell width stands for 100%.

Table 5 Logistic Regression of Age# and Risks of Abnormality Metabolic Metrics (Mean ± S.E.)

	Lean	Overweight	obesity	p-trend
High SBP	0.604±0.019*	0.493±0.011*	0.354±0.016*	<0.001
High DBP	0.120±0.021*	0.075±0.012*	**−0.026±0.016**	<0.001
High GLU	0.517±0.022*	0.463±0.013*	0.380±0.018*	<0.001
High GHB	0.593±0.024*	0.526±0.016*	0.498±0.024*	<0.001
High TC	0.133±0.021*	**0002±0.014**	**0.001±0.022**	<0.001
High TG	**0.000±0.018**	−0.106±0.012*	−0.099±0.018*	<0.001
Low HDL	−0.129±0.026*	−0.162±0.015*	−0.166±0.020*	<0.001
High LDL	**−0.004±0.019**	−0.086±0.012*	−0.152±0.018*	0.061
High UA	−0.131±0.021*	−0.197±0.012*	−0.269±0.017*	<0.001
High AST	−0.246±0.031*	−0.391±0.017*	−0.478±0.023*	<0.001
High ALT	−0.231±0.030*	−0.278±0.016*	−0.368±0.021*	<0.001

Notes: #Age was categorized into 7 groups with code of 1 to 7. Each age group has a 10-year width. It was adjusted by gender and birthplace. *Significant with p<0.05; bold number showed P>0.05 without significance. P_trend: for the linear trend among BMI categories.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; GHB, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SE, Standard error.

Table 6 The Numbers of Abnormal Metabolic Factors Stratified by Age (mean ± SD)

Age group	N	Lean (n=12,158)	Overweight (n=30,896)	Obesity (n=13,442)	p	P_trend
85–95	508	3.0±1.6	2.9±1.4	2.8±1.6	0.726	0.429
75–85	2751	2.9±1.6	2.9±1.6	3.1±1.6	0.051	0.041
65–75	7465	2.7±1.6a	2.9±1.6b	3.2±1.7c	<0.001	<0.001
55–65	17,232	2.6±1.7a	3.0±1.8b	3.4±1.8c	<0.001	<0.001
45–55	18,043	2.4±1.7a	2.9±1.8b	3.5±1.9c	<0.001	<0.001
35–45	8971	2.1±1.6a	2.8±1.8b	3.6±2.0c	<0.001	<0.001
25–35	1526	1.9±1.6a	2.5±1.7b	3.3±1.9c	<0.001	<0.001
Total	56,496	2.5±1.7a	2.9±1.8b	3.4±1.9c	<0.001	<0.001

Notes: In each age group, same letter of a, b, c means insignificant comparison between BMI categories. P is for overall difference among 3 BMI categories. P: P value for overall difference among 3 BMI categories. P_trend: P value for the linear trend among BMI categories.
Abbreviations: SD, Standard Deviation; N, number of participants.

Discussion

This study screened appeared healthy people visited the health center during the year of 2019–2022, and 56,496 fatty livers diagnosed by ultrasound were included. BMI categorized subjects as lean (21.5%), overweight (54.7%), and obese (23.8%) which were comparable with other reports.[18] In addition, more lean subjects were older, female and born in urban areas than those obese, which indicated that older females and those with high socioeconomic status might be more susceptible to a lean type of fatty liver, the same as those found in a study by Li et al.[21] This may indicate that lean fatty liver may be the benign type of fatty liver.

The fatty liver itself is a sign of metabolic dysfunction, and insulin resistance was the pivot driver of NAFLD.[22] When obesity, another indicator of metabolic dysfunction, co-existed with fatty liver, it is reasonable to assume that metabolic indexes will worsen. But some study should that lean fatty liver may increase the risk of cardiovascular diseases and mortalities. In this study, we tried to prove those claims, and 11 measurements of routine health check-ups were included in the metabolic profile analysis. We found that lean fatty liver in total had lower average SBP, DBP, GLU, TG, UA, AST, and ALT but higher HDL ("good" cholesterol) and TC compared to overweight and obesity. The

abnormality rate of those eight measurements (SBP, DBP, GLU, TG, UA, AST, ALT and HDL) was also lower in the lean group except TC. As for GHB and LDL, no differences of average value and abnormality rate were found in lean, overweight and obese fatty liver. After adjusting birth year, gender and birthplace. Lean fatty liver had lower risk of GHB than overweight/obesity, but LDL still was not found different in all type of fatty livers.

The logistic regression analysis found that BMI influenced SBP, DBP, UA, ALT, AST, GLU and HDL the most but the least for LDL, TC, TG and GHB after adjusting birth year, gender and birthplace. A systematic review partly supported our results, in which 18 studies/comparisons with 1966 lean cases and 5938 obese cases were included. This systematic review showed that SBP, DBP, GLU, AST, and ALT were significantly lower in lean fatty livers than obese ones, and no differences were found for TC and TG.[3] However, we detected that TC was higher ($P < 0.001$) while TG was lower in lean fatty liver ($P < 0.001$) with a big sample of over 50 thousand subjects.

Unexpectedly and interestingly, TC was found higher in lean fatty liver ($P < 0.001$, P-trend < 0.001), contrary to other measurements in this study. It supplied an important clue that lean fatty liver may be TC-dependent. Regarding the role of TC in the development of fatty liver, high-cholesterol diet induced NAFLD animals were less obese, but had greater levels of hepatic inflammation and fibrosis,[23] and human study showed TC was also a predictor of NAFLD in lean Chinese.[24] In a population-based study, dietary cholesterol intake rather than energy and carbohydrates (more common in obese) was found to be significantly higher in non-obese fatty livers.[25] As for the high TC to fatty liver prognosis, a popular opinion is that hypercholesterolemia is the major risk factor for atherosclerosis and cardiovascular diseases,[26] and high TC also may result in cholesterol-associated steatohepatitis.[27] Therefore, LDL lowering intervention or therapy should be considered as cornerstone for the reduction of fatty liver development.

Moreover, it is also necessary to note that the metabolic profile in fatty livers is progressive and age-related. With visualized data, all type of fatty liver showed nearly the same shape age-related patterns in term of prevalence of abnormal metrics as overweight and obesity. However, lean fatty liver at young age had more favorable metabolic profile but tend to reach the same as overweight/obesity at elder age with a higher speed of progression. This may indicate a "catch-up" effect of lean fatty liver in progressing metabolic dysfunction. This "catch-up" effect may be due to the fact that lean fatty liver had smaller buffer for metabolic dysfunction.[19] "Catch-up" effect can be testified in advanced metabolic disease such as diabetes which can be treated as a load test, for example, the same cardiometabolic profiles were found in both non-obese and obese fatty liver with diabetes.[28] In a study predicting carotid intima-media thickness and carotid plaque in ten years of age increasing, the lean fatty liver patients had a higher risk of carotid intima-media thickness and carotid plaque than obese fatty liver, which may be attributed to the accelerating development of cardiometabolic factors in lean NAFLD.[29] This hypothesis we proposed here also can explain the results from long-term follow-ups, in which lean fatty liver had no difference with obese fatty liver in diabetes, mortality, liver-related events, or cardiovascular events.[30,31] Due to the possible "catch-up" effects in lean fatty liver, the early stage of evaluation and intervention may be crucial for lean fatty liver management to slowdown the progress.

However, further cohort studies are warranted to directly test this so-called "catch-up" effect owned by lean fatty liver. Because the metabolic profile of fatty liver is age-dependent, age sub-type fatty liver may be taken into account in future studies. Furthermore, in this study, we found TC was reversely high in lean fatty liver after adjusting possible covariables, and its pathological implication needs further study to clarify. We also identified that LDL, the well-known risk factors of atherosclerosis and cardiovascular diseases, was also independent of BMI in the context of fatty liver, its role need further investigations.

There are some strengths of this study. First, this study is the first time to systematically describe the metabolic profile in fatty liver with multiple dimensions, which may give us insight into fatty liver. Second, this study had a big sample size, and these comparisons in other studies were inconsistent and robust in our study with this big sample. Third, the subjects covered a wide range of ages; this allowed us to have a bigger view of the metabolic profile and proposed the "catch-up" hypothesis in the progress of lean fatty liver.

However, we must admit that this study has some limitations. Firstly, we did not discriminate the aetiology of fatty liver, such as alcohol, hepatitis virus and another secondary hepatic steatosis. It is also the reason we did not use the term NAFLD/MAFLD in this study. Because NAFLD is a major part of fatty liver, it still can be referred to as NAFLD. Second, the subjects came from just a health care centre; it may not be representative of fatty liver in whole populations

in Chongqing city or other ethnic groups. Therefore, our findings should be explained with caution. Third, fatty liver was diagnosed by ultrasound, which cannot diagnose mild steatosis and may underestimate the prevalence of fatty liver. However, ultrasound is still widely used for steatosis definition in community-based studies, making our study comparable with other studies. Fourth, cardiometabolic or liver-related diseases were not included as outcomes. Therefore, we cannot evaluate the disease profiles. Fifth, this is a cross-sectional study, subjects at different age categories may have different demographic characteristics, therefore metabolic profiles by age categories may not present the natural history of fatty liver. Lastly, some important confounders such as diet, comorbidity, medication for lipids lowering or weight loss, or physical activity were not available in this study. The results of this study should be explained with caution.

Conclusions

The lean type of fatty livers at a younger age has a relatively favourable metabolic profile compared to overweight and obese fatty livers in blood pressure, insulin resistance, blood lipids, UA, and liver enzymes. However, NAFLD patients with lean phenotype had higher TC level compared to those with obesity/overweight. The "catch-up" effects may exist in young lean fatty liver to erase those metabolic differences between lean and obese fatty livers. The evaluation and intervention may be critical for young lean fatty liver management to slowdown the progress of metabolic abnormalities.

Abbreviations

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; GHB, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease.

Data Sharing Statement

The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy reasons.

Ethical Approval

The original data collection was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

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Disclosure

The authors report no conflicts of interest in this work.

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