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RESEARCH ARTICLE

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Independent markers of nonalcoholic fatty liver disease in a gentrifying population-based Chinese cohort

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Abstract

Background: Prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing in developing countries, but its causes are not known. We aimed to ascertain the prevalence and determinants of NAFLD in a new largely unmedicated population-based cohort from the rapidly gentrifying region of Pinggu, China.

Methods: We randomized cluster sampled 4002 Pinggu residents aged 26 to 76 years. Data from 1238 men and 1928 women without significant alcohol drinking or hepatitis virus B or C infection were analysed. NAFLD was defined using a liver-spleen ratio (L/S ratio) $\leq$1.1 on unenhanced abdominal computed tomography (CT) scanning.

Results: Of men and women, 26.5% and 20.1%, respectively, had NAFLD. NAFLD prevalence was highest in younger men and older women. In multivariate logistic regression models, higher body mass index, waist circumference, serum triglyceride, alanine transaminase, and haemoglobin A1c independently increased the odds of NAFLD in both men and women separately. Higher annual household income and systolic blood pressure for men and higher serum uric acid and red meat intake and lower physical activity levels for women also independently associated with higher odds of NAFLD. Individuals with L/S ratio $\leq$1.1 had linearly increasing rates of obesity, diabetes, and metabolic syndrome that paralleled fatty liver increase.

Conclusions: NAFLD is common in a gentrifying Chinese population particularly in younger men of high socioeconomic status and older women with sedentary behaviour who eat red meat. Demographic factors add independent risk of NAFLD above traditional metabolic risk factors. A CT L/S ratio of $\leq$1.1 identifies individuals at high risk of metabolic disease.

KEYWORDS

nonalcoholic fatty liver disease, diabetes, obesity, physical activity, red meat

Xianghai Zhou and Yufeng Li are joint first authors. Elizabeth K. Speliotes and Linong Ji are joint senior authors.

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disease that develops in the presence of more than 5% triglyceride content in the liver in the absence of excessive alcohol intake. NAFLD is a risk factor for both incident[1,2] and prevalent[3] cardiovascular disease independent of conventional risk factors. NAFLD also predisposes to cirrhosis[4] and hepatocellular carcinoma.[5] NAFLD prevalence has increased over the last 30 years particularly in developed and now developing countries worldwide[6,7]; causes of this increase in prevalence are only now being elucidated. The prevalence of NAFLD in the population based on histology is not known as a biopsy cannot be justified in otherwise healthy individuals. NAFLD estimates in the population have been determined using noninvasive markers of the disease such as alanine aminotransferase (ALT) or imaging, most commonly ultrasound. Both of these methods however have been shown to be highly inaccurate for quantitating NAFLD. Magnetic resonance spectroscopy (MRS) and magnetic resonance imaging quantify liver fat well but are cumbersome and expensive to implement clinically in large populations. Computed tomography (CT) allows for accurate quantification of liver fat while also being clinically available and cost-effective to implement in large populations to estimate the prevalence of this disease. A CT liver-spleen density ratio (L/S ratio) $\leq$1.1 corresponds to more than 30% liver steatosis found in a biopsy specimen among living donors for liver transplantation.[8] In small studies,[9-12] NAFLD has been associated with obesity and development of related metabolic diseases and some demographic and lifestyle factors, but whether those contribute to the disease independently of each other in large cohorts is not known. Further, the effects of rapid modernization associate with development of obesity and related metabolic disorders, but what components of that gentrification contribute to disease are not known.

Here, we use CT to measure liver fat in a largely unmedicated population-based cohort outside of Beijing in Pinggu, China. We chose this area as it has undergone gentrification and within a limited geographic area contains individuals with diverse exposures that may be able to give us insights into what determinants in developing regions contribute to higher levels of NAFLD. In this population with measured NAFLD, we also measured many metabolic and demographic variables and examined the relationship of these to NAFLD.

2 | MATERIALS AND METHODS

2.1 | Study population

We used two-stage cluster random sampling to recruit participants aged 25 to 74 years from 25 villages out of five towns and seven residents' committees out of one street in Pinggu district located in Beijing China, from March 2012 to May 2013. Five thousand four residents were invited, and 3350 initially participated.[13] In the second round, the 5004 originally selected residents were reinvited to participate, and 1579 residents were additionally invited between September 2013 to July 2014 for a total of 6583 invited residents. A total of 4002 individuals aged 26 to 76 years were enrolled, which gave a response rate of 60.8%. We excluded individuals who were hepatitis B or C positive (n = 139), had a history of hepatitis B infection (n = 1), had significant alcohol consumption (men >210 g/week or women >140 g/week[14]) (n = 656), were missing a CT scan (including four women who planned to conceive and three with positive β-human chorionic gonadotropin) (n = 18), or glucose (n = 5) or physical activity (PA) (n = 17) data. We analysed 3166 individuals with complete data.

The Pinggu metabolic disease study was approved by the ethics committees of Peking University Medical Center and University of Michigan. All participants gave written informed consent.

2.2 | Nonlaboratory assessments

Participants were interviewed by trained doctors and nurses in the local clinics. Height and weight were measured when participants stand without shoes and light clothing. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the middle point level between lower rib margin and the iliac crest. Blood pressure was measured three times after 10-minute resting, and the mean of the three measures was used. Education was divided into elementary school or lower, middle school, college, or higher education. Annual household income was divided into <25 000, $\geq$25 000 and <75 000, and $\geq$75 000 Chinese Yuan (CNY, 1000 CNY = 155 USD) and response as "do not know." Long-form International Physical Activity Questionnaire[15] was administered to classify the PA level. Participants reported the frequency and duration of walking, moderate and vigorous activities during work, transportation, domestic/yard work, and leisure time in the previous 7 days. PA scores expressed as metabolic equivalents (METs) minutes/week were calculated for intensity-specific PAs. PA level was classified into low, moderate, and high.[16] Smoking status was divided into nonsmoker, ex-smoker if smoking was stopped or averaged <1 cigarette daily, and current smoker if averaged $\geq$1 cigarette daily. An interviewer-administered 103-item food frequency questionnaire containing questions about meat and alcohol consumption was used. Participants reported the intake frequency and the amount of food during the past year on a daily, weekly, monthly, or yearly basis. Red meat intake was defined as the total amount of pork, beef, and mutton intake per week which was divided into low consumption and high consumption according to the median amount. Food frequency questionnaire (FFQ) was validated before the survey. There was a positive linear relationship between FFQ and 24-hour food recall for meat intake (Spearman Correlation 0.18) which indicates good agreement (Guan et al unpublished). For assessing alcohol consumption (g/week), ethanol content was assumed to be 5.3% by volume for beer, 12.9% by volume for wine, 30.8% by weight for low-alcohol liquor, and 50.1% by weight for high-alcohol liquor. Significant alcohol consumption was defined as >210 g/week in men and >140 g/week in women.[14] Individuals with significant alcohol consumption were excluded from the data analysis. Alcohol

consumption was categorized into 0, >0 and ≤140, >140, and ≤210 g/week in men and 0, >0 and ≤70, >70, and ≤140 g/week in women.

2.3 | Laboratory measurements

Blood samples were drawn in the morning after a 10 to 12-hour fast. Participants without known diabetes underwent a 75-g 2-hour oral glucose tolerance test, and those with known diabetes had fasting plasma glucose measured. Plasma glucose, serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), ALT, aspartate aminotransferase (AST), and uric acid were measured using an automated clinical chemistry analyser (UnicelDxC 800; Beckman Coulter, Miami, FL, USA). Haemoglobin A1c (HbA1c) was measured using cation-exchange high-pressure liquid chromatography (Adams A1c HA-8160; Arkray, Kyoto, Japan) which conforms to the Diabetes Control and Complications Trial standards. Serum hepatitis B virus surface antigen and hepatitis C antibodies were tested using an enhanced chemiluminescence assays (Ortho-Clinical Diagnostics, NJ, USA).

2.4 | Definition of diseases or conditions

Known diabetes was defined by a self-reported history of diabetes diagnosed by a doctor and/or on glucose-lowering treatment. Undiagnosed diabetes was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L and/or 2-hour plasma glucose (2-hPG) ≥11.1 mmol/L.[17] Impaired glucose tolerance (IGT) was defined as FPG < 7.0 mmol/L and 7.8 ≤ 2-hPG < 11.1 mmol/L. Impaired fasting glucose (IFG) was defined as 6.1 ≤ FPG < 7.0 mmol/L and 2-hPG < 7.8 mmol/L. Normal glucose tolerance was defined as FPG < 6.1 mmol/L and 2-hPG < 7.8 mmol/L.[17]

Overweight was defined as BMI between 23.0 and 27.49 kg/m^2 and obesity as BMI ≥ 27.5 kg/m^2 according to the World Health Organization Asian-specific BMI cutpoints.[18] According to the International Diabetes Federation criteria in 2005,[19] central obesity was defined by waist circumference ≥90 cm for men or ≥80 cm for women.[19] Metabolic syndrome was defined if central obesity plus any two of the following four components were present: (1) triglycerides ≥1.7 mmol/L, (2) HDL-C <1.03 mmol/L in men or <1.29 mmol/L in women, (3) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension, and (4) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes.[19]

2.5 | Abnormal CT scan and definition of NAFLD

Individuals underwent unenhanced abdominal CT scan using a 64-slice multidetector scanner (LightSpeed VCT, General Electric Healthcare, Milwaukee, WI, USA). Continuous 5-mm-thick slices (120 kVp, 120-150 mA) from the lung base to the pubic symphysis were acquired in the supine position. The Hounsfield units (HUs) of three 1-cm^2 areas from liver avoiding vessels and two areas in spleen were measured similar to what was done in the Framingham Heart Study.[20,21] The mean of the liver and spleen measurements was used to calculate the L/S ratios. NAFLD was defined as L/S ratio ≤1.1.[8]

2.6 | Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 22 (SPSS, Inc., Chicago, IL). Continuous variables with normal distribution were presented as means ± SD and compared using *t* tests. Variables with skewed distribution were presented as median (25th, 75th percentage) and compared using Mann-Whitney *U* tests. Categorical data were presented as number and percentage and compared using chi-squared tests. A multivariable logistic regression model was used to estimate the odds ratio and its 95% confidence interval (OR [95% CI]) of candidate factors for prevalent NAFLD. Interaction between annual house income and alcohol consumption, PA level or red meat intake in men, and interaction between postmenopausal status and PA level or red meat intake in women were examined. The difference was considered significant if the *P* value of interaction was $P < .05$.

3 | RESULTS

3.1 | NAFLD prevalence and associated factors

The prevalence of NAFLD was 26.5% (95% CI 24.1, 29.0), 20.1% (95% CI 18.4, 22.0), and 22.6% (95% CI 21.2, 24.1) in men, women, and men and women together in the overall study population, respectively. Individuals with NAFLD were more obese, hypertensive, hyperglycaemic, hyperuricaemic, and had a higher proportion of individuals with hypertriglycaemia and metabolic syndrome and a lower proportion of individuals with a high PA level. They had higher ALT and AST levels, and more individuals with NAFLD consumed red meat above the median level. A higher proportion of men with NAFLD had an annual household income ≥75 000 CNY. Women with NAFLD had a higher concentration of total cholesterol, higher proportion of postmenopausal status, and lower proportion of them had received a college or higher education (Table 1). Only 16.9% individuals with NAFLD (23.5% men and 11.3% women) had an abnormal ALT >40 U/L.

The prevalence of NAFLD in men aged 26 to 35, 36 to 45, 46 to 55, 56 to 65, and ≥66 years was 31.0%, 29.4%, 22.9%, 26.1%, and 23.1% (*P* for the category [P_{cat}] was .171), respectively, and in women, it was 17.5%, 14.0%, 19.9%, 25.9%, and 24.6% ($P_{cat} < .001$), respectively (Figure 1). Younger men aged ≤45 years have a higher prevalence than older men aged >45 years (30.1% vs 24.2%, $P = .021$), whereas younger women aged ≤45 years have a lower prevalence of NAFLD compared with older women aged >45 years (15.2% vs 22.8%, $P < .001$). Men who consumed more red meat had a higher prevalence of NAFLD only in 46 to 55-year age group ($P = .003$). Women who consumed more or less red meat had a similar prevalence of NAFLD in each age group. Alcohol drinkers and nondrinkers had a similar prevalence of NAFLD in each age group in men (Figure 2). The prevalence of NAFLD between women alcohol drinkers

TABLE 1 Characteristics of men and women according to with or without nonalcoholic fatty liver disease

	Men				Women			
	Total	Non-NAFLD	NAFLD	*P* Value	Total	Non-NAFLD	NAFLD	*P* Value
N, %	1238	910 (73.5)	328 (26.5)		1928	1540 (79.9)	388 (20.1)	
Age, y	49.1 ± 12.4	49.6 ± 12.3	47.9 ± 12.5	.034	50.0 ± 11.6	49.5 ± 11.6	51.8 ± 11.4	<.001
BMI, kg/m^2	26.1 ± 3.8	25.6 ± 3.5	27.5 ± 4.1	<.001	26.1 ± 4.0	25.6 ± 3.7	28.0 ± 4.2	<.001
BMI category, kg/m^2				<.001				<.001
<23.0	254 (20.5)	211 (23.2)	43 (13.1)		426 (22.1)	381 (24.7)	45 (11.6)	
23.0-27.49	564 (45.6)	442 (48.6)	122 (37.2)	.122	856 (44.4)	722 (46.9)	134 (34.5)	.014
≥27.5	420 (33.9)	257 (28.2)	163 (49.7)	<.001	646 (33.5)	437 (28.4)	209 (53.9)	<.001
Waist circumference, cm	89.1 ± 10.3	87.9 ± 9.8	92.7 ± 10.7	<.001	84.3 ± 10.8	82.9 ± 10.1	90.0 ± 11.5	<.001
≥90 cm in men or ≥80 cm in women	607 (49.0)	395 (43.4)	212 (64.6)	<.001	1241 (64.4)	928 (60.3)	313 (80.7)	<.001
Systolic blood pressure, mmHg	130 ± 16	129 ± 16	133 ± 17	<.001	128 ± 19	127 ± 19	133 ± 19	<.001
Diastolic blood pressure, mmHg	80 ± 11	79 ± 11	82 ± 12	.001	76 ± 11	76 ± 10	79 ± 12	<.001
Glucose tolerance				<.001				<.001
Normal	673 (54.4)	546 (60.0)	127 (38.7)		1107 (57.4)	980 (63.6)	127 (32.7)	
IGT/IFG	301 (24.3)	206 (22.6)	95 (29.0)	<.001	507 (26.3)	370 (24.0)	137 (35.3)	<.001
Previously undiagnosed diabetes	117 (9.5)	65 (7.1)	52 (15.9)	<.001	138 (7.2)	76 (4.9)	62 (16.0)	<.001
Known diabetes	147 (11.9)	93 (10.2)	54 (16.5)	<.001	176 (9.1)	114 (7.4)	62 (16.0)	<.001
FPG, mmol/L	6.3 ± 1.9	6.2 ± 1.8	6.6 ± 2.0	<.001	5.9 ± 1.5	5.8 ± 1.3	6.5 ± 1.9	<.001
HbA1c, %	5.9 ± 1.0	5.8 ± 1.0	6.1 ± 1.1	<.001	5.8 ± 0.9	5.7 ± 0.8	6.2 ± 1.1	<.001
Total cholesterol, mmol/L	4.8 ± 0.9	4.8 ± 0.9	4.8 ± 1.1	.368	5.0 ± 1.0	4.9 ± 1.0	5.2 ± 1.0	<.001
Triglycerides ≥1.7 mmol/L	410 (33.1)	254 (27.9)	156 (47.6)	<.001	488 (25.3)	308 (20.0)	180 (46.4)	<.001
HDL-C, mmol/L	1.05 ± 0.28	1.08 ± 0.28	0.99 ± 0.26	<.001	1.21 ± 0.29	1.23 ± 0.28	1.13 ± 0.30	<.001
LDL-C, mmol/L	2.83 ± 0.81	2.83 ± 0.80	2.83 ± 0.83	.994	2.92 ± 0.82	2.90 ± 0.81	3.01 ± 0.85	.017
ALT, U/L	23 (17, 31)	22 (17, 28)	28 (20, 40)	<.001	17 (14, 23)	17 (14, 21)	23 (16, 31)	<.001
ALT by quartile, U/L				<.001				<.001
<17 (men) or <14 (women)	242 (19.5)	201 (22.1)	41 (12.5)		383 (19.9)	348 (22.6)	35 (9.0)	
17-22 (men) or 14-16 (women)	356 (28.8)	294 (32.3)	62 (18.9)	.880	473 (24.5)	408 (26.5)	65 (16.8)	.038
23-30 (men) or 17-22 (women)	324 (26.2)	233 (25.6)	91 (27.7)	.002	583 (30.2)	489 (31.8)	94 (24.2)	.002
≥31 (men) or ≥23 (women)	316 (25.5)	182 (20.0)	134 (40.9)	<.001	489 (25.4)	295 (19.2)	194 (50.0)	<.001
AST, U/L	22 (19, 25)	21 (18, 25)	23 (19, 28)	<.001	20 (18, 24)	20 (18, 23)	22 (19, 27)	<.001
Uric acid, μmol/L	322 ± 78	317 ± 76	337 ± 83	<.001	249 ± 62	241 ± 59	278 ± 65	<.001
Metabolic syndrome	503 (40.6)	314 (34.5)	189 (57.6)	<.001	925 (48.0)	650 (42.2)	275 (70.9)	<.001
Postmenopausal status	-	-	-	-	977 (50.7)	745 (48.4)	232 (59.8)	<.001
Annual household income, CNY				.001				.926
<25 000	178 (14.4)	145 (15.9)	33 (10.1)		429 (22.3)	341 (22.1)	88 (22.7)	
25 000-74 999	688 (55.6)	514 (56.5)	174 (53.0)	.061	1061 (55.0)	853 (55.4)	208 (53.6)	.691
≥75 000	349 (28.2)	232 (25.5)	117 (35.7)	<.001	388 (20.1)	306 (19.9)	82 (21.1)	.827
Did not report	23 (1.9)	19 (2.1)	4 (1.2)	.894	50 (2.6)	40 (2.6)	10 (2.6)	.932
Education				.119				.003
Elementary school or lower	153 (12.4)	118 (13.0)	35 (10.7)		475 (24.6)	360 (23.4)	115 (29.6)	
Middle school	864 (69.8)	641 (70.4)	223 (68.0)	.442	1197 (62.1)	959 (62.3)	238 (61.3)	.051
College or higher	221 (17.9)	151 (16.6)	70 (21.3)	.064	256 (13.3)	221 (14.4)	35 (9.0)	.001
Physical activity level				.021				.064
Low	176 (14.2)	119 (13.1)	57 (17.4)		106 (5.5)	86 (5.6)	20 (5.2)	

(Continues)

TABLE 1 (Continued)

	Men				Women			
	Total	Non-NAFLD	NAFLD	*P* Value	Total	Non-NAFLD	NAFLD	*P* Value
Moderate	484 (39.1)	346 (38.0)	138 (42.1)	.335	735 (38.1)	567 (36.8)	168 (43.3)	.358
High	578 (46.7)	445 (48.9)	133 (40.5)	.013	1087 (56.4)	887 (57.6)	200 (51.5)	.905
Smoking[a]				.317				-
Nonsmoker	306 (24.7)	221 (24.3)	85 (25.9)		1909 (99.0)	1521 (98.8)	388 (100.0)	
Ex-smoker	237 (19.1)	167 (18.4)	70 (21.3)	.653	3 (0.2)	3 (0.2)	0 (0.0)	-
Current smoker	695 (56.1)	522 (57.4)	173 (52.7)	.336	16 (0.8)	16 (1.0)	0 (0.0)	-
Red meat intake by median (g/wk)				.062				.037
≥325 (men) or ≥200 (women)	621 (50.2)	442 (48.6)	179 (54.6)		1022 (53.0)	798 (51.8)	224 (57.7)	
Alcohol drinking (g/wk)				.775				.379
0	412 (33.3)	308 (33.8)	104 (31.7)		1741 (90.3)	1386 (90.0)	355 (91.5)	
0.1-140 for men or 0.1-70 for women	695 (56.1)	506 (55.6)	189 (57.6)	.477	164 (8.5)	137 (8.9)	27 (7.0)	.231
140.1-210 for men or 70.1-140 for women	131 (10.6)	96 (10.5)	35 (10.7)	.736	23 (1.2)	17 (1.1)	6 (1.5)	.503

Note. Data were expressed as means ± SD for continuous data with normal distribution, median (25th, 75th percentage) for continuous data with skewed distribution, and n (%) for categorical data. *P* value was for the difference between the non-NAFLD and NAFLD using *t* test for normal distributed data, Mann-Whitney *U* test for skewed distributed data, and chi-squared test for categorical data. For multicategorical variables, *P* value taken from univariate logistic regression models comparing the categories with the lowest category in each variable.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; IGT/IFG, impaired glucose tolerance and/or impaired fasting glucose; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNY, Chinese Yuan.

[a]Comparing between categories was not performed in women because of the small number of women smokers.

and nondrinkers in each age group was not compared because of the small number of women drinkers in some categories.

3.2 | Cardiovascular risk factors across the spectrum of NAFLD

Men and women were categorized into groups according to L/S ratio. There were 181 (14.6%), 119 (9.6%), 177 (14.3%), 252 (20.4%), 181 (14.6%), 135 (10.9%), 92 (7.4%), and 101 (8.2%) men with L/S ratio >1.5, >1.4 to ≤1.5, >1.3 to ≤1.4, >1.2 to ≤1.3, >1.1 to ≤1.2, >1.0 to ≤1.1, >0.9 to ≤1.0, and ≤0.9, respectively, and for women, they were 286 (14.8%), 232 (12.0%), 346 (17.9%), 370 (19.2%), 306 (15.9%), 181 (9.4%), 81 (4.2%), and 126 (6.5%), respectively.

The prevalence of metabolic complications of obesity, diabetes, and metabolic syndrome began to increase at a cut-off of L/S ratio ≤1.1 in both men and women (Figure 3).

3.3 | Factors independently associated with NAFLD

Increased age was associated with a decreased risk of having NAFLD in men (OR 0.87 [95% CI 0.77-0.99], model 1 in Table 2) and an increased risk in women (1.22 [1.09-1.36], model 1 in Table 2). However, the association was no longer significant after adjustment for BMI or waist circumference, systolic blood pressure HbA1c, total cholesterol, hypertriglycerides, and uric acid (model 2 in Table 2, model 1 in Table S1). In the full model (model 3 in Table 2, model 2 in Table S1) that was fitted with postmenopausal status (for women), annual household income, education background, PA level, smoking status (for men), red meat intake and alcohol drinking, increased BMI, waist circumference, HbA1c, elevated serum triglycerides, and ALT were independently associated with the presence of NAFLD in both men and women. Increased systolic blood pressure and annual household income ≥75 000 CNY were independently associated with the presence of NAFLD in men, whereas increased uric acid, low PA level, and red meat intake ≥200 g/week were independently associated with the presence of NAFLD in women. Low/moderate alcohol consumption did not statistically significantly increase or decrease the odds of NAFLD in this population (Table 2).

We tested whether annual house income and alcohol consumption ($P = .804$), PA level ($P = .425$), or red meat intake ($P = .550$) in men and postmenopausal status and PA level ($P = .449$) or red meat intake ($P = .096$) in women nonlinearly increased the prevalence of NAFLD using interaction modelling, but none were statistically significant.

There were 10 women and 5 men who had other data except for CT scan. As compared with the 3166 participants included in the study, participants who did not perform CT scan were younger (40.5 vs 49.7 years, $P = .003$). No significant differences were found in BMI (25.2 vs 26.1 kg/m^2, $P = .344$), systolic blood pressure (122 vs 129 mmHg, $P = .122$), and fasting blood glucose (5.9 vs 6.1 mmol/L, $P = .662$).

4 | DISCUSSION

Our study showed that 26.5% men and 20.1% women had NAFLD in Pinggu, China. Men aged ≤45 years or women aged >45 years were

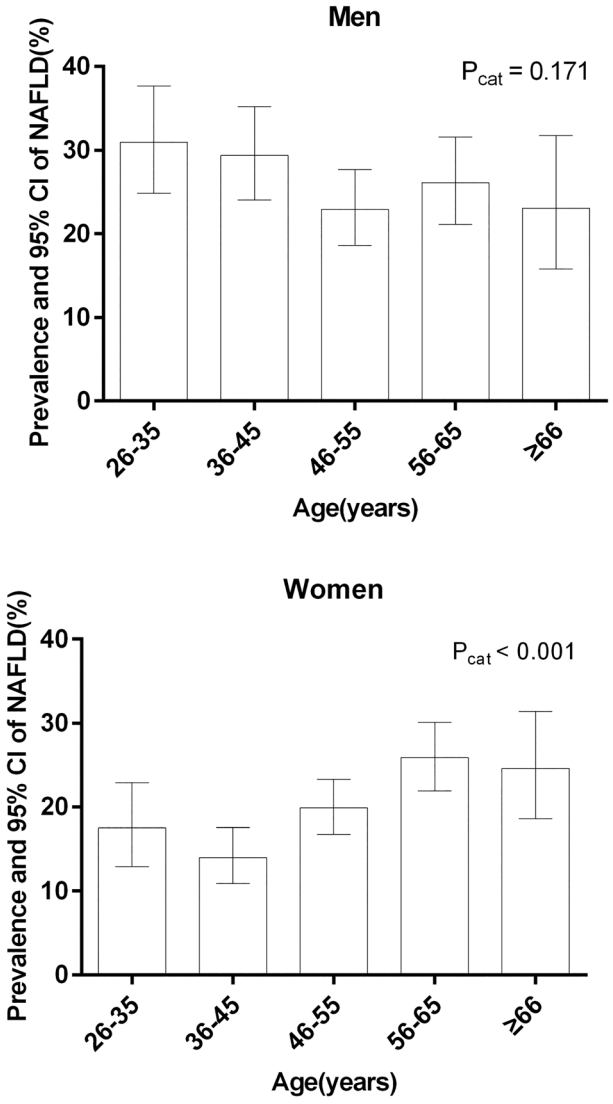

FIGURE 1 Prevalence of nonalcoholic fatty liver disease (NAFLD) and 95% confidence interval (CI) according to age in men and women. P_{cat} was for the difference among age groups using a chi-squared test

more likely to have NAFLD than their older/younger counterparts, respectively. Obesity, hyperglycaemia, hypertriglycaemia, and high ALT concentration were all independently associated with the presence of NAFLD in both men and women. High annual household income and systolic blood pressure for men and low physical activity level and high serum uric acid and consumption of red meat for women were also independent risk factors for the presence of NAFLD.

Our finding that NAFLD is prevalent in an Asian population and associates with metabolic diseases is consistent with other reported studies.[21-23] In a Caucasian population, the Framingham Offspring and the Third Generation study, the prevalence of fatty liver detected by CT was 19%, 15%, and 17% in men, women, and the whole study population, respectively.[21] Individuals with NAFLD in Pinggu had a lower BMI on average than individuals in Framingham but were about the same average age.[21] This result is consistent with observations that individuals of Asian ancestry develop metabolic disease at lower BMIs than individuals of European ancestry.[24] We found that obesity, hyperglycaemia, high blood pressure, and hypertriglycerides were all associated with NAFLD as also noted in Caucasian[21,25] and Asian[23,26] populations. Our study, however, also identified demographic and dietary factors as contributing to the disease independently of metabolic factors. In particular, we found that high intake of red meat was independently associated with NAFLD in women. Two small sample-sized studies reported that a higher intake of meat[11] or red meat[27] increased the risk of the presence of NAFLD. However, these two studies did not take gender into consideration when observing the association between red meat intake and NAFLD.

To our knowledge, this is the first large population-based study in Chinese people using unenhanced abdominal CT scan to detect NAFLD. Our findings that fatty liver is prevalent and associates with metabolic disease support that CT can reliably measure NAFLD in an Asian population. CT-based quantitation of liver fat is correlated (r = 0.92) with histologic-based fatty infiltration.[28] It is less expensive and clinically more widely available than proton MRS currently and less operator dependent and accurate than ultrasound.[29] The L/S ratio provided a more accurate evaluation for liver fat content than ultrasound. Further, we show that only 16.9% of those with NAFLD had abnormally elevated ALT (>40 U/L) suggesting that ALT is not a good marker of the disease despite its widespread use.

From a public health perspective, our results suggest that screening, prevention, and intervention strategies for NAFLD should be focused on young and middle-aged men as well as elder women who were at a higher risk of NAFLD in this cohort. Our data demonstrate that an L/S ratio $\leq$1.1 is an appropriate cut-off point for discriminating a population with a higher prevalence of metabolic disorders in both men and women. Thus, screening for metabolic disorders in individuals found to have a low L/S ratio on abdominal CT should be considered.

Moreover, our study provides current information on the prevalence of NAFLD in men and women from a largely unmedicated general population in mainland China. In this study, although men and women had similar prevalence of obesity defined by BMI, NAFLD is more prevalent in men than in women, consistent with one previous report.[22] Such a result is consistent with the fact that a higher proportion of men than women had metabolic complications of obesity, specifically hypertriglycaemia and diabetes. In several studies,[26,30,31] the prevalence of NAFLD increased as age increased in women, and only one study among the above[31] showed the same result in men. The other two studies[26,30] including ours showed the peak prevalence of NAFLD in young or middle-aged men. The reason why the peak prevalence of NAFLD differs between men and women is not clear. In our study, the peak in NAFLD prevalence in men corresponded with increased sedentary behaviour, increased alcohol consumption, increased eating of red meat, and high household income. Only high household income, however, independently associated with NAFLD in men in a multivariate model. This variable although clearly not pathophysiologically plausible may best capture behaviours such as alcohol consumption, increased sedentary behaviour, and eating red meat that could be more directly contributing to NAFLD pathophysiology in men. Although we identified distinct unique demographic

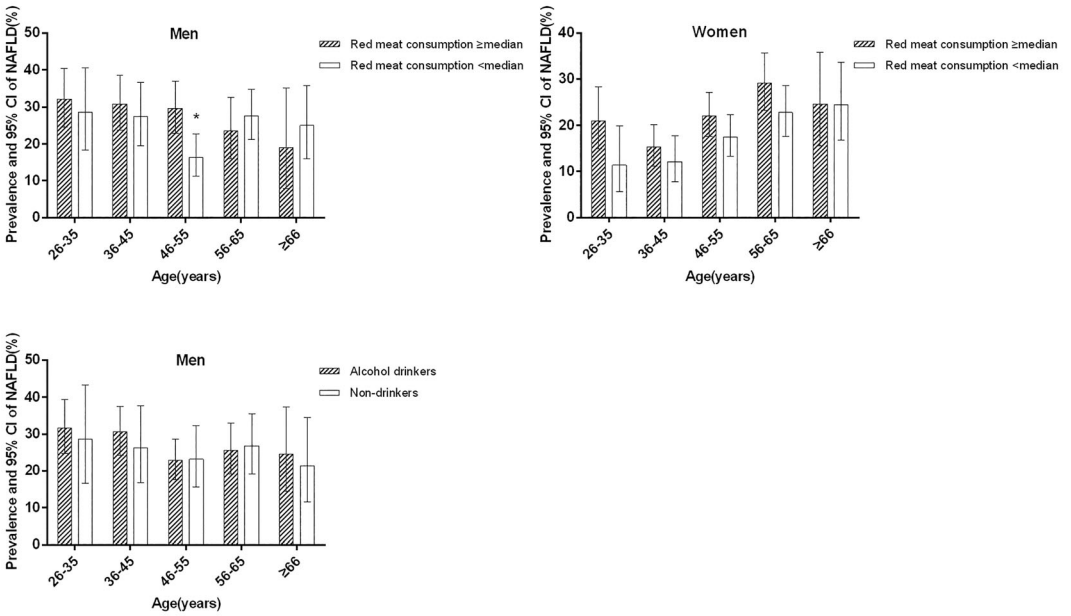

FIGURE 2 Prevalence of nonalcoholic fatty liver disease (NAFLD) by red meat consumption and alcohol drinking according to age and sex. Red meat consumption ≥ median indicates ≥325 g/w for men and ≥200 g/w for women; *P = .003 for the difference between red meat consumption ≥ median and < median in men ages 45 to 55

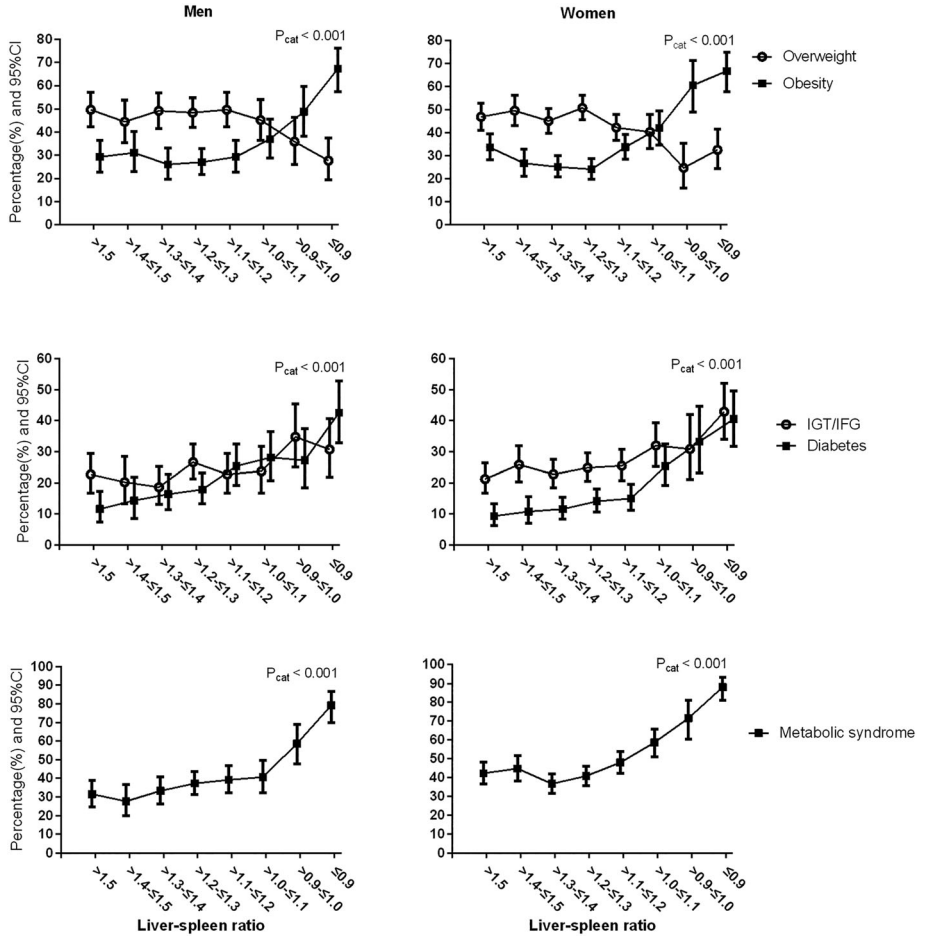

FIGURE 3 Percentage of metabolic disorders in men and women according to liver-spleen ratio. Overweight indicates body mass index (BMI) 23.0 to 27.49 kg/m^2, and obesity indicates BMI ≥27.5 kg/m^2; IGT/IFG, impaired glucose tolerance and/or impaired fasting glucose; P_{cat} was for the difference among liver-spleen ratio groups using a chi-squared test

TABLE 2 Odds ratio (95% CI) for nonalcoholic fatty liver disease of candidate factors corresponding to a one standard deviation increase in continuous variables and categorical data as indicated using logistic regression analysis

	Men			Women		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age, y	0.87 (0.77, 0.99)	1.00 (0.86, 1.17)	1.02 (0.86, 1.21)	1.22 (1.09, 1.36)	0.88 (0.76, 1.03)	0.84 (0.66, 1.06)
BMI, kg/m^2		1.26 (1.08, 1.47)	1.23 (1.05, 1.44)		1.30 (1.13, 1.48)	1.27 (1.11, 1.45)
Systolic blood pressure, mmHg		1.18 (1.03, 1.36)	1.22 (1.05, 1.41)		1.05 (0.91, 1.21)	1.07 (0.92, 1.24)
HbA1c, %		1.26 (1.11, 1.44)	1.26 (1.11, 1.44)		1.28 (1.15, 1.44)	1.29 (1.15, 1.44)
Total cholesterol, mmol/L		0.89 (0.78, 1.02)	0.90 (0.78, 1.03)		1.00 (0.88, 1.14)	1.00 (0.88, 1.13)
Triglycerides ≥1.7 vs <1.7 mmol/L		1.60 (1.19, 2.15)	1.58 (1.17, 2.13)		2.15 (1.65, 2.81)	2.13 (1.62, 2.79)
ALT, U/L						
<17 (men) or <14 (women)		1.00	1.00		1.00	1.00
17-22 (men) or 14-16 (women)		0.86 (0.55, 1.35)	0.85 (0.54, 1.33)		1.28 (0.81, 2.02)	1.28 (0.81, 2.02)
23-30 (men) or 17-22 (women)		1.37 (0.88, 2.12)	1.38 (0.89, 2.14)		1.17 (0.75, 1.81)	1.16 (0.75, 1.81)
≥31 (men) or ≥23 (women)		2.29 (1.46, 3.58)	2.30 (1.46, 3.62)		3.56 (2.34, 5.42)	3.57 (2.33, 5.47)
Uric acid, μmol/L		1.14 (0.99, 1.31)	1.13 (0.98, 1.31)		1.44 (1.27, 1.63)	1.44 (1.27, 1.64)
Postmenopausal status yes vs no			-			1.06 (0.70, 1.58)
Annual household income, CNY, n (%)						
<25 000			1.00			1.00
25 000-74 999			1.36 (0.85, 2.18)			1.05 (0.76, 1.46)
≥75 000			1.96 (1.15, 3.34)			1.41 (0.91, 2.18)
Did not report			0.70 (0.20, 2.39)			0.92 (0.40, 2.10)
Education						
Elementary school or lower			1.00			1.00
Middle school			0.73 (0.45, 1.19)			0.86 (0.61, 1.21)
College or higher			0.79 (0.43, 1.46)			0.58 (0.32, 1.06)
Physical activity level						
High			1.00			1.00
Moderate			1.30 (0.86, 1.96)			1.23 (0.70, 2.18)
Low			1.05 (0.78, 1.43)			1.35 (1.04, 1.75)
Smoking						
Nonsmoker			1.00			-
Ex-smoker			1.04 (0.70, 1.56)			-
Current smoker			0.92 (0.66, 1.27)			-
Red meat intake ≥325 vs <325 (men) or ≥200 vs <200 (women) g/wk			1.00 (0.76, 1.33)			1.41 (1.09, 1.82)
Alcohol drinking, g/wk						
0			1.00			1.00
0.1-140 for men or 0.1-70 for women			0.93 (0.69, 1.27)			0.91 (0.57, 1.46)
140.1-210 for men or 70.1-140 for women			0.98 (0.60, 1.59)			1.33 (0.45, 3.86)

Note. Model 1 fitted with age. Model 2 fitted with model 1 + BMI, systolic blood pressure, HbA1c, total cholesterol, triglycerides, ALT, and uric acid. Model 3 fitted with model 2 + postmenopausal status (for women), annual house income, education level, physical activity level, smoking status (for men), red meat intake, and alcohol consumption.

Abbreviations: BMI, body mass index; HbA1c, haemoglobin A1c; ALT, alanine aminotransferase; CNY, Chinese Yuan.

determinants that independently correlated with NAFLD in men versus women, we cannot rule out that biological variables also contributed to the differences between men and women and can be studied through future work on the genetics of NAFLD in this population.

Strength of the current study includes that it is the largest nonmedicated population-based study using CT scanning to measure NAFLD in Asia. The study is also contemporary and focuses on a region undergoing rapid gentrification which allowed us to capture a wide diversity of exposures to be able to identify demographic and dietary factors that also associate with NAFLD. Limitations include that this region may not be representative of all of China and that based on cross-sectional data, we cannot infer causality between associated factors and NAFLD. Although we excluded individuals with excess alcohol drinking from the analysis and controlled for any residual alcohol consumption using regression, we cannot rule out that there was under-reporting of drinking which may have contributed to fatty liver on CT scanning. We do not see a protection from development of fatty liver with low levels of alcohol consumption as some have reported.[32]

In conclusion, we found that 26.5% men and 20.1% women had NAFLD in Pinggu, China. NAFLD was independently associated with obesity, hyperglycaemia, hypertriglycaemia, and elevated ALT in both men and women. Higher annual household income and blood pressure for men and higher serum uric acid, lower physical activity level, and higher red meat intake for women were also independently associated with NAFLD in multivariate models. An L/S ratio $\leq$1.1 indicated a high risk of metabolic disorders in general populations, and individuals with such findings on CT scanning may want to be screened for concomitant metabolic disease.

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CONFLICT OF INTEREST

The authors have declared no conflict of interests.

AUTHOR CONTRIBUTIONS

Xianghai Zhou—drafting of the manuscript, analysis and interpretation of data, and approved final submission. Yufeng Li—acquisition of data and approved final submission. Xiuying Zhang—acquisition of data and approved final submission. Ying Ying Guan—acquisition of data and approved final submission. Yindra Puentes—acquisition of data and approved final submission. Fang Zhang—analysis and interpretation of images and approved final submission. Elizabeth K. Speliotes—study concept and design, critical revision of the manuscript, and approved final submission. Linong Ji—study concept and design, critical revision of the manuscript, approved final submission, study supervision, and obtained funding.

All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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