Original Article

Higher consumption of animal organ meat is associated with a lower prevalence of nonalcoholic steatohepatitis

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Background: Animal organ meat (offal) is a food with high nutrient density that is popular in different parts of the world, but its relationship with nonalcoholic steatohepatitis (NASH) is unclear. We aimed to examine whether daily animal organ meat consumption is associated with the presence of NASH in individuals with nonalcoholic fatty liver disease (NAFLD).

Methods: A total of 136 Chinese adults with biopsy-proven NAFLD were included. Definite NASH was defined as NAFLD activity score ≥4 and at least one point for steatosis, ballooning, and lobular inflammation. Daily animal organ meat consumption was estimated using a self-administered validated food frequency questionnaire. Logistic regression analysis was performed to assess the association between animal organ meat intake and liver disease severity.

Results: The 136 participants (80.9% men) of the study had a mean ± standard deviation (SD) age of 39.0±12.5 years and body mass index of 27.4±3.6 kg/m^2. Prevalence of definite NASH was 65.4%. Daily median organ meat consumption was 1.30 g/1,000 kcal. Animal organ meat consumption was inversely associated with the presence of NASH even after adjustment of demographics, lifestyle variables, metabolic and dietary factors, as well as liver fibrosis stage; adjusted-odds ratios (95% confidence intervals) for NASH were 0.15 (0.03, 0.69) for the highest tertile and 0.18 (0.05, 0.70) for the medium tertile, compared to the lowest (reference) tertile of animal organ meat intake (P value for trend =0.024).

Conclusions: Our results suggest for the first time that higher animal organ meat consumption is associated with a lower prevalence of NASH in Chinese individuals with biopsy-proven NAFLD.

Keywords: Nonalcoholic fatty liver disease (NAFLD); nonalcoholic steatohepatitis (NASH); diet; organ meat; red meat; metabolic dysfunction-associated fatty liver disease (MAFLD)

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Introduction

Nonalcoholic fatty liver disease (NAFLD) and its progressive form nonalcoholic steatohepatitis (NASH) are recognized causes of cirrhosis and hepatocellular carcinoma (1). Convincing evidence indicates that NAFLD is not only associated with a greater risk of developing liver-related complications, but also with an increased risk of cardiovascular disease (CVD) (2) and chronic kidney disease (CKD) (3). Considering that China has experienced an unexpectedly rapid increase in the burden of NAFLD in recent years (4), and China contains almost 20% of the global population, there is an urgent need for effective ways to prevent this common and burdensome liver disease.

Lifestyle modifications, including a Mediterranean diet, are effective when treating NAFLD or NASH (5). Animal organ meat (offal) is considered similar to red meat (skeletal muscle) as a foodstuff, because it contains nutrients similar to red meat, such as proteins, zinc, iron, saturated fat and cholesterol. Unlike fish or beans, red meat is often considered to be unhealthy, mainly because of its high content of saturated fats (6), cholesterol (7), and heme-iron (8). However, animal organ meat is a more nutrient dense food than most plant foods and skeletal muscle, and also provides high quantities of vitamin E, folic acid, biotin, and n-3 fatty acids (9). The progression from NAFLD to NASH is mainly related to increased oxidative stress, inflammatory response and mitochondrial dysfunction (10,11). Mitochondrial dysfunction is one of the main cellular alterations that explains the development of NASH (12). Increasing evidence also suggests that vitamin E, folic acid, biotin, n-3 fatty acids and docosahexaenoic acid and hydroxytyrosol co-administration can attenuate systemic chronic inflammation and oxidative stress and prevent mitochondrial dysfunction (12-17). The reported potential hepato-protective effects of these factors may highlight a strategy for focusing on foods that are rich in these factors to ameliorate risk of NASH.

In the past decade, several studies have attempted to establish an association between red meat intake and risk of incident NAFLD. For example, a nested case-control study conducted in African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites showed that higher dietary intakes of red meat and processed red meat were associated with a higher risk of NAFLD (18). A meta-analysis of observational studies also reported a significant association between higher red meat consumption and risk of NAFLD in seven homogeneous cross-sectional studies and a case-control study from the United States, Israel, South Korea and China (19).

Differences in daily meat consumption between countries can be substantial because of differences in either meat availability or dietary habits (20). In the Middle, East and West of China, daily meat consumption is markedly different in these regions (21). In fact, people in different countries or regions have different levels of daily meat consumption, which may lead to inconsistent or even opposite results in studies investigating the relationship between daily meat consumption and risk of certain chronic diseases, such as, for example, the relationship between red meat consumption and CVD. Although most of the previously published studies have shown that higher red meat consumption is a risk factor for CVD in Western countries, the results obtained from Asian studies have been conflicting (22,23). For example, a community-based cohort study showed an inverse association between unprocessed red meat consumption and cardiac mortality in Japanese individuals (23).

Given that animal organ meat (offal) is widely consumed in China, and there is a scarcity of studies available that have investigated the association between animal organ meat consumption and risk of having NASH, we aimed to investigate whether animal organ meat consumption is associated with the presence of NASH in Chinese adults with biopsy-proven NAFLD. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-468/rc).

Methods

Study population

In this cross-sectional study, all participants were recruited at the First Affiliated Hospital of Wenzhou Medical University (China) from a well characterized cohort of individuals [namely the Prospective Epidemic Research Specifically of NASH (PERSONS) cohort (24,25)], who consecutively attended our Liver clinic for suspected NAFLD from April 2018 to January 2020. From an initial sample of 209 adults with suspected NAFLD (mainly based on the evidence of hepatic steatosis on imaging techniques and/or persistently elevated serum liver enzyme levels), we subsequently excluded 73 individuals for the following main reasons: missing self-administered food frequency questionnaire (FFQ) data (n=15), positivity for serum

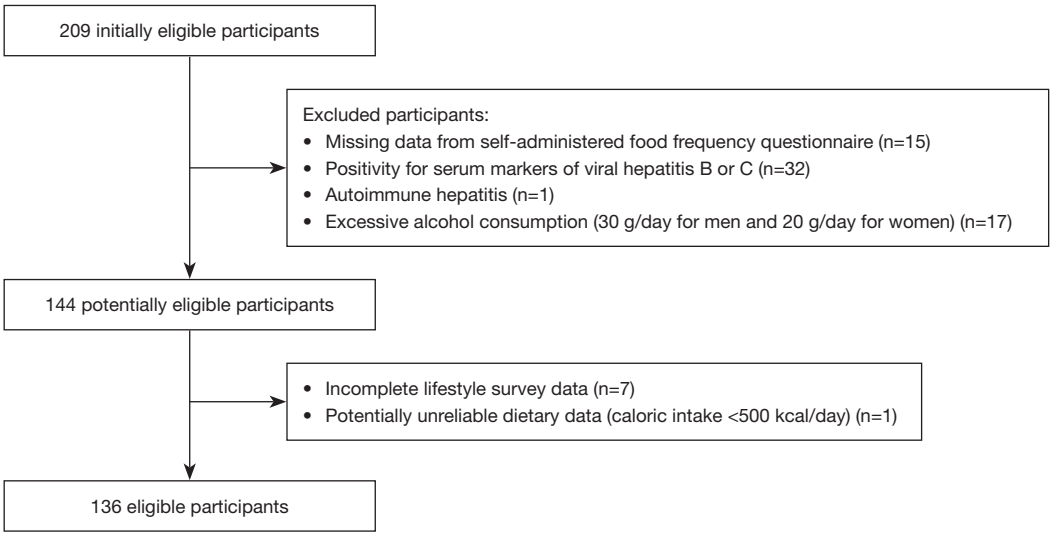

Figure 1 The flow-chart of the study.

markers of viral hepatitis B or C (n=32), autoimmune hepatitis (n=1), excessive alcohol consumption (defined as 30 g/day for men and 20 g/day for women) (n=17), incomplete lifestyle survey data (n=7), or extremely low calorie intake (defined as less than 500 kcal/day) (n=1). As a consequence of these exclusion criteria (*Figure 1*), a total of 136 adults with biopsy-proven NAFLD were included in the final analysis.

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (Issuing Number 2016-246). The protocol conformed to the ethical guidelines of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each participant included in the study.

Liver histology

Liver histology specimens were assessed according to the NASH-Clinical Research Network (CRN) Scoring System (26) as described in detail previously (27). The NAFLD activity score (NAS) was calculated as the sum of three histological components, including steatosis (grades 0–3), ballooning (grades 0–2), and lobular inflammation (grades 0–3). Fatty liver was histologically defined by the presence of more than 5% of steatotic hepatocytes. Individuals with NAS score ≥4 and at least one point for steatosis, ballooning, or lobular inflammation were diagnosed as having definite NASH (28). Stages of hepatic fibrosis were graded from zero to 4, according to the Brunt's histological criteria (26).

Dietary assessment

Data on dietary intake were obtained from a self-administered FFQ, which was assembled by the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention and tailored for the Chinese population, which was composed of 118 items of food with specified serving sizes. The reliability and validity of the FFQ were tested on 300 Chinese adults (50% men) in Beijing, Jiangsu for 1 year. The results showed that assessment of food consumption and nutrient intake by the questionnaire were highly reproducible (29). The FFQ from Chinese Center for Disease Control and Prevention has also provided new dietary evaluation methods for large-scale epidemiological studies in China, such as the Chinese Health and Nutrition Survey (30).

In China, the meat of animal organs that people eat are mainly animal viscera, for example, heart, lung, stomach, liver, large intestine, small intestine or kidney (31). Assessment of animal organ meat intake in the FFQ included seven specific items: (I) liver; (II) kidney; (III) heart; (IV) tripe; (V) intestine; (VI) gizzard; and (VII) other animal organ meat. Animal organ meat intake was calculated by the summation of the intake of these 7 items. Trained registered dieticians asked each participant the FFQ questions in person. The FFQ assessed the average consumption frequency of each food item over the past year

in terms of the number of specified serving sizes consumed per day/week/month, less than once a month, or never. The energy and nutrient components of each food item were calculated based on the Chinese Food Composition Table (9). Food item intake was calculated by multiplying the frequency of consumption per day by the portion size of each food item. Participants with incomplete or unreliable FFQs, defined as either a daily caloric intake of less than 500 or more than 7,500 kcal/day, were excluded. As all self-administered FFQs can be subject to measurement error, we used the nutrient density method for energy adjustments of dietary variables and alcohol. Food intake was presented as grams per 1,000 kcal (32). One gram of alcohol equals 7 kcal, hence, we calculated the energy percent of alcohol (E%) as follows = [total alcohol intake (g) × 7/total kcal intake] × 100 (32).

Additionally, to account for confounding by overall dietary quality, the Chinese Diet Balance Index (DBI) was also derived from the FFQs and added to multivariable regression models. According to the "Chinese Dietary Guidelines" and "Chinese Food Pagoda", the DBI selects eight food-based components, including the intake of cereals, vegetables and fruits, dairy products and soybean, animal food, alcohol, salt, oil as well as dietary variety. Cereals, meat, poultry and eggs are recommended to "eat in moderation" in the guidelines. If the intake is lower than the recommended amount, the value is negative; if the intake is higher than the recommended amount, the value is positive; otherwise, the value is 0. Vegetables, fruits, dairy products, beans and seafood are recommended to "eat more" or "eat often" in the guideline, so there is no upper limit. If the intake is insufficient, the value is negative; otherwise, it is 0. Alcohol, salt and oil are not recommended to be over-consumed. If the intake exceeds the recommended amount, take a positive value; otherwise, take 0. Food diversity includes cereals, animal foods, beans and their products, vegetables and fruits. When the intake of food subgroup is greater than 25 g, the highest score is 0; otherwise, the lowest score is obtained. The DBI is obtained by accumulating the scores of all the above food-based components. A negative score indicates the subject did not reach the lowest recommended intake of some food groups, while a positive score indicates over-intake of the recommended level of some food groups (33,34).

Biochemistry and additional parameters

In all participants blood samples were collected after an overnight fasting. Plasma levels of glucose, hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), liver enzymes [gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)] were centrally analyzed by an automated analyzer (Abbott AxSYM, Park, IL, USA).

Data on demographics, anthropometric variables, physical activity (PA), smoking status, and educational levels were obtained from all participants within 24 hours before liver biopsy examinations. Body mass index (BMI) was calculated using the formula weight (kilograms) divided by height (meters) squared. Waist circumference (WC) was measured at the umbilical level with the subject standing and breathing normally. Smoking status (never *vs.* past/current) was recorded in all participants. PA in the most recent week was assessed using the validated short International Physical Activity Questionnaire (IPAQ) (35). If the subject had performed any activities, further questions were asked about the frequency and duration of walking, moderate activity, and vigorous activity. The metabolic equivalent (MET)-hours per week were calculated as duration × frequency per week × MET intensity (i.e., 3.3 for walking; 4.0 for moderate activity; and 8.0 for vigorous activity), which were summed across different PA to produce an estimate of total PA from all reported activities per week.

Metabolic comorbidities

Type 2 diabetes mellitus (T2DM) was diagnosed as either self-reported history of disease, fasting glucose ≥7.0 mmol/L, HbA1c ≥6.5% (≥48 mmol/mol) or use of any anti-hyperglycemic drugs. Hypertension and dyslipidemia were diagnosed according to widely used diagnostic criteria (36). The metabolic syndrome was diagnosed when at least three of the following metabolic risk abnormalities were present: (I) abdominal obesity, defined as WC ≥90 cm in men and ≥80 cm in women (for Chinese individuals); (II) serum TG ≥150 mg/dL (≥1.7 mmol/L) or drug treatment; (III) HDL-C ≤40 mg/dL (≤1.0 mmol/L) in men and ≤50 mg/dL (≤1.3 mmol/L) in women, or drug treatment; (IV) blood pressure ≥130/85 mmHg or drug treatment; and (V) fasting glucose ≥100 mg/dL (≥5.6 mmol/L) or drug treatment (37).

Statistical analysis

Data were expressed as percentages for categorical variables

and as means ± standard deviation (SD) or medians with 25th and 75th percentiles (P25 to P75) for continuous variables, according to the distribution of each variable. Two independent samples of participant characteristics were compared using the unpaired Student's *t*-test or the Wilcoxon rank sum test, while multiple independent samples of participant characteristics were compared using the one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for normally or not normally distributed continuous variables, as well as the χ^2 test for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) of definite NASH across the tertiles of animal organ meat intake were calculated using multivariable logistic regression analyses, with the lowest tertile of animal organ meat intake as the reference category. We performed three progressive multivariable logistic regression models. Model 1 was adjusted for age, sex, BMI, WC, presence of metabolic syndrome and education levels; model 2 was further adjusted for smoking status, daily alcohol intake and PA levels; and, finally, model 3 was additionally adjusted for intakes of eggs, total energy and processed red meat, DBI, serum TC levels and histological stages of liver fibrosis. Linear trends were tested by assigning median values for each category of organ meat consumption as an ordinal variable in the aforementioned logistic regression models. Statistical analyses were performed using SPSS version 23 (IBM-SPSS, Armonk, NY, USA) software. The criteria for statistical significance of the likelihood ratio test of interaction effects was P<0.05.

Results

Baseline characteristics of participants

In our sample of Chinese adults with biopsy-proven NAFLD, 65.4% of participants had definite NASH on histology and 80.9% were men, with a mean ± SD age of 39.0±12.5 years and a mean BMI of 27.4±3.6 kg/m^2. Their daily median intake was 1.30 g/1,000 kcal for animal organ meat and 29.7 g/1,000 kcal for unprocessed and processed red meats, respectively.

Table 1 shows the participant characteristics stratified by tertiles of daily animal organ meat consumption. Participants in the upper tertile of organ meat consumption were more likely to be male and had higher energy intake and lower education levels. Age, daily alcohol intake, PA level, smoking status, adiposity measures, serum liver enzymes, lipid profile, as well as metabolic comorbidities did not significantly differ across tertiles of daily organ meat consumption.

As shown in *Table 2*, patients with biopsy-proven NASH were younger and had higher proportions of metabolic syndrome and hypertension compared to those with non-NASH. In addition, those with NASH were more likely to be centrally obese and had higher serum liver enzyme levels and a more atherogenic lipid profile.

Dietary data

Dietary characteristics based on the presence or absence of NASH and the tertiles of animal organ meat intake are presented in *Table 1* and *Table 2*. Participants belonging to the 3rd tertile of organ meat consumption had higher total meat (unprocessed meat, processed meat, animal organ meat and poultry) and energy intake compared with those in the 1st and 2nd tertiles.

Patients with definite NASH had a lower animal organ meat intake and consumed more processed red meats and eggs compared with those with non-NASH. No significant differences were found in the intakes of other food groups, total energy and DBI between the two groups.

Liver histology

Table 1 shows that there were no significant differences in liver steatosis, ballooning, lobular inflammation, as well as hepatic fibrosis stages across tertiles of daily organ meat consumption. As shown in *Table 2*, patients with definite NASH had significantly higher individual histological scores of steatosis, ballooning, lobular inflammation and fibrosis compared to those with non-NASH.

Organ meat intake and NASH

In univariable and multivariable logistic regression models (*Table 3*), there was a significant trend (P=0.005) for the association between higher animal organ meat consumption and lower risk of having definite NASH. After adjustment for age, sex, adiposity measures, metabolic syndrome and education levels, the ORs for NASH across tertiles of animal organ meat consumption were 1 (reference) for T1 (<0.51 g/1,000 kcal), 0.24 (95% CI: 0.07–0.81) for T2 (0.51–2.25 g/1,000 kcal) and 0.12 (95% CI: 0.03–0.43) for T3 (>2.25 g/1,000 kcal), respectively (P value for trend =0.005). Importantly, this significant association persisted even after additional adjustment for smoking status, alcohol

Table 1 Characteristics of participants stratified by tertiles of animal organ meat intake[a]

Characteristics	1st tertile (<0.51 g/1,000 kcal)	2nd tertile (0.51–2.25 g/1,000 kcal)	3rd tertile (>2.25 g/1,000 kcal)	P value[b]
No. subjects	46	45	45	
Demographics				
Age (years)	41.15±13.65	38.62±11.53	37.33±12.14	0.334
Male sex	36 (78.3)	32 (71.1)	42 (93.3)	0.024
Education				0.020
≤ Elementary school	13 (28.3)	8 (17.8)	4 (8.9)	
Middle school	14 (30.4)	25 (55.6)	28 (62.2)	
≥ College	19 (41.3)	12 (26.7)	13 (28.9)	
Smoking[c]	16 (34.8)	16 (35.6)	24 (53.3)	0.128
Total alcohol (% of energy)	0.0 (0.0–0.37)	0.0 (0.0–0.62)	0.0 (0.0–0.41)	0.793
Physical activity (≥150 min/week)	16 (34.8)	14 (31.1)	13 (28.9)	0.830
Metabolic comorbidities				
Metabolic syndrome	24 (52.2)	29 (64.4)	33 (73.3)	0.110
Type 2 diabetes	14 (30.4)	15 (33.3)	15 (33.3)	0.943
Hypertension	24 (52.2)	21 (46.7)	15 (33.3)	0.178
Dyslipidemia	20 (43.5)	19 (42.2)	21 (46.7)	0.909
Physical examination				
Body mass index (kg/m^2)	27.43±4.18	27.56±3.06	27.28±3.61	0.933
Waist circumference (cm)	93.47±9.22	93.19±8.26	94.36±8.91	0.804
Biochemistry				
Alanine aminotransferase (U/L)	72.0 (39.75–118.5)	60.0 (27.0–92.5)	52.0 (33.0–106.0)	0.455
Aspartate aminotransferase (U/L)	51.0 (29.25–65.5)	34.0 (25.5–58.0)	30.0 (25.0–58.50)	0.235
Gamma-glutamyl transferase (U/L)	45.0 (27.5–121.5)	60.0 (29.0–99.0)	58.0 (35.50–98.0)	0.679
Glucose (mmol/L)	5.30 (4.88–7.63)	5.30 (4.90–6.25)	5.40 (4.95–6.20)	0.929
Glycated hemoglobin (%)	5.70 (5.38–6.70)	5.60 (5.35–6.30)	5.90 (5.40–6.70)	0.604
Total cholesterol (mmol/L)	5.49±1.37	5.27±1.12	5.16±1.06	0.415
Triglycerides (mmol/L)	1.69 (1.26–2.80)	1.78 (1.12–2.81)	2.08 (1.36–2.54)	0.511
High-density lipoprotein cholesterol (mmol/L)	1.04±0.25	1.01±0.25	0.97±0.19	0.368
Low-density lipoprotein cholesterol (mmol/L)	3.18±1.11	3.12±0.87	3.14±0.92	0.945
Dietary data				
Total meats[d] (g/1,000 kcal)	33.37 (15.84–54.10)	38.12 (20.98–53.02)	48.25 (30.97–67.46)	0.019
Total energy (kcal/day)	2,310 (2,050–3,084)	2,652 (2,258–3,234)	2,945 (2,618–3,766)	0.002
Chinese Diet Balance Index[e] (points)	–9.57±8.69	–8.51±8.49	–6.89±7.51	0.300

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	1st tertile (<0.51 g/1,000 kcal)	2nd tertile (0.51–2.25 g/1,000 kcal)	3rd tertile (>2.25 g/1,000 kcal)	P value[b]
Liver histology[f]				
Steatosis: grades 0/1/2/3	13.0/28.3/30.4/28.3	11.1/22.2/22.3/44.4	15.6/37.8/13.3/33.3	0.321
Hepatocyte ballooning: grades 0/1/2	6.5/50.0/43.5	20.0/48.9/31.1	13.3/46.7/40.0	0.387
Lobular inflammation: grades 0/1/2/3	4.3/56.5/37.0/2.2	6.7/64.5/24.4/4.4	8.9/71.1/20.0/0.0	0.415
Fibrosis[g]: stages 0/1/2/3	19.6/45.7/28.3/6.4	11.1/60.0/22.2/6.7	20.0/57.7/15.6/6.7	0.676

[a], categorical variables are expressed as percentage or number (percentage), while continuous variables are expressed as means ± standard deviation or medians (25th percentile to 75th percentile); [b], based on the χ^2 test for categorical variables, and the analysis of variance (one-way ANOVA) or the Kruskal-Wallis test for continuous variables (as appropriate); [c], smoking status includes the former and current smoker; [d], total meats include unprocessed meat, processed meat, animal organ meat and poultry; [e], Chinese Diet Balance Index includes eight food components and the negative score indicates the subject did not reach the lowest recommended intake of some food components; [f], liver steatosis, ballooning, lobular inflammation and fibrosis stages are graded as 0–3, 0–2, 0–3 and 0–4, respectively, according to the NASH-Clinical Research Network Scoring System; [g], fibrosis score 3 includes fibrosis stage 3 and 4, because of the small sample size of these two stages. ANOVA, analysis of variance; NASH, nonalcoholic steatohepatitis.

Table 2 Characteristics of participants stratified by presence or absence of definite NASH on histology[a]

Demographics	Non-NASH (n=47)	NASH (n=89)	P value[b]
Age (years)	42.64±11.41	37.16±12.68	0.014
Male sex	38 (80.9)	72 (80.9)	0.582
Education			0.054
≤ Elementary school	11 (23.4)	14 (15.7)	
Middle school	27 (57.4)	40 (44.9)	
≥ College	9 (19.2)	35 (39.4)	
Smoking[c]	21 (44.7)	35 (39.3)	0.336
Total alcohol (% of energy)	0.07 (0.0–0.68)	0.0 (0.0–0.30)	0.114
Physical activity (≥150 min/week)	14 (29.8)	29 (32.6)	0.447
Metabolic comorbidities			
Metabolic syndrome	22 (46.8)	64 (71.9)	0.004
Type 2 diabetes	18 (38.3)	26 (29.2)	0.282
Hypertension	15 (31.9)	45 (50.6)	0.037
Dyslipidemia	17 (36.2)	43 (48.3)	0.175
Physical examination			
Body mass index (kg/m^2)	25.75±2.69	28.31±3.75	<0.001
Waist circumference (cm)	88.40±7.23	96.46±8.22	<0.001
Biochemistry			
Alanine aminotransferase (U/L)	34.0 (23.0–57.0)	77.0 (46.0–131.5)	<0.001
Aspartate aminotransferase (U/L)	27.0 (21.0–33.0)	52.0 (32.0–73.0)	<0.001
Gamma-glutamyl transferase (U/L)	40.0 (23.0–62.0)	64.0 (36.0–130.0)	0.001

Table 2 (*continued*)

Table 2 (*continued*)

Demographics	Non-NASH (n=47)	NASH (n=89)	P value[b]
Glucose (mmol/L)	5.20 (4.90–6.40)	5.40 (4.90–6.30)	0.533
Glycated hemoglobin (%)	5.70 (5.30–6.50)	5.70 (5.40–6.45)	0.752
Total cholesterol (mmol/L)	4.89±1.09	5.53±1.19	0.003
Triglycerides (mmol/L)	1.56 (0.91–2.91)	1.92 (1.46–2.69)	0.043
High-density lipoprotein cholesterol (mmol/L)	1.0±0.23	1.01±0.23	0.935
Low-density lipoprotein cholesterol (mmol/L)	2.81±0.88	3.32±0.97	0.003
Dietary data (g/1,000 kcal)			
Rice	106.52±45.62	104.63±35.09	0.805
Wheaten	26.64 (11.94–43.74)	17.87 (7.21–40.16)	0.327
Soybean	8.18 (3.34–14.45)	9.18 (3.36–17.72)	0.768
Tubers	3.63 (0.47–8.00)	2.71 (0.72–6.12)	0.725
Vegetables	70.64 (39.64–120.38)	59.98 (42.18–110.35)	0.497
Edible fungi	4.05 (2.06–5.93)	3.08 (1.19–9.01)	0.677
Fruits	102.62 (60.41–174.49)	103.59 (57.93–180.40)	0.925
Nuts	1.37 (0.32–3.48)	1.19 (0.27–3.15)	0.951
Unprocessed and processed red meat	27.07 (15.37–47.20)	32.09 (19.56–46.31)	0.488
Unprocessed red meat	26.02 (15.21–46.52)	30.61 (16.70–46.31)	0.620
Processed red meat	0.0 (0.0–0.55)	6.14 (0.0–4.21)	0.025
Animal organ meat	1.73 (0.64–4.52)	0.83 (0.0–2.38)	0.006
Poultry	3.87 (2.17–10.29)	3.49 (1.81–7.31)	0.217
Dairy products	6.70 (0.00–18.66)	4.73 (0.00–21.87)	0.772
Eggs	8.41 (4.10–14.81)	12.05 (6.27–17.12)	0.048
Fish	11.65 (6.03–25.92)	13.56 (5.71–20.82)	0.954
Seafoods	17.96 (11.08–45.99)	19.44 (12.17–36.08)	0.889
Soft drinks	6.69 (0.39–44.17)	15.97 (1.22–61.20)	0.282
Total energy (kcal/day)	2,652 (2,264–2,991)	2,763 (2,186–3,561)	0.800
Diet Balance Index[d] (points)	–8.70±8.62	–8.14±8.10	0.705
Liver histology[e]			
Steatosis: grades 0/1/2/3	18 (38.3)/22 (46.8)/2 (4.3)/5 (10.6)	0 (0.0)/18 (20.2)/28 (31.5)/43 (48.3)	<0.001
Hepatocyte ballooning: grades 0/1/2	18 (38.3)/24 (51.1)/5 (10.6)	0 (0.0)/42 (47.2)/47 (52.8)	<0.001
Lobular inflammation: grades 0/1/2/3	9 (19.1)/36 (76.6)/2 (4.3)/0 (0.0)	0 (0.0)/51 (57.3)/35 (39.3)/3 (3.4)	<0.001
Fibrosis[f]: stages 0/1/2/3	14 (29.8)/23 (48.9)/7 (14.9)/3 (6.4)	9 (10.1)/51 (57.3)/23 (25.8)/6 (6.7)	0.028

[a], categorical variables are expressed as number (percentage), while continuous variables are expressed as means ± standard deviation or medians (25th percentile to 75th percentile); [b], based on the χ^2 test for categorical variables and the unpaired Student's *t*-test or the Wilcoxon rank-sum test for normally and not-normally distributed continuous variables (as appropriate); [c], smoking status includes the former and current smoker; [d], Chinese Diet Balance Index includes eight food components and the negative score indicates the subject did not reach the lowest recommended intake of some food components; [e], liver steatosis, ballooning, lobular inflammation and fibrosis stages are graded 0–3, 0–2, 0–3 and 0–4, respectively, according to the NASH-Clinical Research Network Scoring System; [f], fibrosis stage 3 includes fibrosis stages 3 and 4 (cirrhosis), because of the small number of patients with these two stages. NASH, nonalcoholic steatohepatitis.

Table 3 ORs (95% CIs) for definite NASH by increasing levels of animal organ meat consumption

Animal organ meat consumption	Non-NASH/NASH	Unadjusted model, OR (95% CI)	Adjusted model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Per doubling (g)	47/89	0.93 (0.87 to 0.98)	0.88 (0.82 to 0.95)	0.88 (0.81 to 0.95)	0.87 (0.80 to 0.96)
P value		0.008	0.001	0.001	0.003
By tertiles					
T1	10/36	1 (reference)	1 (reference)	1 (reference)	1 (reference)
T2	16/29	0.50 (0.20 to 1.28)	0.24 (0.07 to 0.81)	0.24 (0.07 to 0.81)	0.18 (0.05 to 0.70)
T3	21/24	0.32 (0.13 to 0.79)	0.12 (0.03 to 0.43)	0.12 (0.03 to 0.44)	0.15 (0.03 to 0.69)
P value for trend[a]		0.048	0.005	0.006	0.024

The cutoff points for animal organ meat intake tertiles were as follows: T1 <0.51 g/1,000 kcal, T2 0.51–2.25 g/1,000 kcal, and T3 >2.25 g/1,000 kcal, respectively. Model 1 was adjusted for age, sex, adiposity measures (body mass index and waist circumference), metabolic syndrome and education levels; model 2 was further adjusted for smoking, alcohol (% of energy) and physical activity; model 3 was adjusted for the same covariates of model 2 plus eggs intake, Diet Balance Index, total energy, processed red meat and total cholesterol concentration, and histologic liver fibrosis stage. [a], P value for trend was calculated across tertiles of organ meat consumption. OR, odds ratio; CI, confidence interval; NASH, nonalcoholic steatohepatitis.

intake, PA level, total energy, eggs and processed red meat intakes, DBI, as well as total cholesterol concentrations and histological stages of liver fibrosis (adjusted model 3). In particular, the fully adjusted ORs for NASH across tertiles of daily organ meat consumption were 1 (reference) for T1, 0.18 (95% CI: 0.05–0.70) for T2 and 0.15 (95% CI: 0.03–0.69) for T3, respectively (P value for trend =0.024). Almost similar results were observed when we analyzed the risk of having NASH for every doubling in animal organ meat consumption (*Table 3*).

Discussion

In this cross-sectional study of Chinese individuals with biopsy-confirmed NAFLD, we showed that there was a significant association between higher animal organ meat consumption (offal) and lower risk of having definite NASH. Notably, this association remained statistically significant even after adjusting for established risk factors and potential confounders, including socio-demographic variables, lifestyle habits, metabolic and dietary factors, histologic stages of liver fibrosis, as well as DBI. DBI is designed to assess under- and over-nutrition, which are two important risk factors for the rise of non-communicable chronic diseases, such as CVD, T2DM and cancers, in China's large population that is undergoing rapid economic change.

To our knowledge, only two cross-sectional studies have examined the relationship between daily animal organ meat consumption and presence of NAFLD (as assessed by ultrasonography), and they provided results that are apparently in contrast to those reported in our study. In the Golestan cohort study, involving 1,340 Iranian individuals with low red meat consumption, a higher daily organ meat consumption was associated with a higher prevalence of ultrasound-defined NAFLD (the highest *vs.* the lowest quartile OR =1.70, 95% CI: 1.2–2.4), and the median intake of organ meat in the highest quartile was 7.0 g/day (38). Another study from Chengdu, China, showed that individuals with ultrasound-defined NAFLD consumed more animal organ meat than those without NAFLD (9.7 *vs.* 3.4 g/day, P<0.05) (39).

In our study, the median intake of animal organ meat among patients with biopsy-proven NASH was 2.40 g/day. Similar results were also found in previous CVD studies. Although most of these studies conducted in the North America (40) and Europe (41) reported that higher consumption of unprocessed red meat was associated with a greater risk of CVD mortality, while a moderately higher consumption of unprocessed red meat (beef, pork, and organ meat) was found to be associated with a lower risk of CVD events in South Korean adults (22). The average red meat consumption among Chinese people in 15 provinces (autonomous regions and municipalities) was 74.4 g/day, and in the middle, East and West of China, the average red meat consumption was approximately 64.2, 70.9, and 94.3 g/day, respectively (21). According to the Organization for Economic Co-operation and Development (OECD) report,

the red meat consumption was estimated to be 50.6 and 39.6 kg per capita in the USA and OECD countries in 2020, respectively. It is much higher than that reported in China (about 30.2 kg per capita in 2020) (42). We believe that these observed differences in daily red meat consumption might also partly explain the inconsistent associations observed between animal organ meat intake and the risk for NAFLD in different countries and regions (as reported above).

Animal organ meat (offal) is one of the most nutrient dense foods. Compared with skeletal meat, the levels of coenzyme (CoQ10), L-carnosine, anserine, L-carnitine, conjugated linoleic acid, glutathione, taurine, creatine and dietary fibres in animal organ meat are higher (43). Moreover, animal organ meat is rich in some nutrients, such as vitamin E, vitamin A, vitamin C, vitamin B_{12}, niacin, choline. Low levels of vitamin B_{12} were significantly associated with greater NASH activity and fibrosis stage in people with NAFLD (44). It was also shown from the results of the PIVENS trial that vitamin E therapy (at a daily dose of 800 IU) was associated with a significant improvement in NASH compared with placebo (45). Experimentally, niacin inhibits fat accumulation, oxidative stress, and inflammatory cytokine interleukin 8 (IL-8) production in cultured hepatocytes (46). Choline, which is a phospholipid and neurotransmitter precursor, is also present in the liver where it offers protection against oxidative stress (43). That said, since different animal organ meats contain different ingredients with variable anti-inflammatory and antioxidant effects, it would be better to examine the specific effect of each kind of organ meat and the key ingredient contained therein. Therefore, we suggest further studies are needed to elucidate whether any of the aforementioned mechanisms may mediate the protective effect of animal organ meat consumption on NASH that we observed.

The prevalence of NAFLD is highest in the Middle East (32%) and South America (31%), followed by Asia (27%) and Europe (23%), and lowest in Africa and India (approximately 10%) (47). Apart from ethnic variables, differences in dietary factors may also contribute to the different NAFLD distribution around the world. Dietary patterns and food items, such as the Western diet, high energy diet, high saturated fatty acids and refined carbohydrates, may adversely affect obesity, oxidative stress and inflammatory response, which are all closely related to the development and progression of NAFLD (48,49).

Our study has important strengths. Unlike other studies, we used liver biopsy, which is the 'gold standard' method for diagnosing and staging NAFLD. Furthermore, trained dietitians and laboratory assistants collected data on anthropometry, diet and lifestyle variables through 'face-to-face' interviews.

Some important limitations of this study should also be mentioned. Firstly, the sample size of the study is relatively small. Secondly, cross-sectional design of the study does not allow us to make any causal inferences about the observed associations. Thirdly, it is possible that health-conscious individuals may over-report or under-report some food items. However, we enrolled subjects, who were initially diagnosed with NAFLD and, thus, there should not be differential recall bias. Fourthly, although we did not find any significant interaction between animal organ meat intake and other potentially protective dietary risk factors, we cannot comprehensively exclude this effect. Fifthly, the study sample consisted mainly of men accounting for ~80% of cases. However, we also adjusted our results for sex to reduce this potential bias. Finally, as our sample consisted of Chinese adults of a predominantly single ethnic group, our results might not be applicable to different ethnic groups, who may have different lifestyle habits.

Conclusions

The results of our study suggest that in Chinese adult individuals with biopsy-proven NAFLD, there is a significant association between higher daily consumption of animal organ meat and lower prevalence of NASH. However, larger studies are needed to further corroborate these findings in other ethnic groups and to better elucidate the mechanistic links between higher animal organ meat consumption and lower risk of having NASH.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (No. 2016-246). Written informed consent was obtained from each participant included in the study.

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