Organ meat consumption and risk of nonalcoholic fatty liver disease: the TCLSIH study

Huiping Li[1], Xiaoxi Zheng[1], Sabina Rayamajhi[1], Amrish Thapa[1], Ge Meng[1,2], Qing Zhang[3], Li Liu[3], Hongmei Wu[1], Yeqing Gu[4], Shunming Zhang[1], Tingjing Zhang[1], Xuena Wang[1], Jun Dong[1], Zhixia Cao[1], Xu Zhang[1], Xinrong Dong[1], Shaomei Sun[3], Xing Wang[3], Ming Zhou[3], Qiyu Jia[3], Kun Song[3], and Kaijun Niu[1,5,6,7]*

[1]Nutritional Epidemiology Institute and School of Public Health, Tianjin Medical University, Tianjin, China

[2]Department of Toxicology and Sanitary Chemistry, School of Public Health, Tianjin Medical University, Tianjin, China

[3]Health Management Centre, Tianjin Medical University General Hospital, Tianjin, China

[4]Institute of Radiation Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

[5]School of Public Health, Tianjin Medical University, Tianjin, China

[6]Tianjin Key Laboratory of Environment, Nutrition and Public Health, Tianjin, China

[7]Center for International Collaborative Research on Environment, Nutrition and Public Health, Tianjin, China

***Correspondence author:** Kaijun Niu, MD, PhD, Nutritional Epidemiology Institute and School of Public Health, Tianjin Medical University, 22 Qixiangtai Road, Heping District, Tianjin 300070, China, Phone: +86-22-83336613, E-mail: nkj0809@gmail.com

Running Title: Organ meat and NAFLD

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI
10.1017/S0007114522000629
The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

Abstract

Prospective cohort studies linking organ meat consumption and nonalcoholic fatty liver disease (NAFLD) are limited, especially in Asian populations. This study aimed to prospectively investigate the association between organ meat consumption and risk of NAFLD in a general Chinese adult population. This prospective cohort study included a total of 15,568 adults who were free of liver disease, cardiovascular disease, and cancer at baseline. Dietary information was collected at baseline using a validated food frequency questionnaire. NAFLD was diagnosed by abdominal ultrasound after excluding other causes related to chronic liver disease. Cox proportional regression models were used to assess the association between organ meat consumption and risk of NAFLD. During a median of 4.2 years of follow-up, we identified 3,604 incident NAFLD cases. After adjusting for demographic characteristics, lifestyle factors, vegetable, fruit, soft drink, seafood, and red meat consumption, the multivariable hazard ratios (95% confidence intervals) for incident NAFLD across consumption of organ meat were 1.00 (reference) for almost never, 1.04 (0.94, 1.15) for tertile 1, 1.08 (0.99, 1.19) for tertile 2, and 1.11 (1.01, 1.22) for tertile 3, respectively (*P* for trend <0.05). Such association did not differ substantially in the sensitivity analysis. Our study indicates that organ meat consumption was related to a modestly higher risk of NAFLD among Chinese adults. Further investigations are needed to confirm this finding.

Keywords: organ meats; fatty liver; NAFLD; prospective study

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver disease worldwide, with a prevalence of as high as 30% in the general population and up to 70% in patients with type 2 diabetes mellitus [1]. NAFLD is characterized by the hepatic accumulation of lipids in the absence of excessive alcohol consumption or established liver disease [2]. The spectrum of abnormalities in NAFLD can range from simple steatosis to nonalcoholic steatohepatitis (NASH), which may progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma [3; 4]. However, its clinical burden is not confined to the liver. For example, studies have shown that NAFLD was associated with increased risks of diabetes, cardiovascular disease (CVD), and all-cause mortality [5-7]. While various clinical trials are in progress, there is currently no standard treatment for NAFLD [8]. Dietary factors associated with NAFLD are potentially modifiable and thus represent targets for primary prevention of the condition [9; 10].

Organ meats, such as animal liver and gut, are mainly consumed in Asia and the Middle East, due to the prevailing fact that they are cheap, delicious, and provide several nutrients, such as folic acid, vitamin A, and vitamin B12 [11-14]. Despite these advantages, several characteristics of organ meats might be involved in causing disease, especially NAFLD. First, organ meats are high in saturated fat and cholesterol [15], both of which have been associated with an increased risk of NAFLD [16]. Second, organ meats are rich in N-glycolylneuraminic acid, a chemical that can potentially incite inflammation [17], while chronic inflammation plays important role in the development of NAFLD [18]. Finally, organ meats contain high levels of heme iron. In vivo and human studies, dietary heme iron can increase oxidative stress and lipid peroxidation, implying that heme iron may increase the risk of NAFLD [19; 20]. Therefore, we hypothesized that high consumption of organ meats might increase the risk of NAFLD.

Although previous studies have shown that high red meat consumption was associated with an increased risk of NAFLD [21; 22], epidemiological evidence linking intake of organ meats to the risk of the disease was still very scarce. Only two cross-sectional studies have reported that higher consumption of organ meats was associated with a higher prevalence of NAFLD [22; 23]. To our knowledge, there is no prospective study examining the association between organ meats and NAFLD. Thus, the current study aimed to prospectively examine the association of organ meat consumption with the risk of NAFLD in a large population of Chinese adults.

Methods

Study design and population

The Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSIH) Cohort Study is a dynamic prospective cohort study launched in 2007 focusing on the associations between chronic low-grade systemic inflammation and the health status of a population living in Tianjin, China [24; 25]. In the TCLSIH cohort study, participants were recruited from the Tianjin general population of men and women (excluding pregnant women) aged 18 years or older who participated in annual health examinations. Participants who had received health examinations including abdominal ultrasound and blood draw and had completed questionnaires regarding their smoking and alcohol-consumption habits and disease history since January 2010. Moreover, a detailed dietary and lifestyle questionnaire was administered to randomly selected participants from this population since May 2013. All participants were invited to complete follow-up assessments during annual health examinations (including ultrasonography) that happened in the same month every year. Participants are followed from the date of diet questionnaire completion to 31 December 2019. All participants had completed a written informed consent form, which was witnessed and formally recorded. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Institutional Review Board of Tianjin Medical University (reference number: TMUhMEC 201430).

In the current analysis, we included a total of 30,391 participants. To minimize reverse causal bias and reduce the impact of measurement errors, we excluded participants with extreme values for total energy intake (below the 2.5 or over the 97.5 percentiles) or those with missing data on the exposure variables (n=2,618) or those with a history of CVD (n=1,588), cancer (n=210), alcoholic fatty liver disease (n=1,129), other liver diseases (n=178), NAFLD (n=7,097) at baseline. We further excluded those who were lost to follow-up (n=2,003, retention rate: 88.8%). Data from 15,568 participants were available for the final analysis. The study population flow chart is described in **Figure 1**.

Diagnosis of NAFLD

Abdominal sonography was performed using TOSHIBA SSA-660A (Toshiba, Tokyo, Japan) by experienced radiologists. Ultrasound images were assessed by senior hepatologists with over 10 years of experience. The ultrasound technician and hepatologist were unaware of the study aims and blinded to the participant's information. All

participants were unaware of the presence of steatosis before completing the food frequency questionnaire (FFQs). The diagnosis of fatty liver was based on at least two of three abnormal findings on abdominal ultrasonography, diffusely increased echogenicity ('bright') liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal [26]. NAFLD was defined according to ultrasound-diagnosed fatty liver disease after excluding excessive alcohol consumption (≥210 g/week for men and ≥140 g/week for women), chronic hepatitis B or C, and long-term steatogenic medicine use.

Assessment of dietary intake

Diet was assessed using a 100-item food frequency questionnaire (FFQ) with specified serving sizes that were described by natural portions or standard weight and volume measures of the servings commonly consumed in this study population [27]. All participants were asked how often, on average, they had consumed a particular amount of a specific type of food during the previous month. Daily energy and nutrient intakes were extracted from the questionnaires using the China Food Composition database that includes information on nutrient content per gram or serving per product [14]. The reproducibility and validity of the FFQ in measuring food intake have been described in detail previously [24]. The Spearman correlation coefficients between the FFQ and dietary records were 0.49 for energy and 0.68 for organ meats. Spearman correlation coefficients between the two FFQs collected around 3 months apart were 0.68 for energy and 0.70 for organ meats. Our previous study showed that despite the FFQ investigating the dietary habits during the last month, the long-term dietary intake of the participants could be inferred [28]. To evaluate overall diet quality, principal component analysis with orthogonal rotation was conducted to extract dietary patterns. Eigenvalues (>1.5), scree plots, factor interpretability, and percentage of variance were used to identify key patterns. Food items with absolute factor loadings ≥0.45 were considered to be the main contributors to the dietary pattern. Factors were named descriptively according to the food items showing high loading (absolute value) as follows: vegetable-rich pattern, sugar-rich pattern, and animal food pattern. These patterns were consistent with dietary patterns previously derived in the TCLSIH Cohort Study [29].

On our FFQ, organ meats included animal liver, kidney, lung, and large/small intestine. To correct for potential measurement error, organ meat consumption was adjusted for total energy intake using the nutrient density method and expressed as g/1000 kcal per day [30]. Because the majority of participants (40.8%) almost never consumed organ meats, we set the

reference group as "almost never". The remaining participants with organ meat consumption were ranked into tertiles.

Assessment of other covariates

Data on potential covariates, including age, sex, smoking status, alcohol drinking status, education level, occupation, family history of disease (including CVD, hypertension, hyperlipidemia, and diabetes), hypertension, diabetes, and hyperlipidemia were collected with self-administered questionnaires at the baseline survey. Physical activity in the most recent week was assessed using the short form of the International Physical Activity Questionnaire [31]. Total physical activity was estimated as MET-hours per week (MET-hour/week). Height and body weight were measured using a standard protocol, and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Waist circumference (WC, cm) was assessed at the level of the umbilicus with participants standing and breathing normally.

Blood samples were collected from the ante-cubital vein in siliconized vacuum plastic tubes after an overnight fast. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using an automatic biochemical analyzer (Roche Cobas 8000 modular analyzer, Mannheim, Germany). Participants were classified as having diabetes if their FBG was ≥7.0 mmol/L or they had a self-reported history of diabetes. Participants were defined as having hyperlipidemia if they had increased levels of blood lipids (TC ≥5.17 mmol/L, or TG ≥1.7 mmol/L, or LDL-C ≥3.37mmol/L) or they took lipid-lowering medication [32]. Blood pressure was measured from the upper right arm using the TM-2655 oscillometric device (A&D, Tokyo, Japan). Hypertension was defined as having a self-reported history of hypertension, or systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg [33].

Statistical Analysis

Baseline characteristics of the analytic sample were presented as means (± standard deviation, SD) for continuous variables and percentages for categorical variables. This study calculated each individual's person-years from the date of the return of the baseline questionnaire to the date of the first NAFLD diagnosis, end of follow-up (December 2019), or lost to follow-up, whichever occurred first. Cox proportional hazards models were applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the

association of energy-adjusted organ meat consumption (g/1000 kcal per day) and risk of NAFLD. The proportional hazards assumption was evaluated with a likelihood ratio test comparing the model with and without an interaction term between follow-up time and exposure. In multivariate models, we adjusted for age (continuous), sex (men or women), smoking status (current/past/never), drinking status (everyday/sometime/past/never), BMI (continuous), physical activity (continuous), educational level (college graduate or not), occupation (managers, professionals, or others), household income (< or ≥10,000 Yuan), hypertension (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), and family history of disease (including CVD, hypertension, hyperlipidemia, and diabetes [each yes or no]), total energy intake (continuous), vegetable intake (continuous), fruit intake (continuous), seafood intake (continuous), soft drink intake (<1 serving/week, 1 serving/week, 2-3 servings/week and ≥4 servings/week), and red meat intake (continuous).

To avoid reverse causality bias, we did a sensitivity analysis by excluding NAFLD cases that occurred within the first years of follow-up. In addition, the final multivariable model was rerun by adjusting for vegetable-rich pattern, sugar-rich pattern, and animal food pattern instead of vegetable, fruit, seafood, soft drink, and red meat consumption. Moreover, we stratified the participants by potential effect modifiers including age (<40 or ≥40 years), sex (male or female), BMI (<24.0 or ≥24.0 kg/m$^{2)}$, physical activity (< or ≥23 MET/week), smoking status (current/past/never), drinking status (everyday/sometime/past/never), hypertension (yes or no), hyperlipidemia (yes or no), and diabetes (yes or no). The interactions were tested by using the likelihood ratio test comparing models with and without cross-product terms.

All analyses were performed using SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA.). All statistical tests were two-sided, and *P* <0.05 was considered statistically significant.

Results

During a median follow-up of 4.2 years of 15,568 participants, we identified 3,604 incident NAFLD cases. **Table 1** displays baseline characteristics of participants by NAFLD status. Participants with NAFLD were older, tended to be men, had higher BMI, WC, TC, TG, LDL-C, SBP, DBP, FBG, total energy intake, PA, organ meat intake, and lower HDL-C (all $P<0.001$). They also were more likely to be current smokers and ex-smokers, current drinkers, tended to have more comorbidities, and had a family history of CVD, HBP, and diabetes. Furthermore, participants with NAFLD had lower education levels.

The median (range) intakes of organ meats in each tertile were 1.53 (0.59-2.24), 3.12 (2.24-4.43), and 7.87 (4.43-66.8) g/1000 kcal per day, respectively. The associations between organ meat consumption and NAFLD risk were analyzed in three adjustment models. In the age, sex, and BMI adjusted model, organ meat consumption was positively associated with the risk of NAFLD (comparing the third tertile with almost never eating: HR 1.17; 95% CI 1.07 to 1.29, *P* for trend<0.001) (**Table 2**). After further adjustment for non-dietary NAFLD risk factors, we observed similar results. Adjusting for intakes of vegetable, fruit, seafood, soft drink, and red meat, such association remained statistically significant but attenuated (comparing the third tertile with almost never eating: HR 1.11, 95% CI 1.01 to 1.22, *P* for trend<0.05)

We found no evidence that the associations between meat intake and NAFLD varied by age (*P* for interaction= 0.69), sex (*P* for interaction= 0.42), BMI (*P* for interaction= 0.66), smoking status (*P* for interaction= 0.59), drinking status (*P* for interaction= 0.87), PA (*P* for interaction= 0.71), hyperlipidemia (*P* for interaction= 0.68), diabetes (*P* for interaction= 0.87) and HBP (*P* for interaction= 0.64) (**Table 3**).

In sensitivity analysis, the associations remained similar when we excluded incident NAFLD cases in the first year of follow-up (n=861, **Supplementary Table 1**); In the fully adjusted model, compared with almost never eating, the highest tertile of intake was significantly associated with a higher risk of the NAFLD (HR=1.15, 95% CI 1.02 to 1.29; *P* for trend=0.01). Similar results were observed when adjusting for three main dietary patterns instead of intakes of vegetable, fruit, seafood, soft drink, and red meat consumption (**Supplementary Table 2)**.

Discussion

The prospective findings from the present study support the hypothesis that organ meat was associated with a modestly increased risk of incident NAFLD in Chinese adults, independent of other dietary or non-dietary NAFLD risk factors. To our knowledge, this was the first large prospective cohort study investigating the association between organ meat consumption and the risk of NAFLD.

In this large-scale population-based study, we adjusted for multiple potentially confounding factors, including age, sex, BMI, smoking status, drinking status, physical activity, socioeconomic status, personal and family history of disease, and total energy intake. These adjustments did not change the positive association between organ meat consumption and NAFLD. In addition, to test for the potential influence of nutritional quality of overall diets on the association between organ meat consumption and NAFLD, we additionally adjusted vegetable, fruit, soft drink, seafood, and red meat intake. However, the adjustment for these dietary factors also did not change the positive association between organ meat consumption and NAFLD, implying that the association between organ meat and NAFLD was independent of these dietary factors.

In our study, the mean consumption of organ meat was 6.61 g/day, similar to that of Chengdu, China [23]. Our findings are in line with a previous case-control study, which showed that NAFLD patients consumed significantly more organ meat than controls (9.7 vs 3.4 g/day, $P<0.05$) [23]. In this study, however, energy intake was not taken into account as a covariate. Another study in Iran observed similar results, showing that organ meat consumption was associated with the increased odds of NAFLD (odds ratio Q4 vs Q1=1.70, 95% CI 1.19 to 2.44, *P* for trend trend=0.0025) [22]. It is worth noting that, in this study, ultrasound assessments were not performed at baseline but in 6 years after the dietary data collection, and the participants might have changed their diet during this period. Therefore, it was not clear whether participants had fatty liver disease at baseline. Our current cohort study provides prospective evidence that organ meat consumption was associated with an increased risk of NAFLD.

Several hypotheses could be put forward to explain our findings. Firstly, organ meats are commonly high in saturated fat and cholesterol. Saturated fat ingestion was reported to augment hepatic lipid storage and impaired insulin sensitivity, both of which were accompanied by regulation of hepatic gene expression and signaling that predispose to the development of NAFLD [34]. Among hepatic lipid species, cholesterol is considered a major lipotoxic molecule in nonalcoholic steatohepatitis development [35]. Recently, studies in

animal models have demonstrated that dietary cholesterol could induce both reactive oxygen species and proinflammatory cytokines, thereby promoting NAFLD development [36; 37]. A second interpretation concerns the heme iron in organ meats. Heme iron may exert effects on the synthesis and secretion of insulin and interfere with insulin receptors, thus reducing insulin sensitivity [38]. This could lead to NAFLD because insulin resistance is the key dysfunction in this disease [39]. In addition, heme iron was associated with increased oxidative stress and lipid peroxidation [40]. A large prospective cohort study also found that heme iron intake was associated with a higher risk of chronic liver disease [41]. Finally, the sialic acid N-glycolylneuraminic acid in organ meats has been hypothesized to generate a proinflammatory cascade [17]. It is worth noting that the human liver is an organ that can readily incorporate dietary N-glycolylneuraminic acid [42; 43].

The strengths of the current study include its large sample size, prospective study design, and the robustness of the results in a series of analyses. However, several limitations need to be considered when interpreting our results. First, NAFLD diagnosis was based on abdominal ultrasound rather than the gold standard liver biopsy. However, a meta-analysis showed that the sensitivity and specificity of ultrasonography for assessment of fatty liver, compared to CT, MRI, or magnetic resonance spectroscopy, were 93.6% (95% CI: 60.5, 99.3) and 80.1% (95% CI: 53.3, 93.4), respectively [44]. Moreover, to reduce inter- and intra-observer variation, all ultrasonographic exams were examined by board-certified radiologists using standard methods. Second, bias in self-reported organ meat consumption is inevitable; and such bias might have led to some degree of nondifferential misclassification of exposure, which could have attenuated the observed associations. Third, organ meat consumption was collected once at baseline, which did not take into account the changes in dietary habits during the follow-up time. Therefore, future studies need to evaluate the association of long-term changes in organ meat consumption with subsequent risk of NAFLD. Fourth, as in all observational studies, although we have carefully controlled for the potential confounding factors, we cannot exclude the possibility of residual confounding. Finally, since the study results only represent the study region, caution must be taken when generalizing the findings to other populations. Therefore, further studies are needed to verify the results in other populations.

In conclusion, in this large cohort study of Chinese adults, we found a positive association between organ meat consumption and the risk of NAFLD. Further large-scale, population-based studies are needed to confirm the generalizability of these findings in different populations and settings.

Acknowledgments

The authors gratefully acknowledge all the people that have made this study.

Financial Support

This study was supported by grants from the National Natural Science Foundation of China (No. 91746205, 81673166, and 81372118).

Authorship

The authors' responsibilities were as follows: H.L. analyzed the data and wrote the paper. H.L., X.Z., S.R., A.T., G.M., Q.Z., L.L., H.W., Y.G., S.Z., T.Z., X.W., J.D., S.S., Z.C., X.Z., X.R., S.S., X.W., M.Z., Q.J., and K.S. conducted research. K.N. designed the research and had primary responsibility for the final content. All authors had full access to all the data in the study and read and approved the final manuscript.

Conflict of interest

None.

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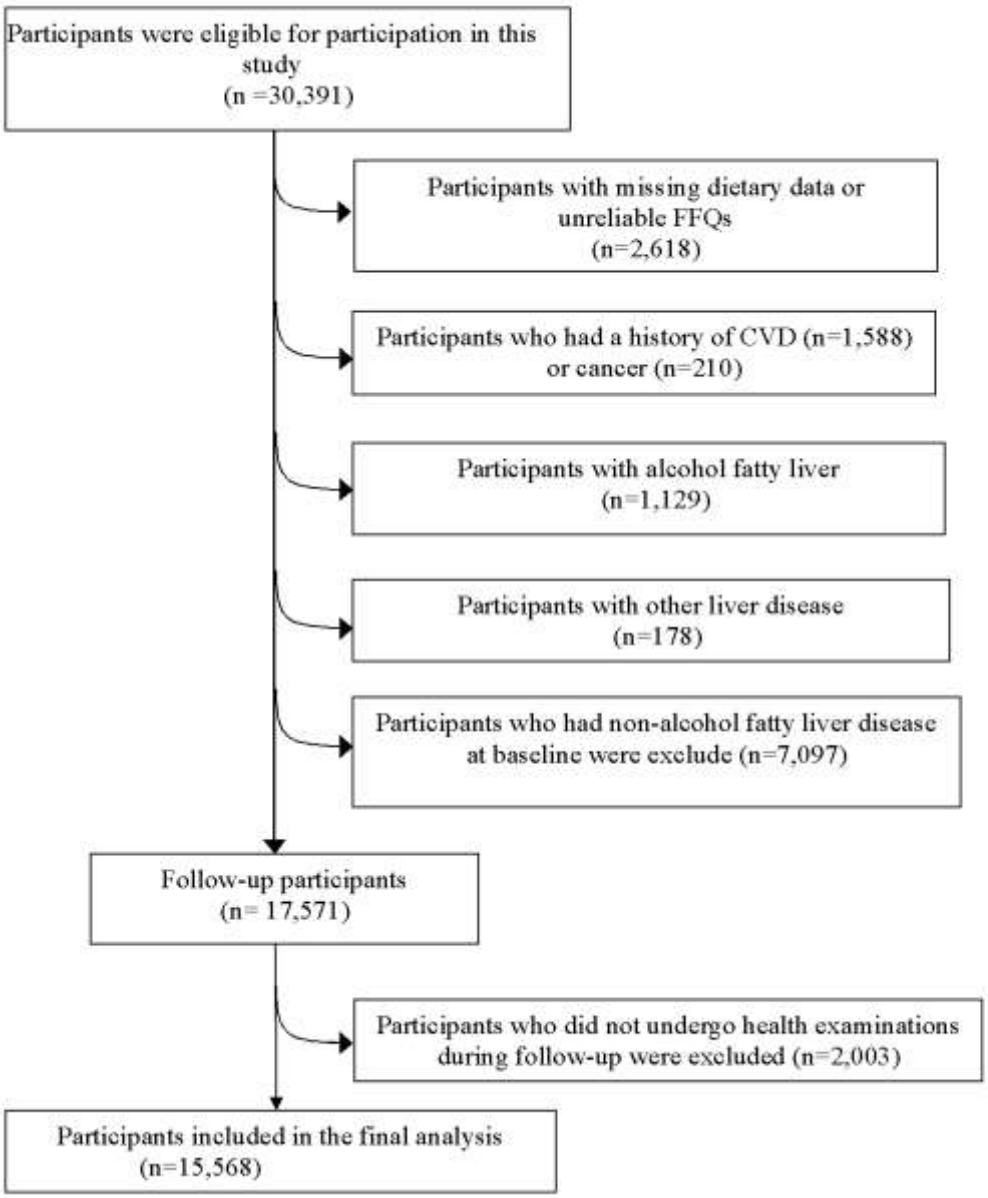

Figure 1. Selection of study participants. CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease

Table 1. Baseline characteristics of the participants according to NAFLD status (n=15,568) [a]

Characteristics	NAFLD status		*P* value [b]
	No	Yes	
No. of participants	11,964	3,604	-
Age (years)	39.0±11.2	42.0±12.1	<.0001
Sex (men, %)	36.5	61.9	<.0001
BMI (kg/m^2)	22.4±2.85	25.0±2.90	<.0001
WC (cm)	76.0±9.05	84.0±8.88	<.0001
TC (mmol/L)	4.57±0.85	4.76±0.87	<.0001
TG (mmol/L)	0.97±0.54	1.38±0.85	<.0001
LDL-C (mmol/L)	2.63±0.75	2.85±0.76	<.0001
HDL-C (mmol/L)	1.53±0.38	1.31±0.32	<.0001
SBP (mmHg)	115.6±14.3	122.4±15.1	<.0001
DBP (mmHg)	72.6±10.0	77.2±10.5	<.0001
FBG (mmol/L)	4.94±0.70	5.13±0.76	<.0001
PA (MET-hour/week)	18.6±30.0	21.0±31.6	<.0001
Total energy intake (kcal/day)	2425.9±1121.4	2549.7±1229.1	<.0001
Organ meat intake (g/1000 kcal/day)	2.99±5.33	3.27±5.40	<0.01
Smoking status (%)			
Smoker	12.3	22.5	<.0001
Ex-smoker	3.20	5.58	<.0001
Non-smoker	84.5	71.9	<.0001
Drinking status (%)			
Everyday	3.02	4.69	<.0001
Sometime	51.4	58.0	<.0001
Ex-drinker	9.02	9.3	0.69
Non-drinker	36.6	28.1	<.0001
Education level (college or higher, %)	76.2	73.0	<.0001
Occupation (%)			
Managers	47.2	46.8	0.69
Professionals	16.1	16.8	0.34
Other	36.8	36.5	0.78

Household income (≥10,000 Yuan, %)	38.9	38.0	0.33
Hypertension (%)	11.3	23.3	<.0001
Hyperlipidemia (%)	29.3	47.3	<.0001
Diabetes (%)	2.16	4.44	<.0001
Family history of disease (%)			
CVD	29.2	35.2	<.0001
Hypertension	49.4	55.6	<.0001
Hyperlipidemia	0.38	0.53	0.23
Diabetes	23.5	28.3	<.0001

[a] BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; NAFLD, nonalcoholic fatty liver disease; PA, physical activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

[b] *P* values were calculated using t test for continuous variables and χ^2 test for categorical variables.

[c] Continuous variables are expressed means (± standard deviation) and categorical variables are expressed as percentages.

Table 2. The association of organ meat consumption with NAFLD (n=15,568) [a]

	Organ meat consumption				*P* for trend [b]
	Almost never	Tertile 1	Tertile 2	Tertile 3	
Median, min-max (g/1000 kcal/day)	0	1.53 (0.59-2.24)	3.12 (2.24-4.43)	7.87 (4.43-66.8)	
Number of participants	6,360	3,067	3,074	3,067	-
Cases/Person-years	1,455/22,306	648/111,35	707/10,789	794/10,695	
Model 1	1.00 (reference)	1.05 (0.95, 1.15) [c]	1.10 (1.00, 1.21)	1.17 (1.07, 1.29)	<0.001
Model 2	1.00 (reference)	1.05 (0.95, 1.15)	1.11 (1.01, 1.22)	1.17 (1.06, 1.28)	<0.001
Model 3	1.00 (reference)	1.04 (0.94, 1.15)	1.08 (0.99, 1.19)	1.11 (1.01, 1.22)	0.02

[a] NAFLD, nonalcoholic fatty liver disease.

[b] Obtained by using multivariable Cox regression model.

[c] Hazard ratios (95% confidence interval) (all such values).

Model 1 was adjusted for age, sex, and BMI.

Model 2 was adjusted for age, sex, BMI, smoking status, drinking status, education level, occupation, household income, physical activity, total energy intake, family history of disease (including cardiovascular disease, hypertension, hyperlipidemia, and diabetes), hypertension, hyperlipidemia, and diabetes.

Model 3 was adjusted for variables in model 2 plus intakes of vegetable, fruit, seafood, soft drink, and red meat.

Because the majority of participants (40.8%) almost never consumed organ meats, we set it as “almost never” as the reference group. The remaining participants with organ meat consumption were ranked into tertiles.

Table 3. Association between organ meat consumption and risk of NAFLD stratified by major covariates [a]

	Organ meat consumption				*P* for trend [b]	*P* for interaction [c]
	Almost never	Tertile 1	Tertile 2	Tertile 3		
Age, y						0.69
<40	1.00 (reference)	1.08 (0.94, 1.24) [d]	1.14 (1.00, 1.3)	1.03 (0.90, 1.18)	0.48	
≥40	1.00 (reference)	1.05 (0.91, 1.21)	1.01 (0.87, 1.17)	1.23 (1.07, 1.41)	0.01	
Sex						0.42
Male	1.00 (reference)	1.04 (0.92, 1.17)	1.14 (1.01, 1.28)	1.15 (1.01, 1.30)	0.01	
Female	1.00 (reference)	1.05 (0.90, 1.23)	1.05 (0.89, 1.22)	1.06 (0.90, 1.25)	0.45	
BMI (kg/m ^{2})						0.66
<24.0	1.00 (reference)	1.06 (0.91, 1.24)	1.04 (0.89, 1.21)	1.12 (0.96, 1.30)	0.20	
≥24.0	1.00 (reference)	1.05 (0.93, 1.19)	1.13 (1.00, 1.27)	1.13 (1.00, 1.28)	0.03	
Smoking status						0.59
Current	1.00 (reference)	1.06 (0.87, 1.30)	1.14 (0.93, 1.40)	1.21 (0.98, 1.48)	0.06	
Never	1.00 (reference)	1.28 (0.85, 1.94)	1.24 (0.82, 1.86)	1.31 (0.84, 2.05)	0.19	
Former	1.00 (reference)	1.02 (0.91, 1.14)	1.03 (0.92, 1.15)	1.10 (0.98, 1.23)	0.14	
Alcohol drinking status						0.87
Everyday	1.00 (reference)	0.79 (0.50, 1.25)	1.14 (0.73, 1.76)	0.98 (0.62, 1.55)	0.84	
Sometime	1.00 (reference)	1.02 (0.90, 1.16)	1.07 (0.94, 1.21)	1.10 (0.97, 1.25)	0.11	
Ex-drinker	1.00 (reference)	0.98 (0.69, 1.39)	1.08 (0.78, 1.51)	1.34 (0.96, 1.85)	0.10	

Non-drinker	1.00 (reference)	1.11 (0.92, 1.33)	1.07 (0.89, 1.29)	1.13 (0.93, 1.37)	0.22	
PA (MET × hour/week)						0.71
≥23.0	1.00 (reference)	1.03 (0.90, 1.19)	1.05 (0.91, 1.20)	1.12 (0.97, 1.30)	0.13	
<23.0	1.00 (reference)	1.07 (0.95, 1.20)	1.14 (1.02, 1.28)	1.12 (1.00, 1.26)	0.03	
Hyperlipidemia						0.68
Yes	1.00 (reference)	1.03 (0.89, 1.19)	1.12 (0.98, 1.29)	1.20 (1.04, 1.39)	0.01	
No	1.00 (reference)	1.06 (0.93, 1.21)	1.03 (0.91, 1.18)	1.05 (0.92, 1.19)	0.52	
Diabetes						0.87
Yes	1.00 (reference)	0.79 (0.47, 1.32)	0.88 (0.53, 1.47)	0.76 (0.44, 1.33)	0.34	
No	1.00 (reference)	1.06 (0.96, 1.17)	1.10 (1.00, 1.21)	1.12 (1.02, 1.24)	0.01	
Hypertension						0.64
Yes	1.00 (reference)	1.16 (0.95, 1.42)	1.13 (0.92, 1.40)	1.17 (0.94, 1.44)	0.13	
No	1.00 (reference)	1.02 (0.92, 1.14)	1.06 (0.96, 1.19)	1.11 (1.00, 1.24)	0.05	

[a] NAFLD, nonalcoholic fatty liver disease; PA, physical activity

[b] Obtained by using multivariable Cox regression model. Adjusted for age, sex, BMI, smoking status, drinking status, education level, occupation, household income, physical activity, total energy intake, family history of disease (including cardiovascular disease, hypertension, hyperlipidemia, and diabetes), hypertension, hyperlipidemia, diabetes, intakes of vegetable, fruit, seafood, soft drink and red meat.

[c] *P* for interaction was calculated using likelihood ratio test.

[d] Hazard ratios (95% confidence interval) (all such values).