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Raw orange intake is associated with higher prevalence of non-alcoholic fatty liver disease in an adult population

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ABSTRACT

Objectives: Non-alcoholic fatty liver disease (NAFLD) is one of the most common public health issues worldwide. Oranges are the most popular fruit consumed in the world. Admittedly, flavonoids in oranges act as antioxidants and improve liver steatosis. However, oranges also are rich in fructose, which is a risk factor in the progress of NAFLD. Therefore, we hypothesize that orange intake may be a double-edged sword in the development of NAFLD. To our knowledge, there currently is little evidence of the effect of dietary orange intake on NAFLD. The aim of this study was to investigate how orange intake is related to NAFLD in a general adult population.

Methods: We randomly recruited 27,214 adults into the Tianjin Chronic Low-Grade Systemic Inflammation and Health Cohort Study. NAFLD was diagnosed by liver ultrasonography. Raw orange intake was assessed by a validated self-administered food frequency questionnaire. Multiple logistic regression analysis was used to evaluate the association between orange intake and the prevalence of NAFLD.

Results: There was a 27.18% prevalence of NAFLD among the participants. Consumption of orange was positively associated with the prevalence of NAFLD after adjustment for all potential confounding factors ($P_{trend} = 0.04$). The odds ratios (95% confidence interval) of the categories of orange intake in the NAFLD were 1.00 (reference) for less than once per week, 1.02 (0.95–1.11) for 1 to 6 times per week, and 1.17 (1.03–1.33) for ≥7 times per week, respectively.

Conclusions: The present study demonstrated that orange intake is positively associated with the prevalence of NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common public health issues worldwide, with high prevalence estimates ranging from 25% to 45% [1], and has potentially serious sequelae such as hepatic insulin resistance (IR), type 2 diabetes, and liver cancer [2]. In China, the prevalence of NAFLD among adults in the general population is >20% and has paralleled the increase in both obesity and type 2 diabetes [3]. Unfortunately, there is no conclusive evidence for any particular treatment approach for NAFLD. Thus, more studies for modifiable risk factors to decrease the prevalence of NAFLD are essential.

NAFLD is a generic term that refers to a spectrum of lesions ranging from pure steatosis to a complex pattern with active lesions of hepatocyte injury, apoptosis, cell death, and significant inflammation in the absence of alcohol intake [4]. Knowledge

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about the pathogenesis of NAFLD is still incomplete [5], and inflammatory injury [6] is widely seen as the common pathophysiological determinant in the progression of NAFLD [7].

Several studies have shown that healthy eating can benefit liver health [8,9]. Orange is the most popular fruit consumed worldwide, and according to the United States Department of Agriculture (USDA), global orange production for 2016 to 2017 was forecast at 49.6 million metric tons, an increase from >2.4 million metric tons from the previous year [10]. It has consistently ranked as the third most consumed fresh fruit [11]. As a nutritious food, each orange contains about 86.8% water and 9.4% sugars and other nutrients like flavonoids [12]. Indeed, the flavonoid in orange is a polyphenolic compound with antioxidant actions [13]. Previous studies have suggested that citrus flavonoids may have beneficial effects in preventing hepatic steatosis [14–16] and IR [17–19]. Despite their antioxidant ingredient content, however, it is an inescapable fact that oranges also are high in fructose [20], a lipogenic, proinflammatory dietary factor that results in oxidative stress [21]. Intake of food and beverages containing fructose is linked to weight gain and dysregulation of glucose metabolism [22] and consequently increases the risk for NAFLD [23,24]. Furthermore, oranges have a higher glycemic index (GI, 43) than apples (GI, 36) and pears (GI, 36), both of which are consumed in high quantities in China [25]. Previous studies suggested that a high GI diet is associated with obesity and inflammation [26] and is consequently linked to NAFLD [27]. Thus, it is conceivable that orange intake may be a double-edged sword in the development of NAFLD. However, to our knowledge, no study has yet assessed the association between raw orange intake and NAFLD. Meanwhile, according to data from the UN Food and Agriculture Organization, the consumption and production of oranges is high worldwide [28]. For example, orange consumption in marketing year 2016 to 2017 in China has been revised up significantly and orange consumption in marketing year 2017 to 2018 was expected to increase as a result of a larger crop and continued robust Chinese consumer demand for high-quality fresh fruit [29]. Thus, the objective of the present study was to determine how raw orange intake is associated with the prevalence of NAFLD in a large general adult population in China.

Materials and methods

Study design

This cross-sectional study is based on the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIHealth) Cohort Study. Participants were recruited during their annual health examinations at the Tianjin Medical University General Hospital-Health Management Center, the largest and most comprehensive physical examination center in Tianjin. All participants were asked to complete a structured, self-administered health status questionnaire used in the TCLSIHealth Cohort Study before their annual health examinations and received reports of their health examination 3 d later. Thus, the results of the examinations did not influence the interviews. More information on the research design and data collection of the TCLSIHealth has been detailed elsewhere [30–32].

Ethical approval was given by the Medical Ethics Committee of Institutional Review Board of the Tianjin Medical University, and each participant had written informed consent before the study.

Eligibility criteria

This cross-sectional study used data from the TCLSIHealth, ranging from 2012 to 2016. During the research period, 31 485 participants took part in the health examinations that included abdominal ultrasound detection. The eligibility criteria are shown in Figure 1. Participants with sonographic fatty liver and a self-reported a weekly alcohol intake of ≥140 g for men and ≥70 g for women were classified as having AFLD [33] and were excluded in present study (n = 2075). In addition,

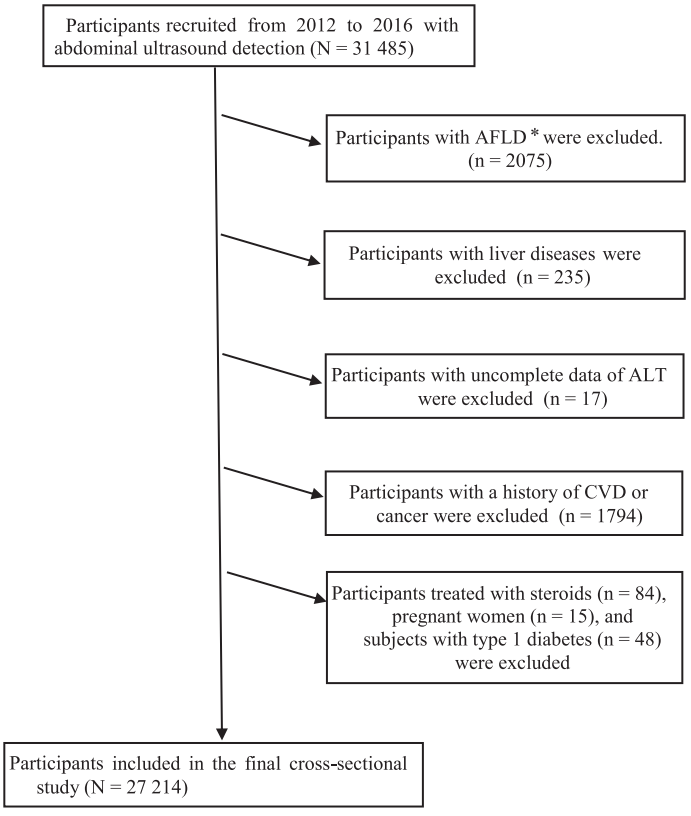

Fig. 1. Participant flowchart. AFLD, alcoholic fatty liver disease; ALT, alanine aminotransferase; CVD, cardiovascular diseases.
*Participants with sonographic fatty liver and a self-reported weekly alcohol intake of ≥140 g for men and ≥70 g for women were classified as having AFLD. †Liver diseases include chronic hepatitis B or C, liver surgery, autoimmune liver diseases, and liver cancer.

participants who had liver diseases like chronic hepatitis B or C, had autoimmune liver diseases or liver cancer, and those who had previous liver surgery also were excluded (n = 235). In addition, we excluded participants who did not complete data collection on alanine aminotransferase (ALT; n = 17) or those with a history of cardiovascular disease (n = 1481) or cancer (n = 313). Furthermore, participants treated with steroids (n = 84), pregnant women (n = 15), and participants with type 1 diabetes (n = 48) were excluded. Based on these exclusions, the final cross-sectional study population comprised 27 214 participants (mean ± standard deviation age: 41.39 ± 12.02).

Assessment of NAFLD

The diagnosis of fatty liver was based on the result of real-time ultrasonography using standardized criteria performed by experienced sonographers [34]. Images were captured in a standard fashion with the patient in the supine position with the right arm raised above the head. Diagnosis of fatty liver disease required at least two of the following abnormal findings [35]: 1) diffusely increased liver near-field ultrasound echo ("bright liver") and increased liver echotexture compared with the kidneys and 2) vascular blurring and the gradual attenuation of far-field ultrasound echo. Participants with sonographic fatty liver and a self-reported weekly alcohol intake of <140 g for men and <70 g for women were classified as having NAFLD [36].

Assessment of dietary

Information on usual intake of foods and beverages was assessed using a 100-item validated semiquantitative food frequency questionnaire (FFQ) with specified serving sizes, although the FFQ originally included 81 items [37]. The FFQ was designed to measure the food and beverage intake of the participants in the previous month. Because the reproducibility and validity of the questionnaire have been assessed, the FFQ represents the long-term food and beverage intake of the participants. Furthermore, seasonal food intake, such as orange and watermelon, included intake of participants in the previous month and in the natural mature season. Responses in the FFQ for food intake included a range of seven frequencies from *almost never* to *2 or more times per day*. Responses to beverage intake questions included eight frequencies ranging from *almost never drink* to *4 or more times per day*.

The daily intake of nutrients was calculated using an ad hoc computer program developed to analyze the questionnaire. Intake of food items were calculated from portion size (g/time) and the frequency of each food item consumed per day [38,39]. We calculated each daily food intake by multiplying the frequency of consumption by the portion size of each food. Furthermore, valid and reliable Chinese food composition tables [40] were used as the nutrient database to acquire the nutrient content of each food item. By combining the information from the FFQ with the Chinese food composition table, the nutrient intake was calculated by first multiplying the amount of consumption for each food item by its nutrient content and then summing nutrient contributions across all food items [41].

Validity and reproducibility

We randomly selected 150 participants from the TCLSIHealth cohort to assess the reproducibility and validity of the FFQ by comparing the data from the questionnaire with the data from two dietary questionnaires collected approximately 3 mo apart and weighed dietary records (WDRs). Spearman's rank correlation coefficient for energy intake between the two FFQ administered 3 mo apart was 0.68. Correlation coefficients for food items (fruits, vegetables, fish, meat, and beverages) between two FFQ administered 3 mo apart ranged from 0.62 to 0.79. Spearman's rank correlation coefficient for energy intake by the WDRs and the FFQ was 0.49. Correlation coefficients for nutrients (quercetin, vitamin C, vitamin E, polyunsaturated fats, saturated fats, carbohydrates, and calcium) between the WDRs and the FFQ ranged from 0.35 to 0.54.

Assessment of other variables

Waist circumference (WC) was measured at the umbilical level with participants standing and breathing normally. The anthropometric variables (height and body weight) were recorded using a standard protocol. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in squared meters (m^2). Sociodemographic variables, including age, sex, educationl levels, employment status, and household income, also were assessed.

Detailed information about personal and family history of physical illness, smoking behavior (never, former, and current smoker) and drinking behavior (never, former, sometimes, and every day) was provided by each participant.

Blood samples for analysis of fasting blood glucose (FBG) and lipids were collected in siliconized vacuum plastic tubes. FBG was measured using the glucose oxidase method, total cholesterol and triacylglycerol (TG) was measured by enzymatic methods, low-density lipoprotein cholesterol was measured by the polyvinyl sulfuric acid precipitation method, high-density lipoprotein cholesterol was measured by chemical precipitation, and ALT was measured by the International Federation of Clinical Chemists method using reagents from Roche Diagnostics on an automatic biochemistry analyzer (Roche Cobas 8000 modular analyzer, Mannheim, Germany). Blood pressure (BP) was measured twice from the upper right arm using an automatic device (KD598, Andon, Tianjin, China) after the individual had rested for 5 min in a seated position, and the average of these two measurements was taken as the BP value. Additional measurements were made until stabilization if the first two results were substantially different [42]. The average of the two closest readings (including the last reading) was calculated to determine the reported BP for each participant.

Physical activity (PA) in the most recent week was assessed using the validated Chinese version of the International Physical Activity Questionnaire [43]. If participants had performed any activities, further questions were asked about the frequency and duration of walking, moderate activity, and vigorous activity. According to the following formula, metabolic equivalents (MET) hours per week were calculated using corresponding METs coefficients (3.3, 4, and 8, respectively):MET coefficient of activity × duration (h/d) × frequency (d/wk).

The weekly MET hours were calculated by combining separate hours for different activities. Total PA levels were assessed according to weekly MET hours.

Metabolic syndrome (MetS) was defined according to the criteria of the 2009 American Heart Association scientific statements [44]. The diagnosis criterion contained at least three of the following listed:

- Elevated WC for Chinese individuals (≥85 cm in men; ≥80 cm in women).
- Elevated TGs (≥1.7 mmol/L), or drug treatment for elevated TGs.
- Reduced HDL (<1 mmol/L in men; <1.3 mmol/L in women) or drug treatment for reduced HDL.
- Elevated BP (systolic BP [SBP] ≥130 mm Hg or diastolic BP [DBP] ≥85 mm Hg) or antihypertensive drug treatment.
- Elevated FBG (≥5.56 mmol/L) or drug treatment for elevated glucose.

Statistical analysis

The final categories of the frequency of orange intake according to the frequency distribution of the responses were as follows: less than once per week, 1 to 6 times per week, and ≥7 times per week. Participants were divided into ordered categorical variables (less than once per week was coded as "1"; 1–6 times per week was coded as "2"; and ≥7 times per week was coded as "3") by the frequency of orange intake. The descriptive data were presented as the mean (with 95% confidence interval [CI]) or as percentages. P_{trend} for proportional variables across increasing quartiles of the orange intake were calculated using logistic regression. P_{trend} for continuous variables across increasing quartiles of the orange intake were calculated using analysis of variance. For further analysis, the NAFLD was used as dependent variable, and the frequency of orange intake was used as independent variables. Multiple logistic regression models were used to assess the association between orange intake and the presence of NAFLD, using the lowest category of orange intake (less than once per week) as the reference group. For analysis, crude model was conducted without any adjustment, and then the analysis-adjusted age, sex, and BMI was performed. In addition, multiple-adjusted model was adjusted for age; sex; BMI; smoking status; drinking status; education level; employment status; household income; PA; MetS; total energy intake; intake of protein, carbohydrates, fats, eicosapentaenoic acid (EPA) + docosahexenoic acid (DHA), fruits, vegetables, soft drinks and juice; and family history of CVD, hypertension, hyperlipidemia, and diabetes. The interactions between orange intake and confounders of NAFLD were tested by addition of cross-product terms to the regression analysis. A linear trend for the prevalence of NAFLD across increasing quartiles of orange intake was calculated using the ordered categorical variable value of each quartile as a continuous variable based on logistic regression. All tests presented were two-tailed and $P < 0.05$ was considered statistically significant. Data were analyzed by using the SAS 9.3 edition for Microsoft Windows (SAS Institute Inc., Cary, NC, USA).

Results

For this study, 50.5% (13 743) of participants were men and 49.5% (13 471) were women. The prevalence of NAFLD was 27.18% (7396). Table 1 shows the sociodemographic, dietary, and clinical data to compare those variables between participants with and without NAFLD. As shown, participants with NAFLD tended to be men ($P < 0.0001$) and older ($P < 0.0001$). Compared with the participants without NAFLD, the patients in the present study tended to have higher BMI ($P < 0.0001$), WC ($P < 0.0001$), total cholesterol ($P < 0.0001$), TG ($P < 0.0001$), LDL ($P < 0.0001$), SBP ($P < 0.0001$), DPB ($P < 0.0001$), FBG ($P < 0.0001$), and ALT ($P < 0.0001$), but a lower HDL ($P < 0.0001$). Moreover, participants with NAFLD participated in more PA ($P < 0.0001$), had higher total protein intake

Table 1
Participant characteristics by NAFLD

	Participants without NAFLD	Participants with NAFLD	*P*-value*
Participants (n)	19 818	7396	-
Age (y)	38.47 (38.32–38.62)†	43.38 (43.11–43.66)	<0.0001
Sex (males, %)	41.88	73.61	<0.0001
BMI (kg/m^2)	22.86 (22.82–22.90)	27.52 (27.44–27.60)	<0.0001
Waist circumference (cm)	77.71 (77.59–77.84)	91.57 (91.33–91.81)	<0.0001
TC (mmol/L)	4.60 (4.58–4.61)	5.02 (4.99–5.04)	<0.0001
TG (mmol/L)	0.94 (0.94–0.95)	1.71 (1.69–1.73)	<0.0001
LDL (mmol/L)	2.62 (2.61–2.63)	2.97 (2.95–2.99)	<0.0001
HDL (mmol/L)	1.43 (1.42–1.43)	1.14 (1.14–1.15)	<0.0001
SBP (mm Hg)	115.93 (115.73–116.13)	127.11 (126.75–127.46)	<0.0001
DBP (mm Hg)	72.89 (72.76–73.03)	80.93 (80.68–81.18)	<0.0001
FBG (mm Hg)	4.85 (4.84–4.86)	5.28 (5.26–5.30)	<0.0001
ALT (U/L)	15.14 (15.03–15.25)	28.01 (27.68–28.35)	<0.0001
Physical activity (MET × h/wk)	9.91 (9.73–10.10)	10.76 (10.44–11.09)	<0.0001
Total energy intake (kcal/d)‡	1992.22 (1984.18–2000.28)	1991.69 (1978.56–2004.91)	0.95
Total protein intake (g/d)‡	83.64 (83.16–4.12)	85.62 (84.81–86.44)	<0.0001
Total carbohydrate intake (g/d)‡	358.09 (355.96–360.24)	356.24 (352.77–359.74)	0.37
Total fat intake (g/d)‡	44.80 (44.50–45.09)	46.13 (45.63–46.63)	<0.0001
EPA+DHA (g/d)‡	3.89 (3.86–3.93)	4.05 (3.99–4.11)	<0.0001
Total fiber intake (g/d)‡	18.96 (18.85–19.08)	19.12 (18.93–19.31)	0.16
Total fruit consumption (g/d)§	294.22 (291.02–297.47)	287.30 (282.19–292.51)	0.03
Total vegetable consumption (g/d)§	247.06 (245.16–248.96)	251.41 (248.26–254.60)	0.02
Metabolic syndromes (yes, %)	11.63	52.48	<0.0001
Smoking status (%)			
Smoker	15.49	27.87	<0.0001
Former smoker	4.15	7.58	<0.0001
Drinker (%)			
Everyday	3.80	1.97	<0.0001
Sometimes	53.41	63.63	<0.0001
Former drinker	9.76	10.77	0.01
Soft drink			
<1 × /wk	56.13	56.28	0.93
1–6 × /wk	17.34	16.67	0.21
≥1 × /wk	26.53	27.05	0.32
Education level (college graduate or higher, %)	68.13	61.41	<0.0001
Household income (>10,000 Yuan, %)	34.88	34.27	0.36
Employment status (%)			
Managers	42.62	42.17	0.51
Professionals	16.72	17.62	0.09
Other	40.66	40.21	0.52
Family history of diseases (%)			
CVD	27.75	32.72	<0.0001
Hypertension	47.41	54.37	<0.0001
Hyperlipidemia	0.31	0.49	0.03
Diabetes	23.08	31.26	<0.0001

ALT, alanine aminotransferase; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DHA, docosahexenoic acid; EPA, eicosapentaenoic acid; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerols

*Analysis of variance or χ^2 test.

†Geometric mean (95% CI; all such values).

‡Nutrient intake was calculated by first multiplying the amount of consumption for each food item by its nutrient content and then summing up nutrient contributions across all food items.

§Food item intake was calculated by multiplying the frequency of consumption per day by the portion size of each food item.

($P < 0.0001$), fat intake ($P < 0.0001$), EPA + DHA intake ($P < 0.0001$), and vegetable intake ($P = 0.02$), but less total fruit intake ($P = 0.03$). The participants with NAFLD also had lower education level ($P < 0.0001$). More of the NAFLD population were current smokers ($P < 0.0001$) and current drinkers (drinking sometimes; $P < 0.0001$); had MetS ($P < 0.0001$); and reported a family history of CVD ($P < 0.0001$), hypertension ($P < 0.0001$), hyperlipidemia ($P = 0.03$), and diabetes ($P < 0.0001$).

The participant characteristics according to frequency of orange intake (less than once per week, 1–6 times per week, ≥7 times per week) are presented in Table 2. Compared with participants with the lowest frequency of orange intake, those with the higher frequency tended to be women ($P_{trend} < 0.0001$), younger ($P_{trend} < 0.0001$), and to have lower WC ($P_{trend} < 0.0001$), DBP ($P_{trend} < 0.0001$), TG ($P_{trend} < 0.0001$), LDL ($P_{trend} = 0.02$), FBG ($P_{trend} < 0.01$), and ALT ($P_{trend} = 0.02$), but higher HDL ($P_{trend} < 0.0001$). In addition, the frequency of orange intake was positively associated with PA ($P_{trend} < 0.0001$), total energy intake ($P_{trend} < 0.0001$), protein intake ($P_{trend} < 0.0001$), carbohydrate intake ($P_{trend} < 0.0001$), fat intake ($P_{trend} < 0.0001$), fiber intake ($P_{trend} < 0.0001$), EPA + DHA intake ($P_{trend} < 0.0001$), fruit ($P_{trend} < 0.0001$) and vegetable intake ($P_{trend} < 0.0001$), but lower soft drink intake (≥1 times per day; $P_{trend} < 0.01$). Fewer participants with high orange intake were current smokers ($P_{trend} < 0.0001$) and drinkers ($P_{trend} < 0.0001$), had MetS ($P_{trend} < 0.0001$) and a family history of CVD ($P_{trend} < 0.0001$), had hypertension ($P_{trend} = 0.02$) and diabetes ($P_{trend} < 0.001$), and a higher educational level (college graduate or higher; $P_{trend} < 0.0001$) and household income (>10,000 Yuan; $P_{trend} < 0.0001$). Otherwise, no significant differences were observed between participants in different frequency of orange intake.

Table 2
Participant characteristics by frequency of dietary orange intake

	Frequency of dietary orange intake			
	1 × /wk	1–6 × /wk	≥7 × /wk	P_{trend}*
Participants (n)	8215	15 966	3033	-
Age (y)	40.87 (40.62–41.11)	39.26 (39.09–39.43)†	39.38 (38.98–39.77)	<0.0001
Sex (males, %)	56.04	49.44	41.08	<0.0001
BMI (kg/m^2)	24.12 (24.04–24.20)	24.01 (23.95–24.07)	23.98 (23.85–24.11)	0.07
Waist circumference (cm)	82.04 (81.80–82.28)	80.99 (80.82–81.16)	80.56 (80.17–80.95)	<0.0001
TC (mmol/L)	4.72 (4.70–4.74)	4.70 (4.69–4.71)	4.70 (4.67–4.73)	0.27
TG (mmol/L)	1.15 (1.13–1.16)	1.10 (1.09–1.11)	1.07 (1.05–1.10)	<0.0001
LDL (mmol/L)	2.73 (2.71–2.75)	2.72 (2.70–2.73)	2.69 (2.66–2.72)	0.02
HDL (mmol/L)	1.32 (1.31–1.33)	1.34 (1.34–1.35)	1.37 (1.36–1.38)	<0.0001
SBP (mm Hg)	119.12 (118.79–119.45)	118.76 (118.52–119.00)	118.73 (118.18–119.28)	0.23
DBP (mm Hg)	75.50 (75.26–75.73)	74.84 (74.67–75.00)	74.47 (74.09–74.85)	<0.0001
FBG (mm Hg)	5.00 (4.99–5.02)	4.94 (4.93–4.95)	4.96 (4.93–4.98)	<0.01
ALT (U/L)	18.08 (17.85–18.31)	17.88 (17.71–18.04)	17.54 (17.18–17.91)	0.02
Physical activity (MET × h/wk)	9.84 (9.56–10.13)	10.12 (9.91–10.33)	11.07 (10.56–11.61)	<0.0001
Total energy intake (kcal/d)‡	1836.48 (1825.21–1847.82)	2042.51 (2033.51–2051.54)	2176.76 (2154.83–2198.92)	<0.0001
Protein intake (g/d)‡	76.17 (75.50–76.85)	86.14 (85.59–86.69)	97.70 (96.29–99.14)	<0.0001
Carbohydrate intake (g/d)‡	313.92 (311.10–316.76)	368.08 (365.71–370.47)	437.00 (430.56–443.53)	<0.0001
Fat intake (g/d)‡	40.22 (39.82–40.62)	46.49 (46.16–46.83)	52.99 (52.12–53.87)	<0.0001
EPA + DHA intake (g/d)‡	3.49 (3.45–3.54)	4.12 (4.08–4.16)	4.28 (4.18–4.37)	<0.0001
Fiber intake (g/d)‡	15.94 (15.79–16.08)	19.79 (19.67–19.92)	24.72 (24.36–25.09)	<0.0001
Fruit intake (g/d)§	197.74 (194.60–200.92)	320.21 (316.61–323.85)	506.13 (493.17–519.42)	<0.0001
Vegetable intake (g/d)§	216.31 (213.78–218.87)	257.52 (255.35–259.70)	296.99 (291.30–302.79)	<0.0001
Metabolic syndromes (yes, %)	25.13	22.32	22.41	<0.0001
Smoking status (%)				
Smoker	22.68	17.77	14.36	<0.0001
Former smoker	6.21	4.67	4.24	<0.0001
Drinker (%)				
Everyday	4.31	2.92	2.62	<0.0001
Sometime	58.12	56.59	48.81	<0.0001
Former drinker	10.32	9.75	10.75	0.94
Soft drink				
<1 × /wk	57.97	54.81	58.44	0.08
1–6 × /wk	17.55	17.18	16.01	0.07
≥1 × /day	24.47	28.01	25.56	<0.01
Education level (college graduate or higher, %)	62.25	68.8.63	65.08	<0.0001
Household income (>10,000 Yuan, %)	30.59	36.46	36.61	<0.0001
Employment status (%)				
Managers	42.96	42.37	41.93	0.28
Professionals	17.43	17.02	15.38	0.03
Other	39.60	40.61	42.69	<0.01
Family history of diseases (%)				
CVD	30.65	28.91	25.91	<0.0001
Hypertension	50.10	49.22	47.58	0.02
Hyperlipidemia	0.41	0.38	0.13	0.06
Diabetes	26.31	25.23	22.98	<0.001

ALT, alanine aminotransferase; BMI, body mass index; CVD, cardiovascular diseases; DBP, diastolic blood pressure; DHA, docosahexenoic acid; EPA, eicosapentaenoic acid; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerols

*Analysis of variance or logistic regression analysis.

†Geometric mean (95% CI) (all such values).

‡Nutrient intake was calculated by first multiplying the amount of consumption for each food item by its nutrient content and then summing up nutrient contributions across all food items.

§Food item intake was calculated by multiplying the frequency of consumption per day by the portion size of each food item.

Table 3 shows the characteristics of participants with NAFLD according to the frequency of orange intake. Compared with participants with NAFLD who had the lowest frequency of orange intake, those with the higher frequency trended to be younger (P_{trend} = 0.02), female (P_{trend} < 0.0001), and to have lower WC (P_{trend} < 0.01) and TG (P_{trend} = 0.03), but higher HDL (P_{trend} < 0.01). In addition, the frequency of orange intake was positively associated with PA (P_{trend} < 0.0001), total energy intake (P_{trend} < 0.0001), protein intake (P_{trend} < 0.0001), carbohydrate intake (P_{trend} < 0.0001), fat intake (P_{trend} < 0.0001), fiber intake (P_{trend} < 0.0001), EPA + DHA intake (P_{trend} < 0.0001), fruit intake (P_{trend} < 0.0001), and vegetable intake (P_{trend} < 0.0001). Fewer participants with high orange intake were current smokers (P_{trend} < 0.0001), current drinkers (sometimes; P_{trend} < 0.0001), managers (P_{trend} < 0.001), and had a family history of CVD (P_{trend} < 0.001) and hypertension (P_{trend} = 0.01). The participants with high orange intake also had a higher level of education (college graduate or higher; P_{trend} = 0.02) and household income (>10,000 Yuan; P_{trend} < 0.0001). Otherwise, no significant differences were observed between participants with NAFLD in different frequency of orange intake.

Table 4 shows the crude and adjusted associations between orange intake and NAFLD. In the crude model, orange intake was significantly associated with a lower risk for NAFLD: The odds ratios (ORs; 95% CI) for NAFLD across increasing frequency of orange intake were 1.00 (reference), 0.89 (0.84–0.94), and 0.90 (0.82–0.99; P_{trend} < 0.01). However, the inverse association for

Table 3
Characteristics of participants with NAFLD by frequency of dietary orange intake

	Frequency of dietary orange intake			
	1 × /wk	1–6 × /wk	≥7 × /wk	P_{trend}*
No. of participants (n)	2366	4218	812	-
Age (y)	44.34 (43.87–44.83)†	42.88 (42.54–43.23)	43.23 (42.44–44.03)	0.02
Sex (males, %)	76.92	73.38	65.15	<0.0001
BMI (kg/m^2)	27.52 (27.39–27.65)	27.50 (27.41–27.60)	27.58 (27.36–27.80)	0.67
Waist circumference (cm)	92.02 (91.66–92.38)	91.42 (91.15–91.68)	91.03 (90.43–91.64)	<0.01
TC (mmol/L)	5.01 (4.97–5.05)	5.02 (4.99–5.05)	5.03 (4.96–5.09)	0.63
TG (mmol/L)	1.75 (1.71–1.78)	1.70 (1.67–1.73)	1.67 (1.61–1.73)	0.03
LDL (mmol/L)	2.96 (2.92–2.99)	2.97 (2.95–3.00)	2.98 (2.93–3.04)	0.45
HDL (mmol/L)	1.13 (1.12–1.14)	1.15 (1.14–1.15)	1.17 (1.15–1.19)	<0.01
SBP (mm Hg)	127.12 (126.49–127.76)	126.87 (126.39–127.34)	128.29 (127.20–129.40)	0.07
DBP (mm Hg)	81.30 (80.86–81.74)	80.76 (80.43–81.09)	80.76 (80.01–81.52)	0.23
FBG (mm Hg)	5.32 (5.28–5.36)	5.26 (5.23–5.29)	5.30 (5.23–5.37)	0.53
ALT (U/L)	27.73 (27.10–28.37)	28.16 (27.68–28.65)	28.08 (27.00–29.21)	0.58
Physical activity (MET × h/wk)	10.14 (9.61–10.71)	10.77 (10.34–11.22)	12.68 (11.56–13.92)	<0.0001
Total energy intake (kcal/d)‡	1843.24 (1822.21–1864.52)	2048.59 (2031.06–2066.28)	2156.26 (2114.42–2198.93)	<0.0001
Protein intake (g/d)‡	78.05 (76.79–79.33)	87.57 (86.51–88.64)	99.75 (97.02–102.56)	<0.0001
Carbohydrate intake (g/d)‡	315.40 (310.13–320.77)	366.97 (362.36–371.63)	435.38 (423.03–448.10)	<0.0001
Fat intake (g/d)‡	3.62 (3.53–3.71)	4.24 (4.16–4.32)	4.47 (4.28–4.67)	<0.0001
EPA + DHA intake (g/d)‡	16.17 (15.90–16.44)	19.95 (19.70–20.20)	25.03 (24.32–25.75)	<0.0001
Fiber intake (g/d)‡	193.73 (187.92–199.73)	317.99 (310.93–325.21)	515.81 (490.04–542.93)	<0.0001
Fruit intake (g/d)§	223.37 (218.57–228.26)	260.19 (256.00–264.45)	296.87 (286.08–308.06)	<0.0001
Vegetable intake (g/d)§	54.51	51.27	52.77	0.09
Metabolic syndromes (yes, %)	2202	3929	783	-
Smoking status (%)				
Smoker	31.70	26.90	21.97	<0.0001
Former smoker	8.99	7.08	6.13	<0.01
Drinker (%)				
Everyday	2.46	1.65	2.23	0.20
Sometime	65.79	64.41	53.23	<0.0001
Former drinker	10.41	10.68	12.28	0.21
Soft drink				
<1 × /wk	58.55	54.51	58.90	0.12
1–6 × /wk	16.93	16.81	15.16	0.33
≥1 × /wk	24.52	28.68	25.94	0.05
Educational level (college graduate or higher, %)	58.43	63.31	60.27	0.02
Household income (>10,000 Yuan, %)	29.57	36.80	34.88	<0.0001
Employment status (%)				
Managers	45.11	40.98	39.69	<0.001
Professionals	17.18	18.26	15.62	0.78
Other	37.72	40.76	44.69	<0.001
Family history of diseases (%)				
CVD	34.74	32.46	28.20	<0.001
Hypertension	56.30	53.75	51.97	0.01
Hyperlipidemia	0.59	0.50	0.12	0.15
Diabetes	31.83	31.77	26.97	0.05

ALT, alanine aminotransferase; BMI, body mass index; CVD, cardiovascular diseases; DBP, diastolic blood pressure; DHA, docosahexenoic acid; EPA, eicosapentaenoic acid; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; NAFLD, non-alcoholic fatty liver disease SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerols

*Analysis of variance or logistic regression analysis.

†Geometric mean (95% CI) (all such values).

‡Nutrient intake was calculated by first multiplying the amount of consumption for each food item by its nutrient content and then summing up nutrient contributions across all food items.

§Food item intake was calculated by multiplying the frequency of consumption per day by the portion size of each food item.

orange intake was no longer statistically significant after multivariable adjustments of age, sex, and BMI. In the final multivariate model, the ORs (95% CI) for NAFLD across increasing orange intake were 1.00 (reference), 1.02 (0.95–1.11), and 1.17 (1.03–1.33; P_{trend} = 0.04).

The tests for interaction between the frequency of orange intake and other confounders in the final models were not statistically significant ($P_{interaction}$ >0.05 for all).

Discussion

In this large-scale study, increasing consumption frequency of orange was associated with a higher prevalence of NAFLD in Chinese adults. After adjustments for confounding variables, compared with participants who consumed orange less than once a week, those who consumed >7 times per week had a 1.17-fold higher prevalence of NAFLD.

Oranges are one of the most popular fruits in China. Compared with other popular fruits in China, like pears and apples, oranges have a higher GI [25], which could be linked to the prevalence of NAFLD [26]. Moreover, orange production is forecast at 7.3 million metric tons in marketing year (MY) 2017 to 2018, up 4% from the previous year's revised production of 7 million metric tons [29]. Orange consumption in MY 2017 to 2018 was expected to increase as a result of the larger crop and continued, robust Chinese consumer demand for high-quality fresh fruit. Furthermore, as

Table 4
Adjusted association between orange intake and NAFLD

	Frequency of dietary orange intake			
	<1 × /wk	1–6 × /wk	≥7 × /wk	P_{trend}*
Participants (n)	8215	15966	3033	
Participants with NAFLD (n)	2366	4218	812	
Model 1†	1.00 (ref.)	0.89 (0.84–0.94)‡	0.90 (0.82–0.99)	<0.01
Model 2§	1.00 (ref.)	1.00 (0.93–1.08)	1.12 (0.99–1.26)	0.16
Model 3‖	1.00 (ref.)	1.02 (0.95–1.11)	1.17 (1.03–1.33)	0.04

NAFLD, non-alcoholic fatty liver disease
*Multiple logistic regression analysis.
†Crude model.
‡Adjusted odds ratios (95% CI) (all such values).
§Adjusted for age, sex, and BMI.
‖Additionally adjusted for smoking status, drinking status, education level, employment status, household income, physical activity, metabolic syndrome, total energy intake, intake of protein, carbohydrate, fat, eicosapentaenoic acid + docosahexenoic acid, fruit, vegetable, soft drink and juice, and family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes.

improving logistics, cold storage, and distribution infrastructure throughout the country helps to connect orange suppliers with more of the vast Chinese population, it is expected that steady growth in consumer demand will continue for several years to come. MY 2016 to 2017 consumption has been increased significantly to reflect recently released Chinese government production data [29]. Given that consumption of oranges is increasing in China and the association between orange consumption and NAFLD remains unclear, we decided to explore the effects of consumption of orange on NAFLD. The primary hypothesis was that orange intake may be a potentially double-edged sword effect on the prevention of NAFLD.

Previous studies reported that age [45] and BMI [46] were closely associated with the prevalence of NAFLD. The sex difference in the prevalence of NAFLD was also widely reported [47]. Thus, we first adjusted for age, sex, and BMI. After adjustment, the inverse association between orange intake and NAFLD was attenuated toward the null, leading us to conclude that age, sex, and BMI were major confounding factors. Second, previous studies demonstrated that NAFLD was associated with sociodemographic conditions such as education level, employment status, and household income [48,49]. In addition, nutritional intake can affect energy metabolism and subsequently affect NAFLD [23]. Metabolic syndromes was also reported an influence on the development of NAFLD [50]. Besides, several studies demonstrated that smoking and drinking status could affect the prevalence of NAFLD [51-53]. Family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes was also associated with the prevalence of NAFLD [54]. Thus, we made adjustments for educational level; employment status and household income; total energy intake; intake of protein, carbohydrates, fats, EPA + DHA, fruit, vegetables, soft drinks, and juice; smoking status; drinking status; PA; MetS; and family history of CVD, hypertension, hyperlipidemia, and diabetes. After these adjustments, a positive association was found between higher orange intake (≥7 times per week) and the prevalence of NAFLD.

We also explored the differences in characteristics of NAFLD patients by frequency of dietary orange intake. The frequency of dietary orange intake was positively associated with PA; HDL; total energy intake; intake of protein, carbohydrates, fats, fiber, EPA + DHA, fruits, and vegetables; education level; and household income, but negatively associated with age, WC, TG, and family history of diseases (CVD and hypertension). Meanwhile, NAFLD patients with the highest frequency of orange intake tended to be women and non-smokers, but had a lower proportion of the current drinkers (sometimes) and managers. These results suggested that these variables may explain the associations between orange intake and the prevalence of NAFLD.

Many studies have demonstrated that the macronutrient composition of the diet is very important in the onset and progression of NAFLD [55–57]. Compared with individuals without hepatosteatosis, patients with NAFLD have a higher caloric intake [58]. A study also has shown that high-fat diets, despite being isocaloric, increased the amount of intrahepatic TGs in rats [59]. Moreover, carbohydrate consumption plays a key role in the NAFLD because it contributed to the progression of IR [57]. The results presented in Tables 2 and 3 show that orange intake is closely associated with total energy intake, carbohydrate intake, and fat intake, respectively. Thus, these nutrients were likely to be the factors that account for the association between the orange intake and NAFLD. However, after adjustment for these factors, the positive association between the orange intake and the prevalence of NAFLD remained statistically significant. Alternatively, we assumed that the high amounts of fructose in oranges may partly explain the positive association here. Indeed, fructose is metabolized in the liver and plays an important role in the pathogenesis of NAFLD. Recently, animal models have suggested that fructose induces peroxisome proliferator-activated receptor γ coactivator 1 β, sterol regulatory element-binding protein 1 c (SREBP-1 c), and carbohydrate response element-binding protein (ChREBP) [60,61]. Both SREBP-1 c and ChREBP are transcription factors for proteins involved in lipogenesis, and their upregulation by fructose may increase de novo lipogenesis, which contributes to the progression of fatty liver [62]. In parallel, evidence from studies of humans also made this assumption plausible. Two studies in adults demonstrated that fructose consumption is increased in individuals with NAFLD [23,56]. Schwarz et al. reported that short-term fructose intake (25% of energy content) was associated with increased hepatic fatty acid synthesis and liver fat in healthy men, implying that fructose intake may contribute to the onset of NAFLD [63]. Moreover, studies also suggested that fructose may increase the severity of NAFLD. In a study including 427 NAFLD patients reported by Abdelmalek et al., daily fructose consumption was associated with hepatic inflammation and ballooning as well as fibrosis [64]. Based on these studies, it is considered that fructose is most likely to be a factor that explains the association between orange intake and the prevalence of NAFLD. Further study is needed to investigate this issue.

This study had several strengths. First, although several previous studies have indicated that some antioxidant ingredients in oranges may be a benefit for improving hepatic steatosis and obesity [13,65], evidence for raw orange intake with the risk for NAFLD in the general population is very limited. The present study extended the evidence in this regard, and first observed that higher orange intake (≥7 times per week) is positively associated with a

higher prevalence of NAFLD. Second, orange is also a source of polyphenolic compounds, a protective factor against developing NAFLD. However, the present results demonstrate that the protective effect of orange intake on the prevalence of NAFLD is inferior to its ability to cause NAFLD in the general population. Although a clear mechanism remains unknown, an unhealthy effect of orange intake is clear.

There were several limitations in this study. First, this was a cross-sectional study, which made it impossible to infer causality. We should establish a causal relationship between orange intake and NAFLD by prospective studies and intervention trials in the future. Second, liver biopsy, the gold standard in the diagnosis of liver disease, was not available in the present study because of the apparently healthy study population. Instead, we used hepatic ultrasonography scanning to detect fatty liver. This technique has a sensitivity of 89% and a specificity of 93% and is widely used in population-based studies because of its noninvasiveness and easy accessibility [66]. Third, because of the nature of the self-reporting questionnaire, recall bias, overreporting, and incorrect estimations of portion sizes exist. Thus, food intake may not be exact. Finally, although in the multivariable analysis we considered a multitude of lifestyle and dietary factors, residual or unmeasured confounding may still exist. Future large clinical trials are needed to confirm the mechanisms involved in association between dietary orange intake and NAFLD.

Conclusion

In support of these findings, we can conclude that higher orange intake is significantly associated with a higher prevalence of NAFLD in the general adult population. Further studies are needed to clarify the causality and the precise mechanisms.

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