ARTICLE

Epidemiology

Association between habitual yogurt consumption and newly diagnosed non-alcoholic fatty liver disease

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Abstract

Background/Objectives Many studies have suggested that probiotics may be applied as a therapeutic agent for non-alcoholic fatty liver disease (NAFLD). However, the effects of frequent yogurt consumption (as a natural probiotic source) on NAFLD remain poorly understood. This study was to examine the association of habitual yogurt consumption with newly diagnosed NAFLD in the general adult population.

Subject/Methods Overall, 24,389 adults were included in this cross-sectional study. Yogurt consumption was estimated by using a validated self-administered food frequency questionnaire. NAFLD was diagnosed by abdominal ultrasonography. We used logistic regression models to assess the association between yogurt consumption categories and newly diagnosed NAFLD.

Results The multivariable odds ratios with 95% confidence interval of newly diagnosed NAFLD were 1.00 (0.88, 1.14) for 1 time/week, 0.91 (0.81, 1.02) for 2–3 times/week, and 0.86 (0.76, 0.98) for ≥4 times/week (P for trend = 0.01), compared with those who consumed <1 time/week yogurt. The inverse association was observed in a sensitivity analysis.

Conclusion Higher yogurt consumption was inversely associated with the prevalence of newly diagnosed NAFLD. These results are needed to be confirmed in randomized controlled trials or prospective studies.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of hepatic fat in the absence of significant alcohol intake. It is a common cause of liver diseases, affecting approximately one-quarter of adults all over the world [1]. About 20% of adults have NAFLD in the mainland of China, and its prevalence is increasing [2]. It

has been reported that NAFLD is associated with an increased risk of cardiovascular disease (CVD) [3, 4]. To date, there is lacking efficacy and safety profiles of pharmacotherapies for NAFLD. Fortunately, lifestyle modification (including diet and exercise) is beneficial for the prevention of NAFLD [5].

Yogurt is a food produced by bacterial fermentation of milk. The consumption of yogurt delivers a large number of probiotics to the gastrointestinal tract [6]. A growing body of evidence shows that probiotics have therapeutic effects for NAFLD [7–10]. Potential mechanisms for these effects include reducing the oxidative and inflammatory liver damage, as well as lowering hepatic triglycerides (TG) and hepatic steatosis [7, 9, 11]. Moreover, probiotics can improve insulin resistance and dyslipidemia, both of which have a prominent role in the pathogenesis of NAFLD [11–13]. Hence, we hypothesized habitual yogurt consumption may protect against the development of NAFLD mainly due to the numerous probiotics contained in yogurt.

To date, two randomized controlled trials (RCTs) have shown that probiotic yogurt consumption could ameliorate

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hepatic steatosis and liver enzyme concentrations in NAFLD patients [14, 15]. However, there is no study that investigated the association between dietary yogurt intake and NAFLD in a general adult population. Thus, we designed this cross-sectional study to assess whether habitual yogurt consumption is inversely associated with the prevalence of newly diagnosed NAFLD in a large general Chinese adult population.

Methods

Study design and participants

The Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIH) Cohort Study is an ongoing large prospective study. This study was launched in 2007. Participants were drawn from health management centers and community management centers during annual health examinations in Tianjin, China. All participants received medical examinations such as abdominal ultrasonography and blood tests. In addition, participants completed questionnaires, regarding their smoking and alcohol drinking status, and provided their disease history since January 2010. All participants provided written informed consent before the study. The study was approved by the Institutional Review Board of Tianjin Medical University. This trial was registered at UMIN Clinical Trials Registry as UMIN000027174.

In this cross-sectional study, we used the baseline data of the TCLSIH Study from May 2013, when participants were administered a detailed lifestyle questionnaire including dietary intake as a standard part of the health checkup process, to December 2016. During the research period, a total of 32,308 subjects received health examinations. Participants with a history of CVD ($n = 1694$) or cancer ($n = 346$) or other liver diseases (including fatty liver disease, chronic hepatitis B or C, operation on liver, autoimmune liver diseases, or cirrhotic) ($n = 2177$) were excluded. We also excluded those with previously diagnosed NAFLD ($n = 3464$). Moreover, we excluded participants who had missing diet data ($n = 238$). Finally, this cross-sectional sample included 24,389 participants (Fig. 1).

NAFLD diagnosis

Fatty liver disease was assessed through a standardized abdominal ultrasound examination during annual health examinations. Participants meeting at least two of the following three parameters were diagnosed as fatty liver disease: hyperechogenicity of liver tissue compared to the renal cortex, vascular blurring, and diffuse echogenicity of the liver [16]. Participants with fatty liver disease and no
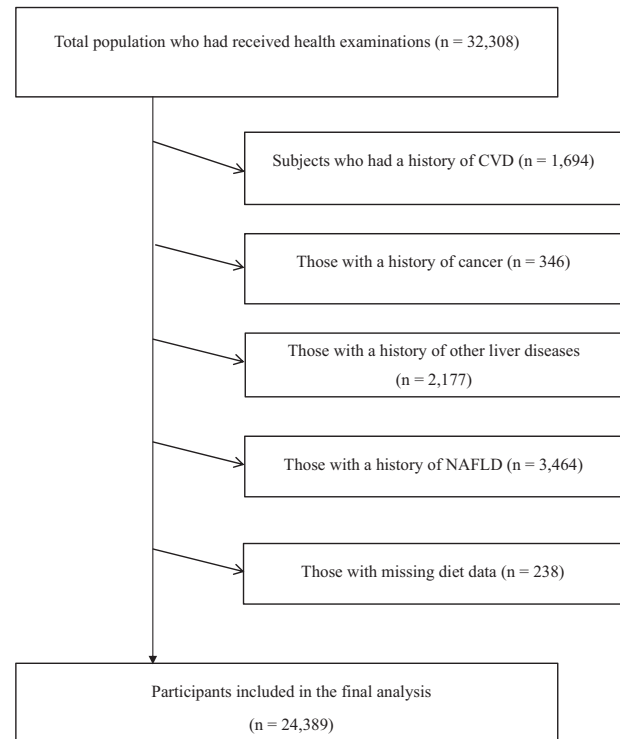

Fig. 1 Participant flow diagram. NAFLD non-alcoholic fatty liver disease, CVD cardiovascular disease

significant alcohol intake (<140 g/week for men and 70 g/week for women, respectively) were defined as having NAFLD [17]. The newly diagnosed NAFLD was detected in accordance with annual ultrasonic examination results [18].

Assessment of dietary intake

Data on diet was collected using a validated self-administered food frequency questionnaire (FFQ). This questionnaire included 100 food items with specified serving sizes, covering 7 response frequency categories ranging from 'almost never eat' to 'twice or more per day' for foods and 8 response frequency categories ranging from 'almost never drink' to 'four or more times per day' for drinks. Daily total energy and nutrient intake were calculated based on the latest available Chinese Food Composition Table [19]. The reproducibility and validity of the FFQ were assessed in a random sample of 150 participants from the TCLSIH Cohort Study [20].

The consumption frequency of dairy products (milk and yogurt) in the previous month was assessed using 7 possible response categories as follows: almost never eat, <1 time/week, 1 time/week, 2–3 times/week, 4–6 times/week, 1 time/day, and ≥2 times/day. For the analyses, intake frequency of yogurt was categorized as (times/week): <1 (reference), 1, 2–3, and ≥4.

Assessment of other variables

During health examinations, all participants completed a structured questionnaire in regard to their lifestyle factors, including smoking status, alcohol drinking status, and medical history. This questionnaire also collected information on demographics, including birth date (age), sex, household income, educational level, and occupation. Physical activity (PA) in the previous week was determined via the short form of the International Physical Activity Questionnaire [21]. PA was estimated as the total hours of metabolic equivalents per week (MET-h/week).

Body weight, height, and waist circumference (WC) were measured by trained staff using a standardized protocol. Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Blood pressure (BP) was measured following a standardized protocol using TM-2655P (A&D Company, Ltd., Tokyo, Japan). Participants sat at rest for at least 5 min in a quiet room before BP measurements, and then kept their upper right arms at heart level with their feet on the ground and their backs supported. Additional measurements were taken if the first two results differed by more than 5 mmHg [22]. At least 1 min elapsed between the measurements. Average values of the two closest readings were used to report BP value of each participant. Participants were defined as having hypertension if they had systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg or a history of hypertension based on the criteria of the JNC 7 [23].

Venous blood samples were collected in siliconized vacuum plastic tubes after an overnight fast. Fasting blood glucose (FBG), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using appropriate kits on Roche Cobas 8000 modular analyzer (Mannheim, Germany). Participants were considered to have diabetes if they had FBG ≥ 7.0 mmol/L, or had a self-reported history of diabetes or antidiabetic drug use [24]. Participants were considered to have hyperlipidemia if they met at least one of the following criteria: TC ≥ 5.17 mmol/L or TG ≥ 1.7 mmol/L or LDL-C ≥ 3.37 mmol/L or a history of hyperlipidemia or taking antihyperlipidemic drugs. Metabolic syndrome (MS) was determined in accordance with the criteria for China of the American Heart Association and International Diabetes Federation scientific statement of 2009 [25]. White blood cell (WBC) count was determined by an automated hematology analyzer XE-2100 (Sysmex, Kobe, Japan) and expressed as ×1000 cells/mm³ [26].

Statistical analysis

To improve the normality of the data, we used the natural logarithm for continuous variables before analysis. Baseline characteristics were presented as geometric means with 95% confidence interval (CI) for continuous variables and percentages for categorical variables. Baseline participant characteristics between groups were assessed by analysis of variance and logistic regression analysis, as appropriate. Multiple comparisons were corrected using the Bonferroni method. The odds ratios (ORs) and 95% CI of newly diagnosed NAFLD were estimated using logistic regression models. We fitted five models in the analyses. The first model was unadjusted. The second model was adjusted for age, sex, and BMI. In model 3, we adjusted for smoking status, alcohol drinking status, educational level, occupation, household income, PA, family history of CVD, family history of hypertension, family history of hyperlipidemia, family history of diabetes, and intake of total energy, carbohydrate, and total fat, EPA and DHA, soft drinks, vegetables, fruits, sweet foods, and milk. In model 4, we additionally adjusted for hypertension, diabetes, and hyperlipidemia. In a final model, we further adjusted for WBC count (×1000 cells/mm³: continuous). The linear trend was tested by assigning yogurt consumption category as an ordinal variable in the logistic models.

Interactions between yogurt consumption and potential confounders were examined by including the quadratic terms in the final model (model 5). Multicollinearity among covariates was tested by the variance inflation factor (VIF). Moreover, we conducted a sensitivity analysis after excluding participants with MS from the analysis. Data analysis was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population by yogurt consumption categories are shown in Table 1. Participants with more frequent consumption of yogurt tended to be younger, were women, had lower BMI, WC, TC, TG, LDL-C, SBP, DBP, FBG level, and WBC count, but had higher HDL-C level (P for all trend < 0.0001), and were more likely to exercise (P for trend < 0.001). They also consumed more total energy, carbohydrate intake, total fat, vegetables, fruits, sweet foods, EPA and DHA, and soft drinks (P for all trend < 0.0001). In addition, participants with higher yogurt consumption were less likely to be current smokers, ex-smokers, everyday drinkers, sometime drinkers, ex-drinkers, employed as professionals or other, and to have MS, hypertension, hyperlipidemia, diabetes, or a family history of CVD (P for all trend < 0.05). Participants with higher yogurt consumption were more likely to be non-smokers, non-drinkers, employed as managers, and to have a family history of hyperlipidemia or diabetes (P for all trend < 0.05).

Table 1 Participant characteristics according to frequency of yogurt consumption ($n = 24{,}389$)

Characteristics	Yogurt consumption				P for trend[a]
	<1 time/week	1 time/week	2–3 times/week	≥4 times/week	
No. of subjects	10,271	3389	5959	4770	–
Age (years)	41.7 (41.4, 41.9)[b]	37.0 (36.7, 37.4)	36.8 (36.5, 37.0)	37.7 (37.4, 38.0)	<0.0001
Men (%)	56.5	49.3	38.5	35.4	<0.0001
BMI (kg/m^2)	24.1 (24.1, 24.2)	23.5 (23.4, 23.6)	23.3 (23.2, 23.4)	23.3 (23.2, 23.4)	<0.0001
WC (cm)	82.3 (82.1, 82.5)	79.8 (79.4, 80.2)	78.5 (78.3, 78.8)	78.4 (78.1, 78.7)	<0.0001
TC (mmol/L)	4.72 (4.71, 4.74)	4.60 (4.57, 4.63)	4.60 (4.58, 4.62)	4.62 (4.59, 4.64)	<0.0001
TG (mmol/L)	1.15 (1.13, 1.16)	1.02 (1.00, 1.03)	0.98 (0.97, 0.99)	0.97 (0.95, 0.98)	<0.0001
LDL-C (mmol/L)	2.74 (2.72, 2.75)	2.65 (2.62, 2.67)	2.63 (2.61, 2.65)	2.63 (2.61, 2.65)	<0.0001
HDL-C (mmol/L)	1.32 (1.31, 1.33)	1.36 (1.35, 1.37)	1.39 (1.38, 1.40)	1.41 (1.40, 1.42)	<0.0001
SBP (mmHg)	120.3 (120.0, 120.6)	117.1 (116.6, 117.7)	116.3 (115.9, 116.7)	116.8 (116.4, 117.2)	<0.0001
DBP (mmHg)	76.0 (75.8, 76.2)	73.6 (73.3, 74.0)	73.0 (72.8, 73.3)	73.2 (72.9, 73.5)	<0.0001
FBG (mmol/L)	5.05 (5.04, 5.07)	4.90 (4.87, 4.92)	4.89 (4.87, 4.91)	4.88 (4.86, 4.90)	<0.0001
WBC count (×1000 cells/mm^3)	5.72 (5.70, 5.75)	5.69 (5.65, 5.74)	5.62 (5.59, 5.66)	5.61 (5.57, 5.65)	<0.0001
Physical activity (MET × hour/week)	9.60 (9.40, 9.90)	9.30 (8.90, 9.70)	10.4 (10.1, 10.8)	11.2 (10.8, 11.6)	<0.001
Total energy intake (kcal/day)	1869.9 (1859.4, 1880.4)	1961.8 (1942.7, 1981.1)	2058.2 (2043.0, 2073.4)	2180.1 (2162.2, 2198.1)	<0.0001
Carbohydrate intake (g/day)	326.4 (323.7, 329.1)	344.1 (339.2, 349.0)	369.4 (365.5, 373.5)	425.2 (420.1, 430.4)	<0.0001
Total fat intake (g/day)	39.9 (39.5, 40.2)	44.5 (43.8, 45.2)	47.3 (46.7, 47.9)	54.7 (54.0, 55.4)	<0.0001
Total vegetables intake (g/day)	223.8 (221.1, 226.5)	234.0 (229.1, 239.0)	250.2 (246.2, 254.2)	288.9 (283.8, 294.1)	<0.0001
Total fruits intake (g/day)	208.1 (203.8, 212.6)	271.8 (262.0, 281.9)	310.4 (301.9, 319.1)	351.5 (340.8, 362.6)	<0.0001
Sweet foods intake (g/day)	11.4 (11.1, 11.8)	21.9 (20.8, 23.1)	23.7 (22.8, 24.7)	23.1 (22.1, 24.1)	<0.0001
EPA and DHA intake (g/day)	3.53 (3.48, 3.57)	4.06 (3.97, 4.14)	4.15 (4.08, 4.22)	4.37 (4.29, 4.45)	<0.0001
Soft drinks intake (mL/day)	4.00 (3.85, 4.15)	6.71 (6.29, 7.15)	5.94 (5.66, 6.24)	4.91 (4.65, 5.18)	<0.0001
Smoking status (%)					
Smoker	23.8	17.0	12.8	10.8	<0.0001
Ex-smoker	6.37	3.81	2.83	3.31	<0.0001
Non-smoker	69.8	79.2	84.4	85.9	<0.0001
Alcohol drinking status (%)					
Everyday	5.27	2.79	1.62	2.05	<0.0001
Sometime	55.6	56.6	54.7	52.0	<0.0001
Ex-drinker	10.8	10.3	9.81	9.24	<0.01
Non-drinker	28.3	30.3	33.9	36.7	<0.0001
Education level (college or higher, %)	56.7	73.9	73.6	71.8	<0.0001
Working status (%)					
Managers	36.9	43.9	44.2	47.9	<0.0001
Professionals	17.5	18.3	17.0	13.6	<0.0001
Other	45.7	37.9	38.8	38.6	<0.0001
Household income (≥10,000 Yuan, %)	32.9	36.1	37.6	34.0	<0.01
Metabolic syndrome (%)	25.5	16.6	16.6	15.6	<0.0001
Hypertension (%)	25.3	16.1	14.3	15.3	<0.0001
Hyperlipidemia (%)	44.3	36.0	34.7	36.0	<0.0001
Diabetes (%)	3.89	1.80	1.73	1.59	<0.0001
Family history of disease (%)					
CVD	27.7	25.7	25.8	26.7	0.049
Hypertension	47.8	46.3	46.6	47.2	0.29
Hyperlipidemia	0.11	0.30	0.32	0.31	<0.01
Diabetes	22.8	24.3	25.0	24.1	0.01

BMI body mass index, *WC* waist circumference, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *WBC* white blood cell, *MET* metabolic equivalent, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *CVD* cardiovascular disease

[a]Analysis of variance or logistic regression analysis

[b]Geometric mean (95% confidence interval) (all such values)

As shown in Table 2, those with NAFLD tended to be older and were more likely to have a higher BMI, WC, TC, TG, LDL-C, SBP, DBP, FBG, PA, and WBC count, but a lower HDL-C (all P values < 0.0001). In addition, those

Table 2 Participant characteristics according to NAFLD status ($n = 24,389$)

Characteristics	NAFLD status		P value[a]
	No	Yes	
No. of subjects	19,731	4658	–
Age (years)	38.3 (38.2, 38.5)[b]	42.0 (41.7, 42.4)	<0.0001
Men (%)	41.2	71.6	<0.0001
BMI (kg/m^2)	22.8 (22.8, 22.8)	27.8 (27.7, 27.9)	<0.0001
WC (cm)	77.6 (77.4, 77.7)	92.7 (92.4, 93.0)	<0.0001
TC (mmol/L)	4.59 (4.58, 4.60)	4.95 (4.92, 4.97)	<0.0001
TG (mmol/L)	0.93 (0.93, 0.94)	1.70 (1.68, 1.72)	<0.0001
LDL-C (mmol/L)	2.62 (2.60, 2.63)	2.93 (2.91, 2.96)	<0.0001
HDL-C (mmol/L)	1.43 (1.42, 1.43)	1.12 (1.11, 1.13)	<0.0001
SBP (mmHg)	115.9 (115.7, 116.1)	128.7 (128.3, 129.2)	<0.0001
DBP (mmHg)	72.8 (72.7, 72.9)	81.5 (81.1, 81.8)	<0.0001
FBG (mmol/L)	4.85 (4.84, 4.86)	5.43 (5.41, 5.46)	<0.0001
WBC count (×1000 cells/mm^3)	5.51 (5.49, 5.53)	6.41 (6.37, 6.46)	<0.0001
Physical activity (MET × h/week)	9.90 (9.70, 10.1)	11.0 (10.5, 11.4)	<0.0001
Total energy intake (kcal/day)	1985.9 (1977.7, 1994.2)	1985.0 (1968.2, 2002.0)	0.92
Carbohydrate intake (g/day)	357.1 (354.9, 359.3)	356.0 (351.5, 360.5)	0.66
Total fat intake (g/day)	44.6 (44.3, 44.9)	46.1 (45.5, 46.8)	<0.0001
Total vegetables intake (g/day)	243.6 (241.4, 245.8)	241.8 (237.4, 246.2)	0.47
Total fruits intake (g/day)	267.2 (263.1, 271.4)	250.2 (242.3, 258.3)	<0.001
Sweet foods intake (g/day)	18.1 (17.7, 18.5)	13.7 (13.1, 14.3)	<0.0001
EPA and DHA intake (g/day)	3.87 (3.84, 3.91)	4.02 (3.95, 4.10)	<0.001
Soft drinks intake (mL/day)	4.83 (4.70, 4.96)	5.37 (5.08, 5.67)	<0.001
Smoking status (%)			
Smoker	15.2	28.3	<0.0001
Ex-smoker	4.01	6.88	<0.0001
Non-smoker	80.8	64.8	<0.0001
Alcohol drinking status (%)			
Everyday	3.71	2.09	<0.0001
Sometime	53.1	62.1	<0.0001
Ex-drinker	9.78	11.8	<0.0001
Non-drinker	33.4	24.0	<0.0001
Education level (college or higher, %)	68.1	57.9	<0.0001
Working status (%)			
Managers	42.6	38.3	<0.0001
Professionals	16.6	17.1	0.37
Other	40.8	44.6	<0.0001
Household income (≥10,000 Yuan, %)	35.0	33.8	0.13
Metabolic syndrome (%)	11.2	55.5	<0.0001
Hypertension (%)	14.3	40.9	<0.0001
Hyperlipidemia (%)	32.6	67.0	<0.0001
Diabetes (%)	1.31	8.18	<0.0001
Family history of disease (%)			
CVD	27.4	24.1	<0.0001
Hypertension	47.0	48.1	0.19
Hyperlipidemia	0.27	0.02	0.01
Diabetes	22.9	27.7	<0.0001

BMI body mass index, *WC* waist circumference, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *WBC* white blood cell, *MET* metabolic equivalent, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *CVD* cardiovascular disease

[a]Analysis of variance or logistic regression analysis

[b]Geometric mean (95% confidence interval) (all such values)

with NAFLD had a higher intake of total fat, EPA and DHA, and soft drinks, and a lower intake of fruits, and sweet foods (all *P* values < 0.001). A higher proportion of these participants were men, current smokers, ex-smokers, sometime drinkers, ex-drinkers, employed as other, and had chronic conditions and family history of diabetes (all *P* values

Table 3 The association of yogurt consumption with NAFLD (n = 24,389)

Logistic regression models	Yogurt consumption				P for trend[a]
	<1 time/week	1 time/week	2–3 times/week	≥4 times/week	
No. of subjects	10,271	3389	5959	4770	–
No. of NAFLD	2383	626	941	708	–
Model 1	1.00 (reference)	0.75 (0.68, 0.83)[b]	0.62 (0.57, 0.67)	0.58 (0.53, 0.63)	<0.0001
Model 2	1.00 (reference)	1.01 (0.89, 1.14)	0.93 (0.84, 1.03)	0.85 (0.76, 0.96)	<0.01
Model 3	1.00 (reference)	0.97 (0.85, 1.10)	0.89 (0.80, 0.99)	0.84 (0.74, 0.95)	<0.01
Model 4	1.00 (reference)	0.99 (0.87, 1.13)	0.90 (0.81, 1.01)	0.85 (0.75, 0.97)	<0.01
Model 5	1.00 (reference)	1.00 (0.88, 1.14)	0.91 (0.81, 1.02)	0.86 (0.76, 0.98)	0.01

Model 1: crude model

Model 2: adjusted for age, sex, and body mass index

Model 3: model 2 plus further adjusted for smoking status, alcohol drinking status, education level, working status, household income, physical activity, family history of disease (including cardiovascular disease, hypertension, hyperlipidemia, and diabetes), total energy intake, carbohydrate intake, total fat intake, eicosapentaenoic acid + docosahexaenoic acid intake, soft drinks intake, vegetables intake, fruits intake, sweet foods intake, and milk intake

Model 4: model 3 plus further adjusted for hypertension, diabetes, and hyperlipidemia

Model 5: model 4 plus further adjusted for WBC count

NAFLD non-alcoholic fatty liver disease

[a]Obtained by using multiple logistic regression analysis

[b]Odds ratio (95% confidence interval) (all such values)

< 0.0001). A lower proportion of these participants were non-smokers, everyday drinkers, non-drinkers, had lower education level, were employed as managers, and had a family history of CVD or hyperlipidemia (all *P* values < 0.05).

Association between yogurt consumption and newly diagnosed NAFLD are presented in Table 3. The unadjusted ORs (95% CI) for newly diagnosed NAFLD comparing the 1 time/week, 2–3 times/week, and ≥4 times/week of yogurt consumption as the < 1 time/week were 0.75 (0.68, 0.83), 0.62 (0.57, 0.67), and 0.58 (0.53, 0.63) (*P* for trend < 0.0001). After adjusting for age, sex, and BMI, the ORs (95% CI) for NAFLD across increasing consumption categories of yogurt were 1.00 (reference), 1.01 (0.89, 1.14), 0.93 (0.84, 1.03), and 0.85 (0.76, 0.96) (*P* for trend < 0.01). Similar results were also observed after further adjustment for possible confounding and mediating factors (Table 3).

No significant interactions between yogurt consumption and covariates were observed in the fully adjusted model (*P* for interaction > 0.10). There was no multicollinearity in the model 5, as all VIF values were < 4.00. In the sensitivity analysis, we excluded participants who had MS (n = 4520). However, results did not change substantially (data not shown).

Discussion

The main findings of the present study were that higher yogurt consumption was dose-dependently associated with a lower prevalence of newly diagnosed NAFLD. The large-scale cross-sectional study is the first study performed to assess the association of yogurt consumption with NAFLD in a general population.

In this cross-sectional study, we included only newly diagnosed NAFLD, which reduced the potential influence of reverse causation on our analyses [18]. Moreover, we adjusted for many confounding factors. First, we adjusted for age, sex, and BMI because these factors were significantly different between groups. Adjustments for these factors substantially attenuated the observed association. This suggests that there is also the possibility of residual confounding since the subjects were quite different in terms of these important characteristics. In particular, BMI is a crude measure of body fat which is associated with NAFLD. However, data on body fat were not available for the present study. Therefore, imperfect measurement of body fat may cause a large bias in the estimated effects. Future studies should investigate the impact of yogurt consumption on NAFLD was independent of mediating by body fat. Second, we made adjustments for lifestyle factors and dietary intakes. However, there were similar results when we adjusted for smoking and alcohol drinking status, educational level, occupation, household income, PA, family medical history, total energy, carbohydrate, and total fat, EPA + DHA, soft drinks, vegetables, fruits, sweet foods, and milk intake. Thus, the observed association between yogurt consumption and newly diagnosed NAFLD was independent of these lifestyle and dietary factors. Third,

yogurt consumption was associated with a lower risk of chronic diseases, which may contribute to a reduction of NAFLD [27, 28]. However, adjustments for hypertension, diabetes, and hyperlipidemia did not alter this inverse association. Furthermore, we excluded subjects with MS in a sensitivity analysis. However, a similar association was also observed. Therefore, yogurt consumption may be negatively associated with NAFLD independent of individual chronic diseases. Finally, we further adjusted for WBC count. After adjustment for the marker of subclinical inflammation, this inverse association was slightly attenuated and remained significant. This means that this inverse association was at least in part mediated through inflammation.

A double-blind RCT showed that probiotics (yogurt is one of the best sources) can improve liver aminotransferases levels in patients with NAFLD [29]. Accumulated evidence also indicated yogurt consumption was associated with improved metabolic profiles in humans, which might have preventive effects against NAFLD [30, 31]. Moreover, a double-blind 8-week RCT and an open-label 24-week RCT collectively showed that probiotic yogurt consumption could improve steatosis among NAFLD patients [14, 15]. However, to our knowledge, few studies have focused on the association of yogurt consumption and NAFLD in a general population. Therefore, our study filled this knowledge gap of association between yogurt consumption and NAFLD. These results need to be replicated in further investigations.

Although the exact mechanisms behind this inverse association remain unknown, these following several aspects may partly explain the observed results. First, yogurt is a rich source of probiotics. Animal experiments have suggested that probiotics may delay NAFLD development by suppressing the lipopolysaccharide and hepatic toll-like receptor 4 signaling pathway [32]. Second, previous studies have been proven that probiotics from yogurt to own anti-inflammatory, anti-oxidant, and immune-modulating activity, which might mediate the lower prevalence of NAFLD among individuals with higher yogurt consumption [33, 34]. Third, yogurt is one of the most nutrient-dense foods that are rich in proteins, minerals (e.g., calcium, magnesium, potassium), and vitamins. Evidence has shown that a higher intake of calcium contained in yogurt is associated with increased whole-body fat oxidation [35, 36]. Thus, the inverse association might partly be explained by increased whole-body fat oxidation rates. Fourth, an animal study found that calcium and vitamin D combinations could prevent NAFLD development [37]. Finally, yogurt is seen as a nutrient-dense food linked with healthy diet habitats. Therefore, this association was partly explained by a healthier diet.

This study has several important advantages including the large sample size, and extensive information on lifestyle and dietary factors, which allowed us to control for many potential confounders. Several limitations of this study should also be noted. First, dietary information was self-reported. Thus, recall bias exists and the information on dietary intake may not be exact. Second, fatty liver disease was diagnosed by abdominal ultrasound rather than the gold standard liver biopsy. However, liver ultrasonography scanning is wildly used in large-scale population-based studies due to its non-invasiveness, easy accessibility, and high sensitivity and specificity [38]. Third, although we controlled for many confounders, we cannot rule out imprecision in the measurement of confounding factors included or residual confounding [39]. For example, varieties of PA and undocumented dietary factors could confound the observed associations. Thus, further confirmatory RCTs are needed to confirm the present findings. Finally, different yogurt types (such as whole fat or low-fat yogurt) may have a differential effect on NAFLD. However, low-fat yogurt was generally less common in China. Therefore, the effect of yogurt types on our results may be ignorable.

Conclusions

Our study results indicated that higher consumption of yogurt is associated with the reduced prevalence of NAFLD among Chinese adults. These results suggest that yogurt consumption may potentially contribute to the reduction of NAFLD. Future longitudinal studies are warranted to confirm this finding.

Author contributions SZ drafted the manuscript. JF, QZ, LL, ML, GM and ZY interpreted the results and contributed to the discussions. HW, YX, XB, YG, SS, XW, MZ, QJ, KS, YW, and HX contributed to collect the data. KN designed the study, analyzed the data, reviewed, and edited the manuscript. KN had full access to all the data and took responsibility for the integrity of the data. All authors approved the final version.

Compliance with ethical standards

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