Dietary Fructose and Risk of Metabolic Syndrome in Chinese Residents Aged 45 and Above: Results From the China National Nutrition and Health Survey

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Abstract

Background

A growing number of researches supported that dietary fructose was associated with all the key features of metabolic syndrome (MetS). However, there was no large epidemiological study among Chinese population although the prevalence of MetS increased sharply. This study explores the relationship between dietary fructose and MetS among Chinese residents aged 45 and above.

Methods

A total of 25528 participants (11574 males and 13954 females) were included in this nationwide representative cross-sectional study of China National Nutrition and Health Survey. Dietary fructose intake was assessed by 3-day 24-h dietary records. MetS was defined according to the International Diabetes Federation and Chinese Diabetes Society criteria.

Results

The consumption of dietary fructose for urban residents was 11.6 g/day and for rural residents was 7.6 g/day. Fruits and vegetables as well as their products were the main food sources. There was no association between dietary fructose intake and the risk of MetS in both urban ($P = 0.315$) and rural residents ($P = 0.230$) after adjustment for confounding factors. Moreover, for urban residents who participating in physical activity, the risk of MetS in the fourth quartiles (OR: 0.67; 95%CI: 0.52–0.86) was reduced compared with the first quartile. In the sensitivity analysis, the risk of MetS was also found a significant reduction in the fourth quartiles (OR, 95%CI: 0.67, 0.51–0.89; 0.63, 0.46–0.85; 0.74, 0.56–0.98) compared with the first quartile when excluding smokers, alcohol users, and underweight/obesity, respectively. And there was no association between dietary fructose intake and the risk of MetS after multivariate adjustment stratified by gender, smoking and alcohol use.

Conclusions

Under the current dietary fructose intake status, there was no association between dietary fructose intake and the risk of MetS among Chinese residents aged 45 and above. Physical activity and relatively low fructose intake may have a beneficial synergistic effect on MetS.

Introduction

Metabolic syndrome (MetS) is a constellation of cardio-metabolic risk factors conveying high risk of developing cardiovascular disease, type 2 diabetes, non-alcoholic fatty liver, and chronic kidney disease, characterized by abdominal obesity, hyperglycemia, hypertension, and dyslipidemia (1, 2). Over the past

few decades, the prevalence of MetS has increased dramatically and has become one of the major public-health challenges in China and worldwide (2–4). The overall standardized prevalence of MetS among Chinese adults was 24.2%, and it was over 32% for those who aged 45 and above (5).

Increased sugar intake was widely recognized as a contributor to the worldwide epidemics of obesity, diabetes, and their associated cardio-metabolic risks (6). Due to its unique set of biochemical, metabolic, and endocrine responses, fructose was regarded to be the main bad actor in sugars and associated with all the key features of MetS (6, 7). A series of systematic reviews and meta-analysis discussed the relationship between fructose and components of MetS. Some of them concluded that intakes of fructose were associated with increased risk of obesity, dyslipidemia, and hypertension (8–10). However, some of them found that a certain dose of fructose has no adverse or even some positive effects on fasting glucose, blood pressure, and blood lipids (11–15). Most of the studies included in these meta-analyses were interventional studies with high-dose fructose intake. In the “real world” study, a cross-sectional population-based research of Iranians reported that higher consumption of dietary fructose increased the risk of MetS, while no such association was found in the US population (16, 17). Differences in dietary intake may be an important reason for the different results. Our previous research found that the average dietary fructose intake of Chinese residents aged 45 and above was 8.29 g/d, which is lower than that of Americans (48.07 g/d) and Iranians (46.50 g/d for male and 37.30 g/d for female) (18). Up to now, there is no large epidemiological study to explore the relationship between dietary fructose and MetS under the current intake status of Chinese population although the prevalence of MetS increased sharply.

Based on data of nationally representative cross-sectional survey of China National Nutrition and Health Survey (CNNHS) in 2010–2012, this study aims to investigate the effect of dietary fructose on MetS among Chinese residents aged 45 and above. Furthermore, we stratified analyzed the variables (gender, physical activity, smoking, and alcohol use) that might influence the risk of MetS.

Materials And Method

Study Design and Subjects

The nationwide representative cross-sectional study of CNNHS was conducted between 2010 to 2012 by Chinese Center for Disease Control and Prevention to assess the nutrition and health status of Chinese population. This survey covered all 31 provinces, autonomous regions, and municipalities directly under the Chinese central government (excluding Taiwan, Hong Kong, and Macao). A stratified multistage random cluster sampling method was conducted at 150 surveys sites of 4 types: 34 large cities, 41 small-to-medium cities, 45 general rural areas and 30 poor rural areas. The survey procedure has been described in detail elsewhere (19). Three consecutive 24-h dietary records combined with food weighting, survey questionnaires, physical examination, and fasting blood collection were completed for all participants.

In this study, we included all participants aged 45 and above who had complete demographic information, medical history, lifestyle factors and dietary intake data. We excluded those with implausible energy

intakes (< 800 kcal/day or > 4800 kcal/day for male and < 500 kcal/day or > 4000 kcal/day for male). A total of 25528 participants (11574 males and 13954 females) were included (19).

This survey was ethically approved by the Ethical Committee of the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention (2013-018). Written informed consent was obtained from all participants.

Data collection and definition

Data were collected by trained health workers or nurses in health examination centers from local health stations or community clinics according to a standard protocol. Questionnaires including demographic information, medical history, and lifestyle factors, were conducted by trained interviewers. Marital status was categorized into three statues (single, married, divorced/widowed). We classified education level into primary schools or below, junior high school, senior high school, and college or above. Current smoking was defined as “having smoked 100 cigarettes during lifetime” and “current smoking”. Current alcohol drinking was referred to “alcohol intake more than once per month during the past 12 months”. Physical activity was defined as “moderate physical activity for more than 10 minutes at least once per week” (20). According to the grading standards of national residents’ net income levels by National Bureau of Statistics in 2009, high income was “≥ 20000 per person per year for urban residents or ≥ 10000 for rural”, middle income was “15000 ~ 19999 for urban or 5000 ~ 9999 for rural”, and low income was “< 15000 for urban or < 5000 for rural”.

Height, weight, waist circumference (WC) and blood pressure (BP) were measured in the morning following standardized procedures. Height was measured with no shoes to the nearest 0.1 cm. With the participant standing and wearing a single layer of clothing, weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. WC was measured on midway between the lower edge of the costal arch and the upper edge of the iliac crest among standing participants. BP levels were measured at the nondominant arm with seated participants after 5 minutes of rest using a standard mercury sphygmomanometer, for 3 times in succession with 1-minute interval between the measurements. Systolic blood pressure (SBP) was measured at the first appearance of a pulse sound (Korotkoff phase 1) and diastolic blood pressure (DBP) at the disappearance of the pulse sound (Korotkoff phase 5). The mean of the three measurements was used for analysis.

Dietary Data and Assessment of Dietary fructose intake

Individual dietary recall data and household food consumption were collected over three consecutive days. Individual dietary data including all food consumed at home and away from home (type, amounts, type of meal, and place of consumption), were collected by trained dietary investigator. Weighting method was used to assess household food consumption, which including all foods and condiments. The Chinese Food Composition was used to calculate individual daily intake of energy, protein, fat, and carbohydrate for each food item in the dietary data.

Since there was no fructose content data in the Chinese Food Composition (1460 food items), we used fructose content data of the American Food Composition Database (2183 food items) and Chinese Sugar

Content Database in Pre-packaged Foods (363 food items) to assign the value of fructose content for each food item (21, 22). The principle of food fructose content assignment was described in detail in our previous study (18).

Dietary total fructose was composed of free-fructose and bound-fructose. Free-fructose intake for each person was calculated from added and naturally occurring sources on the food basis. Bound-fructose intake for each person was calculated by applying one-half of dietary total sucrose, because fructose accounts for one-half of the sucrose molecule. The intake of all forms of fructose from food-fructose and food-sucrose were summed to give the total intake of fructose for each person on a food-group basis (16).

According to the major ingredients of the food and food-grouping system used in the Chinese Food Composition Table, all foods were divided into 13 categories: grain and grain products; fruits and fruit products; vegetables and vegetable products; milk and milk products; meat, poultry, fish, and related products; eggs and egg products; legumes and legume products; nuts, seed, and related products; sugars and sweets; nonalcoholic beverages; alcoholic beverages; snacks; and miscellaneous foods.

Anthropomorphic and Blood Biochemical Methods

Blood samples were collected by trained nurses from all participants undergoing an overnight fast of at least 10 hours. Samples were centrifuged at 1500 rpm for 10 minutes after being left standing for 30 to 60 minutes. The centrifuged serum sample were transported to the central laboratory of the National Institute for Nutrition and Health and stored at -80 degrees centigrade. The blood collection procedure, processing, and determination were standardized. Fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured by a Hitachi automatic biochemical analyzer with reagents from Wako Pure Chemical Industries, Ltd (Tokyo, Japan).

Definition of MetS

According to the recommendation from the International Diabetes Federation and Chinese Diabetes Society criteria (23, 24), a person who met three or more of the following five criteria were diagnosed with MetS: (1) abdominal obesity (WC $\geq$ 90 cm in male or $\geq$ 85 cm in female); (2) hyperglycemia (FPG $\geq$ 6.1 mmol/L or diagnosed diabetes); (3) hypertension (SBP $\geq$ 130 mmHg or DBP $\geq$ 85 mmHg or diagnosed hypertension); (4) TG $\geq$ 1.70 mmol/L; (5) HDL-C $<$ 1.04 mmol/L.

Statistical Analysis

Data were collected using specialized software, and data cleaning and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Due to the differences of dietary total fructose and the prevalence of MetS between urban and rural, we performed all analyses separately for the urban and rural. Categorical variables were presented as percentage (95% confidence interval, 95%CI) and examined with a chi-square test. Continuous variables with normal distribution were presented as mean (95%CI) and compared between groups using z test. Skewed distribution variables were indicated with quartiles and examined non-parametric statistical hypothesis test. The Cochran and Mantel-Haenszel test were used to analyze the characteristics of normal and MetS in urban and rural. Univariate and

multivariable-adjusted logistic regression were performed to explore the association between dietary fructose intake and risk of MetS. The first quartile of dietary total fructose intake was set as the reference. Three models were involved in this study: model 1 did not adjust any variables; model 2 adjusted for gender, age, education, marital status, smoking, alcohol, physical activity, income, energy, protein, fat, carbohydrate, and TC; model 3 adjusted for all variables in model 2 plus BMI. Odds ratios (OR) and 95%CI were measured. A value of $P < 0.05$ was considered statistically significant.

Results

Basic Characteristics of the Study population

A total of 25528 participants were included in the study with an average age of 59.1 years. Of these, 13067 (44.1% males) were urban residents and 12461 (46.6% males) were rural residents. There were significant differences between urban and rural in age, gender, marital status, education, smoking, alcohol, physical activity, and income. BMI, WC, TC, TG, and FPG were higher in urban than in rural ($P < 0.001$), whereas HDL-C was the opposite ($P < 0.001$, Table 1). Table 2 shows that the prevalence of MetS in urban 32.4% was higher than that in rural 24.7% ($P < 0.001$).

Table 1
Basic characteristics of the study population in urban and rural

	Total	Urban	Rural	*p*-Value
N	25528	13067	12461	
Age, years	59.1 (59.0, 59.2)	59.7 (59.5, 59.8)	58.5 (58.3, 58.7)	< 0.001
Gender, n (%)				
Male	11574 (45.3)	5762 (44.1)	5812 (46.6)	
Female	13954 (54.7)	7305 (55.9)	6649 (53.4)	
Marital status, n (%)				0.011
Single	181 (0.7)	84 (0.6)	97 (0.8)	
Married	23093 (90.5)	11767 (90.1)	11326 (90.9)	
Divorced or Widowed	2254 (8.8)	1216 (9.3)	1038 (8.3)	
Education, n (%)				< 0.001
Primary schools or below	12407 (48.6)	4426 (33.9)	7981 (64.1)	
Junior high school	7980 (31.3)	4556 (34.9)	3424 (27.5)	
Senior high school	3963 (15.5)	2975 (22.8)	988 (7.9)	
College or above	1178 (4.6)	1110 (8.5)	68 (0.6)	
Smoking, n (%)				< 0.001
Ever/Never	6830 (26.8)	3065 (23.5)	3765 (30.2)	
Current	18698 (73.2)	10002 (76.5)	8696 (69.8)	
Alcohol, n (%)				< 0.001
Ever/Never	8169 (32.0)	4189 (32.1)	3980 (31.9)	
Current	17359 (68.0)	8878 (67.9)	8481 (68.1)	
Physical activity, n (%)				< 0.001
Yes	4012 (15.7)	3309 (25.3)	703 (5.6)	
No	21516 (84.3)	9758 (74.7)	11758 (94.4)	
Income, n (%)				< 0.001

Mean value (95% confidence interval) or n (%) were shown; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose

	Total	Urban	Rural	*p*-Value
Low	11940 (46.8)	7024 (53.8)	4916 (39.5)	
Middle	5202 (20.4)	1833 (14.0)	3369 (27.0)	
High	7276 (28.5)	3456 (26.5)	3820 (30.7)	
Unanswered	1110 (4.4)	754 (5.8)	356 (2.9)	
BMI, kg/m^2	24.1 (24.1, 24.2)	24.6 (24.6, 24.7)	23.6 (23.6, 23.7)	< 0.001
WC, cm	82.9 (82.7, 83.0)	84.2 (84.0, 84.3)	81.5 (81.3, 81.6)	< 0.001
SBP, mmHg	130.9 (130.6, 131.1)	130.7 (130.4, 131.1)	131.0 (130.6, 131.4)	0.640
DBP, mmHg	81.0 (80.8, 81.1)	80.9 (80.7, 81.1)	81.1 (81.9, 81.3)	0.929
TC, mmol/L	4.79 (4.78, 4.80)	4.89 (4.87, 4.90)	4.70 (4.68, 4.72)	< 0.001
HDL-C, mmol/L	1.19 (1.19, 1.20)	1.18 (1.18, 1.19)	1.20 (1.20, 1.21)	< 0.001
TG, mmol/L	1.50 (1.49, 1.51)	1.55 (1.53, 1.57)	1.44 (1.42, 1.46)	< 0.001
FPG, mmol/L	5.52 (5.50, 5.54)	5.67 (5.64, 5.69)	5.36 (5.34, 5.39)	< 0.001

Mean value (95% confidence interval) or n (%) were shown; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose

Table 2
Basic characteristics of normal and MetS in urban and rural

	Urban		Rural		*p*-Value
	Normal	MetS	Normal	MetS	
Case, n (%)	8830 (67.6)	4237 (32.4)	9388 (75.3)	3073 (24.7)	< 0.001
Age, n (%)					< 0.001
45–59 years	5078 (57.5)	2004 (47.3)	5598 (59.6)	1702 (55.4)	
60–74 years	3353 (38.0)	1997 (47.1)	3420 (36.4)	1247 (40.6)	
75- years	399 (4.5)	236 (5.6)	370 (3.9)	124 (4.0)	
Gender, n (%)					0.248
Male	3788 (42.9)	1974 (46.6)	4526 (48.2)	1286 (41.9)	
Female	5042 (57.1)	2263 (53.4)	4862 (51.8)	1787 (58.2)	
Marital status, n (%)					0.246
Single	63 (0.7)	21 (0.5)	88 (0.9)	9 (0.3)	
Married	7956 (90.1)	3811 (90.0)	5811 (90.7)	2815 (91.6)	
Divorced or Widowed	811 (9.2)	405 (9.6)	789 (8.4)	249 (8.1)	
Education, n (%)					< 0.001
Primary schools or below	3022 (34.2)	1404 (33.1)	6092 (64.9)	1889 (61.5)	
Junior high school	3062 (34.7)	1494 (35.3)	2546 (27.1)	878 (28.6)	
Senior high school	2035 (23.1)	940 (22.2)	709 (7.6)	279 (9.1)	
College or above	711 (8.1)	399 (9.4)	41 (0.4)	27 (0.9)	
Smoking, n (%)					< 0.001
Ever/Never	6725 (76.2)	3277 (77.3)	6248 (66.6)	2233 (72.7)	
Current	2105 (23.8)	960 (22.7)	3140 (33.4)	840 (27.3)	
Alcohol, n (%)					< 0.001
Ever/Never	5926 (67.1)	2952 (69.7)	6374 (67.9)	2322 (75.6)	
Current	2904 (32.9)	1285 (30.3)	3014 (32.1)	751 (24.4)	
Physical activity, n (%)					< 0.001
Yes	2149 (24.3)	1160 (27.4)	460 (4.9)	243 (7.9)	
No	6681 (75.7)	3077 (72.6)	8928 (95.1)	2830 (92.1)	

	Urban		Rural		*p*-Value
	Normal	MetS	Normal	MetS	
Income, n (%)					0.004
Low	4835 (54.8)	2189 (51.7)	3713 (39.6)	1203 (39.2)	
Middle	1195 (13.5)	638 (15.1)	2594 (27.6)	775 (25.2)	
High	2273 (25.7)	1183 (27.9)	2819 (30.0)	1001 (32.6)	
Unanswered	527 (6.0)	227 (5.4)	262 (2.8)	94 (3.1)	

Dietary Fructose Intake Level and Food Sources

The average daily dietary total fructose intake for urban residents was 11.6 g and for rural residents was 7.6 g. Dietary total fructose intake level was significantly higher in urban residents than in rural residents, as well as free-fructose and bound-fructose levels ($P < 0.001$). Intakes of protein and fat were significantly higher in urban residents while energy and carbohydrate were higher in rural residents ($P < 0.001$). Table 3 shows the basic characteristics of dietary fructose and nutrients with mean and quartiles.

Table 3
Intake status of dietary fructose and nutrients in urban and rural residents

	City				Rural				*p*-Value
	Mean	P_{25th}	Median	P_{75th}	Mean	P_{25th}	Median	P_{75th}	
Total Fructose, g/d	11.6	4.8	8.3	14.5	7.6	3.4	5.3	8.8	< 0.001
Free-Fructose, g/d	6.7	2.2	4.2	8.4	4.6	1.6	2.7	5.1	< 0.001
Bound-Fructose, g/d	4.9	2.4	3.7	6.0	3.1	1.6	2.4	3.7	< 0.001
Energy, kcal/d	1887	1454	1780	2204	2159	1648	2041	2547	< 0.001
Protein, g/d	61.2	44.8	56.6	72.5	59.3	43.6	55.4	71.2	< 0.001
Fat, g/d	76.1	50.2	69.2	94.1	70.8	44.0	64.0	90.2	< 0.001
Carbohydrate, g/d	240.3	178.0	224.9	284.3	322.7	238.7	299.4	378.7	< 0.001

We further investigated the food sources of dietary fructose. Fruits and products, vegetables and vegetable products, and snacks were the top three food sources in urban residents and their contribution to dietary

total fructose intake was 69.02%, while vegetables and vegetable products, Fruits and products, and grain and grain products were the top three food sources in rural residents and their contribution was 73.45% (Fig. 1). Food sources of dietary total fructose in urban and rural areas with mean and quartiles were shown in the table S1.

The Association between Dietary Fructose Intake and Risk of MetS

For urban residents, in addition to FPG, there were significant differences in WC, SBP, DBP, TG and HDL-C between the quartiles. The prevalence of MetS was higher in the third quartile than that in the first and forth quartiles ($P < 0.05$). For rural residents, we found significant differences in FPG, SBP, DBP, TG, and HDL-C between the quartiles except for WC. There was no significant difference in the prevalence of MetS between quartiles (Table 4).

Table 4
Basic characteristics of components of MetS by the quartiles of dietary fructose intake

	Q1	Q2	Q3	Q4	*p*-Value
Urban	3266	3268	3266	3267	
Dietary fructose	3.4 (3.4, 3.4)	6.4 (6.4, 6.4)	11.1 (11.1, 11.1)	25.6 (25.1, 26.2)	
WC, cm	83.5 (83.2, 83.8)	84.5 (84.1, 84.8)[1]	84.4 (84.1, 84.8) [1]	84.3 (83.9, 84.6) [1]	< 0.001
FPG, mmol/L	5.68 (5.63, 5.73)	5.72 (5.67, 5.78)	5.64 (5.59, 5.69)	5.62 (5.57, 5.67)	0.081
SBP, mmHg	131.8 (131.1, 132.5)	132.0 (131.3, 132.7)	130.3 (129.7, 131.0) [1,2]	128.8 (128.2, 129.4) [1,2,3]	< 0.001
DBP, mmHg	81.0 (80.6, 81.4)	81.5 (81.2, 81.9)	80.8 (80.5, 81.2)	80.2 (79.9, 80.6) [1,2]	< 0.001
TG, mmol/L	1.49 (1.46, 1.53)	1.56 (1.53, 1.60) [1]	1.59 (1.55, 1.62) [1]	1.56 (1.53, 1.60)	0.002
HDL-C, mmol/L	1.20 (1.19, 1.22)	1.19 (1.18, 1.20)	1.18 (1.16, 1.18) [1]	1.17 (1.16, 1.18) [1]	< 0.000
MetS, n (%)	1019 (31.2)	1083 (33.1)	1109 (34.0)[1]	1027 (31.4)[3]	0.048
Rural	3115	3116	3115	3115	
Dietary fructose	2.5 (2.5, 2.5)	4.3 (4.3, 4.3)	6.8 (6.8, 6.8)	16.8 (16.4, 17.2)	
WC, cm	81.1 (80.7, 81.4)	81.5 (81.1, 81.8)	81.7 (81.3, 82.1)	81.6 (81.3, 81.9)	0.087
FPG, mmol/L	5.37 (5.32, 5.42)	5.44 (5.39, 5.49)	5.32 (5.28, 5.37)[2]	5.32 (5.27, 5.37) [2]	0.001
SBP, mmHg	132.6 (131.9, 133.4)	131.2 (130.5, 131.9)[1]	130.9 (130.2, 131.7) [1]	129.3 (128.5, 130.0) [1,2,3]	< 0.001
DBP, mmHg	81.6 (81.2, 82.0)	81.0 (80.6, 81.4)	81.0 (80.6, 81.4)	80.7 (80.3, 81.1) [1]	0.017
TG, mmol/L	1.39 (1.35, 1.42)	1.43 (1.39, 1.47)	1.43 (1.39, 1.47)	1.52 (1.48, 1.57) [1,2,3]	< 0.001
HDL-C, mmol/L	1.22 (1.21, 1.24)	1.22 (1.21, 1.23)	1.20 (1.18, 1.21) [1,2]	1.18 (1.16, 1.19) [1,2]	< 0.001

[1]: compared with Q1, $p < 0.05$; [2]: compared with Q2, $p < 0.05$; [3]: compared with Q3, $p < 0.05$

	Q1	Q2	Q3	Q4	*p*-Value
MetS, n (%)	764 (24.5)	772 (24.8)	805 (25.8)	732 (23.5)	0.199
[1]: compared with Q1, $p < 0.05$; [2]: compared with Q2, $p < 0.05$; [3]: compared with Q3, $p < 0.05$					

Compared with the first quartile, the risk of MetS was increased in the third quartile among urban residents (OR: 1.13; 95%CI: 1.02–1.26). After adjustment for confounding factors (gender, age, education, marital status, smoking, alcohol, physical activity, income, energy, protein, fat, carbohydrate, TC and BMI), there was no statistical significance. For rural residents, whether confounding factors were adjusted or not, we did not find an association between dietary fructose intake and the risk of MetS (Table 5).

Table 5
The association between dietary fructose intake and risk of MetS

	Dietary fructose intake				*p*-Value
	Q1	Q2	Q3	Q4	
Urban					
Mode1	1.00	1.09 (0.98, 1.21)	1.13 (1.02, 1.26)	1.01 (0.91, 1.12)	**0.048**
Mode2	1.00	1.08 (0.97, 1.20)	1.10 (0.99, 1.22)	0.97 (0.87, 1.09)	**0.059**
Mode3	1.00	1.03 (0.92, 1.16)	1.07 (0.95, 1.21)	0.96 (0.85, 1.10)	0.315
Rural					
Mode1	1.00	1.01 (0.90, 1.14)	1.07 (0.96, 1.20)	0.95 (0.84, 1.06)	0.199
Mode2	1.00	1.04 (0.95, 1.17)	1.15 (1.02, 1.29)	1.06 (0.93, 1.19)	0.148
Mode3	1.00	1.03 (0.90, 1.18)	1.14 (1.00, 1.31)	1.03 (0.90, 1.19)	0.230
Mode1: crude; Mode2: adjusted gender, age, education, marital status, smoking, alcohol, physical activity, income, energy, protein, fat, carbohydrate, TC; Mode3: mode2 plus BMI.					

Stratified analysis of the Association between Dietary Fructose Intake and Risk of MetS

We further analyzed the association between dietary fructose intake and the risk of MetS stratified by gender, physical activity, smoking, and alcohol use. For urban residents who participating in physical activity, the prevalence, and the risk of MetS decreased with the increase of the quartile levels of dietary fructose intake ($P < 0.001$). Compared with the first quartile, the risk of MetS in the fourth quartile (OR: 0.67; 95%CI: 0.52–0.86) was reduced after adjustment for confounding factors (Table 6). In the sensitivity analysis, we also found the risk of MetS with a significant reduction in the fourth quartile (OR, 95%CI: 0.67, 0.51–0.89; 0.63, 0.46–0.85; 0.74, 0.56–0.98) compared with the first quartile when excluding smokers, alcohol users, and BMI < 18.5 or BMI ≥ 28, respectively (Table 7). For urban residents who did not

participate in physical activity, the prevalence of MetS increased with the increase of dietary fructose intake ($P = 0.007$). There was no significant difference for the relationship between dietary fructose intake and the risk of MetS after multivariate adjustment, as was the case in the sensitivity analysis (Table 6, Table 7).

Table 6
Stratified analysis of the association between dietary fructose intake and risk of MetS by physical activity in urban residents

	Dietary fructose intake				*p*-Value
	Q1	Q2	Q3	Q4	
Physical activity					
MetS, n (%)	233 (42.1)	236 (36.2)	324 (35.9)	367 (30.6)	**< 0.001**
Mode1	1.00	0.78 (0.62, 0.99)	0.77 (0.62, 0.96)	0.61 (0.49, 0.75)	**< 0.001**
Mode2	1.00	0.79 (0.63, 1.01)	0.79 (0.63, 0.99)	0.64 (0.51, 0.80)	**0.001**
Mode3	1.00	0.79 (0.61, 1.03)	0.81 (0.62, 1.04)	0.67 (0.52, 0.86)	**0.016**
Non-physical activity					
MetS, n (%)	786 (29.0)	846 (32.3)	785 (33.2)	660 (32.0)	**0.007**
Mode1	1.00	1.17 (1.04, 1.32)	1.22 (1.08, 1.37)	1.15 (1.02, 1.30)	**0.007**
Mode2	1.00	1.15 (1.02, 1.30)	1.17 (1.04, 1.33)	1.09 (0.95, 1.25)	**0.046**
Mode3	1.00	1.01 (0.96, 1.26)	1.14 (0.99, 1.32)	1.07 (0.92, 1.25)	0.276

Mode1: crude; Mode2: adjusted gender, age, education, marital status, smoking, alcohol, income, energy, protein, fat, carbohydrate, TC; Mode3: mode2 plus BMI.

Table 7
Sensitivity analysis of the association between dietary fructose intake and risk of MetS by physical activity in urban residents

	Dietary fructose intake				*p*-Value
	Q1	Q2	Q3	Q4	
Physical activity					
MetS, n (%)*	188 (41.3)	185 (34.9)	256 (35.1)	313 (30.1)	**< 0.001**
Mode1*	1.00	0.76 (0.59, 0.99)	0.77 (0.60, 0.98)	0.61 (0.49, 0.77)	**< 0.001**
Mode2*	1.00	0.78 (0.60, 1.02)	0.79 (0.61, 1.01)	0.63 (0.49, 0.81)	**0.004**
Mode3*	1.00	0.77 (0.57, 1.03)	0.81 (0.62, 1.07)	0.67 (0.51, 0.89)	**0.039**
MetS, n (%)#	168 (42.5)	166 (37.8)	207 (34.2)	230 (30.1)	**< 0.001**
Mode1#	1.00	0.82 (0.62, 1.08)	0.70 (0.54, 0.91)	0.58 (0.45, 0.75)	**< 0.001**
Mode2#	1.00	0.83 (0.63, 1.11)	0.70 (0.53, 0.91)	0.58 (0.44, 0.76)	**0.001**
Mode3#	1.00	0.86 (0.63, 1.17)	0.73 (0.54, 0.99)	0.63 (0.46, 0.85)	**0.019**
MetS, n (%)$	147 (33.2)	166 (30.8)	234 (31.0)	268 (26.0)	**0.017**
Mode1$	1.00	0.90 (0.69, 1.17)	0.90 (0.70, 1.16)	0.71 (0.56, 0.90)	**0.017**
Mode2$	1.00	0.84 (0.63, 1.11)	0.70 (0.53, 0.91)	0.58 (0.44, 0.76)	**0.001**
Mode3$	1.00	0.89 (0.66, 1.19)	0.92 (0.70, 1.22)	0.74 (0.56, 0.98)	**0.119**
Non- physical activity					
MetS, n (%)*	602 (29.6)	650 (34.36)	590 (33.50)	493 (31.58)	**0.008**
Mode1*	1.00	1.25 (1.09, 1.42)	1.20 (1.05, 1.38)	1.10 (0.95, 1.27)	**0.008**

Mode1: crude; Mode2: adjusted gender, age, education, marital status, smoking, alcohol, income, energy, protein, fat, carbohydrate, TC; Mode3: mode2 plus BMI. * excluded smokers; # excluded alcohol; $ excluded BMI < 18.5, and BMI ≥ 28.

	Dietary fructose intake				*p*-Value
	Q1	Q2	Q3	Q4	
Mode2*	1.00	1.22 (1.07, 1.40)	1.16 (1.01, 1.34)	1.06 (0.90, 1.24)	**0.020**
Mode3*	1.00	1.15 (0.99, 1.34)	1.14 (0.97, 1.34)	1.06 (0.89, 1.26)	0.231
MetS, n (%)#	602 (31.1)	620 (34.0)	542 (33.8)	417 (31.8)	0.182
Mode1#	1.00	1.14 (0.99, 1.31)	1.13 (0.98, 1.30)	1.03 (0.89, 1.20)	0.182
Mode2#	1.00	1.12 (0.98, 1.29)	1.08 (0.93, 1.25)	0.98 (0.83, 1.15)	0.210
Mode3#	1.00	1.07 (0.92, 1.26)	1.06 (0.89, 1.25)	0.95 (0.79, 1.14)	0.511
MetS, n (%)$	541 (24.3)	572 (27.0)	534 (27.6)	450 (26.3)	0.073
Mode1$	1.00	1.16 (1.01, 1.33)	1.19 (1.03, 1.37)	1.12 (0.97, 1.29)	0.073
Mode2$	1.00	1.12 (0.98, 1.29)	1.08 (0.93, 1.25)	0.98 (0.83, 1.15)	0.210
Mode3$	1.00	1.12 (0.96, 1.30)	1.12 (0.96, 1.32)	1.04 (0.88, 1.24)	0.380

Mode1: crude; Mode2: adjusted gender, age, education, marital status, smoking, alcohol, income, energy, protein, fat, carbohydrate, TC; Mode3: mode2 plus BMI. * excluded smokers; # excluded alcohol; $ excluded BMI < 18.5, and BMI ≥ 28.

Whether rural residents participated in physical activity or not, there was no association between dietary fructose intake and the risk of MetS (Table S2). When stratified by gender, the prevalence of MetS was lowest in the first quartile of dietary fructose intake for urban males, but in the fourth quartile for urban females (Table S3). There was no association between dietary fructose intake and the risk of MetS after multivariate adjustment stratified by gender, smoking and alcohol (Table S3, Table S4, Table S5).

Discussion

In this nationally representative cross-sectional study, we discussed the association between dietary fructose intake and the risk of MetS among Chinese residents aged 45 and above. The consumption of dietary fructose for urban residents was 11.6 g/day and for rural residents was 7.6 g/day. Under the current dietary fructose intake status, we did not find an association between dietary fructose intake and the risk of MetS in both urban and rural residents aged 45 and above. However, there was a significant inverse

association between dietary fructose intake and MetS for urban residents who participating in physical activity.

A large number of researches suggested that fructose was a culprit in the occurrence of MetS through several metabolic pathways, such as increasing hepatic *de novo* lipogenesis in the liver(25), depleting ATP stores which resulting in increasing generation of uric acid via purine pathway(26, 27), affecting on plasma lipids, lipoprotein, and apolipoproteins (28, 29), and host-gastrointestinal microbe interactions (30, 31). However, there were still disputes between mechanism studies and population epidemiological studies. According to the systematic reviews and meta-analysis, high doses of fructose (≥ 100 g/day) increases serum TG concentration (10, 32), low to middle doses of fructose (0 ~ 90 g/day) have a benefit effect in HbA1c (13, 33). But fructose did not increase the risk of hypertension and type 2 diabetes (12, 34), also, it did not affect serum HDL-C concentration (32) and cause weight gain when it was substituted for other carbohydrate in diets providing similar calories (35).

In present study, we did not find an association between dietary fructose intake and the risk of MetS among Chinese residents aged 45 and above. The results of this study were similar to the study from the NHANES 1999–2006 which showed fructose ordinary consumption (approximately 37% of total sugars and 9% of daily energy in the US population) had no association with the risk of MetS (17). Both two studies were population-based cross-sectional studies. However, a systematic review and meta-analysis discussing the association of fructose consumption and components of metabolic syndrome reported that fructose consumption was positively associated with FPG, TG and SBP, and negatively associated with HDL-C (9). We supposed several reasons for the difference. On the one hand, the fructose sources were different. Food sources of fructose in this meta-analysis were from industrialized foods. In our study, however, fruits and products, vegetables and vegetable products were the most dominant food sources, accounting for more than 50% of dietary fructose. One study reported that most food sources of dietary fructose (especially fruits) did not have a harmful effect on indicators of health (HbA1c, fasting insulin), but several food sources of fructose (especially sugars-sweetened beverages) adding excess energy to diets showed negative effects (36). On the other hand, the fructose intake was different. Fructose provided at least 15% of daily energy requirements in the 15 studies included in this meta-analysis. In our study, however, the average dietary fructose intakes for urban and rural residents were 11.6 g/day and 7.6 g/day, respectively. They contributed less than 3% of energy requirements. Several systematic reviews reported that a continuous exposure to high fructose intake may have adverse health effects (37, 38). Previous study has shown that the percentage of total calories from added sugar containing food of Chinese residents in 2010–2010 was 9.09%, which was under the recommended limits (10%) of WHO (39, 40). In addition, some researchers argued that the before-after design used by the authors, the lack of adjustment for energy as an important confounding variable, and unclear statistical methods render their results uninterpretable. Under calorie-matched conditions, this systematic review and meta-analysis cannot infer that fructose uniquely affects most components of MetS (41). In this study, we not only adjusted the confounding factors, including energy, but also stratified analyze the variables (gender, physical activity, smoking, and alcohol use) that might influence the risk of MetS.

Interestingly, we found that the risk of MetS decreased with the increase of the quartile levels of dietary fructose intake for urban residents who participating in physical activity. In recent years, a growing number of researches supported the idea that physical activity might play a role of modulator for fructose's health effects (37, 38, 42–44). Fructose was generally processed in splanchnic organs (small bowel, liver, kidneys) to glucose, lactate, and fatty acids, which serve as metabolic energy substrates in extra-splanchnic organs and tissues (37). As fructose uptake and fructolysis were unregulated processes, the amount of metabolic energy substrates was proportionate to fructose intake (42). For sedentary subjects, high fructose intake caused an overflow of metabolic energy substrates which resulted in increased gluconeogenesis, *de novo* lipogenesis, and triglyceride-rich lipoprotein secretion in the liver (42). In contrast, for physically active subjects with high fructose intake and high energy expenditure, fructose was mainly metabolized into glucose and lactate that can be readily oxidized to support ATP synthesis, resulting in a net lactate release from splanchnic organs (mostly the liver) to the working muscle (42). This 'reverse Cori cycle' may be advantageous to improve performance by acting on central fatigue and/or alter metabolic regulation (43, 44). An animal study showed that the naked mole-rat can resist hypoxia and acidosis by increasing fructolysis (45). In our study, dietary fructose intake in the fourth quartile of urban and rural residents was 25.6 g/day and 16.8 g/day, respectively, both of which were relatively low dosage. A series of systematic reviews and meta-analyses have reported that small doses of fructose, or fructose in substitution for glucose or sucrose, may have beneficial effects or not any adverse effects on the components of the MetS (12–15, 33, 46, 47). Based on the above points, we suggested that physical activity and relatively low fructose intake may have a beneficial synergistic effect on MetS.

Several limitations should be considered in the present study. First, this cross-sectional study has a natural disadvantage to address causal relationship between dietary fructose intake and MetS. Second, added fructose was not distinguished in this study. In previous studies, the intake status of added fructose and its relationship with metabolic disease were the focus of attention. However, the consumption of added fructose was very low in our study population. Third, the accuracy of dietary information was limited by the accuracy of recall of the participants and the specificity with which the reported foods were mapped in the dietary recall records. To minimize this situation, all interviewers completed a strict training program with detailed methodologies on administration of the dietary questionnaire. Forth, three consecutive 24-h dietary records may not reflect long-term dietary habits. More high-quality cohort studies and randomized controlled trials were needed to evaluate the association between dietary fructose intake and the risk of MetS.

Conclusions

To our knowledge, the present study was the first one discussing the association between dietary fructose and the risk of MetS among Chinese residents aged 45 and above. Fruits and products, vegetables and vegetable products were the main food sources, and the dietary fructose intake was relatively low. Under the current dietary fructose intake status, there was no association between dietary fructose intake and the risk of MetS in both urban and rural residents. Interestingly, there was a significant inverse association between dietary fructose intake and MetS for urban residents who participating in physical activity. Our

results indicated that physical activity and relatively low fructose intake may have an advantageous synergistic effect on MetS.

Abbreviations

MetS, metabolic syndrome; CNNHS, China National Nutrition and Health Survey; WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Declarations

Ethical approval and Consent to participant: This survey was ethically approved by the Ethical Committee of the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention (2013-018). Written informed consent was obtained from all participants.

Consent for publication: All authors have read and agreed to the published version of the manuscript.

Availability of data and materials: Not applicable.

Conflicts of Interest: The authors declare that they have no competing interests.

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Author Contributions: The authors contributions were as follow: Conceptualization, J.Z. and W.Q.; methodology, S.P.; software, S.P.; validation, P.S., C.Y., G.S, and Y.W.; formal analysis, S.P.; investigation, S.P., P.S., C.Y., G.S, and Y.W.; resources, J.Z.; data curation, P.S.; writing—original draft preparation, S.P.; writing—review and editing, J.Z. and W.Q.; visualization, S.P.; supervision, J.Z.; project administration, W.Q.; funding acquisition, W.Q.

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Figures

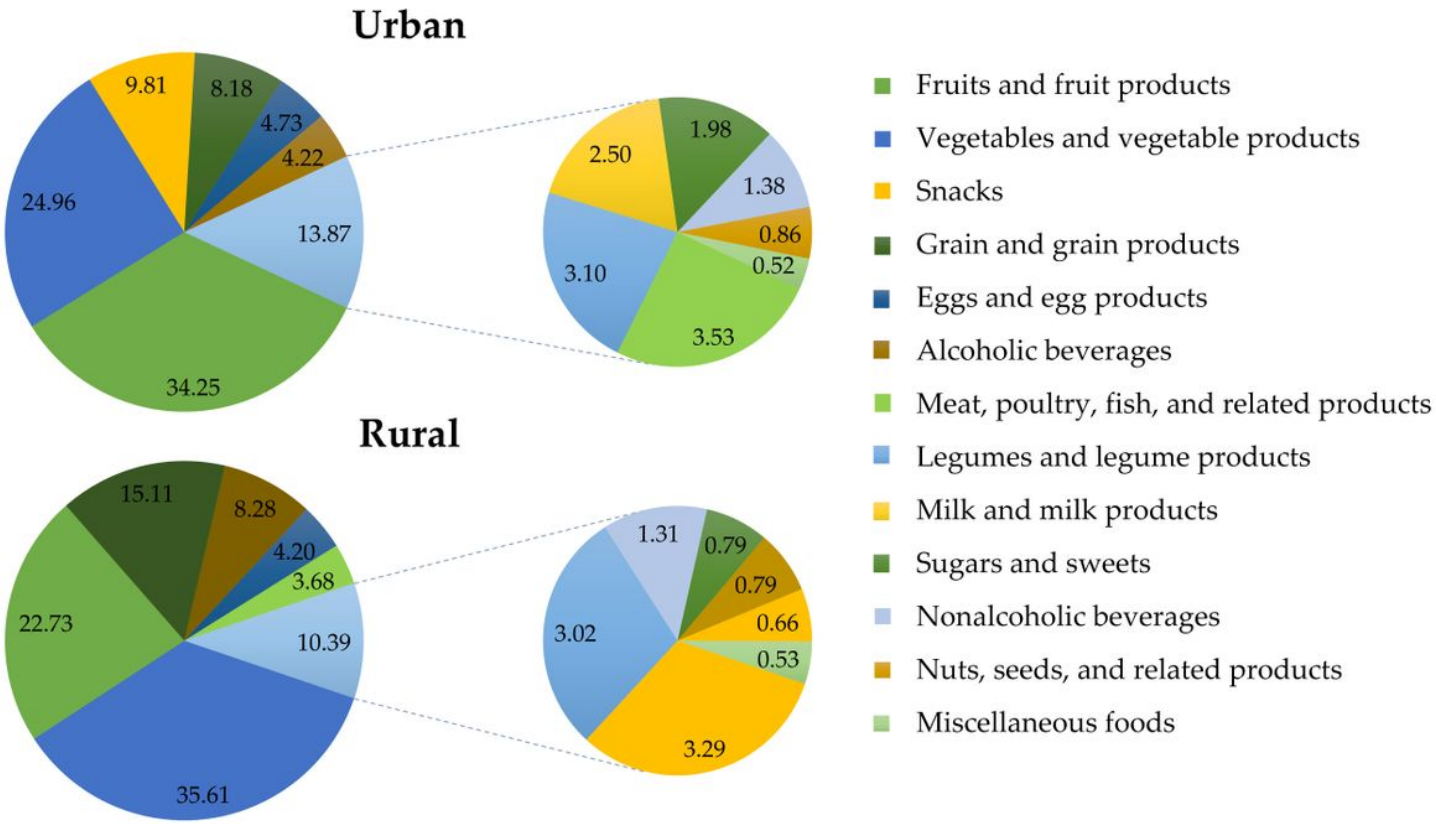

Figure 1

Distribution of dietary fructose from various foods in urban and rural residents

Supplementary Files

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- Supplementarydata.docx