



Relationship between seaweeds consumption and hyperuricaemia in general adults: a Population-based study from the Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSIH) cohort study

Tingjing Zhang^{1†}, Yawen Wang^{1†}, Yeqing Gu², Ge Meng^{1,3}, Qing Zhang⁴, Li Liu⁴, Hongmei Wu¹, Shunming Zhang¹, Xuena Wang¹, Shaomei Sun⁴, Xing Wang⁴, Ming Zhou⁴, Huanli Jiao⁴, Qiyu Jia⁴, Kun Song⁴, Yuntang Wu¹, Xiao-Hui Wu⁵ and Kaijun Niu^{1,4,6,7*}

¹Nutritional Epidemiology Institute and School of Public Health, Tianjin Medical University, 22 Qixiangtai Road, Heping District, Tianjin 300070, People's Republic of China

²Institute of Radiation Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

³Department of Toxicology and Sanitary Chemistry, School of Public Health, Tianjin Medical University, Tianjin, People's Republic of China

⁴Health Management Centre, Tianjin Medical University General Hospital, Tianjin, People's Republic of China

⁵College of Pharmacy, Tianjin Medical University, Tianjin 300070, People's Republic of China

⁶Tianjin Key Laboratory of Environment, Nutrition and Public Health, Tianjin, People's Republic of China

⁷Center for International Collaborative Research on Environment, Nutrition and Public Health, Tianjin, People's Republic of China

(Submitted 1 November 2020 – Final revision received 14 February 2021 – Accepted 5 March 2021 – First published online 15 March 2021)

Abstract

Seaweeds have numerous biologically active ingredients, such as polysaccharides, polyphenols and carotenoids, that are beneficial to human health. Although these benefits might be related to the synthesis, secretion or reabsorption of uric acid, no studies have explored the relationship between seaweeds consumption and hyperuricaemia (HUA) in the general population. The aim of this study was to investigate whether seaweeds consumption is related to HUA in a large-scale adult population. A cross-sectional study was conducted with 32 365 adults (17 328 men and 15 037 women) in Tianjin, People's Republic of China. Frequency of seaweeds consumption was assessed by a validated self-administered FFQ. HUA was defined as serum uric acid levels >420 µmol/L in men and >350 µmol/L in women. The association between seaweeds consumption and HUA was assessed by multiple logistic regression analysis. Restricted cubic spline functions were used for non-linearity tests. The prevalence of HUA in men and women was 21.17% and 5.93%, respectively. After adjustments for potential confounding factors, the OR (95% CI) for HUA across seaweed consumption (g/1000 kcal per d) were 1.00 (reference) for level 1, 0.91 (95% CI 0.81, 1.02) for level 2; 0.90 (95% CI 0.81, 1.01) for level 3; 0.86 (95% CI 0.78, 0.97) for level 4 in men and 0.90 (95% CI 0.73, 1.10) for level 2; 0.82 (95% CI 0.67, 1.00) for level 3; 0.84 (95% CI 0.68, 1.03) for level 4 in women, respectively. A negative correlation between seaweeds consumption and HUA in males but not in females was observed. Further studies are needed to explore the causal relationship.

Key words: Seaweeds; Hyperuricaemia; Adult population

Uric acid is the end product of purine metabolism. Increased production or reduced excretion of serum uric acid level causes hyperuricaemia (HUA) and gout⁽¹⁾. Most patients with HUA are asymptomatic and do not receive treatment. HUA is the causative agent of gout⁽²⁾ and is an independent risk factor for cardiovascular events^(3,4), hypertension⁽⁵⁾, diabetes⁽⁶⁾, cancer⁽⁷⁾

and renal disease⁽⁸⁾ and independently predicts myocardial infarction and premature death⁽⁹⁾. In recent decades, the prevalence of HUA has significantly increased in Western countries⁽¹⁰⁾. Economic growth and resulting lifestyle changes in China have rapidly increased the prevalence of HUA^(11,12). In particular, from 1980 to 2014, the prevalence of HUA increased from 1.4% to

Abbreviations: BP, blood pressure; HUA, hyperuricaemia; PA, physical activity.

* **Correspondence author:** Kaijun Niu, email nkj0809@gmail.com

† These authors contributed equally to this work.

19.4 % in men and 1.3 % to 7.9 % in women^(12,13). Genetics, lifestyle, environment and diet are factors contributing to the development of HUA, and diet also plays a major role in the HUA management^(14,15).

Seaweeds are an important dietary contributor in countries such as China, Japan, Korea and those in Southeast Asia. Historically, Chinese utilisation of seaweeds is one of the longest and most extensive of any country. In coastal northern China, the average household may consume seaweed two to three times a week and it is estimated that each year in China, 50 million kg of fresh and dried seaweed is used for food⁽¹⁶⁾. Epidemiological and experimental animal studies have suggested that seaweeds show hypocholesterolaemic, antithrombotic, antioxidant and antidiabetic effects and that seaweeds can reduce the prevalence of chronic diseases including obesity, coronary diseases, hyperlipidaemia, type 2 diabetes and cancer^(17–19). Seaweeds contain polysaccharides (20–76 % of dry weight), proteins (15–40 % of dry weight), mineral ions (36 % of dry weight) and *n*-3 fatty acids, usually EPA and DHA. Finally, one of the principal nutritional characteristics of seaweeds is their high antioxidant content, such as polyphenols and carotenoids^(18,20,21). Previous studies have suggested that antioxidants significantly reduced xanthine oxidase activity and expression in liver, as well as decreased urate-anion transporter 1 expression, increased organic anion transporter 1 and 3 expressions, and thus inhibited the uric acid production and reabsorption and enhanced urate secretion^(22,23).

To date, studies on the contribution of dietary seaweeds to uric acid levels and HUA are limited. Additionally, current understanding of the health-promoting activities of seaweeds is derived mainly from *in vitro* studies and *in vivo* animal studies. Therefore, we designed a cross-sectional study to explore whether consumption of seaweeds is related to HUA in a large-scale adult population.

Materials and methods

Participants

Tianjin Chronic Low-grade Systemic Inflammation and Health cohort is a prospective dynamic cohort focusing on the relationship between chronic low-grade inflammation and the health status of a population living in Tianjin⁽²⁴⁾, a city which is located in the North China, east of Bohai Sea, with approximately 15.59 million inhabitants. Participants who had received health examinations had completed questionnaires regarding their smoking and alcohol consumption habits and disease history over the course of January 2007 to December 2016. Moreover, a structured lifestyle questionnaire was administered to randomly selected subjects from this population since May 2013. The protocol of this study was approved by the Institutional Review Board of the Tianjin Medical University, and participants gave written informed consent prior to participation in the study.

This cross-sectional study used data from Tianjin Chronic Low-grade Systemic Inflammation and Health cohort ranging from 2013 to 2016. The participant selection process is described in Fig. 1. During the survey period, there were 37 988 subjects aged over 18 years who had received health examinations and handgrip strength test and participants were asked to answer

questionnaires that included questions relating to their lifestyle and provided written informed consent for their data to be analysed. We excluded participants with incomplete measurement results and questionnaires (*n* 3707), or those with a history of CVD (*n* 1652) or cancer (*n* 264). As a result of these exclusions, the final cross-sectional study population comprised 32 365 subjects.

Uric acid assessment

A fasting venous blood sample with fasting time longer than 8 h was collected from the antecubital vein, while subjects were in the sitting position. Serum uric acid levels were measured by an enzymatic colorimetric test using the Roche 912 analyzer (Roche Diagnostics); the lower limit of detection was 0.2 mg/dl. HUA was defined as uric acid levels >420 µmol/L in men and >350 µmol/L in women⁽²⁵⁾.

Dietary assessment

Dietary intake was assessed using a FFQ with specified serving sizes that were described by natural portions or standard weight and volume measures of the servings commonly consumed in this study population⁽²⁶⁾. For the assessment of dietary intake, data were based on a validated eighty-one-item self-administered FFQ (including fruits, vegetables, animal food, seafood, sugared beverages, teas, refined grain and grain products, etc.). The participants were asked how often (almost never, <1 time/week, 1 time/week, 2–3 times/week, 4–6 times/week, 1 time/d and ≥2 times/d) they had eaten specific food items over the last month. The reproducibility and validity of the questionnaire were assessed in a random sample of 150 participants from our cohort using data from repeated measurements of the FFQ approximately 3 months apart and 4-d weighed diet records. The Spearman correlation coefficients between FFQ and weighed diet record were 0.49 for energy intake and 0.35–0.54 for nutrients (vitamin C, vitamin E, polyunsaturated fats, saturated fats, carbohydrate and Ca). Spearman's rank correlation coefficients between two FFQ were 0.68 for energy intake, 0.62–0.79 for food items (fruits, vegetables, sweet foods and beverages) and 0.61 for seaweeds. Energy and nutrient intakes were calculated by using an *ad hoc* computer programme developed to analyse the FFQ.

The FFQ included an item about typical seaweed intake and contained seven frequency categories for seaweeds (*Wakame*, *Konbu*, *Nori* and more): almost never or rarely, <once per week, once per week, 2–3 times/week, 4–6 times/week, 1 time/d and ≥2 times/d. Consumption of seaweeds was calculated by multiplying portion sizes by the frequency at which each food item was consumed per d. To correct for potential measurement error, total seaweed consumption was adjusted for total energy intake according to the nutrient density method and expressed as g/1000 kcal per d⁽²⁷⁾. For analysis, we summarised the categories of seaweeds in quantiles in the following way: <0.52 g/1000 kcal per d for level 1, 0.52–0.93 g/1000 kcal per d for level 2, 0.94–1.55 g/1000 kcal per d for level 3 and >1.55 g/1000 kcal per d for level 4 in males; and <0.47 g/1000 kcal per d for level 1, 0.47–0.87 g/1000 kcal per d for level 2, 0.88–1.52 g/1000 kcal



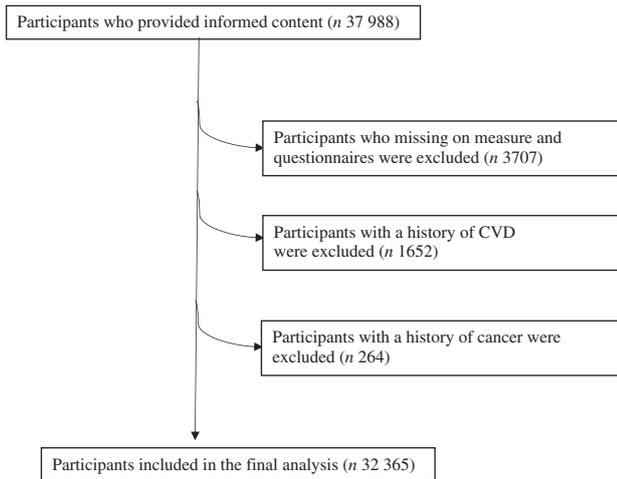


Fig. 1 Flow diagram showing the selection of the study population

per d for level 3 and >1.53 g/1000 kcal per d for level 4 in females.

The nutrient database was from the valid and reliable Chinese Food Composition Tables, and we analyse the questionnaire by using an *ad hoc* computer programme. By combining the information obtained from the FFQ with the Chinese Food Composition Tables, total energy intake for each participant was computed. Factor analysis (principal component analysis) was used to derive dietary patterns and to determine factor loadings for each of the food and beverages subgroups (in g/d). Evaluation of the eigenvalues and scree plot test was used in determining the number of retained factors. Varimax rotation was used to maintain uncorrelated factors and enhance interpretability. After evaluation of eigenvalues (>1.0) and the screen test, three factors were determined. Food items with a factor loading $>|0.30|$ were the main contributors to dietary pattern and representative of the character of each pattern. Factors were named descriptively according to the food items showing high loading (absolute value) with respect to each dietary pattern as follows: 'sweet food pattern (factor 1), healthy pattern (factor 2), and animal food pattern (factor 3)'. Similar dietary patterns were also observed in our previous study⁽²⁸⁾. For each of the dietary patterns, a higher score indicates stricter adherence to that dietary pattern.

Assessment of other variables

Levels of fasting blood glucose were measured by glucose oxidase method. As for lipids, TAG and total cholesterol were measured by enzymatic methods. LDL was measured by the polyvinyl sulphuric acid precipitation method, and HDL was measured by the chemical precipitation method using appropriate kits on a Cobas 8000 analyzer (Roche). Blood pressure (BP) was measured twice at the upper left arm using an automatic device (TM-2655P, A&D Company, Ltd) after 5 min of rest in a sitting position. The BP value was the mean of these two measurements. Waist circumference was measured at the umbilical level with participants standing and breathing normally. The

metabolic syndrome was defined in accordance with the criteria of the American Heart Association scientific statements of 2009⁽²⁹⁾. Participants were considered to have the metabolic syndrome when they presented three or more of the following components: (1) elevated waist circumference for Chinese individuals (≥ 85 cm in males; ≥ 80 cm in females), (2) elevated TAG (≥ 1.7 mmol/l), or drug treatment for elevated TAG, (3) reduced HDL (<1.0 mmol/l in males; <1.3 mmol/l in females) or drug treatment for reduced HDL, (4) elevated BP (systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg) or antihypertensive drug treatment and (5) elevated fasting glucose (≥ 5.56 mmol/l) or drug treatment for elevated glucose.

The anthropometric variables (height and body weight) were recorded using a standard protocol. The BMI was calculated by dividing the weight in kg by the square of the height in metres. Physical activity (PA) was evaluated by using the short form of the International Physical Activity Questionnaire⁽³⁰⁾. The questionnaire surveyed whether subjects had performed any type of activities during the previous week: walking, moderate activity (household activity, riding or child care), vigorous activity (running, swimming or other sports activities). Metabolic equivalent h/week was calculated using corresponding metabolic equivalent coefficients (3.3, 4.0 and 8.0) according to the following formula: metabolic equivalent coefficient of activity \times duration (h) \times frequency (d). Total PA levels were assessed by combining separate scores for different activities. The other information including demographical and socio-economic characteristics, physical health status, lifestyle and health-related factors were collected using the health status questionnaire.

Statistical analysis

All statistical analyses were performed by using the Statistical Analysis System 9.3 edition for Windows (SAS Institute Inc.). Males and females were analysed separately in this study because of the significant difference of prevalence of HUA and eating habits in each sex^(31,32). The frequency of seaweeds consumption was used as independent variable in three categories, and HUA was used as dependent variable. Data were expressed as the mean (95% CI) for continuous variables and percentages for categorical variables. Because the distribution of all continuous variables was non-normal, the natural logarithm was applied to normalise the data before ANOVA and multiple logistic regression analysis. The association between seaweeds consumption categories and prevalence of HUA was examined by multiple logistic regression analysis after adjustment for covariates: Model 1 was adjusted for age and BMI. Model 2 was additionally adjusted for smoking status, alcohol consumption status, socio-economic status (including education level, employment status and household income per month), PA and family or individual history of disease (hypertension, hyperlipidaemia, diabetes). Model 3 (full model) was additionally adjusted for total energy intake, sweet food pattern score, healthy pattern score and animal food pattern score. Multiple linear regression models, adjusting for the same covariates (models 1, 2 and 3), were also used to evaluate the



association between serum uric acid level and intakes of seaweeds. To avoid potentially arbitrary categorisation, restricted cubic splines evaluated the likelihood of HUA in each participant according to the factors evaluated⁽³³⁾. Non-linearity was tested using the likelihood ratio, comparing the model with only the linear term with the model with both linear and cubic spline terms. We specified three knot positions at the 5th, 50th and 90th percentiles of seaweeds consumption. The reference level was set to the lower value of seaweeds consumption. OR and 95 % CI were calculated. All *P* values for linear trends were calculated by using the categories of seaweeds consumption (almost never, <1 time/week, 1 time/week and ≥ 2 –3 times/week). All tests were two-tailed, and $P < 0.05$ was defined as statistically significant.

Results

Participant characteristics delineated by sex are summarised in Table 1. A total of 32 365 participants (17 328 men and 15 037 women) were enrolled in the cross-sectional study, and the prevalence of HUA was 14.10 % (21.17 % in men and 5.93 % in women). Compared with females, males had a higher BMI, total cholesterol, TAG, LDL, systolic BP, diastolic BP and fasting blood glucose. They were also more likely to engage in PA, consumed more total energy and had higher sweet food pattern score and animal food pattern score. In addition, males were more likely to be smokers and drinkers. Compared with females, males were more highly educated, were more likely to be managers, had a higher income and had a higher prevalence of hypertension, hyperlipidaemia and diabetes.

The relationship between the categories of seaweeds consumption (g/1000 kcal per d) and HUA is presented in Table 2. In males, the prevalence of HUA decreases across the increased consumption of seaweeds in all models. The OR (95 % CI) for HUA across seaweeds consumption categories in the final multivariate models were 1.00 (reference), 0.91 (95 % CI 0.81, 1.02) for level 2 ($P = 0.24$); 0.90 (95 % CI 0.81, 1.01) for level 3 ($P = 0.19$); 0.86 (95 % CI 0.78, 0.97) for level 4 ($P = 0.02$), and significant relationships were observed between the highest category of seaweeds consumption and HUA. In females, the OR (95 % CI) for HUA across seaweeds consumption categories in the final multivariate models were 1.00 (reference), 0.91 (95 % CI 0.73, 1.10) for level 2 ($P = 0.35$); 0.82 (95 % CI 0.67, 1.00) for level 3 ($P = 0.06$); 0.84 (95 % CI 0.68, 1.03) for level 4 ($P = 0.09$).

Multiple linear regression models were used to confirm the association between seaweeds consumption and serum uric acid level (Table 3). After adjusting for multiple confounding factors, significant associations between seaweeds consumption and serum uric acid level in males (standard regression coefficient = -0.017 , $P = 0.02$) were observed. However, we found no significant association in females (standard regression coefficient = -0.01 , $P = 0.11$).

Next, we analysed seaweeds consumption as a continuous variable using restricted cubic spline models to further confirm the relationship between seaweeds consumption and HUA by

sex. As shown in Figure 2, as the seaweeds consumption increased, Ln(OR) for HUA displayed decreasing trends in males (P for the non-linear association = 0.60, P for overall association = 0.05). However, no significant trends in correlations between seaweeds consumption and HUA were observed in females (P for the non-linear association = 0.16, P for overall association = 0.37, Fig. 3)

Discussion

While previous studies have underlined the beneficial effects of seaweeds consumption on human health, to the best of our knowledge, no study has assessed the effect of seaweeds consumption on HUA in humans. The present study was the first to discover that higher seaweeds consumption was significantly related to lower prevalence of HUA in males. This effect was not observed in females.

We adjusted for multiple potentially confounding factors in our analysis. First, since studies have shown that HUA is related to age⁽³⁴⁾ and BMI⁽³⁵⁾, we adjusted for these two variables. Second, sociodemographic factors, lifestyle factors, chronic diseases and nutritional status^(36,37) can also influence the relationship between seaweeds and HUA; thus, we subsequently adjusted for smoking status, alcohol consumption status, education level, employment status, household incomes, PA, hypertension, hyperlipidaemia, diabetes and total energy intake. However, the adjustment for these factors did not change the significant relationship between seaweeds consumption and HUA. Finally, to avoid dietary factors influencing the results, we additionally adjusted for dietary pattern. After all adjustments were made, the observed association between seaweeds consumption frequency and HUA was not confounded by covariates.

Although the exact mechanisms of seaweeds consumption in HUA have not been elucidated, biologically active ingredients in seaweeds might be the candidates for this negative relationship in males. Ingredients of seaweeds contain proteins, polysaccharides, dietary fibre, polyphenols and various micronutrients, such as antioxidants⁽³⁸⁾. First, the kidney is crucial for the uric acid excretion, about 2/3 of uric acid is excreted via urination in the kidney, decreased renal function aggravates uric acid excretion impairment⁽³⁹⁾. Seaweed polysaccharides have been shown to have good repair and protective effect on kidney cells and a significant effect on promoting the excretion of uric acid⁽⁴⁰⁾. Second, one of the principal nutritional characteristics of seaweeds is high polyphenol antioxidant content⁽³⁸⁾. Polyphenols may prevent uric acid disorder through the following mechanisms: (i) inhibit xanthine oxidase and reduce serum or liver uric acid synthesis⁽⁴¹⁾, (ii) increase excretion of uric acid and prevent kidney reabsorption⁽⁴²⁾ and (iii) ameliorate uric acid excretion via the intestine⁽⁴³⁾. Third, evidence suggested that natural carotenoid extracted from the plants ameliorated inflammation in kidneys and lowered uric acid levels by reducing the levels of TNF- α and IL-1 β ⁽⁴⁴⁾. Further studies will be required to clarify the exact mechanisms of seaweeds consumption in HUA.

The present study first assessed the relationship between seaweeds consumption and HUA in a large-scale adult population.



Table 1. Participant characteristics by sex (Odds ratios and 95 % confidence intervals; percentages, *n* 32 365) (Percentages; Odds ratio and 95 % confidence intervals)

	Male			Female		
	%	OR	95 % CI	%	OR	95 % CI
No. of subjects		17 328		15 037		
Age (years)		40.8	40.6, 41.0	39.1		38.9, 39.3
BMI (kg/m ²)		25.6	25.5, 25.6	22.8		22.7, 22.8
TC (mmol/l)		4.88	4.86, 4.89	4.75		4.73, 4.76
TAG (mmol/l)		1.69	1.67, 1.71	1.05		1.04, 1.06
LDL (mmol/l)		2.93	2.92, 2.95	2.75		2.73, 2.76
SBP (mmHg)		124.5	124.2, 124.7	116.0		115.7, 116.2
DBP (mmHg)		79.7	79.5, 79.9	72.4		72.3, 72.6
FBG (mmol/l)		5.19	5.17, 5.21	4.91		4.89, 4.92
Total energy intake (kcal/d)		2084.1	2076.0, 2092.2	1914.0		1904.7, 1923.3
PA (MetS × h/week)		22.9	22.4, 23.5	18.3		17.8, 18.8
Smoking status (%)						
Current smoker	38.2			1.6		
Ex-smoker	9.9			0.7		
Non-smokers	51.9			97.7		
Drinker (%)						
Everyday drinkers	8.8			0.7		
Sometimes drinkers	70.9			38.9		
Ex-drinkers	9.5			9.2		
Non-drinkers	10.8			51.2		
Employment status (%)						
Managers	44.9			41.3		
Professionals	20.0			12.9		
Others	35.1			45.8		
Household income (≥10 000 yuan per month, %)	35.1			31.8		
Educational level (≥college graduate, %)	60.6			56.5		
Hypertension (%)	29.7			12.9		
Hyperlipidaemia (%)	51.9			33.1		
Diabetes (%)	4.4			1.8		

TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; PA, physical activity; MetS, metabolic syndrome.

Table 2. Adjusted associations of energy-adjusted seaweeds consumption with hyperuricaemia (Odds ratio and 95 % confidence intervals, percentages, *n* 32 365)*

	Quartiles of energy-adjusted seaweed consumption (g/1000 kcal per d)							
	Level 1		Level 2		Level 3		Level 4	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Male								
No. of case		811		947		958		954
No. of subjects		3846		4494		4494		4494
Model 1†	1.00	Reference	0.94‡	0.85, 1.05	0.95	0.85, 1.06	0.90	0.81, 1.01
Model 2§	1.00	Reference	0.93	0.83, 1.05	0.93	0.83, 1.04	0.87	0.79, 0.99
Model 3	1.00	Reference	0.91	0.81, 1.02	0.90	0.81, 1.01	0.86	0.78, 0.97
Female								
No. of case		235		226		206		225
No. of subjects		3431		3852		3877		3877
Model 1	1.00	Reference	0.95	0.78, 1.15	0.85	0.70, 1.04	0.92	0.76, 1.12
Model 2	1.00	Reference	0.94	0.77, 1.14	0.85	0.69, 1.04	0.89	0.74, 1.09
Model 3	1.00	Reference	0.90	0.73, 1.10	0.82	0.67, 1.00	0.84	0.68, 1.03

* Obtained by using multiple logistic regression analysis.

† Adjusted for age and BMI.

‡ OR (95 % CI) (all such values).

§ Additionally adjusted for smoking status, alcohol consumption status, education level, employment status, household incomes, physical activity, hypertension, hyperlipidaemia and diabetes.

|| Additionally adjusted for total energy intake and dietary patterns.

Furthermore, we controlled for various potential confounders, such as age, BMI, smoking status, alcohol consumption status, education level, employment status, household incomes, PA, hypertension, hyperlipidaemia, diabetes, total energy intake and dietary pattern.

In this study, since sex-specific differences were observed in HUA⁽⁴⁵⁾, we analysed the relationship between seaweeds consumption and HUA by sex. Our results showed a negative relationship between seaweeds consumption and HUA in males but not in females (see Table 2). Although detailed molecular

Table 3 Adjusted associations of energy-adjusted seaweeds consumption with serum uric acid levels (*n* 32 265) (β -coefficients and standard errors)

	Dependent variable: Serum uric acid level			
	Standardised β	Standard error	<i>t</i> Value	<i>P</i> Value*
Male (<i>n</i> 17 328)				
Model 1†	-0.017	0.322	-2.36	0.02
Model 2‡	-0.014	0.316	-2.05	0.04
Model 3§	-0.017	0.349	-2.22	0.02
Female (<i>n</i> 15 037)				
Model 1	-0.004	0.252	-0.55	0.58
Model 2	-0.006	0.250	-0.81	0.42
Model 3	-0.013	0.272	-1.60	0.11

* Multiple linear regression model.

† Adjusted for age and BMI.

‡ Additionally adjusted for smoking status, alcohol consumption status, education level, employment status, household incomes, physical activity, hypertension, hyperlipidaemia and diabetes.

§ Additionally adjusted for total energy intake and dietary patterns.

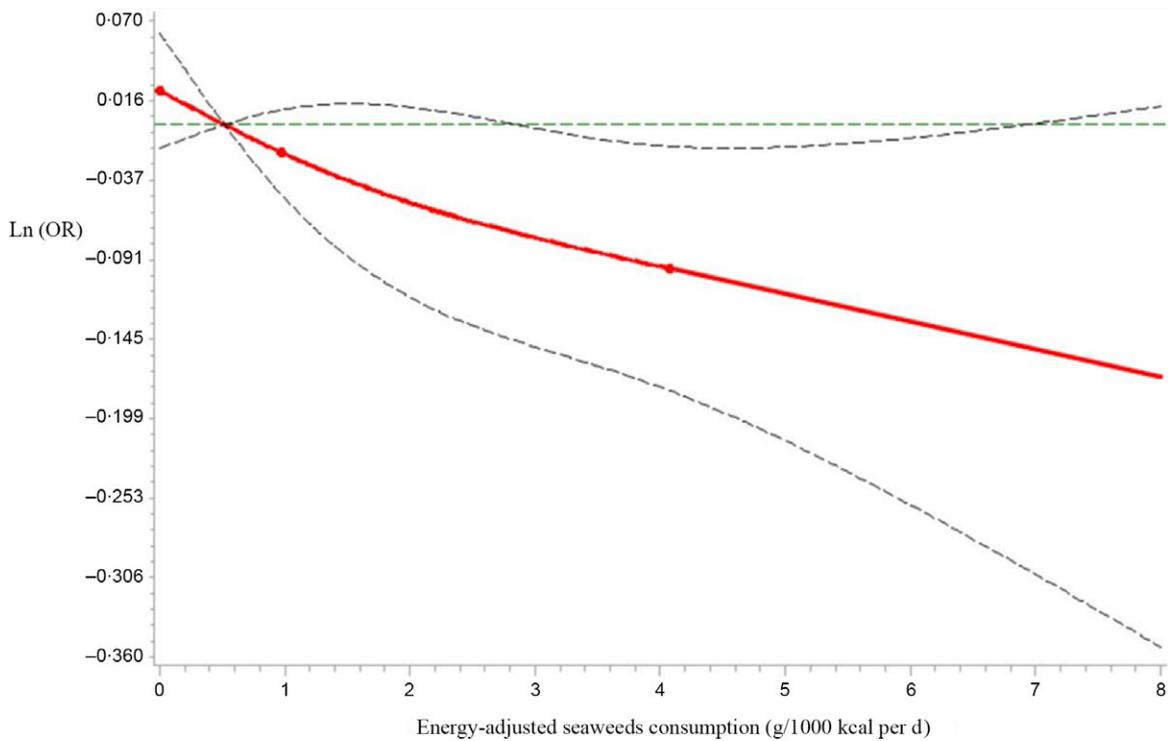


Fig. 2 Restricted cubic spline models representing the associations of seaweeds consumption (g/1000 kcal per d) with OR for prevalence of hyperuricaemia (HUA) in males, after adjusting for age, BMI, smoking status, alcohol consumption status, education level, employment status, household incomes, physical activity, hypertension, hyperlipidaemia, diabetes, total energy intake and dietary patterns (seaweeds intake was not included in the calculation). The reference value for seaweeds consumption (g/1000 kcal per d) was 0.52 g/1000 kcal per d. The three knots were set at 5th, 50th and 95th percentiles. Estimation; — Lower_CL; --- Upper_CL; --- knots

mechanisms remain unclear, seaweeds are found to associate with decreased plasma oestradiol level⁽⁴⁶⁾. Because the effects of oestradiol on uric acid were different for males and females⁽⁴⁷⁾, the seaweeds consumption-inducing oestradiol may partly explain the differences in the correlation between seaweeds consumption and HUA in males and females.

Some limitations merit further discussion. First, the relationship between seaweeds consumption and HUA comes from a cross-sectional design, which does not allow for causal

relationships, since the temporal relationships of these events cannot be determined, and further longitudinal studies will be needed for confirmation. Second, even though many potential confounders have been taken into consideration, there are still other factors which might confound the association between seaweeds and HUA, which have not been fully captured. Third, potential recall bias exists, which occurs when subjects fail to recall the frequency in which they completed the FFQ, and this recall bias could affect the results.

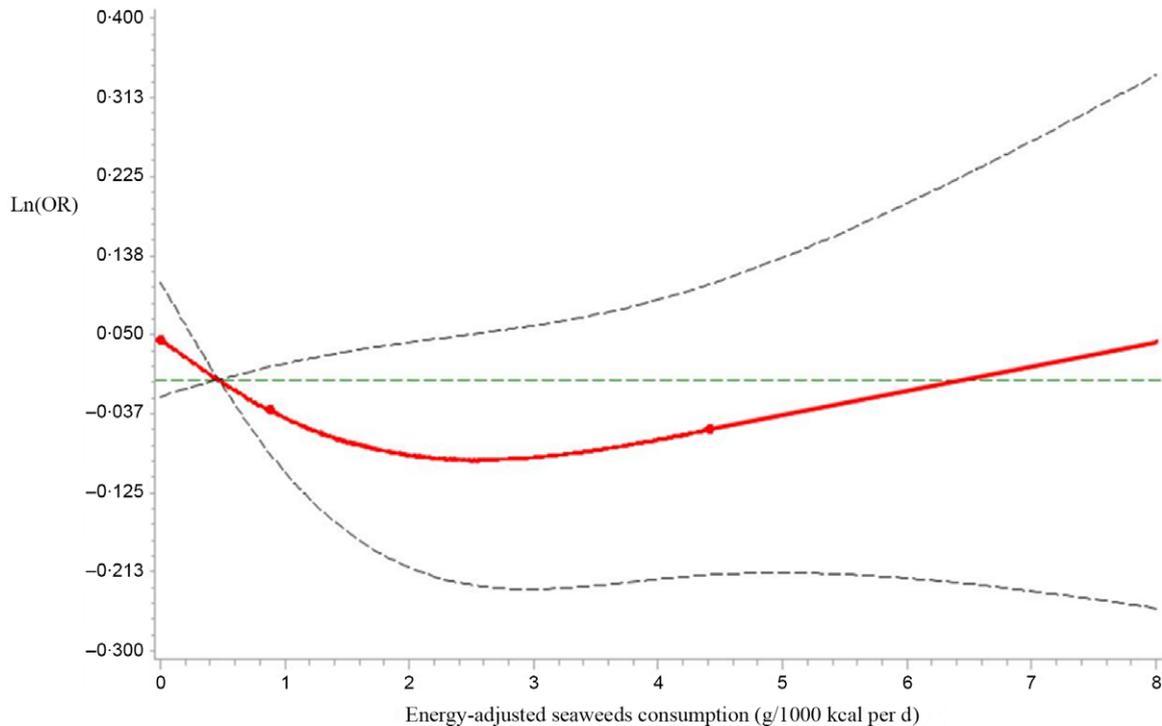


Fig. 3 Restricted cubic spline models representing the associations of seaweeds consumption (g/1000 kcal per d) with OR for prevalence of hyperuricaemia (HUA) in males, after adjusting for age, BMI, smoking status, alcohol consumption status, education level, employment status, household incomes, physical activity, hypertension, hyperlipidaemia, diabetes, total energy intake and dietary patterns (seaweeds intake was not included in the calculation). The reference value for seaweeds consumption (g/1000 kcal per d) was 0.47 g/1000 kcal per d. The three knots were set at 5th, 50th and 95th percentiles. Estimation; — Lower_CL; --- Upper_CL; --- knots

Conclusion

In conclusion, this study revealed that a higher consumption of seaweeds can reduce the prevalence of HUA in males but not in females in a large-scale adult population. This finding suggested that the consumption of seaweeds may have a potentially beneficial effect on reducing the prevalence of HUA. A prospective study or randomised trials are required to clarify the causality.

Acknowledgements

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

This study was supported by grants from the National Natural Science Foundation of China (no. 91746205, 81941024, 81872611, and 81673166).

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

None of the authors has any potential conflict of interest.

References

- Garrel DR, Verdy M, PetitClerc C, *et al.* (1991) Milk- and soy-protein ingestion: acute effect on serum uric acid concentration. *Am J Clin Nutr* **53**, 665–669.
- Choi HK, Mount DB, Reginato AM, *et al.* (2005) Pathogenesis of gout. *Ann Intern Med* **143**, 499–516.
- Hoiegggen A, Alderman MH, Kjeldsen SE, *et al.* (2004) The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* **65**, 1041–1049.
- Holme I, Aastveit AH, Hammar N, *et al.* (2009) Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417 734 men and women in the Apolipoprotein Mortality Risk Study (AMORIS). *J Intern Med* **266**, 558–570.
- Sundstrom J, Sullivan L, D'Agostino RB, *et al.* (2005) Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. *Hypertension* **45**, 28–33.
- Bhole V, Choi JW, Kim SW, *et al.* (2010) Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am J Med* **123**, 957–961.
- Strasak AM, Rapp K, Hilbe W, *et al.* (2007) Serum uric acid and risk of cancer mortality in a large prospective male cohort. *Cancer Causes Control: CCC* **18**, 1021–1029.
- Obermayr RP, Temml C, Gutjahr G, *et al.* (2008) Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol: JASN* **19**, 2407–2413.
- Fang J & Alderman MH (2000) Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. *JAMA* **283**, 2404–2410.
- Uaratanawong S, Suraamornkul S, Angkeaw S, *et al.* (2011) Prevalence of hyperuricemia in Bangkok population. *Clin Rheumatol* **30**, 887–893.
- Liu H, Zhang XM, Wang YL, *et al.* (2014) Prevalence of hyperuricemia among Chinese adults: a national cross-sectional survey using multistage, stratified sampling. *J Nephrol* **27**, 653–658.



12. Liu R, Han C, Wu D, *et al.* (2015) Prevalence of hyperuricemia and gout in Mainland China from 2000 to 2014: a systematic review and meta-analysis. *Biomed Res Int* **2015**, 762820.
13. Chen S, Du H, Wang Y, *et al.* (1998) The epidemiology study of hyperuricemia and gout in a community population of Huangpu District in Shanghai. *Chin Med J* **111**, 228–230.
14. Singh JA, Reddy SG & Kundukulam J (2011) Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol* **23**, 192–202.
15. Zhang W, Doherty M, Bardin T, *et al.* (2006) EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheumatic Dis* **65**, 1312–1324.
16. Abbott XIA (1987) Edible seaweeds of China and their place in the Chinese diet. *Econ Bot* **41**, 341–353.
17. Iwai K (2008) Antidiabetic and antioxidant effects of polyphenols in brown Alga *Ecklonia stolonifera* genetically diabetic KK-AyMice. *Plant Food Hum Nutr* **63**, 163–169.
18. Brown ES, Allsopp PJ, Magee PJ, *et al.* (2014) Seaweed and human health. *Nutr Rev* **72**, 205–216.
19. Sharifuddin Y, Chin YX, Lim PE, *et al.* (2015) Potential bioactive compounds from seaweed for diabetes management. *Mar Drugs* **13**, 5447–5491.
20. Lordan S, Ross RP & Stanton C (2011) Marine bioactives as functional food ingredients: potential to reduce the incidence of chronic diseases. *Mar Drugs* **9**, 1056–1100.
21. Rajapakse N & Kim SK (2011) Nutritional and digestive health benefits of seaweed. *Adv Food Nutr Res* **64**, 17–28.
22. Chen G, Tan ML, Li KK, *et al.* (2015) Green tea polyphenols decreases uric acid level through xanthine oxidase and renal urate transporters in hyperuricemic mice. *J Ethnopharmacol* **175**, 14–20.
23. Coulibaly AY, Kiendrebeogo M, Kehoe PG, *et al.* (2011) Antioxidant and anti-inflammatory effects of *Scoparia dulcis* L. *J Med Food* **14**, 1576–1582.
24. Sun S, Wu H, Zhang Q, Wang C, *et al.* (2014) Subnormal peripheral blood leukocyte counts are related to the lowest prevalence and incidence of metabolic syndrome: tianjin chronic low-grade systemic inflammation and health cohort study. *Mediators Inflammation* **2014**, 412386.
25. Li H, Qin X, Xie D, *et al.* (2015) Effects of combined enalapril and folic acid therapy on the serum uric acid levels in hypertensive patients: a multicenter, randomized, double-blind, parallel-controlled clinical trial. *Intern Med* **54**, 17–24. doi: [10.2169/internalmedicine.54.2931](https://doi.org/10.2169/internalmedicine.54.2931).
26. Yu B, Yu F, Su Q, Zhang Q, *et al.* (2018) A J-shaped association between soy food intake and depressive symptoms in Chinese adults. *Clin Nutr* **37**, 1013–1018.
27. Willett WC, Howe GR & Kushi LH (1977) Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* **65**, 1220S–1228S.
28. Xia Y, Wang N, Yu B, *et al.* (2017) Dietary patterns are associated with depressive symptoms among Chinese adults: a case-control study with propensity score matching. *Eur J Nutr* **56**, 2577–2587.
29. Alberti KG, Eckel RH, Grundy SM, *et al.* (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **120**, 1640–1645.
30. Qu NN & Li KJ (2004) Study on the reliability and validity of international physical activity questionnaire (Chinese Version, IPAQ). **25**, 265–268.
31. Steele P, Dobson A, Alexander H, *et al.* (1991) Who eats what? a comparison of dietary patterns among men and women in different occupational groups. *Aust J Public Health* **15**, 286–295.
32. Dong X, Zhang H, Wang F, *et al.* (2020) Epidemiology and prevalence of hyperuricemia among men and women in Chinese rural population: the Henan Rural Cohort Study. *Mod Rheumatol* **30**, 910–920.
33. Desquilbet L & Mariotti FO (2010) Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med* **29**, 1037–1057.
34. Ryckwaert A, Dry J & Paolaggi F (1965) Hyperuricemia. II. Influence of race, heredity, age, height, weight, diet, diuresis, muscular effort, living conditions on blood uric acid levels. *Rev Rhum Mal Osteoartic* **32**, 783–789.
35. Dalbeth N, Phipps-Green A, House ME, *et al.* (2015) Body mass index modulates the relationship of sugar-sweetened beverage intake with serum urate concentrations and gout. *Arthritis Res Ther* **17**, 263.
36. McAdams-DeMarco MA, Law A, Maynard JW, *et al.* (2013) Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. *BMC Musculoskelet Disord* **14**, 347.
37. Raja S, Kumar A, Aahooja RD, *et al.* (2019) Frequency of hyperuricemia and its risk factors in the adult population. *Cureus* **11**, e4198.
38. Lordan S, Ross RP & Stanton C (2011) Marine bioactives as functional food ingredients: potential to reduce the incidence of chronic diseases. *Mar Drugs* **9**, 1056–1100.
39. Liu YW, Sun WF, Zhang XX, *et al.* (2015) Compound Tufuling Granules (〔characters: see text〕) regulate glucose transporter 9 expression in kidney to influence serum uric acid level in hyperuricemia mice. *Chin J Integr Med* **21**, 823–829.
40. Jia RB, Wu J, Li ZR, *et al.* (2020) Comparison of physicochemical properties and antidiabetic effects of polysaccharides extracted from three seaweed species. *Int J Biol Macromol* **149**, 81–92.
41. Mittal A, Phillips AR, Loveday B, *et al.* (2008) The potential role for xanthine oxidase inhibition in major intra-abdominal surgery. *World J Surg* **32**, 288–295.
42. Zhang ZC, Su GH, Luo CL, *et al.* (2015) Effects of anthocyanins from purple sweet potato (*Ipomoea batatas* L. cultivar Eshu No. 8) on the serum uric acid level and xanthine oxidase activity in hyperuricemic mice. *Food Funct* **6**, 3045–3055.
43. Kamatani Y, Matsuda K, Okada Y, *et al.* (2010) Genome-wide association study of hematological and biochemical traits in a Japanese population. *Nat Genet* **42**, 210–215.
44. Ma JQ, Zhang YJ, Tian ZK, *et al.* (2020) Bixin attenuates carbon tetrachloride induced oxidative stress, inflammation and fibrosis in kidney by regulating the Nrf2/TLR4/MyD88 and PPAR-gamma/TGF-beta1/Smad3 pathway. *Int Immunopharmacol* **90**, 107117.
45. Peichl P (1997) Epidemiology, incidence and sex specific differences in primary gout. *Wien Med Wochenschr* **147**, 370–372.
46. Skibola CF (2004) The effect of *Fucus vesiculosus*, an edible brown seaweed, upon menstrual cycle length and hormonal status in three pre-menopausal women: a case report. *BMC Complement Altern Med* **4**, 10.
47. Yahyaoui R, Esteva I, Haro-Mora JJ, *et al.* (2008) Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab* **93**, 2230–2233.

