Public Health Nutrition: 24(8), 2205–2214 doi:10.1017/S1368980020000324

Association between retinol intake and hyperuricaemia in adults

Peipei Zhang[1], Jianping Sun[2,3], Yan Guo[4], Minghui Han[5], Fan Yang[1] and Yongye Sun[1,*]

[1]Department of Nutrition and Food Hygiene, School of Public Health, Qingdao University, Qingdao, People's Republic of China: [2]Qingdao Municipal Center for Disease Control and Prevention, Qingdao, People's Republic of China: [3]Basic Medical College, Qingdao University, Qingdao, People's Republic of China: [4]Qingdao No. 6 People's Hospital, Qingdao, People's Republic of China: [5]Huangdao District Central Hospital, Qingdao, People's Republic of China

Submitted 30 May 2019: Final revision received 28 December 2019: Accepted 20 January 2020: First published online 21 May 2020

Abstract

Objective: Current evidences on the association between hyperuricaemia and retinol intake remain inconsistent. Furthermore, no known studies have investigated the relationship between hyperuricaemia and retinol intake from animal food and plant food separately. This study aimed to assess the relationship between different sources of retinol intake and risk of hyperuricaemia among US adults.

Design: Univariate and multivariate weighted logistic regression models and restricted cubic spline models were used to assess the associations of total, animal-derived and plant-derived retinol intakes with the risk of hyperuricaemia. Dietary retinol was measured through two 24-h dietary recall interviews. Hyperuricaemia was defined as serum uric acid level ≥7·0 and ≥6·0 mg/dl in men and women, respectively.

Setting: Data from the National Health and Nutrition Examination Survey 2009–2014 were used in this cross-sectional study.

Participants: Overall, 12 869 participants aged ≥20 years were included.

Results: Compared with the lowest quintile, the multivariable OR of hyperuricaemia for the highest quintile intake of total, animal-derived and plant-derived retinol were 0·71 (95 % CI 0·52, 0·96), 0·76 (95 % CI 0·59, 0·96) and 0·92 (95 % CI 0·72, 1·17), respectively. The inverse association between dietary intake of total retinol and the risk of hyperuricaemia was observed in men. Dose–response analyses revealed a novel linear trend between the risk of hyperuricaemia and total, animal-derived retinol intake separately.

Conclusions: Our findings indicated that intakes of total and animal-derived retinol were negatively associated with hyperuricaemia in US adults.

Keywords
Retinol
Hyperuricaemia
Uric acid
Dose–response
National Health and Nutrition Examination Survey

Uric acid is the ultimate product of purine metabolism in humans. Hyperuricaemia occurs when serum uric acid level exceeds the normal level. As a precursor of gout symptoms[1], hyperuricaemia is also associated with the development of hypertension[2], CVD[3,4], type II diabetes[5], metabolic syndrome[6] and premature deaths[7]. The current prevalence of hyperuricaemia ranges from 8·9 to 24·4 % in different populations[8–11]. Nevertheless, the aetiology of hyperuricaemia remains unknown.

Besides genetic variations[12,13] and environmental factors[14], several dietary factors have been associated with hyperuricaemia[12]. Purine-rich foods[15–17], alcohol[18] and even high fructose and sugar-sweetened beverages[19,20] may definitively increase the risk of hyperuricaemia[21]. The intakes of some antioxidant nutrients, including vitamin C[22–24], vitamin E[25] and Zn[26], are negatively associated with hyperuricaemia. The common mechanism of lowering uric acid level was because of the antioxidant property of these nutrients which could reduce oxidative stress and further decrease uric acid synthesis[23,26]. Vitamin A, also called retinol, is a potent exogenous antioxidant for humans[27,28] that is presumed to be linked to uric acid metabolism. Several studies aimed to assess the relationship between dietary retinol intake and hyperuricaemia with inconsistent results. A Korean study revealed that subjects with hyperuricaemia had lower retinol intakes

*Corresponding author: Email yongye.sun@126.com

than controls[29]. However, a previous study conducted to compare data from two cohorts of homogenous ethnicity but different food traditions (Australia and Norway)[30] revealed that retinol intake was positively associated with the uric acid level in the Australian cohort, although this association was not significant in the Norwegian cohort. In a cross-sectional survey in Taiwan, retinol intake was not significantly associated with hyperuricaemia[31]. Thus, the limited evidences associating retinol intake with hyperuricaemia are controversial and need to be further assessed.

To our knowledge, previous studies on the associations of dietary retinol intake and hyperuricaemia have less stratified evidence when retinol intakes from animal food and plant food were referred to. Additionally, no known studies have investigated the dose–response relationship. Therefore, the current study aimed to assess the associations and dose–response relationship between risk of hyperuricaemia and dietary intakes of total, animal-derived and plant-derived retinol among the US adult population using data from the National Health and Nutrition Examination Survey (NHANES) 2009–2014.

Methods

Study populations

In this cross-sectional study, data were gathered from three 2-year cycles (2009–2014) of NHANES. A stratified, multistage sampling design was used to produce a sample that represented American civilians of the non-institutionalised population[32]. The programme covers clinical, physical, laboratory and interviews to obtain dietary and health indicators. NHANES participants are first interviewed at home and then undergone a health check at the mobile examination centre. More details of this study design are available on the NHANES official website[33]. Overall, 30 468 individuals participated in the NHANES during 2009–2014. Our analyses were limited to 17 547 individuals aged ≥20 years. We excluded 1652 participants with incomplete uric acid results, 2739 with incomplete or unreliable 24-h recall data, 149 pregnant women and 138 with total energy intake >mean + 3 SD (18 853·104 kJ) or <mean − 3 SD (0 kJ). Finally, 12 869 subjects (6158 men and 6711 women) were included (Fig. 1).

Measures

Hyperuricaemia was defined as serum uric acid level ≥7·0 and ≥6·0 mg/dl in men and women, respectively. The method of detecting serum uric acid level was described elsewhere[24]; serum uric acid concentration was detected on a Beckman Synchron LX20 or Beckman UniCel® DxC800 Synchron after oxidisation with the specific enzyme uricase to form allantoin and H_2O_2. The detailed measurement methods for weight and height are available in https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/manuals/Anthropometry_Procedures_Manual.pdf. The detailed measurement methods for blood pressure are available in https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/BPX_H.htm; Dietary vitamin A intake in retinol activity equivalents (mcg) was the main measure of retinol intake and was calculated through two 24-h dietary recall interviews. The first dietary recall interview was collected in-person in the mobile examination centre, and the second interview was collected by telephone 3–10 d later. Sources of dietary retinol were identified using US Department of Agriculture Food and Nutrient Database for Dietary Studies (2009–2010, 2011–2012 and 2013–2014, respectively). Intakes of animal-derived retinol (milk and milk products; meat, poultry, fish and mixtures; eggs) and plant-derived retinol (legumes, nuts and seeds; grain products; fruits; vegetables; fats, oils and salad dressings; sugars, sweets and beverages) were calculated according to the food code. As for 'animal-derived retinol', 1 mcg retinol activity equivalents = 1 mcg all-trans retinol from animal foods. To calculate retinol activity equivalents for 'plant-derived retinol', we used the equation: retinol activity equivalents for plant-derived retinol (mcg) = 1/12 beta carotene (mcg) + 1/24 other provitamin A (mcg).

Covariates

Based on the literatures and the assessed correlations in our data, the following factors that correlated with hyperuricaemia and retinol intakes were included to control for potential effects of confounding: age, gender, race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic black and others), educational background (<high school, high school and >high school), BMI, smoking status (smoking at least 100 cigarettes in life or not), drinking status (having at least twelve alcohol drinks/year or not), total energy intake, vitamin C intake, dietary fibre intake, Mg intake, levels of total cholesterol, hypertension status (mean systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg[34] or self-reported physician diagnosis) and diabetes status (fasting blood sugar level ≥7·0 mmol/l or 2-h plasma glucose level ≥11·1 mmol/l or taking anti-diabetic pills or insulin).

Statistical analyses

All statistical analyses were conducted using Stata 15.0. To carry out nationally representative estimates, appropriate sampling weights, primary sampling units and stratified information were considered in the study. Following the NHANES analysis guide available on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/tutorials/module3.aspx), the new 6-year sample weight was created using one-third of the 2-year dietary weighted. Baseline characteristics of the participants with and without hyperuricaemia were compared with respect to gender. The continuous variables were presented as mean ± SD, and the categorical

https://doi.org/10.1017/S1368980020000324 Published online by Cambridge University Press

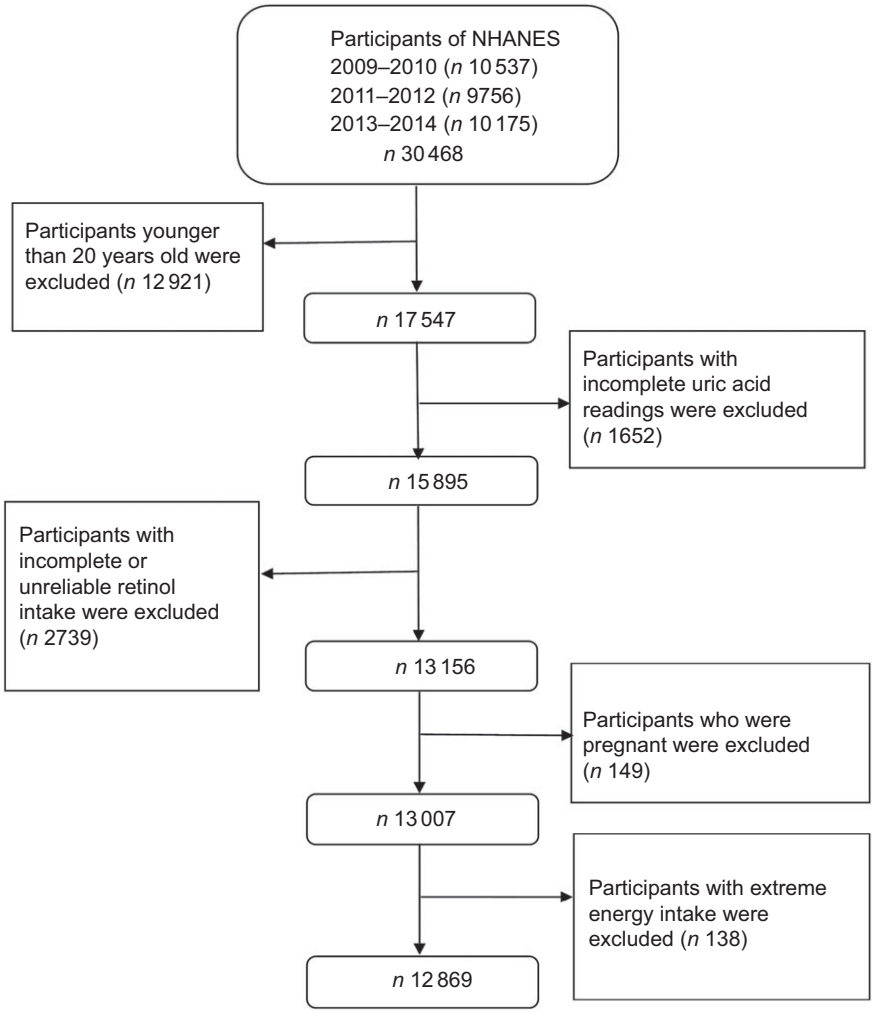

Fig. 1 Flow chart showing the population selection of the study. NHANES, National Health and Nutrition Examination Survey

variables were presented as participants (percentage). χ^2 tests and Student's t test were used to examine the differences in percentages and means, respectively. We also performed univariate and multivariate logistic regression analyses to estimate OR (95 % CI) of hyperuricaemia according to quintiles of dietary retinol intake. The lowest quintile of dietary intake was used as the reference. In the multivariate logistic regression analysis, model 1 was adjusted for age and gender and model 2 was adjusted for age, gender, race, BMI (continuous), smoking status, drinking status, education background, hypertension status, diabetes status, total energy intake, vigorous activities, total cholesterol, vitamin C intake, dietary fibre intake and Mg intake. The dose–response relationship was assessed using restricted cubic spline functions with three knots located at the 5th, 50th and 95th percentiles of the exposure distribution in the multivariate-adjusted model 2. In addition, we calculated sex-specific quintiles for the retinol intake; stratified analyses were performed based on genders (men and women) to evaluate the association between retinol intake and hyperuricaemia. All P values were two-sided, and $P < 0{\cdot}05$ is considered statistically significant.

Results

In 12 869 participants (47·85 % was men), the mean values of age, BMI and retinol intake were 49·62 (SD 17·49) years, 29·20 (SD 6·94) kg/m^2 and 618·18 (SD 543·59) mcg/d, respectively. Serum uric acid level was 5·42 mg/dl (6·07 and 4·84 mg/dl in men and women, respectively). The prevalence of hyperuricaemia was 19·35 % (22·32 and 16·67 % in men and women, respectively). The baseline characteristics of the study population according to hyperuricaemia status are presented in Table 1. Compared with controls, participants with hyperuricaemia tended to be older, non-Hispanic black and smoke at least 100 cigarettes in life and were more likely to have hypertension, diabetes, higher BMI, total cholesterol levels, lower total energy intake, vigorous activity and retinol intake (all P values $< 0{\cdot}05$). Additionally, the characteristics of the study population according to quintiles of retinol intake are shown in Appendix 1 in supplementary material.

The weighted OR (95 % CI) of hyperuricaemia based on the quintiles of total, animal-derived and plant-derived

https://doi.org/10.1017/S1368980020000324 Published online by Cambridge University Press

Table 1 Characteristics of participants with or without hyperuricaemia, US adults aged ≥20 years, National Health and Nutrition Examination Survey (NHANES) 2009–2014†

	Total					Male					Female				
	Non-hyperuricaemia (*n* 10 257)		Hyperuricaemia (*n* 2612)			Non-hyperuricaemia (*n* 4761)		Hyperuricaemia (*n* 1397)			Non-hyperuricaemia (*n* 5496)		Hyperuricaemia (*n* 1215)		
Characteristics	*n*	%	*n*	%		*n*	%	*n*	%		*n*	%	*n*	%	
Age (years)					*										*
Mean	42·29		51·40			47·64		47·02			46·99		56·71		
SD	16·34		17·91			16·54		17·09			16·17		17·37		
Age (years)					*					*					*
20–44	4514	44·01	832	31·85		1971	41·40	584	41·80		2543	46·27	248	20·41	
45–59	2669	26·02	616	23·58		1221	25·65	318	22·76		1448	26·35	298	24·53	
60–74	2196	21·41	743	28·45		1098	23·06	315	22·55		1098	19·98	428	35·23	
≥75	878	8·56	421	16·12		471	9·89	180	12·88		407	7·41	241	19·84	
Race					*					*					*
Mexican American	1545	15·06	244	9·34		724	15·21	155	11·10		821	14·94	89	7·33	
Other Hispanic	1054	10·28	183	7·01		442	9·28	102	7·30		612	11·14	81	6·67	
Non-Hispanic white	4607	44·92	1265	48·43		2166	45·49	673	48·17		2441	44·41	592	48·72	
Non-Hispanic black	1949	19·00	648	24·81		909	19·09	305	21·83		1040	18·92	343	28·23	
Other races	1102	10·74	272	10·41		520	10·92	162	11·60		582	10·59	110	9·05	
Education background															*
<High School	921	8·98	234	8·96		445	9·35	122	8·73		476	8·66	112	9·22	
High School	1404	13·69	380	14·55		685	14·39	192	13·74		719	13·08	188	15·47	
>High School	7919	77·21	1995	76·38		3627	76·18	1081	77·38		4292	78·09	914	75·23	
Alcohol drinking status															*
Have at least 12 alcohol drinks/year	7101	69·23	1809	69·26		3868	81·24	1148	82·18		3233	58·82	661	54·40	
No	2535	24·71	680	26·03		697	14·64	188	13·46		1838	33·44	492	40·49	
Smoking status					*										*
Smoked at least 100 cigarettes in life	4429	43·18	1231	47·13		2513	52·78	720	51·54		1916	34·86	511	42·06	
No	5824	56·78	1380	52·83		2246	47·17	676	48·39		3578	65·10	704	57·94	
Hypertension status					*					*					*
Yes	4579	44·64	1762	67·46		2350	49·36	873	62·49		2229	40·56	889	73·17	
No	5678	55·36	850	32·54		2411	50·64	524	37·51		3267	59·44	326	26·83	
Diabetes status					*										*
Yes	673	6·56	303	11·60		383	8·04	132	9·45		290	5·28	171	14·07	
No	9584	93·44	2309	88·40		4378	91·96	126590·55			5206 (94·72)		1044	85·93	
Vigorous activity					*					*					*
Yes	2283	22·26	420	16·08		1275	26·78	318	22·76		1008	18·34	102	8·40	
No	7974	77·74	2192	83·92		3486	73·22	1079	77·24		4488	81·66	1113	91·60	
BMI (kg/m^2)					*					*					*
Mean	28·15		32·45			28·15		31·35			28·15		33·80		
SD	6·31		7·68			5·56		6·45			6·86		8·80		

Table 1 *Continued*

	Total				Male				Female			
	Non-hyperuricaemia (*n* 10 257)		Hyperuricaemia (*n* 2612)		Non-hyperuricaemia (*n* 4761)		Hyperuricaemia (*n* 1397)		Non-hyperuricaemia (*n* 5496)		Hyperuricaemia (*n* 1215)	
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total energy intake (kcal/d)‡				*				*				*
Mean	2075·19		2022·55		2397·06		2310·41		1803·3		1673·17	
SD	725·99		779·55		749·35		782·31		583·78		600·60	
TC (mg/dl)				*				*				*
Mean	191·75		197·59		188·19		195·16		194·83		200·38	
SD	40·60		43·24		40·94		44·22		40·05		41·92	
Retinol intake (RAE, mcg/d)				*				*				*
Mean	665·92		599·90		720·69		623·24		619·66		571·57	
SD	632·69		483·27		813·87		444·93		423·95		526·47	
Vitamin C (mg/d)				*				*				*
Mean	85·00		76·50		90·18		80·37		80·62		71·80	
SD	79·56		71·40		90·87		77·32		68·54		62·59	
Total fibre intake (mg/d)				*				*				*
Mean	17·81		15·88		19·63		17·24		16·26		14·25	
SD	9·19		8·58		10·24		9·32		7·89		7·16	
Mg intake (mg/d)				*				*				*
Mean	306·87		286·59		344·16		320·75		275·37		245·12	
SD	128·62		121·88		142·74		131·39		106·14		91·41	
Uric acid (mg/dl)				*				*				*
Mean	4·95		7·42		5·57		7·79		4·42		6·96	
SD	1·02		0·98		0·86		0·79		0·83		0·99	

TC, total cholesterol; RAE, retinol activity equivalents.
†Data are presented as mean and standard deviation for continuous variables or participants (percentage) for categorical variable.
‡To convert kcal into kJ, multiply it by 4·184.
*$P < 0·05$.

Table 2 Weighted OR (95 % CI) of hyperuricaemia across quintiles of retinol intake, National Health and Nutrition Examination Survey (NHANES) 2009–2014†

		Cases/participants	Weighted prevalence (%)	Crude		Model 1		Model 2	
				OR	95 % CI	OR	95 % CI	OR	95 % CI
Total retinol intake (RAE, mcg/d)									
Q1	<283·50	614/2581	23·59	1·00 (Ref.)		1·00 (Ref.)		1·00 (Ref.)	
Q2	283·50, 436·00	525/2568	19·90	0·80*	0·66, 0·98	0·77*	0·63, 0·94	0·77*	0·62, 0·94
Q3	436·00, 601·00	542/2575	20·68	0·84*	0·71, 0·99	0·79*	0·67, 0·93	0·86	0·67, 1·10
Q4	601·00, 861·00	487/2574	17·59	0·69*	0·59, 0·81	0·61*	0·52, 0·72	0·75*	0·58, 0·96
Q5	≥861·00	444/2571	16·14	0·62*	0·51, 0·75	0·54*	0·45, 0·66	0·71*	0·52, 0·96
Animal-derived retinol intake (RAE, mcg/d)									
Q1	<98·00	564/2583	20·88	1·00 (Ref.)		1·00 (Ref.)		1·00 (Ref.)	
Q2	98·00, 168·00	543/2558	20·21	0·96	0·80, 1·15	0·93	0·77, 1·11	0·96	0·79, 1·16
Q3	168·00, 249·50	525/2573	20·55	0·98	0·86, 1·11	0·90	0·79, 1·03	0·92	0·79, 1·08
Q4	249·50, 371·50	478/2568	17·50	0·80*	0·68, 0·95	0·73*	0·61, 0·87	0·76*	0·62, 0·93
Q5	≥371·50	495/2562	17·84	0·82*	0·69, 0·97	0·70*	0·60, 0·83	0·76*	0·59, 0·96
Plant-derived retinol intake (RAE, mcg/d)									
Q1	<102·50	613/2583	23·44	1·00	Ref.	1·00	Ref.	1·00	Ref.
Q2	102·50, 202·00	530/2576	19·63	0·80*	0·67, 0·94	0·79*	0·67, 0·94	0·91	0·75, 1·11
Q3	202·00, 333·00	526/2567	19·92	0·81*	0·68, 0·97	0·81*	0·68, 0·96	0·97	0·77, 1·22
Q4	333·00, 544·50	493/2573	18·31	0·73*	0·61, 0·87	0·70*	0·59, 0·84	0·96	0·75, 1·23
Q5	≥544·50	450/2570	16·45	0·64*	0·54, 0·76	0·61*	0·52, 0·72	0·92	0·72, 1·17

RAE, retinol activity equivalents.
†Model 1: adjusted for age, gender. Model 2: adjusted for age, gender, race/ethnicity, BMI, smoking status, drinking status, education background, hypertension status, diabetes status, total energy intake, vigorous activities, total cholesterol, vitamin C intake, dietary fibre intake and Mg intake. Results are survey-weighted.
*$P < 0·05$.

Table 3 Weighted OR (95 % CI) of hyperuricaemia across quintiles of retinol, stratified by gender, National Health and Nutrition Examination Survey (NHANES) 2009–2014†

		Cases/participants	Weighted prevalence (%)	Crude		Model 1		Model 2	
				OR	95 % CI	OR	95 % CI	OR	95 % CI
Retinol intake (RAE, mcg/d)									
Men									
Q1	<295·00	336/1232	27·60	1·00 (Ref.)		1·00 (Ref.)		1·00 (Ref.)	
Q2	295·00, 454·00	289/1232	23·81	0·82	0·65, 1·03	0·82	0·65, 1·04	0·81	0·63, 1·02
Q3	454·00, 632·50	284/1232	23·54	0·81	0·64, 1·02	0·81	0·64, 1·03	0·82	0·59, 1·13
Q4	632·50, 907·60	253/1231	19·59	0·64*	0·51, 0·80	0·64*	0·51, 0·81	0·69*	0·50, 0·94
Q5	≥907·60	235/1231	18·79	0·61*	0·47, 0·78	0·61*	0·47, 0·79	0·68*	0·48, 0·95
Women									
Q1	<272·70	266/1342	19·28	1·00 (Ref.)		1·00 (Ref.)		1·00 (Ref.)	
Q2	272·70, 418·00	260/1343	19·06	0·98	0·76, 1·28	0·95	0·73, 1·23	0·95	0·65, 1·38
Q3	418·00, 578·00	245/1345	16·56	0·83	0·63, 1·09	0·75*	0·57, 0·97	0·75	0·50, 1·11
Q4	578·00, 817·50	238/1343	16·24	0·81	0·63, 1·04	0·67*	0·52, 0·87	0·88	0·60, 1·30
Q5	≥817·50	206/1338	13·12	0·63*	0·50, 0·80	0·51*	0·40, 0·66	0·68	0·46, 1·01

RAE, retinol activity equivalents.
†Model 1: adjusted for age. Model 2: adjusted for age, race/ethnicity, BMI, smoking status, drinking status, education background, hypertension status, diabetes status, total energy intake, vigorous activities, total cholesterol, vitamin C intake, dietary fibre intake and Mg intake. Results are survey-weighted.
*$P < 0·05$.

retinol intakes are shown in Table 2. In the univariate logistic regression analyses, for the highest *v.* lowest quintiles, intakes of total retinol (0·62, 95 % CI 0·51, 0·75), animal-derived retinol (0·82, 95 % CI 0·69, 0·97) and plant-derived retinol (0·64, 95 % CI 0·54, 0·76) were all inversely associated with the risk of hyperuricaemia. After adjustment for age and gender (model 1), the results remained unchanged. After further adjustment for race, BMI, smoking status, drinking status, education background, hypertension status, diabetes status, total energy intake, vigorous activities, total cholesterol, vitamin C intake, dietary fibre intake and Mg intake (model 2), the OR of quintile 5 of intake of total, animal-derived and plant-derived retinol were 0·71 (95 % CI 0·52, 0·96), 0·76 (95 % CI 0·59, 0·96) and 0·92 (95 % CI 0·72, 1·17), respectively. The association between retinol intake and hyperuricaemia in stratified analyses by gender is shown in Table 3. For the highest *v.* lowest quintiles, the OR (95 % CI) of hyperuricaemia were 0·61 (95 % CI 0·47, 0·78) for men and 0·63 (95 % CI 0·50, 0·80) for women. After adjustment for age (model 1), the OR (95 % CI) of hyperuricaemia were 0·61 (95 % CI 0·47, 0·79) for men and 0·51 (95 % CI 0·40, 0·66) for women. After further adjustment for multiple covariates (model 2), the OR (95 % CI) of hyperuricaemia were 0·68 (95 % CI 0·48, 0·95) for men and 0·68 (95 % CI 0·46, 1·01) for women. After excluding participants with hypertension or diabetes, a total of 5871 individuals were included in the final analysis. We re-assessed the association between retinol intake and hyperuricaemia; the association remained unchanged after further adjustment for multiple covariates (Appendix 2 in supplementary material).

The results of the dose–response relationship analysis between dietary retinol intake and risk of hyperuricaemia are shown in Figs 2 and 3. Using the restricted cubic spline model, a linear negative association between total dietary retinol intake and hyperuricaemia was found ($P_{\text{for nonlinearity}} = 0{\cdot}235$). As the total dietary retinol intake increased, the OR of hyperuricaemia decreased. Dietary total retinol intake showed significant inverse association with the odds of hyperuricaemia when the intake of total retinol reached 115 mcg/d (OR 0·97, 95 % CI 0·94, 0·99). Similarly, animal-derived retinol intake also had a liner negative association with hyperuricaemia when the intake of animal-derived retinol reached 187 mcg/d (OR 0·83, 95 % CI 0·70, 0·99).

Discussion

In this national representative population study, total retinol intake was inversely associated with the risk of hyperuricaemia in both genders of the US adult population. After adjustment for multiple covariates (age, gender, race/ethnicity, BMI, smoking status, *et al.*), the association remained significant in men. Interestingly, we found a linear trend towards intake of animal-derived retinol and the risk of hyperuricaemia.

Several studies have examined the association between retinol intake and hyperuricaemia. Similar to our results, a

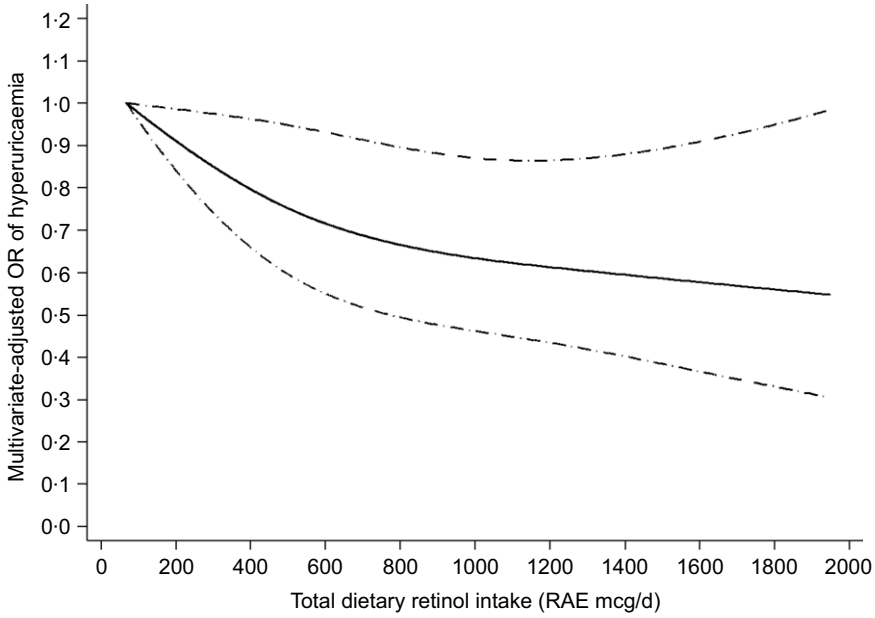

Fig. 2 Linear dose–response relationship between retinol intake and hyperuricaemia, $P_{\text{for nonlinearity}} = 0{\cdot}235$. The lowest intake level (67 mcg/d) was used as the reference group. Adjusted for age, gender, race/ethnicity, BMI, smoking status, drinking status, education background, hypertension status, diabetes status, total energy intake, vigorous activities, total cholesterol, vitamin C intake, dietary fibre intake and Mg intake. The solid line and dashed line represent the estimated OR and its 95 % CI, respectively. RAE, retinol activity equivalents

https://doi.org/10.1017/S1368980020000324 Published online by Cambridge University Press

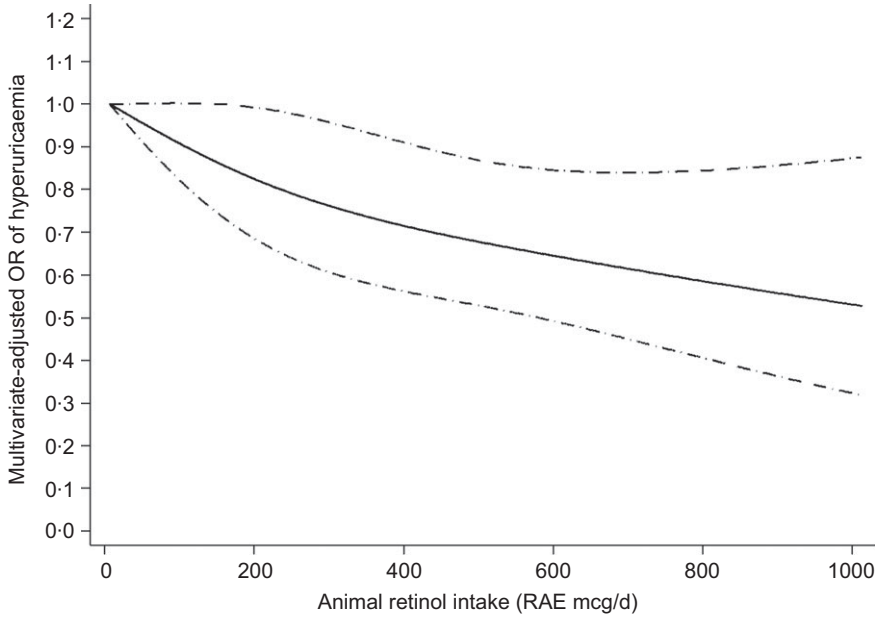

Fig. 3 Linear dose–response relationship between animal-derived retinol intake and risk of hyperuricaemia, $P_{\text{for nonlinearity}} = 0{\cdot}510$. The lowest intake level (7 mcg/d) was used as the reference group. Adjusted for age, gender, race/ethnicity, BMI, smoking status, drinking status, education background, hypertension status, diabetes status, total energy intake, vigorous activities, total cholesterol, vitamin C intake, dietary fibre intake and Mg intake. The solid line and dashed line represent the estimated OR and its 95 % CI. RAE, retinol activity equivalents

Korean study revealed that patients with hyperuricaemia had a lower intake of retinol than controls[29]. Additionally, a cross-sectional study conducted in two Caucasian cohorts proposed that retinol intake was positively associated with the risk of hyperuricaemia for women without abdominal obesity among Australian subjects, whereas even no correlation was observed among Norwegian subjects[30]. In a cross-sectional survey in Taiwan, retinol intake was not significantly associated with hyperuricaemia. Several factors may account for the inconsistent results. First, the participants in our analysis were adults aged ≥20 years, and pregnant women were excluded, whereas the subjects in the Taiwan study were aged 4–96 years. Second, based on a previous study[31], there was significant difference in retinol intakes when calculated by a semi-quantitative FFQ compared with two 24-h diet recall survey. Retinol intakes were calculated using a semi-quantitative FFQ in the above Caucasian studies, whereas 24-h dietary recall interviews were used in our study. Finally, ethnic background and differences in dietary patterns might also contribute to the inconsistent results. Moreover, a previous cross-sectional study proposed that serum retinol level was positively associated with the risk of hyperuricaemia in the Third NHANES[32]. Further studies are needed to clarify the differences.

The biological mechanism underlying the association between retinol intake and hyperuricaemia remains poorly understood. The underlying mechanism could be that retinol intake modulates serum uric acid via antioxidant and anti-inflammatory mechanism. Uric acid may function as a pro-oxidant in hyperuricaemia, despite acting as an antioxidant under physiological conditions[35]. Retinol has well-established antioxidant properties and has the potential to retard the oxidative process[27]. Several studies suggested that hyperuricaemia was positively associated with serum C-reactive protein, inflammatory cytokines IL-6 and TNF-α levels, which were generally viewed as biomarkers of inflammation[36–38]. The reversed relationship was also reported between retinol status and inflammatory response[39,40]. In a cross-sectional study, retinol-rich foods significantly reduced inflammation in peritoneal dialysis patients[41]. Therefore, retinol intake reduced oxidative stress and inflammatory response and further decreased uric acid synthesis, thereby providing a potential mechanism for retinol to reduce the risk of hyperuricaemia[42].

In our study, intake of animal-derived retinol was inversely associated with hyperuricaemia among US adults. Currently, available studies on the associations between different sources of dietary retinol intake and hyperuricaemia are very limited. Therefore, the underlying mechanism remains undetermined. A possible explanation may be that the absorption of retinol from animal sources is relatively more effective and not affected by food substrate[43], while the bioavailability of retinol from plant sources is greatly affected by food substrate[44–47]. Additional research is needed to elucidate the relationship between animal-derived retinol intake and the risk of hyperuricaemia.

Our study has several strengths. First, the large nationally representative sample increased the statistical power

https://doi.org/10.1017/S1368980020000324 Published online by Cambridge University Press

for assessing the relationship between retinol intake and the risk of hyperuricaemia. Second, we explored the dose–response relationship of retinol intake with the risk of hyperuricaemia. Finally, the association between various sources of dietary retinol intake and hyperuricaemia was examined for the first time.

Notably, our study also has some limitations. First, because of the cross-sectional study design, addressing the causal interpretations of the relationship between retinol intake and risk of hyperuricaemia is unfeasible and thus adds only limited information to the overall question how dietary retinol is associated with hyperuricaemia. Simultaneously, dietary retinol intake was calculated by two 24-h diet recall survey, which may not have accurately reflected an individual's usual dietary intake. In addition, we could not exclude the possibility of residual confusion owing to unmeasured confounding factors.

Conclusion

Intakes of total and animal-derived retinol were inversely associated with hyperuricaemia among US adults. Furthermore, large prospective cohort studies need to be performed to support our findings.

Acknowledgements

Acknowledgements: The authors would like to thank all subjects, investigators and study personnel who participated in this study. *Financial support:* This work was supported by the grant from the Natural Science Foundation of China (no. 81703206) and China Postdoctoral Science Foundation (no. 2015M580575). *Conflicts of interest:* The authors declare no conflicts of interest. *Authorship:* P.Z. and Y.S. designed the research; P.Z. and J.S. conducted and wrote the manuscript; P.Z., J.S., Y.G., M.H. and F.Y. analysed and interpreted the data; Y.S. was primarily responsible for the final content; and all authors read and approved the final manuscript. *Ethics of human subject participation:* This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Research Ethics Review Board of National Center for Health Statistics. All participants provided written informed consent both before the interview and examination stages. The security, anonymity and privacy of the participants were strictly respected.

Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S1368980020000324

References

1. Luk AJ & Simkin PA (2005) Epidemiology of hyperuricemia and gout. *Am J Manag Care* **11**, S435–S442; quiz S465–438.
2. Wang J, Qin T, Chen J *et al.* (2014) Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. *PLoS One* **9**, e114259.
3. Feig DI, Kang DH & Johnson RJ (2008) Uric acid and cardiovascular risk. *N Engl J Med* **359**, 1811–1821.
4. Kodama S, Saito K, Yachi Y *et al.* (2009) Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* **32**, 1737–1742.
5. Sluijs I, Beulens JW, van der AD *et al.* (2013) Plasma uric acid is associated with increased risk of type 2 diabetes independent of diet and metabolic risk factors. *J Nutr* **143**, 80–85.
6. Zhang Q, Lou S, Meng Z *et al.* (2011) Gender and age impacts on the correlations between hyperuricemia and metabolic syndrome in Chinese. *Clinical Rheumatology* **30**, 777–787.
7. Cohen SD, Kimmel PL, Neff R *et al.* (2008) Association of incident gout and mortality in dialysis patients. *J Am Soc Nephrol* **19**, 2204–2210.
8. Zhu Y, Pandya BJ & Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* **63**, 3136–3141.
9. Wallace KL, Riedel AA, Joseph-Ridge N *et al.* (2004) Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *J Rheumatol* **31**, 1582–1587.
10. 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.
11. Uaratanawong S, Suraamornkul S, Angkeaw S *et al.* (2011) Prevalence of hyperuricemia in Bangkok population. *Clin Rheumatol* **30**, 887–893.
12. Kuo CF, Grainge MJ, Zhang W *et al.* (2015) Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol* **11**, 649–662.
13. Ebrahimpour-Koujan S, Saneei P, Larijani B *et al.* (2018) Consumption of sugar sweetened beverages and dietary fructose in relation to risk of gout and hyperuricemia: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr* **60**, 1–10.
14. Boyle JA, Greig WR, Jasani MK *et al.* (1967) Relative roles of genetic and environmental factors in the control of serum uric acid levels in normouricaemic subjects. *Ann Rheum Dis* **26**, 234–238.
15. Choi HK, Liu S & Curhan G (2005) Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum* **52**, 283–289.
16. Villegas R, Xiang YB, Elasy T *et al.* (2012) Purine-rich foods, protein intake, and the prevalence of hyperuricemia: the Shanghai Men's Health Study. *Nutr Metab Cardiovasc Dis* **22**, 409–416.
17. Richette P & Bardin T (2012) Purine-rich foods: an innocent bystander of gout attacks? *Ann Rheum Dis* **71**, 1435–1436.
18. Rai SK, Fung TT, Lu N *et al.* (2017) The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: prospective cohort study. *BMJ (Clinical Research Ed)* **357**, j1794.
19. Choi HK, Willett W & Curhan G (2010) Fructose-rich beverages and risk of gout in women. *JAMA* **304**, 2270–2278.
20. Choi HK & Curhan G (2008) Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ (Clinical Research Ed)* **336**, 309–312.
21. Emmerson BT (1996) The management of gout. *N Engl J Med* **334**, 445–451.

22. Bae J, Shin DH, Chun BY *et al.* (2014) The effect of vitamin C intake on the risk of hyperuricemia and serum uric acid level in Korean Multi-Rural Communities Cohort. *Joint Bone Spine* **81**, 513–519.
23. Gao X, Curhan G, Forman JP *et al.* (2008) Vitamin C intake and serum uric acid concentration in men. *J Rheumatol* **35**, 1853–1858.
24. Sun Y, Sun J, Wang J *et al.* (2018) Association between vitamin C intake and risk of hyperuricemia in US adults. *Asia Pac J Clin Nutr* **27**, 1271–1276.
25. Onyesom I, Uzuegbu UE, Nwangwa EK *et al.* (2007) Effect of Vitamin E on ethanol-induced increase in some cardiovascular parameters and blood uric acid levels in man. *Int JBiol Chem* **1**, 156–161.
26. Zhang Y, Liu Y & Qiu H (2018) Association between dietary Zinc intake and hyperuricemia among adults in the United States. *Nutrients* **10**, 568.
27. Goodman DS (1984) Vitamin A and retinoids in health and disease. *N Engl J Med* **310**, 1023–1031.
28. Imam MU, Zhang S, Ma J *et al.* (2017) Antioxidants mediate both Iron homeostasis and oxidative stress. *Nutrients* **9**, 671.
29. Ryu KA, Kang HH, Kim SY *et al.* (2014) Comparison of nutrient intake and diet quality between hyperuricemia subjects and controls in Korea. *Clin Nutr Res* **3**, 56–63.
30. Zykova SN, Storhaug HM, Toft I *et al.* (2015) Cross-sectional analysis of nutrition and serum uric acid in two Caucasian cohorts: the AusDiab Study and the Tromso study. *Nutr J* **14**, 49.
31. Yu KH, See LC, Huang YC *et al.* (2008) Dietary factors associated with hyperuricemia in adults. *Semin Arthritis Rheum* **37**, 243–250.
32. Choi WJ, Ford ES, Curhan G *et al.* (2012) Independent association of serum retinol and beta-carotene levels with hyperuricemia: a national population study. *Arthritis Care Res (Hoboken)* **64**, 389–396.
33. Centers for Disease Control and Prevention (2014) National Health and Nutrition Examination Survey. https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx (accessed February 2018).
34. Whelton PK, Carey RM, Aronow WS *et al.* (2018) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension (Dallas, Tex: 1979)* **71**, 1269–1324.
35. Kadowaki D, Sakaguchi S, Miyamoto Y *et al.* (2015) Direct radical scavenging activity of benzbromarone provides beneficial antioxidant properties for hyperuricemia treatment. *Biol Pharma Bull* **38**, 487–492.
36. Lyngdoh T, Marques-Vidal P, Paccaud F *et al.* (2011) Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. *PLoS One* **6**, e19901.
37. Kirilmaz B, Asgun F, Alioglu E *et al.* (2010) High inflammatory activity related to the number of metabolic syndrome components. *J Clin Hypertens* **12**, 136–144.
38. Ruggiero C, Cherubini A, Ble A *et al.* (2006) Uric acid and inflammatory markers. *Eur Heart J* **27**, 1174–1181.
39. Sauer JM, Hooser SB & Sipes IG (1995) All-trans-retinol alteration of 1-nitronaphthalene-induced pulmonary and hepatic injury by modulation of associated inflammatory responses in the male Sprague-Dawley rat. *Toxicol Appl Pharmacol* **133**, 139–149.
40. Swamidas GP, Basaraba RJ & Baybutt RC (1999) Dietary retinol inhibits inflammatory responses of rats treated with monocrotaline. *J Nutr* **129**, 1285–1290.
41. Martin-del-Campo F, Batis-Ruvalcaba C, Gonzalez-Espinoza L *et al.* (2012) Dietary micronutrient intake in peritoneal dialysis patients: relationship with nutrition and inflammation status. *Perit Dial Int* **32**, 183–191.
42. Hayden MR & Tyagi SC (2004) Uric acid: A new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: the urate redox shuttle. *Nutr Metab* **1**, 10.
43. van Vliet T, Boelsma E, de Vries AJ *et al.* (2001) Retinoic acid metabolites in plasma are higher after intake of liver paste compared with a vitamin A supplement in women. *J Nutr* **131**, 3197–3203.
44. Edwards AJ, You CS, Swanson JE *et al.* (2001) A novel extrinsic reference method for assessing the vitamin A value of plant foods. *Am J Clin Nutr* **74**, 348–355.
45. Edwards AJ, Nguyen CH, You CS *et al.* (2002) Alpha- and beta-carotene from a commercial puree are more bioavailable to humans than from boiled-mashed carrots, as determined using an extrinsic stable isotope reference method. *J Nutr* **132**, 159–167.
46. Yeum KJ & Russell RM (2002) Carotenoid bioavailability and bioconversion. *Ann Rev Nutr* **22**, 483–504.
47. Hickenbottom SJ, Follett JR, Lin Y *et al.* (2002) Variability in conversion of beta-carotene to vitamin A in men as measured by using a double-tracer study design. *Am J Clin Nutr* **75**, 900–907.

https://doi.org/10.1017/S1368980020000324 Published online by Cambridge University Press