

## Original Article

# Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review

Rongrong Li MD<sup>1</sup>, Kang Yu MD<sup>1</sup>, Chunwei Li MD<sup>2</sup><sup>1</sup>Department of Clinical Nutrition, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences and Peking Union Medical College, China<sup>2</sup>Department of Clinical Nutrition, Tianjin Union Medical Center, China

**Background and Objectives:** To evaluate the associations of dietary factors and the risk of gout and hyperuricemia. **Methods and Study Design:** PubMed and Embase databases were searched from inception to June 2017 for eligible studies. Nineteen prospective cohort or cross-sectional studies with adequate sample sizes are included, all involving red meat, seafoods, alcohol, fructose, dairy products, soy foods, high-purine vegetables and coffee. **Results:** Meta-analysis revealed several dietary associations with gout risk: red meat: OR 1.29 (95% CI 1.16-1.44); seafoods: OR 1.31 (95% CI 1.01-1.68); alcohol: OR 2.58 (95% CI 1.81-3.66); fructose: OR 2.14 (95% CI 1.65-2.78); dairy products: OR 0.56 (95% CI 0.44-0.70); soy foods: OR 0.85 (95% CI 0.76-0.96); high-purine vegetables: OR 0.86 (95% CI 0.75-0.98); coffee: OR 0.47 (95% CI 0.37-0.59). Dietary association with hyperuricemia risk (red meat: OR 1.24 (95% CI 1.04-1.48); seafoods: OR 1.47 (95% CI 1.16-1.86); alcohol: OR 2.06 (95% CI 1.60-2.67); fructose: OR 1.85 (95% CI 1.66-2.07); dairy products: OR 0.50 (95% CI 0.37-0.66); soy foods: OR 0.70 (95% CI 0.56-0.88); high-purine vegetables ingestion: OR 1.10 (95% CI 0.88-1.39),  $P=0.39$ ; coffee: OR 0.76 in men (95% CI 0.55-1.06), OR 1.58 in women (95% CI 1.16-2.16). **Conclusion:** The risk of hyperuricemia and gout is positively correlated with the intake of red meat, seafoods, alcohol or fructose, and negatively with dairy products or soy foods. High-purine vegetables showed no association with hyperuricemia, but negative association with gout. Coffee intake is negatively associated with gout risk, whereas it may be associated with increased hyperuricemia risk in women but decreased risk in men.

**Key Words:** gout, hyperuricemia, risk, nutrition, dietary factors

## INTRODUCTION

Gout is a monosodium urate monohydrate crystal deposit disease, and hyperuricemia plays a role as one of the key intermediary steps. Both of the diseases are considered elements of purine metabolic disturbances and are usually associated with other metabolic disorders (metabolic syndrome, diabetes mellitus, dyslipidemia, stroke and cardiovascular diseases). As modern society develops, the global incidence of gout and hyperuricemia has also increased, especially in developed regions.<sup>1</sup> A population-based survey in 2011 revealed that the morbidity of gout and asymptomatic hyperuricemia was 3.9% and 21.4% in the United States, respectively.<sup>2</sup> Dietary association to this global burdensome health problem, attracted attention as early as in 1970s.<sup>3</sup> However, it was not until the last decade that the clinical relevance was extensively reviewed in a number of population-based observational studies.<sup>3-6</sup> Although it is now generally accepted that nutrition intervention plays a critical role in synthetic treatment of gout and hyperuricemia, controversy still remains in view of specific food selection among studies performed on different populations. For instance, some researchers have even suggested it be necessary for gout or hyperuricemia patients to avoid purine-rich vegetables or soy foods, while some latest epidemiologic studies found opposite conclusions. Thus, to guide decision-making for Nutritional therapeutic

strategies, we conducted a meta-analysis to determine relationship between different dietary factors and incidence of gout and hyperuricemia. Although previous systematic reviews had depicted the association among a variety of dietary factors and risk of gout and hyperuricemia, the present review identified newer studies and adds to the mounting evidence of the impact of foods on risk of gout and hyperuricemia.

## PARTICIPANTS AND METHODS

### Search strategy

This study was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology guideline.<sup>7</sup> We systematically retrieved literature from the PubMed (from 1966 to June 2017) and Embase (from 1980 to June 2017) databases. In order to collect as many

**Corresponding Author:** Dr Kang Yu, Department of Clinical Nutrition, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No.1 in Shuaifuyuan Street, Dongdan Street, Dongcheng District, Beijing 100730, China.

Tel: +861069155550; +8613801130457

Email: yuk1997@sina.com

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relevant studies as possible, we set the following search terms: “gout”, “gouty attacks”, “hyperuricemia”, “urate”, “uric acid”, “dietary”, “diet”, “nutrition”, “nutritional”, “food”, “lifestyle”, “meat”, “seafoods”, “alcohol”, “fructose”, “sugar”, “sweetened”, “milk”, “dairy products”, “vegetables”, “coffee”. In addition, the reference lists of relevant publications were manually screened for identifying more eligible citations. No language restriction was imposed. Two researchers (LRR and LCW) reviewed the titles, abstracts and full texts of all retrieved studies independently. Disagreements, if any, were resolved by discussions and mutual consultations.

### Criteria for Inclusion

Observational studies that met the following conditions were included in our meta-analysis. (1) Since clinical randomized controlled trials have rarely been performed, observational studies (prospective cohort design or cross-sectional study) with large sample sizes are included. Given that there is no specific criteria for adequacy of sample size of observational studies included in a meta-analysis, we estimated appropriate study size by different formulas. For cross-sectional studies, sample size was calculated by formula of  $n = Z^2 * \frac{p(1-p)}{e^2}$ .  $Z$  is the standard normal variate;  $p$  is the expected prevalence of gout or hyperuricemia based on previous studies;  $e$  is the absolute error or desired level of precision. For cohort studies, sample size was estimated by

$$n = \frac{\left( Z_{\alpha} \sqrt{\frac{p_0 + p_1}{2} * \frac{2 - p_0 - p_1}{2}} \right) + \left( Z_{\beta} \sqrt{p_0 * (1 - p_0) + p_1 * (1 - p_1)} \right)}{(p_1 - p_0)^2}$$

$Z_{\alpha}$  is the standard normal variate for level of significance;  $Z_{\beta}$  is the standard normal variate for power;  $p_0$  and  $p_1$  are event rates in control groups and exposed groups based on previous studies, respectively. It was estimated sample size of cross-sectional studies should be more than 811 participants, while that of cohort studies should be more than 1298 subjects.

(2) The exposure of interest should be high intake of red meat, seafoods, alcohol, fructose, dairy products, soy foods, high-purine vegetables or coffee. (3) For cohort studies which comprised longitudinal follow-up, the subjects from the study population should not have hyperuricemia or gout at baseline. (4) The risk of hyperuricemia or gout associated with dietary factors was presented as adjusted odds ratio (OR), risk ratio (RR), or hazard ratio (HR). (5) Full-text publication was accessible. Reviews, comments, pooled analyses, or observational studies with inadequate samples were excluded.

### Data collection and quality assessment

Two authors (LRR and LCW) independently extracted the characteristics of the studies, including first author, publication year, study population, sample size, location, exposure factors, study design, outcomes (OR, RR or HR for gout or hyperuricemia) and follow-up durations. The quality of the included studies was assessed according to the Newcastle-Ottawa Scale (NOS)<sup>8</sup> within 3 main domains: study group selection (4 points), comparability between groups (2 points) and ascertainment of outcomes (3 points). Studies with NOS score of 7 or higher were regarded as “high quality”, studies with score of 4 to 6 were considered

as “moderate quality”, while studies with score <4 were regarded as “low quality”. Any disagreements in the process of data extraction and methodologic quality assessment were resolved by discussion with a third reviewer (YK).

### Statistical Analysis

Data analyses were realized by using RevMan (Review Manager) statistical software, version 5.1 (Cochrane Community). We calculated the pooled ORs with related 95% confidential interval (CI). The heterogeneity across studies was evaluated by the Chi-square-based Q-test with a significant level of  $p \leq 0.10$  and quantified by the  $I^2$  statistic. Substantial heterogeneity was reflected by a value of  $I^2 > 50\%$ ; moderate heterogeneity was regarded as  $I^2 = 25\%$  to  $50\%$ ; while low heterogeneity was considered as  $I^2 < 25\%$ . When  $I^2$  was larger than 50%, a random effects model was used; otherwise, the fixed effects model was used. A 2-sided  $p < 0.05$  was considered as significant. Potential publication bias was appraised through funnel plots. Sensitivity analysis was performed by approach of changing one-factor-at-a-time for meta-analysis involving multiple studies. Data of every study was moved and then returned subsequently, with sensitivity measured by monitoring changes in outputs of meta-analysis. The study procedures were approved by the Ethics Committee of Peking Union Medical College Hospital.

## RESULTS

### Search results

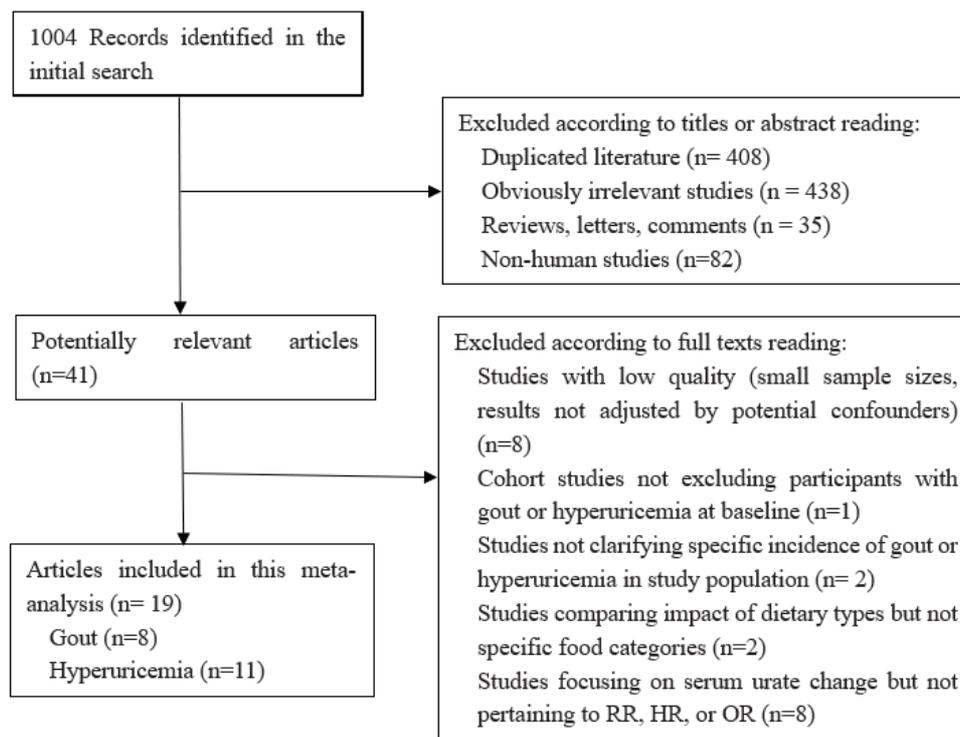
The literature search process is shown in Figure 1. Overall, of the initial 1,004 records, 963 were excluded according to the title or abstract. The remaining 41 studies were selected for full-text screening, of which 22 articles that failed to meet the inclusion criteria were eliminated. As a consequence, 10 cohort studies and 9 cross-sectional studies were selected in this meta-analysis.

### Study characteristics and quality

In our meta-analysis, the publication year of included literature ranged from 2004 to 2017; the regions included 6 countries (U.S., Japan, Korea, Brazil, Mexico and China); the sample size ranged from 483 to 100,226. As for the included 10 cohort studies, the follow-up duration ranged from 6 years to 26 years. Of all the studies, 10 studies<sup>5,9-17</sup> selected individuals from a community-based population, and the remaining 9 studies<sup>4,6,18-24</sup> recruited professional workers as participants. All studies included only adults. Table 1 summarizes the main characteristics of these 20 included studies. Based on the Newcastle-Ottawa Scale (NOS), the quality assessment of included studies yielded a mean NOS score of 7.1, suggesting the presence of high methodologic quality (Table 2). With regard to association between dietary factors and risk of hyperuricemia and gout, the results of included studies were aggregated and analyzed (Table 3 and Figure 2)

### Dietary factors and risk of hyperuricemia and gout Red meat

Two cross-sectional studies<sup>9,17</sup> and 2 prospective cohort studies<sup>4,11</sup> reported risk of gout or hyperuricemia for the highest versus the lowest red meat intake category. Two



**Figure 1.** Flow diagram for inclusion of studies.

studies<sup>4,11</sup> were related to gout, and the other 2 studies<sup>9,17</sup> were about hyperuricemia. There was no heterogeneity across the included studies ( $p=0.88$ ,  $I^2=0\%$ ). Data pooling under a fixed-effect model revealed that high intake of red meat was associated with a significant increased risk of incident gout and hyperuricemia, respectively (Figure 2-A, Table 3).

### Seafoods

Choi,<sup>4</sup> Villegas,<sup>9</sup> Poletto<sup>17</sup> and Teng<sup>11</sup> also referred to the risk of gout or hyperuricemia for the highest versus the lowest seafoods intake, with 2 studies<sup>4,11</sup> focusing on gout and remaining 2 studies<sup>9,17</sup> about hyperuricemia. Data pooling under a random-effects model demonstrated that high intake of seafoods pertains to increased risk of gout and hyperuricemia (Figure 2-B, Table 3). There was substantial heterogeneity across the 2 studies referring to risk of gout ( $p=0.06$ ,  $I^2=73\%$ ), which might be explained by ethnic difference, given the fact that one study<sup>4</sup> was performed in the USA whereas the other in Singapore.<sup>9</sup> However, the sensitivity analyses showed that exclusion of anyone of the 2 studies did not change our result.

### Alcohol

Three cross-sectional studies<sup>10,17,21</sup> and 4 prospective cohort studies<sup>5,18-20</sup> reported the OR or RR for the prevalence of gout and hyperuricemia in population with large consumption of alcohol. Choi<sup>5</sup> focused on the risk of gout, while the other studies were related to the risk of hyperuricemia. The studies were performed in America, Korea, China and Japan. There was significant heterogeneity across the studies ( $p<0.00001$ ,  $I^2=91\%$ ). Data pooling under a random-effects model confirmed that alcohol consumption is positively associated to increased risk of gout and hyperuricemia (Figure 2-C, Table 3). Sensitivity analysis indicated ethnic origin might have interaction with the

aggregated ORs, which may account for the heterogeneity. In the subgroup analysis by ethnicity, the ORs of gout and hyperuricemia were 2.48 (95% CI 1.22-5.03,  $p=0.01$ ), 2.48 (95% CI 2.18-2.83,  $p<0.00001$ ), 1.27 (95% CI 1.13-1.43,  $p<0.0001$ ) and 2.58 (95% CI 1.81-3.66,  $p<0.00001$ ) for Chinese, Japanese, Koreans, and Americans, respectively ( $p$  for subgroup difference  $<0.00001$ ,  $I^2=91\%$ ).

### Sweetened soft drinks or fructose

Four cross-sectional studies<sup>10,12,13,23</sup> and 2 cohort studies<sup>6,22</sup> reported the ORs of the prevalence of gout or hyperuricemia. The included studies originated from Singapore, Korea, America and Mexico, with 2 studies<sup>6,22</sup> about gout and 4 studies<sup>10,12,13,23</sup> about hyperuricemia. No heterogeneity was observed among the included studies ( $p=0.27$ ,  $I^2=21\%$ ). Data pooling and subgroup analysis under a fixed-effects model revealed that high intake of fructose or sweetened soft drinks was associated with increased risk of incident gout or hyperuricemia (Figure 2-D, Table 3).

### Dairy products

One cross-sectional<sup>17</sup> studies and 2 cohort studies<sup>4,11</sup> performed separately in America, Brazil and Singapore were included in the meta-analysis. Of these studies, 2 studies<sup>4,11</sup> were related to gout while the other 1 study<sup>17</sup> focused on hyperuricemia. Because of significant heterogeneity across the studies ( $p<0.00001$ ,  $I^2=94\%$ ), data pooling under a random-effects model was conducted. As the result, inverse association between dairy product consumption and risk of hyperuricemia was proved, while correlation between dairy product intake and gout risk was not found (Figure 2-E, Table 3). After we excluded the study<sup>11</sup> with participants having generally lower milk ingestion, the risk of gout in subjects with substantial dairy product consumption (OR, 0.56 (95% CI 0.44-0.70);  $p<0.00001$ ) was modified and the heterogeneity across the studies disappeared

**Table 1.** General characteristics of included studies

First author, publication year	Study design	Location; population source	Dietary exposure	Male (%)	Age (years)	Sample size; no. of cases of gout or HUA	Follow-up (years)	Exposure measures and definitions	OR, RR or HR for risk of HUA or gout (95%CI)
Choi, 2004 <sup>4</sup>	cohort	America; health professional workers	Red meat, seafoods, dairy products, purine-rich vegetables	100	40-75	47, 150; 730 (gout cases)	12	The highest quintile of red meat intake vs the lowest quintile	1.41 (1.07-1.86)
								The highest quintile of sea food intake vs the lowest quintile	1.51 (1.17-1.95)
								The highest quintile of dairy products intake vs the lowest quintile	0.56 (0.42-0.74)
								The highest quintile of purine-rich vegetables intake vs the lowest quintile	0.96 (0.74-1.24)
Poletto, 2011 <sup>17</sup>	Cross-sectional	Brazil; Japanese-Brazilian community	Alcohol, red meat, fish, dairy product	46.2	≥30	1,330; 470 (HUA cases)	NA	The highest tertile of alcohol intake vs the lowest tertile	1.56 (1.26-1.92)
								The highest tertile of red meat intake vs the lowest tertile	1.13 (0.90-1.42)
								The highest tertile of fish intake vs the lowest tertile	1.18 (0.93-1.48)
								The highest tertile of dairy products intake vs the lowest tertile	0.64 (0.51-0.81)
Villegas, 2012 <sup>9</sup>	Cross-sectional	China; community	Animal protein, vegetable protein, seafoods, red meat, purine-rich vegetables	100	40-74	3, 978; 996 (HUA cases)	NA	The highest quintile of red meat intake vs the lowest quintile	1.29 (0.99-1.69)
								The highest quintile of sea food intake vs the lowest quintile	1.56 (1.20-2.02)
								The highest quintile of purine-rich vegetables intake vs the lowest quintile	1.14 (0.89-1.48)
Teng, 2013 <sup>10</sup>	Cross-sectional	Singapore; Chinese community	Alcohol, coffee, soda	44	45-74	483; 171 (HUA cases)	NA	The heaviest alcohol intake vs no alcohol intake	4.83 (1.10-21.2)
								The heaviest coffee intake vs no coffee intake	0.93 (0.49-1.76)
								The heaviest soda intake vs no soda intake	1.51 (0.30-7.72)
Teng, 2015 <sup>11</sup>	Cohort	Singapore; Chinese community	Soy foods, non-soy legumes, red meat, fish and shellfish, dairy products	42.5	45-74	51,114; 2,167 (gout cases)	11.1±3.7	The highest quartile of soy foods intake vs the lowest quartile	0.86 (0.75-0.98)
								The highest quartile of non-soy legumes intake vs the lowest quartile	0.83 (0.73-0.95)
								The highest quartile of red meat intake vs the lowest quartile	1.08 (0.94-1.24)
								The highest quartile of fish and shellfish intake vs the lowest quartile	1.16 (1.02-1.32)
								The highest quartile of dairy products intake vs the lowest quartile	0.99 (0.87-1.13)

HUA: hyperuricemia.

**Table 1.** General characteristics of included studies (cont.)

First author, publication year	Study design	Location; population source	Dietary exposure	Male (%)	Age (years)	Sample size; no. of cases of gout or HUA	Follow-up (years)	Exposure measures and definitions	OR, RR or HR for risk of HUA or gout (95%CI)
Choi,2004 <sup>5</sup>	Cohort	America; community	Alcohol	100	40-75	47,150; 730(gout cases)	12	Alcohol intake $\geq 50$ g / day	RR for risk of gout: 2.53 (1.73-3.70)
Nakamura, 2012 <sup>18</sup>	Cohort	Japan; professional workers	Alcohol	100	38.5 $\pm$ 9.6	3,310; 529 (HUA cases)	6	Alcohol intake $\geq 30$ g / day	1.98 (1.40-2.80)
Ryu, 2012 <sup>19</sup>	Cohort	Korea; professional workers	Alcohol	100	30-59	10,802; 2,496 (HUA cases)	7	Alcohol intake $\geq 20$ g / day	1.20 (1.08-1.34)
Makinouchi, 2016 <sup>20</sup>	Cohort	Japan; professional workers	Alcohol	100	42.9 $\pm$ 12.0	8,097; 1,907 (HUA cases)	8	An increase in alcohol consumption per 22 g/day	1.29 (1.22-1.36)
Cui, 2017 <sup>21</sup>	Cross-sectional	China; professional employees	Alcohol	79.9	18-97	100,226; 8,289 (HUA cases)	NA	Alcohol intake $\geq 50$ g / day (for men)	1.380 (1.32-1.44)
								Alcohol intake $\geq 50$ g / day (for women)	1.265 (1.01-1.58)
Choi,2008 <sup>6</sup>	Cohort	America; health professional workers	Sweetened soft drinks, fructose	100	40-75	46,393; 755 (gout cases)	12	The highest quintile of total fructose intake vs the lowest quintile	1.81 (1.31-2.50)
								Sugar sweetened soft drink intake $\geq 2$ servings / day	1.85 (1.08-3.16)
Choi, 2008 <sup>12</sup>	Cross-sectional	America; urban community	Sweetened soft drinks	46.79	$\geq 20$	14,761; 2,657 (HUA cases)	NA	Sugar-sweetened soft drink intake $\geq 4$ servings / day	OR for risk of HUA: 1.82
Choi, 2010 <sup>22</sup>	Cohort	America; registered nurses	Sweetened soft drinks	0	30-55	78,906; 778 (gout cases)	22	The highest quintile of free fructose intake vs. the lowest quintile	1.43 (1.09-1.88)
								Sugar-sweetened soda intake $\geq 2$ servings / day	2.39 (1.34-4.26)
Bae, 2014 <sup>13</sup>	Cross-sectional	Korea; rural community	Sugar-sweetened soft drinks	37.9	$\geq 40$	9,400; 1,021 (HUA cases)	NA	The highest quintile of soft drink intake vs. the lowest quintile (for men)	1.35 (1.07-1.71)
								The highest quintile of soft drink intake vs. the lowest quintile (for women)	1.40 (1.03-1.90)
Meneses-Leon, 2014 <sup>23</sup>	Cross-sectional	Mexico; health workers	Sweetened beverage	29.2	18-70	8,514; 1,057 (HUA cases)	NA	Sweetened beverage intake $\geq 3$ servings / day (for men)	2.40 (1.63-3.53)
								Sweetened beverage intake $\geq 3$ servings / day (for women)	1.32 (1.02-1.71)
Choi,2007 <sup>14</sup>	Cohort	America; community	Coffee	100	40-75	45,869; 757 (gout cases)	12	Total coffee intake $\geq 6$ cups / day	0.41(0.19-0.88)
								Decaffeinated coffee intake $\geq 4$ cups / day	0.73 (0.46-1.17)

HUA: hyperuricemia.

**Table 1.** General characteristics of included studies (cont.)

First author, publication year	Study design	Location; population source	Dietary exposure	Male (%)	Age (years)	Sample size; no. of cases of gout or HUA	Follow-up (years)	Exposure measures and definitions	OR, RR or HR for risk of HUA or gout (95%CI)
Choi, 2010 <sup>24</sup>	cohort	America; registered nurses	Coffee	0	30-55	89, 433; 896 (gout cases)	26	Total coffee intake $\geq$ 4 cups / day Decaffeinated coffee intake $>$ 1 cup / day	0.43(0.30-0.61) 0.77 (0.63-0.95)
Pham, 2010 <sup>15</sup>	Cross-sectional	Japan; community	Coffee	49.88	49-76	11,662; 1,020 (HUA cases)	NA	Coffee intake $\geq$ 7 cups / day in men Coffee intake $\geq$ 4 cups / day in women	0.71 (0.39-1.30) 1.30 (0.50-3.38)
Bae, 2015 <sup>16</sup>	Cross-sectional	Korea; rural community	Coffee	37.9	$\geq$ 40	9,400; 1021 (HUA cases)	NA	The highest quintile of coffee intake vs the lowest quintile (for men) The highest quintile of coffee intake vs the lowest quintile (for women)	0.92 (0.47–1.83) 1.57 (0.76–3.27)

HUA: hyperuricemia.

**Table 2.** The quality assessment of included studies by Newcastle-Ottawa Scale (NOS)

Included studies	The selection of the study groups	The comparability of the groups	The ascertainment of exposure or outcome of interest	Total score
Choi, 2004 <sup>4</sup>	3	1	3	7
Poletto, 2011 <sup>17</sup>	4	2	1	7
Villegas, 2012 <sup>9</sup>	4	2	1	7
Teng, 2013 <sup>10</sup>	4	2	1	7
Teng, 2015 <sup>11</sup>	4	1	3	8
Choi, 2004 <sup>5</sup>	4	2	3	9
Nakamura, 2012 <sup>18</sup>	3	1	3	7
Ryu, 2012 <sup>19</sup>	3	1	3	7
Makinouchi, 2016 <sup>20</sup>	3	1	3	7
Cui, 2017 <sup>21</sup>	3	2	1	6
Choi, 2008 <sup>6</sup>	3	2	3	8
Choi, 2008 <sup>12</sup>	4	2	1	7
Choi, 2010 <sup>22</sup>	3	2	3	8
Bae, 2014 <sup>13</sup>	3	2	1	6
Meneses-Leon, 2014 <sup>23</sup>	4	2	1	7
Choi, 2007 <sup>14</sup>	4	2	1	7
Choi, 2010 <sup>24</sup>	3	2	3	8
Pham, 2010 <sup>15</sup>	4	2	1	7
Bae, 2015 <sup>16</sup>	3	2	1	6

( $p=0.55$ ,  $I^2=0\%$ ). Other variables, such as population size, ethnicity or region, had no interaction with the aggregated ORs.

### Purine-rich vegetables

One cross-sectional studies<sup>9</sup> and 2 cohort studies<sup>4,11</sup> were included. All were related to purine-rich vegetables. Two studies<sup>4,11</sup> concerned the risk of gout, and the remaining one<sup>9</sup> referred to hyperuricemia. According to data pooling under a random-effects model and subgroup analysis, purine-rich vegetable intake is negatively associated with gout risk (Figure 2-F, Table 3).

### Soy foods

One cross-sectional study<sup>9</sup> and 1 cohort study<sup>11</sup> were included. One<sup>11</sup> referred to the risk of gout, and the other<sup>9</sup> was related to the risk hyperuricemia as for consumption of large amounts of soy foods. Since there was considerable heterogeneity among the included studies ( $p=0.13$ ,  $I^2=56\%$ ), data pooling under a random-effects model was conducted, showing higher consumption of soy foods was related with lower risk of hyperuricemia and gout (Figure 2-G, Table 3).

### Coffee

Two prospective cohort studies<sup>14,24</sup> and 3 cross-sectional studies<sup>10,15,16</sup> reported ORs of the risk of gout or hyperuricemia for the highest versus lowest coffee consumption category. Two studies<sup>14,24</sup> were about the risk of gout, while the remaining 3 referred to hyperuricemia. Data aggregation under a random-effects model was performed and found coffee intake was negatively associated with risk of gout whereas had no interaction on hyperuricemia risk (Figure 2-H, Table 3). Subsequently, the data about men and women of all the included studies was extracted separately into this meta-analysis. In the subgroup analysis, substantial coffee consumption was testified to be related with reduced risk of gout, without significant difference between women and men (men: OR, 0.54; 95% CI 0.40-0.74,  $p=0.0001$ ; women: OR, 0.43; 95% CI 0.34-0.53,  $p<0.00001$ ;  $p$  for subgroup difference =0.20,  $I^2=38.4\%$ ). Meanwhile, significant distinction was revealed in ORs for the risk of hyperuricemia in men and women. Coffee intake had no correlation with the risk of hyperuricemia in men, whereas seemed positively associated with risk of hyperuricemia in women (women: OR, 1.58; 95% CI 1.16-2.16,  $p=0.004$ ; men: OR, 0.76; 95% CI 0.55-1.06,  $p=0.11$ ;  $p$  for subgroup difference <0.0001).

### Sensitivity analysis and publication bias

The influence of each included study on the pooled risk estimate was assessed by repeating the meta-analysis after omitting each study in turn, showing that no single study significantly affected our final conclusion. As for all comparisons of the included study outcomes, the funnel plots were visually symmetrical, suggesting the absence of publication bias.

## DISCUSSION

It has been accepted by many researchers that dietary modification has been an effective strategy for prevention and

management for gout or hyperuricemia. Moreover, specific suggestions on diet and lifestyle choices for gout or hyperuricemia patients have been recommended by clinical guidelines.<sup>25,26</sup> This present work pooling all eligible cohort studies and cross-sectional studies, evaluated association of consumption of red meat, seafoods, alcohol, fructose, vegetables, dairy products, soy foods and coffee with risk of gout and hyperuricemia.

### Effect of red meat, seafoods, fructose and alcohol

Owing to high purines content, substantial consumption of red meat and seafoods has been confirmed by a number of studies to be positively correlated with development of hyperuricemia and gout flares.<sup>27</sup> Fructose, a major constituent of high-fructose corn syrup in sugar-sweetened beverages, can also facilitate ATP depletion through phosphorylation and result in an elevation of circulating uric acid level. A recent meta-analysis<sup>28</sup> including 2 prospective cohort studies has verified the effect of fructose on increasing vulnerability to gout and hyperuricemia. Alcohol intake was also regarded as one of important precipitating factors for development or exacerbation of hyperuricemia and gout. Ethanol ingestion has been proven to increase uric acid production by ATP degradation to AMP; furthermore, dehydration and metabolic acidosis associated with alcoholism might contribute to decreased urinary excretion of urate.<sup>29</sup> Along the line, a number of observational studies as well as a meta-analysis<sup>30</sup> has suggested that substantial alcohol consumption may significantly predispose people to gout and hyperuricemia. Based on this published evidence, American College of Rheumatology has recommended patients with gout or hyperuricemia to avoid or limit high-purine organ meat, seafood, alcohol, high fructose corn syrup-sweetened beverages or foods.<sup>26</sup> In accordance with the previous literature, our work demonstrated significant influence of meat, seafood, alcohol and fructose in increasing susceptibility to gout and hyperuricemia.

### Effect of dairy products

It has been pointed out by literature that urinary excretion of uric acid and xanthine was increased after ingestion of dairy products.<sup>31</sup> Low purine content of milk, in combination with the uricosuric effect of casein, whey protein and calcium in milk may lead to decreased urate concentration. Some cross-sectional studies and intervention studies have observed this urate-lowering effect of dairy products.<sup>31,32</sup> A randomized clinical trial<sup>31</sup> testified that skim milk powder (SMP) enriched with glycomacropeptide (GMP) and G600, standard SMP and lactose powder could all significantly lower serum urate levels, alleviate gouty arthralgia, and reduce the frequency of gout flares over a three-month period. After adjusting the confounder of volume of milk intake per day, this meta-analysis demonstrated the negative association between dairy products and risk of gout and hyperuricemia.

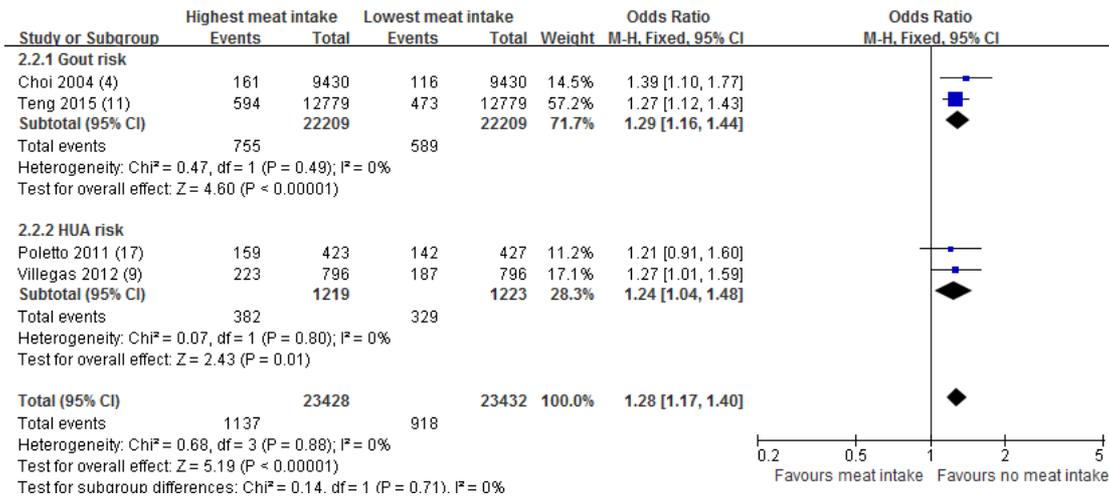
### Effect of high-purine vegetables

As was reported by population-based epidemiological studies, substantial vegetable intake contributed to lower serum urate level.<sup>27,33</sup> However, as for purine-rich vegetables (cauliflower, spinach, peas, beans, mushrooms, lentil

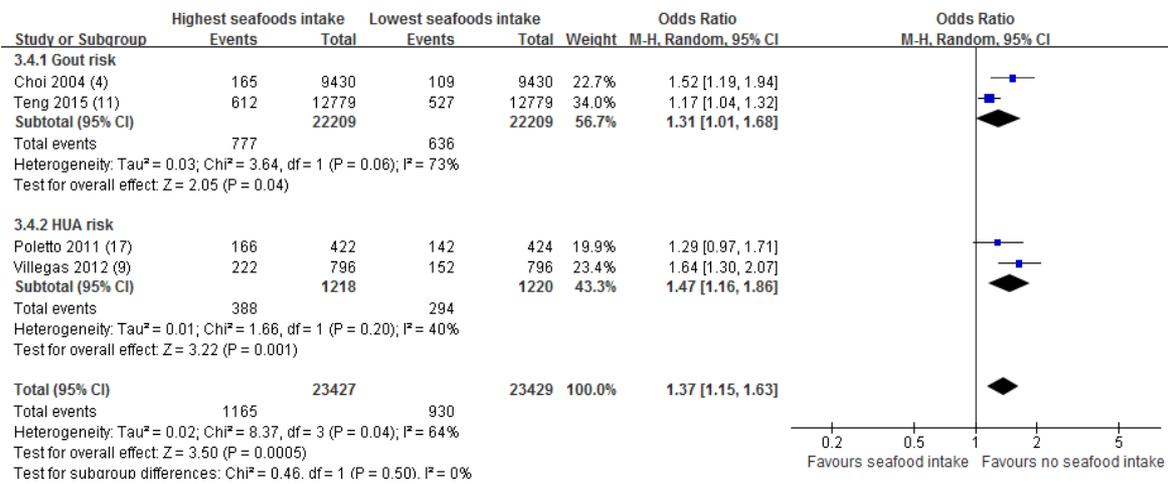
**Table 3.** The association of various dietary factors with risk of gout and hyperuricemia

Dietary factors	Risk of gout				Risk of HUA				Overall risk of gout and HUA	
	OR (95% CI)	<i>p</i>	No. of pooled studies	<i>p</i> for heterogeneity; <i>I</i> <sup>2</sup>	OR (95% CI)	<i>p</i>	No. of pooled studies	<i>p</i> for heterogeneity; <i>I</i> <sup>2</sup>	OR (95% CI)	<i>p</i>
Red meat	1.29 (1.16-1.44)	<0.00001	2	0.49; 0%	1.24 (1.04-1.48)	0.01	2	0.80; 0%	1.28 (1.17-1.40)	<0.00001
Seafoods	1.31 (1.01-1.68)	0.04	2	0.06; 73%	1.47 (1.16-1.86)	0.001	2	0.20; 40%	1.37 (1.15-1.63)	0.0005
Alcohol	2.58 (1.81-3.66)	<0.00001	1	NA	2.06 (1.60-2.67)	<0.00001	6	<0.00001; 93%	2.12 (1.68-2.69)	<0.00001
Fructose	2.14 (1.65-2.78)	<0.00001	2	0.35; 0%	1.85 (1.66-2.07)	<0.00001	4	0.23; 31%	1.89 (1.70-2.09)	<0.00001
Dairy products	0.75 (0.42-1.32)	0.31	2	<0.0001; 95%	0.50 (0.37-0.66)	<0.00001	1	NA	0.66 (0.41-1.06)	0.08
Vegetable	0.86 (0.75-0.98)	0.02	2	0.37; 19%	1.10 (0.88-1.39)	0.39	1	NA	0.94 (0.78-1.12)	0.48
Soy foods	0.85 (0.76-0.96)	0.01	1	NA	0.70 (0.56-0.88)	0.002	1	NA	0.79 (0.66-0.95)	0.01
Coffee	0.47 (0.37-0.59)	<0.00001	2	0.2; 39%	0.96 (0.76-1.22)	0.75	3	0.12; 52%	0.72 (0.48-1.08)	0.11

2-A



2-B



2-C

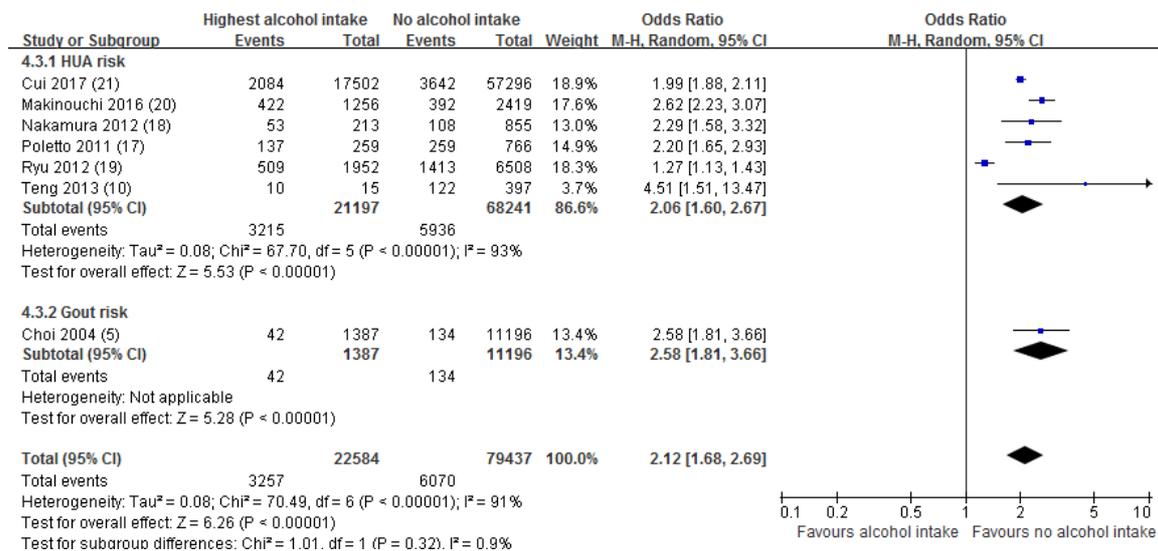
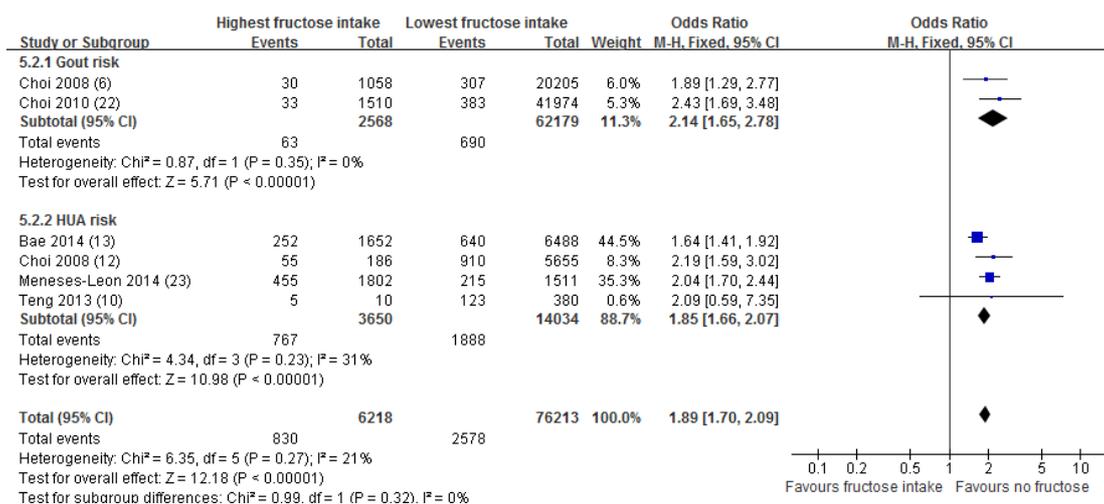


Figure 2. Forest plots of effects of dietary preferences (red meat (2-A), seafoods (2-B), alcohol (2-C), fructose (2-D), dairy products (2-E), purine-rich vegetables (2-F), soy foods (2-G), coffee (2-H) on risk of having gout and hyperuricemia.

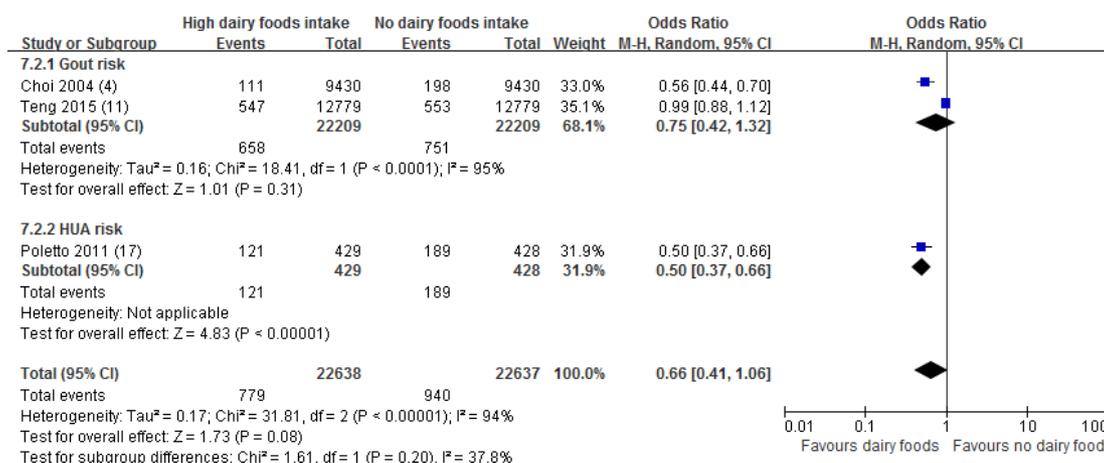
and so on), disagreement has existed. Some researchers have even suggested it be necessary for gout or hyperuricemia patients to avoid purine-rich vegetables. Nevertheless, contrary to the belief, our work verified that purine-rich vegetables intake was not correlated with gout risk, and further, was associated with lowered risk of hyperuricemia.

In agreement with our findings, several recent population-based epidemiologic studies<sup>4,31</sup> also found no association between high-purine vegetables and risk of gout and hyperuricemia. This phenomenon might be, in part, explained by the variant bioavailability of purines from different dietary source.<sup>31</sup>

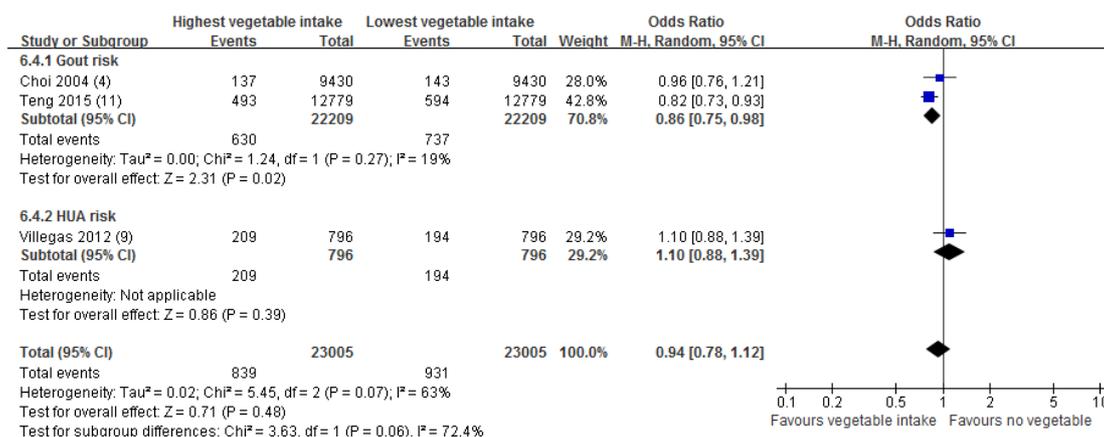
## 2-D



## 2-E



## 2-F



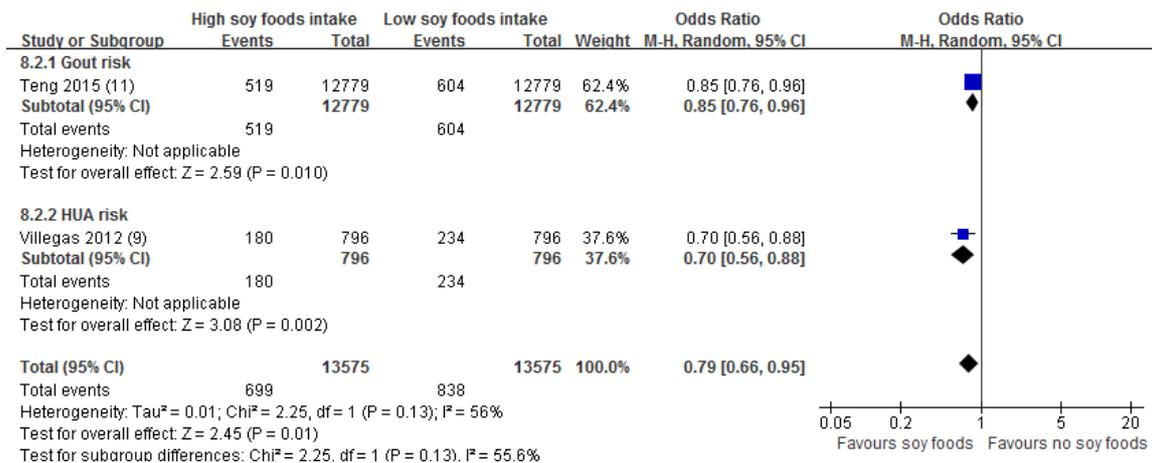
**Figure 2.** Forest plots of effects of dietary preferences (red meat (2-A), seafoods (2-B), alcohol (2-C), fructose (2-D), dairy products (2-E), purine-rich vegetables (2-F), soy foods (2-G), coffee (2-H)) on risk of having gout and hyperuricemia (cont.)

### Effect of soy foods

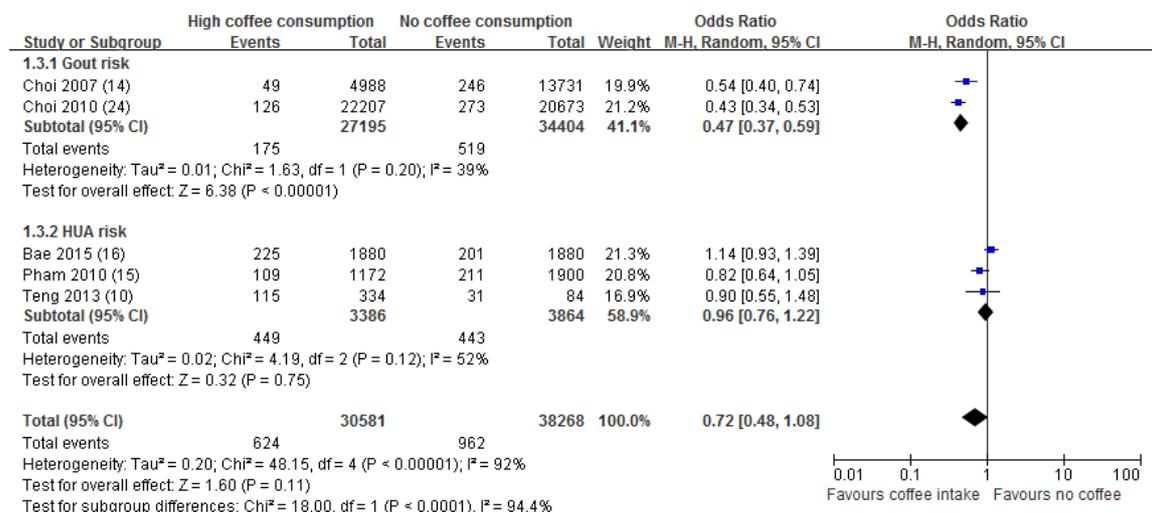
As a part of traditional Asian diets, soy foods are frequently consumed by Chinese. Due to the fact that they usually contain a moderate amount of purines, soy foods are conventionally advised to be contraindicated for gout or hyperuricemia patients. However, a number of epidemiologic researches and clinical studies could not justify the commonly-held concern. The former studies uncovered that soy foods intake did not increase the risk of developing gout or hyperuricemia, but conversely reduced the risk of

other related comorbidities.<sup>34</sup> To explain the inconsistency between rich purine content of soy foods and their non-injurious impact on prevalence odds, some researchers speculated that purine bases and metabolites might be involved in the endogenous synthesis of purines, so that dietary purine content could not simply affect serum urate level.<sup>34</sup> In conformity with previous studies, our work also demonstrated that soy foods consumption exerted beneficial effects and was related with reduced risk of gout and hyperuricemia.

## 2-G



## 2-H



**Figure 2.** Forest plots of effects of dietary preferences (red meat (2-A), seafoods (2-B), alcohol (2-C), fructose (2-D), dairy products (2-E), purine-rich vegetables (2-F), soy foods (2-G), coffee (2-H) on risk of having gout and hyperuricemia (cont.)

### Effect of coffee

Though the mechanisms underlying the correlation between coffee and serum urate remain yet undefined, several potential explanations were speculated. Caffeine (1,3,7-trimethyl-xanthine) in coffee may competitively inhibit xanthine oxidase, increase renal blood flow, and enhance urinal excretion of urate. In addition, the phenol chlorogenic acid, another component of coffee may improve insulin resistance and thereby decrease serum urate.<sup>15</sup> In line with previous literature,<sup>14</sup> our study observed significant reduction of gout risk among people with substantial coffee consumption. A recent meta-analysis<sup>35</sup> including 11 observational studies, also validated the significant inverse association between coffee consumption and gout risk (RR, 0.43, 95% CI 0.31-0.59,  $p < 0.001$ ).

Meanwhile, with regard to association of coffee and hyperuricemia risk, studies have yielded inconsistent results. A cross-sectional study has depicted association of coffee intake with lower risk of hyperuricemia in men and analogous but weaker association in women.<sup>15</sup> However, the aforementioned meta-analysis<sup>35</sup> found no correlation between hyperuricemia risk and coffee consumption (OR, 0.84, 95% CI 0.65-1.09;  $p = 0.20$ ), which did not investigate the effect of sex on the result. Inconsistent with former studies, our finding disclosed the coffee intake had no cor-

relation with hyperuricemia risk in men while seemed associated with elevated risk in women. In view of the distinction, the interaction between sex and risk of hyperuricemia for high coffee consumption category is intriguing and deserves further discussion. However, there are limited studies on this topic, and more well-designed long-term prospective studies need to be conducted separately for men and women.

As the primary strength of the present meta-analysis, all included studies were analyzed based on multivariable adjusted results and large samples, allowing a possibility of avoiding confounders and reaching reasonable conclusions. What is more important, this is the first meta-analysis clarifying association between red meat, seafoods, soy foods and vegetables and the risk of gout and hyperuricemia. Furthermore, this work discloses deficiency of current evidence, which can serve as a clue for further study. However, some limitations should not be ignored. First, the observational nature of studies limits the precise estimation for the risk of gout or hyperuricemia. Second, the ascertainment methods for gout or hyperuricemia were different across the primary studies, which may also influence the observed association in our meta-analysis. Third, the confounders adjusted in the included studies were not identical. Considerable heterogeneity among various studies might

have distorted the results of this meta-analysis. Fourth, renal function is another potential factor that may interact with the incidence of gout or hyperuricemia. Nevertheless, because of the lack of relevant data, it is not feasible to conduct a subgroup analysis by estimated glomerular filtration rate (eGFR). Finally only limited number of studies were included and qualified for this meta-analysis. These limitations might weaken the strengths of this study.

### Conclusion

In summary, evidence from this meta-analysis indicated that intake of red meat, seafoods, fructose and alcohol may increase the risk of hyperuricemia and gout. On the contrary, consumption of dairy products or soy foods decreases the risk of hyperuricemia and gout. Purine-rich vegetables may not predispose people to gout, and even exert protecting effect on hyperuricemia risk. Coffee consumption may decrease risk of gout, but have opposing effect on men and women's risk of hyperuricemia. The present review adds to the mounting evidence which could provide more clues for prevention and intervention of gout and hyperuricemia. However, owing to the limited number of studies, further well-designed prospective research and randomized controlled trials is needed to elaborate these issues.

### AUTHOR DISCLOSURES

The authors have no financial disclosures or conflicts of interest to declare.

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