



# Modification of Plant-Based Food Intake for Prevention of Gout in Japanese People in 2019:2022 Update

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**Abstract:** The number of patients with gout has been increasing in Japan. A previous report showed modification of dietary habits for the prevention of gout in Japanese people in 2016 through the trends in food intake of Japanese people in 1946-2016. The aim of this article is to suggest what food intake is important for the prevention of gout in Japanese people in 2019 referencing the results of clinical research reported. As the previous report, the author used the data of the Comprehensive Survey of Living Conditions in Japan for the number of gout patients (1986-2019) and the data of the National Health and Nutrition Survey in Japan (1946-2019) for the intake of foods. Food intake of Japanese people in 2019 was compared with that in 2016. The relationship between the number of gout patients and food intake in Japanese people was examined. The daily intake of mushrooms, total legumes, and total vegetables of Japanese people in 2019 were higher compared to those in 2016, respectively. Whereas the daily intake of total grains, total potatoes, seaweed, and total fruit of Japanese people in 2019 were lower compared to those in 2016, respectively. The intake of seeds and nuts of Japanese people in 2019 was the same as that in 2016. The significance of the correlation between the number of gout patients and food intake in 1986-2016 were also observed that in 1986-2019. This article indicates the importance of recognizing the intake of plant-based foods for the prevention of gout in Japanese people (especially adults). Modification of food intake for the prevention of gout in Japanese people in 2019 is also suggested as follows: limiting intake of meat; limiting alcohol beverage consumption; limiting or decreasing intake of salt, oils and fats and confectioneries; avoidance of excessive intake of sugar-sweetened beverages and sugary foods including desserts and sweets; increasing the intake of fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), milk and dairy products (particularly low-fat dairy products), mushrooms, seaweed, legumes, seeds and nuts, fruit, vegetables, which contain rich in carbohydrate (particularly dietary fiber), vitamin A, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, vitamin C, calcium, potassium, magnesium, zinc, and polyphenol.

**Keywords:** Diet, Food, Gout, Hyperuricemia, Nutrient, Plant-Based Food, Uric Acid

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## 1. Introduction

The prevalence of gout in Japan has increased markedly since the 1960s [1, 2]. The westernization of the Japanese diet from 1955 is thought to be one factor the increase in the prevalence of gout [3]. Recently, the Ministry of Health, Labour and Welfare in Japan [4-7] has shown the number of gout patients and the intake of nutrients or foods in 2019. The number of gout patients of Japanese people in 2019 was higher compared to that in 2016 and increased 4.92-fold compared to that in 1986 (1986: 0.255 million; 2016: 1.105 million; 2019: 1.254 million) [4].

To explore means of the dietary control for the prevention of gout, the author [3, 8-13] has proposed the modification of intake of nutrients and certain foods for the prevention of gout in Japanese people in 2016 and 2019. In the contents of previous reports [11-13], modification of intake of nutrients, animal products, seasonings, condiments and spices, confectioneries, and beverages for the prevention of gout in Japanese people in 2019 is suggested as follows: reduce the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy); limiting or

decreasing intake of fat (particularly animal fat), saturated fatty acids, cholesterol, salt, oils and fats and confectioneries; decreasing intake of phosphorus and copper; increase intake of carbohydrate (particularly dietary fiber), vitamin A, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, calcium, potassium, magnesium, and zinc; increase intake of vitamin B<sub>2</sub> and vitamin C in Japanese men (aged 20-59 years) and women (aged 20-59 years); limiting intake of meat; limiting alcohol beverage consumption; avoidance of excessive intake of sugar-sweetened beverages and sugary foods including desserts and sweets; increasing the intake of milk and dairy products (particularly low-fat dairy products). In the previous report [10], modification of food intake for the prevention of gout in Japanese people in 2016 suggests increasing intake of foods rich in dietary fiber, vitamin A, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, calcium, potassium, magnesium and encouraging intake of fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), eggs, milk and dairy products (especially high-fat dairy products), legumes, seeds and nuts, fruit, vegetables, and coffee. It is necessary to recognize what plant-based food (i.e., grains, potatoes, mushrooms, seaweed legumes, seeds and nuts, fruit, and vegetables) intake is important for the prevention of gout in Japanese people in 2019.

The author [14] suggests encouraging high fruit and soybean products diet, less protein-rich and more vegetable/fruit-rich materials diet, soybean products and fruit dietary pattern, polyphenol-rich dietary pattern, higher adherence to the Mediterranean diet (the traditional Mediterranean diet) and its dietary pattern, higher adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and its dietary pattern, and vegetarian diet (plant-based diet). Referring to or adopting dietary patterns such as the Mediterranean diet, the DASH diet, and vegetarian diet (plant-based diet), the author [14] wishes to emphasize that Japanese people in 2016 should eat a diet in which consciously selects foods rich in dietary fiber, vitamin A, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, calcium, potassium, magnesium, and zinc and decreases intakes of fat (especially animal fat) and salt.

This article shows the relationship between the number of gout patients and plant-based food intake in Japanese people in 2019 and suggests modification of plant-based food intake for the prevention of gout in Japanese people referencing the results of clinical research reported. In addition, considering the contents of previous reports [11-13], this article suggests modification of food intake and selection of food in beneficial diet and dietary pattern for the prevention of gout in Japanese people in 2019.

## 2. Methods

### 2.1. The Number of Gout Patients

The number of gout patients was estimated in the

Comprehensive Survey of Living Conditions performed by the Ministry of Health, Labour and Welfare in Japan (1986-2019) [4]. The Comprehensive Survey of Living Conditions was based on self-reporting by residents. This article showed the rate of hospital visits due to gout from 1986 to 2019 based on the Comprehensive Survey of Living Conditions.

### 2.2. The Trends in Nutrient or Food Intake in Japanese People

The intake of nutrients or foods was searched in the National Health and Nutrition Survey Japan (1946-2019) performed by the Ministry of Health, Labour and Welfare in Japan [5-7].

Data were extracted from the series of Japanese National Nutrition Surveys that have been carried out every year throughout Japan since 1946 [7]. In these surveys, food consumption by families enrolled in the study was assessed by weighing food items consumed on three consecutive weekdays (until 1994) or one weekday (from 1995).

The daily nutrient or food intakes of Japanese people are shown as the mean values reported by the National Health and Nutrition Survey Japan (1946-2019) [5].

### 2.3. Food Composition

The food composition was extracted from a standard tables of food composition in Japan -2020- (Eighth Revised Edition) of the Council for Science and Technology, Ministry of Education, Culture, Sports, Science and Technology in Japan. The Ministry of Education, Culture, Sports, Science and Technology [15] and the National Institutes of Health in the U.S. Department of Health & Human Services [16].

### 2.4. Statistical Analysis

The correlation efficient and the significance of the correlation between the number of gout patients and food intake in 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, 2016, and 2019 were analyzed by Pearson Product Moment Correlation. A SigmaPlot 12.0 software program (version 12.0, Systat Software Inc, San Jose, CA) was used for statistical analysis. Differences were considered significant at  $p < 0.05$ .

## 3. Relationship Between the Number of Gout Patients and Plant-Based Food Intake in Japanese People

The results on the correlation between the number of gout patients and food intake in Japanese people are shown in Table 1 and 2. Table 1 and 2 showed that the significance of the correlation between the number of gout patients and food intake in 1986-2016 were also observed that in 1986-2019.

**Table 1.** Correlation between number of gout patients and intake of food group in Japanese people in 1986-2016 and 1986-2019.

Food group	Year	1986-2016*		1986-2019	
		coefficient	p-value	coefficient	p-value
Grains		0.813	0.002	0.774	0.003
Potatoes		- 0.782	0.005	- 0.829	< 0.001
Mushrooms		0.963	< 0.001	0.955	< 0.001
Seaweed		0.793	0.004	0.735	0.006
Animal Products**		- 0.412	0.208	- 0.349	0.266
Meat**		0.805	0.003	0.843	< 0.001
Seafood**		- 0.884	< 0.001	- 0.911	< 0.001
Eggs**		- 0.937	< 0.001	- 0.731	0.007
Milk and Dairy products**		- 0.036	0.917	0.032	0.921
Legumes		- 0.726	0.011	- 0.688	0.013
Seeds and Nuts		0.706	0.015	0.774	0.003
Fruit		- 0.855	< 0.001	- 0.876	< 0.001
Vegetables		- 0.0687	0.841	0.339	0.281
Seasonings, Condiments, and Spices		-0.905	< 0.001	-0.919	< 0.001
Oils and Fats		- 0.928	< 0.001	- 0.892	< 0.001
Confectioneries		0.711	0.014	0.670	0.017
Alcoholic Beverages		0.861	< 0.001	0.873	< 0.001

\* Adapted from Koguchi [10]. \*\* Adapted from Koguchi [13].

**Table 2.** Correlation between number of gout patients and food item intake in Japanese people in 1986-2016 and 1986-2019.

Food	Year	1986-2016**		1986-2019	
		coefficient	p-value	coefficient	p-value
Grains					
Rice		0.793	0.004	0.752	0.005
Wheat and Wheat Processed Foods		0.864	< 0.001	0.828	< 0.001
Breads		- 0.616	0.044	- 0.581	0.047
Rice and Rice Processed Foods		0.280	0.405	0.205	0.522
Meat***					
Pork***		0.886	< 0.001	0.913	< 0.001
Poultry***		0.838	0.001	0.848	< 0.001
Ham and Sausage***		0.949	< 0.001	0.960	< 0.001
Beef***		- 0.629	0.038	- 0.606	0.037
Wheat Meat***		- 0.406	0.216	- 0.346	0.271
Seafood***					
Raw Fish***		- 0.883	< 0.001	- 0.911	< 0.001
Raw Seafood***		- 0.894	< 0.001	- 0.919	< 0.001
Shellfish***		- 0.710	0.014	- 0.747	0.005
Seafood Processed Foods***		- 0.702	0.016	- 0.754	0.005
Milk and Dairy Products***					
Cheese***		0.932	< 0.001	0.926	< 0.001
Milk***		- 0.901	< 0.001	- 0.913	< 0.001
Legumes					
Soybeans and Soybeans Processed Foods		- 0.714	0.014	- 0.671	0.017
Fermented Soybean Paste		- 0.986	< 0.001	- 0.987	< 0.001
Soybean Curd (Tofu)		- 0.210	0.536	- 0.373	0.233
Fruit					
Citruses		- 0.921	< 0.001	- 0.929	< 0.001
Bananas		0.967	< 0.001	0.962	< 0.001
Apples		- 0.918	< 0.001	- 0.938	< 0.001
Strawberries		- 0.902	< 0.001	- 0.721	0.008
Other Fruit		- 0.706	0.015	-0.720	0.008
Vegetables					
Green and Yellow Vegetables		0.356	0.283	0.228	0.476
Carrots		0.507	0.112	0.459	0.134
Green Peppers		0.460	0.155	0.566	0.055
Onions		0.950	< 0.001	0.941	< 0.001
Cabbages		0.737	0.010	0.804	0.002
Tomatoes		0.695	0.018	0.707	0.010
Radishes		- 0.857	< 0.001	- 0.892	< 0.001
Cucumbers		- 0.828	0.002	- 0.836	< 0.001
Chinese Cabbages		- 0.640	0.0340	- 0.395	0.204
Spinach		- 0.748	0.008	- 0.803	0.002
Pickles		- 0.971	< 0.001	- 0.975	< 0.001

Food	Year	1986-2016**		1986-2019	
		coefficient	p-value	coefficient	p-value
Seasonings, Condiments, and Spices***					
Salt*		- 0.903	< 0.001	- 0.913	< 0.001
Soy Sauce***		- 0.905	< 0.001	- 0.919	< 0.001
Sauce***		- 0.917	< 0.001	- 0.914	< 0.001
Mayonnaise***		- 0.898	< 0.001	- 0.854	< 0.001
Oils and Fats***					
Margarine***		- 0.850	< 0.001	- 0.873	< 0.001
Vegetable Oils and Fats***		- 0.856	< 0.001	- 0.760	0.004
Animal Oils and Fats***		- 0.643	0.033	- 0.421	0.173
Butter***		- 0.0445	0.897	0.0385	0.905
Confectioneries***					
Jam***		0.617	0.043	0.657	0.020
Alcoholic Beverages***					
Beer***		0.695	0.018	0.702	0.011
Rice Wine***		- 0.929	< 0.001	- 0.946	< 0.001
Other Liquors***		0.967	< 0.001	0.974	< 0.001

\* Adapted from Koguchi [9, 12]. \*\* Adapted from Koguchi [10]. \*\*\* Adapted from Koguchi [13].

### 3.1. Grains

The daily intake of total grains of Japanese people in 2019 was lower compared to that in 2016 (2016: 422.1 g/day; 2019: 410.7 g/day). The daily intake of total grains of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r=0.774$ ,  $p=0.00311$ ).

The intake of total grains of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were lower compared to those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 424.3 g/day; 2019: 410.5 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 499.0 g/day; 2019: 480.6 g/day; Japanese adult women (aged  $\geq 20$  years): 2016: 361.8 g/day; 2019: 349.3 g/day]. In Japanese adult people (aged  $\geq 20$  years) or Japanese adult men (aged  $\geq 20$  years), the daily intake of total grains was negatively correlated with the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq 20$  years):  $r=-0.982$ ,  $p=0.000461$ ; Japanese adult men (aged  $\geq 20$  years):  $r=-0.991$ ,  $p=0.000115$ ]. Whereas the daily intake of total grains of Japanese adult women (aged  $\geq 20$  years) did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r=0.684$ ,  $p=0.134$ ). This result suggests that the correlation of daily intake of total grains with the number of gout patients tends to vary with gender.

The daily intake of rice plus rice processed foods of Japanese people in 2019 was lower compared to that in 2016 (2016: 310.8 g/day; 2019: 301.4 g/day). The daily intake of rice plus rice processed foods did not show a significant correlation with the number of gout patients in 1986-2019 ( $r=0.205$ ,  $p=0.522$ ).

The daily rice intake of Japanese people in 2019 was lower compared to that in 2016 (2016: 307.3 g/day; 2019: 292.6 g/day). The daily rice intake of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r=0.752$ ,  $p=0.00480$ ).

The daily intake of wheat plus wheat processed foods of Japanese people in 2019 was lower compared to that in 2016

(2016: 100.7 g/day; 2019: 99.4 g/day). The daily intake of wheat plus wheat processed foods of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r=0.828$ ,  $p=0.000875$ ).

The daily intake of breads of Japanese people in 2019 was higher compared to that in 2016 (2016: 38.6 g/day; 2019: 39.9 g/day). The daily intake of breads of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r=-0.581$ ,  $p=0.0474$ ).

The daily intake of other grains plus other grains processed foods of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r=0.924$ ,  $p=0.0000175$ ).

In epidemiological studies, increased intake of bread and/or margarine (including low-fat margarine, i.e., 40% fat) [17, 18], high-fiber bread [18, 19], cereals [18, 19] were associated with decreased SUA concentrations, respectively. Higher intake of whole grains [20] and dietary fiber [21] were associated with decreased gout risk, respectively. Conscious intake of cereals, whole grains, and high-fiber bread seems to be important for the prevention of gout through reduced serum uric acid (SUA) concentrations.

A novel rice-derived peptide, which was isolated and identified from extract of shelled fruits of *Oryza sativa*, suppressed SUA concentrations in hyperuricemic rats or mice via suppressing xanthine oxidase activity [22, 23]. A novel rice-derived peptide alleviated renal damage through inhibiting the activation of the nucleotide-binding and oligomerization domain-like receptor, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome in hyperuricemic mice and alleviated paw swelling and inflammatory reactions in mice with acute gouty arthritis after subcutaneous injection of monosodium urate crystals [23].

In a randomized, crossover clinical trial in adult male subjects with risk factors for metabolic syndrome for 4 weeks, intake of rice endosperm protein (10 g/day) significantly decreased SUA concentrations compared with the casein group or the baseline [24]. Increase in intake of rice is important for a decrease in SUA concentrations.

The Australian Dietary Guidelines [25] has proposed that

the general recommended minimal intake of grain foods is 6 servings per day for a healthy 70-kg man.

### 3.2. Potatoes, Mushrooms and Seaweed

#### 3.2.1. Potatoes

The daily intake of total potatoes of Japanese people in 2019 was lower compared to that in 2016 (2016: 53.8 g/day; 2019: 50.2 g/day). The daily intake of total potatoes of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.829$ ,  $p = 0.000846$ ).

The daily intake of total potatoes of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were lower compared to those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 54.0 g/day; 2019: 50.0 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 56.3 g/day; 2019: 52.0 g/day; Japanese adult women (aged  $\geq 20$  years): 2016: 52.1 g/day; 2019: 48.3 g/day]. In Japanese adult people (aged  $\geq 20$  years) or Japanese adult men (aged  $\geq 20$  years), the daily intake of total potatoes was negatively correlated with the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq 20$  years):  $r = -0.897$ ,  $p = 0.0154$ ; Japanese adult men (aged  $\geq 20$  years):  $r = -0.937$ ,  $p = 0.00575$ ]. Whereas the daily intake of total potatoes of Japanese adult women (aged  $\geq 20$  years) tended to be positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r = 0.809$ ,  $p = 0.0514$ ). This result suggests that the correlation of daily intake of total potatoes with the number of gout patients tends to vary with gender.

The daily intake of potato plus potato processed foods of Japanese people in 2019 was lower compared to that in 2016 (2016: 51.4 g/day; 2019: 46.9 g/day). The daily intake of potato plus potato processed foods of Japanese people was negatively correlated with the number of gout patients in 2001-2019 ( $r = -0.949$ ,  $p = 0.00112$ ).

The daily intake of other potato plus potato processed foods of Japanese people was negatively correlated with the number of gout patients in 2001-2019 ( $r = -0.826$ ,  $p = 0.0221$ ).

The daily intake of sweet potato plus sweet potato processed foods of Japanese people did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.543$ ,  $p = 0.208$ ).

Considering the data of mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) and the daily dietary fiber, vitamin A, vitamin B<sub>6</sub>, pantothenic acid, potassium, magnesium, phosphorus, iron intake, the daily potatoes intake seems to be appropriate.

#### 3.2.2. Mushrooms

The mushroom intake of Japanese people in 2019 was higher compared to that in 2016 (2016: 16.0 g/day; 2019: 16.9 g/day). The daily mushroom intake of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r = 0.955$ ,  $p = 0.00000129$ ).

The mushroom intake of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were higher compared

to those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 16.9 g/day; 2019: 17.7 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 17.0 g/day; 2019: 17.6 g/day; Japanese adult women (aged  $\geq 20$  years): 2016: 17.0 g/day; 2019: 17.8 g/day]. In Japanese adult people (aged  $\geq 20$  years) or Japanese adult men (aged  $\geq 20$  years), there was no significant correlation between the daily mushroom intake and the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq 20$  years):  $r = 0.521$ ,  $p = 0.289$ ; Japanese adult men (aged  $\geq 20$  years):  $r = 0.276$ ,  $p = 0.597$ ]. Whereas the daily mushroom intake Japanese adult women (aged  $\geq 20$  years) was negatively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.831$ ,  $p = 0.0406$ ). This result suggests that the correlation of daily mushroom intake with the number of gout patients tends to vary with gender and is stronger in adult women than in adult men.

Mushrooms contain fiber, protein, vitamins, minerals and some phenolic compounds [26]. In in vitro study, xanthine oxidase inhibitory activities of the water extracts from fruiting bodies of *Pleurotus ostreatus* and *Pleurotus salmoneo-stramineus* are 78.3% and 67.2%, respectively [27]. In a review reported by Kozarski et al. [28], they have stated that edible mushrooms have been related to significant antioxidant properties due to their bioactive compounds, such as polyphenols, polysaccharides, vitamins (vitamin C, E, A), carotenoids and minerals (zinc, copper, manganese, iron, selenium). Anti-inflammatory and antioxidant properties of edible mushrooms were highlighted by Muszyńska et al. [29].

Though mushrooms excluding shiitake mushrooms, king trumpet mushrooms, nameko mushrooms are high in purine, increased mushroom intake was associated with reduced serum uric acid (SUA) concentrations [30] and decreased hyperuricemia risk [31]. In a large-scale prospective cohort study, mushroom consumption was inversely associated with the incident hyperuricemia [serum uric acid (SUA) level  $> 420$   $\mu\text{mol/L}$  in men and  $> 350$   $\mu\text{mol/L}$  in women] in general population during the 6-year follow-up period (median follow-up of 4.2 years); that is to say, the highest quartile of mushroom intake ( $> 5.52$  g per 1000 kcal per day) was 12.0% reduced risk of hyperuricemia compared with the lowest quartile of mushroom intake ( $< 1.76$  g per 1000 kcal per day) in adjusted model [OR = 0.88, (95% confidence interval, 0.80-0.96),  $p$  for trend = 0.007] [32].

Considering the daily dietary fiber, vitamin D, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, pantothenic acid, folate, potassium, iron, zinc intake, the daily mushroom intake seems better to increase.

#### 3.2.3. Seaweed

The daily seaweed intake of Japanese people in 2019 was lower compared to that in 2016 (2016: 10.9 g/day; 2019: 9.9 g/day). The daily seaweed intake of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r = 0.735$ ,  $p = 0.00647$ ).

The daily seaweed intake of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were lower compared

to those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 11.5 g/day; 2019: 10.6 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 12.1 g/day; 2019: 11.1 g/day; Japanese adult women (aged  $\geq 20$  years): 2016: 11.1 g/day; 2019: 10.1 g/day]. The daily seaweed intake of Japanese adult people (aged  $\geq 20$  years) tended to be negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.780$ ,  $p = 0.0676$ ). In Japanese adult men (aged  $\geq 20$  years) or Japanese adult women (aged  $\geq 20$  years), there was no significant correlation between the daily seaweed intake and the number of gout patients in 2004-2019 [Japanese adult men (aged  $\geq 20$  years):  $r = -0.748$ ,  $p = 0.0876$ ; Japanese adult women (aged  $\geq 20$  years):  $r = 0.691$ ,  $p = 0.129$ ]. This result suggests that the correlation of daily seaweed intake with the number of gout patients tends to vary with gender.

Though seaweed (e.g., nori, wakame) are high in purine, increased seaweed intake was associated with decreased serum uric acid (SUA) concentrations in an epidemiological study [30]. Considering the daily dietary fiber, vitamin A, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, folate, vitamin C, magnesium, iron, zinc intake, the daily seaweed intake seems better to increase.

### 3.2.4. Potatoes, Mushrooms and Seaweed

The Dietary guidelines for Japanese (the Japanese food guide spinning top) by Ministry of Health, Labour and Welfare and Ministry of Agriculture, Forestry and Fisheries has recommended that the daily total intake of potatoes, mushrooms and seaweed must be 1-2 servings (approximately 70-140 g), depending on an individual's caloric intake [33]. The daily total intake of potatoes, mushrooms and seaweed of Japanese people in 2019 was lower compared to that in 2016 (2016: 80.7 g/day; 2019: 77.0 g/day). This tendency was observed in Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) [Japanese adult people: 2016: 82.4 g/day; 2019: 78.3 g/day; Japanese adult men: 2016: 85.4 g/day; 2019: 80.7 g/day; Japanese adult women: 2016: 80.2 g/day; 2019: 76.2 g/day]. The daily total intake of potatoes, mushrooms and seaweed of Japanese people seems better to increase to reach approximately 140 g.

### 3.3. Legumes

The daily intake of total legumes of Japanese people in 2019 was higher compared to that in 2016 (2016: 58.6 g/day; 2019: 60.6 g/day). The daily intake of total legumes of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.688$ ,  $p = 0.0134$ ).

The daily intake of total legumes of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 62.2 g/day; 2019: 64.6 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 63.5 g/day; 2019: 64.0 g/day; Japanese adult women (aged  $\geq 20$  years): 2016: 61.2 g/day; 2019: 65.1 g/day]. In Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), or Japanese

adult women (aged  $\geq 20$  years), there was no significant correlation between the daily intake of total legumes and the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq 20$  years):  $r = 0.384$ ,  $p = 0.452$ ; Japanese adult men (aged  $\geq 20$  years):  $r = 0.232$ ,  $p = 0.658$ ; Japanese adult women (aged  $\geq 20$  years):  $r = 0.376$ ,  $p = 0.462$ ].

The daily intake of soybeans and soybean processed foods, natto of Japanese people in 2019 were higher compared to those in 2016, respectively (soybeans and soybean processed foods: 2016: 57.2 g/day; 2019: 59.2 g/day; natto: 2016: 8.8 g/day; 2019: 9.0 g/day). The daily intake of soybeans and soybean processed foods of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.671$ ,  $p = 0.0169$ ). The daily intake of natto of Japanese people was positively correlated with the number of gout patients in 2001-2019 ( $r = 0.839$ ,  $p = 0.0183$ ).

The daily intake of soybean curd (tofu), deep-fried tofu, and fermented soybean paste (miso) of Japanese people in 2019 were lower compared to those in 2016, respectively [soybean curd (tofu): 2016: 33.7 g/day; 2019: 33.0 g/day; deep-fried tofu: 2016, 7.2 g/day; 2019: 6.9 g/day; fermented soybean paste (miso): 2016: 10.4 g/day; 2019: 9.8 g/day]. The daily soybean curd (tofu) intake of Japanese people did not show a significant correlation with the number of gout patients in 1986-2019 ( $r = -0.373$ ,  $p = 0.233$ ). The daily intake of deep-fried tofu of Japanese people did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.420$ ,  $p = 0.349$ ). The daily intake of fermented soybean paste of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.986$ ,  $p = 0.0000000273$ ).

The daily intake of other legumes plus other legumes processed foods of Japanese people in 2019 was the same as that in 2016 (2016: 1.4 g/day; 2019: 1.4 g/day). The daily intake of other legumes plus other legumes processed foods of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.770$ ,  $p = 0.00336$ ).

Common beans, broad bean seeds, soybeans and soy products (soy paste, soy bacon, soy flour, soy meat, soy tempe, tofu) contain polyphenols that suppress uric acid (UA) production by inhibition of xanthine oxidase activity [34]. Generally speaking, legumes are rich in protein, complex carbohydrates, dietary fiber, folate, flavonoid, and various micronutrients (e.g., phytochemicals) [35]. In epidemiological studies, increased intake of legumes was associated with decreased serum uric acid (SUA) concentrations [30, 36] and hyperuricemia risk [37]. There was no increased risk of gout associated with the intake of legumes [38].

Intake of soy [39-41] and soybean curd (tofu) [42] increased postprandial plasma UA (PUA) or SUA concentrations. Difference of effect of soy and tofu on postprandial SUA concentrations in healthy and gouty subjects was largely influenced by the content of protein and purine [42]. On the other hand, in epidemiological studies, increased intake of soy and soy products was associated with decreased hyperuricemia risk [31, 43-46]. Soy promotes renal oxypurine excretion, thereby reducing the availability of precursor substrates necessary for urate production [41].

These results suggest that increase in daily intake of legumes and soy products in Japanese people is essential for the prevention of gout through reduced SUA concentrations and decreased hyperuricemia risk.

Legume intake was inversely associated with serum concentrations of inflammatory biomarkers [high sensitive C-reactive protein (hs-CRP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6)] in a cross-sectional study among Iranian women [47]. Bitzer et al. [48] have stated that soy may prevent gout through the anti-inflammatory pathway, as a mouse study found that soy protein concentrates lower the nucleotide-binding and oligomerization domain-like receptor, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome and caspase-1 enzyme activity.

The daily intake of total legumes of Japanese people in 2019 was 60.6 g. The Ministry of Health, Labour and Welfare in Japan has recommended an intake of legumes of 100 g or more per day [6]. Higher intake of legumes [49, 50], non-soy legumes [50], soy foods [43, 50], legumes and nuts [20] were associated with decreased gout risk, respectively. This result suggests that increase in daily intake of legumes and soy foods in Japanese people is essential for the prevention of gout. Considering the result from the balance of the caloric ratio of protein, fat and carbohydrate in Japanese people in 2019 (protein: 15.1%, fat: 28.6%, and carbohydrates: 56.3%) and the daily dietary fiber, vitamin A, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, pantothenic acid, folate, potassium, magnesium, phosphorus, zinc intake, it seems better to increase the daily intake of legumes for the prevention of gout.

### 3.4. Seeds and Nuts

The intake of seeds and nuts of Japanese people in 2019 was the same as that in 2016 (2016: 2.5 g/day; 2019: 2.5 g/day). The daily intake of seeds and nuts of Japanese people was positively correlated with the number of gout patients in 1986-2019 ( $r=0.774$ ,  $p=0.00313$ ).

The intake of seeds and nuts of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were the same as those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 2.7 g/day; 2019: 2.7 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 2.6 g/day; 2019: 2.6 g/day; Japanese adult women (aged  $\geq 20$  years) Japanese adult women (aged  $\geq 20$  years): 2016: 2.8 g/day; 2019: 2.8 g/day]. In Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), or Japanese adult women (aged  $\geq 20$  years), there was no significant correlation between the daily intake of seeds and nuts and the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq 20$  years):  $r=0.680$ ,  $p=0.137$ ; Japanese adult men (aged  $\geq 20$  years):  $r=0.645$ ,  $p=0.167$ ; Japanese adult women (aged  $\geq 20$  years):  $r=-0.507$ ,  $p=0.305$ ].

Almonds, hazelnuts, pecan nuts, and pistachio nuts contain polyphenols that suppress uric acid (UA) production by inhibition of xanthine oxidase activity [34]. Generally speaking, nuts are rich in unsaturated fatty acids, plant protein, dietary fiber, antioxidant vitamins (e.g., folate, vitamin E),

minerals (e.g., magnesium and potassium), and phytochemicals (e.g., flavonoids) [35].

In an epidemiological study, increased intake of peanuts was associated with decreased serum uric acid (SUA) concentrations [18]. It seems important to actively choose above nuts in order to maintain SUA concentration at normal levels in healthy people. In a cross-sectional study, increased intake of walnuts or pine nuts was inversely associated with decreased hyperuricemia risk [51]; that is to say, a cross-sectional study using the data from the Health Check Program of Undergraduates collected for 6,862 males and 7,194 females (aged 15-25 years) in China showed that increased intake of walnuts was inversely associated with decreased the risk of hyperuricemia [serum uric acid (SUA) level  $\geq 7.0$  mg/dL (416.4  $\mu\text{mol/L}$ ) in males and  $\geq 6.0$  mg/dL (356.9  $\mu\text{mol/L}$ ) in females] and the highest quartile of walnut intake was 22.0% reduced risk of hyperuricemia compared with the lowest quartile of walnut intake in adjusted model, which is adjusted for dietary information (intakes of energy, carbohydrate, protein, fat, candies, meat, soup and seafood) and physical activity [OR = 0.78, (95% confidence interval, 0.58-1.05),  $p$  for trend = 0.047] [51]. The highest quartile of pine nuts intake was also 29.0% reduced risk of hyperuricemia compared with the lowest quartile of pine nut intake in adjusted model [OR = 0.71, (95% confidence interval, 0.51-0.98),  $p$  for trend = 0.061] [51]. No significant association was found between hyperuricemia risk and intake of peanuts, melon seeds, cashews, or total nuts [51].

Celery seed aqueous extract and celery seed oil extract suppressed the elevation of SUA, xanthine oxidase, reactive oxygen species (ROS) levels and increased serum superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in mice with hyperuricemia induced by potassium oxonate and yeast extract [52]. Superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are antioxidant enzyme [53]; that is to say, superoxide dismutase (SOD) catalyzes the rapid conversion of  $\text{O}_2^-$  and  $\cdot\text{O}_2$  to  $\text{H}_2\text{O}_2$ , following which  $\text{H}_2\text{O}_2$  can be converted to  $\text{H}_2\text{O}$  by glutathione peroxidase (GSH-Px) catalysis inside cells. Celery seed aqueous extract and celery seed oil extract suppressed the elevation of serum interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which are pro-inflammatory cytokines, levels and the ankle joint swelling rate and increased serum interleukin-10 (IL-10), which is anti-inflammatory cytokines, levels in rats with acute gouty arthritis induced by intra-articular injection of monosodium urate crystals [52]. These results examined by Li et al. [52] suggest that celery seed extracts may have anti-gout properties, partially through anti-inflammatory and antioxidative effects.

Intake of seeds and nuts of Japanese people in 2019 was 2.5 g. Saag and Choi [54] have recommended that intake of nuts and legumes should be 1 to 3 servings. The Ministry of Health, Labour and Welfare in Japan has recommended an intake of legumes of 100 g or more per day [6]. Schlesinger [55] has recommended intake of nuts 1-3 times per day (13-15 g per ounce). Stuetz et al. [56] have stated that the recommended nut

intake is less than 25g/day. It is considered that intake of seeds and nuts of Japanese people was too low. Higher intake of legumes and nuts was associated with decreased gout risk [20]. Considering the result from the balance of the caloric ratio of protein, fat and carbohydrate in Japanese people in 2019 (protein: 15.1%, fat: 28.6%, and carbohydrates: 56.3%) and the daily dietary fiber, vitamin A, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, pantothenic acid, folate, potassium, magnesium, phosphorus, zinc intake, it seems that increase in daily intake of seeds and nuts is needed for the prevention of gout.

### 3.5. Fruit and Vegetables

Fruit and vegetables are a rich source of carbohydrates, dietary fiber, vitamin A ( $\beta$ -carotene), vitamin C, vitamin E, potassium, and magnesium [15, 16, 57]. Other important constituents are phytochemicals such as antioxidants, is flavones, flavonoids, and polyphenols [57]. Saura-Calixto and Goñi [57] have stated that the intake of antioxidant (polyphenols and carotenoids) and nonantioxidant (phytosterols) bioactive compounds and dietary fiber have been strongly linked with the high consumption of fruit and vegetables and may have a significant role in health.

#### 3.5.1. Fruit

The daily total fruit intake of Japanese people in 2019 was lower compared to that in 2016 (2016: 98.9 g/day; 2019: 96.4 g/day). The daily intake of total fruit of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.876$ ,  $p = 0.000183$ ).

The daily intake of total fruit of Japanese adult people (aged  $\geq 20$  years), Japanese adult men (aged  $\geq 20$  years), and Japanese adult women (aged  $\geq 20$  years) in 2019 were lower compared to those in 2016, respectively [Japanese adult people (aged  $\geq 20$  years): 2016: 102.2 g/day; 2019: 100.2 g/day; Japanese adult men (aged  $\geq 20$  years): 2016: 90.9 g/day; 2019: 87.5 g/day; Japanese adult women (aged  $\geq 20$  years): 2016: 111.7 g/day; 2019: 111.2 g/day]. In Japanese adult people (aged  $\geq 20$  years) or Japanese adult men (aged  $\geq 20$  years), there was no significant correlation between the daily intake of total fruit and the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq 20$  years):  $r = -0.703$ ,  $p = 0.119$ ; Japanese adult men (aged  $\geq 20$  years):  $r = -0.694$ ,  $p = 0.126$ ]. Whereas the daily intake of total fruit of Japanese adult women (aged  $\geq 20$  years) was positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r = 0.955$ ,  $p = 0.000298$ ). This result suggests that the correlation of daily fruit intake with the number of gout patients varies with gender and is stronger in adult women than in adult men.

The daily intake of citruses, bananas, strawberries of Japanese people in 2019 were higher compared to those in 2016, respectively (citruses: 2016: 19.1 g/day; 2019: 19.5 g/day; bananas: 2016: 15.7 g/day; 2019: 16.1 g/day; strawberries: 2016: 0.1 g/day; 2019: 0.3 g/day). The daily intake of citruses and strawberries of Japanese people were negatively correlated with the number of gout patients in 1986-2019, respectively (citruses:  $r = -0.929$ ,  $p = 0.0000123$ ;

strawberries:  $r = -0.721$ ,  $p = 0.00810$ ). The daily intake of bananas of Japanese people was positively correlated with the number of gout patients in 1986-2019 (bananas:  $r = 0.962$ ,  $p = 0.000000595$ ).

The daily apple intake of Japanese people in 2019 was lower compared to that in 2016 (2016: 20.0 g/day; 2019: 17.7 g/day). The daily apple intake of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.938$ ,  $p = 0.0000066$ ).

The daily intake of other fruit of Japanese people in 2019 was higher compared to that in 2016 (2016: 32.1 g/day; 2019: 32.8 g/day). The daily intake of other fruit of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.720$ ,  $p = 0.00821$ ).

The daily intake of fruit juices of Japanese people in 2019 was lower compared to that in 2016 (2016: 10.7 g/day; 2019: 8.7 g/day). The daily intake of fruit juices of Japanese people was negatively correlated with the number of gout patients in 1986-2019 ( $r = -0.732$ ,  $p = 0.00683$ ).

Blackberries, black currants, black elderberries, European cranberries, apricots, grapes, fox grapes, nectarines, peaches, plums, red raspberries, sour cherries, strawberries, sweet cherries, quinces, loquats, apples, pears, and custard apples contain polyphenols that suppress uric acid (UA) production by inhibition of xanthine oxidase activity [34]. It seems important to actively choose above fruit in order to maintain serum uric acid (SUA) concentration at normal levels in healthy people.

Tart cherry (*prunus cerasus*) juice decreased SUA concentrations in rats with hyperuricemia by inhibiting the xanthine oxidase/xanthine oxidoreductase activity in the liver [58]. In clinical trials, cherries and cherry products [59-61], *Terminalia chebula* or *Terminalia bellerica* [62] decreased SUA concentrations. In epidemiological studies, increased intake of fruit [19, 36, 63] and noncitrus fruit [18] was associated with decreased SUA concentrations. Eating 280 g of cherries in healthy volunteers reduced plasma UA (PUA) concentration by 0.031 mmol/L over a 5-h period [60]. Cherries contain vitamins A, C, E, and phenolic compounds (e.g., anthocyanins and quercetin) and have antioxidant and anti-inflammatory properties [64, 65]. In a case-crossover study, cherry intake over a two-day period was associated with a 35% lower risk of recurrent gout attacks compared with no cherry intake, and cherry extract intake over a two-day period was associated with a 45% lower risk of recurrent gout attacks compared with no cherry extract intake [66]. Clinical case reports of three patients with gout showed that consumption of 227 g of cherry products daily for 3 days to 3 months reduced PUA to normal levels and alleviated attacks of gouty arthritis [59]. A systematic review reported by Chen et al. [67] has revealed that cherry intake is associated with decreased risk of gout attacks and consumption of tart cherry juice decrease SUA concentrations.

Kelley et al. [68] assessed the effect of consuming Bing sweet cherries on multiple biomarkers for several chronic inflammatory diseases in healthy humans with modestly

elevated plasma C-reactive protein (CRP; range, 1-14 mg/L; mean, 3.5 mg/L; normal < 1.0 mg/L) for 28 days. Cherry consumption (280g/day) significantly decreased plasma C-reactive protein (CRP) compared with the baseline (levels before the treatment). Collins et al. [65] have stated that anthocyanins are linked to the inhibition of interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-8 (IL-8), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and may have the ability to reduce recurrent gout flares. A retrospective study demonstrated that regular use of cherry juice concentrate led to a significant reduction in flares over a minimum period of 4 months [69]. The antioxidant and anti-inflammatory effects of cherry juice concentrate inhibited secretion of interleukin-1 $\beta$  (IL-1 $\beta$ ) by monosodium urate (MSU)-stimulated monocytes in *in vitro* study [69]. The guidelines recommended encourage intake of cherries for patients with gout [70].

There is a relatively small amount of fructose in an individual fruit and the presence of other nutrients in the fruit (e.g., fiber, vitamin C, and many important secondary metabolites) may slow fructose absorption or partially block the fructose metabolic effect of UA formation and inhibit superoxide generation [71].

In a randomized, controlled, crossover trial in healthy mildly hypercholesterolemic adults for 8 weeks, Koutsos et al. [72] have shown that daily intake of two whole apples (340 g/day) decreased serum total cholesterol, LDL cholesterol, triacylglycerol, and plasma intracellular cell adhesion molecule-1 concentrations, and increased SUA concentrations (whole apples: 341.4  $\mu$ mol/L; a sugar-matched apple control beverage: 330.0  $\mu$ mol/L) compared with a sugar-matched apple control beverage. However, SUA concentrations in healthy mildly hypercholesterolemic individuals consuming apples was 341.4  $\mu$ mol/L and was within the normal physiological range (standard range) of SUA concentrations [SUA concentration 3.4 < 7.0 mg/dL (202.3 < 416.4  $\mu$ mol/L) in males and 2.4 < 6.0 mg/dL (142.8 < 356.9  $\mu$ mol/L) in females]. In a randomized crossover trials in young Chinese individuals, postprandial SUA concentrations at 120 min of participants consuming apple returned baseline (before consuming apple) [73]. Uric acid (UA) is the primary antioxidant in human plasma and accounts for more than 60% of the capacity to scavenge free oxidative radicals in serum [74]. UA at normal levels is associated with scavenging free radicals, thus, UA is an important endogenous antioxidant at physiologically appropriate concentrations [71]. Therefore, it is speculated that circulating UA acts an antioxidant in human plasma in both healthy mildly hypercholesterolemic individuals consuming apples and a sugar-matched apple control beverage.

The Dietary Guidelines for Americans established by the U.S. Department of Agriculture recommended that adult population (aged  $\geq$  19 years) eat fruit of 1.5 to 2.5 servings (i.e., cup or ounce equivalents) per day, depending on an individual's caloric intake [75]. The Dietary guidelines for Japanese (the Japanese food guide spinning top) has recommended that daily consumption of fruit must be 2-3 servings (approximately 200-300 g), depending on an

individual's caloric intake [33]. The daily intake of fruit of Japanese people in 2019 (96.4 g/day) was less than the daily recommended fruit intake by the U.S. Department of Agriculture [75] and the Ministry of Health, Labour and Welfare in Japan [6]. Higher intake of fruit [63], less sugary fruit [20], cherries [66] were associated with decreased gout risk, respectively. Considering the daily dietary fiber, vitamin A, vitamin B<sub>6</sub>, vitamin C, folate, potassium, magnesium, phosphorus, iron intake, it seems better to increase the daily intake of fruit (especially less sugary fruit and cherries) for the prevention of gout.

### 3.5.2. Vegetables

The daily intake of total vegetables of Japanese people in 2019 was higher compared to that in 2016 (2016: 265.9 g/day; 2019: 269.8 g/day). The daily intake of total vegetables of Japanese people did not show a significant correlation with the number of gout patients in 1986-2019 ( $r=0.339$ ,  $p=0.281$ ).

The daily intake of total vegetables of Japanese adult people (aged  $\geq$  20 years), Japanese adult men (aged  $\geq$  20 years), and Japanese adult women (aged  $\geq$  20 years) in 2019 were higher compared to those in 2016, respectively [Japanese adult people (aged  $\geq$  20 years): 2016: 276.5 g/day; 2019: 280.5 g/day; Japanese adult men (aged  $\geq$  20 years): 2016: 283.7 g/day; 2019: 288.3 g/day; Japanese adult women (aged  $\geq$  20 years): 2016: 270.5 g/day; 2019: 273.6 g/day]. In Japanese adult people (aged  $\geq$  20 years), Japanese adult men (aged  $\geq$  20 years), or Japanese adult women (aged  $\geq$  20 years), there was no significant correlation between the daily intake of total vegetables and the number of gout patients in 2004-2019 [Japanese adult people (aged  $\geq$  20 years):  $r=0.0140$ ,  $p=0.979$ ; Japanese adult men (aged  $\geq$  20 years):  $r=0.0141$ ,  $p=0.979$ ; Japanese adult women (aged  $\geq$  20 years):  $r=-0.385$ ,  $p=0.452$ ].

The daily intake of green and yellow vegetables, carrots, green peppers, onions, tomatoes, radishes, pickles of Japanese people in 2019 were lower compared to those in 2016, respectively (green and yellow vegetables: 2016: 84.4 g; 2019: 81.8 g/day; carrots: 2016: 19.8 g; 2019: 19.5 g/day; green peppers: 2016: 5.1 g; 2019: 4.7 g/day; onions: 2016: 34.4 g; 2019: 32.1 g/day; tomatoes: 2016: 17.3 g; 2019: 16.2 g/day; radishes: 2016: 25.8 g; 2019: 25.7 g/day; pickles: 2016: 8.7 g; 2019: 8.1 g/day). The daily intake of cabbages, Chinese cabbages, and spinach of Japanese people in 2019 were higher compared to those in 2016, respectively (cabbages: 2016: 29.0 g; 2019: 31.4 g/day; Chinese cabbages: 2016: 15.6 g; 2019: 23.5 g/day; spinach: 2016: 8.3 g; 2019: 9.0 g/day). The daily intake of cucumbers of Japanese people in 2019 was the same as that in 2016 (cucumbers: 2016: 9.0 g; 2019: 9.0 g/day). The daily intake of green and yellow vegetables, carrots, and Chinese cabbages of Japanese people did not show a significant correlation with the number of gout patients in 1986-2019 (green and yellow vegetables:  $r=0.228$ ,  $p=0.476$ ; carrots:  $r=0.459$ ,  $p=0.134$ ; Chinese cabbages:  $r=-0.395$ ,  $p=0.204$ ). The daily intake of green peppers of Japanese people tended to be positively correlated with the number of gout patients in 1986-2019 (green peppers:  $r=0.566$ ,  $p=0.0551$ ). The daily intake of onions, tomatoes, and

cabbages of Japanese people was positively correlated with the number of gout patients in 1986-2019 (onions:  $r=0.941$ ,  $p=0.00000528$ ; tomatoes:  $r=0.707$ ,  $p=0.0102$ ; cabbages:  $r=0.804$ ,  $p=0.00163$ ). The daily intake of radishes, spinach, cucumbers, and pickles of Japanese people was negatively correlated with the number of gout patients in 1986-2019 (radishes:  $r= -0.892$ ,  $p=0.0000953$ ; spinach:  $r= -0.803$ ,  $p=0.00165$ ; cucumbers:  $r= -0.836$ ,  $p=0.000696$ ; pickles:  $r= -0.975$ ,  $p=0.00000684$ ).

The daily intake of tomatoes of Japanese people in 2019 was 16.2 g. The daily intake of tomatoes was positively correlated with the number of gout patients in 1986-2019 ( $r=0.707$ ,  $p=0.0102$ ). In epidemiological studies, increased intake of tomatoes and tomato juice were associated with increased serum uric acid (SUA) concentrations, respectively [18, 76]. However, a prospective clinical trial in 35 young women showed that raw ripe tomato intake (90 g) before lunch for 4 weeks has been significantly associated with a decrease in SUA concentration with 0.16 mg/dL [77]. In a crossover study, consumption of tomato sauce (150 g) increased plasma UA (PUA) concentration by 46  $\mu\text{mol/L}$  at 48 h compared with the baseline (before consuming tomato sauce) [78]. The intervention study showed no significant difference in PUA or SUA concentrations after consumption of tomato sauce [79], tomato extract [80] or tomato juice [81]. These differences in outcomes may be attributed to the amount of tomato intake per week and the method of tomato preparation, which can influence the contents of chemicals that affect SUA levels.

The daily intake of carrots of Japanese people in 2019 was 19.5 g. In an epidemiological study, increased intake of carrots was associated with decreased SUA concentrations [30]. The daily intake of carrots did not show a significant correlation with the number of gout patients in 1986-2019 ( $r=0.459$ ,  $p=0.134$ ). Conscious intake of carrots seems to be important for the prevention of gout.

Spinach intake (294 g) increased SUA concentrations in elderly women [82]. The daily intake of spinach was negatively correlated with the number of gout patients in 1986-2019 ( $r= -0.803$ ,  $p=0.00165$ ). The daily intake of spinach of Japanese people in 2019 was 9.0 g. It seems better to increase the daily spinach intake slightly but must not take in excessive.

In an epidemiological study, increased intake of bamboo shoots was associated with increased SUA concentrations [30]. Though bamboo shoots contain high in dietary fiber, protein, and potassium (dietary fiber: 3.3 g/100 g; protein: 3.5 g/100 g; potassium: 470 mg/100 g) [15], they are purine-rich foods (30.8-63.3 mg/100 g) [83]. The Ministry of Health, Labour and Welfare in Japan has not investigated the daily intake of bamboo shoots.

Intake of purine-rich vegetables (peas, beans, lentils, cauliflowers, and spinach) was not associated with PUA concentrations in a population-based case-control study conducted in Scotland (1999-2006) [84]. In epidemiological studies, there was no association between intake of purine-rich vegetables (peas, beans, lentils, spinach, mushrooms, and cauliflowers) and hyperuricemia risk [43] or gout risk [38, 49].

On the other hand, higher intake of high-purine vegetables was associated with decreased gout risk [43].

Black olives, broad bean pods, broccoli, and globe artichokes contain polyphenols that suppress UA production by inhibition of xanthine oxidase activity [34]. It seems important to choose these vegetables in order to maintain SUA concentrations at normal levels in healthy people.

Increased intake of vegetables was associated with decreased hyperuricemia risk [31, 85]. This phenomenon can probably explain that increased intake of vegetable protein [49] and dietary fiber [21] protect against risk of gout through decreased hyperuricemia risk.

Garlic (*Allium sativum*) (raw garlic, dried garlic, garlic oil or a prepared commercial product) has been widely used for gout and rheumatism [86].

Vegetables contain many nutrients, including folate, antioxidants, and dietary fiber, which contribute to reducing the risk of chronic disease [87]. The guidelines recommended encourage intake of vegetables for patients with gout [70, 88].

The Dietary Guidelines for Americans established by the U.S. Department of Agriculture recommended that adult population (aged  $\geq 19$  years) eat vegetables of 2.5 to 4 servings (i.e., cup or ounce equivalents) per day, depending on an individual's caloric intake [75]. The Ministry of Health, Labour and Welfare in Japan has recommended that daily consumption of vegetables must be 350 g or more (green-yellow vegetables, 120 g or more) [6]. The daily intake of vegetables of Japanese people in 2019 (269.8 g/day) was less than the daily recommended vegetables intake by the Ministry of Health, Labour and Welfare in Japan [6]. Considering the daily dietary fiber, vitamin A, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, vitamin C, pantothenic acid, folate, calcium, potassium, magnesium, phosphorus, iron intake, it seems better to increase the daily intake of vegetables for the prevention of gout.

### 3.5.3. Fruit and Vegetables

In epidemiological studies, increased intake of fruit and vegetables was associated with decreased serum uric acid (SUA) concentrations [30], hyperuricemia risk [89], and gout risk [21, 45].

The World Health Organization [90] has recommended increasing fruit and vegetables (to 400-500 g daily) for the prevention of cardiovascular disease (CVD) in healthy adults. The World Health Organization [91] has also stated that eating at least 400 g, or five portions, of fruit and vegetables per day reduces the risk of noncommunicable diseases (NCDs), including such as diabetes, heart disease, stroke and cancer, and helps to ensure an adequate daily intake of dietary fiber. The Australian government [92] has proposed that the minimum recommended number of serves of fruit per day is 2 for people (aged  $\geq 9$  years) and the minimum recommended number of serves of vegetables per day is 5-6 for people [males (aged 19-50 years): 6; males (aged 51-70 years): 5.5; males (aged  $> 70$  years): 5; females (aged  $\geq 12$  years): 5]. The daily intake of total fruit and vegetables of Japanese people in 2019 (366.2 g/day) was less than the daily recommended fruit

intake by the World Health Organization [90, 91] and the Australian government [92]. Increase in daily intake of fruit and vegetables of Japanese people seems to be essential for the prevention of gout through reduced SUA concentrations and decreased hyperuricemia risk.

## 4. Conclusion

The number of patients with gout has been increasing in Japan [1, 2, 4]. The daily intake of mushrooms, total legumes, and total vegetables of Japanese people in 2019 were higher compared to those in 2016, respectively. Whereas the daily intake of total grains, total potatoes, seaweed, and total fruit of Japanese people in 2019 were lower compared to those in 2016, respectively. The intake of seeds and nuts of Japanese people in 2019 was the same as that in 2016. The significance of the correlation between the number of gout patients and food intake in 1986-2016 were also observed that in 1986-2019. Modification of food intake for the prevention of gout in Japanese people in 2019 is suggested as follows: limiting intake of meat; limiting alcohol beverage consumption; limiting or decreasing intake of salt, oils and fats and confectioneries; avoidance of excessive intake of sugar-sweetened beverages and sugary foods including desserts and sweets; increasing the intake of fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), milk and dairy products (particularly low-fat dairy products), mushrooms, seaweed, legumes, seeds and nuts, fruit, vegetables, which contain rich in carbohydrate (particularly dietary fiber), vitamin A, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, vitamin C, calcium, potassium, magnesium, zinc, and polyphenol.

In the previous report [14], the author suggests what foods should be chosen in proper diet or dietary pattern for the prevention of gout in Japanese people in 2016 referencing the results of clinical research reported; that is to say, avoidance of purine-rich diet, uric acid-prone dietary pattern, animal foods dietary pattern, and the Western diet; encourage high fruit and soybean products diet, less protein-rich and more vegetable/fruit-rich materials diet, soybean products and fruit (high in soybean products, fruit, vegetables and starchy tubers) dietary pattern, polyphenol-rich dietary pattern (e.g., the Mediterranean diet), higher adherence to the Mediterranean diet (the traditional Mediterranean diet) and its dietary pattern, higher adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and its dietary pattern, and vegetarian diet (plant-based diet).

Referring to or adopting dietary patterns such as the Mediterranean diet, the DASH diet, and vegetarian diet (plant-based diet), the author wishes to emphasize that Japanese people in 2019 should eat a diet in which consciously selects foods rich in carbohydrate (particularly dietary fiber), vitamin A, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, vitamin C, calcium, potassium, magnesium, zinc, and polyphenol [11, 12, 14-16, 34]. To properly choose and consume the following foods that contain the above-mentioned nutrients may play a helpful role in the

prevention of gout for Japanese people; that is to say, meat (poultry), seafood (salmon, sardines, anchovy, tuna, trout, mackerel), seeds and nuts (pumpkin seeds, chia seeds, sunflower seeds, almonds, sesame seeds, pistachio nuts, hazelnuts, peanuts, pecan nuts, walnuts, flaxseeds, pine nuts, chia seeds), grains (white rice, buckwheat, bread), whole grains (brown rice, brown cereal, fortified ready-to-eat cereals, oatmeal), potatoes (konjac), mushrooms (maitake mushrooms, shiitake mushrooms), legumes (black-eyed peas, common beans, green peas, kidney beans, soybeans, chickpeas, lentils), seaweed, fruit (acerolas, apples, apricots, avocados, bananas, blackberries, black currants, black elderberries, cherries, European cranberries, kiwi fruits, mangos, oranges, papayas, raisins, red raspberries, strawberries, watermelons), vegetables (asparaguses, black olives, broad bean pods, broccoli, curly kale, garlic, brussels sprouts, carrots, globe artichokes, Jew's mallow, lettuces, mustard greens, okra, onions, spinach, carrots, parsley, tomatoes, peppers, radishes, cucumbers, zucchinis, pumpkins, leafy greens, Chinese cabbages, pickles), soy products (soy milk, tofu, soy meat), dairy products (low-fat milk, low-fat yogurt), eggs, spices (capers, caraways, cloves, cumin), oils (olive oil), coffee and tea (black tea, green tea), and chocolates and cocoa powders [15, 16]. Furthermore, it should consider to reduce the intake of one serving of high-phosphorus foods (e.g., yogurt, milk, cheese, salmon, scallops, sardines, flying fish, dried squid, chicken, lentils, cashew nuts, potatoes [15, 16]) and high-copper foods (e.g., beef liver, oysters, baking chocolate, potatoes, shiitake mushrooms, cashew nuts, crab, sunflower seeds, turkey giblets, squid, mantis shrimp, sakura shrimp, octopus [15, 16]) and decrease intakes of animal fat (e.g., beef, beef tallow, pork, margarine, butter [15]), saturated fatty acids (e.g., coconut oil, coconut powder, butter, shortening, beef, beef tallow, pork, margarine, whipped cream, cheese [15]), cholesterol (e.g., eggs, herring roe, dried squid, anchovy, anchovy liver, foie gras, sakura shrimp, dried shrimp, sand lance, caviar, lamprey, salmon roe [15]), and salt and limit the intake of one serving of purine-rich foods (e.g., beef, pork, lamb, organ meats, and meat extracts, seafood, yeast extracts, peas, beans, lentils, asparaguses, cauliflowers, spinach, mushrooms, bamboo shoots, nori, wakame, soup stock, oyster sauce, consommé, Chinese soup) [11, 12, 14, 83, 93]. Based on the view for modification of food intake for the prevention of gout in Japanese people in 2019, choosing and eating the above foods in the Mediterranean diet, the DASH diet, and vegetarian diet (plant-based diet) may play a helpful role in the prevention of gout in Japanese people.

The guidelines for the management of gout highlight the importance of limiting or avoiding the intake of purines [93, 94], purine-rich foods (meat, seafood, organ meats, yeast extract) [70, 88], high-fructose [94], sugar-sweetened drinks [95], desserts [88], table sugar [88], sauces and gravies [88], alcohol (especially beer and spirits) [93-95], and heavy meals [95]. The Centers for Disease Control and Prevention (CDC) [96] has recommended that avoid foods that may trigger a gout flare, including foods high in purines (like a diet rich in red meat, organ meat, and seafood), and limit alcohol intake

(particularly beer and hard liquor). It is speculated that recommendations for nutrition and diet in the above guidelines and CDC apply to the prevention of gout. Furthermore, the guidelines have stated that important lifestyle changes in gout patients include weight control [88, 93-95], physical activity [88, 93, 95], smoking cessation [88], and proper hydration [88, 93]. The important points of behavior for the prevention and management of gout in the general population (especially adults) is suggested as follows: limiting intake of foods high in purines (e.g., meat, seafood and organ meats); limiting or decreasing alcohol beverage consumption; limiting or decreasing intake of salt, oils and fats, confectioneries (sugary foods including desserts and sweets), and sugar-sweetened beverages; recognizing the intake of fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), eggs, milk and dairy products (particularly low-fat dairy products), mushrooms, seaweed, legumes, seeds and nuts, fruit, vegetables, coffee, and tea; weight management including proper calorie intake; weight loss for overweight and obese people; adequate physical exercise (e.g., moderate intensity aerobic exercise for 30 minutes on 5-7 days per week, vigorous intensity aerobic physical activity for 75 minutes per week); smoking cessation; and maintenance of good hydration. The above behavior may be a beneficial strategy both for prevention and management of gout in the general population (especially adults).

## Conflict of Interest Statement

The author declares that there are no conflicts of interest.

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