American Journal of Health Research
2022; 10(3): 83-106
http://www.sciencepublishinggroup.com/j/ajhr
doi: 10.11648/j.ajhr.20221003.15
ISSN: 2330-8788 (Print); ISSN: 2330-8796 (Online)

Modification of Macronutrient Intake for Prevention of Gout in Japanese People in 2019: 2022 Update

Takashi Koguchi

Department of Human Education, Kokugakuin Tochigi Junior College, Tochigi, Japan

Email address:
echo130@nifty.com

To cite this article:
Takashi Koguchi. Modification of Macronutrient Intake for Prevention of Gout in Japanese People in 2019: 2022 Update. *American Journal of Health Research*. Vol. 10, No. 3, 2022, pp. 83-106. doi: 10.11648/j.ajhr.20221003.15

Received: May 10, 2022; **Accepted**: May 27, 2022; **Published**: May 31, 2022

Abstract: The prevalence of gout in Japan has increased markedly since the 1960s because of the westernization of the Japanese diet from 1955. A previous report showed modification of dietary habits for the prevention of gout in Japanese people through the trends in macronutrient intakes of Japanese people in 1946-2016. The aim of this article is to suggest what macronutrient 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 macronutrients. Macronutrient intake of Japanese people in 2019 were compared with those in 2016. The relationship between the number of gout patients and macronutrient intake in Japanese people was examined. The number of gout patients of Japanese people in 2019 was higher compared to that in 2016 (2016: 1.105 million; 2019: 1.254 million). The mean ratio of energy intake from protein in total energy intake (Protein/Energy), the mean ratio of energy intake from fat in total energy intake (Fat/Energy), the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) and the daily intake of energy, dietary fiber, total protein, animal protein, vegetable protein, total fat, animal fat, vegetable fat, saturated fatty acids, polyunsaturated fatty acids (n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids), and cholesterol of Japanese people in 2019 were higher compared to those in 2016, respectively. Whereas the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) and the daily intake of carbohydrate were lower compared to those in 2016, respectively. Fat/Energy and Saturated fatty acids/Energy were positively correlated with the number of gout patients, respectively. Whereas Protein/Energy and the daily intake of energy, total carbohydrate, total protein, animal protein, vegetable protein, and vegetable fat were negatively correlated with the number of gout patients, respectively. Modification of macronutrient intake for the prevention of gout in Japanese people (especially adults) 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, and cholesterol; increase intake of carbohydrate (particularly dietary fiber).

Keywords: Carbohydrate, Fat, Gout, Hyperuricemia, Protein, Saturated Fatty Acids, Uric Acid

1. Introduction

Gout is the most common form of inflammatory arthritis, and it is characterized by the deposition of monosodium urate (MSU) crystals that form in the presence of increased uric acid (UA) concentrations [1, 2]. There is a strong association between serum uric acid (SUA) concentration and the risk of developing gout [3, 4]. A high SUA concentration (hyperuricemia) is frequently associated with gout [5]. Though hyperuricemia is a strong predictor of incident gout but not all patients with asymptomatic hyperuricemia will develop gout [6], management of SUA concentrations is important for the prevention and suppression of hyperuricemia and/or gout.

The global burden of gout is substantial and seems to have been increasing in many parts of the world including Japan over the past 50 years [7-10]. In Japan, most of gout patients are adults [11]. The number of gout patients was higher in men than in women [8, 11-18].

The prevalence of gout in Japan has increased markedly since the 1960s [7, 11-13, 19]. The Japanese economy revived to pre-World War II levels around 1955 and the eating habits in the

1960s became stable [20]. The menu of Japanese food has been rapidly expanded with a variety of dishes due to the westernization of meals from 1955 to 1965 [20]. One of the factors of the increase in the prevalence of gout is thought to be due to the westernization of the Japanese diet from 1955 [19, 20]. For example, the introduction of the Western lifestyle to Japanese people, such as a diet containing greater amounts of meat and saturated fatty acids, has been associated with the increases in SUA levels and the incidence of hyperuricemia [21]. The Japanese Society of Gout and Uric & Nucleic Acids [14] has stated that an increase in hyperuricemia and gout patients is attributed to changes in environmental factors (e.g., purine intake, fructose intake, meat and visceral intake, alcohol consumption, strenuous muscle exercise, stress, obesity) rather than genetic factors.

To explore means of the dietary control for the prevention of gout, the author [19, 22, 23] previously suggested modification of nutrient intake for the prevention of gout in Japanese people in 2016 as described below: energy-providing nutrient balance (percentages of proteins, fats, and carbohydrates of total energy intake) should be within the range of the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG); reduce fat (especially animal fat) intake and maintain the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) within the range of the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG); replacement of saturated fatty acids with mono- and polyunsaturated ones (especially n-3 polyunsaturated fatty acids); avoidance of excessive intake of saturated fatty acids and cholesterol; limiting or decreasing salt intake; pay attention to sucrose and fructose intake; increase intake of dietary fiber, vitamin A, vitamin B_1, vitamin B_2, vitamin B_6, calcium, potassium, magnesium, and zinc; and maintenance of good hydration.

Recently, the Ministry of Health, Labour and Welfare in Japan [11, 24-28] has shown the number of gout patients and the intake of nutrients or foods in 2019. Macronutrient intake of Japanese people in 2019 were compared with those in 2016. This article shows the relationship between the number of gout patients and macronutrient intake in Japanese people and suggests modification of macronutrient intake for the prevention of gout in Japanese people referencing the results of clinical research through comparison with macronutrient intake in 2016 and 2019.

2. Methods

2.1. The Number of Gout Patients

The number of gout patients and serum uric acid (SUA) concentration was estimated in the Comprehensive Survey of Living Conditions performed by the Ministry of Health, Labour and Welfare in Japan (1986-2019)[11, 24, 25]. 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 [26, 27].

Data were extracted from the series of Japanese National Nutrition Surveys that have been carried out every year throughout Japan since 1946 [27]. 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) [26].

2.3. Dietary Reference Intakes for Japanese People

The Ministry of Health, Labour and Welfare in Japan [28] evaluated the intake of nutrients as described below: (1) the Estimated Average Requirement (EAR) indicates the amount that would meet the nutrient requirements of 50% of the population; (2) the Recommended Dietary Allowance (RDA) indicates the amount that would meet the nutrient requirement of most of the population; (3) the Adequate Intake (AI) indicates the amount adequate to maintain a certain level of nutritional status; (4) the Tolerable Upper Intake Level (UL) was determined for the purpose of avoiding adverse health effects due to excessive intake; and (5) the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) was developed for the purpose of prevention of lifestyle-related diseases.

Dietary Reference Intakes definitions set by Institute of Medicine of the National Academy of Sciences in the U.S. [29] are as follows: (1) the Estimated Average Requirement (EAR) indicates the average daily nutrient intake level that is estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group; (2) the Recommended Dietary Allowance (RDA) indicates the average daily nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97-98 percent) healthy individuals in a particular life stage and gender group; (3) the Adequate Intake (AI) indicates the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate; used when an RDA cannot be determined; and (4) the Tolerable Upper Intake Level (UL) indicates the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.

2.4. 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 [30] and the National Institutes of Health in the U.S. Department of Health & Human Services [31].

2.5. Statistical Analysis

The correlation efficient and the significance of the correlation between the number of gout patients and nutrient 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. Gout

3.1. Serum Uric Acid Concentration in Japanese Adult Men and Women

Physiological effects of uric acid (UA) have been reviewed in detail by Koguchi [19, 32], Doherty [33], and Lin et al. [34]. In brief, UA is a weak acid with a pKa of 5.75 and, at the physiological pH of 7.40 it exists mainly in the ionized form as urate [33]. UA can exert, along with its extracellular antioxidant activity, an intracellular prooxidant effect [34]. UA is the primary antioxidant in human plasma and accounts for more than 60% of the capacity to scavenge free oxidative radicals in the serum [35]. On the other hand, the antioxidant activity of UA is overcome by the pro-oxidant and proinflammatory effects of reactive oxygen species accumulation under ischemic conditions [36]. The serum uric acid (SUA) concentration is determined by the amount of production of UA and the efficiency of urinary UA excretion [37, 38]. The SUA concentrations have been associated with several inflammatory markers [neutrophil count, C-reactive protein (CRP), interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factor-alpha (TNF-α)] in individuals with or without hyperuricemia [SUA concentration > 7.5 mg/ dL (446.1 μmol/L) in men and > 6.2 mg/dL (368.8 μmol/L) in women] [39]. Mean SUA concentration in Japanese adult men (aged ≥ 20 years) and Japanese adult women (aged ≥ 20 years) in 2019 was 5.8 mg/dL (345.0 μmol/L) and 4.6 mg/dL (273.6 μmol/L), respectively [25]. Mean SUA concentration in Japanese adult men (aged ≥ 20 years) was 5.5 mg/dL (327.2 μmol/L) in 1989, 5.6 mg/dL (333.1 μmol/L) in 1990, 5.8 mg/dL (345.0 μmol/L) in 2010, 2011, 2013, 2014, 2017, 2018, and 2019 and 5.9 mg/dL (351.0 μmol/L) in 2015 [25]. Mean SUA concentration in Japanese adult women (aged ≥ 20 years) was 4.0 mg/dL (237.9 μmol/L) in 1989 and 1990, 4.4 mg/dL (261.7 μmol/L) in 2010, 2013 and 4.5 mg/dL (267.7 μmol/L) in 2011, 2014, 2015, 2017 and 4.6 mg/dL (273.6 μmol/L) in 2018 and 2019 [25]. Mean SUA concentration in Japanese adult men (aged ≥ 20 years) and Japanese adult women (aged ≥ 20 years) in 2019 were higher compared to those in 1989 and 1990, respectively. Mean SUA concentration in Japanese adult men (aged ≥ 20 years) in 1989-2019 were higher than those in Japanese adult women (aged ≥ 20 years), respectively.

3.2. Prevalence of Gout in Japan

The number of gout patients going to hospitals estimated based on the Comprehensive Survey of Living Conditions conducted by the Ministry of Health, Labour and Welfare in Japan was 0.255 million in 1986, 0.283 million in 1989, 0.338 million in 1992, 0.423 million in 1995, 0.590 million in 1998, 0.696 million in 2001, 0.874 million in 2004, 0.854 million in 2007, 0.957 million in 2010, 1.063 million in 2013, 1.105 million in 2016, and 1.254 million in 2019 [11, 24, 25] (Table 1). These values clearly indicate a steady increase in the number of patients with gout in Japan.

The number of gout patients in Japanese adult population (aged ≥ 20 years) in 2019 was estimated to be 1.253 million [24, 25]. The number of gout patients in Japanese adult men (aged ≥ 20 years) and Japanese adult women (aged ≥ 20 years) in 2019 were estimated to be 1.195 million and 0.059 million, respectively [24, 25].

Table 1. *Trends in estimated number of gout patients in Japan in 2004-2019.*

Disease/Year	2004	2007	2010	2013	2016	2019
	million					
Total	0.874	0.854	0.957	1.063	1.105	1.254
Men	0.790	0.779	0.904	0.993	1.048	1.195
Women	0.083	0.074	0.053	0.069	0.057	0.059

Adapted from the Ministry of Health, Labour and Welfare in Japan [11, 24, 25].

Table 2. *Trends in estimated number of gout patients by generations in Japan in 1998, 2016, and 2019.*

Year	1998	2016	2019
Years old	Thousand		
Total			
15-24	2	4	3
25-34	15	17	19
35-44	68	84	83
45-54	124	180	206
55-64	159	270	296
65-74	152	340	393
75-84	61	173	216
< 85	9	35	38
Men			
15-24	2	4	2
25-34	14	16	19
35-44	67	81	82
45-54	116	177	204
55-64	137	261	288
65-74	125	326	373
75-84	43	155	199
< 85	6	27	28
Women			
15-24	0	0	0
25-34	1	1	0
35-44	1	1	0
45-54	8	4	1
55-64	22	9	9
65-74	27	14	20
75-84	18	19	17
< 85	3	8	10

Adapted from the Ministry of Health, Labour and Welfare in Japan [11, 24, 25].

Association between dietary factor and serum uric acid (SUA) concentration, hyperuricemia or gout seems to be attributed to differences in participant ages [40], gender [41, 42], race [43], ethnic backgrounds [40], demographic factors [42], kidney urate clearance [42], and dietary habits [40]. Smith and Ebrahim [44] have stated that the observational findings are difficult to interpret because the results are affected by a variety of confounding factors, such as occupational and environmental exposures, diet, and supplement use. Clebak et al. [45] have stated that risk factors for gout include male sex, obesity, hypertension, alcohol consumption, diuretic use, a diet rich in meat and seafood, chronic kidney disease, a diet heavy in fructose-rich food and beverages, being a member of certain ethnic groups including Taiwanese, Pacific Islander, and New Zealand Maori, and living-income countries [45].

3.3. Relationship Between Prevalence of Gout and Age in Japan

The number of gout patients, especially men, increased with age in 1998-2019 [11, 24, 25] (Table 2). Compared to the number of gout patients (aged > 15 years) in 1998, the number of gout patients (aged > 15 years) in 2019 increased [11, 24, 25] (Table 2). Compared to the number of gout patients (aged > 45 years) in 2016, the number of gout patients (aged > 45 years) in 2019 increased [11, 24, 25] (Table 2).

Compared to the number of gout patients in men (aged > 25 years) in 1998 and 2016, the number of gout patients in men (aged > 25 years) in 2019 increased [11, 24, 25] (Table 2). Whereas compared to the number of gout patients in women (aged > 25 years) in 1998, the number of gout patients in women (aged > 25 years) in 2019 decreased [11, 24, 25] (Table 2). Compared to the number of gout patients (aged > 15 years) in 2016, the number of gout patients in women (aged 65-74 years, > 85 years) in 2019 increased and the number of gout patients in women (aged 25-54 years, 75-84 years) in 2019 decreased [11, 24, 25] (Table 2).

The number of gout patients in the young adulthood (aged < 35 years) in the middle adulthood (35-54 years) in 1998 increased 17-fold and 3.59-fold in 2019, approximately 20 years later, respectively [11, 24, 25]. The number of gout patients in the young-aged men (aged < 35 years) in the middle-aged men (35-54 years) in 1998 increased 17.9-fold and 3.61-fold in 2019, approximately 20 years later, respectively [11, 24, 25]. The number of gout patients in the middle-aged women (35-54 years) in 1998 increased 3.22-fold in 2019, approximately 20 years later [11, 24, 25].

4. Relationship Between the Number of Gout Patients and Macronutrient Intake

The results on the correlation between the number of gout patients and macronutrient intake in Japanese people are shown in Tables 3 and 4.

4.1. Energy

The daily energy intake of Japanese people in 2019 was lower compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, 1998, and 2001 and was higher compared to that in 2004, 2007, 2010, 2013, and 2016 (1960: 2096 kcal/day; 1965: 2184 kcal/day; 1975: 2188 kcal/day; 1986: 2075 kcal/day; 1989: 2061 kcal/day; 1992: 2058 kcal/day; 1995: 2042 kcal/day; 1998: 1979 kcal/day; 2001: 1954 kcal/day; 2004: 1902 kcal/day; 2007: 1898 kcal/day; 2010: 1849 kcal/day; 2013: 1873 kcal/day; 2016: 1865 kcal/day; 2019: 1903 kcal/day). The daily energy intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 1878 kcal/day; 2019: 1915 kcal/day). The daily energy intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 2097 kcal/day; 2019: 2141 kcal/day; women: 2016: 1684 kcal/day; 2019: 1717 kcal/day).

In Japanese adult men (aged ≥ 20 years), the daily energy intake of Japanese adult men (aged 20-29 years, ≥ 40 years) in 2019 were higher compared to those in 2016, respectively, whereas the daily energy intake of Japanese adult men (aged 30-39 years) in 2019 was lower compared to that in 2016. In Japanese adult women (aged ≥ 20 years), the daily energy intake of Japanese adult women (aged 40-49 years, ≥ 60 years) in 2019 were higher compared to those in 2016, respectively, whereas the daily energy intake of Japanese adult women (aged 20-39 years, 50-59 years) in 2019 were lower compared to those in 2016, respectively. The mean daily intake of energy for Japanese men (20-59 years) and women (20-49 years) in 2019 were 2081-2199 kcal/day and 1600-1729 kcal/day, respectively, and were below the Estimated Energy Requirements (EERs) of low physical activity levels established by the Ministry of Health, Labour and Welfare in Japan [physical activity levels: low: 2300 kcal/day; medium: 2650-2700 kcal/day; high: 3050 kcal/day among men; low: 1700-1750 kcal/day; medium: 2000-2050 kcal/day; high: 2300-2350 kcal/day among women] [28]. In Japanese men and women in 2019, the mean daily intake of energy for men (≥ 60 years) and women (≥ 50 years) were 2078-2177 kcal/day and 1695-1784 kcal/day, respectively, and were within the Estimated Energy Requirements (EERs) of medium physical activity levels, and below the Estimated Energy Requirements (EERs) of high physical activity levels established by the Ministry of Health, Labour and Welfare in Japan [physical activity levels: low: 1800-2200 kcal/day; medium: 2100-2600 kcal/day; high: 2750-2950 kcal/day among men; low: 1400-1650 kcal/day; medium: 1650-2190 kcal/day; high: 2100-2250 kcal/day among women] [28]. The Institute of Medicine of the National Academy of Sciences in the U.S. has established the Estimated Energy Requirements (EERs), which is defined as the average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, gender, weight, height, and a level of physical activity that is consistent with good health [29].

The daily consumption of energy was negatively correlated with the number of gout patients in 1986-2016 (r= -0.984,

p=0.0000000514) and in 1986-2019 (r= -0.938, p=0.0000065). The daily consumption of energy did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.610, p=0.275) and in 2004-2019 (r= -0.0133, p=0.980). The daily consumption of energy did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.610, p=0.275) and in 2004-2019 (r= -0.125, p=0.814). The daily consumption of energy did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.826, p=0.0847) and in 2004-2019 (r=0.599, p=0.209).

4.2. Carbohydrates

4.2.1. Carbohydrate

The daily carbohydrate intake of Japanese people in 2019 was lower compared to that in 1959, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 (1959: 405 g/day; 1965: 384 g/day; 1975: 337 g/day; 1986: 295 g/day; 1989: 290 g/day; 1992: 289 g/day; 1995: 280 g/day; 1998: 271 g/day; 2001: 274 g/day; 2004: 266 g/day; 2007: 264 g/day; 2010: 258 g/day; 2013: 259 g/day; 2016: 253 g/day; 2019: 248 g/day). The daily carbohydrate intake of Japanese adult population (aged ≥ 20 years) in 2019 was lower compared to that in 2016 (2016: 253.8 g/day; 2019: 248.7 g/day). The daily carbohydrate intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were lower compared to those in 2016, respectively (men: 2016: 281.1 g/day; 2019: 275.3 g/day; women: 2016: 231.0 g/day; 2019: 225.5 g/day). The Ministry of Health, Labour and Welfare in Japan [28] has not set the Recommended Dietary Allowances (RDAs) for the daily carbohydrate intake in Japanese people. The Recommended Dietary Allowances (RDAs) for carbohydrates (sugars and starches) in the U.S. population (aged ≥ 1 year) established by the Institute of Medicine of the National Academy of Sciences in the U.S. is 130 g/day [29].

The daily carbohydrate intake was negatively correlated with the number of gout patients in 1986-2016 (r= -0.978, p=0.00000215) and in 1986-2019 (r= -0.982, p=0.0000000144). The daily carbohydrate intake was negatively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.909, p=0.0327) and in 2004-2019 (r= -0.955, p=0.00301). The daily carbohydrate intake was negatively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.909, p=0.0323) and in 2004-2019 (r= -0.959, p=0.00249). The daily carbohydrate intake tended to be positively correlated with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.864, p=0.0590) and in 2004-2019 (r=0.788, p=0.0624). This result suggests that the correlation of daily carbohydrate intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women.

4.2.2. Fructose and Sugars

1. Fructose

The Ministry of Health, Labour and Welfare in Japan has not investigated the daily fructose intake of Japanese people.

In a randomized crossover trials in young Chinese individuals, fructose powder intake increased postprandial serum uric acid (SUA) concentrations at 30 min and 60 min compared with baseline (before consuming fructose powder) [46]. In a double-blinded, randomized, crossover trial in healthy young subjects, ingestion of a 75 g fructose increased SUA concentrations and the area under the curve (AUC) within 3 h (3h-AUC) of SUA concentrations when compared with the same amount of ingested glucose [47]. Emmerson [48] indicated that intake of fructose (250-290 g/day) increased SUA concentrations 8-41% compared to glucose in three healthy men. In a systematic review and meta-analysis of controlled feeding trials, high fructose intake (213-219 g/day) under hypercaloric feeding conditions (+35% excess energy) raised SUA concentrations in people with and without diabetes mellitus [49]. In epidemiological studies, increased fructose intake was associated with increased SUA concentrations [50, 51], hyperuricemia risk [50-53], and gout risk [33, 52, 54-57]. In a randomized crossover trial in healthy subjects, high-fructose corn syrup intake increased postprandial SUA concentrations at 60 min, 120 min, 180 min, and 300 min compared with sucrose intake [58]. Wang et al. [49] have stated that high fructose intake (213-219 g/day) under hypercaloric feeding conditions (+35% excess energy) leads to increased risk of hyperuricemia and gout.

Higher intake of foods high in fructose was associated with increased SUA concentrations [10, 50, 59-65], hyperuricemia risk [64, 66, 67], and gout risk [40, 67]. These results suggest that excessive intake of fructose and fructose-rich foods (e.g., high-fructose corn syrup and sugar-sweetened beverages, soft drinks) may lead to hyperuricemia and gout.

Caliceti et al. [68] have stated that it is not yet possible to conclude whether fructose intake alone is the main contributor to increased blood UA concentration. However, the 2020 American College of Rheumatology (ACR) Guideline [69] has conditionally recommended for limiting high-fructose for patients with gout, regardless of disease activity. The Japanese Society of Gout and Uric & Nucleic Acids Guidelines [14] has recommended avoidance of fructose overdose in patients of gout.

2. Sugars

The Ministry of Health, Labour and Welfare in Japan has not investigated the daily intake of sucrose, glucose and fructose of Japanese people.

The Ministry of Health, Labour and Welfare in Japan [28] has not set the Recommended Dietary Allowances (RDAs) for the daily intake of sugars (monosaccharides, disaccharides, sugar alcohols) in Japanese people. The World Health Organization (WHO) has stated that the term “sugars” includes intrinsic sugars, which are those incorporated within the structure of intact fruit and vegetables; sugars from milk (lactose and galactose); and free sugars, which are monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates [70]. On the other hand, the 2015-2020 Edition

of the Dietary Guidelines for Americans [71] recommends consuming less than 10% calories per day from added sugar and does not include sugars fruit juices added sugars.

Sucrose intake (1.5 g/kg of body weight) increased plasma uric acid (PUA) concentrations in healthy subjects through increase in purine degradation [72]. In epidemiological studies, added sugars were related to serum uric acid (SUA) concentration among Whites [43]. Increased intake of sugars [73], added sugars which are fructose-containing sugars, sucrose and high fructose corn syrup [66] was associated with increased hyperuricemia risk. A meta-analysis reported by Schwingshackl et al. [74] have indicated that replacing fructose with an equivalent energy amount of glucose reduced insulin resistance (HOMA-IR) and PUA or SUA concentrations. This result suggests that substitution of fructose with glucose has beneficial effect for prevention and suppression of hyperuricemia and/or gout. Therefore, increased daily sugars intake do not appear to be appropriate for the prevention of gout. Effects of sucrose, glucose and fructose on SUA levels and hyperuricemia risk are reviewed in detail by Koguchi [22, 32], Caliceti et al. [68], Sun and Empie [75], and Dornas et al. [76].

Tappy et al. [73] have proposed to set a maximum limit to the intake of total sugars containing fructose (sucrose, glucose fructose syrups, honey or other syrups, and natural concentrates, etc.) of 100 g/day. Recommendation for added sugars naturally present in established by the Institute of Medicine of the National Academy of Sciences in the U.S. suggests limit to a maximal intake of no more than 25 percent total energy [29]. The World Health Organization (WHO) recommends reducing the intake of free sugars to less than 10% of total energy intake in both adults and children and suggests a further reduction of the intake of free sugars to below 5% of total energy intake [70].

The 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout [5] has recommended limiting intake of table sugar in all gout patients. The Italian Society of Rheumatology clinical practice guidelines for the diagnosis and management of gout [77] has recommended low in added sugars.

It should pay attention to not to excessive intake of sugars (particularly fructose and sucrose) to prevent hyperuricemia and/or gout.

4.2.3. Dietary Fiber

The daily intake of dietary fiber of Japanese people in 2019 was lower compared to that in 1951, 1955, and 1960 and was higher compared to that in 1966, 1975, 1986, 1989, 1992, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 (1951: 23.3 g/day; 1955: 23.0 g/day; 1960: 19.9 g/day; 1966: 18.1 g/day; 1975: 18.3 g/day; 1986: 16.6 g/day; 1989: 16.4 g/day; 1992: 16.4 g/day; 1998: 15.0 g/day; 2001: 14.6 g/day; 2004: 13.9 g/day; 2007: 14.6 g/day; 2010: 14.0 g/day; 2013: 14.2 g/day; 2016: 14.2 g/day; 2019: 18.4 g/day). The daily intake of dietary fiber of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 14.7 g/day; 2019: 18.8 g/day). The daily dietary fiber intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 15.0 g/day; 2019: 19.9 g/day; women: 2016: 14.4 g/day; 2019: 18.0 g/day).

The daily intake of dietary fiber of Japanese men (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 12.5-16.9 g/day; 2019: 17.5-21.4 g/day). The daily intake of dietary fiber of Japanese women (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 11.3-16.5 g/day; 2019: 14.6-19.8 g/day). The daily dietary fiber intake of Japanese men (aged 20-59 years) and women (aged 20-59 years) in 2019 were 17.5-19.4 g/day (7.96-8.79 g/1000kcal) and 14.6-16.8 g/day (9.13-9.91 g/1000kcal), respectively, and were below the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 18-64 years): ≥ 21 g/day; women (aged 15-64 years): ≥ 18 g/day][28]. The daily dietary fiber intake of Japanese men (aged ≥ 70 years) and women (aged ≥ 60 years) were 21.4 g/day (10.30 g/1000kcal) and 19.6-19.8 g/day (11.10-11.42 g/1000kcal), respectively, and were above the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 65 years): ≥ 20 g/day; women (aged 15-64 years): ≥ 18 g/day; women (aged ≥ 65 years): ≥ 17 g/day][28]. The daily dietary fiber intake of adult men and women tended to increase as age increased.

The U.S. Department of Agriculture (USDA) has recommended that dietary fiber intake is 14 g/1000kcal, for an average age adult, this means a daily intake of 25 g (female) or 38 g (male) in the U.S. [71]. The Recommended Adequate Intakes (AIs) for total fiber in the U.S. population (aged ≥ 1 year) established by the Institute of Medicine of the National Academy of Sciences in the U.S. is 14 g/1,000 kcal [men (aged 14-50 years): 38 g/day; men (aged ≥ 51 years): 30 g/day; women (aged 9-18 years): 26 g/day; women (aged 19-50 years): 25 g/day; women (aged ≥ 51 years): 21 g/day][29]. The daily dietary fiber intake for Japanese adult men and women (aged ≥ 20 years) were below the recommendation by the U.S. Department of Agriculture (USDA) and the Institute of Medicine of the National Academy of Sciences in the U.S..

The daily intake of dietary fiber was negatively correlated with the number of gout patients in 1986-2016 (r= -0.946, p=0.000036). Whereas the daily dietary fiber intake did not show a significant correlation with the number of gout patients in 1986-2019 (r= -0.214, p=0.476). The daily intake of dietary fiber did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.133, p=0.831) and in 2004-2019 (r= 0.730, p=0.0994). The daily intake of dietary fiber did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.0701, p=0.911) and in 2004-2019 (r=0.742, p=0.0913). The daily intake of dietary fiber did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.108, p=0.862) and in 2004-2019 (r= -0.270, p=0.605).

In epidemiological studies, increased dietary fiber intake was associated with decreased serum uric acid (SUA) concentrations [41, 42, 78-80], hyperuricemia risk [41, 42, 78, 80-82], and gout risk [83]. Dietary fiber intake may prevent gout through reduced SUA concentrations and decreased hyperuricemia risk. Though the daily dietary fiber intake of Japanese adult men and women in 2019 were higher compared to those in 1986-2016, respectively, it seems that Japanese adult population (aged ≥ 20 years) need to take in more dietary fiber. A cross-sectional survey using Australian Diabetes, Obesity and Lifestyle Study (AusDiab) data (1999-2000) collected for 4,295 males and 5,439 females (aged ≥ 25 years) showed that dietary fiber intake had a significant inverse relationship with SUA concentration and the highest quartiles of dietary fiber intake was associated with 0.25-0.45 mg/dL (15-27 μmol/L) reduction in SUA level compared to the lowest quartiles in all AusDiab gender- and obesity-subgroups [41]. In the National Health and Nutrition Examination Survey (NHANES) 1999-2004, dietary fiber intake had a significantly inverse relationship with SUA concentration and the highest quartiles of the daily dietary fiber intake (> 9.5 g/1000 kcal) was associated with 0.15 mg/dL reduction in SUA concentration compared to the lowest quartiles of the daily dietary fiber intake (≤ 4.6 g/1000 kcal) [42]. A cross-sectional study survey using the seventh Korean National Health and Nutrition Examination Survey 2016-2017 data collected for 4300 men (aged ≥ 19 years) showed that dietary fiber intake was inversely associated with SUA concentrations and the highest quartiles of the daily dietary fiber intake were associated with 0.23 mg/dL reduction in SUA concentration compared to the lowest quartiles of the daily dietary fiber intake [78]. In the National Health and Nutrition Examination Survey (NHANES) 1999-2004, the daily dietary fiber intake was inversely associated with hyperuricemia risk among U.S. adult men and women (aged 20-80 years) [42]. This article revealed that participants in the highest level of the daily dietary fiber intake (> 9.5 g/1000 kcal/day) were 55.2% less likely to be hyperuricemia [SUA concentration > 8.4 mg/dL (499.7 μmol/L) in men and > 7.5 mg/dL (446.1 μmol/L) in women] compared to those in the lowest intake level (≤ 4.6 g/1000 kcal/day) [OR = 0.448 (95% confidence interval, 0.291-0.690)][42]. In the seventh Korean National Health and Nutrition Examination Survey 2016-2017, participants in the highest quartiles of the daily dietary fiber intake had a 8% lower likelihood of having hyperuricemia [SUA concentration > 6.0 mg/dL (356.9 μmol/L) in men and women] compared to those in the lowest quartiles of the daily dietary fiber intake in Korean men [OR = 0.92 (95% confidence interval, 0.85-0.99)] [78]. In the National Health and Nutrition Examination Survey (NHANES) 2009-2014, the daily dietary fiber intake was inversely associated with hyperuricemia risk among U.S. general adult population (aged ≥ 20 years) [82]. This article revealed that participants in the highest level of the daily dietary fiber intake (≥ 21.50 g/day) were 42% less likely to be hyperuricemia [SUA concentration > 7.0 mg/dL (416.4 μmol/L) in men and > 6.0 mg/dL (356.9 μmol/L) in women] compared to those in the lowest intake level (< 10.75 g/day) [OR = 0.58 (95% confidence interval, 0.46-0.74)][82]. Cereal fiber intake was inversely associated with hyperuricemia risk, but no association between fruit fiber intake or vegetable fiber intake and hyperuricemia risk among U.S. general adult population (aged ≥ 20 years) [82]. The data from the China Adult Chronic Disease and Nutrition Surveillance 2015 in Chinese adults (aged ≥ 18 years) revealed that the association of dietary fiber from different food sources with SUA concentrations and risk of hyperuricemia [SUA concentration ≥ 7.0 mg/dL (416.4 μmol/L) in men and ≥ 6.0 mg/dL (356.9 μmol/L) in women] showed different results [80]: Increased total dietary fiber intake and cereal fiber intake was associated with lower SUA levels and hyperuricemia risk, respectively [80]. Whereas no significant association between SUA levels or hyperuricemia risk with intake of dietary fiber from legumes, fruits and vegetables was observed [80]. This article also showed that the highest quartiles of daily total dietary fiber intake (≥ 11.66 g/day) was associated with 0.06 mg/dL reduction in SUA concentration and 12% reduction of hyperuricemia risk compared to the lowest quartiles of the daily total dietary fiber intake (≤ 5.85 g/day) and the highest quartiles of daily cereal fiber intake (≥ 6.10 g/day) was associated with 0.18 mg/dL reduction in SUA concentration and 33% reduction of hyperuricemia risk compared to the lowest quartiles of the daily total dietary fiber intake (≤ 2.36 g/day) [80]. The exact mechanism for the beneficial effect of dietary fiber intake on hyperuricemia remains largely unknown.

In a clinical trial, dietary fiber intake decreased SUA concentrations [84.85]. A double-blind, placebo-controlled clinical study showed that SUA concentration on the dose of 1.83 g chitosan per day for 12 weeks was significantly lower than that at baseline (before chitosan intake) in adult men with hyperuricemia [SUA concentration 7.5 - < 8.0 mg/dL (446.1 - < 475.8 μmol/L)] ($p < 0.05$) [84]. In a randomized, double-blind, placebo controlled clinical study, 27 healthy subjects (14 males and 13 females) ingested a maximum dose level of 10 g per day of PolyGlycoplex, which is composed of konjac powder, sodium alginate, and xanthan gum, for 21 days [85]. Plasma uric acid (PUA) levels on the dose of 10 g PolyGlycoplex per day were approximately 9% lower than those on the dose of 2.5 g PolyGlycoplex per day as the baseline ($p = 0.0316$) [85].

Although the underlying mechanism for the suppression of elevation of SUA concentrations and decrease in hyperuricemia risk by dietary fiber intake is not fully elucidated, a possible mechanism of higher dietary fiber intake associated with lower SUA concentration and reduced hyperuricemia risk are presumed to be due to the following four reasons: (1) dietary fiber suppresses digestion and/or absorption of dietary purines in the digestive system [22, 32, 86-88]; (2) inulin [89, 90] and konjac glucomannan [91, 92] suppresses uric acid (UA) production through inhibition of xanthine oxidase activity; (3) agarose increases the renal excretion efficiency of UA [87]; (4) inulin alleviates the inflammatory state because of increased short chain fatty acids

(SCFAs) concentrations (acetate, propionate and butyrate concentrations) and SCFAs-producing bacteria (e.g., *Akkermansia*, *Ruminococcus*, *Bifidobacterium*, *Parasutterella*) in the feces and modulation of gut microbiota, resulting in reduced SUA levels in *Uox*-knockout (urate oxidase) mice [90]. The mechanism may be related to SCFAs, especially propionate and butyrate, providing ATP to the cells of the intestinal wall to show beneficial effects on UA excretion [93, 94], and butyrate improves metabolism of UA through lowering UA concentrations in the colonic mucosa [95]. Dietary fiber increases production of SCFAs, which are acetate, propionate, and butyrate, by increasing bacteria that are beneficial to health [96, 97]. Butyrate can play a role in inhibiting the pathways that lead to the production of pro-inflammatory cytokines [98]. The mechanism responsible for the anti-inflammatory effect of dietary fiber has not been fully elucidated but might involve the production of SCFAs by colonic fermentation in rodents [90, 99, 100]. Future investigations are needed to clarify how dietary fiber suppresses elevation of SUA concentrations and lowers hyperuricemia risk, other than the above-mentioned mechanisms.

Judging from the data of food composition [30, 31], it is important for Japanese people to eat seeds and nuts (pumpkin seeds, chia seeds, almonds, pistachio nuts, hazelnuts, peanuts), whole grains (high fiber-bran ready-to-eat cereals, shredded wheat ready-to-eat cereals, whole grain bread, oats, barley, rye), legumes (navy beans, small white beans, yellow beans, cranberry beans, adzuki beans, French beans, split peas, chickpeas, lentils, pinto beans), seaweed, mushrooms (wood ear, shiitake mushrooms, maitake mushrooms), potatoes (konjac, potato with skin), fruit (avocados, apples, raspberries, blackberries, prunes, oranges, bananas, guavas), and vegetables (artichokes, pumpkins, tomatoes, broccoli, carrots, sweet corn, pears) to take in more dietary fiber to reach the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan and the Recommended Adequate Intakes (AIs) established by the Institute of Medicine of the National Academy of Sciences in the U.S..

4.2.4. The Mean Ratio of Energy Intake from Carbohydrate in Total Energy Intake (Carbohydrate/Energy)

The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese people in 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, 2016, and 2019 were 57.8-60.3% of energy, respectively. The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese people in 2019 was lower compared to that in 1975, 1980, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 (1975: 63.1%; 1980: 61.5%; 1986: 60.3%; 1989: 58.7%; 1992: 58.9%; 1995: 57.8%; 1998: 57.8%; 2001: 59.7%; 2004: 59.7%; 2007: 59.3%; 2010: 59.4%; 2013: 58.9%; 2016: 57.8%, 2019: 56.3%). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese adult population (aged ≥ 20 years) in 2019 was lower compared to that in 2016 (2016: 58.0%; 2019: 56.4%). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were lower compared to those in 2016, respectively (men: 2016: 59.3%; 2019: 57.8%; women: 2016: 57.0%; 2019: 55.3%).

The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were 55.8-59.1% of energy and 53.6-57.7% of energy, respectively, and were within the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 1 year): 50-65% of energy; women (aged ≥ 1 year): 50-65% of energy] [28]. The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese adult men (aged ≥ 20 years) in 2019 was lower compared to that in 2016 (2016: 59.3% of energy; 2019: 57.8% of energy). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese adult women (aged ≥ 20 years) in 2019 was lower compared to that in 2016 (2016: 57.0% of energy; 2019: 55.3% of energy).

The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) did not show a significant correlation with the number of gout patients in 1986-2016 (r= -0.058, p=0.865) and in 1986-2019 (r= -0.358, p=0.253). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) tended to be negatively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.875, p=0.0518). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) was negatively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2019 (r= -0.932, p=0.00687). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) was negatively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.899, p=0.0377) and in 2004-2019 (r= -0.954, p=0.00314). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.591, p=0.294) and in 2004-2019 (r=0.541, p=0.268). This result suggests that the correlation of the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) with the number of gout patients varies with gender.

The ideal balance of the caloric ratio of protein, fat, and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrates: 60% [20]. The Institute of Medicine of the National Academy of Sciences in the U.S. has determined that the Acceptable Macronutrient Distribution Ranges (AMDRs), which is defined as a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients, for carbohydrates both adults (aged ≥ 19 years) and children (aged 1-18 years) is 45-65 percent of total

calories [29]. Since the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese people in 2019 was 56.3%, it seems better to increase the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) until 60-65%. Intake of fiber-rich foods (e.g., whole grains, legumes, seeds and nuts, fruit, vegetables) seems to be important for the prevention of gout.

4.3. Proteins

4.3.1. Total Protein

The daily total protein intake of Japanese people in 2019 was lower compared to that in 1975, 1986, 1989, 1992, 1995, 1998, and 2001 and was higher compared to that in 1960, 1965, 2004, 2007, 2010, 2013, and 2016 (1960: 69.7 g/day; 1965: 71.3 g/day; 1975: 80.0 g/day; 1986: 78.9 g/day; 1989: 80.2 g/day; 1992: 80.1 g/day; 1995: 81.5 g/day; 1998: 79.2 g/day; 2001: 73.4 g/day; 2004: 70.8 g/day; 2007: 69.8 g/day; 2010: 67.3 g/day; 2013: 68.9 g/day; 2016: 68.5 g/day; 2019: 71.4 g/day). The daily total protein intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 69.3 g/day; 2019: 72.2 g/day). The daily total protein intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 75.7 g/day; 2019: 78.8 g/day; women: 2016: 64.0 g/day; 2019: 66.4 g/day).

In Japanese men (aged ≥ 1 year), the daily total protein intake of Japanese men (aged 1-14 years) was lower compared to that in 2016 (2016: 45.1-75.4 g/day; 2019: 47.2-74.3 g/day). Whereas the daily total protein intake of Japanese men (aged ≥ 15 years) in 2019 was higher compared to that in 2016 (aged ≥ 15 years: 2016: 73.6-85.7 g/day; 2019: 74.8-88.7 g/day). In Japanese women (aged ≥ 1 year), the daily total protein intake of Japanese women (aged 1-6 years, 30-39 years, 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016, 43.1 g/day; 2019: 42.5 g/day; aged 30-39 years: 2016, 62.1 g/day; 2019: 61.6 g/day; aged 50-59 years: 2016, 65.2 g/day; 2019: 64.1 g/day). Whereas the daily total protein intake of Japanese women (aged 7-29 years, 40-49 years, ≥ 60 years) in 2019 were higher compared to those in 2016, respectively (aged 7-29 years: 2016: 60.5-65.8 g/day; 2019: 61.1-71.8 g/day; aged 40-49 years: 2016: 60.7 g/day; 2019: 65.9 g/day; aged ≥ 60 years: 2016: 64.1-67.8 g/day; 2019: 68.0-70.2 g/day). The mean daily total protein intake of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were 47.2-88.7 g/day and 42.5-71.8 g/day, respectively, and exceeded the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 1 year): 20-65 g/day; women (aged ≥ 1 year): 20-55 g/day] [28]. The Recommended Dietary Allowances (RDAs) for protein in the U.S. adults (aged ≥ 19 years) established by the Institutes of Medicine is 0.8 g/kg body weight for the reference body weight [29, 101].

The daily total protein intake was negatively correlated with the number of gout patients in 1986-2016 (r= -0.937, p=0.0000215) and in 1986-2019 (r= -0.887, p=0.000118). The daily intake of total protein did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.559, p=0.327) and in 2004-2019 (r= 0.159, p=0.764). The daily intake of total protein did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.577, p=0.308) and in 2004-2019 (r=0.077, p=0.885). The daily total protein intake was positively correlated with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.896, p=0.0399). Whereas the daily intake of total protein did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2019 (r=0.527, p=0.283).

In a prospective cohort study in a Chinese population, higher intake of total protein, protein from poultry, protein from seafood (fish and shellfish) was associated with increased gout risk, respectively, whereas higher intake of protein from soy foods and protein from nonsoy legumes was associated with decreased gout risk, respectively [102]. Protein intake from red meat, eggs, dairy products, grain products, or nuts and seeds had no association with gout risk, respectively [102]. This population-based cohort study in a Chinese adult population (aged 45-74 years) revealed that the daily total protein intake of subjects with gout was significantly higher than that of subjects without gout (subjects with gout: 15.4±2.5% energy; subjects without gout: 15.2±2.4% energy) and the daily soy protein intake of subjects with gout tended to decrease compared to that of subjects without gout (subjects with gout: 1.47±0.99% energy; subjects without gout: 1.50±1.01% energy) [102]. The daily total protein intake (the mean ratio of energy intake from protein in total energy intake) of Japanese adult population (aged ≥40 years) in 2019 was 14.8-15.5% energy. The daily total protein intake of Japanese adult population (aged ≥40 years) was as same as that of Chinese adult population without gout (aged 45-74 years).

The Ministry of Health, Labour and Welfare in Japan [28] has not set a Tolerable Upper Intake Levels (ULs) for healthy Japanese individuals because there are insufficient reports of clear scientific evidence for health problems due to excessive daily intake of protein. However, excessive intake of protein can reduce renal function. A meta-analysis concluded that higher protein intake (≥ 20% but < 35% of energy or ≥ 10% higher than a comparison intake) within the range of recommended intakes for protein was consistent with normal renal function in healthy individuals in the short term (and did not reduce renal function) [103]. In healthy adults, consuming a higher-protein diet did not cause changes in kidney function compared with lower- or normal-protein diets [104]. In healthy adult men and women, protein intake should not exceed the World Health Organization (WHO) recommendation (0.83 g/ kg body weight/day for adults [105]).

4.3.2. Animal Protein

The daily animal protein intake of Japanese people in 2019

was higher compared to that in 1960 1965, 1975, 2001, 2004, 2007, 2010, 2013, and 2016 and was lower compared to that in 1989, 1992, 1995, and 1998, and was the same as that in 1986 (1960: 24.7 g/day; 1965: 28.5 g/day; 1975: 38.9 g/day; 1986: 40.1 g/day; 1989: 42.4 g/day; 1992: 42.5 g/day; 1995: 44.4 g/day; 1998: 42.8 g/day; 2001: 39.9 g/day; 2004: 38.0 g/day; 2007: 38.0 g/day; 2010: 36.0 g/day; 2013: 37.2 g/day; 2016: 37.4 g/day; 2019: 40.1 g/day). The daily animal protein intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 37.4 g/day; 2019: 40.1 g/day). The daily animal protein intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 41.2 g/day; 2019: 44.3 g/day; women: 2016: 34.2 g/day; 2019: 36.4 g/day).

The daily animal protein intake of Japanese men (aged ≥ 15 years) in 2019 was higher compared to that in 2016 (2016: 39.2-50.8 g/day; 2019: 42.2-54.3 g/day). In Japanese women (aged ≥ 15 years), the daily animal protein intake of Japanese women (aged 15-49 years, ≥ 60 years) in 2019 were higher compared to those in 2016, respectively (aged 15-49 years: 2016: 32.9-38.3 g/day; 2019: 34.1-44.1 g/day; aged ≥ 60 years: 2016: 33.7-36.0 g/day; 2019: 36.8-37.6 g/day), whereas the daily animal protein intake of Japanese women (aged 50-59 years) in 2019 was lower compared to that in 2016 (aged 50-59 years: 2016: 34.9 g/day; 2019: 34.8 g/day).

The daily intake of animal protein was negatively correlated with the number of gout patients in 1986-2016 (r= -0.823, p=0.00185) and in 1986-2019 (r= -0.709, p=0.00985). The daily intake of animal protein did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.241, p=0.696) and in 2004-2019 (r= 0.541, p=0.267). The daily intake of animal protein did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.376, p=0.532) and in 2004-2019 (r=0.451, p=0.369). The daily intake of animal protein did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.717, p=0.173) and in 2004-2019 (r=0.154, p=0.771).

In a clinical trial, animal sources of protein (e.g., casein, lactalbumin [106, 107]) decreased serum uric acid (SUA) concentrations. An increase in intake of milk and cheese seems to be important for the prevention of gout through a decrease in SUA concentrations. In a prospective cohort study in a Chinese population, higher intake of total protein, protein from poultry, protein from seafood (fish and shellfish) was associated with increased gout risk, respectively, whereas protein intake from red meat, eggs, and dairy products had no association with gout risk, respectively [102].

4.3.3. Vegetable Protein

The vegetable protein is from grains, potatoes, legumes, seeds, nuts, fruit, vegetables, mushrooms, and seaweed. The daily vegetable protein intake of Japanese people in 2019 was lower compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, and 2013 and was higher compared to that in 2016 and was the same as that in 2010 (1960: 45.0 g/day; 1965: 42.8 g/day; 1975: 41.1 g/day; 1986: 38.8 g/day; 1989: 37.8 g/day; 1992: 37.6 g/day; 1995: 37.1 g/day; 1998: 36.4 g/day; 2001: 33.5 g/day; 2004: 32.8 g/day; 2007: 31.8 g/day; 2010: 31.3 g/day; 2013: 31.7 g/day; 2016: 31.1 g/day; 2019: 31.3 g/day). The daily vegetable protein intake of Japanese adult population (aged ≥ 20 years) was higher compared to that in 2016 (2016: 32.0 g/day; 2019: 32.1 g/day). The daily vegetable protein intake of Japanese adult men (aged ≥ 20 years) in 2019 was the same as that in 2016 (2016: 34.5 g/day; 2019: 34.5 g/day). The daily vegetable protein intake of Japanese adult women (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 29.8 g/day; 2019: 30.0 g/day).

In Japanese men (aged ≥ 15 years), the daily vegetable protein intake of Japanese men (aged 15-19 years, 40-69 years) were lower compared to those in 2016, respectively (aged 15-19 years: 2016: 34.9 g/day; 2019: 34.4 g/day; 40-69 years: 2016: 33.1-36.6 g/day; 2019: 32.5-35.8 g/day). Whereas the daily vegetable protein intake of Japanese men (aged 20-29 years, ≥ 70 years) were higher compared to those in 2016, respectively (aged 20-29 years: 2016: 31.8 g/day; 2019: 32.2 g/day; aged ≥ 70 years: 2016: 35.2 g/day; 2019: 35.6 g/day). The daily vegetable protein intake Japanese men (aged 30-39 years) was as same as that in 2016 (32.6 g/day). In Japanese women (aged ≥ 15 years), the daily vegetable protein intake of Japanese women (aged 20-39 years, 50-59 years) were lower compared to those in 2016, respectively (aged 20-39 years: 2016: 26.6-29.0 g/day; 2019: 25.7-27.5 g/day; 50-59 years: 2016: 30.3 g/day; 2019: 29.3 g/day). Whereas the daily vegetable protein intake of Japanese men (aged 15-19 years, 40-49 years, ≥ 60 years) were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 26.5 g/day; 2019: 27.7 g/day; aged 40-49 years: 2016: 27.8 g/day; 2019: 28.2 g/day; aged ≥ 60 years: 2016: 30.4-31.8 g/day; 2019: 31.2-32.6 g/day).

The daily vegetable protein intake was negatively correlated with the number of gout patients in 1986-2016 (r= -0.974, p=0.000000417) and in 1986-2019 (r= -0.960, p=0.000000715). The daily intake of vegetable protein did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.674, p=0.312) and in 2004-2019 (r= -0.507, p=0.304). The daily intake of vegetable protein did not show a significant correlation with the number of gout patients in the adult men (aged ≥ 20 years) in 2004-2016 (r= -0.740, p=0.153). The daily intake of vegetable protein tended to be negatively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2019 (r= -0.788, p=0.0628). The daily intake of vegetable protein tended to be positively correlated with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.854, p=0.0656). The daily intake of vegetable protein was positively correlated with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2019 (r=0.865, p=0.0262). This result suggests that the correlation of daily vegetable protein intake with the number of gout patients tends to vary with gender.

Vegetable sources of protein (e.g., wheat gluten [108], rice endosperm protein [109]) decreased serum uric acid (SUA) concentrations. An increase in intake of wheat gluten and rice endosperm protein seems to be important for the prevention of gout through a decrease in SUA concentrations. In a prospective cohort study in a Chinese population, higher intake of protein from soy foods and protein from nonsoy legumes was associated with decreased gout risk, respectively, while protein intake from grain products, and nuts and seeds had no association with gout risk, respectively [102].

4.3.4. The Mean Ratio of Energy Intake from Protein in Total Energy Intake (Protein/Energy)

The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese people in 1986, 1989, 1992, 1995, 1998, 2002, 2005, 2007, 2010, 2013, 2016 and 2019 were 14.7-16.1% of energy, respectively. The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese people in 2019 was higher compared to that in 1975, 1980, 2007, 2010, 2013, and 2016 was lower compared to that in 1986, 1989, 1992, 1995, and 1998 and was about the same as that in 2002 and 2005 (1975: 14.6%; 1980: 14.9%; 1986: 15.2%; 1989: 15.6%; 1992: 15.6%; 1995: 16.1%; 1998: 16.1%; 2002: 15.1%; 2005: 15.1%; 2007: 14.8%; 2010: 14.7%; 2013: 14.8%; 2016: 14.8%, 2019: 15.1%). The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 14.9% of energy; 2019: 15.2% of energy). The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 14.6% of energy; 2019: 14.8% of energy; women: 2016, 15.2% of energy; 2019, 15.5% of energy).

The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were 14.2-15.2% of energy and 14.1-15.9% of energy, respectively, and were within the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [men (≥ 1 year): 13-20% of energy; women (aged ≥ 1 year): 13-20% of energy] [28]. The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 14.6% of energy; 2019: 14.8% of energy; women: 2016: 15.2% of energy; 2019: 15.5% of energy).

The mean ratio of energy intake from protein in total energy intake (Protein/Energy) was negatively correlated with the number of gout patients in 1986-2016 (r= -0.697, p=0.0172) and in 1986-2019 (r= -0.661, p=0.0192). The mean ratio of energy intake from protein in total energy intake (Protein/Energy) did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.405, p=0.499) and in 2004-2019 (r=0.458, p=0.361). The mean ratio of energy intake from protein in total energy intake (Protein/Energy) did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.147, p=0.813) and in 2004-2019 (r=0.470, p=0.347). The mean ratio of energy intake from protein in total energy intake (Protein/Energy) did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.855, p=0.0648) and in 2004-2019 (r=0.275, p=0.598).

The mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) were 14.2-15.2% of energy and 14.1-15.9% of energy, respectively. The ideal balance of the caloric ratio of protein, fat, and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrates: 60% [20]. The Institute of Medicine of the National Academy of Sciences in the U.S. has determined that the Acceptable Macronutrient Distribution Ranges (AMDRs) for total protein at 10-35 percent of total calories for adults (aged ≥ 19 years) and at 10-30 percent of total calories for children (aged 4-18 years) and 5-20 percent of total calories for children (aged 1-3 years) [29]. The mean ratio of energy intake from protein in total energy intake (Protein/Energy) seems to be appropriate or it seems better to increase it slightly.

4.4. Fats

4.4.1. Total Fat

The daily total fat intake of Japanese people in 2019 was higher compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 (1960: 24.7 g/day; 1965: 36.0 g/day; 1975: 52.0 g/day; 1986: 56.6 g/day; 1989: 58.9 g/day; 1992: 58.4 g/day; 1995: 59.9 g/day; 1998: 57.9 g/day; 2001: 55.3 g/day; 2004: 54.1 g/day; 2007: 55.1 g/day; 2010: 53.7 g/day; 2013: 55.0 g/day; 2016: 57.2 g/day; 2019 61.3 g/day). The daily total fat intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 56.9 g/day; 2019: 61.2 g/day). The daily total fat intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 61.4 g/day; 2019: 66.3 g/day; women: 2016: 53.2 g/day; 2019: 56.7 g/day).

The daily total fat intake of Japanese men (aged ≥ 1 years) in 2019 was higher compared to that in 2016 (2016: 40.9-76.6 g/day; 2019: 43.2-84.4 g/day). The daily total fat intake of Japanese women (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 48.3-61.4 g/day; 2019: 53.8-67.7 g/day). The Ministry of Health, Labour and Welfare in Japan [28] has not set the Recommended Dietary Allowances (RDAs) for the daily total fat intake in Japanese people. The Estimated Average Requirements (EARs), the Recommended Dietary Allowances (RDAs), the Adequate Intakes (AIs), and the Tolerable Upper Intake Levels (ULs) for total fat for individuals aged 1 year and older in the U.S. established by the Institutes of Medicine has not been set [29, 101].

The daily intake of total fat was negatively correlated with the number of gout patients in 1986-2016 (r= -0.677, p=0.0221). Whereas the daily intake of total fat did not show a significant correlation with the number of gout patients in 1986-2019 (r= -0.210, p=0.512). The daily intake of total fat did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r=0.771, p=0.127). Whereas the daily intake of total fat was positively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2019 (r=0.904, p=0.0133). The daily intake of total fat did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r=0.805, p=0.100). Whereas the daily intake of total fat was positively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2019 (r=0.912, p=0.0113). The daily intake of total fat did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r= -0.387, p=0.519) and in 2004-2019 (r= -0.437, p=0.387). This result suggests that the correlation of daily total fat intake with the number of gout patients varies with gender and is stronger in adult men than in adult women.

4.4.2. Animal Fat

The daily animal fat intake of Japanese people in 2019 was higher compared to that in 1972, 1975, 1980, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 (1972: 27.0 g/day; 1975: 27.4 g/day; 1980: 26.9 g/day; 1986: 27.9 g/day; 1989: 28.3 g/day; 1992: 28.5 g/day; 1995: 29.8 g/day; 1998: 29.2 g/day; 2001: 27.2 g/day; 2004: 26.8 g/day; 2007: 27.7 g/day; 2010: 27.1 g/day; 2013: 28.1 g/day; 2016: 29.1 g/day; 2019: 32.4 g/day). The daily animal fat intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 28.5 g/day; 2019: 31.9 g/day). The daily animal fat intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 31.4 g/day; 2019: 35.2 g/day; women: 2016: 26.2 g/day; 2019: 28.9 g/day).

The daily animal fat intake of Japanese men (aged ≥ 1 years) in 2019 was higher compared to that in 2016 (2016: 22.2-42.9 g/day; 2019: 25.1-48.9 g/day). The daily animal fat intake of Japanese women (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 20.5-33.0 g/day; 2019: 21.0-36.5 g/day).

The daily animal fat intake did not show a significant correlation with the number of gout patients in 1986-2016 (r= -0.285, p=0.396) and in 1986-2019 (r= 0.242, p=0.339). The daily animal fat intake did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r=0.848, p=0.0692). Whereas the daily animal fat intake was positively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2019 (r=0.921, p=0.00905). The daily animal fat intake did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r=0.860, p=0.0617). Whereas the daily animal fat intake was positively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2019 (r=0.921, p=0.00919). The daily animal fat intake did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r= -0.426, p=0.474) and in 2004-2019 (r= -0.446, p=0.375). This result suggests that the correlation of daily animal fat intake with the number of gout patients varies with gender and is stronger in adult men than in adult women.

4.4.3. Vegetable Fat

The vegetable fat is from grains, potatoes, legumes, seeds, nuts, fruit, vegetables, mushrooms, and seaweed. The daily vegetable fat intake of Japanese people in 2019 was lower compared to that in 1989, 1992, and 1995 and was higher compared to that in 1986, 1998, 2007, 2010, 2013, and 2016 (1986: 28.7 g/day; 1989: 30.6 g/day; 1992: 29.9 g/day; 1995: 30.2 g/day; 1998: 28.7 g/day; 2007: 27.3 g/day; 2010: 26.7 g/day; 2013: 26.9 g/day; 2016: 28.1 g/day; 2019: 28.9 g/day). The daily vegetable fat intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 28.4 g/day; 2019: 29.3 g/day). The daily vegetable fat intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 30.0 g/day; 2019: 31.1 g/day; women: 2016: 27.0 g/day; 2019: 27.7 g/day).

The daily vegetable fat intake of Japanese men (aged ≥ 15 years) in 2019 was higher compared to that in 2016 (2016: 26.6-33.7 g/day; 2019: 28.2-35.4 g/day). In Japanese women (aged ≥ 15 years), the daily vegetable fat intake of Japanese women (aged 15-19 years, 30-39 years, ≥ 60 years) in 2019 were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 28.5 g/day; 2019: 31.2 g/day; aged 30-39 years: 2016: 28.2 g/day; 2019: 29.6 g/day; aged ≥ 60 years: 2016: 24.2-27.9 g/day; 2019: 26.4-29.0 g/day), whereas the daily vegetable fat intake of Japanese women (aged 20-29 years, 40-59 years) in 2019 were lower compared to those in 2016, respectively (aged 20-29 years: 2016: 27.8 g/day; 2019: 26.3 g/day; aged 40-59 years: 2016: 28.8 g/day; 2019: 28.5 g/day).

The daily intake of vegetable fat was negatively correlated with the number of gout patients in 1986-2016 (r= -0.840, p=0.00121) and in 1986-2019 (r= -0.676, p=0.0157). The daily intake of vegetable fat did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r=0.580, p=0.306). Whereas the daily intake of vegetable fat was positively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2019 (r=0.835, p=0.0388). The daily intake of vegetable fat did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r=0.691, p=0.197). Whereas the daily intake of vegetable fat was positively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2019 (r=0.872, p=0.0235). The daily intake of vegetable fat did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20

years) in 2004-2016 (r= -0.240, p=0.698) and in 2004-2019 (r= -0.371, p=0.470). This result suggests that the correlation of daily vegetable fat intake with the number of gout patients varies with gender and is stronger in adult men than in adult women.

4.4.4. Saturated Fatty Acids

The daily saturated fatty acids intake of Japanese in 2019 was lower compared to that in 1995 and was higher compared to that in 1998, 2002, 2005, 2007, 2010, 2013, and 2016 (1995: 18.4 g/day; 1998: 17.7 g/day; 2002: 14.3 g/day; 2005: 14.8 g/day; 2007: 15.0 g/day; 2010: 14.7 g/day; 2013: 15.1 g/day; 2016: 15.7 g/day; 2019: 18.3 g/day). The daily saturated fatty acids intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 15.3 g/day; 2019: 17.9 g/day). The daily saturated fatty acids intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 16.2 g/day; 2019: 19.1 g/day; women: 2016: 14.5 g/day; 2019: 16.7 g/day).

The daily saturated fatty acids intake of Japanese men (aged ≥ 1 years) in 2019 was higher compared to that in 2016 (2016: 12.8-21.9 g/day; 2019: 14.9-26.3 g/day). The daily saturated fatty acids intake of Japanese women (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 12.2-19.2 g/day; 2019: 13.3-21.1 g/day). The Estimated Average Requirements (EARs), the Recommended Dietary Allowances (RDAs), the Adequate Intakes (AIs), and the Tolerable Upper Intake Levels (ULs) for saturated fatty acids in the U.S. population established by the Institutes of Medicine has not been set [29, 101]. The Institute of Medicine of the National Academy in the U.S. has stated that recommendation for saturated fatty acids is as low possible while consuming a nutritionally adequate diet [29].

The daily saturated fatty acids intake did not show a significant correlation with the number of gout patients in 1995-2019 (r= -0.360, p=0.428). Japanese adult men (aged 20-49 years) and women (aged ≥ 20 years) should reduce the daily saturated fatty acids intake for the prevention of gout.

4.4.5. The Mean Ratio of Energy Intake from Saturated Fatty Acids in Total Energy Intake (Saturated Fatty Acids/Energy)

The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) of Japanese people in 2019 was higher compared to that in 2016 (2016: 7.54% of energy, 2019: 8.60% of energy). The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 7.32% of energy, 2019: 8.39% of energy). The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 6.94% of energy; 2019: 8.05% of energy; women: 2016: 7.72% of energy; 2019: 8.77% of energy).

The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were higher compared to those in 2016, respectively (men: 2016: 6.50-9.15% of energy; 2019: 7.52-10.23% of energy; women: 2016: 7.01-9.43% of energy; 2019: 8.11-10.45% of energy). The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) of Japanese men (aged ≥ 7 years) and women (aged ≥ 7 years) in 2019 were 7.52-10.23% of energy and 8.11-10.45% of energy, respectively, and exceeded the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan (men and women: 7-14 years, ≤ 10% of energy; 25-17 years, ≤ 8% of energy; ≥ 18 years, ≤ 7% of energy) [28].

The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) did not show a significant correlation with the number of gout patients in 1995-2016 (r= -0.757, p=0.0817) and in 1995-2019 (r= -0.0571, p=0.903). The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) did not show a significant correlation with the number of gout patients in 2007-2016 (r=0.889, p=0.111). Whereas the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) was positively correlated with the number of gout patients in 2007-2019 (r=0.907, p=0.0334). This result suggests that decrease in intake of saturated fatty acids in Japanese people (aged ≥ 7 years) is important for prevention of gout.

4.4.6. Polyunsaturated Fatty Acids

The Ministry of Health, Labour and Welfare of Japan [28] has not set the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) for the daily intake of n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids in Japanese men and women. The Estimated Average Requirements (EARs), the Recommended Dietary Allowances (RDAs), and the Tolerable Upper Intake Levels (ULs) for n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids in the U.S. population established by the Institutes of Medicine has not been set [29, 101].

Urate transporter 1 (URAT1/SLC22A12) and Glucose transporter 9 (GLUT9/SLC2A9), which are key renal urate anion transporters promoting reabsorption by the proximal renal tubule epithelial cell, and ATP-binding cassette transporter G2 (ABCG2), which is the proximal tubule renal urate anion secretory transporter in the human kidney [110]. Urate transporter 1 (URAT1/SLC22A12) is an organic anion exchanger localized at the apical (tubule lumen-facing) membrane of renal proximal tubule epithelial cells [110, 111]. URAT1-transduced urate anion reabsorption is stimulated by intracellular organic anions, including lactate and monocarboxylates [110]. The balance between proximal tubular secretion and reabsorption of filtered urate (mediated partly by GLUT9/SLC2A9 and ABCG2, respectively) ultimately determines net renal uric acid excretion [111]. In vitro using URAT 1-expressing 293A cells, unsaturated fatty

acids inhibited the function of URAT 1 more strongly than saturated fatty acids [112].

Zhang et al. [113] found that higher n-3:n-6 ratio foods such as fatty fish was associated with lower risk of gout flares, more neutral n-3:n-6 ratio foods such as spinach had no effect on gout flare risk, and lower n-3:n-6 ratio foods such as egg was associated with increased risk of gout flares.

1. n-3 polyunsaturated fatty acids

The daily n-3 polyunsaturated fatty acids intake of Japanese people in 2019 was lower compared to that in 2007 and was higher compared to that in 2010, 2013, and 2016 (2007: 2.37 g/day; 2010: 2.24 g/day; 2013: 2.17 g/day; 2016: 2.16 g/day; 2019: 2.36 g/day). The daily n-3 polyunsaturated fatty acids intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 2.26 g/day; 2019: 2.46 g/day). The daily n-3 polyunsaturated fatty acids intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 2.46 g/day; 2019: 2.68 g/day; women: 2016: 2.09 g/day; 2019: 2.27 g/day).

The daily n-3 polyunsaturated fatty acids intake of Japanese men (aged ≥ 1 year) in 2019 was higher compared to that in 2016 (2016: 1.23-2.67 g/day; 2019: 1.31-2.88 g/day). In Japanese women, the daily n-3 polyunsaturated fatty acids intake of Japanese women (aged 1-19 years, ≥ 30 years) in 2019 were higher compared to those in 2016, respectively (aged 1-19 years: 2016: 1.12-1.84 g/day; 2019: 1.14-1.94 g/day; aged ≥ 30 years: 2016: 1.87-2.33 g/day; 2019: 2.01-2.51 g/day), whereas the daily n-3 polyunsaturated fatty acids intake of Japanese women (aged 20-29 years) in 2019 was lower compared to that in 2016 (2016: 1.86 g/day; 2019: 1.82 g/day).

The daily n-3 polyunsaturated fatty acids intake of Japanese men (aged ≥ 7 year) and women (aged ≥ 7 years) in 2019 were 1.99-2.88 g/day and 1.82-2.51 g/day, respectively, and exceeded the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 7 years): 1.5-2.2 g/day; women (aged ≥ 7 years): 1.3-2.0 g/day] [28]. This result suggests that the daily n-3 polyunsaturated fatty acids intake in Japanese men (aged ≥ 7 years) and women (aged ≥ 7 years) appears to be very unlikely to cause a deficiency. The Estimated Average Requirements (EARs) and the Recommended Dietary Allowances (RDAs) for n-6 polyunsaturated fatty acids in the U.S. population established by the Institutes of Medicine has not been set [29, 101]. The Institute of Medicine of the National Academy of Sciences in the U.S. has determined that the Acceptable Macronutrient Distribution Ranges (AMDRs) for n-3 polyunsaturated fatty acids (α-linolenic acid) both adults (aged ≥ 19 years) and children (aged 4-18 years) is 0.6-1.2 percent of total calories [29].

The daily n-3 polyunsaturated fatty acids intake was negatively correlated with the number of gout patients in 2007-2016 (r= -0.975, p=0.0246) and in 2007-2019 (r= -0.0978, p=0.876).

Diets enriched in both linolenic acid and eicosapentaenoic acid (EPA) significantly suppressed urate crystal-induced inflammation in a rat model [114]. These fatty acids show a potential protective role against gout flares.

Plant-based sources such as flax, canola, soybean, and walnuts containsα-linolenic acid [30, 31]. Eicosapentaenoic acid (EPA), alpha linolenic acid (ALA), and docosahexaenoic acid (DHA) strongly inhibited URAT 1 activities and n-3 polyunsaturated fatty acids inhibited the function of URAT 1 more effectively than n-6 polyunsaturated fatty acids [112]. Saito et al. [112] have stated that n-3 polyunsaturated fatty acids will be preferable to n-6 polyunsaturated fatty acids for the prevention of hyperuricemia/gout as uricosuric agents.

Fatty fish, such as tuna, mackerel, and salmon, contains rich in n-3 polyunsaturated fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] [30, 31]. Nuts and seeds contain rich in n-3 polyunsaturated fatty acids [alpha linolenic acid (ALA)] [30, 31]. One should consume at least 250 mg/day of long-chain n-3 polyunsaturated fatty acids or at least 2 servings/week of oily fish [115].

It seems important for Japanese people to eat fatty fish, nuts, and seeds to take in more n-3 polyunsaturated fatty acids for the prevention and management of gout.

2. n-6 polyunsaturated fatty acids

The daily n-6 polyunsaturated fatty acids intake of Japanese people in 2019 was higher compared to that in 2007, 2010, 2013, and 2016 (2007: 9.45 g/day; 2010: 9.27 g/day; 2013: 9.28 g/day; 2016: 9.61 g/day; 2019: 10.50 g/day). The daily n-6 polyunsaturated fatty acids intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 9.73 g/day; 2019: 10.66 g/day). The daily n-6 polyunsaturated fatty acids intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 10.62 g/day; 2019: 11.61 g/day; women: 2016: 8.98 g/day; 2019: 9.84 g/day).

The daily n-6 polyunsaturated fatty acids intake of Japanese men (aged ≥ 1 year) in 2019 was higher compared to that in 2016 (2016: 6.24-12.37 g/day; 2019: 6.54-13.45 g/day). In Japanese women, the daily n-6 polyunsaturated fatty acids intake of Japanese women (aged 7-19 years, ≥ 30 years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 9.18-9.89 g/day; 2019: 9.48-11.40 g/day; aged: 2016: 8.15-9.45 g/day; 2019: 9.41-11.32g/day), whereas the daily n-6 polyunsaturated fatty acids intake of Japanese women (aged 1-6 years, 20-29 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 6.13 g/day; 2019: 5.98 g/day; aged 20-29 years: 2016: 9.16 g/day; 2019: 9.13 g/day). The daily n-6 polyunsaturated fatty acids intake of Japanese men (aged ≥ 15 years) and Japanese women (aged ≥ 7 years) in 2019 were 10.47-13.45 g/day and 9.41-11.40 g/day, respectively, and exceeded the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 15 years): 8.0-13.0 g/day; women (aged ≥ 7 years): 7.0-8.0 g/day] [28]. This result suggests that the daily n-6 polyunsaturated fatty acids intake in Japanese men (aged ≥ 15 years) appears to be very unlikely to cause a deficiency, but the daily n-6 polyunsaturated fatty acids intake in Japanese women (aged ≥

7 years) is high. The Estimated Average Requirements (EARs) and the Recommended Dietary Allowances (RDAs) for n-6 polyunsaturated fatty acids in the U.S. population established by the Institutes of Medicine has not been set [29, 101]. The Institute of Medicine of the National Academy of Sciences in the U.S. has determined that the Acceptable Macronutrient Distribution Ranges (AMDRs) for n-6 polyunsaturated fatty acids (linoleic acid) both adults (aged ≥ 19 years) and children (aged 4-18 years) is 5-10 percent of total calories [29].

The daily n-6 polyunsaturated fatty acids intake did not show a significant correlation with the number of gout patients in 2007–2016 (r=0.221, p=0.779) and in 2007–2019 (r=0.776, p=0.123).

4.4.7. Cholesterol

The daily cholesterol intake of Japanese people in 2019 was lower compared to that in 1995, 1998, and 2001 and was higher compared to that in 2004, 2007, 2010, 2013 and 2016 (1995: 383 mg/day; 1998: 370 mg/day; 2001: 346 mg/day; 2004: 320 mg/day; 2007: 323 mg/day; 2010: 307 mg/day; 2013: 307 mg/day; 2016: 311 mg/day; 2019 335 mg/day). The daily cholesterol intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 313 mg/day; 2019: 340 mg/day). The daily cholesterol intake of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 339 mg/day; 2019: 366 mg/day; women: 2016: 292 mg/day; 2019: 317 mg/day).

The daily cholesterol intake for men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were 206-474 mg/day and 174-381 mg/day, respectively. The daily intake of cholesterol of Japanese men (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 320-431 mg/day; 2019: 324-474 mg/day). The daily intake of cholesterol of Japanese women (aged ≥ 7 years) in 2019 was higher compared to that in 2016 (2016: 290-351 mg/day; 2019: 304-381 mg/day).

The daily cholesterol intake did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r= -0.609, p=0.216) and in 2004-2019 (r=0.461, p=0.357). The daily cholesterol intake did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r= -0.610, p=0.275) and in 2004-2019 (r=0.398, p=0.447). The daily cholesterol intake did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r=0.544, p=0.343) and in 2004-2019 (r= -0.0160, p=0.976).

The Ministry of Health, Labour and Welfare of Japan [28] has not set an index for the daily intake of cholesterol in Japanese adults. The Estimated Average Requirements (EARs), the Recommended Dietary Allowances (RDAs), the Adequate Intakes (AIs), and the Tolerable Upper Intake Levels (ULs) for cholesterol in the U.S. population established by the Institutes of Medicine has not been set [29, 101]. The Institute of Medicine of the National Academy of Sciences in the U.S. has stated that recommendation for dietary cholesterol is as low possible while consuming a nutritionally adequate diet [29]. The Ministry of Health, Labour and Welfare in Japan [28] has stated that, for the daily cholesterol intake, it is desirable to take less than 200 mg from the viewpoint of preventing aggravation of dyslipidemia. Thus, it is important for Japanese people to reduce daily cholesterol intake to prevent the aggravation of dyslipidemia. It seems that decreasing intake of cholesterol and/or avoidance of excessive intake of cholesterol in Japanese adults is important for the prevention of lifestyle-related diseases including gout.

4.4.8. The Mean Ratio of Energy Intake from Fat in Total Energy Intake (Fat/Energy)

The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese people in 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, 2016, and 2019 were 24.5-28.6% of energy. The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese people in 2019 was higher compared to that in 1975, 1980, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 (1975: 22.3%; 1980: 23.6%; 1986: 24.5%; 1989: 25.7%; 1992: 25.5%; 1995: 26.2%; 1998: 26.1%; 2001: 25.2%; 2004: 25.3%; 2007: 25.8%; 2010: 25.9%; 2013: 26.2%; 2016: 27.4%, 2019: 28.6%). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 27.1% of energy, 2019: 28.4% of energy). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese adult men (aged ≥ 20 years) and adult women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 26.1% of energy; 2019: 27.4% of energy; women: 2016: 27.9% of energy; 2019: 29.2% of energy).

The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese men (aged ≥ 1 year) and women (aged 1-6 years and ≥ 50 years) in 2019 were 25.7-29.8% of energy, 28.2% of energy, and 27.5-29.9% of energy, respectively. and were within the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 1 year): 20-30% of energy; women (aged ≥ 1 year): 20-30% of energy] [28]. The mean ratio of energy intake from fat in total energy intake (Fat/Energy) for women (7-49 years) was 30.2-31.1% of energy and exceeded the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [women (aged ≥ 1 year): 20-30% of energy] [28]. The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese adult men (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 26.1% of energy; 2019: 27.4% of energy). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese adult women (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 27.9% of energy; 2019: 29.2% of energy).

The mean ratio of energy intake from fat in total energy intake (Fat/Energy) did not show a significant correlation with

the number of gout patients in 1986-2016 (r=0.514, p=0.106). Whereas the mean ratio of energy intake from fat in total energy intake (Fat/Energy) was positively correlated with the number of gout patients in 1986-2019 (r=0.660, p=0.0195). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) was positively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 (r=0.856, p=0.0453) and in 2004-2019 (r=0.953, p=0.00328). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) was positively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 (r=0.924, p=0.0247) and in 2004-2019 (r=0.966, p=0.00170). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 (r= -0.677, p=0.209) and in 2004-2019 (r= -0.619, p=0.190). This result suggests that the correlation of the mean ratio of energy intake from fat in total energy intake (Fat/Energy) with the number of gout patients varies with gender and is stronger in adult men than in adult women.

In epidemiological studies, increased intake of fat was associated with increased serum uric acid (SUA) concentrations [41].

The Institute of Medicine of the National Academy of Sciences in the U.S. has determined that the Acceptable Macronutrient Distribution Ranges (AMDRs) for total fat at 20-35 percent of total calories for adults (aged ≥ 19 years) and at 25-35 percent of total calories for children (aged 4-18 years) and 30-40 percent of total calories for children (aged 1-3 years) [29]. The mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese adult men (aged ≥ 20 years) and Japanese adult women (aged ≥ 20 years) in 2019 were 27.4% of energy and 29.2% of energy, respectively, and were within the Acceptable Macronutrient Distribution Ranges (AMDRs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [29]. However, the mean ratio of energy intake from fat in total energy intake (Fat/Energy) was positively correlated with the number of gout patients in 1986-2019 (r=0.660, p=0.0195). The ideal balance of the caloric ratio of protein, fat, and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrates: 60% [20]. It seems better to decrease the mean ratio of energy intake from fat in total energy intake (Fat/Energy).

4.5. Caloric Ratio of Protein, Fat, and Carbohydrate

The balance of the caloric ratio of protein, fat, and carbohydrate of Japanese people in 2019 was protein: 15.1%, fat: 28.6%, and carbohydrates: 56.3%. The balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 1965 was protein: 13.1%, fat: 14.8%, and carbohydrates: 70.3% [20]. The balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 1975 was near the ideal balance for healthy life (protein: 14.6%, fat: 21.4%, and carbohydrates: 61.6%)[20]. Compared to the Japanese diet in 1965, in the Japanese diet in 1975-2019, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased.

Compared to the Japanese diet in 2016, in the Japanese diet in 2019, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased by 0.3% and 1.2%, respectively and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased by 1.5%. In Japanese men and women (aged ≥ 1 year), compared to the Japanese diet in 2016, in the Japanese diet in 2019, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased by 1.34% and 4.38%, respectively and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased by 2.60%. In Japanese adult men (aged ≥ 20 years), compared to the Japanese diet in 2016, in the Japanese diet in 2019, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased by 1.37% and 4.98%, respectively and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased by 2.53%. In Japanese adult women (aged ≥ 20 years), compared to the Japanese diet in 2016, in the Japanese diet in 2019, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased by 1.97% and 4.66%, respectively and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased by 2.98%. The balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 2019 was weighted toward fat (protein: 15.1%, fat: 28.6%, and carbohydrates: 56.3%). Japanese people need to decrease fat (especially saturated fatty acids and cholesterol) intake. The Institute of Medicine of the National Academy of Sciences in the U.S. has determined that the Acceptable Macronutrient Distribution Ranges (AMDRs) for carbohydrates is 45-65 percent of total calories for adults (aged ≥ 4 years) and total protein is 10-35 percent of total calories for adults (aged ≥ 19 years) and at 10-30 percent of total calories for children (aged 4-18 years), respectively [29]. It seems that Japanese population (aged ≥ 1 year) need to take in more carbohydrates and protein (e.g., casein, lactalbumin, wheat gluten, rice endosperm protein).

4.6. Alcohol Consumption

The Ministry of Health, Labour and Welfare of Japan [28] has not determined dietary reference intakes for alcohol in Japanese people.

In epidemiological studies, increased intake of alcohol was associated with increased serum uric acid (SUA) concentrations [10, 41-43, 78, 116-120], hyperuricemia risk [42, 52, 78, 118, 119, 121-124], and gout risk [10, 52, 54, 83, 116, 125-129]. The Health Professionals Follow-up Study

(HPFS) of middle-aged males without gout at the onset of the prospective observation period of 26 years found that participants consuming in the second quintile (0.1-4.9 g/day), third quintile (5.0-9.9 g/day), fourth quintile (10.0-29.9 g/day), and highest quartile of alcohol consumption (≥ 30 g/day) were 5%, 20%, 57%, 2.1-fold increased risk of gout compared to those consuming in the lowest quintile of alcohol consumption (0 g/day) [129].

Heavy alcohol (ethanol) consumption increases the production of uric acid (UA), which resulted in increases in SUA concentration and urinary UA excretion, leads to hyperuricemia [130]. Proposed mechanisms of higher alcohol consumption associated with increased SUA levels and hyperuricemia risk are presumed to be due to the following reasons reviewed in detail by Yamamoto et al. [130]: (1) alcohol consumption increases UA liver production through ATP degradation, leading to accumulation of ADP and AMP [131], and it increases lactic acid production, which has a competitive inhibitory effect on UA excretion and ethanol can increase the rate of sputum synthesis in humans and increase UA production [132]; (2) alcohol consumption leads to dehydration and metabolic acidosis, resulting in decreased UA excretion [133].

Excessive alcohol consumption was associated with increased risk of gout attacks [134-136]. All forms of alcohol promote gout flares when ingested in a condensed period of time (e.g., more than three servings in a 24-hour period) [137]. Terkeltaub and Edwards [137] have stated that the patient can help lessen gout flares by moderating food portion sizes and content, by not drinking alcohol in excess in short time periods, and by staying well hydrated (five or eight 250-mL servings of water daily unless medically contraindicated).

The guidelines for the management of gout recommended the following for alcohol consumption: (1) limit alcohol consumption for patients with gout [14, 69]; (2) reduced consumption of alcohol (particularly beer, but also wine and spirits) and avoidance of alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients [5, 77]; (3) avoidance of alcohol (especially beer and spirits) for patients with gout [6].

4.7. Water Intake

The mean total water intake of Japanese adults (aged 30-76 years), Japanese men (aged 30-76 years), Japanese women (aged 30-69 years) were 2230 g/day, 2423 g/day, and 2037 g/day, respectively [138]. Since there is only this report on water intake of Japanese people, the Ministry of Health, Labour and Welfare in Japan [28] has not set the Adequate Intakes (AIs) for water intake of Japanese people. The Recommended Adequate Intakes (AIs) for water in the U.S. population (aged ≥ 0 month) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are based on the median water intake U.S. survey data (total water intake includes drinking water, water in beverages and formula, and water that is contained in food) [Total water intake: males (aged 14-18 years): 3.3 L g/day (approximately 2.6 L as total beverages, including drinking water); males (aged ≥ 19 years): 3.7 L/day (approximately 3.0 L as total beverages, including drinking water); females (aged 14-18 years): 2.3 L/day (approximately 1.8 L as total beverages, including drinking water); females (aged ≥ 19 years): 2.7 L/day (approximately 2.2 L as total beverages, including drinking water)] [29].

Consumption of water to maintain hydration was associated with decreased risk of gout flares in an internet-based case-crossover study [139]. Specifically, consumption of five to eight glasses (250 mL each) of water in a 24-hour period or drinking more than eight glasses of water in a 24-hour period was associated with decreased risk of gout flares [139]. The guidelines [5, 14] and Terkeltaub and Edwards [137] have stated importance of fluid intake for management in patients with gout [5, 14].

Table 3. *Correlation between number of gout patients and macronutrient intake in Japanese people in 1986-2016 and 1986-2019.*

Year	1986-2016		1986-2019	
Macronutrient	**coefficient**	**p-value**	**coefficient**	**p-value**
Energy	- 0.984	<0.001	- 0.938	<0.001
Total Carbohydrate	- 0.978	<0.001	- 0.982	<0.001
Dietary Fiber	- 0.946	<0.001	- 0.214	0.476
Carbohydrate/Energy	- 0.058	0.865	- 0.358	0.253
Total Protein	- 0.937	<0.001	- 0.887	<0.001
Animal Protein	- 0.823	0.002	- 0.709	0.010
Vegetable Protein	- 0.974	<0.001	- 0.960	<0.001
Protein/Energy	- 0.697	0.017	- 0.661	0.019
Total Fat	- 0.677	0.022	- 0.210	0.512
Animal Fat	- 0.285	0.396	0.242	0.339
Vegetable Fat	- 0.840	0.001	- 0.676	0.016
Fat/Energy	0.514	0.106	0.660	0.020

Abbreviation: Carbohydrate/Energy, The mean ratio of energy intake from carbohydrate in total energy intake; Protein/Energy, The mean ratio of energy intake from protein in total energy intake; Fat/Energy, The mean ratio of energy intake from fat in total energy intake.

Table 4. *Correlation between number of gout patients in adult men (aged ≥ 20 years) or adult women (aged ≥ 20 years) and macronutrient intake in Japanese people in 2004-2019.*

Gender	Men		Women	
Macronutrient	**coefficient**	**p-value**	**coefficient**	**p-value**
Energy	- 0.125	0.814	0.599	0.209
Total Carbohydrate	- 0.959	0.003	0.788	0.062
Dietary Fiber	0.742	0.091	- 0.270	0.605
Carbohydrate/Energy	- 0.954	0.003	0.541	0.268
Total Protein	0.077	0.885	0.527	0.283
Animal Protein	0.451	0.369	0.154	0.771
Vegetable Protein	- 0.788	0.063	0.865	0.026
Protein/Energy	0.470	0.347	0.275	0.598
Total Fat	0.912	0.011	- 0.437	0.387
Animal Fat	0.921	0.009	- 0.446	0.375
Vegetable Fat	0.872	0.024	- 0.371	0.470
Fat/Energy	0.966	0.002	-0.619	0.190

Abbreviation: Carbohydrate/Energy, The mean ratio of energy intake from carbohydrate in total energy intake; Protein/Energy, The mean ratio of energy intake from protein in total energy intake; Fat/Energy, The mean ratio of energy intake from fat in total energy intake.

5. Limitation

Smith and Ebrahim [44] have stated that the observational findings are difficult to interpret because the results are affected by a variety of confounding factors, such as occupational and environmental exposures, diet, and supplement use. Jakše et al. [140] have stated that a patient's individual risk likely represents a complex interplay between nonmodifiable factors (e.g., age, gender, race, and genetics) and modifiable factors (e.g., diet, body weight, and lifestyle). Lifestyle-related diseases including gout are not caused or prevented by a single nutrient, but they involve environmental and genetic factors. As the previous report [22], the relationship between the number of gout patients and macronutrient intake in Japanese people was examined using the mean values of the number of gout patients and macronutrient intake reported by the Comprehensive Survey of Living Conditions performed by the Ministry of Health, Labour and Welfare in Japan (1986-2019) [11, 24, 25] and the National Health and Nutrition Survey Japan (1946-2019) [26]. The number of patients with gout estimated from the Comprehensive Survey of Living Conditions was based on self-reporting by residents. In the National Health and Nutrition Survey performed by the Ministry of Health, Labour and Welfare in Japan, the daily intake of nutrients, etc. was calculated using the Standard Tables of Food Composition in Japan prepared by the Ministry of Education, Culture, Sports, Science and Technology in Japan. Regarding the method of quantifying nutrients contained in food, it is unavoidable that there will be discrepancies in the calculated values depending on which ingredient table is used. The Standard Tables of Food Composition in Japan are revised every five years. It is necessary to consider that the content of nutrients in foods reported in the Standard Tables of Food Composition in Japan fluctuates because the analysis method is different or is improved due to technological progress. It must be also taken into account that the content of nutrients in foods differ from the cooked meals that the person actually consumes.

6. Conclusion

In Japan, the westernization of the Japanese diet from 1955 is thought to be one factor the remarkable increase in the prevalence of gout [7, 11-13, 19, 20]. 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).

The mean ratio of energy intake from protein in total energy intake (Protein/Energy), the mean ratio of energy intake from fat in total energy intake (Fat/Energy), the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) and the daily intake of energy, dietary fiber, total protein, animal protein, vegetable protein, total fat, animal fat, vegetable fat, saturated fatty acids, polyunsaturated fatty acids (n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids), and cholesterol of Japanese people in 2019 were higher compared to those in 2016, respectively. Whereas the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) and the daily intake of carbohydrate were lower compared to those in 2016, respectively. The mean ratio of energy intake from fat in total energy intake (Fat/Energy) was positively correlated with the number of gout patients in 1986-2019. Whereas the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the daily intake of energy, total carbohydrate, total protein, animal protein, vegetable protein, and vegetable fat were negatively correlated with the number of gout patients in 1986-2019, respectively. The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) was positively correlated with the number of gout patients in 2007-2019. The increase in the number of gout patients between 2016 and 2019 is presumed to be due to increased fat intake.

As the previous report [22], this article also suggests the importance of macronutrient for the prevention of gout in Japanese people referencing the results of clinical research reported. Modification of macronutrient intake for the prevention of gout in Japanese people (particularly adults) 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, and cholesterol; increase intake of carbohydrate (particularly dietary fiber). The important points of macronutrient intake for the prevention of gout in Japanese people (especially adults) is suggested as follows: The percentage of carbohydrate, protein, fat, and n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids in total energy intake should be within the range of the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan or the Acceptable Macronutrient Distribution Ranges (AMDRs) set by the Institute of Medicine of the National Academy of Sciences in the U.S.; maintain the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) within the range of the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan; recognizing increased intake of dietary fiber, animal sources of protein (e.g., casein, lactalbumin), and vegetable sources of protein (e.g., wheat gluten, rice endosperm protein); avoidance of excessive intake of saturated fatty acids and cholesterol; replacement of saturated fatty acids (e.g., dairy fats, meat fat) with mono- and polyunsaturated fatty acids (particularly n-3 polyunsaturated fatty acids) (e.g., macadamia nuts, almonds, peanuts and peanut butter, olive oil, canola oil, avocados); pay attention to not to excessive intake of sugars (particularly fructose and sucrose); limiting alcohol consumption; and maintenance of good hydration. It is necessary to recognize what micronutrient (vitamin and mineral) intake is important as potential dietary habits to prevent gout in Japanese people.

Conflict of Interest Statement

The author declares that there are no conflicts of interest.

Acknowledgements

The author thanks Prof. Eiko Ota (Kokugakuin University Tochigi Junior College), Ms. Yuko Itabashi, Ms. Tamae Yanagita, Ms. Nao Uzuka, and Ms. Yumi Kuwabara for furnishing references at Kokugakuin University Tochigi Gakuen Library.

References

[1] Dalbeth, N., Merrriman, T. R., & Stamp, L. K. (2016) Gout. Lancet, 388, 2039-2052.

[2] Zhu, Y., Pandya, B. J., & Choi, H. K. (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum, 63, 3136-3141.

[3] Duskin-Bitan, H., Cohen, E., Goldberg, E., Shochat, T., Levi, A., Garty, M., & Krause, I. (2014) The degree of asymptomatic hyperuricemia and the risk of gout: A retrospective analysis of a large cohort. Clin Rheumatol, 33, 549-553.

[4] Vedder, D., Walrabenstein, W., Heslinga, M., de Vries, R., Nurmohamed, M., van Schaardenburg, D., & Gerritsen, M. (2019) Dietary interventions for gout and effect on cardiovascular risk factors: A systematic review. Nutrients, 11, 2955.

[5] Khanna, D., Fitzgerald, J. D., Khanna, P. P., Bae, S., Singh, M. K., Neogi, T., Pillinger, M. H., Merill, J., Lee, S., Prakash, S., Kaldas, M., Gogia, M., Perez-Ruiz, F., Taylor, W., Lioté, F., Choi, H., Singh, J. A., Dalbeth, N., Kaplan, S., Niyyar, V., Jones, D., Yarows, S. A., Roessler, B., Kerr, G., King, C., Levy, G., Furst, D. E., Edwards, N. L., Mandell, B., Schumacher, H. R., Robbins, M., Wenger, N., & Terkeltaub, R. (2012) 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Research, 64, 1431-1446.

[6] Richette, P., Doherty, M., Pascual, E., Barskova, V., Becce, F., Castaneda, J. Coyfish, M., Guillo, S., Jansen, T., Janssens, H., Lioté, F., Mallen, C. D., Nuki, G., Perez-Ruiz, F., Pimentao, J., Punzi, L., Pywell, A., So, A., Tausche, A. K., Uhlig, T., Zavada, J., Zhang, W., Tubach, F., & Bardin, T. (2020) 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis, 79, 31-38.

[7] Mikanagi, K. (1963) Gout in Japan. The Kyosai Medical Journal, 12, 14-37 (in Japanese).

[8] Nishioka, K., Mikanagi, K., & Hirose, K. (1974) Clinical study of gout and hyperuricemia: Epidemiology and pathogenesis. Rheum, 14, 95-105.

[9] Kuo, C. F., Grainge, M. J., Zhang, W., & Doherty, M. (2015) Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol, 11, 649-662.

[10] Xia, Y., Wu, Q., Wang, H., Zhang, S., Jiang, Y., Gong, T., Xu, X., Chang, Q., Niu, K., & Zhao, Y. (2020) Global, regional and national burden of gout:, 1990-2017: a systematic analysis of the Global Burden of Disease Study. Rheumatology (Oxford), 59, 1529-1538.

[11] The Ministry of Health, Labour and Welfare. Household Statistics Office. (2022) Comprehensive Survey of Living Conditions [Internet]. Available from: https://www.mhlw.go.jp/toukei/list/20-21kekka.html.

[12] Kawasaki, T., & Shichikawa, K. (2006) Epidemiological survey of gout by resident examination. Gout and nucleic acid metabolism, 30, 66.

[13] Hakoda, M., & Kasagi, F. (2018) Trends in gout and hyperuricemia in Japan. Gout and nucleic acid metabolism, 42, 110 (in Japanese).

[14] Hisatome, I., Ichida, K., Mineo, I., Ohtahara, A., Ogino, K., Kuwabara, M., Ishizaka, N., Uchida, S., Kurajoh, M., Kohagura, K., Sato, Y., Taniguchi, A., Tsuchihashi, T., Terai, C., Nakamura, T., Hamaguchi, T., Hamada, T., Fujimori, S., Masuda, I., Moriwaki, Y., Yamamoto, T. on behalf of guideline development group. (2018) Japanese Society of Gout and Uric & Nucleic Acids Guidelines for Management of Hyperuricemia and Gout: 3 rd edition. SHINDAN TO CHIRYO SHA, Inc. pp. 1-169. Tokyo (in Japanese).

[15] Nishioka, K., & Mikanagi, K. (1980) Hereditary and environmental factors influencing on the serum uric acid throughout ten years population study in Japan. Adv Exp Med Biol, 122A, 155-159.

[16] Smith, E., Hoy, D., Cross, M., Merriman, T. R., Vos, T., Buchbinder, R., Woolf, A., & March, L. (2014) The global burden of gout: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis, 73, 1470-1476.

[17] Castro, K. E., Corey, K. D., Raymond, D. L., Jiroutek, M. R., & Holland, M. A. (2018) An evaluation of gout visits in the United States for the years 2007 to 2011. BMC Rheumatology, 2, 14.

[18] Akizuki, S. (1982) A population study of hyperuricemia and gout in Japan: analysis of sex, age and occupational differences in thirty-four thousand people living in Nagano prefecture. Ryumachi, 22, 201-208 (in Japanese).

[19] Koguchi, T. (2021) Modification of dietary habits for prevention of gout in Japanese people: Gout and the Japanese diet. Am J Health Res, 9, 117-127.

[20] The Ministry of Agriculture, Forestry and Fisheries. (2020) WASHOKU, traditional dietary cultures of the Japanese [Internet]. Available from: https://www.maff.go.jp/e/japan_food/washoku/pdf/wasyoku_english.pdf.

[21] Kagan, A., Harris, B. R., Winkelstein, W. Jr., Johnson, K. G., Kato, H., Syme, S. L., Rhoads, G. G., Gay, M. L., Nichaman, M. Z., Hamilton, H. B., & Tillotson, J. (1974) Epidemiologic studies on coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics. J Chronic Dis, 27, 345-364.

[22] Koguchi, T. (2021) Modification of dietary habits for prevention of gout in Japanese people: Gout and macronutrient intake. Am J Health Res, 9, 128-142.

[23] Koguchi, T. (2021) Modification of dietary habits for prevention of gout in Japanese people: Gout and micronutrient intake or alcohol consumption. Am J Health Res, 9, 143-157.

[24] The Ministry of Health, Labour and Welfare. Household Statistics Office. (2022) Comprehensive Survey of Living Conditions [Internet]. Available from: https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450061&tstat=000001141126&cycle=7&tclass1=000001141142&tclass2=000001142126&stat_infid=000031964417&tclass3val=0

[25] The Ministry of Health, Labour and Welfare. Household Statistics Office. (2022) Comprehensive Survey of Living Conditions [Internet]. Available from: https://www.e-stat.go.jp/dbview?sid=0003223900

[26] The Ministry of Health, Labour and Welfare. Health Service Bureau. (2020) National Health and Nutrition Survey Japan, 1946-2017 [Internet]. Available from: https://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html.

[27] National Institute of Health and Nutrition [Internet]. Available from: www.nibiohn.go.jp/eiken/kenkounippon21/eiyouchousa/keinen_henka_time.html.

[28] The Ministry of Health, Labour and Welfare, Japan. (2020) Dietary Reference Intakes for Japanese, 2020 [Internet]. Available from: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/Overview.pdf.

[29] Institute of Medicine of the National Academy of Sciences. Food and Nutrition Board. Dietary Reference Intakes: The essential guide to nutrient requirements. (2021) Washington, D.C. The National Academy Press. [Internet]. Available from: https://www.nap.edu/catalog/11537.html

[30] The Council for Science and Technology, Ministry of Education, Culture, Sports, Science and Technology in Japan. (2020) Standard tables of food composition in Japan -2020- (Eighth Revised Edition), Report of the Subdivision Resources [Internet]. Available from: https://www.mext.go.jp/content/20201225-mxt_kagsei-mext_01110_011.pdf.

[31] U.S. Department of Health & Human Services. National Institutes of Health. Office of Dietary Supplements. Dietary Supplement Fact Sheets [Internet]. Available from: https://ods.od.nih.gov/factsheets/list-all/

[32] Koguchi, T. (2018) Essentials of dietary habits for prevention and suppression of hyperuricemia. Curr Top Pharmacol, 22, 77-133.

[33] Doherty, M. (2009) New insights into epidemiology of gout. Rheumatology. (Oxford), 48 (suppl 2), ii2-ii8.

[34] Lin, K-M., Lu, C-L., Hung, K-C., Wu, P-C., Pan, C-F., Wu, C-J., Syu, R-S., Chen, J-S., Hsiao, P-J., & Lu, K-C. (2019) The paradoxical role of uric acid in osteoporosis. Nutrients, 11, 2111.

[35] Fabbrini, E., Serafini, M., Colic Baric, C., Hazen, S. L., & Klein, S. (2014) Effect of plasma uric acid on antioxidant capacity, oxidative stress, and insulin sensitivity in obese subjects. Diabetes, 63, 976-981.

[36] Lippi, G., Montagnana, M., Franchini, M., Favaloro, E. J., & Targher, G. (2008) The paradoxical relationship between serum uric acid and cardiovascular disease. Clin Chim Acta, 392, 1-7.

[37] Itakura, M. (2009) Metabolic pathway and regulation of uric acid production. Hyperuricemia and Gout, 17, 106-111.

[38] Taniguchi, A., & Kamatani, N. (2008) Control of renal uric acid excretion and gout. Curr Opin Rheumatol, 20, 192-197.

[39] Ruggiero, C., Cherubini, A., Ble, A., Bos, A. J., Maggio, M., Dixit, V. D., Lauretani, F., Bandinelli, S., Senin, U., & Ferrucci, L. (2006) Uric acid and inflammatory markers. Eur Heart J, 27, 1174-1181.

[40] Zhang, L., Shi, X., Yu, J., Zhang, P., Ma, P., & Sun, Y. (2020) Dietary vitamin E intake was inversely associated with hyperuricemia in US adults: NHANES 2009-2014. Ann Nutr Metab, 76, 354-360.

[41] Zykova, S. N., Storhaug, H. M., Toft, I., Chadban, S. J., Jenssen, T. G., & White, S. L. (2015) Cross-sectional analysis of nutrition and serum uric acid in two Caucasian cohorts: the AusDiab Study and the Tromsø study. Nutr J, 14, 49.

[42] Sun, S. Z., Flickinger, B. D., Williamson-Hughes, P. S., & Empie, M. W. (2010) Lack of association between dietary fructose and hyperuricemia risk in adults. Nutr Metab (Lond), 7, 16.

[43] Beydoun, M. A., Fanelli-Kuczmarski, M. T., Canas, J-A., Beydoun, H. A., Evans, M. K., & Zonderman, A. B. (2018) Dietary factors are associated with serum uric acid trajectory differentially by race among urban adults. Br J Nutr, 120, 935-945.

[44] Smith, G. D., & Ebrahim, S. (2002) Data dredging, or confounding. BMJ, 325, 1437-1438.

[45] Clebak, K. T., Morrison, A., & Croad, J. R. (2020) Gout: Rapid evidence review. Am Fam Physician, 102, 533-538.

[46] Cheng, Y., Zhang, H., Zhu, Y., Xue, Z., Yan, M., Wang, H., Sun, S., & Zhang, X. (2022) Effects of fructose from apple and honey on serum uric acid in young Chinese: Randomized crossover trials. Asia Pac J Clin Nutr, 31, 87-96.

[47] Cai, W., Li, J., Shi, J., Yang, B., Tang, J., Truby, H., & Li, D. (2018) Acute metabolic and endocrine response induced by glucose and fructose in healthy young subjects: A double-blinded, randomized, crossover trial. Clin Nutr, 37, 459-470.

[48] Emmerson, B. T. (1974) Effect of oral fructose on urate production. Ann Rheum Dis, 33. 276-280.

[49] Wang, D. D., Sievenpiper, J. L., de Souza, R. J., Chiavaroli, L., Ha, V., Cozma, A. I., Mirrahimi, A., Yu, M. E., Carleton, A. J., Buono, M. D., Jenkins, A. L., Leiter, L. A., Wolever, T. M. S., Beyene, J., Kendall, C. W. C., & Jenkins, D. J. A. (2012) The effects of fructose intake on serum uric acid vary among controlled dietary trials. J Nutr, 142, 916-923.

[50] Choi, J. W. J., Ford, E. S., Gao, X., & Choi, H. K. (2008) Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: The third national health and nutrition examination survey. Arthritis. Rheum, 59, 109-116.

[51] Zhang, Z., Harman, J. L., Coresh, J., Köttgen, A., McAdams-DeMarco, M. A., Correa, A., Young, B. A., Katz, R., & Rebholz, C. M. (2018) The dietary fructose: vitamin C intake ratio is associated with hyperuricemia in African-American adults. J Nutr, 148, 419-426.

[52] Li, R., Yu, K., & Li, C. (2018) Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. Asia Pac J Clin Nutr, 27, 1344-1356.

[53] Zhang, C., Li, L., Zhang, Y., & Zeng, C. (2020) Recent advances in fructose intake and risk of hyperuricemia. Biomed Pharmacother, 131, 110795.

[54] Nielsen, S. M., Zobbe, K., Kristensen, L. E., & Christensen, R. (2018) Nutritional recommendations for gout: An update from clinical epidemiology. Autoimmun Res, 17, 1090-1096.

[55] Choi, H. K., & Curhan, G. (2008) Soft drinks, fructose consumption, and the risk of gout in men; Prospective cohort study. BMJ, 336, 309-312.

[56] Choi, H. K., Willett, W., & Curhan, G. (2010) Fructose-rich beverages and the risk of gout in women. JAMA, 304, 2270-2278.

[57] Jamnik, J., Rehman, S., Mejia, S. B., de Souza, R. J., Khan, T. A., Leiter, L. A., Wolever, T. M. S., Kendall, C. W. C. Jenkins, D. J. A., & Sievernpiper, J. L. (2016) Fructose intake and risk of gout and hyperuricemia: a systematic review and meta-analysis of prospective cohort studies. BMJ Open, 6, e013191.

[58] Le, M. T., Frye, R. F., Rivard, C. J., Cheng, J., McFann, K. K., Segal, M. S., Johnson, R. J., & Johnson, J. A. (2012) Effects of high-fructose corn syrup and sucrose on the pharmacokinetics of fructose and acute metabolic and hemodynamic responses in healthy subjects. Metabolism, 61, 641-651.

[59] Chuang, S. Y., Lee, S. C., Hsieh, Y. T., & Pan, W. H. (2011) Trends in hyperuricemia and gout prevalence: Nutrition and Health Survey in Taiwan from 1993-1996 to 2005-2008. Asia Pac J Clin Nutr, 20, 301-308.

[60] Merriman, T. R., Dalbeth, N., & Johnson, R. J. (2014) Sugar-sweetened beverages, urate, gout and genetic interaction. Pac Health Dialog, 20, 31-38.

[61] Kontogianni, M. D., Chrysohoou, C., Panagiotakos, D. B., Tsetsekou, E., Zeimbekis, A., Pitsavos, C., & Stefanadis, C. (2012) Adherence to the Mediterranean diet and serum uric acid: the ATTICA study. Scand J Rheumatol, 41, 442-449.

[62] Zgaga, L., Theodoratou, E., Kyle, J., Farrington, S. M., Agakov, F., Tenesa, A., Walker, M., McNeill, G., Wright, A. F., Rudan, I., Dunlop, M. G., & Campbell, H. (2012) The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. PLoS One, 7, e38123.

[63] Nguyen, S., Choi, H. K., Lustig, R. H., & Hsu, C. Y. (2009) Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. J Pediatr, 154, 807-813.

[64] Siqueira, J., Pereira, T. S. S., Veiasquez-Melendez, G., Barreto, S. M., Benseñor, I. M., Mill, J. G., & Molina, M. C. B. (2021) Sugar-sweetened soft drinks consumption and risk of hyperuricemia: Results of the ELSA-Brasil study. Nutr Metab Cardiovasc Dis, 31, 2004-2013.

[65] Ebrahimpour-Koujan, S., Saneei, P., Larijani, B., & Esmaillzadeh, A. (2021) Consumption of sugar-sweetened beverages and serum uric acid concentrations: a systematic review and meta-analysis. J Hum Nutr Diet, 34, 305-313.

[66] Stanhope, K. L. (2016) Sugar consumption, metabolic disease and obesity: The state of the controversy. Crit Rev Clin Lab Sci, 53, 52-67.

[67] Ebrahimpour-Koujan, S., Saneei, P., Larijani, B., & Esmaillzadeh, A. (2020) Consumption of sugar sweetened beverages and dietary fructose in relation to risk of gout and hyperuricemia: a systematic review and meta-analysis. Crit Rev Food Sci Nutr, 60, 1-10.

[68] Caliceti, C., Calabria, D., Roda, A., & Cicero, A. (2017) Fructose intake, serum uric acid, and cardiometabolic disorders: A critical review. Nutrients, 9, 395.

[69] FitzGerald, J. D., Dalbeth, N., Mikuls, T., Brignardello-Petersen, R., Guyatt, G., Abeles, A. M., Gelber, A. C., Harrold, L. R., Khanna, D., King, C., Levy, G., Libbey, C., Mount, D., Pillinger, M. H., Rosenthal, A., Singh, J. A., Sims, J. E., Smith, B. J., Wenger, N. S., Bae, S. S., Danve, A., Khanna, P. P., Kim, S. C., Lenert, A., Poon, S., Qasim, A., Sehra, S. T., Sharma, T. S. K., Toprover, M., Turgunbaev, M., Zeng, L., Zhang, M. A., Turner, A. S., & Neogi, T.(2020) 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Research, 72, 744-760.

[70] World Health Organization (2015) Guideline: Sugars intake for adults and children. pp. 1-49. WHO Press. Geneva, Switzerland.

[71] U.S. Department of Agriculture. (2021) Dietary Guidelines for Americans 2015-2020, 8th ed. [Internet]. Available from: https://health.gov/sites/default/files/2019-09/2015-2020_Dietary_Guidelines.pdf

[72] Kobayashi, T., Inokuchi, T., Yamamoto, A., Takahashi, S., Ka, T., Tsutsumi, Z., Saito, H., Moriwaki, Y., & Yamamoto, T. (2007) Effects of sucrose on plasma concentrations and urinary excretion of purine bases. Metabolism, 56, 439-443.

[73] Tappy, L., Morio, B., Azzout-Mamiche, D., Champ, M., Gerber, M., Houdart, S., Mas, E., Rizkalia, S., Slama, G., Mariotti, F., & Margaritis, I. (2018) French recommendations for sugar intake in adults: a novel approach chosen by ANSES. Nutrients, 10, 989.

[74] Schwingshackl, L., Neuenschwander, M., Hoffmann, G., Buyken, A., & Schlesinger, S. (2020) dietary sugars and cardiometabolic risk factors: a network meta-analysis on isocaloric substitution interventions. Am J Clin Nutr, 111, 187-196.

[75] Sun, S. Z., & Empie, M. W. (2012) Fructose metabolism in humans-what isotopic tracer studies tell us. Nutr. Metab (Lond), 9, 89.

[76] Dornas, W. C., de Lima, W. G., Pedrosa, M. L., & Silva, M. E. (2015) Health implications of high-fructose intake and current research. Adv Nutr, 6, 729-737.

[77] Ughi, N., Prevete, I., Ramonda, R., Cavagna, L., Filippou, G., Manara, M., Bortoluzzi, A., Parisi, S., Ariani, A., & Scirè, C. A. (2019) The Italian Society of Rheumatology clinical practice guidelines for the diagnosis and management of gout. Reumatismo, 71 (S1), 50-79.

[78] So, M. W., Lim, D-H., Kim, S-H., & Lee, S. (2020) Dietary and nutritional factors associated with hyperuricemia: The seventh Korean National Health and Nutrition Examination Survey. Asia Pac J Clin Nutr, 29, 609-617.

[79] Shatat, I. F., Abdallah, R. T., Sas, D. J., & Hailpern, S. M. (2012) Serum uric acid in US adolescents: distribution and relationship to demographic characteristics and cardiovascular risk factors. Pediatric Research, 72, 95-100.

[80] Zhu, Q., Yu, L., Li, Y., Man, Q., Jia, S., Zhou, Y., Zuo, H., & Zhang, J. (2022) Association between dietary fiber intake and hyperuricemia among Chinese adults: Analysis of the China Adult Chronic Disease and Nutrition Surveillance (2015). Nutrients, 14, 1433.

[81] Yu, K-H., See, L-C., Huang, Y-C., Yang, C-H., & Sun, J-H. (2008) Dietary factors associated with hyperuricemia in adults. Semin Arthritis Rheum, 37, 243-250.

[82] Sun, Y., Sun, J., Zhang, P., Zhong, F., Cai, J., & Ma, A. (2019) Association of dietary fiber intake with hyperuricemia in U.S. adults. Food Funct, 10, 4932-4940.

[83] Lyu, L. C., Hsu, C. Y., Yeh, C. Y., Lee, M. S., Huang, S. H., & Chen, C. L. (2003) A case-control study of the association of diet and obesity with gout in Taiwan. Am J Clin Nutr, 78, 690-701.

[84] Yamaguchi, Y., Ando, C., Tsukamoto, S., Nagao, J., Ueda, T., Yamaguchi, H., & Akaoka, I. (2007) The effect on the serum uric acid level of long-term intake of chitosan-supplemented food and its safety in adults. J Jpn Soc Clin Nutr, 29, 104-113 (in Japanese).

[85] Carabin, I. G., Lyon, M. R., Wood, S., Pelletier, X., Donazzolo, Y., & Burdock, G. A. (2009) Supplementation of the diet with the functional fiber PolyGlycoplex is well tolerated by healthy subjects in a clinical trial. Nutr J, 8, 9.

[86] Koguchi. T., & Tadokoro, T. (2019) Beneficial effect of dietary fiber on hyperuricemia in rats and humans: A review. Int. J. Vitam. Nutr. Res, 89, 89-108.

[87] Koguchi, T., Nakajima, H., Takano, S., Ota, T., Wada, M., Innami, S., & Tadokoro, T. (2016) Suppressive effect of agarose and cellulose on hyperuricemia induced by dietary RNA in rats. Curr Top Pharmacol, 20, 57-66.

[88] Koguchi, T., Nakajima, H., Takano, S., Ota, T., Wada, M., Innami, S., & Tadokoro, T. (2018) Suppressive effect of carboxymethyl-chitin and chitin on hyperuricemia induced by dietary RNA in rats. Chitin and Chitosan Research, 24, 11-22 (in Japanese).

[89] Lin, Z., Zhang, B., Liu, X., Jin, R., & Zhu, W. (2014) Effects of chicory inulin on serum metabolites of uric acid, lipids, glucose, and abdominal fat deposition in quails induced by purine-rich diets. J Med Food, 17, 1214-1221.

[90] Guo, Y., Yu, Y., Li, H., Ding, X., Li, X., Jing, X., Chen, J., Liu, G., Lin, Y., Jiang, C., Liu, Z., He, Y., Li, C., & Tian, Z. (2020) Inulin supplementation ameliorates hyperuricemia and modulates gut microbiota in *Uox*-knockout mice. Eur J Nutr [Internet]. Available from: https://doi.org/10.1007/s00394-020-02414-x.

[91] Zhang, Y., Shuai, T. G., Wu, C. M., Shen, J. J., & Zhong, G. (2016) Effect of konjac glucomannan on hyperuricemic rats. Research & Reviews: Journal of Food and Dairy Technology, 4, 18-25.

[92] Zhang, Y., Deng, L., Wu, C. M., Zheng, L., & Zhong, G. (2018) Konjac glucomannan improves hyperuricemia through regulating xanthine oxidase, adenosine deaminase and urate transporters in rats. Journal of Functional Foods, 48, 566-575.

[93] Hosomi, A., Nakanishi, T., Fujita, T., Tamai, I., & Hosomi, A (2012) Extra-renal elimination of uric acid via intestinal efflux transporter BCRP/ABCG2. PLoS ONE, 7, e30456.

[94] Nieuwdorp, M., Gilijamse, P. W., Pai, N., & Kaplan, L. M. (2014) Role of the microbiome in energy regulation and metabolism. Gastroenterology, 146, 1525-1533.

[95] Hamer, H. M., Jonkers, D. M., Bast, A., Vanhoutvin, S. A., Fischer, M. A., Kodde, A., Troost, F., Venema, K., & Brummer, R-J. M. (2009) Butyrate modulates oxidative stress in the colonic mucosa of healthy humans. Clin Nutr, 28, 88-93.

[96] Lattimer, J. M., & Haub, M. D. (2010) Effects of dietary fiber and its components on metabolic health. Nutrients, 2, 1266-1289.

[97] Schariau, D., Borowicki, A, Habermann, N., Hofmann, T., Klenow, S., Miene, C., Munjal, U., Stein, K., & Glei, M. (2009) Mechanisms of primary cancer prevention by butyrate and other products formed during gut flora-mediated fermentation of dietary fiber. Mutat Res, 582, 39-53.

[98] Bander, Z. A., Nitert, M. D., Mousa, A., & Naderpoor, N. (2020) The gut microbiota and inflammation: An overview. Int J Environ Res Public Health, 17, 7618.

[99] Ando, A., Bamba, T., & Sasaki, M (1999) Physiological and anti-inflammatory roles of dietary fiber and butyrate in intestinal functions. JPEN J Parenter Enteral Nutr, 23, S70-S73.

[100] Hijova E., Szabadosova, V., Štofilová, J., & Hrčková, G. (2013) Chemopreventive and metabolic effects of inulin on colon cancer development. J Vet Sci, 14, 387-393.

[101] Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Recommended Dietary Allowances and Adequate Intakes, Total Water and Macronutrients. (2011) Washington, D. C. The National Academy Press. [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56068/table/summarytables.t4/?report=objectonly

[102] Teng, G. G., Pan, A., Yuan, J. M., & Koh, W. P. (2015) Food sources of protein and risk of incident gout in the Singapore Chinese Health Study. Arthritis Rheumatol, 67, 1933-1942.

[103] Van Elswyk, M. E., Weatherford, C. A., & McNeill, S. H. (2018) A systematic review of renal health in healthy individuals associated with protein intake above the US Recommended Allowance in randomized controlled trials and observational studies. Adv Nutr, 9, 404-418.

[104] Devries, M. C., Sithamparapillai, A., Brimble, K. S., Banfield, L., Morton, R. W., & Phillips, S. M. (2018) Changes in kidney function do not differ between healthy adults consuming higher- compared with lower- or normal-protein diets: A systematic review and meta-analysis. J Nutr, 148, 1760-1775.

[105] The World Health Organization, Food and Agriculture Organization, and United Nations University. (2007) Protein and amino acid requirements in human nutrition. Tech Rep Ser, 935.

[106] Dalbeth, N., Wong, S., Gamble, G. D., Horne, A., Mason, B., Pool, B., Fairbanks, L., McQueen, F. M., Cornish, J., Reid, I. R., & Palmano, K. (2010) Acute effect of milk on serum urate concentrations: a randomized controlled crossover trial. Ann Rheum Dis, 69. 1677-1682.

[107] Garrel, D. R., Verdy, M., PetitClerc, C. Martin, C., Brulé, D., & Hamet, P. (1991) Milk-and soy-protein ingestion; Acute effect on serum uric acid concentration. Am J Clin Nutr, 53, 665-669.

[108] Jenkins, D. J., Kendall, C. W., Vidgen, E., Augustin, L. S., van Erk, M., Geelen, A., Parker, T., Faulkner, D., Vuksan, V., Josse, R. G., Leiter, L. A., & Connelly, P. W. (2001) High-protein diets in hyperlipidemia: effect of wheat gluten on serum lipids, uric acid, and renal function. Am J Clin Nutr, 74, 57-63.

[109] Hosojima, M., Kaseda, R., Kondo, H., Fujii, M., Kubota, M., Watanabe, R., Tanabe, N., Kadowaki, M., Suzuki, Y., & Saito, A. (2016) Beneficial effects of rice endosperm protein intake in Japanese men with risk factors for metabolic syndrome: a randomized, crossover clinical trial. BMC Nutr, 2, 25.

[110] Terkeltaub, R. (2010) Update on gout.; new therapeutic strategies and options. Nat Rev Rheumatol, 6, 30-38.

[111] Terkeltaub, R., & Edwards, N. L. (2010) Uric acid metabolism and pathogenesis of hyperuricemia. Gout; Diagnosis and management of gouty arthritis and hyperuricemia. p. 28-33. Professional Communications, Inc. NY.

[112] Saito, H., Toyoda, Y., Takada T., Hirata, H., Ota-kontani, A., Miyata, H., Kobayashi, N., Tsuchiya, Y., & Suzuki, H. (2020) n-3 polyunsaturated fatty acids inhibit the function of human URAT 1, a renal urate re-absorber. Nutrients, 12, 1601.

[113] Zhang, M., Zhang, Y., Terkeltaub, R., Chen, C., & Neogi, T. (2019) Effect of dietary and supplemental omega-3 polyunsaturated fatty acids on risk of recurrent gout flares. Arthritis Rheumatol, 71, 1580-1586.

[114] Tate, G. A., Mandell, B. F., Karmali, R. A., Laposata, M., Baker, D. G., Schumacher, H. R. Jr., & Zurier, R. B. (1988) Suppression of monosodium urate crystal-induced acute inflammation by diets enriched with gamma-linolenic acid and eicosapentaenoic acid. Arthritis Rheum, 31, 1543-1551.

[115] Mozaffarian, D., & Wu, J. H. Y. (2011) Omega-3 fatty acids and cardiovascular disease. J Am Coll Cardiol, 58, 2047-2067.

[116] Williams, P. T. (2008) Effects of diet, physical activity and performance, and body weight on incident gout in ostensibly healthy, vigorously active men. Am J Clin Nutr, 87, 1480-1487.

[117] Loenen, H. M. J. A., Eshuis, H., Löwik, M. R. H., Schouten, E. G., Hulshof, K. F. A. M., Odink, J., & Kok, F. J. (1990) Serum uric acid correlates in elderly men and women with special reference to body composition and dietary intake (Dutch Nutrition Surveillance System). J Clin Epidemiol, 43, 1297-1303.

[118] Villegas, R., Xiang, Y. -B., Elasy, T., Xu, W. H., Cai, H., Cai, Q., Linton, M. F., Fazio, S., Zheng, W., & Shu, X. -O. (2012) Purine-rich foods, protein intake, and the prevalence of hyperuricemia: the Shanghai Men's Health Study. Nutr Metab Cardiovasc Dis, 22, 409-416.

[119] Shadick, N. A., Kim, R., Weiss, S., Liang, M. H., Sparrow, D., & Hu, H. (2000) Effect of low level lead exposure on hyperuricemia and gout among middle aged and elderly men: the normative aging study. J Rheumatol, 27, 1708-1712.

[120] Choi, H. K., & Curhan, G. (2004) Beer, liquor, and wine consumption and serum uric acid level; The Third National Health and Nutrition Examination Survey. Arthritis Rheum, 51, 1023-1029.

[121] Campion, E. W., Glynn, R. J., & DeLabry, L. O. (1987) Asymptomatic hyperuricemia: Risks and consequences in the Normative Aging Study. Am J Med, 82, 421-426.

[122] Liu, H., Zhang, X. M., Wang, Y. L., & Liu, B. C. (2014) Prevalence of hyperuricemia among Chinese adults: a national cross-sectional survey using multistage, stratified sampling. J Nephrol, 27, 653-658.

[123] Sigie, T., Imatou, T., Miyazaki, M., & Une, H. (2005) The effect of alcoholic beverage type on hyperuricemia in Japanese male office workers. J Epidemiol, 15, 41-47.

[124] Xiong, Z., Zhu, C., Qian, X., Zhu, J., Wi, Z., & Chen, L. (2013) Serum uric acid is associated with dietary and lifestyle factors in elderly women in suburban Guangzhou in Guangdong province of south China. J Nutr Hralth Aging, 17, 30-34.

[125] Torralba, K. D., De Jesus, E., & Rachabattula, S. (2012) The interplay between diet, urate transporters and the risk for gout and hyperuricemia: current and future directions. Int J Rheum Dis, 15, 499-506.

[126] Choi, H. K., Atkinson, K., Karlson, E. W., Willett, W., & Curhan, G. (2004) Alcohol intake and risk of incident gout in men: a prospective study. Lancet, 363, 1277-1281.

[127] Soriano, L. C., Rothenbacher, D., Choi, H. K., & Rodriguez, G. (2011) Contemporary epidemiology of gout in the UK general population. Arthritis Res Ther, 13, R39.

[128] Wang M, Jiang X, Wu W., & Zhang, D. (2013) A meta-analysis of alcohol consumption and the risk of gout. Clin Rheumatol, 32, 1641-1648.

[129] McCormick, N., Rai, S. K., Lu, N., Yokose, C., Curhan, G. C., & Choi, H. K. (2020) Estimation of primary prevention of gout in men through modification of obesity and other key lifestyle factors. JAMA Netw Open, 3, e2027421.

[130] Yamamoto, T., Moriwaki, Y., & Takahashi, S. (2005) Effect of ethanol on metabolism of purine bases (hypoxanthine, xanthine, and uric acid). Clin Chim Acta, 356, 35-57.

[131] Roman, Y. M. (2019) Perspectives on the epidemiology of gout and hyperuricemia. Hawaii J Med Public Health, 78, 71-76.

[132] Eastmond, C. J., Garton, M., Robins, S., & Riddoch, S. (1995) The effects of alcoholic beverages on urate metabolism in gout sufferers. Br J Rheumatol, 34, 756-759.

[133] Choi, H. K., Mount, D. B., Reginato, A. M., American College of Physicians; American Physiological Society (2005) Pathogenesis of gout. Ann. Intern. Med, 143, 499-516.

[134] Zhang, Y., Woods, R., Chaisson, C. E., Neogi, T., Niu, J., McAlndon, T. E., & Hunter, D. (2006) Alcohol consumption as a trigger of recurrent gout attacks. Am J Med, 119, 800, e13-18.

[135] Zhang, Y., Chen, C., Choi, H., Chaisson, C., Hunter, D., Niu, J., & Neogi, T. (2012) Purine-rich foods intake and recurrent gout attacks. Ann Rheum Dis, 71, 1448-1453.

[136] Neogi, T., Chen, C., Niu, J., Chaisson, C., Hunter, D., & Zhang, Y. (2014) Alcohol quantity and type on risk of recurrent gout attacks: an internet-based case-crossover study. Am J Med, 127, 311-318.

[137] Terkeltaub, R., & Edwards, N. L. (2013) Gout: Diagnosis and management of gouty arthritis and hyperuricemia. 3rd edition, p. 1-336. Professional Communications, Inc. NY.

[138] Tani, Y., Asakura, K., Sasaki, S., Hirota, N., Notsu, A., Todoriki, H., Miura, A., Fukui M., & Date, C. (2015) The influence of season and air temperature on water intake by food groups in a sample of free-living Japanese adults. Eur J Clin Nutr, 69, 907-913.

[139] Neogi, T., Chen, C., Chiasson, C., Hunter, D. J., & Zhang, Y. (2009) Drinking water can reduce the risk of recurrent gout attacks. Arthritis Rheum, 60 (suppl), S762.

[140] Jakše, B., Jakše, B., Pajek, M., & Pajek, J. (2019) Uric acid and plant-based nutrition. Nutrients, 11, 1736.