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# Modification of Micronutrient 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

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**Abstract:** The prevalence of gout in Japan has increased markedly since the 1960s. The westernization of the Japanese diet from 1955 is thought to be one factor the increase in the prevalence of gout. In Japan, most of gout patients are adults, and the number of gout patients are higher in men than in women. A previous report showed modification of dietary habits for the prevention of gout in Japanese people through the trends in micronutrient (vitamin and mineral) intake of Japanese people in 1946-2016. The aim of this article is to suggest what micronutrient 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 micronutrients. Micronutrient intakes of Japanese people in 2019 was compared with those in 2016. The relationship between the number of gout patients and micronutrient 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 daily intake of vitamin A, vitamin E, vitamin K, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, niacin, pantothenic acid, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, vitamin C, sodium, salt, calcium, potassium, magnesium, phosphorus, iron, copper, and zinc of Japanese people in 2019 were higher compared to those in 2016, respectively. Whereas the daily vitamin D intake of Japanese people in 2019 was lower compared to that in 2016. The daily intake of vitamin A, vitamin D, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>12</sub>, vitamin C, salt, calcium, iron, and copper were negatively correlated with the number of gout patients, respectively. Modification of micronutrient intake for the prevention of gout in Japanese people (especially adults) in 2019 is suggested as follows: limiting or decreasing salt intake; decreasing intake of phosphorus and copper; increase intake of vitamin A, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, calcium, potassium, magnesium, and zinc; increase intake of vitamin B<sub>2</sub> and vitamin C in Japanese men (aged 20-59 years) and women (aged 20-59 years).

**Keywords:** Dietary Reference Intakes, Food, Gout, Hyperuricemia, Mineral, Uric Acid, Vitamin

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## 1. Introduction

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 [1-4]. Furthermore, the burden of gout has increased between 1990 and 2017 globally, especially in high sociodemographic index countries [4]. A remarkable increase in gout patients in Japan has been observed since the 1960s [2, 3]. In particular, the increase in gout patients was remarkable after 1965 [3]. This phenomenon is thought to be attributed to the westernization of the Japanese diet since 1955. The phenomenon that the number of gout patients has

increased with the westernization of the Japanese diet since 1955 has been described in the previous report [5]. Recently, the Ministry of Health, Labour and Welfare in Japan [6-11] has shown the number of gout patients and the intake of nutrients or foods in 2019. The number of gout patients of Japanese people in 2019 was higher compared to that in 2016 and increased 4.92-fold compared to that in 1986 (1986: 0.255 million; 2016: 1.105 million; 2019: 1.254 million) [12]. The author previously examined comparison with the daily macronutrient intake in 2016 and 2019 [12]. Considering from the results, 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, cholesterol; increase intake of carbohydrate (particularly dietary fiber).

In the previous report [13], Japanese people (aged  $\geq 15$  years) in 2016 should take in more vitamin A, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>6</sub>, calcium, potassium, magnesium, and zinc to reach the Recommended Dietary Allowances (RDAs) [13]. It is necessary to recognize what micronutrient (vitamin and mineral) intake is important as potential dietary habits to prevent gout in Japanese people in 2019.

This article shows the relationship between the number of gout patients and micronutrient (vitamin and mineral) intake in Japanese people and suggests modification of micronutrient (vitamin and mineral) intake for the prevention of gout in Japanese people referencing the results of clinical research through comparison with micronutrient intake in 2016 and 2019.

## 2. Methods

### 2.1. The Number of Gout Patients

The number of gout patients was estimated in the Comprehensive Survey of Living Conditions performed by the Ministry of Health, Labour and Welfare in Japan (1986-2019) [6-8]. 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 [9-11]. Data were extracted from the series of Japanese National Nutrition Surveys that have been carried out every year throughout Japan since 1946 [11]. 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) [9].

### 2.3. Dietary Reference Intakes for Japanese People

The Ministry of Health, Labour and Welfare in Japan [10] 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 the Institute of Medicine of the National Academy of Sciences in the U.S. [14] 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 [15] and the National Institutes of Health in the U.S. Department of Health & Human Services [16].

### 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. Relationship Between the Number of Gout Patients and Vitamin Intake in Japanese People

The results on the correlation between the number of gout patients and vitamin intake in Japanese people are shown in Tables 1 and 2.

### 3.1. Fat-soluble Vitamins

#### 3.1.1. Vitamin A

The daily vitamin A (retinol equivalent) intake of Japanese

people in 2019 was higher compared to that in 1960, 1965, 1975, 2010, 2013, and 2016 and was lower compared to that in 1986, 1989, 1992, 1995, 1998, 2001, 2004, and 2007 (1960: 354.0 µgRAE; 1965: 397.2 µgRAE; 1975: 480.6 µgRAE; 1986: 650.7 µgRAE; 1989: 806.1 µgRAE; 1992: 794.7 µgRAE; 1995: 852.0 µgRAE; 1998: 810.3 µgRAE; 2001: 981.0 µgRAE; 2004: 879.0 µgRAE; 2007: 615.0 µgRAE; 2010: 529.0 µgRAE; 2013: 516.0 µgRAE; 2016: 524.0 µgRAE; 2019: 534.0 µgRAE). The daily vitamin A intake of Japanese adult population (aged ≥ 20 years) was higher compared to that in 2016 (2016: 529.0 µgRAE; 2019: 547.0 µgRAE). The daily vitamin A intake of Japanese adult men (aged ≥ 20 years) and women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 541.0 µgRAE; 2019: 564.0 µgRAE; women: 2016: 520.0 µgRAE; 2019: 532.0 µgRAE).

The daily vitamin A (retinol equivalent) intake of Japanese men (aged 30-49 years, aged ≥ 60 years) in 2019 were higher compared to those in 2016, respectively (aged 30-49 years: 2016: 465-523 µgRAE/day; 2019: 474-555 µgRAE/day; aged ≥ 60 years: 2016: 559-568 µgRAE/day; 2019: 596-621 µgRAE/day). The daily vitamin A (retinol equivalent) intake of Japanese men (aged 1-29 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-29 years: 2016: 397-542 µgRAE/day; 2019: 356-532 µgRAE/day; aged 50-59 years: 2016: 574 µgRAE/day; 2019: 528 µgRAE/day). The daily vitamin A (retinol equivalent) intake of Japanese women (aged ≥ 50 years) in 2019 was higher compared to that in 2016 (aged ≥ 50 years: 2016: 520-569 µgRAE/day; 2019: 543-604 µgRAE/day). The daily vitamin A (retinol equivalent) intake of Japanese women (aged 1-49 years) in 2019 was lower compared to that in 2016 (aged 1-49 years: 2016: 391-519 µgRAE/day; 2019: 345-491 µgRAE/day).

The daily vitamin A (retinol equivalent) intake of Japanese men (aged 15-69 years) and women (aged 15-49 years) were 451-596 µgRAE/day and 409-458 µgRAE/day, respectively, and were below the Estimated Average Requirements (EARs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 15-69 years): 600-650 µgRAE/day; women (aged 15-49 years): 450-500 µgRAE/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 15-69 years): 625-630 µgRAE/day; women (aged 15-49 years): 485-500 µgRAE/day] [14]. Thus the daily vitamin A (retinol equivalent) intake of Japanese men (aged 15-69 years) and women (aged 15-49 years) were below the Recommended Dietary Allowances (RDAs) for vitamin A established both the Ministry of Health, Labour and Welfare in Japan [men (aged 15-69 years): 850-900 µgRAE/day; women (aged 15-49 years): 650-700 µgRAE/day] [10] and the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged ≥ 14 years): 900 µgRAE/day; women (aged ≥ 14 years): 700 µgRAE/day] [14, 16, 17]. The daily vitamin A (retinol equivalent) intake of Japanese men (aged 1-6 years), men (aged ≥ 70 years), and women (aged ≥ 50 years) in 2019 were 356 µgRAE/day, 621 µgRAE/day, and 543-604

µgRAE/day, respectively, and were above the Estimated Average Requirements (EARs) [men (1-6 years): 300-350 µgRAE/day; men (aged ≥ 70 years): 550-600 µgRAE/day; women (aged ≥ 50 years): 450-500 µgRAE/day] and were below the Recommended Dietary Allowances (RDAs) [men (aged 1-6 years): 400-450 µgRAE/day; men (aged ≥ 70 years): 800-850 µgRAE/day; women (aged ≥ 50 years): 650-700 µgRAE/day] [10]. The daily vitamin A (retinol equivalent) intake of Japanese men (aged ≥ 14 years) and women (aged ≥ 14 years) were below the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

The daily vitamin A intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.899$ ,  $p = 0.000164$ ) and in 1986-2019 ( $r = -0.893$ ,  $p = 0.0000933$ ). The intake of vitamin A did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 ( $r = -0.669$ ,  $p = 0.217$ ) and in 2004-2019 ( $r = -0.585$ ,  $p = 0.222$ ). The intake of vitamin A did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 ( $r = -0.731$ ,  $p = 0.161$ ) and in 2004-2019 ( $r = -0.636$ ,  $p = 0.175$ ). The intake of vitamin A did not show a significant correlation with number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 ( $r = 0.797$ ,  $p = 0.106$ ). The intake of vitamin A tended to be positively correlated with number of gout patients in adult women (aged ≥ 20 years) in 2004-2019 ( $r = 0.806$ ,  $p = 0.0526$ ). This result suggests that the daily vitamin A intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

Judging from the data of food composition [15, 16], it is important for Japanese people (aged ≥ 14 years) to eat organ meats (liver, breast), seafood (salmon, tuna, herring, firefly squid, eel, conger eel, sablefish), potatoes, whole grains (fortified ready-to-eat cereals), nuts (pistachio nuts), legumes (black-eyed peas, baked beans), seaweed, fruit (apricots, mangos, cantaloupes), vegetables (spinach, carrots, peppers, broccoli, Jew's mallows, perillas), dairy products (milk, cheese, yogurt), eggs, green tea to take in more vitamin A to reach the Recommended Dietary Allowances (RDAs) established both the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

### 3.1.2. Vitamin D

The daily vitamin D of Japanese people in 2019 was lower compared to that in 2001, 2004, 2007, 2010, 2013, and 2016 (2001: 8.4 µg/day; 2004: 7.9 µg/day; 2007: 7.6 µg/day; 2010: 7.3 µg/day; 2013: 7.5 µg/day; 2016: 7.5 µg/day; 2019: 6.9 µg/day). The daily vitamin D intake of Japanese adult population (aged ≥ 20 years) was lower compared to that in 2016 (2016: 7.8 µg/day; 2019: 7.2 µg/day). The daily vitamin D intake of Japanese adult men (aged ≥ 20 years) and women (aged ≥ 20 years) in 2019 were lower compared to those in 2016, respectively (men: 2016: 8.2 µg/day; 2019: 7.9 µg/day; women: 2016: 7.5 µg/day; 2019: 6.6 µg/day).

The daily vitamin D intake of Japanese men (aged 1-6 years,

aged  $\geq 70$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 3.9  $\mu\text{g}/\text{day}$ ; 2019: 4.1  $\mu\text{g}/\text{day}$ ; aged  $\geq 70$  years: 2016: 9.9  $\mu\text{g}/\text{day}$ ; 2019: 10.3  $\mu\text{g}/\text{day}$ ). The daily vitamin D intake of Japanese men (aged 7-69 years) in 2019 was lower compared to that in 2016 (2016, 6.2-9.3  $\mu\text{g}/\text{day}$ ; 2019, 5.5-7.9  $\mu\text{g}/\text{day}$ ). The daily vitamin D intake of Japanese women (aged  $\geq 1$  year) in 2019 was lower compared to that in 2016 (2016, 3.6-8.9  $\mu\text{g}/\text{day}$ ; 2019, 3.4-8.4  $\mu\text{g}/\text{day}$ ).

The daily vitamin D intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were 4.1-10.3  $\mu\text{g}/\text{day}$  and 3.4-8.4  $\mu\text{g}/\text{day}$ , respectively, and were below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 1$  year): 20-100  $\mu\text{g}/\text{day}$ ; women (aged  $\geq 1$  year): 20-100  $\mu\text{g}/\text{day}$ ] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 1$  year): 50  $\mu\text{g}/\text{day}$ ; women (aged  $\geq 1$  year): 50  $\mu\text{g}/\text{day}$ ] [14]. The daily vitamin D intake of Japanese men (aged 15-69 years) and women (aged 1-6 years, aged  $\geq 15$  years) in 2019 were 5.5-7.9  $\mu\text{g}/\text{day}$ , 3.4  $\mu\text{g}/\text{day}$  and 4.6-8.4  $\mu\text{g}/\text{day}$ , respectively, and were below the Adequate Intakes (AIs) [men (aged 15-69 years): 8.5-9.0  $\mu\text{g}/\text{day}$ ; women (aged 1-6 years): 3.4-5.0  $\mu\text{g}/\text{day}$ ; women (aged  $\geq 15$  years): 8.5  $\mu\text{g}/\text{day}$ ] [10]. The daily vitamin D intake of Japanese men (aged  $\geq 70$  years) in 2019 was 10.3  $\mu\text{g}/\text{day}$  and was above the Adequate Intakes (AIs) [men (aged  $\geq 70$  years): 8.5  $\mu\text{g}/\text{day}$ ] [10]. The Recommended Dietary Allowances (RDAs) for vitamin D in the U.S. men and women (aged 19-70 years), men and women (aged  $\geq 71$  years) established by the Food and Nutrition Board at Institute of Medicine in the U.S. are 15  $\mu\text{g}/\text{day}$  and 20  $\mu\text{g}/\text{day}$ , respectively [17]. The Adequate Intakes (AIs) for vitamin D in the U.S. men and women (aged 0-50 years), men and women (aged 51-70 years), men and women (aged  $\geq 71$  years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 5  $\mu\text{g}/\text{day}$ , 10  $\mu\text{g}/\text{day}$  and 15  $\mu\text{g}/\text{day}$ , respectively [14]. The daily vitamin D intake of Japanese men (aged 7-49 years) and Japanese women (aged 7-19 years, aged 40-49 years) were 5.5-6.4  $\mu\text{g}/\text{day}$ , 5.3-5.8  $\mu\text{g}/\text{day}$  and 5.3  $\mu\text{g}/\text{day}$ , respectively, and were above the Adequate Intakes (AIs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 0-50 years): 5  $\mu\text{g}/\text{day}$ ; women (aged 0-50 years): 5  $\mu\text{g}/\text{day}$ ] [14]. Whereas the daily vitamin D intake of Japanese men (aged 50-69 years, aged  $\geq 75$  years) and Japanese women (aged 20-39 years, aged 50-69 years, aged  $\geq 70$  years) were 8.0-9.0  $\mu\text{g}/\text{day}$ , 13.4  $\mu\text{g}/\text{day}$ , 4.6-4.9  $\mu\text{g}/\text{day}$ , 5.4-7.1  $\mu\text{g}/\text{day}$ , and 8.4  $\mu\text{g}/\text{day}$ , respectively, and were below the Adequate Intakes (AIs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 50-69 years): 10.0  $\mu\text{g}/\text{day}$ ; men (aged  $\geq 75$  years): 15.0  $\mu\text{g}/\text{day}$ ; women (aged 20-39 years): 5.0  $\mu\text{g}/\text{day}$ ; women (aged 50-69 years): 10.0  $\mu\text{g}/\text{day}$ ; women (aged  $\geq 70$  years): 10.0-15.0  $\mu\text{g}/\text{day}$ ] [14]. The daily vitamin D intake of Japanese adult men and women tended to increase as age increased.

The daily vitamin D intake tended to be negatively correlated with the number of gout patients in 2001-2016 ( $r =$

$-0.809$ ,  $p = 0.0511$ ). The daily vitamin D intake was negatively correlated with the number of gout patients in 2001-2019 ( $r = -0.891$ ,  $p = 0.00709$ ). The intake of vitamin D did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.723$ ,  $p = 0.167$ ). Whereas the intake of vitamin D was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.886$ ,  $p = 0.0187$ ). The intake of vitamin D did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.870$ ,  $p = 0.0552$ ). The intake of vitamin D was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.932$ ,  $p = 0.00677$ ). The intake of vitamin D did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.822$ ,  $p = 0.0876$ ) and in 2004-2019 ( $r = 0.684$ ,  $p = 0.134$ ). This result suggests that the correlation of daily vitamin D intake with the number of gout patients tends to vary with gender.

Vitamin D intake was inversely associated with hyperuricemia risk among U.S. adult participants in the National Health and Nutrition Examination Survey (NHANES) 2007-2014 [18]. This article revealed that male subjects in the highest level of vitamin D intake ( $\geq 14.7$   $\mu\text{g}/\text{day}$ ) were 41% less likely to be hyperuricemia [serum uric acid (SUA) concentration  $\geq 7.0$  mg/dL (416.4  $\mu\text{mol}/\text{L}$ ) in males and  $\geq 6.0$  mg/dL (356.9  $\mu\text{mol}/\text{L}$ ) in females] compared to those subjects in the lowest intake level ( $< 1.3$   $\mu\text{g}/\text{day}$ ) [OR = 0.59 (95% confidence interval, 0.48-0.71)]. Female subjects in the highest level of vitamin D intake ( $\geq 19.6$   $\mu\text{g}/\text{day}$ ) were also 20% less likely to be hyperuricemia compared to those subjects in the lowest intake level ( $< 1.2$   $\mu\text{g}/\text{day}$ ) [OR = 0.80 (95% confidence interval, 0.65-0.98)] [18]. From the result of the above article [18], though the daily vitamin D intake of Japanese men (aged  $\geq 70$  years) was above the Adequate Intakes (AIs), it seems that Japanese adult population (aged  $\geq 20$  years) need to take in more vitamin D.

Vitamin D deficiency can activate the parathyroid to induce the release of parathyroid hormone [19], which was thought to increase SUA levels [20, 21]. Vitamin D deficiency was associated with hyperuricemia [22]. A review reported by Charoenngam [23] suggests that correcting vitamin D deficiency (serum 25-dihydroxyvitamin D concentration  $< 20$  ng/mL) and insufficiency (serum 25-dihydroxyvitamin D concentration 20-  $< 30$  ng/mL) has a mild uric acid (UA) -lowering effect ( $\sim 0.3$ -0.6 mg/dL), which is thought to be mediated by the suppression of parathyroid hormone, which is known to downregulate the ATP-binding cassette transporter G2 (ABCG2) in the kidneys, leading to a reduction in the renal clearance of UA [24]. Serum UA, blood glucose, erythrocyte sedimentation rate, C-reactive protein (CRP), and interleukin-22 (IL-22) levels were significantly higher in acute gouty arthritis patients than in healthy controls [25]. Whereas serum 1,25-dihydroxy vitamin D3 levels were significantly lower in acute gouty arthritis patients than in healthy controls [30]. Luo et al. [26] found that plasma interleukin-22 (IL-22) levels were higher

in patients with acute gouty arthritis than in healthy controls and plasma interleukin-22 (IL-22) levels was positively correlated with serum C-reactive protein (CRP) levels. Chen et al. [25] also observed that serum interleukin-22 (IL-22) levels was positively correlated with serum C-reactive protein (CRP) levels or SUA levels, respectively and serum 1,25-dihydroxy vitamin D3 levels was negatively correlated with serum C-reactive protein (CRP) levels or SUA levels, respectively. They [25] have state that both interleukin-22 (IL-22) and 1,25-dihydroxy vitamin D3 functioned in gouty arthritis-related immune and inflammatory responses, and closely correlated with the level of gouty arthritis-related UA.

Judging from the data of food composition [15, 16] and roles in the body of vitamin D (promotion of calcium absorption, reduction of inflammation, modulation of such processes as cell growth, neuromuscular and immune function, and glucose metabolism) [16], it is important for Japanese men (aged 50-69 years, aged  $\geq 75$  years) and Japanese women (aged 20-39 years, aged 50-69 years, aged  $\geq 70$  years) to eat fish (salmon, trout, swordfish, sturgeon, cisco, whitefish, mackerel, tuna, sardines, rockfish, tilapia, flatfish), fish oil (cod liver), mushrooms, milks (whole milk, whole chocolate milk, soy milk, almond milk), dairy products (yogurt), cereals (fortified ready-to-eat cereals), eggs to take in more vitamin D to reach the Adequate Intakes (AIs) or the Recommended Dietary Allowances (RDAs) set by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 50-69 years): 10.0  $\mu\text{g}/\text{day}$ ; men (aged  $\geq 75$  years): 15.0  $\mu\text{g}/\text{day}$ ; women (aged 20-39 years): 5.0  $\mu\text{g}/\text{day}$ ; women (aged 50-69 years): 10.0  $\mu\text{g}/\text{day}$ ; women (aged  $\geq 70$  years): 10.0-15.0  $\mu\text{g}/\text{day}$ ] [14]. However, it must be careful not to exceed the Tolerable Upper Intake levels (ULs) of the daily vitamin D intake.

### 3.1.3. Vitamin E

The daily vitamin E intake of Japanese people in 2019 was lower compared to that in 2001, 2004, 2007, and 2010 and was higher compared to that in 2013 and 2016 (2001: 8.5 mg/day; 2004: 10.5 mg/day; 2007: 8.6 mg/day; 2010: 7.9 mg/day; 2013: 6.4 mg/day; 2016: 6.4 mg/day; 2019: 6.7 mg/day). The daily vitamin E intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 6.6 mg/day; 2019: 6.9 mg/day). The daily vitamin E intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 6.9 mg/day; 2019: 7.2 mg/day; women: 2016: 6.4 mg/day; 2019: 6.6 mg/day).

The daily vitamin E intake of Japanese men (aged 15-29 years, aged  $\geq 40$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-29 years: 2016: 6.4-6.9 mg/day; 2019: 6.9-7.3 mg/day; aged  $\geq 40$  years: 2016: 6.5-7.3 mg/day; 2019: 6.7-7.5 mg/day). Whereas the daily vitamin E intake of Japanese men (aged 1-14 years) in 2019 was lower compared to that in 2016 (2016: 4.4-6.1 mg/day; 2019: 4.2-6.0 mg/day). The daily vitamin E intake of Japanese men (aged 30-39 years) in 2019 was the same as that in 2016 (2016: 6.6 mg/day; 2019:

6.6 mg/day). The daily vitamin E intake of Japanese women (aged 15-19 years, aged 30-39 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 5.9 mg/day; 2019: 6.6 mg/day; aged 30-39 years: 2016: 5.9 mg/day; 2019: 6.1 mg/day; aged  $\geq 60$  years: 2016: 6.6-6.9 mg/day; 2019: 7.0-7.2 mg/day). Whereas the daily vitamin E intake of Japanese women (aged 1-6 years, aged 20-29 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 4.1 mg/day; 2019: 3.8 mg/day; aged 20-29 years: 2016: 5.7 mg/day; 2019: 5.4 mg/day). The daily vitamin E intake of Japanese women (aged 7-14 years, aged 40-49 years, aged 50-59 years) in 2019 were the same as those in 2016, respectively (aged 7-14 years: 5.9 mg/day; aged 40-49 years: 6.0 mg/day; aged 50-59 years: 6.6 mg/day).

The daily vitamin E intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were 4.2-7.5 mg/day and 3.8-7.2 mg/day, respectively, and were below the Tolerable Upper Intake levels (ULs) [men (aged  $\geq 1$  year): 150-900 mg/day; women (aged  $\geq 1$  year): 150-700 mg/day] [10]. The daily vitamin E intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) in 2019 were 6.6-7.5 mg/day and 5.4-7.2 mg/day, respectively, and were above the Adequate Intakes (AIs) [men (aged  $\geq 15$  years): 6.0-7.5 mg/day; women (aged  $\geq 15$  years): 5.0-6.5 mg/day] [10]. The Estimated Average Requirements (EARs) and the Recommended Dietary Allowances (RDAs) for vitamin E in the U.S. men (aged  $\geq 14$  years) and women (aged  $\geq 14$  years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 12 mg/day and 15 mg/day, respectively [14]. In Dietary Reference Intakes for Japanese established by the Ministry of Health, Labour and Welfare in Japan, the daily vitamin E intake in Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) appears to be very unlikely to cause a deficiency. However, Judging from Dietary Reference Intakes established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14], Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) need to take in more vitamin E to reach the Recommended Dietary Allowances (RDAs).

The daily vitamin E intake did not show a significant correlation with the number of gout patients in 2001-2016 ( $r = -0.686$ ,  $p = 0.132$ ) and in 2001-2019 ( $r = -0.706$ ,  $p = 0.0762$ ). The daily vitamin E intake was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.887$ ,  $p = 0.0446$ ). Whereas the daily vitamin E intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.773$ ,  $p = 0.0712$ ). The daily vitamin E intake tended to be negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.860$ ,  $p = 0.0613$ ) and in 2004-2019 ( $r = -0.793$ ,  $p = 0.0600$ ). The daily vitamin E intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.671$ ,  $p = 0.215$ ) and in 2004-2019 ( $r = 0.703$ ,  $p = 0.119$ ).

Vitamin E inhibits the activity of xanthine oxidase [27].

Vitamin E suppressed the elevation of SUA concentrations and hypertension in deoxycorticosterone-salt-treated hypertensive rats via the uricosuric (increasing or promoting the excretion of UA in urine) effect [28].

In the National Health and Nutrition Examination Survey (NHANES) 2009-2014, dietary vitamin E intake was inversely associated with hyperuricemia risk in U.S. adult population (aged  $\geq 20$  years), especially among males and participants aged  $\geq 60$  years [29]; that is to say, this article revealed that participants in the highest level of the daily vitamin E intake ( $\geq 8.640$  mg/day) were 23.0% less likely to be hyperuricemia [serum uric acid (SUA) concentration  $> 7.0$  mg/dL ( $416.4 \mu\text{mol/L}$ ) in men and  $> 6.0$  mg/dL ( $356.9 \mu\text{mol/L}$ ) in women] compared to those in the lowest intake level ( $< 5.455$  mg/day) [OR = 0.77 (95% confidence interval, 0.63-0.96)] and the risk of hyperuricemia reached a relatively low level when the dietary vitamin E intake was close to 10.0 mg/day [29]. A possible mechanism of higher vitamin E intake associated with lower hyperuricemia risk could be that vitamin E inhibits the activity of xanthine oxidase and has uricosuric effect. The average daily vitamin E intake of Japanese men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were 7.2 mg/day and 6.6 mg/day, respectively. It seems that Japanese adult population (aged  $\geq 20$  years) need to take in 10.0 mg/day of vitamin E or the Adequate Intakes (AIs) set by the Institute of Medicine of the National Academy in the U.S.

Judging from the data of food composition [15, 16], it is important for Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) to eat wheat germ, seeds and nuts (sunflower seeds, almonds, hazelnuts, peanuts), vegetables (spinach, broccoli, tomatoes), and fruit (kiwi fruits, mangos) to take in more vitamin E to reach the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

### 3.1.4. Vitamin K

The daily vitamin K intake of Japanese people in 2019 was lower compared to that in 2001 and 2004, and was higher compared to that in 2007, 2010, 2013, and 2016 (2001: 267  $\mu\text{g/day}$ ; 2004: 242  $\mu\text{g/day}$ ; 2007: 235  $\mu\text{g/day}$ ; 2010: 227  $\mu\text{g/day}$ ; 2013: 220  $\mu\text{g/day}$ ; 2016: 225  $\mu\text{g/day}$ ; 2019: 240  $\mu\text{g/day}$ ). The daily vitamin K intake of Japanese adult population (aged  $\geq 20$  years) in 2019 was higher compared to that in 2016 (2016: 236  $\mu\text{g/day}$ ; 2019: 250  $\mu\text{g/day}$ ). The daily vitamin K intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 245  $\mu\text{g/day}$ ; 2019: 258  $\mu\text{g/day}$ ; women: 2016: 229  $\mu\text{g/day}$ ; 2019: 243  $\mu\text{g/day}$ ).

The daily vitamin K intake of Japanese men (aged 1-6 years, aged 15-19 years, aged  $\geq 30$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 125  $\mu\text{g/day}$ ; 2019: 132  $\mu\text{g/day}$ ; aged 15-19 years: 2016: 210  $\mu\text{g/day}$ ; 2019: 237  $\mu\text{g/day}$ ; aged  $\geq 30$  years: 2016: 217-270  $\mu\text{g/day}$ ; 2019: 228-288  $\mu\text{g/day}$ ). The daily vitamin K intake of Japanese men (aged 20-29 years) in 2019 was lower compared to that in 2016 (2016: 199  $\mu\text{g/day}$ ; 2019: 198  $\mu\text{g/day}$ ). The

daily vitamin K intake of Japanese men (aged 7-14 years) in 2019 was the same as that in 2016 (2016: 196  $\mu\text{g/day}$ ; 2019: 196  $\mu\text{g/day}$ ). The daily vitamin K intake of Japanese women (aged  $\geq 7$  year) in 2019 was higher compared to that in 2016 (2016: 162-259  $\mu\text{g/day}$ ; 2019: 204-270  $\mu\text{g/day}$ ). Whereas the daily vitamin K intake of Japanese women (aged 1-6 years) in 2019 was lower compared to that in 2016 (2016: 130  $\mu\text{g/day}$ ; 2019: 128  $\mu\text{g/day}$ ).

The daily vitamin K intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were 132-288  $\mu\text{g/day}$  and 128-270  $\mu\text{g/day}$ , respectively, and were above the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 1$  year): 60-160  $\mu\text{g/day}$ ; women (aged  $\geq 1$  year): 60-170  $\mu\text{g/day}$ ] [10]. The Adequate Intakes (AIs) for vitamin K in the U.S. men (aged 14-18 years), men (aged  $\geq 19$  years), women (aged 14-18 years), and women (aged  $\geq 19$  years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 75  $\mu\text{g/day}$ , 120  $\mu\text{g/day}$ , 75  $\mu\text{g/day}$ , and 90  $\mu\text{g/day}$ , respectively [14]. This suggests that the daily vitamin K intake in Japanese men (aged  $\geq 14$  year) and women (aged  $\geq 14$  year) appears to be very unlikely to cause a deficiency.

The daily vitamin K intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.923$ ,  $p = 0.00876$ ). Whereas the daily vitamin K intake did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.615$ ,  $p = 0.142$ ). The daily vitamin K intake tended to be negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.861$ ,  $p = 0.0608$ ). The daily vitamin K intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.318$ ,  $p = 0.540$ ). The daily vitamin K intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.826$ ,  $p = 0.0849$ ) and in 2004-2019 ( $r = -0.162$ ,  $p = 0.759$ ). The daily vitamin K intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.630$ ,  $p = 0.255$ ) and in 2004-2019 ( $r = 0.505$ ,  $p = 0.306$ ).

Conscious intake of vitamin K-rich foods (e.g., natto, collards, turnip greens, spinach, kales, broccoli, soybeans, edamame, pumpkins, okra, pine nuts, blueberries, iceberg lettuces, chicken breast, grapes, cashews, carrots, chicken liver, ground beef) [15, 16] seems to be important.

## 3.2. Water-Soluble Vitamins

### 3.2.1. Vitamin B<sub>1</sub>

The daily vitamin B<sub>1</sub> intake of Japanese people in 2019 was lower compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, and 1998 and was higher compared to that in 2001, 2004, 2007, 2010, 2013, and 2016 (1960: 1.05 mg/day; 1965: 0.97 mg/day; 1975: 1.11 mg/day; 1986: 1.35 mg/day; 1989: 1.23 mg/day; 1992: 1.25 mg/day; 1995: 1.22 mg/day; 1998: 1.16 mg/day; 2001: 0.89 mg/day; 2004: 0.86 mg/day; 2007: 0.87 mg/day; 2010: 0.83 mg/day; 2013: 0.80 mg/day; 2016: 0.86 mg/day; 2019: 0.95 mg/day). The daily vitamin B<sub>1</sub> intake of

Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 0.87 mg/day; 2019: 0.95 mg/day). The daily vitamin B<sub>1</sub> intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 0.94 mg/day; 2019: 1.03 mg/day; women: 2016: 0.81 mg/day; 2019: 0.88 mg/day).

The daily vitamin B<sub>1</sub> intake of Japanese men (aged  $\geq 1$  year) in 2019 was higher compared to that in 2016 (2016: 0.58-1.12 mg/day; 2019: 0.68-1.17 mg/day). The daily vitamin B<sub>1</sub> intake of Japanese women (aged 1-19 years, 30-49 years,  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-19 years: 2016: 0.56-0.83 mg/day; 2019: 0.62-0.98 mg/day; 30-49 years: 2016: 0.78 mg/day; 2019: 0.83-0.89 mg/day; aged  $\geq 60$  years: 2016: 0.79-0.85 mg/day; 2019: 0.89-0.9 mg/day). The daily vitamin B<sub>1</sub> intake of Japanese women (aged 50-59 years) in 2019 was lower compared to that in 2016 (2016: 0.84 mg/day; 2019: 0.83 mg/day). The daily vitamin B<sub>1</sub> intake of Japanese women (aged 20-29 years) was the same as that in 2016 (2016: 0.77 mg/day; 2019: 0.77 mg/day).

The daily vitamin B<sub>1</sub> intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) in 2019 were 1.00-1.17 mg/day and 0.77-0.98 mg/day, respectively. In Dietary Reference Intakes for Japanese established by the Ministry of Health, Labour and Welfare in Japan, the Recommended Dietary Allowances (RDAs) for daily vitamin B<sub>1</sub> intake in Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) are 1.2-1.5 mg/day and 0.9-1.2 mg/day, respectively [10]. The Recommended dietary allowances (RDAs) for vitamin B<sub>1</sub> in the U.S. men (aged  $\geq 14$  years), women (aged 14-18 years) and women (aged  $\geq 19$  years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 1.2 mg/day, 1.0 mg/day, and 1.1 mg/day, respectively [14]. Therefore, the daily vitamin B<sub>1</sub> intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) were below the Recommended Dietary Allowances (RDAs).

The daily vitamin B<sub>1</sub> intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.949$ ,  $p = 0.0000799$ ) and in 1986-2019 ( $r = -0.880$ ,  $p = 0.000157$ ). The daily vitamin B<sub>1</sub> intake was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.909$ ,  $p = 0.0327$ ) and in 2004-2019 ( $r = -0.831$ ,  $p = 0.0404$ ). The daily vitamin B<sub>1</sub> intake tended to be negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.860$ ,  $p = 0.0614$ ) and in 2004-2019 ( $r = -0.793$ ,  $p = 0.0599$ ). The daily vitamin B<sub>1</sub> intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.263$ ,  $p = 0.669$ ) and in 2004-2019 ( $r = 0.344$ ,  $p = 0.505$ ). This result suggests that the daily vitamin B<sub>1</sub> intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

In an epidemiological study, increased vitamin B<sub>1</sub> intake was associated with decreased serum uric acid (SUA) concentrations [30]. It is possible that vitamin B<sub>1</sub> intake prevent gout through a decrease in SUA concentrations.

Judging from the data of food composition [15, 16], it is important for Japanese people (aged  $\geq 15$  years) to eat meats (pork), seafood (mussels, trout, tuna, walleye pollock, eel), mushrooms (maitake mushrooms), grains (white rice, egg noodle, bread), whole grains (whole wheat, brown rice, oatmeal, fortified ready-to-eat cereals), seeds (sunflower seeds, sesame seeds, chia seeds), legumes (black beans, soybeans), fruit (avocados), vegetables (broccoli), dairy products (milk), eggs to take in more vitamin B<sub>1</sub> to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

### 3.2.2. Vitamin B<sub>2</sub>

The daily vitamin B<sub>2</sub> intake of Japanese people in 2019 was higher compared to that in 1960, 1965, 1975, 2004, 2007, 2010, 2013, and 2016 and was lower compared to that in 1986, 1989, 1992, 1995, 1998, and 2001 (1960: 0.72 mg/day; 1965: 0.83 mg/day; 1975: 0.96 mg/day; 1986: 1.26 mg/day; 1989: 1.33 mg/day; 1992: 1.36 mg/day; 1995: 1.47 mg/day; 1998: 1.42 mg/day; 2001: 1.22 mg/day; 2004: 1.17 mg/day; 2007: 1.17 mg/day; 2010: 1.13 mg/day; 2013: 1.10 mg/day; 2016: 1.15 mg/day; 2019: 1.18 mg/day). The daily vitamin B<sub>2</sub> intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 1.16 mg/day; 2019: 1.19 mg/day). The daily vitamin B<sub>2</sub> intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 1.20 mg/day; 2019: 1.25 mg/day; women: 2016: 1.12 mg/day; 2019: 1.13 mg/day).

The daily vitamin B<sub>1</sub> intake of Japanese women (aged 1-7 years, 15-29 years, 40-49 years,  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-7 years: 2016: 0.82 mg/day; 2019: 0.85 mg/day; aged 15-29 years: 2016: 1.14-1.24 mg/day; 2019: 1.20-1.32 mg/day; 40-49 years: 2016: 1.10 mg/day; 2019: 1.16 mg/day;  $\geq 60$  years: 2016: 1.28-1.27 mg/day; 2019: 1.30-1.35 mg/day). The daily vitamin B<sub>2</sub> intake of Japanese men (aged 7-14 years, 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 7-14 years: 2016: 1.32 mg/day; 2019: 1.30 mg/day; aged 50-59 years: 2016: 1.20 mg/day; 2019: 1.19 mg/day). The daily vitamin B<sub>2</sub> intake of Japanese men (aged 30-39 years) in 2019 was the same as that in 2016 (2016: 1.10 mg/day; 2019: 1.10 mg/day). The daily vitamin B<sub>1</sub> intake of Japanese women (aged 15-19 years, 40-49 years,  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 1.02 mg/day; 2019: 1.11 mg/day; 40-49 years: 2016: 1.02 mg/day; 2019: 1.05 mg/day;  $\geq 60$  years: 2016: 1.17-1.20 mg/day; 2019: 1.21 mg/day). The daily vitamin B<sub>2</sub> intake of Japanese women (aged 1-7 years, 20-29 years, 40-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-7 years: 2016: 0.79 mg/day; 2019: 0.76 mg/day; aged 20-29 years: 2016: 1.01 mg/day; 2019: 0.97 mg/day; aged 40-59 years: 2016: 1.02-1.13 mg/day; 2019: 1.05-1.09 mg/day). The daily vitamin B<sub>2</sub> intake of Japanese women (aged 7-14 years, 30-39 years) in 2019 were the same

as those in 2016, respectively (aged 7-14 years: 1.18 mg/day; aged 30-39 years: 1.00 mg/day).

The daily vitamin B<sub>2</sub> intake of Japanese men (aged 20-59 years) and women (aged 20-59 years) in 2019 were 1.10-1.20 mg/day and 0.97-1.09 mg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 18-69 years): 1.30-1.60 mg/day; women (aged 18-59 years): 1.20 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged ≥ 19 years): 1.30 mg/day; women (aged ≥ 19 years): 1.10 mg/day] [14]. The daily vitamin B<sub>2</sub> intake of Japanese men (aged ≥ 75 years) and women (aged ≥ 75 years) were 1.31 mg/day and 1.18 mg/day, respectively, and were above the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged ≥ 75 years): 1.30 mg/day; women (aged ≥ 75 years): 1.0 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged ≥ 19 years): 1.30 mg/day; women (aged ≥ 19 years): 1.10 mg/day] [14]. Therefore, the daily vitamin B<sub>1</sub> intake of Japanese men (aged 20-59 years) and women (aged 20-59 years) were below the Recommended Dietary Allowances (RDAs), and those of Japanese men (aged ≥ 75 years) and women (aged ≥ 75 years) were above the Recommended Dietary Allowances (RDAs).

The daily vitamin B<sub>2</sub> intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.799$ ,  $p = 0.00468$ ) and in 1986-2019 ( $r = -0.756$ ,  $p = 0.00447$ ). The daily vitamin B<sub>2</sub> intake was negatively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 ( $r = -0.923$ ,  $p = 0.0256$ ) and in 2004-2019 ( $r = -0.846$ ,  $p = 0.0339$ ). The daily vitamin B<sub>2</sub> intake was negatively correlated with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 ( $r = -0.941$ ,  $p = 0.0170$ ) and in 2004-2019 ( $r = -0.844$ ,  $p = 0.0470$ ). The daily vitamin B<sub>2</sub> intake did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 ( $r = 0.289$ ,  $p = 0.638$ ) and in 2004-2019 ( $r = 0.370$ ,  $p = 0.470$ ). This result suggests that the correlation of daily vitamin B<sub>2</sub> intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women. Furthermore, this result suggests that the daily vitamin B<sub>2</sub> intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

In an epidemiological study, increased vitamin B<sub>2</sub> intake was associated with decreased serum uric acid (SUA) concentrations [30]. It is possible that vitamin B<sub>2</sub> intake prevent gout through a reduction of SUA concentrations.

Judging from the data of food composition [15, 16], it is important for Japanese men (aged 20-59 years) and women (aged 20-59 years) to eat organ meats (kidneys, liver), seafood (clams, salmon, cod), mushrooms (maitake mushrooms, shiitake mushrooms), grains (white rice, egg noodle, bread), whole grains (whole wheat, brown rice, oats, fortified ready-to-eat cereals), seeds (sunflower seeds, almonds),

legumes (kidney beans), seaweed, vegetables (asparagus, tomatoes, cauliflowers), dairy products (milk, cheese, yogurt), eggs to take in more vitamin B<sub>2</sub> to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

### 3.2.3. Niacin (Vitamin B<sub>3</sub>)

The daily intake of niacin equivalent (niacin) of Japanese people in 2019 was higher compared to that in 2001, 2004, 2007, 2010, 2013, and 2016 (2001: 27.0 mg NE /day; 2004: 26.7 mg NE /day; 2007: 26.7 mg NE /day; 2010: 25.4 mg NE /day; 2013: 25.9 mg NE /day; 2016: 25.8 mg NE /day; 2019: 30.7 mg NE /day). The daily niacin intake of Japanese adult population (aged ≥ 20 years) was higher compared to that in 2016 (2016: 26.6 mg NE /day; 2019: 31.3 mg NE /day). The daily niacin intake of Japanese adult men (aged ≥ 20 years) and women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 29.2 mg NE /day; 2019: 34.5 mg NE /day; women: 2016: 24.4 mg NE /day; 2019: 28.5 mg NE /day).

The daily niacin intake of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were higher compared to those in 2016, respectively [men (aged ≥ 1 year): 2016: 15.3-30.9 mg NE /day; 2019: 18.6-36.7 mg NE /day; women (aged ≥ 1 year): 2016: 14.6-26.4 mg NE /day; 2019: 16.9-30.3 mg NE /day]. The daily niacin intake of Japanese men (aged ≥ 1 year) and women (aged ≥ 1 year) in 2019 were 18.6-36.7 mg NE /day and 16.9-30.3 mg NE /day, respectively, and were above the Recommended Dietary Allowances (RDAs) [men (aged ≥ 1 year): 6.0-17.0 mg NE /day; women (aged ≥ 1 year): 5.0-14.0 mg NE /day] [10]. The daily niacin intake in the U.S. men (aged ≥ 1 years) and women (aged ≥ 1 years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. were also above the Recommended Dietary Allowances (RDAs), respectively [men (aged ≥ 1 year): 6.0-16.0 mg NE /day; women (aged ≥ 1 year): 6.0-14.0 mg NE /day; men (aged ≥ 14 years): 16.0 mg NE /day; women (aged ≥ 14 years): 14.0 mg NE /day] [14]. The Tolerable Upper Intake levels (ULs) for niacin in the U.S. men (aged ≥ 19 years) and women (aged ≥ 19 years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 35.0 mg NE /day, respectively [14]. The daily niacin intake of Japanese men (aged 40-49 years and aged 60-69 years) were 35.4 mg NE /day and 35.6 mg NE /day, respectively. It seems that the daily niacin intake of Japanese people except for men (aged 40-49 years and aged 60-69 years) in 2019 are appropriate.

The daily niacin intake did not show a significant correlation with the number of gout patients in 2001-2016 ( $r = 0.113$ ,  $p = 0.831$ ) and in 2001-2019 ( $r = 0.677$ ,  $p = 0.0946$ ). The daily niacin intake did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 ( $r = -0.755$ ,  $p = 0.140$ ) and in 2004-2019 ( $r = 0.725$ ,  $p = 0.103$ ). The daily niacin intake was negatively correlated with the number of gout patients in adult

men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.884$ ,  $p = 0.0467$ ). The daily niacin intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2019 ( $r = 0.702$ ,  $p = 0.120$ ). The daily niacin intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.786$ ,  $p = 0.115$ ) and in 2004-2019 ( $r = -0.250$ ,  $p = 0.633$ ). This result suggests that the correlation of daily niacin intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women.

### 3.2.4. Pantothenic Acid (Vitamin B<sub>5</sub>)

The daily pantothenic acid intake of Japanese people in 2019 was lower compared to that in 2001 and was higher compared to that in 2004, 2007, 2010, 2013, and 2016 (2001: 5.71 mg/day; 2004: 5.52 mg/day; 2007: 5.46 mg/day; 2010: 5.24 mg/day; 2013: 5.41 mg/day; 2016: 5.45 mg/day; 2019: 5.65 mg/day). The daily pantothenic acid intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 5.47 mg/day; 2019: 5.65 mg/day). The daily pantothenic acid intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 5.83 mg/day; 2019: 6.05 mg/day; women: 2016: 5.16 mg/day; 2019: 5.30 mg/day).

The daily pantothenic acid intake of Japanese men (aged 7-14 years, 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 7-14 years: 2016: 6.42 mg/day; 2019: 6.40 mg/day; aged 50-59 years: 2016: 5.85 mg/day; 2019: 5.83 mg/day). Whereas the daily pantothenic acid intake of Japanese men (aged 1-7 years, 15-29 years, 40-49 years,  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-7 years: 2016: 3.96 mg/day; 2019: 4.26 mg/day; aged 15-29 years: 2016: 6.47 mg/day; 2019: 6.85 mg/day; 40-49 years: 2016: 5.58 mg/day; 2019: 5.91 mg/day;  $\geq 60$  years: 2016: 5.95-6.09 mg/day; 2019: 6.21-6.32 mg/day). The daily pantothenic acid intake of Japanese men (aged 30-39 years) was the same as that in 2016 (2016: 5.54 mg/day; 2019: 5.54 mg/day). The daily pantothenic acid intake of Japanese women (aged 1-7 years, 20-39 years, 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-7 years: 2016: 3.84 mg/day; 2019: 3.83 mg/day; aged 20-39 years: 2016: 4.73-4.92 mg/day; 2019: 4.65-4.87 mg/day; aged 50-59 years: 2016: 5.18 mg/day; 2019: 5.12 mg/day). Whereas the daily pantothenic acid intake of Japanese women (aged 7-19 years, 40-49 years,  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 4.97-5.59 mg/day; 2019: 5.60-5.83 mg/day; 40-49 years: 2016: 4.78 mg/day; 2019: 5.06 mg/day;  $\geq 60$  years: 2016: 5.32-5.53 mg/day; 2019: 5.52-5.68 mg/day).

The daily pantothenic acid intake of Japanese men (aged 20-49 years and  $\geq 60$  years) and women (aged  $\geq 40$  years) in 2019 were 5.54-5.92 mg/day, 6.21-6.32 mg/day, and 5.06-5.69 mg/day, respectively, and were above the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 20-49 years): 5.0 mg/day; men

(aged  $\geq 60$  years): 6.0 mg/day; women (aged  $\geq 40$  years): 5.0 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 14$  years): 5.0 mg/day; women (aged  $\geq 14$  years): 5.0 mg/day] [14]. The daily pantothenic acid intake of Japanese men (aged 50-59 years) and women (20-39 years) in 2019 were 5.83 mg/day and 4.65-4.87 mg/day, respectively, and were below the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 50-59 years): 6.0 mg/day; women (aged 1-7 years): 4.0-5.0 mg/day; women (aged 20-39 years): 5.0 mg/day] [10]. However, the daily pantothenic acid intake of Japanese men (aged 50-59 years) was above the Adequate Intakes (AIs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14]. The daily pantothenic acid intake of Japanese men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) were 6.05 mg/day and 5.30 mg/day, respectively, and were above the Adequate Intakes (AIs) in Dietary Reference Intakes for Japanese established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 18$  years): 5.0-6.0 mg/day; women (aged  $\geq 18$  years): 5.0 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 14$  years): 5.0 mg/day; women (aged  $\geq 14$  years): 5.0 mg/day] [14].

The daily pantothenic acid intake did not show a significant correlation with the number of gout patients in 2001-2016 ( $r = -0.663$ ,  $p = 0.151$ ) and in 2001-2019 ( $r = -0.138$ ,  $p = 0.769$ ). The daily pantothenic acid intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.027$ ,  $p = 0.966$ ) and in 2004-2019 ( $r = 0.533$ ,  $p = 0.276$ ). The daily pantothenic acid intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.0376$ ,  $p = 0.952$ ) and in 2004-2019 ( $r = 0.546$ ,  $p = 0.262$ ). The daily pantothenic acid intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.651$ ,  $p = 0.234$ ) and in 2004-2019 ( $r = 0.284$ ,  $p = 0.585$ ).

The daily pantothenic acid intake in Japanese men (aged 20-49 years and  $\geq 60$  years) and women (aged  $\geq 40$  years) appears to be very unlikely to cause a deficiency. Judging from the data of food composition [15, 16], it is important for Japanese men (aged 1-19 years, aged 50-59 years) and women (aged 1-39 years) to eat meats (beef, poultry), seafood, organ meats, mushrooms (shiitake mushrooms), potatoes, whole grains (whole wheat, brown rice, oats), nuts (peanuts), seeds (sunflower seeds), legumes (chickpeas), fruit (avocados), vegetables (broccoli), dairy products (milk), eggs to take in more pantothenic acid.

### 3.2.5. Vitamin B<sub>6</sub>

The daily vitamin B<sub>6</sub> intake of Japanese people in 2019 was lower compared to that in 2004, 2007, and 2010 and was higher compared to that in 2013 and 2016 and was the same as that in 2001 (2001: 1.18 mg/day; 2004: 1.72 mg/day; 2007: 1.67 mg/day; 2010: 1.67 mg/day; 2013: 1.11 mg/day; 2016:

1.11 mg/day; 2019: 1.18 mg/day). The daily vitamin B<sub>6</sub> intake of Japanese adult population (aged ≥ 20 years) in 2019 was higher compared to that in 2016 (2016: 1.14 mg/day; 2019: 1.20 mg/day). The daily vitamin B<sub>6</sub> intake of Japanese adult men (aged ≥ 20 years) and women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 1.23 mg/day; 2019: 1.30 mg/day; women: 2016: 1.07 mg/day; 2019: 1.12 mg/day).

The daily vitamin B<sub>6</sub> intake of Japanese men (aged 1-19 years, ≥ 30 years) in 2019 were higher compared to those in 2016, respectively (aged 1-19 years: 2016: 0.73-1.23 mg/day; 2019: 0.77-1.31 mg/day; aged ≥ 30 years: 2016: 1.11-1.32 mg/day; 2019: 1.13-1.42 mg/day). Whereas the daily vitamin B<sub>6</sub> intake of Japanese men (aged 20-29 years) in 2019 was lower compared to that in 2016 (2016: 1.13 mg/day; 2019: 1.12 mg/day). The daily vitamin B<sub>6</sub> intake of Japanese women (aged 7-19 years, 30-49 years, ≥ 60 years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 0.95-0.98 mg/day; 2019: 1.03-1.09 mg/day; aged 30-49 years: 2016: 0.95 mg/day; 2019: 0.96-1.01 mg/day; aged ≥ 60 years: 2016: 1.14-1.18 mg/day; 2019: 1.23 mg/day). Whereas the daily vitamin B<sub>6</sub> intake of Japanese women (aged 20-29 years, 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 20-29 years: 2016: 0.95 mg/day; 2019: 0.91 mg/day; aged 50-59 years: 2016: 1.07 mg/day; 2019: 1.05 mg/day). The daily vitamin B<sub>6</sub> intake of Japanese women (aged 1-6 years) in 2019 was the same as that in 2016 (2016: 0.69 mg/day; 2019: 0.69 mg/day).

The daily vitamin B<sub>6</sub> intake of Japanese men (aged 15-69 years, ≥ 75 years) and women (aged 15-59 years) in 2019 were 1.31-1.36 mg/day, 1.38 mg/day, and 0.91-1.09 mg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 15-69 years): 1.40-1.50 mg/day; men (aged ≥ 75 years): 1.40 mg/day; women (aged 15-59 years): 1.10-1.30 mg/day] [10]. The daily vitamin B<sub>6</sub> intake of Japanese women (aged ≥ 60 years) in 2019 was 1.23 mg/day and was above the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan (1.10 mg/day) [10], but was below the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. (1.50 mg/day) [14]. The Recommended Dietary Allowances (RDAs) for vitamin B<sub>6</sub> in the U.S. men (aged 14-50 years), men (aged ≥ 51 years), women (aged 19-50 years), and women (aged ≥ 51 years) are 1.3 mg/day, 1.7 mg/day, 1.3 mg/day, and 1.5 mg/day, respectively [14]. The daily vitamin B<sub>6</sub> intake of Japanese men (aged 20-49 years), men (aged ≥ 50 years), women (aged 19-49 years), and women (aged ≥ 50 years) in Japan were 1.12-1.25 mg/day, 1.23-1.42 mg/day, 0.91-1.01 mg/day, and 1.05-1.23 mg/day, respectively. Therefore, the daily vitamin B<sub>6</sub> intake of Japanese men (aged ≥ 20 years) and women (aged ≥ 20 years) were below the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

The daily vitamin B<sub>6</sub> intake did not show a significant

correlation with the number of gout patients in 2001-2016 ( $r = -0.300$ ,  $p = 0.563$ ) and in 2001-2019 ( $r = -0.413$ ,  $p = 0.357$ ). The daily vitamin B<sub>6</sub> intake was negatively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 ( $r = -0.931$ ,  $p = 0.0213$ ) and in 2004-2019 ( $r = -0.857$ ,  $p = 0.0291$ ). The daily vitamin B<sub>6</sub> intake was negatively correlated with number of gout patients in adult men (aged ≥ 20 years) in 2004-2016 ( $r = -0.927$ ,  $p = 0.0232$ ) and in 2004-2019 ( $r = -0.850$ ,  $p = 0.0319$ ). The daily vitamin B<sub>6</sub> intake did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 ( $r = 0.266$ ,  $p = 0.666$ ) and in 2004-2019 ( $r = 0.349$ ,  $p = 0.497$ ). This result suggests that the correlation of daily vitamin B<sub>6</sub> intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women. Furthermore, this result suggests that the daily vitamin B<sub>6</sub> intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

In the National Health and Nutrition Examination Survey (NHANES) 2001-2014, no association between vitamin B<sub>6</sub> intake and hyperuricemia risk in both U.S. adult males and females (aged 20-85 years) [31].

Judging from the data of food composition [15, 16], it is important for Japanese men (aged ≥ 20 years) and women (aged ≥ 20 years) to eat meats (turkey, chicken, pork fin), organ meats (chicken breast, beef liver, pork liver), seafood (tuna, salmon, skipjack, sardines, mackerel, Nile tilapia), grains (white rice, buckwheat), whole grains (fortified ready-to-eat cereals), potatoes, seeds and nuts (sunflower seeds, squid, pistachio nuts, sesame seeds), legumes (chickpeas), seaweed, vegetables (onions, garlic, tomatoes, peppers), fruit (bananas, raisins, watermelons), dairy products (cheese), soy products (tofu) to take in more vitamin B<sub>6</sub> to reach the Recommended Dietary Allowances (RDAs) set by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 19-50 years): 1.3 mg/day; men (aged > 50 years): 1.7 mg/day; women (aged 19-50 years): 1.3 mg/day; women (aged > 50 years): 1.5 mg/day] [14]. However, it must be careful not to exceed the Tolerable Upper Intake levels (ULs) of the daily vitamin B<sub>6</sub> intake.

### 3.2.6. Folate (Vitamin B<sub>9</sub>)

The daily folate intake of Japanese people in 2019 was lower compared to that in 2001, 2004, and 2007 and was higher compared to that in 2010, 2013, and 2016 (2001: 313.0 µg/day; 2004: 294.0 µg/day; 2007: 299.0 µg/day; 2010: 281.0 µg/day; 2013: 280.0 µg/day; 2016: 277.0 µg/day; 2019: 289.0 µg/day). The daily folate intake of Japanese adult population (aged ≥ 20 years) was higher compared to that in 2016 (2016: 290.0 µg/day; 2019: 302.0 µg/day). The daily folate intake of Japanese adult men (aged ≥ 20 years) and women (aged ≥ 20 years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 297.0 µg/day; 2019: 310.0 µg/day; women: 2016: 285.0 µg/day; 2019: 295.0 µg/day).

The daily folate intake of Japanese men (aged 1-19 years, aged ≥ 30 years) in 2019 were higher compared to those in 2016, respectively (aged 1-19 years: 2016: 156.0-252.0

µg/day; 2019: 159.0-260.0 µg/day; aged ≥ 30 years: 2016: 244.0-334.0 µg/day; 2019: 253.0-352.0 µg/day). Whereas the daily folate intake of Japanese men (aged 20-29 years) in 2019 was lower compared to that in 2016 (2016: 244.0 µg/day; 2019: 237.0 µg/day). The daily folate intake of Japanese women (aged 7-19 years, aged ≥ 40 years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 218.0-228.0 µg/day; 2019: 230.0-245.0 µg/day; aged ≥ 40 years: 2016: 244.0-318.0 µg/day; 2019: 247.0-335.0 µg/day). Whereas the daily folate intake of Japanese women (aged 1-6 years, aged 20-39 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 151.0 µg/day; 2019: 148.0 µg/day; aged 20-39 years: 2016: 229.0-240.0 µg/day; 2019: 226.0-233.0 µg/day).

The daily folate intake of Japanese men (aged 1-6 years, aged 15-19 years, aged ≥ 30 years) and women (aged 1-6 years, aged 15-19 years, aged ≥ 40 years) in 2019 were 159.0 µg/day, 260.0 µg/day, 253.0-352.0 µg/day, 148.0 µg/day, 245.0 µg/day, and 247.0-335.0 µg/day, respectively, and were above the Recommended Dietary Allowances (RDAs) [men (aged 1-6 years): 90.0-140.0 µg/day; men (aged 15-19 years): 240.0 µg/day; men (aged ≥ 30 years): 240.0 µg/day; women (aged 1-6 years): 90.0-140.0 µg/day; women (aged 15-19 years): 240.0 µg/day; women (aged ≥ 40 years): 240.0 µg/day] and were below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 1-6 years): 200.0-400.0 µg/day; men (aged 15-19 years): 900.0 µg/day; men (aged ≥ 30 years): 900.0-1000.0 µg/day; women (aged 1-6 years): 200.0-400.0 µg/day; women (aged 15-19 years): 900.0 µg/day; women (aged ≥ 40 years): 900.0-1000.0 µg/day] [10]. The daily folate intake of Japanese men (aged 20-29 years) and women (aged 20-39 years) in 2019 were 237.0 µg/day and 226.0-233.0 µg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 20-29 years): 240.0 µg/day; women (aged 20-39 years): 240.0 µg/day] [10]. The daily folate intake of Japanese adult men and women tended to increase as age increased.

The Institute of Medicine of the National Academy of Sciences in the U.S. [14] has recommended that the daily folate intake for males (aged ≥ 14 years) or females (aged ≥ 14 years) is 400 µg DFE (dietary folate equivalents: 1 DFE = 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of folic acid from a supplement taken on an empty stomach [14]) and has not established a Tolerable Upper Intake Levels (ULs). The Institute of Medicine of the National Academy of Sciences in the U.S. [14] has set that the Estimated Average Requirements (EARs) for folate in the U.S. men and women (aged 14-18 years) and men and women (aged ≥ 19 years) are 330 µg/day and 320 µg/day, respectively, and the Recommended Dietary Allowances (RDAs) for folate in the U.S. men (aged ≥ 14 years) and women (aged ≥ 14 years) are 400 µg/day, respectively. Judging from Dietary Reference Intakes established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14], since the

daily folate intake for Japanese men (aged ≥ 15 years) and women (aged ≥ 15 years) was below the Recommended Dietary Allowances (RDAs), they need to take in more folate to reach the Recommended Dietary Allowances (RDAs).

The daily folate intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.967$ ,  $p = 0.00165$ ). The daily folate intake tended to be negatively correlated with the number of gout patients in 2001-2019 ( $r = -0.748$ ,  $p = 0.0532$ ). The daily folate intake was negatively correlated with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2016 ( $r = -0.947$ ,  $p = 0.0144$ ). The daily folate intake did not show a significant correlation with the number of gout patients in the adult population (aged ≥ 20 years) in 2004-2019 ( $r = -0.594$ ,  $p = 0.214$ ). The daily folate intake was negatively correlated with the number of gout patients in the adult men (aged ≥ 20 years) in 2004-2016 ( $r = -0.922$ ,  $p = 0.0258$ ). Whereas the daily folate intake did not show a significant correlation with the number of gout patients in adult men (aged ≥ 20 years) in 2004-2019 ( $r = -0.610$ ,  $p = 0.199$ ). The daily folate intake did not show a significant correlation with the number of gout patients in adult women (aged ≥ 20 years) in 2004-2016 ( $r = 0.690$ ,  $p = 0.198$ ) and in 2004-2019 ( $r = 0.642$ ,  $p = 0.169$ ). This result suggests that the correlation of daily folate intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women.

In epidemiological studies, increased folate intake was associated with decreased serum uric acid (SUA) concentrations [30], hyperuricemia risk [31], and gout risk [32]. It is possible that folate intake prevent gout through a decrease in SUA concentrations.

In the National Health and Nutrition Examination Survey (NHANES) 2001-2014, folate intake was inversely associated with hyperuricemia risk among U.S. adult males (aged 20-85 years), but no association between folate intake and hyperuricemia risk among U.S. adult females (aged 20-85 years) [31]. This article revealed that male subjects in the highest level of folate intake ( $\geq 621$  µg/day) were 36% less likely to be hyperuricemia [serum uric acid (SUA) concentration  $\geq 7.0$  mg/dL (416.4 µmol/L) in males and  $\geq 6.0$  mg/dL (356.9 µmol/L) in females] compared to those subjects in the lowest intake level ( $\leq 247$  µg/day) [OR = 0.64 (95% confidence interval, 0.53-0.77)] [31]. Whereas female subjects in the highest level of folate intake ( $\geq 477$  µg/day) were also 16% less likely to be hyperuricemia compared to those subjects in the lowest intake level ( $\leq 191$  µg/day) [OR = 0.84 (95% confidence interval, 0.67-1.04)] [31].

From the results of this article [31], though the daily folate intake for Japanese men (aged 1-6 years, aged 15-19 years, aged ≥ 30 years) and women (aged 1-6 years, aged 15-19 years, aged ≥ 40 years) in 2019 were above the Recommended Dietary Allowances (RDAs), it seems that Japanese adult population (aged ≥ 20 years) need to take in more folate. However, it must be careful not to exceed the Tolerable Upper Intake Levels (ULs) of the daily folate intake, which is above 1000 µg/day for Japanese people (aged ≥ 19 years) [14]. Judging from the data of food composition [15, 16], it is important for Japanese men (aged ≥ 15 years) and women

(aged  $\geq 15$  years) to eat meats (beef), organ meats (liver, breast), seafood (crab, halibut, sardines, sea urchin), mushrooms (maitake mushrooms, shiitake mushrooms), grains (white rice, spaghetti, bread, wheat), whole grains (fortified ready-to-eat cereals), seeds (sunflower seeds, peanuts), legumes (black-eyed peas, kidney beans, green peas, soybeans, chickpeas), seaweed, fruit (avocados, oranges, papayas, bananas, mangos), vegetables (asparaguses, spinach, brussels sprouts, lettuces, broccoli, mustard greens, Jew's mallow), dairy products (milk), eggs, green tea.

### 3.2.7. Vitamin B<sub>12</sub>

The daily vitamin B<sub>12</sub> intake of Japanese people in 2019 was lower compared to that in 2001, 2004, and 2007 and was higher compared to that in 2010, 2013, and 2016 (2001: 7.7  $\mu\text{g/day}$ ; 2004: 7.0  $\mu\text{g/day}$ ; 2007: 7.1  $\mu\text{g/day}$ ; 2010: 6.0  $\mu\text{g/day}$ ; 2013: 6.1  $\mu\text{g/day}$ ; 2016: 6.0  $\mu\text{g/day}$ ; 2019: 6.3  $\mu\text{g/day}$ ). The daily vitamin B<sub>12</sub> intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 6.3  $\mu\text{g/day}$ ; 2019: 6.5  $\mu\text{g/day}$ ). The daily vitamin B<sub>12</sub> intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 6.8  $\mu\text{g/day}$ ; 2019: 7.3  $\mu\text{g/day}$ ; women: 2016: 5.8  $\mu\text{g/day}$ ; 2019: 5.9  $\mu\text{g/day}$ ).

The daily vitamin B<sub>12</sub> intake of Japanese men (aged 1-14 years, 20-29 years,  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-14 years: 2016: 3.5-5.6  $\mu\text{g/day}$ ; 2019: 4.4-5.9  $\mu\text{g/day}$ ; aged 20-29 years: 2016: 5.5  $\mu\text{g/day}$ ; 2019: 6.5  $\mu\text{g/day}$ ; aged  $\geq 60$  years: 2016: 7.7-7.8  $\mu\text{g/day}$ ; 2019: 8.2-8.5  $\mu\text{g/day}$ ). Whereas the daily vitamin B<sub>12</sub> intake of Japanese men (aged 15-19 years, 30-59 years) in 2019 were lower compared to those in 2016, respectively (aged 15-19 years: 2016: 5.5  $\mu\text{g/day}$ ; 2019: 4.9  $\mu\text{g/day}$ ; aged 30-59 years: 2016: 5.7-6.4  $\mu\text{g/day}$ ; 2019: 5.3-6.3  $\mu\text{g/day}$ ). The daily vitamin B<sub>12</sub> intake of Japanese women (aged 7-19 years, 30-39 years,  $\geq 70$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 4.1-4.8  $\mu\text{g/day}$ ; 2019: 4.4-5.8  $\mu\text{g/day}$ ; aged 30-39 years: 2016: 4.9  $\mu\text{g/day}$ ; 2019: 5.0  $\mu\text{g/day}$ ; aged  $\geq 70$  years: 2016: 6.7  $\mu\text{g/day}$ ; 2019: 7.0  $\mu\text{g/day}$ ). Whereas the daily vitamin B<sub>12</sub> intake of Japanese men (aged 1-6 years, 20-29 years, 50-69 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 2.9  $\mu\text{g/day}$ ; 2019: 2.7  $\mu\text{g/day}$ ; 20-29 years: 2016: 4.8  $\mu\text{g/day}$ ; 2019: 4.3  $\mu\text{g/day}$ ; aged 50-69 years: 2016: 5.7-6.6  $\mu\text{g/day}$ ; 2019: 5.4-6.5  $\mu\text{g/day}$ ). The daily vitamin B<sub>12</sub> intake of Japanese women (aged 40-49 years) in 2019 was the same as that in 2016 (2016: 4.5  $\mu\text{g/day}$ ; 2019: 4.5  $\mu\text{g/day}$ ).

The Recommended Dietary Allowances (RDAs) for vitamin B<sub>12</sub> in the U.S. men (aged  $\geq 14$  years) and women (aged  $\geq 14$  years) established by the Institute of Medicine of the National Academy in the U.S. are 2.4  $\mu\text{g/day}$ , respectively [14]. In Japanese men and women in 2016 and 2019, the daily vitamin B<sub>12</sub> intake for men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) were 4.4-8.5  $\mu\text{g/day}$  and 2.7-7.0  $\mu\text{g/day}$ , respectively, and were above Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine

of the National Academy of Sciences in the U.S. [14] [men (aged  $\geq 1$  year): 0.9-2.4  $\mu\text{g/day}$ ; women (aged  $\geq 1$  year): 0.9-2.4  $\mu\text{g/day}$ ]. The daily vitamin B<sub>12</sub> intake of Japanese adult men and women tended to increase as age increased. The Ministry of Health, Labour and Welfare in Japan [10] has not set the Tolerable Upper Intake Levels (ULs) for healthy people because there is no scientific evidence for health problems due to excessive daily intake of vitamin B<sub>12</sub>.

The daily vitamin B<sub>12</sub> intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.936$ ,  $p = 0.00599$ ) and in 2001-2019 ( $r = -0.812$ ,  $p = 0.0264$ ). The daily vitamin B<sub>12</sub> intake tended to be negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.851$ ,  $p = 0.0677$ ). The daily vitamin B<sub>12</sub> intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.707$ ,  $p = 0.116$ ). The daily vitamin B<sub>12</sub> intake was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.923$ ,  $p = 0.0255$ ). Whereas the daily vitamin B<sub>12</sub> intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.723$ ,  $p = 0.105$ ). The daily vitamin B<sub>12</sub> intake was positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.880$ ,  $p = 0.0492$ ) and in 2004-2019 ( $r = 0.881$ ,  $p = 0.0205$ ). This result suggests that the correlation of daily vitamin B<sub>12</sub> intake with the number of gout patients varies with gender and is stronger in adult women than in adult men.

In the National Health and Nutrition Examination Survey (NHANES) 2001-2014, vitamin B<sub>12</sub> intake was inversely associated with hyperuricemia risk among U.S. adult males (aged 20-85 years), but no association between vitamin B<sub>12</sub> intake and hyperuricemia risk among U.S. adult females (aged 20-85 years) [31]. This article revealed that male subjects in the highest level of vitamin B<sub>12</sub> intake ( $\geq 8.44$   $\mu\text{g/day}$ ) were 23% less likely to be hyperuricemia [serum uric acid (SUA) concentration  $\geq 7.0$  mg/dL (416.4  $\mu\text{mol/L}$ ) in males and  $\geq 6.0$  mg/dL (356.9  $\mu\text{mol/L}$ ) in females] compared to those subjects in the lowest intake level ( $\leq 2.27$   $\mu\text{g/day}$ ) [OR = 0.77 (95% confidence interval, 0.64-0.93)] [31]. Whereas female subjects in the highest level of vitamin B<sub>12</sub> intake ( $\geq 5.94$   $\mu\text{g/day}$ ) were also 17% less likely to be hyperuricemia compared to those subjects in the lowest intake level ( $\leq 1.56$   $\mu\text{g/day}$ ) [OR = 0.83 (95% confidence interval, 0.67-1.03)] [31].

From the results of this article [31], though the daily vitamin B<sub>12</sub> intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were above the Recommended Dietary Allowances (RDAs), it seems that Japanese adult population (aged  $\geq 20$  years) need to take in more vitamin B<sub>12</sub>. Judging from the data of food composition [15, 16], it is important for Japanese adult population (aged  $\geq 20$  years) to eat meats (beef, turkey, chicken), organ meats (beef liver, angler liver), seafood (clams, tuna, salmon, anchovy, freshwater trout, lamprey, firefly squid, chub mackerel), grains (bread), whole grains (fortified ready-to-eat cereals),

legumes and soybean processed foods (kidney beans, tempeh), seaweed, fruit (bananas, strawberries), vegetables (spinach), dairy products (milk, yogurt, cheese), eggs.

The Ministry of Health, Labour and Welfare in Japan [10] has stated that the recommended daily vitamin B<sub>12</sub> intake in men and women (aged  $\geq 1$  year) of 0.9-2.4  $\mu\text{g/day}$  may be low and has been considered a future issue to address. The daily vitamin B<sub>12</sub> intake seems to be appropriate or it seems better to increase it slightly.

### 3.2.8. Vitamin C

The vitamin C intake of Japanese people in 2019 was higher compared to that in 1960, 1965, 2010, and 2016 was lower compared to that in 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, and 2007 and was the same as that in 2013 (1960: 75.0 mg/day; 1965: 78.0 mg/day; 1975: 117.0 mg/day; 1986: 124.0 mg/day; 1989: 123.0 mg/day; 1992: 122.0 mg/day; 1995: 135.0 mg/day; 1998: 125.0 mg/day; 2001: 106.0 mg/day; 2004: 99.0 mg/day; 2007: 96.0 mg/day; 2010: 90.0 mg/day; 2013: 94.0 mg/day; 2016: 89.0 mg/day; 2019: 94.0 mg/day). The daily vitamin C intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 94.0 mg/day; 2019: 99.0 mg/day). The daily vitamin C intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 92.0 mg/day; 2019: 96.0 mg/day; women: 2016: 97.0 mg/day; 2019: 101.0 mg/day).

The daily vitamin C intake of Japanese men (aged 1-19 years, aged 30-49 years, aged  $\geq 70$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-19 years: 2016: 53.0-71.0 mg/day; 2019: 56.0-75.0 mg/day; aged 30-49 years: 2016: 65.0-70.0 mg/day; 2019: 66.0-76.0 mg/day; aged  $\geq 70$  years: 2016: 119.0 mg/day; 2019: 126.0 mg/day). Whereas the daily vitamin C intake of Japanese men (aged 20-29 years, aged 60-69 years,) in 2019 were lower compared to those in 2016, respectively (aged 20-29 years: 2016: 67.0 mg/day; 2019: 62.0 mg/day; aged 60-69 years: 2016: 105.0 mg/day; 2019: 102.0 mg/day). The daily vitamin C intake of Japanese men (aged 50-59 years) in 2019 was the same as that in 2016 (2016: 82.0 mg/day; 2019: 82.0 mg/day). The daily vitamin C intake of Japanese women (aged 15-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 69.0 mg/day; 2019: 81.0 mg/day; aged 40-49 years: 2016: 71.0 mg/day; 2019: 74.0 mg/day; aged  $\geq 60$  years: 2016: 115.0-121.0 mg/day; 2019: 118.0-129.0 mg/day). Whereas the daily vitamin C intake of Japanese women (aged 1-14 years, aged 20-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-14 years: 2016: 52.0-68.0 mg/day; 2019: 49.0-66.0 mg/day; aged 20-39 years: 2016: 65.0-66.0 mg/day; 2019: 62.0-65.0 mg/day; aged 50-59 years: 2016: 90.0 mg/day; 2019: 88.0 mg/day).

The Recommended dietary allowances (RDAs) for vitamin C in Japanese men (aged  $\geq 12$  years) and women (aged  $\geq 12$  years) established by the Ministry of Health, Labour and Welfare in Japan are 100.0 mg/day, respectively [10]. The daily vitamin C intake of Japanese men (aged 20-59 years) and

women (aged 20-59 years) in 2019 were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 20-59 years): 62.0-82.0 mg/day; women (aged 20-59 years): 62.0-88.0 mg/day] [10]. Whereas the daily vitamin C intake of Japanese men (aged  $\geq 60$  years) and women (aged  $\geq 60$  years) were 102-126 mg/day and 118-129 mg/day, respectively, and were above the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 12$  years): 100.0 mg/day; women (aged  $\geq 12$  years): 100.0 mg/day] [10]. The Recommended dietary allowances (RDAs) for vitamin C in the U.S. men (aged  $\geq 19$  years) and women (aged  $\geq 19$  years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 90.0 mg/day and 75.0 mg/day, respectively [14]. The daily vitamin C intake of Japanese men (aged 20-59 years) and women (aged 20-49 years) were 62.0-82.0 mg/day and 62.0-74.0 mg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14]. Whereas the daily vitamin C intake of Japanese men (aged  $\geq 60$  years) and women (aged  $\geq 50$  years) were 102.0-126.0 mg/day and 88.0-129.0 mg/day, respectively, and exceeded the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14]. Smokers require 35 mg/day more vitamin C than nonsmokers [14]. The Ministry of Health, Labour and Welfare in Japan [10] has not set the Tolerable Upper Intake Levels (ULs) for healthy people because there is no scientific evidence for health problems due to excessive daily vitamin C intake. However, the Institute of Medicine of the National Academy of Sciences in the U.S. [14] has shown the Tolerable Upper Intake Levels (ULs) for healthy individuals [men (aged 14-18 years): 1800 mg/day; men (aged  $\geq 19$  years): 2000 mg/day; women (aged 14-18 years): 1800 mg/day; women (aged  $\geq 19$  years): 2000 mg/day].

The daily vitamin C intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.914$ ,  $p = 0.0000845$ ) and in 1986-2019 ( $r = -0.900$ ,  $p = 0.0000661$ ). The daily vitamin C intake was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.979$ ,  $p = 0.00360$ ) and in 2004-2019 ( $r = -0.879$ ,  $p = 0.0211$ ). The daily vitamin C intake was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.948$ ,  $p = 0.0142$ ) and in 2004-2019 ( $r = -0.873$ ,  $p = 0.0233$ ). The daily intake of vitamin C did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.552$ ,  $p = 0.335$ ) and in 2004-2019 ( $r = 0.600$ ,  $p = 0.208$ ). This result suggests that the correlation of daily vitamin C intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women. Furthermore, this result suggests that the daily vitamin C intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

In clinical trials, vitamin C decreased serum uric acid (SUA) concentrations [33-37]. In epidemiological studies, increased intake of vitamin C was associated with decreased SUA concentrations [38-41], hyperuricemia risk [38, 40, 42], and gout risk [32, 43-45]. Vitamin C intake may prevent gout through reduced SUA concentrations and decreased hyperuricemia risk.

Vitamin C lowers SUA concentration through a uricosuric effect by competing with SUA on the urate transporter 1 (also known as solute carrier family 22, member 12, or SLC22A12) for re-absorption in the kidney proximal tubule [33, 35-37, 46]. Vitamin C inhibits the pro-oxidant actions of uric acid (UA) during copper-mediated low density lipoprotein cholesterol (LDL-cholesterol) oxidation, and could reduce oxidative stress and inflammation, and may be related to lower UA production [47]. Vitamin C, which exerts as an antioxidant, reduced uric acid-induced inflammation by inhibiting activation of responsible nucleotide-binding and oligomerization domain-like receptor, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome in monosodium urate (MSU)-induced inflammation [48]. The role of vitamin C in prophylaxis and treatment of gout was reviewed in detail by Brzezińska et al. [49]. They [49] have stated that a higher serum vitamin C level has a positive effect on purine metabolism and favors the reduction of UA level, thus reducing the risk of monosodium urate crystal deposition in joints structures and soft tissue.

Huang et al. [36] found that supplementation with 500 mg/day of vitamin C for 2 months reduced SUA concentration by 0.5 mg/dL compared to no change in the placebo group in a randomized controlled trial. Gao et al. [41] found that total vitamin C intake of 500 mg/day or higher was associated with a -0.6-0.7 mg/dL lower level of SUA and was over 42% less likely to be hyperuricemia relative to those with intake < 90 mg/day. However, a randomized trial of vitamin C 500 mg daily as an adjunct to allopurinol demonstrated no reduction in SUA levels with vitamin C [50]. Choi et al. [45] found that vitamin C intake associated with lower gout risk have been approximately 500 mg/day or higher compared with vitamin C intake < 250 mg/day. From the results of these articles [36, 41, 45], though the Recommended Dietary Allowances (RDAs) for vitamin C established by the Ministry of Health, Labour and Welfare in Japan [10] and/or the Institute of Medicine of the National Academy of Sciences in the U.S. [14] were below 500.0 mg/day, it seems that Japanese adult population (aged  $\geq 20$  years) with higher SUA levels need to take in more vitamin C.

Judging from the data of food composition [15, 16], it is important for Japanese men (aged 20-59 years) and women (aged 20-59 years) to eat seaweed, fruit (acerolas, guavas, kiwi fruits, lemons, strawberries, papayas, blackcurrants), vegetables (kales, peppers, parsley, broccoli, tomatoes, cauliflowers, peas, eggplants, brussels sprouts, Chinese cabbages, mustard spinach) to take in more vitamin C to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10]

and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

## 4. Relationship Between the Number of Gout Patients and Mineral Intake in Japanese People

The results on the correlation between the number of gout patients and intake of mineral or salt in Japanese people are shown in Tables 1 and 2.

**Table 1.** Correlation between number of gout patients and intake of micronutrient or salt in Japanese people in 1986-2016 and 1986-2019.

Year	1986-2016		1986-2019	
	coefficient	p-value	coefficient	p-value
<b>Vitamins</b>				
Vitamin A*	- 0.899	<0.001	- 0.893	<0.001
Vitamin B <sub>1</sub> *	- 0.949	<0.001	- 0.880	<0.001
Vitamin B <sub>2</sub> **	- 0.799	0.005	- 0.756	0.004
Vitamin C	- 0.914	<0.001	- 0.900	<0.001
<b>Minerals</b>				
Calcium*	- 0.714	0.014	- 0.757	0.004
Iron	- 0.909	<0.001	- 0.894	<0.001
Salt***	- 0.903	<0.001	- 0.913	<0.001

\*The daily micronutrient intake of Japanese people (aged  $\geq 15$  years) in 2016 and 2019 were below the Recommended Dietary Allowances (RDAs). \*\*The daily micronutrient intake of Japanese people (aged  $\geq 15$  years) in 2016 were below the Recommended Dietary Allowances (RDAs). \*\*\*The daily salt intake of Japanese people (aged  $\geq 1$  year) in 2016 and 2019 exceeded the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG).

**Table 2.** Correlation between number of gout patients and micronutrient intake in Japanese people in 2001-2016 and 2001-2019.

Year	2001-2016		2001-2019	
	coefficient	p-value	coefficient	p-value
<b>Vitamins</b>				
Vitamin D	- 0.809	0.051	- 0.891	0.007
Vitamin E	- 0.686	0.132	- 0.706	0.076
Vitamin K	- 0.923	0.009	- 0.615	0.142
Niacin	0.113	0.831	0.677	0.095
Pantothenic acid	- 0.663	0.151	- 0.138	0.769
Vitamin B <sub>6</sub>	- 0.300	0.563	- 0.413	0.357
Folate	- 0.967	0.002	- 0.748	0.053
Vitamin B <sub>12</sub> **	- 0.936	0.006	- 0.812	0.026
<b>Minerals</b>				
Potassium*	- 0.905	0.013	- 0.624	0.134
Magnesium*	- 0.904	0.014	- 0.620	0.137
Phosphorus	- 0.858	0.029	- 0.554	0.197
Copper	- 0.933	0.007	- 0.852	0.015
Zinc*	- 0.868	0.021	- 0.304	0.508

\*The daily micronutrient intake of Japanese people (aged  $\geq 15$  years) in 2016 and 2019 were below the Recommended Dietary Allowances (RDAs). \*\*The daily vitamin B<sub>12</sub> intake of Japanese people (aged  $\geq 1$  year) in 2016 and 2019 were above the Recommended Dietary Allowances (RDAs).

### 4.1. Macrominerals

#### 4.1.1. Sodium and Salt

##### 1. Sodium

The daily sodium intake of Japanese people in 2019 was lower compared to that in 1995, 1998, 2000, 2002, 2005, 2007,

2010, and 2013 and was higher compared to that in 2016 (1995: 5.18 g/day; 1998: 5.00 g/day; 2000: 4.85 g/day; 2002: 4.48 g/day; 2005: 4.32 g/day; 2007: 4.18 g/day; 2010: 4.00 g/day; 2013: 3.87 g/day; 2016: 3.77 g/day; 2019: 3.83 g/day). The daily sodium intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 3.90 g/day; 2019: 3.96 g/day). The daily sodium intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 4.25 g/day; 2019: 4.31 g/day; women: 2016: 3.61 g/day; 2019: 3.65 g/day).

The daily sodium intake of Japanese men (aged 1-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-49 years: 2016: 2097-4139 mg/day; 2019: 2108-4171 mg/day; aged  $\geq 60$  years: 2016: 4243-4494 mg/day; 2019: 4396-4521 mg/day). Whereas the daily sodium intake of Japanese men (aged 50-59 years) in 2019 was lower compared to that in 2016 (aged 50-59 years: 2016: 4269 mg/day; 2019: 4180 mg/day). The daily sodium intake of Japanese women (aged 15-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 3283 mg/day; 2019: 3451 mg/day; aged 40-49 years: 2016: 3366 mg/day; 2019: 3499 mg/day; aged  $\geq 60$  years: 2016: 3713-3842 mg/day; 2019: 3736-3934 mg/day). Whereas the daily sodium intake of Japanese women (aged 1-14 years, aged 20-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-14 years: 2016: 2134-3249 mg/day; 2019: 1962-3216 mg/day; aged 20-39 years: 2016: 3352-3441 mg/day; 2019: 3277-3347 mg/day; aged 50-59 years: 2016: 3614 mg/day; 2019: 3602 mg/day).

The daily sodium intake was negatively correlated with the number of gout patients in 1995-2016 ( $r = -0.990$ ,  $p = 0.000160$ ) and in 1995-2019 ( $r = -0.964$ ,  $p = 0.000474$ ). The daily sodium intake did not show a significant correlation with the number of gout patients in 2007-2019 ( $r = -0.866$ ,  $p = 0.0574$ ). The daily sodium intake of Japanese men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were 4085-4521 mg/day and 3277-3934 mg/day, respectively, and exceeded the Estimated Average Requirements (EARs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 18$  years): 600 mg/day; women (aged  $\geq 18$  years): 600 mg/day] [10]. On the other hand, the Institute of Medicine of the National Academy of Sciences in the U.S. [14] and the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine in the U.S. [51] have not set the Estimated Average Requirements (EARs) and the Recommended Dietary Allowances (RDAs). The Adequate Intakes (AIs) and the Tolerable Upper Intake Levels (ULs) for sodium in the U.S. people (aged  $\geq 14$  years) established by the Institute of Medicine in the U.S. are 1500 mg/day and 2300 mg/day, respectively [14, 51]. It seems that the daily sodium intake of Japanese men and women in 2016 and 2019 are excessive.

## 2. Salt

The daily salt intake of Japanese people in 2019 was lower compared to that in 1975, 1980, 1985, 1986, 1995, 1998, 2001,

2004, 2007, 2010, and 2013 and was higher compared to that in 2016 (1975: 13.5 g/day; 1980: 12.9 g/day; 1985: 12.1 g/day; 1986: 12.1 g/day; 1995: 13.2 g/day; 1998: 12.7 g/day; 2001: 11.5 g/day; 2004: 10.7 g/day; 2007: 10.6 g/day; 2010: 10.2 g/day; 2013: 9.8 g/day; 2016: 9.6 g/day; 2019: 9.7 g/day). The daily salt intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 9.9 g/day; 2019: 10.1 g/day). The daily salt intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 10.8 g/day; 2019: 10.9 g/day; women: 2016: 9.2 g/day; 2019: 9.3 g/day).

The daily salt intake of Japanese men (aged 1-6 years, aged 20-29 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 5.3 g/day; 2019: 5.4 g/day; aged 20-29 years: 2016: 10.2 g/day; 2019: 10.6 g/day; aged 40-49 years: 2016: 10.5 g/day; 2019: 10.6 g/day; aged  $\geq 60$  years: 2016: 10.8-11.4 g/day; 2019: 11.2-11.5 g/day). Whereas the daily salt intake of Japanese men (aged 7-14 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 7-14 years: 2016: 9.1 g/day; 2019: 8.9 g/day; aged 50-59 years: 2016: 10.8 g/day; 2019: 10.6 g/day). The daily salt intake of Japanese men (aged 15-19 years, aged 30-39 years) in 2019 were the same as those in 2016, respectively (aged 15-19 years: 2016: 10.4 g/day; 2019: 10.4 g/day; aged 30-39 years: 2016: 10.4 g/day; 2019: 10.4 g/day). The daily salt intake of Japanese women (aged 15-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-19 years: 2016: 8.3 g/day; 2019: 8.8 g/day; aged 40-49 years: 2016: 8.6 g/day; 2019: 8.9 mg/day; aged  $\geq 60$  years: 2016: 9.4-9.8 g/day; 2019: 9.5-10.0 g/day). Whereas the daily salt intake of Japanese women (aged 1-14 years, aged 20-39 years) in 2019 were lower compared to those in 2016, respectively (aged 1-14 years: 2016: 5.4-8.3 g/day; 2019: 5.0-8.2 g/day; aged 20-39 years: 2016: 8.5-8.7 g/day; 2019: 8.3-8.5 g/day). The daily salt intake of Japanese men (aged 50-59 years) in 2019 were the same as those in 2016, respectively (aged 50-59 years: 2016: 9.2 g/day; 2019: 9.2 g/day).

The daily salt intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were 5.4-11.2 g/day and 5.0-10.0 g/day, 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 (aged  $\geq 1$  year):  $< 3.0$ -7.5 g/day; women (aged  $\geq 1$  year):  $< 3.0$ -6.5 g/day] [10]. The daily salt intake of adult men and women tended to increase as age increased. It is speculated that a decrease in daily salt intake in the situation of exceeding the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) is associated with the number of patients with gout. Thus, it is important for Japanese people to reduce salt intake.

The daily salt intake was negatively correlated with number of gout patients in 1986-2016 ( $r = -0.903$ ,  $p = 0.000141$ ) and in 1986-2019 ( $r = -0.913$ ,  $p = 0.0000331$ ). The daily salt intake was negatively correlated with the number of gout patients in

the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.988$ ,  $p = 0.00164$ ) and in 2004-2019 ( $r = -0.884$ ,  $p = 0.0195$ ). The daily salt intake was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.992$ ,  $p = 0.000801$ ) and in 2004-2019 ( $r = -0.916$ ,  $p = 0.0102$ ). The daily salt intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.722$ ,  $p = 0.169$ ) and in 2004-2019 ( $r = 0.749$ ,  $p = 0.0864$ ). This result suggests that the correlation of daily salt intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women.

The guidelines for management of gout established by 2012 American College of Rheumatology [52] recommended the limit intake of salt in gout patients.

#### 4.1.2. Calcium

The calcium intake of Japanese people in 2019 was higher compared to that in 1960, 1965, 2013, and 2016 and was lower compared to that in 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, and 2010 (1960: 389.0 mg/day; 1965: 465.0 mg/day; 1975: 550.0 mg/day; 1986: 551.0 mg/day; 1989: 540.0 mg/day; 1992: 539.0 mg/day; 1995: 585.0 mg/day; 1998: 568.0 mg/day; 2001: 550.0 mg/day; 2004: 538.0 mg/day; 2007: 531.0 mg/day; 2010: 510.0 mg/day; 2013: 504.0 mg/day; 2016: 502.0 mg/day; 2019: 505.0 mg/day). The daily calcium intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 495.0 mg/day; 2019: 498.0 mg/day). The daily calcium intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 498.0 mg/day; 2019: 503.0 mg/day; women: 2016: 492.0 mg/day; 2019: 494.0 mg/day).

The daily calcium intake of Japanese men (aged 1-6 years, aged 20-29 years, aged  $\geq 70$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 421.0 mg/day; 2019: 446.0 mg/day; aged 20-29 years: 2016: 430.0 mg/day; 2019: 462.0 mg/day; aged  $\geq 70$  years: 2016: 562.0 mg/day; 2019: 572.0 mg/day). Whereas the daily calcium intake of Japanese men (aged 7-19 years, aged 30-69 years,) in 2019 were lower compared to those in 2016, respectively (aged 7-19 years: 2016: 508.0-678.0 mg/day; 2019: 504.0-676.0 mg/day; aged 30-69 years: 2016: 442.0-539.0 mg/day; 2019: 395.0-533.0 mg/day). The daily calcium intake of Japanese women (aged 15-29 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 15-29 years: 2016: 396.0-426.0 mg/day; 2019: 408.0-454.0 mg/day; aged 40-49 years: 2016: 439.0 mg/day; 2019: 441.0 mg/day; aged  $\geq 60$  years: 2016: 531.0 mg/day; 2019: 544.0 mg/day). Whereas the daily calcium intake of Japanese women (aged 1-14 years, aged 30-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-14 years: 2016: 398.0-610.0 mg/day; 2019: 391.0-594.0 mg/day; aged 30-39 years: 2016: 439.0 mg/day; 2019: 406.0 mg/day; aged 50-59 years: 2016: 491.0-543.0 mg/day; 2019: 472.0-539.0 mg/day).

The daily calcium intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) in 2019 were 395-572 mg/day and 406-544 mg/day, respectively, and were below the Estimated Average Requirements (EARs) [men (aged  $\geq 15$  years): 600-650 mg/day; women (aged 15-74 years): 550 mg/day; women (aged  $\geq 75$  years): 500 mg/day] and the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 15$  years): 700-800 mg/day; women (aged  $\geq 15$  years): 600-650 mg/day] [10]. The daily calcium intake of Japanese women (aged 1-6 years) in 2019 was 391.0 mg/day and was below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [women (aged 1-6 years): 400-550 mg/day] [10]. The daily calcium intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) were also below the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine in the U.S. [men (aged 14-18 years): 1300 mg/day; men (aged 19-70 years): 1000 mg/day; men (aged  $> 71$  years): 1200 mg/day; women (aged 14-18 years): 1300 mg/day; women (aged 19-50 years): 1000 mg/day; women (aged  $\geq 51$  years): 1200 mg/day] [16, 17].

The Adequate Intakes (AIs) for calcium in the U.S. men and women (aged 1-3 years), men and women (aged 4-8 years), men and women (aged 9-18 years), men and women (aged 19-50 years), men and women (aged  $\geq 51$  years) established by the Institute of Medicine of the National Academy of Sciences in the U.S. are 500 mg/day, 800 mg/day, 1300 mg/day, 1000 mg/day, and 1200 mg/day, respectively [14]. In the Adequate Intakes (AIs) for calcium established by the Institute of Medicine of the National Academy of Sciences in the U.S., the daily calcium intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) were 395-676 mg/day and 391-594 mg/day, respectively, and were below the Adequate Intakes (AIs) [14]. It seems that Japanese population (aged  $\geq 1$  year) need to take in more calcium.

The daily calcium intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.714$ ,  $p = 0.0136$ ) and in 1986-2019 ( $r = -0.757$ ,  $p = 0.00435$ ). The daily calcium intake was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.952$ ,  $p = 0.0124$ ) and in 2004-2019 ( $r = -0.883$ ,  $p = 0.0396$ ). The daily calcium intake tended to be negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.848$ ,  $p = 0.0693$ ) and in 2004-2019 ( $r = -0.781$ ,  $p = 0.0668$ ). The daily calcium intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.769$ ,  $p = 0.128$ ). The daily calcium intake tended to be positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r = 0.786$ ,  $p = 0.0639$ ). This result suggests that the correlation of daily calcium intake with the number of gout patients tends to vary with gender and tended to be stronger in adult men than in adult women. Furthermore, this result suggests that the daily calcium intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

In a mendelian randomization study, blood calcium concentration had no association with gout risk [53]. In a randomized, placebo controlled clinical trial, 323 healthy men (aged > 40 years) ingested a dose level of 1200 mg per day of calcium for 24 months [20]. No significant differences were detected in serum uric acid (SUA) levels between placebo group and calcium group [20]. Regression analysis indicated that a difference of calcium intake of 1200 mg per day was associated with a difference in SUA levels of 0.022 mmol/L [20]. In epidemiological studies, increased intake of calcium was associated with decreased SUA concentrations [30, 54] and hyperuricemia risk [42]. It is possible that calcium intake prevent gout through reduced SUA concentrations and decreased hyperuricemia risk.

Judging from the data of food composition [15, 16], it is important for Japanese people (aged  $\geq 15$  years) to eat seafood (sardines), cereals (fortified ready-to-eat cereals), milks (almond milk, low-fat milk, skim milk, whole butter milk, whole chocolate milk), vegetables (spinach, okra, curly kale), dairy products (milk, cheese, yogurt), soy products (soy milk, tofu) to take in more calcium to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and the Adequate Intakes (AIs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

#### 4.1.3. Potassium

The daily potassium intake of Japanese people in 2019 was lower compared to that in 2001, 2004, and 2007 and was higher compared to that in 2010, 2013, and 2016 (2001: 2434 mg/day; 2004: 2321 mg/day; 2007: 2306 mg/day; 2010: 2200 mg/day; 2013: 2231 mg/day; 2016: 2219 mg/day; 2019: 2299 mg/day). The daily potassium intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 2279 mg/day; 2019: 2350 mg/day). The daily potassium intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 2356 mg/day; 2019: 2439 mg/day; women: 2016: 2216 mg/day; 2019: 2273 mg/day).

The daily potassium intake of Japanese men (aged 1-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-49 years: 2016: 1489-2257 mg/day; 2019: 1588-2307 mg/day; aged  $\geq 60$  years: 2016: 2556-2603 mg/day; 2019: 2569-2699 mg/day). Whereas the daily potassium intake of Japanese men (aged 50-59 years) in 2019 was lower compared to that in 2016 (2016: 2219 mg/day; 2019: 2290 mg/day). The daily potassium intake of Japanese women (aged 7-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 1782-2050 mg/day; 2019: 2060-2133 mg/day; aged 40-49 years: 2016: 1937 mg/day; 2019: 2033 mg/day; aged  $\geq 60$  years: 2016: 2402-2476 mg/day; 2019: 2506-2529 mg/day). Whereas the daily potassium intake of Japanese women (aged 1-6 years, aged 20-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 1441 mg/day; 2019: 1435

mg/day; aged 20-39 years: 2016: 1829-1925 mg/day; 2019: 1743-1896 mg/day; aged 50-59 years: 2016: 2217 mg/day; 2019: 2153 mg/day).

The daily potassium intake of Japanese men (aged 15-59 years) and women (aged 20-39 years) in 2019 were 2080-2290 mg/day and 1743-1896 mg/day, respectively, and were below the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 15-59 years): 2500-2700 mg/day; women (aged 20-39 years): 2000 mg/day] [10]. Whereas the daily potassium intake of Japanese men (aged  $\geq 60$  years) and women (aged  $\geq 40$  years) were 2569-2699 mg/day and 2033-2529 mg/day, respectively, and were above the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 60$  years): 2500 mg/day; women (aged  $\geq 40$  years): 2000 mg/day] [10]. The daily potassium intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) in 2019 were 2080-2699 mg/day and 1743-2529 mg/day, 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  $\geq 15$  years):  $\geq 3000$  mg/day; women (aged  $\geq 15$  years):  $\geq 2600$  mg/day] [10], but were below the Adequate Intakes (AIs) established by the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine in the U.S. [men (aged 14-18 years): 3000 mg/day; men (aged  $\geq 19$  years): 3400 mg/day; women (aged 14-18 years): 2300 mg/day; women (aged  $\geq 19$  years): 2600 mg/day] [51]. The daily potassium intake of Japanese people tended to increase as age increased. Furthermore, this result suggests that the daily potassium intake below the Recommended Dietary Allowances (RDAs) are related to the increase in the number of gout patients.

The daily potassium intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.905$ ,  $p = 0.0132$ ). The daily potassium intake did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.624$ ,  $p = 0.134$ ). The daily potassium intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.773$ ,  $p = 0.126$ ) and in 2004-2019 ( $r = -0.268$ ,  $p = 0.608$ ). The daily potassium intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.808$ ,  $p = 0.0977$ ) and in 2004-2019 ( $r = -0.326$ ,  $p = 0.529$ ). The daily potassium intake tended to be positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.863$ ,  $p = 0.0594$ ). The daily potassium intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r = 0.0709$ ,  $p = 0.115$ ). This result suggests that the correlation of daily potassium intake with number of gout patients tends to vary with gender.

Judging from the data of food composition [15, 16], it is important for Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) to eat meats (poultry), seafood (tuna, halibut, cod, trout, rockfish), nuts, whole grains (brown and wild rice, brown cereal, whole-wheat bread and pasta), potatoes,

legumes (peas, lima beans, pinto beans, kidney beans, soybeans, lentils), mushrooms, fruit (bananas, oranges, apricots, grapefruits, cantaloupes), vegetables (spinach, broccoli, cucumbers, zucchinis, pumpkins, leafy greens), coffee to take in more potassium to reach the Tentative Dietary Goal for Preventing Lifestyle-related Diseases (DG) established by the Ministry of Health, Labour and Welfare in Japan [10] and the Adequate Intakes (AIs) established by the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine in the U.S. [51]. It is encouraged to replace meat with fish and legumes.

#### 4.1.4. Magnesium

The daily magnesium intake of Japanese people in 2019 was lower compared to that in 2001 and 2004 and was higher compared to that in 2010, 2013, and 2016 and was the same as that in 2007 (2001: 262 mg/day; 2004: 250 mg/day; 2007: 247 mg/day; 2010: 236 mg/day; 2013: 239 mg/day; 2016: 238 mg/day; 2019: 247 mg/day). The daily magnesium intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 246 mg/day; 2019: 255 mg/day). The daily magnesium intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 260 mg/day; 2019: 270 mg/day; women: 2016: 234 mg/day; 2019: 242 mg/day).

The daily magnesium intake of Japanese men (aged 1-14 years, aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-14 years: 2016: 148-232 mg/day; 2019: 158-236 mg/day; aged  $\geq 20$  years: 2016: 222-284 mg/day; 2019: 227-290 mg/day). Whereas the daily magnesium intake of Japanese men (aged 15-19 years) in 2019 was lower compared to that in 2016 (2016: 242 mg/day; 2019: 239 mg/day). The daily magnesium intake of Japanese women (aged 7-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 189-209 mg/day; 2019: 213-214 mg/day; aged 40-49 years: 2016: 210 mg/day; 2019: 219 mg/day; aged  $\geq 60$  years: 2016: 247-259 mg/day; 2019: 216-269 mg/day). Whereas the daily magnesium intake of Japanese women (aged 1-6 years, aged 20-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 146 mg/day; 2019: 143 mg/day; aged 20-39 years: 2016: 194-209 mg/day; 2019: 192-205 mg/day; aged 50-59 years: 2016: 238 mg/day; 2019: 233 mg/day). This tendency of the daily magnesium intake in Japanese women was same that of the daily potassium intake.

The daily magnesium intake of Japanese men (aged 1-6 years), men (aged  $\geq 70$  years), women (aged 1-6 years), and women (aged  $\geq 60$  years) in 2019 were 159 mg/day, 290 mg/day, 143 mg/day, and 261-269 mg/day, respectively, and were above the Estimated Average Requirements (EARs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 1-6 years): 60-110 mg/day; men (aged  $\geq 70$  years): 270-290 mg/day; women (aged 1-6 years): 60-110 mg/day; women (aged  $\geq 60$  years): 220-240 mg/day] [10]. The daily magnesium intake for men (aged 1-6 years) and women

(aged 1-6 years) in 2019 were above the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 1-6 years): 70-130 mg/day; women (aged 1-6 years): 70-130 mg/day] [10]. The daily magnesium intake of Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) in 2019 were 227-290 mg/day and 192-269 mg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 15$  years): 320-370 mg/day; women (aged  $\geq 15$  years): 260-310 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 14$  years): 400-420 mg/day; women (aged  $\geq 14$  years): 310-360 mg/day] [14]. The daily magnesium intake of Japanese men (aged 7-14 years) and women (aged 7-14 years) in 2019 were 236 mg/day and 214 mg/day, respectively. The Ministry of Health, Labour and Welfare in Japan [10] has set the Tolerable Upper Intake Levels (ULs) of daily magnesium intake for men and women (aged 7-14 years) and men and women (aged  $\geq 15$  years) are 5 mg/ kg body weight/day and 350 mg/day, respectively. In healthy men and women (aged 1-14 years), overdose of magnesium-rich foods and/or supplementation should be avoided so as not to exceed the Tolerable Upper Intake Levels (ULs).

The daily magnesium intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.904$ ,  $p = 0.0135$ ). The daily magnesium intake did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.620$ ,  $p = 0.137$ ). The daily magnesium intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.815$ ,  $p = 0.0925$ ) and in 2004-2019 ( $r = -0.259$ ,  $p = 0.620$ ). The daily magnesium intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.839$ ,  $p = 0.0755$ ) and in 2004-2019 ( $r = -0.315$ ,  $p = 0.495$ ). The daily magnesium intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.851$ ,  $p = 0.0672$ ) and in 2004-2019 ( $r = 0.677$ ,  $p = 0.140$ ). This result suggests that the correlation of daily magnesium intake with the number of gout patients tends to vary with gender.

In a mendelian randomization study, blood magnesium concentration was inversely associated with gout risk (OR = 0.26, 95% CI = 0.09, 0.76,  $p = 0.013$ ); that is to say, each 0.16 mmol/L increase in genetically predicted magnesium was associated with a 0.26-fold increased risk of gout [53]. In epidemiological studies, increased magnesium intake was associated with decreased serum uric acid (SUA) concentrations [55] and hyperuricemia risk [55, 56]. A meta-analysis and systematic review reported that dietary magnesium intake was inversely associated with serum C-reactive protein levels as biomarker of inflammation [57]. SUA level is positively associated with several inflammatory markers (e.g., white blood cell count, C-reactive protein, interleukin-6) [58]. This fact suggests that uric acid (UA) may have a role in inflammation and subsequent

inflammatory related disease, such as gout. It is possible that magnesium intake prevent gout through reduced SUA concentrations and decreased hyperuricemia risk.

Increased magnesium intake was significantly associated with decreased risk of hyperuricemia [serum uric acid (SUA) concentration  $\geq 7.0$  mg/dL (416.4  $\mu\text{mol/L}$ ) in males and  $\geq 6.0$  mg/dL (356.9  $\mu\text{mol/L}$ ) in females] by analyses of the U.S. NHANES (2001-2014) databases involving 26,796 adults (aged 20-85 years) [56]. This article revealed that male subjects consuming in the second quintile (200-265 mg/day), third quintile (266-334 mg/day), fourth quintile (335-432 mg/day), and highest quintile ( $\geq 433$  mg/day) of magnesium intake were 17%, 26%, 22%, and 30% decreased risk of hyperuricemia, respectively, compared to those subjects consuming in the lowest quintile of magnesium intake ( $< 200$  mg/day) (p for trend = 0.0003) [56]. This article also revealed that female subjects consuming in the second quintile (158-207 mg/day), third quintile (208-260 mg/day), fourth quintile (261-336 mg/day), and highest quintile ( $\geq 337$  mg/day) of magnesium intake were 5%, 14%, 25%, and 13% decreased risk of hyperuricemia, respectively, compared to those subjects consuming in the lowest quintile of magnesium intake ( $< 158$  mg/day) (p for trend = 0.0242) [56]. In Japanese men and women in 2019, the daily magnesium intake for men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) were 270 mg/day and 242 mg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 20$  years): 320-370 mg/day; women (aged  $\geq 20$  years): 260-290 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 19$  years): 400-420 mg/day; women (aged  $\geq 19$  years): 310-320 mg/day][14]. These results indicate the importance of Recommended Dietary Allowances (RDAs) of magnesium intake for the prevention of hyperuricemia in Japanese adults.

Judging from the data of food composition [15, 16], it is important for Japanese men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) to eat meats (beef), organ meats (chicken breast), seafood (salmon, sardines), seeds and nuts (pumpkin seeds, chia seeds, sunflower seeds, almonds, peanuts, cashew nuts, sesame seeds, flaxseeds), grains (white rice, bread), whole grains (brown rice, cereals, fortified ready-to-eat cereals, whole-wheat bread, oatmeal), potatoes, legumes (black beans, kidney beans, edamame), seaweeds, fruit (bananas, raisins, avocados, apples), vegetables (spinach, broccoli, carrots, parsley), dairy products (milk, yogurt), soy products (soy milk), tea, green tea to take in more magnesium to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

#### 4.1.5. Phosphorus

The daily phosphorus intake of Japanese people in 2019 was lower compared to that in 2001 and 2004 and was higher compared to that in 2007, 2010, 2013, and 2016 (2001: 1057

mg/day; 2004: 1013 mg/day; 2007: 1000 mg/day; 2010: 960 mg/day; 2013: 978 mg/day; 2016: 976 mg/day; 2019: 1007 mg/day). The daily phosphorus intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 982 mg/day; 2019: 1012 mg/day). The daily phosphorus intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 1051 mg/day; 2019: 1084 mg/day; women: 2016: 925 mg/day; 2019: 948 mg/day).

The daily phosphorus intake of Japanese men (aged 1-6 years, aged 20-29 years, aged  $\geq 40$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 692 mg/day; 2019: 728 mg/day; aged 20-29 years: 2016: 983 mg/day; 2019: 1066 mg/day; aged  $\geq 40$  years: 2016: 1004-1119 mg/day; 2019: 1052-1127 mg/day). Whereas the daily phosphorus intake of Japanese men (aged 7-19 years, aged 30-39 years) in 2019 were lower compared to those in 2016, respectively (aged 7-19 years: 2016: 1129-1144 mg/day; 2019: 1128-1181 mg/day; aged 30-39 years: 2016: 988 mg/day; 2019: 981 mg/day). The daily phosphorus intake of Japanese women (aged 7-29 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-29 years: 2016: 827-996 mg/day; 2019: 837-1014 mg/day; aged 40-49 years: 2016: 861 mg/day; 2019: 916 mg/day; aged  $\geq 60$  years: 2016: 951-996 mg/day; 2019: 991-1012 mg/day). Whereas the daily phosphorus intake of Japanese women (aged 1-6 years, aged 30-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 657 mg/day; 2019: 650 mg/day; aged 30-39 years: 2016: 868 mg/day; 2019: 852 mg/day; aged 50-59 years: 2016: 939 mg/day; 2019: 917 mg/day).

The daily phosphorus intake of Japanese men (aged 30-39 years) in 2019 was 981 mg/day and was below the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 30-39 years): 1000 mg/day] [10]. Whereas the daily phosphorus intake of Japanese men (aged 20-29 years,  $\geq 40$  years) and women (aged  $\geq 7$  years) in 2019 were 1066 mg/day, 1052-1127 mg/day, and 837-1014 mg/day, respectively, and were above the Adequate Intakes (AIs) [men (aged  $\geq 20$  years): 1000 mg/day; women (aged  $\geq 7$  years): 800-1000 mg/day] and were below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 20$  years): 3000 mg/day; women (aged  $\geq 20$  years): 3000 mg/day] [10]. The daily phosphorus intake of Japanese men (aged  $\geq 20$  years) and Japanese women (aged  $\geq 20$  years) in 2019 were 981-1127 mg/day and 837-1012 mg/day, respectively, and were above the Recommended Dietary Allowances (RDAs) for phosphorus established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 19$  years): 700 mg/day; women (aged  $\geq 19$  years): 700 mg/day] [14]. Though the daily phosphorus intake for men (aged 30-39 years) was below the Adequate Intakes (AIs) established by the Ministry of Health, Labour and Welfare in Japan [10], it seems that Japanese adult population (aged  $\geq 20$  years) need to decrease intake of phosphorus to reach the Recommended Dietary Allowances (RDAs)

established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

The daily phosphorus intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.858$ ,  $p = 0.0289$ ). The daily phosphorus intake did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.554$ ,  $p = 0.197$ ). The daily phosphorus intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.594$ ,  $p = 0.291$ ) and in 2004-2019 ( $r = -0.0215$ ,  $p = 0.968$ ). The daily phosphorus intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.649$ ,  $p = 0.236$ ) and in 2004-2019 ( $r = -0.151$ ,  $p = 0.775$ ). The daily phosphorus intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.845$ ,  $p = 0.0713$ ) and in 2004-2019 ( $r = 0.593$ ,  $p = 0.215$ ). This result suggests that the correlation of daily phosphorus intake with the number of gout patients tends to vary with gender.

It seems important to reduce the intake of one serving of high-phosphorus food (e.g., yogurt, milk, cheese, salmon, scallops, sardines, flying fish, dried squid, chicken, lentils, cashew nuts, potatoes, [15, 16]).

## 4.2. Microminerals

### 4.2.1. Iron

The daily iron intake of Japanese in 2019 was lower compared to that in 1960, 1975, 1980, 1986, 1995, 1998, 2001, 2004, and 2007 and was higher compared to that in 2013 and 2016 and was the same as that in 2010 (1960: 13.0 mg/day; 1975: 13.4 mg/day; 1980: 10.4 mg/day; 1986: 10.7 mg/day; 1995: 11.8 mg/day; 1998: 11.4 mg/day; 2001: 8.2 mg/day; 2004: 7.9 mg/day; 2007: 7.9 mg/day; 2010: 7.6 mg/day; 2013: 7.4 mg/day; 2016: 7.4 mg/day; 2019: 7.6 mg/day). The daily iron intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 7.7 mg/day; 2019: 7.9 mg/day). The daily iron intake of Japanese adult men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 8.1 mg/day; 2019: 8.3 mg/day; women: 2016: 7.3 mg/day; 2019: 7.5 mg/day).

The daily iron intake of Japanese men (aged 1-6 years, aged 15-29 years, aged  $\geq 40$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 4.4 mg/day; 2019: 4.5 mg/day; aged 15-29 years: 2016: 7.2-7.8 mg/day; 2019: 7.4-7.9 mg/day; aged  $\geq 40$  years: 2016: 7.5-8.7 mg/day; 2019: 7.6-9.0 mg/day). Whereas the daily iron intake of Japanese men (aged 7-14 years, aged 30-39 years) in 2019 were lower compared to those in 2016, respectively (aged 7-14 years: 2016: 6.9 mg/day; 2019: 6.7 mg/day; aged 30-39 years: 2016: 7.3 mg/day; 2019: 7.2 mg/day). The daily iron intake of Japanese women (aged 7-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 6.1-6.5 mg/day; 2019: 6.3-7.0 mg/day; aged 40-49 years: 2016: 6.5 mg/day; 2019: 6.7 mg/day; aged  $\geq 60$  years: 2016: 7.8-8.1 mg/day;

2019: 8.2-8.4 mg/day). Whereas the daily iron intake of Japanese women (aged 1-6 years, aged 20-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 4.3 mg/day; 2019: 4.0 mg/day; aged 20-39 years: 2016: 6.5-6.7 mg/day; 2019: 6.2-6.4 mg/day; aged 50-59 years: 2016: 7.4 mg/day; 2019: 7.2 mg/day).

The daily iron intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were 4.5-9.0 mg/day and 4.0-8.4 mg/day, respectively, and were below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 1$  year): 25-50 mg/day; women (aged  $\geq 1$  year): 20-40 mg/day] [10]. The daily iron intake of Japanese men (aged  $\geq 20$  years) in 2019 was 7.2-9.0 mg/day and was above the Estimated Average Requirements (EARs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 20$  years): 6.0-6.5 mg/day] [10]. The daily iron intake of Japanese men (aged 20-39 years) in 2019 was 7.2-7.4 mg/day and was below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 20-39 years): 7.5 mg/day] [10]. Whereas the daily iron intake of Japanese men (aged  $\geq 40$  years) in 2019 was 7.6-9.0 mg/day and was above the Recommended Dietary Allowances (RDAs) [men (aged  $\geq 40$  years): 7.0-7.5 mg/day] and was below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 50$  years): 50.0 mg/day] [10]. The daily iron intake of Japanese women (aged  $\geq 1$  year) and women (aged 15-59 years) in 2019 were 4.0-8.4 mg/day and 6.2-7.2 mg/day, respectively. The Ministry of Health, Labour and Welfare in Japan [10] has established that the Recommended Dietary Allowances (RDAs) of daily iron intake for women without menstruation (aged  $\geq 1$  year) and women with menstruation (aged 15-59 years) are 4.5-8.5 mg/day and 10.5-11.0 mg/day, respectively. The daily iron intake of Japanese women (aged  $\geq 40$  years) in 2019 was 6.7-8.4 mg/day and was above the Recommended Dietary Allowances (RDAs) in women without menstruation [women without menstruation (aged  $\geq 40$  years): 6.0-6.5 mg/day] or was below the Recommended Dietary Allowances (RDAs) in women with menstruation (aged  $\geq 40$  years) [women with menstruation (aged  $\geq 40$  years): 10.5-11.0 mg/day] and was below the Tolerable Upper Intake levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 40$  years): 40.0 mg/day] [10]. In healthy men (aged  $\geq 40$  years) and women without menstruation (aged  $\geq 40$  year), overdose of iron-rich foods and/or supplementation should be avoided so as not to exceed the Tolerable Upper Intake Levels (ULs). The daily iron intake of Japanese men (aged 15-49 years) and women (aged 15-59 years) in 2019 were 7.2-7.9 mg/day and 6.2-7.2 mg/day, respectively, and were below the Recommended Dietary Allowances (RDAs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 14-18 years): 11 mg/day; men (aged  $\geq 15$  years): 8 mg/day; women (aged 14-18 years): 15 mg/day; women (aged 19-50 years): 18 mg/day; women (aged  $\geq 51$  years): 8 mg/day][14].

Whereas the daily iron intake for men (aged  $\geq 50$  years) and women (aged  $\geq 60$  years) were 8.1-9.0 mg/day and 8.2-8.4 mg/day, respectively, and exceeded the Recommended Dietary Allowances (RDAs) and was below the Tolerable Upper Intake Levels (ULs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 14$  years): 45.0 mg/day; women (aged  $\geq 14$  years): 45.0 mg/day] [14].

The daily iron intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.909$ ,  $p = 0.000107$ ) and in 1986-2019 ( $r = -0.894$ ,  $p = 0.000088$ ). The daily iron intake was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.966$ ,  $p = 0.00757$ ). The daily iron intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.718$ ,  $p = 0.108$ ). The daily iron intake was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.985$ ,  $p = 0.00220$ ). The daily iron intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.721$ ,  $p = 0.106$ ). Whereas the daily iron intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.614$ ,  $p = 0.271$ ) and in 2004-2019 ( $r = 0.623$ ,  $p = 0.186$ ). This result suggests that the correlation of daily iron intake with number of gout patients varies with gender and is stronger in adult men than in adult women.

In a mendelian randomization study, blood iron concentration was inversely associated with gout risk (OR = 0.71, 95% CI = 0.53, 0.95,  $p = 0.047$ ); that is to say, each per-unit increase in genetically predicted iron was associated with a 0.71-fold increased risk of gout [53]. In an epidemiological study, increased iron intake was associated with decreased serum uric acid (SUA) concentrations [30]. It is possible that iron intake prevent gout through a reduction of SUA concentrations.

From the data of food composition [15, 16], it is important for Japanese men (aged 15-49 years) and women (aged 15-59 years) including women with menstruation (aged  $\geq 40$  years) to eat lean meat and meats (poultry), organ meats (liver), seafood (oysters, sardines, tuna, sweetfish, abalone, clams, firefly squid), potatoes (konjac), nuts (cashew nuts, pistachio nuts, sesame seeds, flaxseeds), grains (white rice, bread, spaghetti), whole grains (brown rice, Iron-fortified ready-to-eat cereals and breads), mushrooms (wood ear), legumes (kidney beans, white beans, lentils, peas, green peas), seaweed, fruit (raisins, cantaloupes), vegetables (spinach, broccoli, parsley), dairy products (milk, cheese), soy products (tofu), eggs, tea to take in more iron to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] or those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14]. It must be careful not to exceed the Tolerable Upper Intake Levels (ULs) of the daily iron intake in Japanese men (aged  $\geq 50$  years) and women (aged  $\geq 60$  years).

#### 4.2.2. Copper

The daily copper intake of Japanese people in 2019 was lower compared to that in 2001, 2004, and 2007 and was the same as that in 2010 and 2013 and was higher compared to that in 2016 (2001: 1.25 mg/day; 2004: 1.19 mg/day; 2007: 1.16 mg/day; 2010: 1.12 mg/day; 2013: 1.12 mg/day; 2016: 1.11 mg/day; 2019: 1.12 mg/day). The daily copper intake of Japanese adult population (aged  $\geq 20$  years) was the same as that in 2016 (2016: 1.14 mg/day; 2019: 1.14 mg/day). The daily copper intake of Japanese adult men (aged  $\geq 20$  years) in 2019 was the same as that in 2016 (2016: 1.23 mg/day; 2019: 1.23 mg/day). On the other hand, the daily copper intake of Japanese adult women (aged  $\geq 20$  years) in 2019 was higher compared to that in 2016 (2016: 1.06 mg/day; 2019: 1.07 mg/day).

The daily copper intake of Japanese men (aged 1-6 years, aged  $\geq 70$  years) in 2019 were higher compared to those in 2016, respectively (aged 1-6 years: 2016: 0.69 mg/day; 2019: 0.71 mg/day; aged  $\geq 70$  years: 2016: 1.26 mg/day; 2019: 1.30 mg/day). Whereas the daily copper intake of Japanese men (aged 7-19 years, aged 30-69 years) in 2019 were lower compared to those in 2016, respectively (aged 7-19 years: 2016: 1.13-1.30 mg/day; 2019: 1.11-1.29 mg/day; aged 30-69 years: 2016: 1.16-1.30 mg/day; 2019: 1.15-1.27 mg/day). The daily copper intake of Japanese men (aged 20-29 years) in 2019 was the same as that in 2016 (2016: 1.14 mg/day; 2019: 1.14 mg/day). The daily copper intake of Japanese women (aged 7-19 years, aged 40-49 years, aged  $\geq 60$  years) in 2019 were higher compared to those in 2016, respectively (aged 7-19 years: 2016: 0.97-0.99 mg/day; 2019: 1.00-1.05 mg/day; aged 40-49 years: 2016: 0.97 mg/day; 2019: 0.98 mg/day; aged  $\geq 60$  years: 2016: 1.10-1.13 mg/day; 2019: 1.15 mg/day). Whereas the daily copper intake of Japanese women (aged 1-6 years, aged 20-39 years, aged 50-59 years) in 2019 were lower compared to those in 2016, respectively (aged 1-6 years: 2016: 0.69 mg/day; 2019: 0.66 mg/day; aged 20-39 years: 2016: 0.95-0.99 mg/day; 2019: 0.90-0.96 mg/day; aged 50-59 years: 2016: 1.07 mg/day; 2019: 1.03 mg/day).

The daily copper intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) in 2019 were 0.71-1.30 mg/day and 0.66-1.15 mg/day, respectively, and exceeded the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 1$  year): 0.3-0.9 mg/day; women (aged  $\geq 1$  year): 0.3-0.7 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 1$  year): 0.34-0.90 mg/day; women (aged  $\geq 1$  year): 0.34-0.90 mg/day] [14]. The daily copper intake of Japanese men (aged  $\geq 18$  years) and women (aged  $\geq 18$  years) in 2019 were 1.14-1.30 mg/day and 0.90-1.15 mg/day, respectively, and were below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 18$  years): 7.0 mg/day; women (aged  $\geq 18$  years): 7.0 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 14-18 years): 8 mg/day; men (aged  $\geq 19$  years): 10.0 mg/day; women (aged 14-18 years): 8 mg/day; women (aged  $\geq 19$  years): 10.0

mg/day] [14]. The daily copper intake of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) were below the Tolerable Upper Intake Levels (ULs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged 1-3 years): 1.0 mg/day; men (aged 4-8 years): 3.0 mg/day; men (aged 9-13 years): 5.0 mg/day; men (aged 14-18 years): 8.0 mg/day; men (aged  $\geq 19$  years): 10.0 mg/day; women (aged 1-3 years): 1.0 mg/day; women (aged 4-8 years): 3.0 mg/day; women (aged 9-13 years): 5.0 mg/day; women (aged 14-18 years): 8.0 mg/day; women (aged  $\geq 19$  years): 10.0 mg/day] [14]. The Ministry of Health, Labour and Welfare in Japan [10] has not set the Tolerable Upper Intake Levels (ULs) for healthy men and women (aged 0-17 years) because there is no scientific evidence for health problems due to excessive daily intake of copper and has expressed the view that healthy people do not overdose copper in their normal diet, but overdose of copper can occur due to improper use of supplementation. In healthy men and women, taking of copper supplementation should be careful so as not to exceed the Tolerable Upper Intake Levels (ULs).

The daily copper intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.933$ ,  $p = 0.00652$ ) and in 2001-2019 ( $r = -0.852$ ,  $p = 0.0149$ ). The daily copper intake tended to be negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.877$ ,  $p = 0.0511$ ). The daily copper intake was negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2019 ( $r = -0.818$ ,  $p = 0.0469$ ). The daily copper intake was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.925$ ,  $p = 0.0242$ ) and in 2004-2019 ( $r = -0.890$ ,  $p = 0.0176$ ). The daily copper intake tended to be positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.878$ ,  $p = 0.0503$ ). The daily copper intake was positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2019 ( $r = 0.880$ ,  $p = 0.0207$ ). This result suggests that the correlation of daily copper intake with the number of gout patients varies with gender.

In a mendelian randomization study, blood copper concentration had no association with gout risk [53].

It seems that Japanese adult population (aged  $\geq 1$  year) need to decrease intake of copper to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] or those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

#### 4.2.3. Zinc

The daily zinc intake of Japanese people in 2019 was lower compared to that in 2001 and was higher compared to that in 2004, 2007, 2010, 2013, and 2016 (2001: 8.5 mg/day; 2004: 8.3 mg/day; 2007: 8.2 mg/day; 2010: 7.9 mg/day; 2013: 8.0 mg/day; 2016: 8.0 mg/day; 2019: 8.4 mg/day). The daily zinc intake of Japanese adult population (aged  $\geq 20$  years) was higher compared to that in 2016 (2016: 8.0 mg/day; 2019: 8.4 mg/day). The daily zinc intake of Japanese adult men (aged  $\geq$

20 years) and women (aged  $\geq 20$  years) in 2019 were higher compared to those in 2016, respectively (men: 2016: 8.8 mg/day; 2019: 9.2 mg/day; women: 2016: 7.3 mg/day; 2019: 7.7 mg/day).

The daily zinc intake of Japanese men (aged  $\geq 1$  year) in 2019 was higher compared to that in 2016 (2016: 5.5-10.8 mg/day; 2019: 5.7-11.4 mg/day). The daily zinc intake of Japanese women (aged 7-29 years, aged  $\geq 40$  year) in 2019 were higher compared to those in 2016, respectively (aged 7-29 years: 2016: 7.1-7.9 mg/day; 2019: 7.3-8.6 mg/day; aged  $\geq 40$  year: 2016: 7.1-7.6 mg/day; 2019: 7.5-8.0 mg/day). Whereas the daily zinc intake of Japanese women (aged 1-6 years) in 2019 was lower compared to that in 2016 (2016: 5.3 mg/day; 2019: 5.2 mg/day). The daily zinc intake of Japanese women (aged 20-39 years) in 2019 was the same as that in 2016 (2016: 7.3 mg/day; 2019: 7.3 mg/day).

The daily zinc intake of Japanese men (aged 1-69 years) and women (aged  $\geq 1$  year) in 2019 were 5.7-11.4 mg/day and 5.2-8.6 mg/day, respectively, and exceeded the Estimated Average Requirements (EARs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 1-69 years): 3.0-10.0 mg/day; women (aged  $\geq 1$  year): 2.0-7.0 mg/day] [10]. The daily zinc intake of Japanese men (aged  $\geq 70$  years) in 2019 was 8.9 mg/day and was below the Estimated Average Requirements (EARs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 70$  years): 9.0 mg/day] [10]. The daily zinc intake of Japanese men (1-6 years) and women (aged 1-19 years) in 2019 were 5.7 mg/day, 5.2-8.6 mg/day, respectively, and were above the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged 1-6 years): 3.0-5.0 mg/day; women (aged 1-19 years): 3.0-8.0 mg/day] [10]. The daily zinc intake of Japanese men (aged  $\geq 20$  years) in 2019 was 9.2 mg/day and was below the Estimated Average Requirements (EARs) established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 20$  years): 9.4 mg/day] [14].

The daily zinc intake of Japanese men (aged  $\geq 20$  years) and women (aged 20-59 years, aged  $\geq 70$  years) in 2019 were 8.9-9.8 mg/day, 7.3-7.8 mg/day, and 7.7 mg/day, respectively and were below the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 20$  years): 10.0-11.0 mg/day; women (aged  $\geq 20$  years): 8.0 mg/day] [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [men (aged  $\geq 14$  years): 11.0 mg/day; women (aged 14-18 years): 9.0 mg/day; women (aged  $\geq 19$  years): 8.0 mg/day] [14]. The daily zinc intake of Japanese women (aged 60-69 years) in 2019 was 8.0 mg/day and reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14]. The daily zinc intake of Japanese men (aged  $\geq 18$  years) and women (aged  $\geq 18$  years) were below the Tolerable Upper Intake Levels (ULs) established by the Ministry of Health, Labour and Welfare in Japan [men (aged  $\geq 18$  years):

40.0-45.0 mg/day; women (aged  $\geq 18$  years): 30.0-35.0 mg/day] [10] and those established by the Institute of Medicine of the National Academy in the U.S. [men (aged 14-18 years): 34.0 mg/day; men (aged  $\geq 19$  years): 40.0 mg/day; women (aged 14-18 years): 34.0 mg/day; women (aged  $\geq 19$  years): 40.0 mg/day] [14]. The Ministry of Health, Labour and Welfare in Japan [10] has not set the Tolerable Upper Intake Levels (ULs) for healthy men and women (aged 0-17 years) because there is no scientific evidence for health problems due to excessive daily intake of zinc and has expressed the view that healthy people do not overdose zinc in their normal diet, but overdose of zinc can occur due to improper use of supplementation.

The daily zinc intake was negatively correlated with the number of gout patients in 2001-2016 ( $r = -0.868$ ,  $p = 0.0205$ ). The daily zinc intake did not show a significant correlation with the number of gout patients in 2001-2019 ( $r = -0.304$ ,  $p = 0.508$ ). The daily zinc intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.695$ ,  $p = 0.192$ ) and in 2004-2019 ( $r = 0.162$ ,  $p = 0.759$ ). The daily zinc intake did not show a significant correlation with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.842$ ,  $p = 0.0732$ ) and in 2004-2019 ( $r = -0.0973$ ,  $p = 0.854$ ). The daily zinc intake did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.821$ ,  $p = 0.0881$ ) and in 2004-2019 ( $r = 0.408$ ,  $p = 0.421$ ). This result suggests that the correlation of daily zinc intake with the number of gout patients tends to vary with gender.

In a mendelian randomization study, blood zinc concentration had no association with gout risk [53]. In an epidemiological study, increased zinc intake was associated with decreased hyperuricemia risk [59]. It is possible that zinc intake prevent gout through decreased hyperuricemia risk.

Judging from the data of food composition [15, 16], it is important for Japanese men (aged  $\geq 20$  years) and women (aged 20-59 years, aged  $\geq 70$  years) to eat meats (beef, chicken), processed meats (beef chuck, beef patty, beef jerky, pork chop), organ meats (liver, breast), seafood (oysters, crab, lobster, blue mackerel, anchovy, sardines, snail, scallop, lamprey), seeds and nuts (pumpkin seeds, cashew nuts, almonds, sesame seeds, flaxseeds, chia seeds), whole grains (fortified ready-to-eat cereals, oatmeal), mushrooms (maitake mushrooms), legumes (kidney beans, baked beans, chickpeas, green peas), seaweed, dairy products (low-fat milk, cheese, yogurt) to take in more zinc to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] and those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14]. It seems that Japanese men (aged 1-6 years, 15-19 years) and women (aged 1-6 years) need to decrease intake of zinc to reach the Recommended Dietary Allowances (RDAs) established by the Ministry of Health, Labour and Welfare in Japan [10] or those established by the Institute of Medicine of the National Academy of Sciences in the U.S. [14].

## 5. Conclusion

A remarkable increase in gout patients in Japan has been observed since the 1960s [2, 3]. 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) [12]. The daily intake of vitamin A, vitamin E, vitamin K, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, niacin, pantothenic acid, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, vitamin C, sodium, salt, calcium, potassium, magnesium, phosphorus, iron, copper, and zinc of Japanese people in 2019 were higher compared to those in 2016, respectively. The daily vitamin D intake of Japanese people in 2019 was lower compared to that in 2016. The daily intake of vitamin A, vitamin D, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, vitamin B<sub>12</sub>, vitamin C, salt, calcium, iron, and copper were negatively correlated with the number of gout patients, respectively.

Modification of micronutrient intake for the prevention of gout in Japanese people (especially adults) in 2019 is suggested as follows: limiting or decreasing salt intake; decreasing intake of phosphorus and copper; increase intake of vitamin A, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, calcium, potassium, magnesium, and zinc; increase intake of vitamin B<sub>2</sub> and vitamin C in Japanese men (aged 20-59 years) and women (aged 20-59 years). The important points of micronutrient intake for the prevention of gout in Japanese people (especially adults) is suggested as follows: recognizing intake of vitamin D, vitamin E, vitamin B<sub>1</sub>, vitamin B<sub>2</sub>, folate, vitamin B<sub>12</sub>, vitamin C, calcium, magnesium, iron, and zinc; and pay attention to intake of salt. It is necessary to recognize what food intake is important for the prevention of gout in Japanese people.

## Conflict of Interest Statement

The author declares that there are no conflicts of interest.

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