Dietary Reference Intakes for Japanese (DRIs) is revised every five years, and determines the standard reference values for the energy and nutrients intake in each gender- and age-group. In DRIs 2020, major revision has been made regarding vitamin D (VD). In DRIs, five indices are defined for nutrients: estimated average requirement (EAR), recommended dietary allowance (RDA), and adequate intake (AI) for the prevention of deficiency/insufficiency, tolerable upper intake level (UL) for avoiding excess intake, and tentative dietary goal for preventing life-style related diseases (DG) for the primary prevention of life-style related diseases. For VD, AI has been determined. VD deficiency causes rickets and osteomalacia. VD insufficiency, milder than deficiency, is a risk for various diseases including osteoporotic fracture. Previously, the basis of AI for VD was the prevention of rickets and osteomalacia, but was changed to the median intake of healthy subjects in DRIs 2005. Recent studies have shown, however, that VD deficiency/insufficiency is quite prevalent, and the above basis is considered inadequate. Then in DRIs 2020, AI was defined as the amount necessary for fracture prevention (15 μg/d) minus that possibly produced in Sapporo during winter in the skin by ultraviolet (5 μg/d). UL and AI for infants were revised in DRIs 2015. For the future DRIs, more clinical and epidemiological studies are urgently needed.

Key Words
Dietary Reference Intakes for Japanese (DRIs), adequate intake (AI), vitamin D, fracture prevention, ultraviolet irradiation

Dietary Reference Intakes for Japanese (DRIs) is revised every five years, and determines the standard reference values for the energy and nutrients intake in each gender- and age-group. In DRIs 2020, major revision has been made regarding vitamin D (VD) (1); also available at https://www.mhlw.go.jp/content/1094750/0005886553.pdf, accessed July 9, 2020), which is not merely a change of the values, but includes the alteration of the determination basis. Then in this review, we have described the background for the alteration.

Dietary Reference Intakes for Japanese (DRIs)
First, we will give some brief description on DRIs. Previously up until in the 2000 version; Recommended Dietary Allowances for the Japanese (6th revision), emphasis was mostly put on the prevention of energy and nutrients deficiency (2). The 2005 version was the almost complete revision, and renamed to Dietary Reference Intakes for Japanese (DRIs) (3). In DRIs 2005, theoretical basis was updated as described below, and the prevention of excessive intake and primary prevention of lifestyle-related diseases have come to be targeted in addition to the prevention of deficiency.

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Except for energy, five indices targeted for three purposes are defined as below.

Five indices can be divided into three categories (Table 1). Estimated average requirement (EAR), recommended dietary allowance (RDA), and adequate intake (AI) are for the prevention of deficiency. EAR and RDA refer to an intake corresponding to the 50% and 2.5% possibility of deficiency (Fig. 1). When EAR and RDA could not be defined, AI is determined instead. Median intake of healthy subjects is the most popular way to define AI, as far as most subjects in the population are sufficient regarding the nutrient intake. Tolerable upper intake level (UL) is for the prevention of unfavorable health consequences due to the excessive intake. Since intervention studies with excessive amount with adverse events as the outcome is unethical, it is inevitable to define UL mainly based on the reports from accidental excessive intake rather than the scientific studies. In DRIs, only intake from foods is considered for EAR, RDA, and AI, whereas intake from supplementation is also considered for UL.

Japanese DRIs is characterized by the presence of tentative dietary goal for preventing life-style related diseases (DG), which is not defined in DRIs in other countries. At present, the prevention of hypertension, dyslipidemia, diabetes, and chronic kidney disease (CKD) is
the target of DG.

In DRIs 2010, only minor modification has been made without theoretical alteration (4; also available at https://www.mhlw.go.jp/shingi/2009/05/s0529-4.html, accessed July 9, 2020). In DRIs 2015, the prevention of the progression of lifestyle-related diseases has become the novel target of DRIs (5; also available at https://www.mhlw.go.jp/stf/shingi/0000041824.html, accessed July 9, 2020), and specific values has been defined in DRIs 2020 for cholesterol and sodium (1). In DRIs 2020, the prevention of frailty was added as the additional target of DRIs (1), for which, however, no specific values are not defined yet.

Vitamin Deficiency and Insufficiency

Vitamin deficiency causes various classical deficiency diseases. Examples with the responsible vitamins in the parentheses include beriberi (vitamin B1), pellagra (niacin), scurvy (vitamin C), and coagulation abnormality (vitamin K). Such diseases are generally considered to be mostly overcome in developed countries including Japan, and the significance of vitamins in health promotion tends to be overlooked.

Recently, increasing attention has been paid on vitamin insufficiency. Insufficiency is milder than deficiency, and does not cause the diseases described above, but renders one at an increased risk for various diseases (6). In deficiency, phenotypic changes occur in the affected subjects, and diagnosis can be made individually. In contrast, insufficiency is accompanied with increased risk for diseases as a population, but not with the individual phenotypic abnormalities.

Vitamin D Deficiency and Insufficiency

Bone is formed by the calcium phosphate deposition (mineralization) onto a proteinous matrix mainly composed of collagen. Since the most essential role of vitamin D is to enhance the intestinal absorption of calcium and phosphate, its deficiency causes the mineralization defect; rickets and osteomalacia. In insufficiency, although the mineralization defect does not occur, impaired intestinal absorption of calcium evokes secondary hyperparathyroidism to maintain the serum calcium level, leading to the negative calcium balance, osteoporosis, and increased fracture risk (6).

Parameters for Vitamin D Status

Vitamin D, either from food intake or dermal production, is metabolized in the liver to 25-hydroxy vitamin D [25(OH)D], then in the kidney to the active form: 1α,25-dihydroxy vitamin D[1α,25(OH)2D]. Renal activation is strictly controlled by such as the stimulation by parathyroid hormone (PTH) and suppression by hypercalcemia or increased 1α,25(OH)2D level. Therefore, vitamin D is safe within intakes from usual diet.

Serum 25(OH)D concentration is the best indicator of vitamin D status. According to the recently published guideline, judgement is made as follows (7):

1. Sufficiency when serum 25(OH)D is above 30 ng/mL
2. Insufficiency when serum 25(OH)D is between 20 ng/mL and 30 ng/mL
3. Deficiency when serum 25(OH)D is below 20 ng/mL
### Adequate Intake for Vitamin D in DRIs 2005–2015

Previously, the requirement for vitamin D in adult was 2.5 μg/d, the basis being the prevention of deficiency; rickets and osteomalacia. As written above, DRIs 2005 was a complete revision, and vitamin D was no exception (4). Chronic deficiency of vitamin D is related to bone fragility leading to rickets in children and osteomalacia in adult. Additionally, in adult especially in the elderly, vitamin D insufficiency causes elevated serum parathyroid hormone (PTH), hence increased risk of osteoporosis and fracture. Thus, maintaining serum 25(OH)D concentration high enough to avoid the increased serum PTH level was considered important from the viewpoint of osteoporosis and fracture prevention. Based on these considerations, serum 25(OH)D concentration of 20 ng/mL was considered appropriate, and AI for vitamin D was determined to be 5.0 μg/d based on the median intake of population in which above-mentioned range of serum 25(OH)D was fulfilled. In DRIs 2010 (4) and 2015 (5), the basis for its determination remained the same, although the AI was changed to 5.5 μg/d based on the new data on the median intake (5).

#### Challenges in the Determination in DRIs 2020

Recently, it has repeatedly been reported that the prevalence of vitamin D deficiency/insufficiency is extremely high world-wide including in Japan. For example, in ROAD Study including 1,683 subjects (595 men, 1,088 women), the prevalence of vitamin D deficiency/insufficiency, defined as serum 25(OH)D level less than 30 ng/mL, was as high as 81.3%. The study subjects ranged from less than 40 y old to over 80 y old, and the high prevalence was observed in all age groups (8). Prevalence was even higher in women, which is in accordance with other reports. Tsugawa et al. have also reported that serum 25(OH)D level was less than 30 ng/mL in 90% of girls and 80% of boys in their study in adolescent (9). High prevalence of vitamin D deficiency/insufficiency is a world-wide phenomenon, which is even called an “epidemic.”

Median intake of a healthy subjects can be an AI as far as almost all subjects in the population are sufficient regarding the nutrient. Thus, recent demonstration of high prevalence of vitamin D deficiency/insufficiency has precluded the use of hitherto employed basis for AI and necessitated the revision. In the novel DRIs in USA/Canada 2011, serum 25(OH)D level required for the maintenance of bone health was considered 20 ng/mL, and RDA of 15 μg/d for adult was defined as the intake to achieve this concentration (10). Caution is needed, however, that this value was defined based on data in subjects with little dermal production of vitamin D such as those in Alaska during winter time. Then, such definition was considered directly inapplicable to Japan.

#### Basic Consideration in the Determination of AI for Vitamin D in DRIs 2020

AI for vitamin D was defined as the amount necessary to avoid increased fracture risk subtracted by the amount produced in the skin. Intake needed to avoid increased fracture risk was defined to be 15 μg/d employing the value in DRIs in USA/Canada (10). Miyauchi et al. have studied the amount of vitamin D produced in the skin in July and December in three regions of Japan with their north latitude in the parenthesis; Sapporo (43° north latitude), Tsukuba (36° north latitude), and Naha (26° north latitude) (11). In July, 5.5 μg/d of vitamin D could be produced in the skin from sun exposure by practically attainable duration of time. In contrast, in Sapporo in December, sun exposure time needed to produce 5.5 μg/d of vitamin D was 497.4 min at 9 am, 76.4 min at noon, and 2,741.7 min at 3 pm (Table 2), which indicates that vitamin D production in the skin could be expected to occur only around noon in Sapporo during winter. Since AI is the amount, with which intake most subjects are sufficient regarding the nutrient, the basis for adult AI was defined as 15 μg/d, the amount necessary for fracture prevention, subtracted by 5 μg/d, the amount which is considered producible even in Sapporo during winter. Considering the attainability taking the current vitamin D intake of Japanese into account (12), AI for adult was defined to be 8.5 μg/d (Table 3).

#### AI in the Infant

Recently re-emergence of vitamin D deficient rickets has been reported world-wide including in Japan, for which insufficient sun exposure and breast feeding are
risks. In a study in Kyoto, craniotabes was observed in 22% of infants with marked seasonal variation (13). Of the infants with craniotabes, serum 25(OH)D level was less than 10 ng/mL in significant percentage of them with breast feeding, but not in those with mixed feeding, suggesting that vitamin D content in the breast milk may not be high enough. Indeed, measurement of vitamin D content by newly developed LC/MS/MS has yielded values far lower than that measured by HPLC (14). AI in infant is basically defined as the nutrient concentration in the breast milk multiplied by the typical intake of 0.78 L/d. At present, determining the infant AI based on the vitamin D concentration in the breast milk was considered inappropriate, and it was defined based on the rickets prevention (5).

**UL for Vitamin D**

Hypercalcemia was employed as the index for health problems due to excessive vitamin D intake, since elevated serum 25(OH)D level is not necessarily associated with health problems. A paper employed in the determination of AI for vitamin D in DRIs 2010 was excluded in DRIs 2015, since it included data from patients with granulomatous diseases, which is a condition with susceptibility to hypercalcemia due to ectopic vitamin D activation (5). Intake of 250 μg/d was adopted as the NOAEL (no observable adverse effect level), since hypercalcemia has not been reported at doses less than this amount. UL was decided to be 100 μg/d by dividing 250 μg/d by the uncertainty factor of 2.5 (5). Additionally, there is a paper reporting the occurrence of hypercalcemia by 1,250 μg/d of vitamin D. Adopting this value as the LOAEL (lowest observed adverse effect level) and division by the uncertainty factor of 10 also yields the similar value. Thus, the UL of 100 μg/d was considered appropriate and adopted in DRIs 2020 also.

**Remarks**

Reference values in DRIs are “references,” but not the mandatory values, for which vitamin D is worth special emphasis. Determination of AI for adult to be 8.5 μg/d does not necessarily mean that this amount must be always taken from food. Since significant amount of vitamin D is intrinsically produced by sun exposure, less amount of intake would be satisfactory for those in low latitude region during summer time, whereas more amount would be needed for people with limited chance to going outside, e.g. institutionalized elderly.

**Reports on Fracture Risk and Vitamin D**

Many papers have been available in America or Europe on the relationship between fracture risk and vitamin D including both cohort studies and intervention studies with native vitamin D. Unfortunately, however, papers from cohort studies have been scarce, and there have been no publication of intervention studies on the fracture prevention with native vitamin D in Japan.

In a cohort study in Nagano, 1,470 community-dwelling post-menopausal Japan women aged 63.7 ± 10.7 were followed for the average of 7.2 y. Higher serum 25(OH)D level was associated with lower risk of long bone and hip fracture with the cut-off value of 25 ng/mL, showing that vitamin D insufficiency is a risk for non-vertebral fracture (15).

Recently, vitamin D has reported to be active in organs other than bone. Its relationship with muscle strength has received much attention. Of the osteoporotic fractures, most non-vertebral fracture is triggered by falling. Thus, bone strength and muscle strength are both important determinants of fracture risk, and vitamin D insufficiency is likely to increase the fracture risk both through impaired bone strength and decreased muscle strength.

In a cohort study in Japan with falling as an endpoint including 1,373 women aged 75 and over, the odds ratio of falling in subjects with their serum 25(OH)D higher than 25 ng/mL was significantly higher compared with those with their serum 25(OH)D lower than 25 ng/mL (16).

Vitamin D has been reported to exert actions in other organs, and its insufficiency has been reported to be associated with increased risk of such diversity of diseases as ischemic heart diseases, cancer, and upper respiratory tract infection (17). These actions of VD need to be confirmed in further studies, and are not currently considered in the determination of AI.

**Summary and Conclusion**

Vitamin D in DRIs 2020 is characterized by that the basis for its determination has been changed, not merely the alteration of reference values. Unlike the DRIs in other countries, DG is defined in Japanese DRIs for the

| Table 3. AI and UL for vitamin D in DRIs 2020. |
|-----------------------------------------------|
| Gender | Male | Female |
| Age    | AI (μg) | UL (μg) | AI (μg) | UL (μg) |
| 0 to 5 (mo) | 5.0 | 25 | 5.0 | 25 |
| 6 to 11 (mo) | 5.0 | 25 | 5.0 | 25 |
| 1 to 2 (y) | 3.0 | 20 | 3.5 | 20 |
| 3 to 5 (y) | 3.5 | 30 | 4.0 | 30 |
| 6 to 7 (y) | 4.5 | 30 | 5.0 | 30 |
| 8 to 9 (y) | 5.0 | 40 | 6.0 | 40 |
| 10 to 11 (y) | 6.5 | 60 | 8.0 | 60 |
| 12 to 14 (y) | 8.0 | 80 | 9.5 | 80 |
| 15 to 17 (y) | 9.0 | 90 | 8.5 | 90 |
| 18 to 29 (y) | 8.5 | 100 | 8.5 | 100 |
| 30 to 49 (y) | 8.5 | 100 | 8.5 | 100 |
| 50 to 64 (y) | 8.5 | 100 | 8.5 | 100 |
| 65 to 74 (y) | 8.5 | 100 | 8.5 | 100 |
| Over 75 (y) | 8.5 | 100 | 8.5 | 100 |
| Pregnant women | 8.5 | 100 | |
| Lactating women | 8.5 | 100 | |

Adopted from Ref. 1) with the authors’ translation. AI, UL, and DRIs are the abbreviations for adequate intake, tolerable upper intake level, and dietary reference intakes, respectively.
primary prevention of life-style related diseases. Although AI is defined for vitamin D in DRIs 2020, the basis for it is rather close to DG. Currently, DG is defined for four diseases: hypertension, dyslipidemia, diabetes, and chronic kidney disease. Much more evidence is urgently needed for the determination of indices in future DRIs.

Authorship
KT, AK, and NT have reviewed the related references, and made discussion, and KT is responsible for the final manuscript.

Disclosure of state of COI
The authors have no conflict of interest to declare.

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