A review of vitamin D fortification: Implications for nutrition programming in Southeast Asia

Zhenyu Yang, Arnaud Laillou, Geoffry Smith, Dominic Schofield, and Regina Moench-Pfanner

Abstract

Background. *Vitamin D is vital for bone health and has important roles in nonskeletal health and organ function. Most vitamin D is generated in the body by exposure to sunlight, with limited amounts added by the diet. Despite the presence of regular sunshine in Southeast Asia, vitamin D deficiency or insufficiency is being found there more commonly, primarily due to reduction of sunlight exposure as a result of lifestyle changes. Some of these lifestyle changes are unlikely to be reversed, and foods naturally containing vitamin D are not widely consumed, so fortification of foods with vitamin D may raise vitamin D status.*

Methods. *The literature database was searched for studies of vitamin D fortification, and we estimated potential vitamin D intakes from fortified vegetable oil.*

Results. *Almost all of the studies showed that circulating vitamin D (25-hydroxyvitamin D [(25OHD]) increased in a dose-dependent manner with increased intake of vitamin D–fortified foods. However, in a number of studies the additional intake was insufficient to increase vitamin D levels to 50 nmol/L. Vegetable oil fortified with vitamin D at a level of 10 μg/100 g could provide 3.9% to 21% of the Institute of Medicine Estimated Average Requirement (EAR) of vitamin D for adults in Southeast Asia.*

Conclusions. *Fortification of widely consumed foods, such as edible oil, with vitamin D could contribute to improved vitamin D status in Southeast Asian countries. Intake modeling studies should be conducted to calculate the resulting additional intakes, and fortification of additional foods should be considered. More nationally representative studies of vitamin D status in the region are urgently needed.*

Zhenyu Yang is affiliated with the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control, Xicheng, Beijing; Arnaud Laillou, Dominic Schofield, and Regina Moench-Pfanner are affiliated with the Global Alliance for Improved Nutrition (GAIN), Geneva; Geoffry Smith is affiliated with the Essential Micronutrients Foundation, Singapore, and the International Life Sciences Institute (ILSI), Southeast Asia Region, Singapore.

Please direct queries to the corresponding author: Zhenyu Yang, No 29 Nanwei Road, Xicheng District, Beijing 100050, China; e-mail: yang.zhenyuid@gmail.com.

Key words: Fortification, nutrition impact, Southeast Asia, supplementation, vitamin D

Background

Vitamin D is a fat-soluble "vitamin" and is now recognized as a prohormone. This is because the body can synthesize vitamin D from its precursor (7-dehydrocholesterol) when exposed to ultraviolet light at a wavelength between 290 and 315 nm. Vitamin D in this form is not biologically active and must be converted by two enzymatic hydroxylation reactions to function physiologically. The first of these conversions takes place in the liver and transforms vitamin D to the main circulating form, 25-hydroxyvitamin D (25OHD). This is further converted in the kidney to the active hormonal form 1,25-dihydroxyvitamin D (calcitriol). This hormonal form of the synthesized vitamin D acts at different target organs [1]. The physiological functions of active vitamin D (calcitriol) are related to calcium homeostasis and osteoporosis, with possible roles in diabetes, cancer, ischemic heart disease, and autoimmune and infectious diseases [1]. The major source of body vitamin D is from cutaneous synthesis when the skin is exposed to ultraviolet B.* Season, latitude, time of day, skin pigment, sunscreen use, and aging can affect cutaneous vitamin D synthesis [1]. The natural food sources of vitamin D include oily fish, egg yolk, and fish liver oil, which are not commonly consumed in many diets [2].

A rough estimate indicates that about 1 billion people globally are vitamin D deficient (defined as 25OHD

* Ultraviolet B is one of the three types of invisible light rays (together with ultraviolet A and ultraviolet C) given off by the sun.

< 50 nmol/L) or vitamin D insufficient (defined as 25OHD < 75 nmol/L) [1]. Vitamin D deficiency is quite common in regions and countries including North America, northern Europe, Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon [1]. Vitamin D deficiency is believed to be less common in Southeast Asia than in India [3]; however, it has not been well characterized. The prevalence of vitamin D deficiency varies across countries in Southeast Asia (**table 1**). The reported prevalence was lower in Thailand and Vietnam (5.7% to 7%) in two studies [4, 5] and was higher in Indonesia and Malaysia (41% to 87%) [6–8], but only the Thai study was nationally representative. However, another recent study in Vietnam found that the prevalence of vitamin D deficiency was 40% for women and 37% for children [9].

Some observational studies have shown that vitamin D deficiency is associated with greater risk of cardiovascular diseases (e.g., stroke, sudden cardiac death) and their risk factors (e.g., hypertension, diabetes) [10]. However, few randomized, controlled trials are available, and the evidence from observational studies is not conclusive [10]. A recent systematic review found that the relationship between 25OHD and cancer mortality was mixed [11]. However, cancer patients with higher 25OHD tended to have lower risk of mortality, especially patients with colorectal cancer [11]. There was no significant association between vitamin D supplementation and breast cancer incidence in a randomized, controlled trial [12]. A recent longitudinal polymorphisms study also did not show a conclusive causal relationship between 25OHD and myocardial infarction, type 2 diabetes, cancer, or all-cause mortality [13]. Some of the inconsistency in the evidence may be due to issues of study design and interpretation [14]. Major trials are under way and may address some of these issues (VITAL in the United States, the European DO-HEALTH study on vitamin D and omega 3, FIND in Finland, and ViDA in New Zealand), but the results are not expected until 2017 or later. Thus, it might not be justifiable at present to recommend nutritional vitamin D intervention for the prevention of chronic diseases other than osteoporosis in the general population.

Serum or plasma 25OHD is considered the best indicator of vitamin D status, since it is not tightly regulated by parathyroid hormone and is not affected by dietary calcium and phosphorus intake [15]. Recent meta-analyses and systematic reviews found that vitamin D supplementation could significantly increase serum 25OHD for both pregnant women and elderly subjects [16, 17]. In some countries, vitamin D–fortified foods are an important source of vitamin D. For example, more than 60% of vitamin D intake comes from fortified products in the United States [18]. It is useful to systematically update the impacts of vitamin D fortification on 25OHD and other health outcomes and to evaluate potential food carriers (e.g., edible oil) and dosage for vitamin D fortification globally. During the period of preparation of this review, another similar review and meta-analysis was published [19]. This paper examines the existing evidence on vitamin D fortification and tries to estimate the potential contribution of vitamin D fortification to improve daily vitamin D intake in Southeast Asian countries.

Methods

Sources searched and search strategy for evidence on vitamin D fortification

A meta-analysis of the efficacy of vitamin D fortification in improving 25OHD concentrations was conducted in 2006 [2]. Therefore, we began our search for relevant publications starting with 2006, searching for specific key words on PubMed. All titles and abstracts were assessed for their relevance to vitamin D fortification. The key phrase ("Vitamin D"[MAJR] AND "Food, Fortified"[MAJR]) was used for the search. References were extracted from the search results and included if they met one of the following criteria: randomized clinical trial, quasi-experimental design, or program evaluation. These criteria were used in order to assess both efficacy and effectiveness. A total of 91 papers were found, 13 of which were included in this review. Six were reports of randomized, controlled trials and seven were reports of quasi-experimental designs or program evaluations with preintervention control.

TABLE 1. Prevalence of vitamin D deficiency in Southeast Asia

Country	Sampling site	Age (yr)	Sex	Prevalence (%)[a]	Ref.
Vietnam	Northern	Childbearing age	F	7	[4]
Thailand	National	15–98	M and F	5.7	[5]
Indonesia	Jakarta	18–40	F	63	[6]
Malaysia	Kuala Lumpur	18–40	F	60	[6]
Malaysia	Kuala Lumpur	48.2 ± 5.2	M (42%) and F (58%)	41 (M) 87 (F)	[7]
Malaysia	Kuala Lumpur	7–12	M and F	72.4	[8]

a. Vitamin D deficiency is defined as 25-hydroxyvitamin D (25OHD) < 50 nmol/L [48, 49]

Estimation of vitamin D intakes from fortified foods

The objective of this study was to estimate, based on dietary intakes available from several Southeast Asian countries, whether food fortification has the potential to increase daily vitamin D intakes among women of reproductive age and other targeted groups. The Institute of Medicine (IOM) Estimated Average Requirement (EAR) of 10 μg/day (400 IU) nutrient intake for vitamin D [20] was used to assess the contribution of dietary intakes to the coverage of daily micronutrient requirements.

Results

Existing evidence

Moderate exposure to sunshine and fortification of food with vitamin D can improve the vitamin D status of the population [3]. Fortification with vitamin D has been assessed for the past decade (**table 2**). For example, since 2003 the Finnish Government has recommended vitamin D fortification of milk (0.5 μg/100 mL) and of margarine and spreads (10 μg/100 g). In one study, adolescent girls aged 12 to 18 years ($n = 142$) were followed from 2000 to 2004, one year after the initiation of fortification [21]. The mean 25OHD concentration did not differ between 2000 and 2004 (48.3 and 48.1 nmol/L, respectively). The prevalence of low vitamin D status (defined as 25OHD < 50 nmol/L) was also similar in these two years (60.6% and 65.5%, respectively). Another study assessed the effectiveness of the program among young Finnish men by following them from 2001 to 2004. The median 25OHD concentration was significantly higher in 2004 than in 2001 (27 vs. 24 nmol/L, $p < .0015$) [22]. The third study examined the impact of the vitamin D fortification program on 4-year-old children [23]. 25OHD concentration was significantly higher among children in 2004 than in 2000 (64.9 vs 54.7 nmol/L, $p = .002$). Dietary vitamin D intake was also significantly higher after fortification than before fortification.

In a recent meta-analysis (considering studies up to 2006), eight of nine randomized, controlled trials consistently showed that vitamin D fortification improved 25OHD concentration in both younger and older subjects [2]. The change in 25OHD concentration varied from 14.5 to 34.5 nmol/L after consumption of 3.4 to 25 μg/day of vitamin D from fortified products. Only one study, in which the subjects were given vitamin D–fortified cheese, did not find significant improvement in 25OHD concentration, even though vitamin D intake increased significantly [24].

Since 2006, many studies have evaluated the impact of foods fortified with vitamin D and/or calcium on elderly men or postmenopausal women and have shown improvement [25–30]. Other groups were also studied. In a study in New Zealand, women aged 18 to 45 years were randomly assigned to a group receiving vitamin D–fortified milk (5 μg/day, $n = 37$) or a control milk group ($n = 36$) [31]. After 12 weeks of intervention, the mean serum 25OHD concentration was significantly greater in the fortification group than in the control group (65 vs. 53 nmol/L, $p < .001$). The prevalence of vitamin D insufficiency (defined as 25OHD < 75 nmol/L) was significantly lower in the fortification group than in the control group (53% vs. 79%, $p = .011$). A study in the United States assessed the bioavailability of vitamin D_2 and D_3 in fortified orange juice [32]. Adult subjects (18 to 79 years old, $n = 105$) were randomly assigned to receive vitamin D_2–fortified orange juice, vitamin D_3–fortified orange juice, vitamin D_2 supplement, vitamin D_3 supplement, or placebo, at a level of vitamin D supplementation or fortification of 25 μg/day. There were no significant differences in 25OHD concentration between the groups receiving vitamin D–fortified orange juice and vitamin D supplement, but 25OHD concentrations were significantly higher in both the fortification and the supplementation groups than in the placebo group (28.1 vs. 18.1 ng/mL). In Mongolia, schoolchildren (9–11 years old, $n = 46$) were given vitamin D–fortified (7.5 μg/day) milk for 1 month [33]. The prevalence of low vitamin D status (defined as 25OHD < 50 nmol/L) decreased from 76% to 7% and the prevalence of vitamin D deficiency (defined as 25OHD < 37 nmol/L) decreased from 32% to 0% after 1 month of treatment.

The common food carriers for vitamin D fortification included milk, cheese, and other dairy products (both regular-fat and low-fat); margarine; oil spread; orange juice; and bread. The fortification level in these studies varied from 2.5 to 125 μg/day, and the most common doses were between 5 and 25 μg/day (33% to 166% of EAR [34]). The fortification level for each food depended on the intake and characteristics of that food (e.g., 0.5 μg/100 mL for milk and 10 μg/100 g for margarine in Finland). Two studies showed that the bioavailability of vitamin D used as a fortificant was similar to the bioavailability of supplemental vitamin D [30, 32]. The principal findings are summarized in **table 3**.

Contribution of vitamin D fortification

Dairy products (e.g., milk and cheese), margarine, vegetable oil, and orange juice are the common food carriers for fortification with vitamin D, mainly in Western countries. Vitamin D fortification of those products has been shown to improve 25OHD levels significantly across studies and could be an efficacious way to prevent and control vitamin D deficiency in Southeast Asia. Unfortunately, the consumption of

TABLE 2. Description of studies evaluating the impact of food fortified with vitamin D and calcium on elderly men and postmenopausal women (2006–12)

Country, date, ref	Subjects	Vitamin D level	Calcium level	Duration	Food carrier	25OHD assay	Effect
France, 2009 [25]	Elderly women in nursing homes	Vitamin D3 (2.5 μg/day)	302 mg/day	1 mo	Cheese	RIA	Compared with baseline, 25OHD3 increased significantly; PTH decreased significantly at 1 mo of treatment ($p < .01$). Although vitamin D fortification cannot fully explain the decrease in PTH, it did account for the small but significant increase in 25OHD. However, time effects cannot be excluded because historical controls were used.
Romania, 2009 [26]	Nursing home residents	Vitamin D3 (125 μg/day)	320 mg/day	1 yr	Bread	RIA	After 12 mo of intervention, mean 25OHD significantly increased from 28.5 to 125.6 nmol/L ($p < .001$). BMD at lumbar and hip sites was significantly higher at endline than at baseline (0.863 vs. 0.83 g/cm^2 and 0.906 vs. 0.734 g/cm^2, respectively). There was no significant difference in serum calcium concentration between baseline and endline. Because no true control group was available in this study, the results should be interpreted with caution.
Greece, 2009 [27]	Postmenopausal women (mean age 60.5 yr)	Vitamin D (7.5 μg / day)	1,200 mg/day; 600 mg/day (supplement)	5 mo	Dairy product	Chemiluminescence immunoassay	After 5 mo of treatment, the increase in PTH was marginally lower in the fortification group and the supplementation group ($p = .055$) than in the control group. No significant differences in the amount of change in 25OHD between the treatment groups and the control group were observed, but the treatment and time interaction was significant for 25OHD, which means that the changes over time significantly differed between the group receiving fortified dairy product and the control group [50]. The group receiving fortified dairy product had significantly greater improvements in pelvis, total spine, and total-body BMD than did the other 2 groups ($p < .05$).
Australia, 2009 [28]	Elderly men (> 50 yr)	Vitamin D3 (20 μg/day)	1,000 mg/day	2 yr	Milk	RIA	During the 2-yr treatment, 25OHD and PTH concentration changes were significantly greater in the treatment group (4.8 nmol/L and −1.8 pg/mL, respectively) than in the control group (−14.4 nmol/L and 2.2 pg/mL, respectively). Fortified milk improved femoral neck, ultradistal radius, and total hip BMD at the end of the intervention [51]. In the subsequent follow-up 18 mo after withdrawing from treatment [52], the group receiving fortified milk had consistent benefits in femoral neck and ultradistal radius BMD but not in total hip and lumbar spine BMD.
Australia, 2009 [29]	Elderly men	Vitamin D (20 μg / day)	1,000 mg/day	1 yr	Milk	RIA	25OHD concentration significantly improved by 23% in the milk groups. Lumbar spine BMD increased in all the treatment groups by 1.4% to 1.5% compared with the control group. However, fortified milk did not improve BMD in other skeletal sites.
Canada, 2008 [30]	Elderly men	Vitamin D (100 μg/day)	NA	8 wk	Regular-fat cheese, low-fat cheese, supplements with food	RIA	After 8 wk of intervention, the 25OHD concentration changes were significantly greater in all vitamin D treatment groups (63.3 nmol/L) than in the placebo groups (−4.3 nmol/L). PTH decreased significantly from baseline by 12% to 25% in the vitamin D treatment groups but not in the placebo groups. There were no significant differences between the fortified vitamin D and the supplemented vitamin D groups. No subjects developed hypercalcemia (serum calcium > 2.75 mmol/L) or hypercalciuria. No adverse effects were reported.

BMD, bone mineral density; NA, not available; 25OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone; RIA, radioimmunoassay

TABLE 3. Summary of findings of different surveys (including all category groups)

Places where the studies were implemented	All of these studies except one in Romania and another in Mongolia were conducted in developed countries. Most of these countries were located in high-latitude regions (30°N or higher). Seasonal variation was obvious for vitamin D deficiency, and most studies were conducted during winter.
Food vehicles used	The common food carriers for vitamin D fortification included milk, cheese, and other dairy products (both regular-fat and low-fat); margarine; oil spread; orange juice; and bread.
Fortification levels	The fortification level of these studies varied from 2.5 to 125 μg /day; the most common doses were between 5 and 25 μg/day (1 to 5 times AI). The fortification level for each food depended on the intake and characteristics of that food (e.g., 0.5 μg/100 mL for milk and 10 μg/100 g for margarine in Finland).
Impacts of the studies on 25OHD concentration	20 studies showed beneficial effects of vitamin D fortification on 25OHD concentration or vitamin D deficiency. The magnitude of mean 25OHD concentration improvement varied from 2 to 97.1 nmol/L; the most common improvements were between 9.9 and 34.5 nmol/L. The magnitude was significantly related to the fortification level used ($n = 8$, $r = 0.98$, $p < .01$), which is also supported by the meta-analysis of Black et al. [19]. For example, fortification with the lowest (2.5 μg/day) and the highest (125 μg/day) amounts of vitamin D resulted in the smallest (2 nmol/L) and the largest (97.1 nmol/L) improvements in 25OHD, respectively.
Impact of the studies on other markers	Vitamin D fortification suppressed PTH in 8 of 14 studies. When products fortified with both vitamin D and calcium were consumed, BMD increased in various locations, including hip, femoral neck, ultradistal radius, spine, and pelvis. However, it is difficult to attribute the benefits to vitamin D or calcium alone, due to the design of these studies.
Toxicity	No adverse effects were reported when food fortified with 100 μg/day vitamin D was consumed for 2 months. Serum calcium concentration, a biomarker for vitamin D toxicity, did not increase during 1 year of intervention with 125 μg/day vitamin D, although urinary calcium concentration increased at 3, 6, and 9 months, but not at 12 months. When 25 μg/day vitamin D or less was consumed, some subjects reported gastrointestinal discomfort.

AI, Adequate Intake; BMD, bone mineral density; 25OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone

milk and milk products is still marginal in Southeast Asia, and vegetable oil seems to be more suitable as a potential food vehicle for fortification.

Since vitamin D is a fat-soluble vitamin, it is commonly added to lipid-containing foods, although stabilized forms can be added to a wide variety of foods. For example, vegetable oils are suitable as vehicles for fortification with vitamins A, D, and E, which are easily uniformly distributed in oil [35]. The production and refining of oils is often a centralized process and therefore is suitable for large-scale intervention. In addition, margarine is fortified with vitamin D in Canada [36], Finland [21], and some other European countries.

As shown in **table 4**, in several Southeast Asian countries vitamin D–fortified vegetable oil can contribute to a significant daily vitamin D intake among different age groups. For example, in Vietnam 91.5% of women [37] and 38% of children under 5 years of age [38] consume vegetable oil daily (median consumption, 11.1 and 6 g/day, respectively). Therefore, as shown in **table 4**, vegetable oil fortified at a level of 7.5 to 10 μg/100 g in Vietnam could provide 7% to 9% of the IOM EAR of vitamin D for a woman (400 IU) and 4% to 5% of the IOM EAR for a child under 5 years of age. Overall, in Southeast Asia, if governments decided to support national standards of vitamin D fortification, vitamin D–fortified vegetable oil could provide from 3% to approximately 21% of the IOM EAR for vitamin D for an adult, depending on local practices (**table 4**). In addition, and as discussed more in depth by Laillou et al. in this supplement [39], the exportation of fortified edible oil from Malaysia and Indonesia has a significant potential to increase vitamin A intake in many neighboring countries. The same can apply to vitamin D–fortified exported vegetable oil. For example, in Afghanistan, vitamin D–fortified vegetable oil can provide up to 23.8% of the IOM EAR for vitamin D for an adult, as vegetable oil consumption is high and most of the oil is imported from Malaysia.

Discussion

Over the past decade, Southeast Asian countries have focused nutrition strategies on iron and vitamin A deficiencies. It seems relevant also to include vitamin

TABLE 4. Contribution of vegetable oil fortified with vitamin D at levels from 7.5 to 10 μg/100 g to the Institute of Medicine (IOM) Estimated Average Requirement (EAR) [20]

Target group	Average oil consumption (g/day)	Vitamin D supplied through vegetable oil fortification (μg/day)		% of IOM EAR	
		Level 7.5 μg/100 g	Level 10 μg/100 g	Level 7.5 μg/100 g	Level 10 μg/100 g
National fortification					
Indonesia					
Women	20.5	1.23	1.64	12.3	16.4
Children < 5 yr	17.3	1.04	1.38	10.4	13.8
Rich adults	26.0	1.56	2.08	15.6	20.8
Poor adults	23.0	1.38	1.84	13.8	18.4
Vietnam					
Women of reproductive age	11.1	0.67	0.89	6.7	8.9
Children 6–59.9 mo	6.0	0.36	0.48	3.6	4.8
China					
Adults	25.0	1.50	2.00	15.0	20.0
Pregnant women	25.1	1.51	2.01	15.1	20.1
Lao People's Democratic Republic					
Adults	4.9	0.29	0.39	2.9	3.9
Cambodia					
Adults	6.6	0.40	0.53	4.0	5.3
Philippines					
Adults	13.2	0.79	1.06	7.9	10.6
Malaysia					
Adults	16.1	0.97	1.29	9.7	12.9
Imported vegetable oil from Malaysia and Indonesia					
Bangladesh					
Breastfeeding women	7.3	0.44	0.58	4.4	5.8
Adult women	17.7	1.06	1.42	10.6	14.2
Children 4–6 yr	10.5	0.63	0.84	6.3	8.4
Children 1–3 yr	8.3	0.50	0.66	5.0	6.6
Egypt					
Adults	29.3	1.76	2.34	17.6	23.4
Ethiopia					
Adults	7.1	0.43	0.57	4.3	5.7
Afghanistan					
Adults	29.8	1.79	2.38	17.9	23.8

References: Indonesia [53, 54]; Vietnam [37, 38]; Bangladesh [55]; China [56], Malaysia, Cambodia, Ethiopia, and Philippines (data from 2009) [57]; Afghanistan [58]. A 20% loss of vitamin D during processing, storage, and cooking has been assumed [34].

D among the targets to prevent micronutrient deficiencies in the region, particularly as the Asian population increases their life expectancy and the risk of osteoporosis increases. In the past, the prevalence of vitamin D deficiency in Southeast Asia was usually not expected to be high, as most vitamin D (80% to 90%) is synthesized in the skin under the action of sunlight [40]. Dermal synthesis through exposure to ultraviolet B is the major natural source of vitamin D in all regions. Increasingly, however, even in countries where the amount of regular sunshine is adequate to achieve recommended vitamin D status, lifestyle changes (fewer outdoor workers, more transportation in covered vehicles) are limiting sun exposure. In addition, in some populations Asian tradition favors avoiding sunlight and people take measures to protect themselves from exposure (long gloves, masks, avoiding exposure between noon and 2 p.m., etc.). In some countries, 10% to 20% of vitamin D is acquired from the diet. However, very few unfortified foods contain vitamin D (fatty and oily fish, egg yolk, and fish liver oil are the exceptions), and these are not commonly consumed in most Southeast Asian diets [18]. It is essential to prevent vitamin D deficiency, at least to maintain bone health (while research continues on possible nonskeletal functions of vitamin D) [1]. It is crucial to prevent such deficiency or insufficiency, as low serum 25OHD is significantly associated with low bone mineral density and increased risk of nonvertebral fractures [20] and hip fractures [34]. Evidence on calcium and vitamin D supplementation supports preventive treatment for osteoporosis in adults over 50 years of age [41, 42] and the possibility that calcium and vitamin D supplementation may reduce mortality rates in postmenopausal women. Adequate vitamin D and calcium nutrition throughout life appears to reduce the risk of osteoporosis [43].

The impacts of vitamin D fortification tend to be beneficial, because the majority of studies show positive effects of vitamin D fortification of milk, cheese, bread, margarine, and orange juice on 25OHD concentration. A dose–response relationship can exist between vitamin D dosage and improvement in 25OHD concentration. Recently Black et al. showed a dose–response relationship between vitamin D intake and 25OHD concentration [19]. According to Black et al. [19] and Heaney et al. [19, 44], 1 μg of ingested vitamin D can increase 25OHD concentration by 1 to 1.2 nmol/L. When 10 μg/day or more of vitamin D (1 Adequate Intake [AI]) is used for fortification, the increment in 25OHD concentration can be 10 to 12 nmol/L or more. For example, the fortification level for edible oil could start at 7.5 to 10 μg/100 g, which was suggested as the fortification level for margarine by the international margarine association of the countries of Europe [45]. These levels could contribute to the daily intake of vitamin D, but other interventions will also be needed (supplementation, behavior education on exposure to sunlight, etc.). However, the level of consumption of the oil to be fortified should be taken into account when determining the fortification level. Higher fortification levels should also be considered. A recent review in the United States has proposed a fortification level for vitamin D in edible oil of 42 μg of vitamin D per 100 g of oil [46]. This fortification level would provide 50% or more of the EAR and in some cases 50% of the Dietary Reference Intake (DRI). Additional foods should also be considered for fortification with vitamin D. Although vitamin D status is significantly affected by seasonality in high latitudes, seasonality may not need to be considered in planning vitamin D fortification programs and determining the dosage of vitamin D in Southeast Asia due to relatively constant sunshine levels.

At present, knowledge of vitamin D deficiency is low among most relevant populations in the region. Better understanding of the regional levels of vitamin D deficiency would help to establish a demand for fortified products. In the meantime, education could be encouraged. During an awareness and knowledge study of osteoporosis in Vietnam, more than 90% of women expressed interest in a prevention and treatment program [47]. Consequently, specific interventions to improve food diversity and quality should be implemented.

Conclusions

The current review and literature search on vitamin D fortification has shown that there are limited data on the impact of vitamin D fortification on 25OHD concentrations. Recent nutrition and health surveys have shown that vitamin D deficiency exists in some Southeast Asian countries. There is a strong need for nationally representative studies in more countries in Southeast Asia. Only Thailand has published a nationally representative study of vitamin D status [5]. The Singapore Health Promotion Board has conducted a national survey, which has not yet been published, and a study in Vietnam has been completed and submitted for publication. With growing understanding of the importance of vitamin D for adequate growth and nutritious diet, it is important that countries start to collect data systematically on vitamin D status in the population. The current study has shown the potential of vitamin D–fortified vegetable oil to increase intakes of vitamin D. Southeast Asian countries where vitamin A fortification of vegetable oil is ongoing should consider adding vitamin D to the fortified oil. Adding vitamin D is easy and feasible; people in Southeast Asia, including children within the 1,000-day window of opportunity, consume substantial amounts of oil; and the oil industry is concentrated in Southeast Asia and their exports have significant potential to reach other vitamin D–deficient regions. In addition to fortification, other interventions should be considered for at-risk populations, such as supplementation and behavior change communication to encourage people to increase exposure to sunlight.

Acknowledgments

This work was funded by the Bill & Melinda Gates Foundation and the Department for International Development. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors read and approved the final manuscript.

References

1. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
2. O'Donnell S, Cranney A, Horsley T, Weiler HA, Atkinson SA, Hanley DA, Ooi DS, Ward L, Barrowman N, Fang M, Sampson M, Tsertsvadze A, Yazdi F. Efficacy of food fortification on serum 25-hydroxyvitamin D concentrations: systematic review. Am J Clin Nutr 2008;88:1528–34.
3. Lips P. Worldwide status of vitamin D nutrition. J Steroid Biochem Mol Biol 2010;121:297–300.
4. Hien VT, Lam NT, Skeaff CM, Todd J, McLean JM, Green TJ. Vitamin D status of pregnant and non-pregnant women of reproductive age living in Hanoi City and the Hai Duong province of Vietnam. Maternal & child nutrition 2012;8:533–9.
5. Chailurkit LO, Aekplakorn W, Ongphiphadhanakul B. Regional variation and determinants of vitamin D status in sunshine-abundant Thailand. Bmc Public Health 2011;11:853.
6. Green TJ, Skeaff CM, Rockell JE, Venn BJ, Lambert A, Todd J, Khor GL, Loh SP, Muslimatun S, Agustina R, Whiting SJ. Vitamin D status and its association with parathyroid hormone concentrations in women of childbearing age living in Jakarta and Kuala Lumpur. Eur J Clin Nutr 2008;62:373–8.
7. Moy FM, Bulgiba A. High prevalence of vitamin D insufficiency and its association with obesity and metabolic syndrome among Malay adults in Kuala Lumpur, Malaysia. BMC Public Health 2011;11:735.
8. Khor GL, Chee WS, Shariff ZM, Poh BK, Arumugam M, Rahman JA, Theobald HE. High prevalence of vitamin D insufficiency and its association with BMI-for-age among primary school children in Kuala Lumpur, Malaysia. BMC Public Health 2011;11:95.
9. Laillou A, Wieringa F, Tran TN, Pham VT, Le BM, Fortin S, Le TH, Moench-Pfanner R, Berger J. Hypovitaminosis D and mild hypocalcaemia are highly prevalent among young Vietnamese children and women and related to low dietary intake. PloS ONE 2013;acccepted.
10. Pilz S, Kienreich K, Tomaschitz A, Lerchbaum E, Meinitzer A, Marz W, Zittermann A, Dekker JM. Vitamin D and cardiovascular disease: update and outlook. Scand J Clin Lab Invest Suppl 2012;243:83–91.
11. Pilz S, Kienreich K, Tomaschitz A, Ritz E, Lerchbaum E, Obermayer-Pietsch B, Matzi V, Lindenmann J, Marz W, Gandini S, Dekker JM. Vitamin D and cancer mortality: systematic review of prospective epidemiological studies. Anticancer Agents Med Chem 2013;13:107–17.
12. Chlebowski RT. Vitamin D and breast cancer incidence and outcome. Anticancer Agents Med Chem 2013;13:98–106.
13. Jorde R, Schirmer H, Wilsgaard T, Joakimsen RM, Mathiesen EB, Njolstad I, Lochen ML, Figenschau Y, Berg JP, Svartberg J, Grimnes G. Polymorphisms related to the serum 25-hydroxyvitamin D level and risk of myocardial infarction, diabetes, cancer and mortality. The Tromso Study. PLoS ONE 2012;7:e37295.
14. Lappe J, Heaney R. Why randomized controlled trials of calcium and vitamin D sometimes fail. Dermato-Endocrinology 2012;4:95–100.
15. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. Am J Clin Nutr 2004;80:1710S–6S.
16. De-Regil LM, Palacios C, Ansary A, Kulier R, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev (Online) 2012;2:CD008873.
17. Autier P, Gandini S, Mullie P. A systematic review: influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. J Clin Endocrinol Metab 2012;97:2606–13.
18. Whiting SJ, Calvo MS. Overview of the proceedings from Experimental Biology 2005 symposium: optimizing vitamin D intake for populations with special needs: barriers to effective food fortification and supplementation. J Nutr 2006;136:1114–6.
19. Black LJ, Seamans KM, Cashman KD, Kiely M. An updated systematic review and meta-analysis of the efficacy of vitamin D food fortification. J Nutr 2012;142:1102–8.
20. Institute of Medicine. Dietary reference intakes form calcium and vitamin D. Washington, DC: National Academies Press; 2011.
21. Lehtonen-Veromaa M, Mottonen T, Leino A, Heinonen OJ, Rautava E, Viikari J. Prospective study on food fortification with vitamin D among adolescent females in Finland: minor effects. The Br J Nutr 2008;100:418–23.
22. Valimaki VV, Loyttyniemi E, Valimaki MJ. Vitamin D fortification of milk products does not resolve hypovitaminosis D in young Finnish men. Eur J Clin Nutr 2007;61:493–7.
23. Piirainen T, Laitinen K, Isolauri E. Impact of national fortification of fluid milks and margarines with vitamin D on dietary intake and serum 25-hydroxyvitamin D concentration in 4-year-old children. Eur J Clin Nutr 2007;61:123–8.
24. Johnson JL, Mistry VV, Vukovich MD, Hogie-Lorenzen T, Hollis BW, Specker BL. Bioavailability of vitamin D from fortified process cheese and effects on vitamin D status in the elderly. J Dairy Sci 2005;88:2295–301.
25. Bonjour JP, Benoit V, Pourchaire O, Ferry M, Rousseau B, Souberbielle JC. Inhibition of markers of bone resorption by consumption of vitamin D and calcium-fortified soft plain cheese by institutionalised elderly women. Br J Nutr 2009;102:962–6.
26. Mocanu V, Stitt PA, Costan AR, Voroniuc O, Zbranca E, Luca V, Vieth R. Long-term effects of giving nursing home residents bread fortified with 125 microg (5000 IU) vitamin D(3) per daily serving. Am J Clin Nutr 2009;89:1132–7.
27. Manios Y, Moschonis G, Panagiotakos DB, Farajian P, Trovas G, Lyritis GP. Changes in biochemical indices of bone metabolism in post-menopausal women following a dietary intervention with fortified dairy products. J Hum Nutr Diet 2009;22:156–65.
28. Daly RM, Nowson CA. Long-term effect of calcium-vitamin D(3) fortified milk on blood pressure and serum lipid concentrations in healthy older men. Eur J Clin Nutr 2009;63:993–1000.
29. Kukuljan S, Nowson CA, Bass SL, Sanders K, Nicholson GC, Seibel MJ, Salmon J, Daly RM. Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on bone mineral density in older men: a randomised controlled trial. Osteoporos Int 2009;20:1241–51.
30. Wagner D, Sidhom G, Whiting SJ, Rousseau D, Vieth R. The

bioavailability of vitamin D from fortified cheeses and supplements is equivalent in adults. J Nutr 2008;138:1365–71.
31. Green TJ, Skeaff CM, Rockell JE. Milk fortified with the current adequate intake for vitamin D (5 microg) increases serum 25-hydroxyvitamin D compared to control milk but is not sufficient to prevent a seasonal decline in young women. Asia Pac J Clin Nutr 2010;19:195–9.
32. Biancuzzo RM, Young A, Bibuld D, Cai MH, Winter MR, Klein EK, Ameri A, Reitz R, Salameh W, Chen TC, Holick MF. Fortification of orange juice with vitamin D(2) or vitamin D(3) is as effective as an oral supplement in maintaining vitamin D status in adults. Am J Clin Nutr 2010;91:1621–6.
33. Ganmaa D, Tserendolgor U, Frazier L, Nakamoto E, Jargalsaikhan N, Rich-Edwards J. Effects of vitamin D fortified milk on vitamin D status in Mongolian school age children. Asia Pac J Clin Nutr 2008;17:68–71.
34. Allen L, de Benoist B, Dray O, Hurrell R. Guidelines on food fortification with micronutrients. Geneva:WHO/FAO 2006.
35. DSM. Fortification basis—margarine and oils. Available at: http://www.dsm.com/en_US/downloads/dnp/51609_fort_basics_oils.pdf Accessed 03/14 2013.
36. Health Canada. Food & Drug Act B.09.016. Available at: http://www.hcsc.gc.ca/food-aliment/friia-raaii/food_drugs-aliments_drogues/act-loi/pdf/e_b-text-1.pdf.
37. Laillou A, Berger J, Le BM, Pham VT, Le TH, Nguyen CK, Panagides D, Rohner F, Wieringa F, Moench-Pfanner R. Improvement of the Vietnamese diet for women of reproductive age by micronutrient fortification of staples foods and condiments. PloS ONE 2012;7:e50538.
38. Laillou A, Mai le B, Hop le T, Khan NC, Panagides D, Wieringa F, Berger J, Moench-Pfanner R. An assessment of the impact of fortification of staples and condiments on micronutrient intake in young Vietnamese children. Nutrients 2012;4:1151–70.
39. Laillou A, Panagides D, Garrett G, Moench-Pfanner R. Fortification of exported vegetable oil from Malaysia and Indonesia can significantly contribute to vitamin A intake worldwide. Food Nutr Bull 2013;34:S72–80.
40. Holick M. Evolution, biologic functions, and recommended dietary allowance for vitamin D. In: Holick M, ed. Vitamin D: physiology, molecular biology and clinical applications. Totowa, New Jersey: Osteoporos Int, Humana Press; 1999:1–16.
41. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657–66.
42. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:827–38.
43. Earl S, Cole ZA, Holroyd C, Cooper C, Harvey NC. Session 2: other diseases: dietary management of osteoporosis throughout the life course. Proc Nutr Soc 2010;69:25–33.
44. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204–10.
45. International Margarine Association of the Countries of Europe. Code of practice on vitamin A&D fortification of margarines and fat spreads. Available at: http://imace.org/files/files/public-website/nut-0408-ann-1-imace-cop-on-vit-a-and-d-final-version.pdf.Accessed 03/20/ 2013.
46. Webb P, Rogers B, Rosenberg I, Schlossman N, Wanke C, Bagriansky J, Sadler K, Johnson Q, Tilahun J, Reese Masterson A, Narayan A. Delivering improved nutrition: recommendations for changes to US food aid products and programs. Tufts University Boston, MA: Tufts University, 2011.
47. Nguyen NV, Dinh TA, Ngo QV, Tran VD, Breitkopf CR. Awareness and knowledge of osteoporosis in Vietnamese women. Asia Pac J Public Health 2011, DOI 10.1177/1010539511423569.
48. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293:2257–64.
49. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:551–61.
50. Manios Y, Moschonis G, Trovas G, Lyritis GP. Changes in biochemical indexes of bone metabolism and bone mineral density after a 12-mo dietary intervention program: the Postmenopausal Health Study. Am J Clin Nutr 2007;86:781–9.
51. Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. J Bone Miner Res 2006;21:397–405.
52. Daly RM, Petrass N, Bass S, Nowson CA. The skeletal benefits of calcium- and vitamin D3-fortified milk are sustained in older men after withdrawal of supplementation: an 18-mo follow-up study. Am J Clin Nutr 2008;87:771–7.
53. Drajat Martianto, Komari, Moesijanti Soekatri, Yayat Heryatno, Mudjajanto ES, Soekirman. Possibility of vitamin A fortification of cooking oil in Indonesia: a feasibility analysis. Jakarta: The Indonesia Fortification Coalition/The Micronutrient Initiative, 2005.
54. Central Board of Statistics (BPS) of Indonesia. Indonesian Susenas, 2005. Available at: http://ada.edu.au/international/browse/indonesia/susenas/susenas-2005.
55. Yakes EA, Arsenault JE, Munirul Islam M, Hossain MB, Ahmed T, Bruce German J, Gillies LA, Shafiqur Rahman A, Drake C, Jamil KM, Lewis BL, Brown KH. Intakes and breast-milk concentrations of essential fatty acids are low among Bangladeshi women with 24–48-month-old children. BR J Nutr 2011;105:1660–70.
56. Zhang F, Yi C, Fang G, Sakutombo DN. Dietary intakes and behaviours in pregnant women of Li ethnicity: a comparison of mountainous and coastal populations in southern China. Pac J Clin Nutr 2010;19:236–42.
57. FAOSTAT. Available at: http://faostat.fao.org/site/354/default.aspx 2010.
58. Altai Consulting. Market survey—edible vegetable oil. USAID Kabul: USAID, 2007.