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POSITION PAPER

Vitamin D status and clinical implications in the adult population of Malaysia: a position paper by the Malaysian Vitamin D Special Interest Group

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Abstract

Purpose Vitamin D deficiency and insufficiency is common among populations globally, and in Asia and Malaysia. The purpose of this Position Paper is to propose recommendations for both clinicians and non-clinicians to promote vitamin D sufficiency in Malaysian adults. Formation of a national multisector, multidisciplinary alliance is also proposed to progress initiatives relating to safe sun exposure, adequate vitamin D intake through food fortification, and vitamin D supplementation for high-risk groups.

Methods Literature reviews were undertaken to inform summaries of the following: vitamin D status globally and in Asian and Malaysian populations, vitamin D status among individuals with common medical conditions, and current recommendations to achieve vitamin D sufficiency through sun exposure, food intake and supplementation. Recommendations were based on the findings of the literature reviews, recent European guidance on vitamin D supplementation, the 2018 road map for action on vitamin D in low- and middle-income countries, and research recommendations proposed by the Malaysian Ministry of Health in 2017.

Results Recommendations on assessment of vitamin D in the adult Malaysian population include using serum or plasma 25-hydroxyvitamin D concentration as a biomarker, widespread participation by Malaysian laboratories in the Vitamin D Standardization Program, adoption of the US Endocrine Society definitions of vitamin D deficiency and insufficiency, and development of a comprehensive nationwide vitamin D status study. Specific high-risk groups are identified for vitamin D assessment and recommendations relating to loading doses and ongoing management are also made.

Conclusion This Position Paper provides individual clinicians and national stakeholder organisations with clear recommendations to achieve vitamin D sufficiency in the adult population of Malaysia.

Keywords Deficiency · Diet · Malaysia · Sun exposure · Supplementation · Vitamin D

Introduction

Vitamin D deficiency is the primary cause of nutritional rickets in children and osteomalacia in adults. Epidemiological studies have also reported associations of vitamin D deficiency with a broad array of adverse extra-skeletal outcomes. In recent years, a substantial amount of basic research has been undertaken and clinical studies conducted to evaluate the impact of vitamin D status on both bone and extra-skeletal health. Vitamin D deficiency and insufficiency is common among populations globally, and in Asia and Malaysia.

This Position Paper has the following objectives:

1. To summarise peer-reviewed literature on vitamin D status globally and in Asian and Malaysian populations
2. To summarise vitamin D status among individuals with common medical conditions and pregnancy
3. To summarise current/updates on recommendations on achieving vitamin D sufficiency through sun exposure, food intake and supplementation
4. To propose recommendations to promote vitamin D sufficiency in Malaysia

Extended author information available on the last page of the article

Methods

The online search interface of EndNote software (Clarivate Analytics, Philadelphia and London) was used to query the PubMed database for entries from 1 January 2017 to 27 July 2022 and searches were saved. An initial search was conducted using the following broad terms:

- Vitamin D AND deficiency
- Vitamin D AND deficiency AND Asia
- Vitamin D AND deficiency AND Malaysia

These searches retrieved 18,159, 1664 and 121 PubMed records, respectively. The searches were refined by including the additional term "review" which retrieved 4223, 173 and 32 PubMed records, respectively. To identify literature relating to the second objective of this Position Paper, the following general search terms were used in the PubMed database:

- Vitamin D AND [medical condition] AND review
- Vitamin D AND [medical condition] AND review AND Asia
- Vitamin D AND [medical condition] AND review AND Malaysia

The number of review publications identified in the searches is shown in Table 1.

Abstracts were scrutinised for:

- Global, Asian and Malaysian general review articles on vitamin deficiency
- Global, Asian and Malaysian review articles on vitamin D status among individuals with common medical conditions and pregnancy

Full publications of selected reviews were obtained for full evaluation. Full primary publications of relevance described within the review articles were also obtained for full evaluation. Additional publications provided by members of the Malaysian Vitamin D Special Interest Group, including some studies published in journals not cited on PubMed, were also scrutinised.

Table 1 Summary of literature searches relating to review publications on vitamin D and common medical conditions and pregnancy

Condition	Number of review publications		
	Global	Asia	Malaysia
Cancer	2530	52	30
COVID-19	746	19	8
Diabetes	1677	39	17
Bone health	1025	25	13
Osteoporosis	793	22	16
Fragility fracture	128	4	1
Falls	202	4	1
Sarcopenia	199	6	1
Fibromyalgia	26	0	0
Neurological	420	8	4
Multiple sclerosis	273	1	1
Pregnancy	1088	47	14

Vitamin D metabolism and functions

Vitamin D refers to a group of fat-soluble secosteroids, the most important in humans being vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D is produced in the keratinocytes of two innermost strata of the epidermis, the stratum basale and stratum spinosum [1]. Irradiation of 7-dehydrocholesterol, the precursor of vitamin D_3, with ultraviolet B (UVB) light at wavelengths of 290–315 nm present in sunlight results in photochemical synthesis of vitamin D_3 [2]. Vitamin D_2 is found in foods including mushrooms and alfafa.

Both vitamins D_3 and D_2 are themselves inactive and require two hydroxylations to be activated. Vitamin D_3 is converted in the liver to calcifediol (25-hydroxycholecalciferol) and vitamin D_2 is converted to ercalcidiol (25-hydroxyergocalciferol). The total amount of these two metabolites—referred to as 25-hydroxyvitamin D or 25(OH)D—is measured in serum to determine a person's vitamin D status. Calcifediol is further hydroxylated by the kidneys and some of the immune system cells to form calcitriol (1,25-dihydroxycholecalciferol or 1,25-$(OH)_2D_3$), the biologically active form of vitamin D. Analogously, ercalcidiol undergoes a second hydroxylation in the kidneys to form ercalcitriol (1,25-dihydroxyergocalciferol or 1,25-$(OH)_2D_2$). Calcitriol and ercalcitriol have similar binding affinities to the vitamin D receptor (VDR), a transcription factor that binds to thousands of sites in DNA that regulate hundreds of genes in a cell-specific fashion [3]. The activated form of vitamin D has several physiological functions including increasing absorption of calcium [4] and phosphate [5] in the intestine, increasing mineralisation of bone [6], inducing differentiation of immune cells [7], improving vasodilation [8], and effects on the tumour microenvironment [9].

Measurement of vitamin D

Clinical recommendations and most epidemiological studies focus on levels of total 25-hydroxyvitamin D, which can be measured in serum, plasma, whole blood, or blood spots. The half-life of 25-hydroxyvitamin D_3 may be

slightly longer than that of 25-hydroxyvitamin D_2 (15.1 days vs. 13.9 days) [10]. Total 25(OH)D can be measured using the following methods:

- Liquid chromatography-tandem mass spectrometry (LC-MS/MS)
- Ligand-binding assays:
    - Competitive enzyme-linked immunosorbent assay (ELISA)
    - Competitive chemiluminescent immunoassay
    - Competitive receptor-binding assays

There are pros and cons for each approach. Compared to LC-MS/MS, immunoassay methods have demonstrated bias and increased variability [11]. Also, LC-MS/MS can quantify levels of 25(OH)D_2 and 25(OH)D_3, whereas the immunoassays cannot. However, LC-MS/MS requires expert staff and more expensive equipment, albeit that reagent costs for LC-MS/MS are significantly lower.

On account of reported variability and bias in laboratory measurement of total 25(OH)D [12], in November 2010, the US National Institutes of Health's Office of Dietary Supplements in collaboration with the Centers for Disease Control and Prevention National Center for Environmental Health, National Institute of Standards and Technology and Ghent University established the Vitamin D Standardization Program (VDSP) [13]. The VDSP objectives included:

1. Standardize 25(OH)D concentration measurements in national health surveys around the world
2. Evaluate survey differences
3. Extend standardization efforts to assay manufacturers, and to clinical, commercial, and research laboratories
4. Promote standardization of emerging metabolites of vitamin D status
5. Enable the use of standardized data in patient care and public health

Government and commercial laboratories in Malaysia generally measure 25(OH)D with ELISA or chemiluminescent immunoassays. Peer-reviewed publications or other public domain sources of information documenting the proportion of Malaysian laboratories that standardize their vitamin D assays against the VDSP were not identified. However, several studies that evaluated vitamin D status among Malaysian populations [14–16] noted their use of assays which had been standardized to the University of Ghent ID-LC/MS/MS reference measurement procedure [13] and had achieved the Centers for Disease Control Vitamin D Standardization Certification [17].

Vitamin D status in Asian and Malaysian populations

In 2022, Cashman reviewed global differences in vitamin D status and dietary intake [18]. In light of ongoing debate in the scientific literature regarding definitions of the degree of low vitamin D status, thresholds for the purposes of the review were informed by the following:

- Guidance from expert bodies on vitamin D deficiency in relation to nutritional rickets and osteomalacia [19–22]
- Population health perspectives on the development of dietary recommendations for vitamin D intake, primarily from the perspective of musculoskeletal health outcomes [19, 21, 23, 24]
- Thresholds considered to achieve near universal sufficiency within a population [19, 23]

Accordingly, the review focused primarily on the prevalence of serum 25(OH)D < 25 or 30 nmol/L, between 25/30 and 50 nmol/L, and >50 nmol/L.

The importance of using standardised serum 25(OH)D values for comparisons of the prevalence of vitamin D deficiency between countries was illustrated by findings from national surveys conducted in Germany and Ireland, two European countries resident within comparable ranges of latitude. Prior to standardisation of the *German Health Interview and Examination Survey for Adults*, the prevalence estimate for serum 25(OH)D < 30 nmol/L was 25.9%, which decreased to 15.2% after standardisation [25]. Conversely, the pre-standardisation prevalence of deficiency reported in the *Irish National Nutrition Survey* was 6.6%, which increased to 12.3% after standardisation [26].

The review by Cashman [18] defined major world regions in accordance with those used by the Food and Agriculture Organisation of the United Nations (FAO) [27], i.e. Africa, Asia, the Americas, Europe and Oceania. The prevalence of serum 25(OH)D < 25/30 nmol/L was in the range 5 to 18%, depending on FAO world region, and from 24 to 49% for serum 25(OH)D < 50 nmol/L. While some variation between regions was evident, high levels of inadequate vitamin D intake was the norm. Furthermore, the vast majority of countries do not undertake national surveys on vitamin D intake and status, and standardization should be a priority in the future to ensure that some existing surveys and all new national surveys seek to minimise method-related differences in measurement of 25(OH)D.

The review concluded with reference to the recommendations of a 2018 report that proposed a roadmap for action on vitamin D deficiency in low- and middle-income countries [28]. The roadmap will be considered in the context of the recommendations proposed at the end of this Position Paper.

In 2021, Jiang et al. published a systematic review and meta-analysis to investigate the prevalence of vitamin D

deficiency and its association with different health outcomes in Asia [29]. The review included 472 studies with 746,564 participants from 30 Asian countries. Among the 466 studies that reported serum concentrations of 25(OH)D, the three most well-represented countries were China (168 studies), Saudi Arabia (43 studies) and Turkey (26 studies). A total of 348 studies were included in the meta-analysis of pooled prevalence, the majority of which ($n = 332$) reported a threshold of < 50 nmol/L, almost 44% ($n = 153$) a threshold of < 30 nmol/L, and 35% ($n = 122$) a threshold of < 25 nmol/L. The prevalence of vitamin D levels below the 50 nmol/L, 30 nmol/L and 25 nmol/L thresholds were 57.7%, 22.8% and 20.9%, respectively. Sub-group analyses suggested that gender, age, region, altitude and specific diseases were significant factors related to vitamin D deficiency.

In 2022, Md Isa et al. published a comprehensive review of studies evaluating vitamin D status of Malaysians, including adult men and women, pregnant women, postmenopausal women, adolescents, and children with specific diseases [30]. The studies reviewed used a range of thresholds to define vitamin D deficiency and insufficiency. Those that used the 2011 Institute of Medicine thresholds for deficiency of < 30 nmol/L and/or insufficiency of 30 to 50 nmol/L included the following populations [19]:

- Postmenopausal women ($n = 214$): 49.5% insufficient, 33.2% deficient [14]
- Pregnant women ($n = 535$): 49.3% insufficient, 42.6% deficient [15]
- Men aged ≥20 years ($n = 383$): 22.7% insufficient, 0.5% deficient [31]
- Children ≤18 years with chronic liver disease ($n = 59$): 14% insufficient, 14% deficient [32]

Across the range of study populations reviewed, vitamin D deficiency and insufficiency were particularly common among females, Indians and those of Malay ethnicity, where absorption of UVB radiation by melanin in darker skin [31, 33–36] and sun-avoidant behaviours [37–40] are well-documented contributors to low levels of vitamin D. Other high-risk groups identified included breastfed infants, the elderly, the obese, and those with conditions associated with malabsorption of fat.

In 2022, Saffian et al. published a systematic review and meta-analysis of studies on vitamin D status among Malaysian populations [41]. The systematic review had the following two inclusion criteria:

- The study measured serum 25(OH)D levels in healthy Malaysians
- The study was non-interventional and conducted either as a cross-sectional, case-control, or longitudinal study design

Only data from healthy population subgroups for case-control studies was included in the meta-analysis. Results were reported for studies with the following three thresholds:

- < 30 nmol/L: Based on data from 10 studies with a total of 2,438 participants, the pooled proportion was 21% (95% confidence interval [CI], 9–36%)
- < 50 nmol/L: Based on data from 30 studies with 13,977 participants, the pooled proportion was 64.5% (95% CI, 56.1–72.5%)
- < 75 nmol/L: Based on data from 5 studies with a total of 1,376 participants, the pooled proportion was 85% (95% CI, 61–100%)

Based on a threshold of < 50 nmol/L, higher proportions of vitamin D insufficiency were found for those living in urban areas compared to rural areas (66.8% vs. 45.6%), females compared to males (76% vs. 46%), and Malays (77%) and Indians (77%) compared to Chinese (34.5%).

The recommendations made in the reviews by Md Isa et al. [30] and Saffian et al. [41] will be considered in the context of the recommendations proposed at the end of this Position Paper.

Vitamin D status among individuals with common medical conditions and pregnancy

In recent years, numerous narrative reviews, systematic reviews and meta-analyses have explored associations between vitamin D status and many common medical conditions. These include cancer [42–47], COVID-19 [48–54], diabetes [49, 55, 56], musculoskeletal conditions [57–61] and neurological conditions [62–64]. Vitamin D status in pregnancy has also been evaluated [61, 65]. Table 2 provides an illustration of the purpose and key findings of several studies exploring associations between various cancers and vitamin D status. It is beyond the scope of this Position Paper to comment upon the findings of the plethora of such studies for all medical conditions. However, as noted in the research recommendations of the Ministry of Health's 2017 update to the recommended nutrient intakes (RNIs) for Malaysia [66], rigorous large scale randomised controlled trials are required to test the effects of vitamin D on a range of non-skeletal outcomes.

Approaches to achieving Vitamin D sufficiency

Sun exposure

The 2022 review by Md Isa et al. [30] noted "Malaysia is a tropical country with an ample source of sunshine, but, at the same time, the majority of Malaysia's population consists of Muslims who cover themselves (especially ladies)

Table 2 Summary of findings from publications relating to vitamin D and various cancers [42–46]

Type of cancer	Type of publication	Purpose and key findings	References
Bladder	Systematic review and evaluation of potential mechanism	**Purpose:** To assess the relationship between serum 25(OH)D and bladder cancer risk **Findings:** • Low vitamin D levels were associated with bladder cancer risk in 5 of the 6 studies evaluated. • Higher vitamin D levels also correlated with better survival and outcomes. • Transitional epithelial cells express functional vitamin D signaling and can synthesize sufficient $1,25(OH)_2D$ to stimulate a local immune response. • The authors suggest that in order to maintain optimal immune surveillance within the bladder adequate levels of serum 25(OH)D are required for direct synthesis of $1,25(OH)_2D$ by bladder epithelial cells.	Dunn et al. 2019 [42]
Breast	Systematic review and meta-analysis of observational studies	**Purpose:** To evaluate evidence linking serum 25(OH)D with vitamin D obtained from both food and supplements with breast cancer (BC) occurrence. **Findings:** • A net direct association between 25(OH)D deficiency and BC (relative risk $[RR]_{pooled}$, 1.91; 95% confidence interval [CI], 1.51–1.91, $p < 0.001$). • Total vitamin D intake (RR_{pooled}, 0.99; 95% CI, 0.97–1.00, $p = 0.022$, per 100 IU/day) and supplemental vitamin D (RR_{pooled}, 0.97; 95% CI, 0.95–1.00, $p = 0.026$) were inversely associated with BC. • Randomised clinical trials are warranted.	Hossain et al. 2019 [43]
Colorectal	Systematic review and dose-response meta-analysis	**Purpose:** To assess the association between circulating vitamin D levels and colorectal cancer (CRC) risk in the Asian population. **Findings:** • Pooled Odds Ratios (ORs) of CRC for the highest versus lowest categories of circulating vitamin D levels was 0.75 (95% CI, 0.58-0.97) up to 36.5 ng/mL. • An increment of 16 ng/mL in circulating vitamin D level corresponded to an OR of 0.79 (95% CI, 0.64–0.97). • The dose-response meta-analysis indicated a significant linear relationship ($P_{non\text{-}linearity} = 0.11$).	Zhang et al. 2019 [44]
Liver	Systematic review and dose-response meta-analysis of cohort studies	**Purpose:** To assess available data from cohort studies on the association of 25(OH)D levels with the risk of hepatocellular carcinoma (HCC). **Findings:** • Subjects with the highest serum concentrations of vitamin D had a lower risk of liver cancer versus subjects with the lowest serum concentrations of vitamin D (hazard ratio $[HR]_{pooled,}$ 0.53; 95% CI, 0.41–0.68, $p < 0.001$). • HR_{pooled} from the random-effects dose-response model indicated a significant indirect linear association between serum vitamin D levels and the risk of liver cancer (coef = -0.017, $p < 0.001$). • No significant non-linear dose-response association between vitamin D levels and the risk of liver cancer (coef − 0.0001, $p = 0.342$).	Zhang et al. 2021 [45]

Table 2 (continued)

Type of cancer	Type of publication	Purpose and key findings	References
Prostate	Systematic review and meta-analysis	**Purpose:** To investigate whether there is evidence that an association of vitamin D on prostate cancer progression could be via an effect of vitamin D on circulating levels of testosterone within the normal range. **Findings:** • A meta-analysis of 10 human RCTs showed evidence of an effect of vitamin D on total testosterone (standardized mean difference [SMD], 0.133; 95% CI, − 0.003–0.269, $I^2 = 0.0\%$, $p = 0.056$). • Five human RCTs showed evidence of an effect of vitamin D on free testosterone (SMD, 0.173; 95% CI, − 0.104–0.450, $I^2 = 52.4\%$, $p = 0.220$). • Further research is required to confirm if testosterone mediates the relationship between vitamin D and prostate cancer progression.	Robles et al. 2022 [46]
Thyroid	Meta-analysis of case control studies	**Purpose:** To investigate the association between vitamin D deficiency and thyroid cancer. **Findings:** • Preoperatively, serum 25(OH)D was significantly lower in thyroid cancer patients than in controls (SMD, − 0.22; 95% CI, − 0.36 to − 0.09, $p = 0.001$). • Postoperatively, there was no significant difference in serum 25(OH)D (SMD, -0.19; 95% CI, − 0.47–0.10, $p = 0.21$). • More studies are needed to elucidate the mechanism of vitamin D deficiency related to thyroid cancer.	Liao et al. 2019 [47]

during outdoor activities." In 2011, Moy reported a positive correlation for sun exposure score ($r = 0.27$, $p < 0.001$) and negative correlation for sun protection score ($r = -0.41$, $p < 0.001$) with 25(OH)D levels among Malay adults [67]. Logistic regression demonstrated that females were 2.9 times more likely to have insufficient 25(OH)D levels, defined as < 50 nmol/L. In 2020, Aris et al. described the effects of occupational sunlight exposure and the monsoon season on vitamin D status among outdoor and indoor workers in Malaysia [68]. All participants were Muslims. Outdoor workers had significantly higher sunlight exposure, physical activity, and vitamin D intake than indoor workers regardless of sex and season. Vitamin D status was in accordance with the US Endocrine Society Clinical Practice Guideline 2011 [69], i.e. sufficient = serum 25(OH)D concentration ≥ 75 nmol/L, insufficient = serum 25(OH)D concentration 50–74 nmol/L and deficient = serum 25(OH)D concentration < 50 nmol/L. Mean 25(OH)D levels were as follows:

- Males: Outdoor workers 129.7 nmol/L vs. indoor workers 67.6 nmol/L ($p < 0.001$)
- Females: Outdoor workers 78.2 nmol/L vs. indoor workers 39.2 nmol/L ($p < 0.001$)

The differences between males and females were statistically significant between all groups ($p < 0.001$). Almost three quarters of indoor female workers were classified as deficient as compared to less than 10% of indoor male workers.

A Malaysian study presented at the International Life Sciences Institute Annual Meeting in 2016 suggested that minimum surface exposure (i.e. face and hands) to sunlight for 30 min, twice per week at 11.00 am could increase serum vitamin D levels by 40% [70].

In 2021, Augustine et al. proposed sun exposure as a low-cost sustainable strategy in tropical countries to achieve vitamin D sufficiency for the general population [71]. Key components and considerations for development of national strategies included:

- Season-specific guidelines using satellite data
- Popularization of UV index using mobile applications and monitoring
- Generating high-quality evidence
- Policy directions to promote out-door physical activity
- Facilitative built environment changes conducive for sun exposure especially for females
- Policy directives to reduce pollution

- Native and immigrant populations require separate policy decisions guidelines
- National health policy on holistic approach, establish dose-response relationship with calcium
- Understand the interactions between 7-dehydrocholesterol and 25(OH)D syntheses in the current scenario of malnutrition, including specific guidelines and strategies for elderly

Diet and food fortification

In 2017, the National Coordinating Committee on Food and Nutrition (NCCFN) of the Ministry of Health Malaysia updated the recommended nutrient intakes (RNIs) for Malaysia (see Table 2) [66]. Notably, all eight vitamins in the 2005 edition [72] of the Ministry's RNIs were reviewed and retained except for vitamin D. In 2017, the Technical Sub-Committee (TSC) on Minerals and Trace Elements adapted the values proposed by the Institute of Medicine in 2011 [19] on account of studies at the time reporting unsatisfactory vitamin D status in some population groups. Consequently, 2017 values were generally 2–3 times higher than the 2005 values. Notably, the daily requirements assumed minimal sunlight exposure (Table 3).

Table 3 Vitamin D recommended nutrient intake (RNI) for Malaysia 2017 [66]

Population	Age or stage	Boys and men Vitamin D µg per day	Girls and women Vitamin D µg per day
Infants	0–11 months	10	10
Children	1–9 years	15	15
Adolescents	10–18 years	15	15
Adults	19–65 years	15	15
	> 65 years	20	20
Pregnancy	1st–3rd trimesters	-	15
Lactation	1st Year	-	15

Food fortification

The 2017 RNI for Malaysia stated the following with respect to fortification of foods with vitamin D:

"In Malaysia, the Malaysian Food Regulation permits the addition of vitamin D according to different categories of foods (MOH, 1985). Currently, voluntary vitamin D fortification of milk powder for children and adults are being carried out by manufacturers. The intake of foods fortified with vitamin D can increase vitamin D in the diet."

In 2021, Niedermaier et al. published a modelling study on the potential impact of food fortification with vitamin D on cancer deaths in Germany [73]. The investigators sought to answer two questions:

i. Can vitamin D food fortification achieve similar increases in vitamin D levels as vitamin D supplementation at doses that were reported to be effective in reducing cancer mortality in meta-analyses?
ii. What would be the costs for such food fortification, and how would they compare with saved costs from prevented cancer deaths?

In most studies considered, fortification resulted in serum increases of approximately 20 nmol/L. This was comparable to daily intake of approximately 400 (up to 800) international units (IU) of vitamin D by supplements, as reported in a 2012 systematic review by Autier et al. [74]. A 2019 systematic review and meta-analysis of randomised controlled trials by Keum et al. indicated that cancer mortality was reduced with a daily intake of vitamin D (400 to 2000 IU per day) in the range of 11 to 17% (13% on average) [75]. Accordingly, the economic analysis was based on a fortification program that would result in a daily intake of 400 IU of vitamin D resulting in an 11% reduction in cancer mortality. This would result in net savings of almost Euro 1 billion per year in Germany. A sensitivity analysis suggested that the costs per prevented death would be in the range Euro 38 to Euro 62.

Supplementation

The health effects of vitamin D supplementation has been the subject of debate and controversy in the scientific literature in recent years. Several detailed reviews and commentaries were published in 2022 [76–81]. A summary of the findings of the major vitamin D randomised controlled trials (RCTs), systematic reviews and meta-analyses relating to specific conditions follows. It should be noted that the majority of the large-scale studies have been conducted in European, Oceanian and North American populations, some of which were vitamin D replete at the commencement of the studies. There is also currently a paucity of data on the effectiveness of vitamin D supplementation in vitamin D deficient Asian and Malaysian populations.

Since 2016, several meta-analyses have evaluated the effectiveness of vitamin D supplementation—with and without calcium—on the prevention of falls and fractures [82–85]. The most recent review published in 2020 by Thanapluetiwong et al was based on 47 RCTs [85]. While overall vitamin D supplementation demonstrated a 5% reduction in the risk of falls (relative risk [RR], 0.948; CI, 0.914–0.984, $p = 0.004$, $I^2 = 41.52$), sub-group analysis revealed that the reduction only remained significant when calcium was co-administered with vitamin D (RR, 0.881; 95% CI, 0.821–0.945, $p < 0.001$, $I^2 = 49.19$). Vitamin D

supplementation alone did not reduce the incidence of fractures. However, when co-administered with calcium a 14% reduction was evident (RR, 0.859; 95% CI, 0.741–0.996, $p = 0.045$, $I^2 = 25.48$).

In mid-2022, findings were published from an ancillary study of the Vitamin D and Omega-3 Trial (VITAL) [86]. VITAL was designed as a two-by-two factorial RCT to evaluate whether supplemental vitamin D_3 (2,000 IU per day), n-3 fatty acids (1 g per day), or both would prevent cancer and cardiovascular disease in men aged 50 years or older and women aged 55 years or older in the United States of America. Notably, participants ($n = 25,871$) were not selected on the basis of having vitamin D deficiency, low bone mass or osteoporosis. At baseline, 12.9% of participants had 25(OH)D levels of < 50 nmol/L (20 ng/mL) and 2.4% of participants had 25(OH)D levels of < 30 nmol/L (12 ng/mL). During median follow-up of 5.3 years, supplemental vitamin D_3 did not have a significant effect on total fractures (hazard ratio [HR], 0.98; 95% CI, 0.89–1.08, $p = 0.70$), nonvertebral fractures (HR, 0.97; 95% CI, 0.87–1.07, $p = 0.50$), or hip fractures (HR, 1.01; 95% CI, 0.70–1.47, $p = 0.96$). Post hoc analyses found no benefit among the small group of participants with baseline 25(OH)D levels < 30nmol/L. The authors noted "It would not have been feasible or ethical to study the effects of vitamin D as compared with placebo on incident fractures in a population preselected for vitamin D deficiency."

In addition to VITAL, several other large RCTs have been undertaken to evaluate the effects of vitamin D supplementation on mortality, cardiovascular disease (CVD) and cancer. These include the Vitamin D Assessment (ViDA) study [87], the D-Health trial [88] and the Finnish Vitamin D Trial (FIND) [89]. In 2022, in an editorial [81] related to publication of FIND, Professor Peter Ebeling concluded "… vitamin D supplementation in predominantly vitamin D–replete populations does not reduce CVD events or cancer. Although daily dosing may reduce the likelihood of death from cancer, this was not seen with monthly dosing. Future trials are needed in vitamin D–deficient populations to demonstrate beneficial effects of vitamin D on CVD and cancer, as are proven for musculoskeletal outcomes in this population."

A secondary analysis of the D2d study evaluated the effect of vitamin D_3 supplementation (4000 IU per day) on cardiovascular risk in patients ($n = 2423$) with prediabetes not selected for vitamin D insufficiency [90]. While supplementation did not decrease major adverse cardiovascular events, a favourable change in the atherosclerotic CVD risk score was observed for the vitamin D_3 group (− 0.45%; 95% CI, − 0.75 to − 0.15).

In 2021, a Cochrane systematic review sought to evaluate the effectiveness of vitamin D supplementation in the treatment of COVID-19 [52]. The authors concluded that there was insufficient evidence at the time to determine the benefits and harms of vitamin D for Covid-19 patients. However, results from 21 ongoing studies would provide an opportunity to update the review when more evidence became available. In 2022, the COvid19 and VITamin d TRIAL (COVIT-TRIAL) study evaluated 14-day survival among older adults infected with Covid-19 treated with a single high dose of vitamin D_3 (400,000 IU) within 72 h of diagnosis, compared to a group treated with a standard dose of vitamin D_3 (50,000 IU) [91]. A benefit was observed at 14 days in the high dose group compared to standard dose (adjusted HR, 0.39; 95% CI, 0.16–0.99, $p = 0.049$), after controlling for age, oxygen requirement, hospitalization, use of antibiotics, anti-infective drugs, and/or corticosteroids, and baseline imbalances in prognostic factors. However, the protective effect ceased to be observed at 28 days. Also in 2022, Efird et al. undertook a large-scale analysis ($n = 26,508$) of the interaction of vitamin D and corticosteroids on mortality among military veterans in the USA infected with COVID-19 [92]. Approximately 24% of the sample received vitamin D and/or corticosteroids, with just 1% having received both treatments. Overall, 30-day mortality was 6%. Among hospitalized patients ($n = 7845$, 29.6%), compared to post-index use of corticosteroids without vitamin D, significant decreases in 30-day mortality were observed for:

- Use of vitamin D in the absence of corticosteroids (adjusted relative risk [aRR], 0.30; 95% CI, 0.16–0.58, multiplicity corrected p value [p_{mc}] = 0.0004)
- Use of vitamin D in combination with corticosteroids (aRR, 0.51; 95% CI, 0.27–0.94, $p_{mc} = 0.031$)
- Use of neither treatment (aRR, 0.66; 95% CI, 0.58–0.74, $p_{mc} < 0.0001$)

Vitamin D deficiency during pregnancy has been reported globally [93] and is particularly prevalent in developing countries [94]. In 2022, Irwinda et al. undertook a systematic review and meta-analysis to determine the optimal supplementation dose required to prevent adverse maternal and foetal outcomes [95]. A total of 27 RCTs were included to evaluate the effects of oral vitamin D at a dose of > 2000 IU per day versus ≤ 2000 IU per day, and ≤ 2000 IU per day versus placebo, on preeclampsia, gestational diabetes mellitus, preterm birth and birth weight. Analysis of seven RCTs found a positive effect on gestational diabetes mellitus (risk ratio [RR], 0.70; 95% CI, 0.51–0.95, $I^2 = 0$). Analysis of three RCTs found a reduction in the risk of preeclampsia for vitamin D supplementation of ≤2,000 IU per day (RR, 0.29; 95% CI, 0.09–0.95, $I^2 = 0$), and no statistically significant difference was evident when compared to > 2000 IU per day. No differences were observed in preterm birth risk and birth weight after vitamin D supplementation.

Recommendations to achieve vitamin D sufficiency in Malaysia

The recommendations to achieve vitamin D sufficiency among the population of Malaysia follows. These recommendations are informed by the evidence summarised in this Position Paper, recent guidance from the European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group on vitamin D supplementation [96], the road map for action on vitamin D in low- and middle-income countries published by Roth et al in 2018 [28], and the research recommendations proposed by the Ministry of Health in the 2017 edition of the RNIs for Malaysia [66].

Assessment of vitamin D status in the Malaysian population

1. Serum or plasma 25-hydroxyvitamin D (25[OH]D) concentration should be used as a biomarker of vitamin D status [11].
2. Government, academic and university, and commercial laboratories should participate in the Vitamin D Standardization Program (VDSP) [13].
3. Malaysia to adopt the US Endocrine Society definitions of vitamin D deficiency as 25(OH)D < 50 nmol/L (20 ng/mL) and vitamin D insufficiency as 50 to 74 nmol/L (21–29 ng/mL) and vitamin D sufficiency as ≥ 75 nmol/L [69], which is consistent with the recommendation made in the third edition of the clinical practice guidelines for the management of osteoporosis in Malaysia [97].
4. A comprehensive nationwide vitamin D status study should be funded through the Ministry of Health and findings be published every three years until at least 80% of the population sampled are vitamin D sufficient.
5. Vitamin D status assessment should be incorporated into the National Health and Morbidity Survey (NHMS).

Strategies to achieve vitamin D sufficiency in the Malaysian population

6. For individual clinicians:
    a. To assess vitamin D status in groups at high risk of vitamin D deficiency, including pregnant and lactating mothers, postmenopausal women, the elderly, patients with fragility fracture, patients being treated for osteoporosis, patients presenting with symptoms of fibromyalgia, people who have undergone bariatric surgery, and individuals from communities with cultural practices that may limit sun exposure.
    b. To develop an individualised plan to achieve vitamin D sufficiency for their patients found to be vitamin D insufficient or vitamin D deficient, based on a combination of consumption of foods rich in vitamin D, safe sun exposure, and, where required, vitamin D supplementation.
    c. For patients with vitamin D deficiency (serum 25(OH)D < 50 nmol/L), a loading dose of 25,000 IU vitamin D_3 twice a week or 50,000 IU weekly for eight to twelve weeks is recommended, followed by repeat serum vitamin D level. The subsequent dosage of recommended vitamin D_3 will be adjusted accordingly, maintaining the serum 25(OH)D above 75 nmol/L. Maintenance therapy is likely to be in the range 800–1000 IU vitamin D_3 per day, in accordance with the clinical practice guidelines for the management of osteoporosis in Malaysia [97] and the recent guidance from the European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group on vitamin D supplementation in the management of musculoskeletal diseases [96].
    d. For patients presenting with vitamin D insufficiency (serum 25(OH)D between 50 and 75 nmol/L), a loading dose of 25,000 IU vitamin D_3 weekly is recommended for eight to twelve weeks, followed by repeat serum vitamin D level. The subsequent dosage of recommended vitamin D_3 will be adjusted accordingly, maintaining the serum 25(OH)D above 75 nmol/L. Maintenance therapy should in accordance with bullet 6c. above.
    e. Serum vitamin D level should be assessed yearly for high-risk individuals for vitamin D insufficiency/deficiency. This can be included as part of their yearly health screening blood test. Serum vitamin D level is currently not included in the routine health screening blood test.
    f. Where vitamin D supplementation is required to achieve sufficiency, the recent guidance from the ESCEO working group on vitamin D supplementation can be considered as a guide for clinicians in Malaysia [96].
    g. The ESCEO Working Group stated that daily doses of 800–1000 IU of vitamin D are safe; however, intermittent regimens with doses higher than those equivalent to this daily dosing are not recommended.
7. Formation of an alliance of healthcare professional organisations, universities, patients and medical charities/foundations, government agencies, public and private insurance providers, and private sector companies to collaborate and progress the following initiatives:

a. Sun exposure:

    i. Development and implementation of inclusive and engaging public awareness campaigns on the benefits of safe sun exposure, with consid-

eration given to cultural practices, ethnicity, workplace/study place/home environment, and a life course approach to engage all age groups

ii. Devise and commission research into the possible variations of biological effects of vitamin D on time and duration of sun exposure, adiposity, ethnicity and genetic factors [66]

b. Food composition and fortification:

iii. Advocate that regulatory bodies should mandate presentation of vitamin D content in the Malaysian food composition table [30]

iv. Advocate that vitamin D fortification in Malaysia should be regulated and standardized [30]

v. Advocate that vitamin D analysis should be included as parameter for Malaysian food composition database

vi. To develop a public health campaign to educate the population on vitamin D content in commonly consumed foods in Malaysia

c. Supplementation:

vii. Promote vitamin D supplementation in groups at high risk of vitamin D deficiency including pregnant and lactating mothers, postmenopausal women, the elderly, patients with fragility fracture, patients being treated for osteoporosis, patients presenting with symptoms of fibromyalgia, people who have undergone bariatric surgery, and communities with cultural practices that may limit sun exposure

viii. Design and identify funding to undertake large-scale RCTs to test the effects of vitamin D supplementation on non-skeletal outcomes [66], potentially in collaboration with colleagues in other countries in Asia Pacific

Code availability Not applicable.

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Data Availability Not applicable.

Declarations

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