

University of Wollongong

Research Online

Faculty of Science, Medicine and Health -
Papers: Part B

Faculty of Science, Medicine and Health

2020

Future perspectives in addressing the global issue of vitamin D deficiency

M M. Mendes
University of Surrey

Karen E. Charlton
University of Wollongong, karenc@uow.edu.au

Siddhartha Thakur
North Carolina State University, sthakur@ncsu.edu

Helen Ribeiro
Universidade de Sao Paulo

Susan A. Lanham-New
University of Surrey

Follow this and additional works at: <https://ro.uow.edu.au/smhpapers1>

Publication Details Citation

Mendes, M. M., Charlton, K. E., Thakur, S., Ribeiro, H., & Lanham-New, S. A. (2020). Future perspectives in addressing the global issue of vitamin D deficiency. Faculty of Science, Medicine and Health - Papers: Part B. Retrieved from <https://ro.uow.edu.au/smhpapers1/1557>

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au

Future perspectives in addressing the global issue of vitamin D deficiency

Abstract

Vitamin D is a fundamentally critical nutrient that the human body requires to function properly. It plays an important role in musculoskeletal health due to its involvement in the regulation of calcium and phosphorus. Having a low level of vitamin D in the body may be detrimental for a wide range of health outcomes, including risk of osteoporotic and stress fractures, risk of CVD and some cancers, and lowering of the capability of the immune system. Vitamin D is an unusual nutrient; it is not a vitamin, in the true sense of the word but a pro-hormone. The main source of vitamin D is UV exposure, not dietary intake. Interestingly, there are two forms of vitamin D, vitamin D₂ and vitamin D₃, both of which are metabolised into 25-hydroxyvitamin D (25(OH)D) in the liver, the biomarker of vitamin D status. Vitamin D deficiency is a global public health problem, especially amongst older people and ethnic minority groups. The newest publication from the UK Government's Public Health England Department recommends that vitamin D intake should be 10 µg daily and this recommendation compares well (albeit lower) with other guidelines such as the Institute of Medicine recommendation of 15 µg for those aged 1–70 years and 20 µg for those 70 years or over. Few countries, however, have a specific vitamin D policy to prevent deficiency in populations. Finland leads the way, demonstrating impressive results in reducing population-level vitamin D deficiency through mandatory food fortification programmes. Collaboration between academia, government and industry, including countries from varying latitudes, is essential to identify long-term solutions to the global issue of vitamin D deficiency. This paper provides a narrative review of the evidence related to the role of vitamin D deficiency in health outcomes, outlines controversies regarding setting levels of adequacy, identifies the prevalence of vitamin D deficiency across the globe, and identifies population-level strategies adopted by countries to prevent vitamin D deficiency.

Keywords

perspectives, global, future, issue, vitamin, addressing, deficiency

Publication Details

Mendes, M. M., Charlton, K., Thakur, S., Ribeiro, H. & Lanham-New, S. A. (2020). Future perspectives in addressing the global issue of vitamin D deficiency. *Proceedings of the Nutrition Society*, 79 (2), 246-251.



Conference on ‘Targeted approaches to tackling current nutritional issues’ Symposium 3: Global strategies to improve micronutrient status; current opinion and implications for nutrition policy

Future perspectives in addressing the global issue of vitamin D deficiency

M. M. Mendes¹, K. Charlton², S. Thakur³, H. Ribeiro⁴ and S. A. Lanham-New^{1*}

¹Nutritional Sciences Department, School of Biosciences & Medicine, Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK

²School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, Australia and Illawarra Health and Medical Research Institute, Wollongong, Australia

³College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA

⁴School of Public Health, University of São Paulo, São Paulo, Brazil

Vitamin D is a fundamentally critical nutrient that the human body requires to function properly. It plays an important role in musculoskeletal health due to its involvement in the regulation of calcium and phosphorus. Having a low level of vitamin D in the body may be detrimental for a wide range of health outcomes, including risk of osteoporotic and stress fractures, risk of CVD and some cancers, and lowering of the capability of the immune system. Vitamin D is an unusual nutrient; it is not a vitamin, in the true sense of the word but a pro-hormone. The main source of vitamin D is UV exposure, not dietary intake. Interestingly, there are two forms of vitamin D, vitamin D₂ and vitamin D₃, both of which are metabolised into 25-hydroxyvitamin D (25(OH)D) in the liver, the biomarker of vitamin D status. Vitamin D deficiency is a global public health problem, especially amongst older people and ethnic minority groups. The newest publication from the UK Government's Public Health England Department recommends that vitamin D intake should be 10 µg daily and this recommendation compares well (albeit lower) with other guidelines such as the Institute of Medicine recommendation of 15 µg for those aged 1–70 years and 20 µg for those 70 years or over. Few countries, however, have a specific vitamin D policy to prevent deficiency in populations. Finland leads the way, demonstrating impressive results in reducing population-level vitamin D deficiency through mandatory food fortification programmes. Collaboration between academia, government and industry, including countries from varying latitudes, is essential to identify long-term solutions to the global issue of vitamin D deficiency. This paper provides a narrative review of the evidence related to the role of vitamin D deficiency in health outcomes, outlines controversies regarding setting levels of adequacy, identifies the prevalence of vitamin D deficiency across the globe, and identifies population-level strategies adopted by countries to prevent vitamin D deficiency.

Vitamin D: Deficiency: Global: Future perspectives

Vitamin D is essential for musculoskeletal health, particularly due to its involvement in the regulation of calcium and phosphorus^(1,2). Vitamin D is a unique nutrient in that it is not a vitamin, in the true sense of the word, but actually a pro-hormone, with its main

source being an exposure of skin to UV rays (at 290–315 nm), not dietary intake⁽²⁾. Over the past two decades, there has been mounting scientific and clinical evidence that vitamin D deficiency, defined as 25-hydroxyvitamin D (25(OH)D) concentrations below 25 nmol/l, and

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; RCT, randomised controlled trial.

*Corresponding author: S. A. Lanham-New, email s.lanham-new@surrey.ac.uk

inadequacy, defined as 25(OH)D concentrations below 50 nmol/l, are a major public health issue across all age groups and populations, but especially amongst older people and ethnic minority groups (a group of people who identify with each other, either on the basis of a presumed common genealogy or ancestry or on similarities such as common language, history, society, culture or nation)^(3–7).

The two main forms of vitamin D are naturally present in a few foods and in small quantities, with ergocalciferol (vitamin D₂) from plant and/or fungal sources, such as mushrooms and cholecalciferol (D₃) from animal origin foods such as oily fish, butter, eggs and liver. It is important to appreciate that the vitamin D content in these food sources can vary dramatically between countries due to environmental and agricultural factors and that usual dietary intake of vitamin D-rich foods varies widely between populations⁽²⁾. For instance, the vitamin D content of milk is known to be subjected to seasonal variations, presenting, as expected, higher content in summer months in comparison to wintertime. Several studies have indeed demonstrated a variation in vitamin D concentration in milk, ranging from 0.004 to 0.0014 µg/g fat, across not only different breeds of cattle, but also different locations⁽⁸⁾.

Habitual exposure of the skin to UVB radiation in sunlight (wavelength between 290 and 315 nm) converts the molecule 7-dehydrocholesterol, naturally present in the epidermis, into pre-vitamin D₃^(2,9). Pre-vitamin D₃ is thermodynamically unstable and is thus quickly metabolised to vitamin D₃ through thermal isomerisation. Vitamin D₃ then binds to vitamin-D-binding protein in the bloodstream and is transported to the liver, along with vitamin D absorbed from dietary sources (food and supplements)⁽²⁾. In the liver, these molecules undergo a first hydroxylation by the cytochrome P450 enzyme CYP2R1 (25-hydroxylase) to produce the major circulating form, 25(OH)D⁽²⁾. The molecule 25(OH)D undergoes further hydroxylation in the kidneys, by enzyme CYP27B1 (1α-hydroxylase), resulting in the active form of vitamin D (1α,25(OH)₂D₃), which is the main biological active metabolite⁽²⁾.

Atmospheric conditions, such as cloud, ozone and humidity can cause absorption or deflection of much of the UV rays in sunlight before it reaches the earth's surface^(10,11). Since ozone absorbs UVB radiation, holes in the ozone layer caused by pollution could potentially enhance vitamin D levels of populations due to an increase of UVB radiation passing through these holes. Conversely, air pollution will disperse and absorb UVB radiation, reducing the availability of UVB rays reaching the ground, and consequently reducing the production of vitamin D in the skin.

In the UK, the latest data from the rolling National Diet and Nutrition Survey 2008/2009–2011/2012 provides evidence of an increased risk of vitamin D deficiency in all age/sex groups⁽¹²⁾. Year-round, 7.5% of children aged 1.5–3 years and 24.4% of children aged 11–18 years had serum 25(OH)D concentrations below 25 nmol/l⁽¹²⁾. In adults, 16.9% of men and 24.1% of women, aged 65 years and over, had serum 25(OH)D

concentration below 25 nmol/l, with the prevalence being higher in the wintertime⁽¹²⁾. The recent Scientific Advisory Committee on Nutrition report published in 2016, suggests that the mean intake of vitamin D (from all sources, including supplements) for the general British population is 2–4 µg/d for ages 1.5–64 years and 5 µg/d for adults aged 65 years or over⁽¹³⁾.

Why is vitamin D so important?

The biologically active vitamin D metabolite 1α,25(OH)₂D₃ is involved in bone formation as well as bone maturation^(1,2). Along with parathyroid hormone, it regulates calcium and phosphorus metabolism and enhances the absorption of calcium in the gut and reabsorption of filtered calcium in the kidney^(1,2). Vitamin D is, therefore, essential to help maintain muscle function and an optimal status may help reduce the risk of falls and fractures, particularly in older people. Prolonged and severe vitamin D deficiency may lead to rickets in children and osteomalacia/osteoporosis in adults^(1,2).

Although data is still largely observational, recent evidence also suggests that Vitamin D may have an important role in the pathophysiology of conditions as diverse as inflammatory and heart diseases, type I and II diabetes, various types of cancer and multiple sclerosis^(3,14,15). However, while the essential role of vitamin D in the maintenance of calcium homeostasis and skeletal health is well recognised, there is still a substantial lack of robust evidence, with few well-designed randomised controlled trials (RCT) to elucidate the effect of vitamin D deficiency in other non-skeletal related health outcomes.

The costs associated with vitamin D deficiency in the population are staggering, with a recent National Health Service report estimating that approximately 10 million people in England alone may have low vitamin D status, with treatment costs for vitamin D deficiency calculated to be over £70 million per year for England⁽¹⁶⁾.

Controversy: where to set the cut-point for total 25(OH)D status?

Defining vitamin D deficiency

The most common criteria used for determining the optimal serum 25(OH)D concentration for bone health in adults are the levels that result in (1) suppression of parathyroid hormone secretion; (2) greater bone mineral density; (3) lower rates of bone loss; and (4) decreased incidence of fractures and falls^(17,18). There is still much debate and controversy about which levels of circulating 25(OH)D should be considered to define states of deficiency, insufficiency and sufficiency, and consequently lack of consensus on a definition for optimal vitamin D status. There is, though, general agreement that circulating 25(OH)D concentrations of populations should not decrease below 25 nmol/l in order to preserve bone health^(18,19).



The UK Scientific Advisory Committee on Nutrition classifies vitamin D deficiency as 25(OH)D concentrations below 25 nmol/l⁽¹³⁾, the Institute of Medicine in the US defines insufficiency as 25(OH)D concentrations below 50 nmol/l⁽¹⁹⁾ and the US Endocrine Society proposes 75 nmol/l⁽²⁰⁾ as the minimum level required to prevent detrimental effects to health.

Vitamin D recommendations

Previously in the UK, a reference nutrient intake for vitamin D was set only for population groups deemed to be at high risk of deficiency, assuming that for most people the amount of vitamin D synthesised in the skin by exposure to sunlight was sufficient to reach serum 25(OH)D concentrations ≥ 25 nmol/l throughout the year⁽¹³⁾. However, increasing new evidence proved this not to be the case and the new publication from the UK Government's Public Health England Department recommends a vitamin D daily intake of 10 μ g for the UK population aged 4 years and over, including individuals from minority ethnic groups with darker skin⁽¹³⁾. The Institute of Medicine and the Endocrine Society in the US recommendations are much higher than the UK reference standards, namely an RDA of 15 μ g of vitamin D for individuals aged 1–70 years, increasing to 20 μ g for those older than 70 years^(19,20).

Vitamin D status worldwide

Over the past three decades, the increasing prevalence of inadequate vitamin D status has been reported in different populations worldwide^(3,5,21–23). The majority of the data comes from studies and national surveys in high latitude countries, which is not surprising due to the known challenges of maintaining adequate vitamin D levels in these locations, especially during winter.

A systematic review conducted in 2013, of studies published in the previous 10 years in apparently healthy individuals, reported a remarkably high prevalence of low vitamin D status (in places with available data) in all age groups, but especially in girls and women from the Middle East⁽²⁴⁾. More recently, emerging evidence indicates that low vitamin D concentrations are alarmingly common, also in low latitude countries, despite the abundance of sunlight^(25–27).

In the UK, data from the rolling National Diet and Nutrition Survey programme of 977 individuals showed a mean 25(OH)D level of 44.8 nmol/l in adults aged 19 years or over (Fig. 1). A recent study applying Vitamin D Standardization Program protocols to fourteen studies, combined with four previously standardised studies, from representative European populations, estimated that 40 and 13% of 55 844 individuals had average year-round 25(OH)D concentrations below 50 and 30 nmol/l, respectively. Remarkably, dark-skinned ethnic groups were estimated to have a substantially higher prevalence of levels below 30 nm, ranging from 3- up to 71-fold, compared to white individuals⁽²³⁾.

A multinational study conducted in 2004/2005 that included eighteen countries ranging in latitude from 64° N to 38°S, with 2606 participants, observed that low 25(OH)D concentrations were common among postmenopausal women with osteoporosis, with 64% of this sample having levels below 75 nmol/l. Mean 25(OH)D concentration was 67 (SE 0.75) nmol/l and values ranged from 15 to 607 nmol/l, with regional mean concentrations lowest in the Middle East (51 nmol/l, SE 1.25) and highest in Latin America (74 nmol/l, SE 1.5)⁽⁴⁾.

In the US, data from the National Health and Nutrition Examination Survey population reported a mean 25(OH)D concentration of 65 nmol/l in individuals aged 20–59 years and 62.5 nmol/l within those 60 years or over (Fig. 1). The number of individuals with 25(OH)D concentrations below 75 nmol/l almost doubled from 1994 to 2004, reaching a figure of nearly 75% of the American population by 2004. Within dark-skinned populations (Black, Hispanic and Asians), the prevalence of levels below 75 nmol/l was more than 90% in this cohort⁽²⁸⁾.

A longitudinal cohort study in South Australia (latitude 34°S) with 2413 participants, conducted between 2008 and 2010 (Stage 3 of the Nutrition, Water, Sanitation and Hygiene Study), observed an overall mean serum 25(OH)D of 69.2 nmol/l with 22.7% of the population having concentrations below 50 nmol/l (Fig. 1)⁽²⁹⁾. Another study in Australia in 126 healthy free-living adults (aged 18–87 years) reported a prevalence of 10.2 and 32.3% of individuals with serum 25(OH)D concentrations below 25 and 50 nmol/l, respectively, at the end of winter⁽³⁰⁾. Studies conducted in several different cities in Brazil found a high prevalence of 25(OH)D concentrations below 50 nmol/l, with values as high as 57.3% in the city of São Paulo (latitude 23°S) (Fig. 1), 31.5% in Recife (latitude 8°S), 63.7% in Curitiba (latitude 25°S), with the latter study being conducted in adolescents^(25,31,32).

Strategies for improving vitamin D status in the population

Vitamin D supplementation and/or food fortification have been increasingly discussed worldwide as an effective strategy to tackle low vitamin D levels, particularly since natural food sources are limited in most countries. Vitamin D supplementation has been gaining popularity over recent years, in line with widespread claims of the preventive or therapeutic effects of vitamin D being related to a diverse range of health outcomes. Over the past 15 years, research has been dedicated to determining the best ways of improving vitamin D status of populations, either through the supplemental intake and/or food fortification, and have debated whether vitamin D₂ or D₃ should be the preferred source.

It was previously believed that there were no differences between vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol) in their effectiveness in improving vitamin D concentrations⁽³³⁾. However, a recent randomised, double-blind, placebo-controlled food-fortification

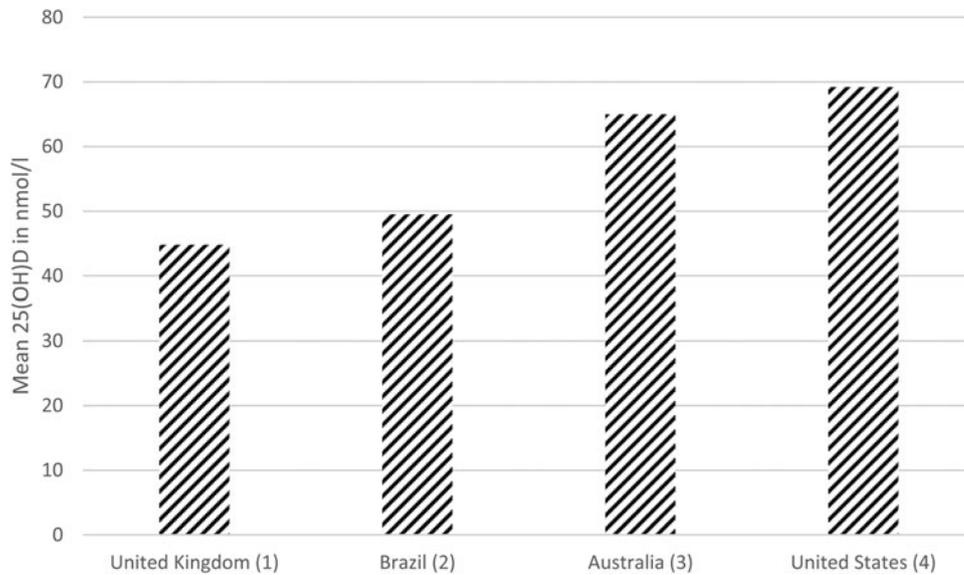


Fig. 1. Mean 25(OH)D (nmol/l) by country.

trial, conducted in 335 healthy South Asian and Caucasian European women (20–64 years) living in Southern England, has demonstrated that vitamin D₃ was more effective than vitamin D₂ in increasing serum 25(OH)D in the wintertime. This suggests that vitamin D₃ might be the better option to optimise vitamin D status within the general population⁽³³⁾. In the trial, study participants received either a placebo, juice supplemented with 15 µg vitamin D₂, biscuit supplemented with 15 µg vitamin D₂, juice supplemented with 15 µg vitamin D₃, or biscuit supplemented with 15 µg vitamin D₃ daily for 12 weeks. Serum 25(OH)D was measured by liquid chromatography–tandem MS at baseline and at weeks 6 and 12 of the study. The findings from this relevant study suggested that both juice and biscuits are viable products for fortification strategies to effectively raise 25(OH)D concentrations.

Regarding strategies to reduce vitamin D deficiency at a population level through mandatory food fortification programmes, Finland has taken the lead by implementing a systematic national fortification programme and has shown this to be an effective approach. A voluntary food fortification policy was introduced in Finland in 2003 advising food manufacturers to add 10 µg/100 g vitamin D to fat spreads and 0.5 µg/100 g to milk products. National reports showed that over a period of 10 years, mean 25(OH)D concentrations increased from 47.6 to 65.4 nmol/l in adults⁽³⁴⁾. Furthermore, the prevalence of 25(OH)D concentrations below 30 nmol/l decreased from 13 to 0.6%. It is worth noting that during the same survey period, reported supplement use also increased, from 11 to 41%⁽³⁴⁾.

In this sense, another key recent project on vitamin D is the European Commission-funded ODIN project (food-based solutions for optimal vitamin D nutrition and health throughout the life cycle), a cross-disciplinary, collaborative project, including thirty partners from nineteen countries. This project aimed to develop evidence-

based solutions to prevent low vitamin D status (25(OH)D <30 nmol/l) using a food-first approach⁽³⁵⁾. The ODIN project is the first internationally standardised dataset of vitamin D status and included almost 56 000 EU residents⁽³⁵⁾. A summary overview published in 2018, reported that across a latitude of regions ranging from 35 to 69°N, 13 and 40% had serum 25(OH)D below 30 and 50 nmol/l, respectively, with the risk of low vitamin D status higher among ethnic minorities⁽³⁵⁾. Within the ODIN project, four dose-response RCT were conducted in Northern Europe, accompanied by a series of food production studies, food-based RCT and dietary modelling experiments. The study collaborators concluded that diverse fortification strategies could safely increase population intakes and prevent low vitamin D status⁽³⁵⁾.

A review discussing the impact of urban living high latitude, urban living and ethnicity on 25(OH)D status, published in 2019, proposes a further discussion on the key role of a multidisciplinary approach on tackling vitamin D deficiency globally⁽³⁶⁾. This multidisciplinary approach would bring together and apply knowledge from dietitians, nutritionists, endocrinologists, psychologists, social scientists, photobiologists, biochemists, engineers, town planners etc. This is crucial to be able to consider all the aspects involved in vitamin D status of populations, with particular relevance for ethnic minority groups⁽³⁶⁾.

Vitamin D supplementation RCT have consistently demonstrated the dependence of the response to vitamin D supplements on initial vitamin D concentrations, although this factor has not been considered in most studies conducted in the past^(37,38). This is an important point to be considered when discussing the benefits of vitamin D supplements, as it might explain the various negative results from vitamin D supplementation studies that have investigated its effect on the incidence and risk of falls and/or fractures. For instance, a recent review



that investigated the proportion of RCT that studied vitamin D deficient populations found that 70% of RCT included participants with baseline 25(OH)D over 40 nmol/l and of the twenty-five large RCT (completed or ongoing), only one investigated a vitamin D deficient population, while three focused on vitamin D insufficient populations. Individuals that are vitamin D sufficient are considered unlikely to benefit from supplementation and could even potentially mask the beneficial effect to those with deficient or insufficient levels⁽³⁹⁾.

Conclusions

This narrative review has demonstrated that vitamin D inadequacy is a global public health issue and that whilst populations at higher latitudes are at greater risk of deficiency, particularly during winter, the concern is now extended to a global level. Targeting intervention strategies specific to each population, country and the ambient setting is important if benefits are to be optimised. Studies specifically designed to investigate the effect of, and requirements for, vitamin D supplements in each country or ethnic group are urgently required to contribute to an improved definition of vitamin D deficiency and more specific and efficient recommendations.

Recommendations for either supplementation or food fortification need to consider the availability of each vitamin D source (dietary intake, either from food or supplements, and endogenous production from sunlight exposure), individual characteristics and lifestyle aspects. Moreover, there are key considerations to be taken into account for the proposal of supplementation and fortification programmes. Firstly, identification of the optimum level of blood concentrations for optimal vitamin D status and recommended daily intake remains controversial, both of which are the bases for determining supplementation or fortification strategies, particularly for programmes implemented at population levels. Moreover, such programmes will also need to be tailored to incorporate culturally and geographically appropriate choices of vehicles for fortification, consider the bioavailability of the fortificant and consider current intake levels for each country and/or ethnic group targeted.

Inter-individual variability in vitamin D status could be reasonably explained by differences in the metabolism of vitamin D. The VDR gene plays an important role in Vitamin D metabolism and polymorphisms in this gene can potentially affect Vitamin D gene expression, meaning that genetic variation could explain the considerable differences in vitamin D levels among population independently of latitude and sunlight exposure⁽⁴⁰⁾. Moreover, some research suggests that some polymorphisms in GC and CYP2R1 genes (involved in vitamin D metabolism) are associated with 25(OH)D concentrations^(40,41). Therefore further research, with robust data from clinical trials, investigating genetic factors influencing vitamin D concentrations could be key in better understanding how to tackle vitamin D deficiency in different populations.

In the near future, climate changes are expected to affect food production and the interactions between environment, agricultural systems and livestock will have a critical impact on future diets and health outcomes. However, the extent and pathways, and potential consequences, are still mainly unclear. Future research will need to consider an approach with an interdisciplinary tactic, linking multiple interactions between environmental changes, agricultural productivity and livestock systems, with a specific focus on vitamin D availability through both food intake and photochemical production in the skin.

Additional research is still required to understand inter-individual variability in the metabolism of vitamin D and differences in response to supplementation, which may be due to genetic polymorphisms. Environmental, cultural and individual factors that influence vitamin D status, including during supplementation, need to be better elucidated. Such factors include adiposity, season, cultural and clothing habits, skin pigmentation, sun exposure and dietary habits also required further investigation to determine what extent each factor affects vitamin D status. Regarding supplementation strategies, particular issues include accessibility to vitamin D supplements and compliance/reluctance with supplement intake.

Most importantly, there is an urgent need for studies that appropriately investigate the response to supplementation or fortification considering initial concentrations of 25(OH)D to interpret the effect of changes between baseline and post-supplementation on the studied outcomes.

Collaborative efforts between academia, government and industry, including countries from several different latitudes, are required to implement effective long-term solutions to this global issue of vitamin D deficiency.

Financial Support

None.

Conflict of Interest

S. L. N. is the Research Director of D3Tex Ltd, which holds the UK and Gulf Corporation Council Patent for the use of UVB transparent material for vitamin D deficiency prevention.

Authorship

M. M. M. and S. L. N. drafted the manuscript; K. C., S. T., H. R. and S. L. N. revised the manuscript. M. M. M., K. C., S. T., H. R. and S. L. N. had primary responsibility for final content. All authors read and approved the final manuscript.

References

1. Reid IR, Bolland MJ & Grey A (2014) Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* **383**, 146–155.
2. DeLuca HF (2004) Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* **80** (6 Suppl), 1689S–1696S.

3. Adams JS & Hewison M (2010) Update in vitamin D. *J Clin Endocrinol Metab* **95**, 471–478.
4. Lips P, Hosking D, Lippuner K *et al.* (2006) The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med* **260**, 245–254.
5. Mithal A, Wahl DA, Bonjour JP *et al.* (2009) Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* **20**, 1807–1820.
6. Lips P, Duong T, Oleksik A *et al.* (2001) A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. *J Clin Endocrinol Metab* **20**, 1807–1820.
7. Darling AL, Hart KH, MacDonald HM *et al.* (2013) Vitamin D deficiency in UK South Asian Women of child-bearing age: a comparative longitudinal investigation with UK Caucasian women. *Osteoporos Int* **24**, 477–488.
8. Weir R, Strain J, Johnston M *et al.* (2017) Environmental and genetic factors influence the vitamin D content of cows' milk. *Proc Nutr Soc* **76**, 76–82.
9. Webb AR, Kift R, Durkin MT *et al.* (2010) The role of sunlight exposure in determining the vitamin D status of the U. K. white adult population. *Br J Dermatol* **163**, 1050–1055.
10. Hosseinpanah F, Pour SH, Heibatollahi M *et al.* (2010) The effects of air pollution on vitamin D status in healthy women: a cross sectional study. *BMC Public Health* **10**, 519.
11. Raiten DJ & Picciano MF (2004) Vitamin D and health in the 21st century: bone and beyond. Executive summary. *Am J Clin Nutr* **80**(6 Suppl), 1673S–1677S.
12. Beverley B, Lennox A, Prentice A *et al.* (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009–2011/2012). London: Crown Copyr.
13. Scientific Advisory Committee on Nutrition. (2016) Vitamin D and Health. Available at <https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report>
14. Theodoratou E, Tzoulaki I, Zgaga L *et al.* (2014) Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *Br Med J* **348**, 1–19.
15. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* **357**, 266–281.
16. Scholes S, Faulding S & Mindell J (2013) *Use of prescribed medicines*. Vol 1, Chapter 5 pp. 1–27. Leeds: Health and Social Care Information Centre. HSE.
17. Vieth R, Ladak Y & Walfish PG (2003) Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* **88**, 185–191.
18. Bouillon R, Van Schoor NM, Gielen E *et al.* (2013) Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. *J Clin Endocrinol Metab* **98**, 1283–1304.
19. Ross AC, Manson JE, Abrams SA *et al.* (2011) The 2011 dietary reference intakes for calcium and vitamin D: what dietetics practitioners need to know. *J Am Diet Assoc* **111**, 524–527.
20. Holick MF, Binkley NC, Bischoff-Ferrari HA *et al.* (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* **96**, 1911–1930.
21. Hossein-nezhad A, Holick MF, Heaney R *et al.* (2013) Vitamin D for health: a global perspective. *Mayo Clin Proc* **88**, 720–755.
22. Prentice A (2008) Vitamin D deficiency: a global perspective. *Nutr Rev* **66**, S153–S164.
23. Cashman KD, Dowling KG, Škrabáková Z *et al.* (2016) Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* **103**, 1033–1044.
24. Palacios C & Gonzalez L (2014) Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol* **144**, 138–145.
25. Mendes MM, Hart KH, Botelho PB *et al.* (2018) Vitamin D status in the tropics: is sunlight exposure the main determinant? *Nutr Bull* **43**, 428–434.
26. Binkley N, Novotny R, Krueger D *et al.* (2007) Low vitamin D status despite abundant sun exposure. *J Clin Endocrinol Metab* **92**, 2130–2135.
27. Wacker M & Holick MF (2013) Sunlight and vitamin D: a global perspective for health. *Dermatoendocrinol* **5**, 51–108.
28. Ginde AA, Liu MC & Camargo CA (2009) Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch Intern Med* **169**, 626–632.
29. Gill TK, Hill CL, Shanahan EM *et al.* (2014) Vitamin D levels in an Australian population. *BMC Public Health* **14**, 1001–1006.
30. Kimlin M, Harrison S, Nowak M *et al.* (2007) Does a high UV environment ensure adequate vitamin D status? *J Photochem Photobiol B Biol* **89**, 139–147.
31. Premaor MO & Furlanetto TW (2006) Vitamin D deficiency in adults: to better understand a new presentation of an old disease. *Arq Bras Endocrinol Metab* **50**, 25–37.
32. Saraiva GL, Cendoroglo MS, Ramos LR *et al.* (2007) Prevalence of vitamin D deficiency, insufficiency and secondary hyperparathyroidism in the elderly inpatients and living in the community of the city of São Paulo, Brazil. *Arq Bras Endocrinol Metab* **51**, 437–442.
33. Tripkovic L, Wilson LR, Hart K *et al.* (2017) Daily supplementation with 15 µg vitamin D₂ compared with vitamin D₃ to increase wintertime 25-hydroxyvitamin D status in healthy South Asian and white European women: a 12-wk randomized, placebo-controlled food-fortification trial. *Am J Clin Nutr* **106**, 481–449.
34. Jaaskelainen T, Itkonen ST, Lundqvist A *et al.* (2017) The positive impact of general vitamin D food fortification policy on vitamin D status in a representative adult Finnish population: evidence from an 11-y follow-up based on standardized 25-hydroxyvitamin D data. *Am J Clin Nutr* **105**, 1512–1520.
35. Kiely M & Cashman KD (2018) Summary outcomes of the ODIN project on food fortification for vitamin D deficiency prevention. *Int J Environ Res Public Health* **15**, 2342.
36. Mendes MM, Darling A, Hart KH *et al.* (2019) Impact of high latitude, urban living and ethnicity on 25-hydroxyvitamin D status: a need for multidisciplinary action? *J Steroid Biochem Mol Biol* **188**, 95–102.
37. Stokes CS & Lammert F (2016) Vitamin D supplementation: less controversy, more guidance needed. *Fl000Res* **5**, 1–18.
38. Heaney RP (2012) Vitamin D – baseline status and effective dose. *N Engl J Med* **367**, 77–78.
39. Bolland MJ, Grey A & Avenell A (2018) Assessment of research waste part 2: wrong study populations- an exemplar of baseline vitamin D status of participants in trials of vitamin D supplementation. *BMC Med Res Methodol* **18**, 101–105.
40. Valdivielso JM & Fernandez E (2006) Vitamin D receptor polymorphisms and diseases. *Clin Chim Acta* **371**, 1–12.
41. Hunter D, De Lange M, Snieder H *et al.* (2001) Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. *J Bone Miner Res* **16**, 371–378.

