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THE GLOBAL EPIDEMIOLOGY OF VITAMIN D STATUS

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Abstract: *Objective:* Vitamin D is an important component of calcium and phosphate metabolism, ensuring, with PTH and FGF23, adequate serum concentrations of these two analytes for optimal cell function and bone mineralisation. Despite a surge of interest in vitamin D physiology over the last decade, a single threshold for deficiency remains uncertain in functional terms, and it is clear that correlation between serum concentration of 25(OH)-vitamin D and disease outcomes is very poor at the level of the individual. In this review, we describe the physiology of vitamin D, its potential associations with disease, and relate, in detail, the epidemiology of vitamin D status across populations worldwide. *Design:* Through a comprehensive literature review, we identified relevant studies from Europe, the Middle East, Africa, Asia, North America, Latin America, and Oceania. *Results:* Although rickets and osteomalacia are established potential consequences of vitamin D deficiency, evidence for low levels of vitamin D as a cause of the multitude of other health outcomes with which they have been linked is lacking. We observed geographical differences in serum 25(OH)-vitamin D concentrations, which may be partly, but not wholly, explained by factors such as sunlight exposure, skin pigmentation, skin coverage, dietary choices, supplements, adiposity, malabsorption, disease, demographics and lifestyle. *Conclusion:* We conclude that low serum concentrations of 25(OH)-vitamin D appear common across the globe; the relevance of this observation to human health remains to be elucidated.

Key words: Vitamin D, epidemiology, global, physiology.

Introduction

Vitamin D is a fat soluble vitamin involved in bone mineralization.. It is unique in that it can not only be ingested in the diet as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) but can also be synthesized in the skin when sunlight exposure is adequate. Despite dual mechanisms of attainment, vitamin D deficiency is not uncommon in many countries throughout the world and can lead to disease. The geographical variation in vitamin D is significant. Particular areas at risk include South Asia and the Middle East. Several factors can affect vitamin D levels on a population and individual basis. Of particular importance are sunlight exposure and modulators of this, such as clothing, sunscreen usage, institutionalization, and latitude. Dietary, lifestyle, and demographic aspects also play a role; specifically, more obese individuals tend to have lower vitamin D levels. This review describes the importance of vitamin D for bone and muscle health and highlights the uncertainties regarding effects on non-musculoskeletal outcomes. It also explores the possible determinants of the geographical variation in vitamin D status which might inform the development and implementation of targeted interventions and future public health policies.

The importance of Vitamin D

Vitamin D has many functions in humans including calcium and phosphate homeostasis. Once absorbed from the gut or produced in the skin, it is then hydroxylated in the liver into 25-hydroxyvitamin D (25(OH)D) and then in the kidney and in extrarenal tissues to 1,25-dihydroxyvitamin D (1,25(OH)2D) and 24,25-dihydroxyvitamin D (24,25(OH)2D). Thereafter, the active metabolite can enter cells and bind to either the vitamin D-receptor or to a responsive gene, such as that of calcium binding protein, and thus assist in calcium absorption (1). Vitamin D also regulates parathyroid hormone (PTH) levels which in turn reduces bone loss (2). Severe vitamin D deficiency causes new bone, the osteoid, not to be mineralized. This can lead to rickets in

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children and osteomalacia in adults.

Vitamin D deficiency has been associated with lower BMD in individuals without frank osteomalacia (3, 4); however a recent meta-analysis showed only a small effect of vitamin D supplementation on femoral neck BMD and no significant effect at other sites (5). This is consistent with studies of vitamin D and fracture which have shown that although there two are associated (6), intervention trials tend to fail to show a benefit of supplementation (7, 8).

Vitamin D acts on muscles through genomic and non-genomic pathways. The genomic pathway involves activation of the 1,25(OH)2D nuclear receptors resulting in messenger RNA production and the synthesis of various proteins (9, 10). The non-genomic pathway acts through a secondary messenger in the cell or by activating protein kinase C (11, 12). It is not surprising therefore that in cases of severe vitamin D deficiency causing rickets or osteomalacia, a myopathy can develop(13-15). When severe, it presents with marked proximal muscle weakness with a predilection for the lower limbs (13).

In contrast, observational studies at the population level have failed to show consistent associations between vitamin D and muscle strength. Although some studies have shown crude associations with leg strength (16, 17) and grip strength (18), these relationships are completely attenuated after adjustment for potential covariates. Furthermore, studies investigating the effects of vitamin D supplementation on muscle function have also found inconsistent results (15).

Recently vitamin D has also been linked with several other conditions. Associations have been shown with colorectal cancer (19), diabetes mellitus (20), infection (21), multiple sclerosis, cardiovascular disease, breast cancer, autoimmunity and allergy (22), depression (23), and postural instability (24). These relationships are found mainly in observational studies which are open to many interpretations. For example, there is the possibility of confounding through several associated factors, such as physical activity, and reverse causality, when the disease may lead to a greater time spent indoors resulting in reduced sunlight exposure. Furthermore, there is evidence that vitamin D levels decrease during an inflammatory response which might partly explain associations with inflammatory conditions (25, 26). Publication bias is also a significant issue as there is a reluctance to publish negative findings which leads to a predominance of positive associations in the literature. It is therefore important to exercise caution when examining the evidence of such relationships. However, the absence of large randomised controlled trial evidence in these areas by no means excludes such causative relationships. Furthermore, bearing these provisos in mind, recently systematic reviews have been carried out assessing multiple potential outcomes. Amongst their findings is emerging evidence of a direct role for vitamin D in regulation of immune function, both innate and adaptive (27, 28).

The assessment of Vitamin D status is also a contentious issue. It is usually best measured by assessment of serum 25(OH)D (29, 30), however, there is disagreement about what level constitutes deficiency. Although levels below 25 nmol/l have been associated with bone metabolic disorders (31), using post-mortem specimens, a recent study found that a large proportion of those individuals with serum levels below 25 nmol/l did not have abnormal bone histology and several with higher levels did (32). Other studies have assessed relationships between 25(OH)D and parathyroid hormone (PTH) levels in relation to bone health, however, it was found that the 25(OH)D level at which PTH reached a plateau varied considerably between 25 nmol/l and 125 nmol/l (33). At present, it is therefore not possible to accurately determine an individual's bone health based on a vitamin D level alone and thus debate on the threshold for deficiency continues. The lack of consensus on a definition of vitamin D deficiency has significantly affected the prevalence rates reported by various studies in different geographical locations. It is important that this is taken into consideration when reviewing the findings of such studies.

Factors affecting Vitamin D levels

When assessing factors that affect Vitamin D levels, it is logical to start with those that influence acquisition; namely skin synthesis and dietary intake. The effectiveness of vitamin D production in the skin is dependent on the intensity of sunlight to which it is exposed. Consequently, in winter vitamin D synthesis may slow and, in some cooler climates, even cease completely. Intuitively, it would be expected that vitamin D levels would be higher closer to the equator where sunlight intensity is greater. However, some studies have shown the contrary, with levels higher in northern than southern Europe (34, 31). This can partly be explained by skin pigmentation. Populations in warmer climates tend to have greater skin pigmentation which can affect their ability to synthesis vitamin D. Migration can therefore have a significant impact. White women living in the south of England had median 25(OH)D levels of 62.5 nmol/l in the summer and 39.9 nmol/l in the winter. In Asian women living in the same geographical location the median levels were considerably less at 24.9 nmol/l and 16.9 nmol/l respectively (35). Furthermore, synthesis only occurs if adequate skin is exposed. In some countries cultural factors influence style of dress with effects on skin vitamin D conversion (36, 37). It has also been shown that the application of sunscreen has a similar effect (38, 39), although a study from Australia found that regular usage did not cause vitamin D levels to fall outside the normal reference range (40).

Vitamin D is additionally obtained from the diet although the contribution to total levels tends to be small in comparison to skin synthesis. It can be ingested as ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3). Ergocalciferol is obtained from plant sources such as mushrooms, whereas cholecalciferol is contained mainly in oily fish and egg yolk. Several supplements are also available although due to a lack of stringent regulation, there may be discrepancies between the label value and the true levels contained within the formulation (41). Cod liver oil contains high levels of Vitamin D and as is taken commonly in Scandinavia. This can partly explain the higher serum levels found in northern Europe (42). In many regions, including Canada and America (43), fortification of foods, including milk and cereals, with vitamin D is routine. There is however significant geographic variation and in some countries, particularly in the developing world, it does not occur at all. This may have significant effects on overall population levels.

Diet is also important in the maintenance of a healthy weight. Obesity is becoming more prevalent and has effects on vitamin D bioavailability. Overall obese people have a lower 25(OH)D level than those of normal weight (44, 45). Vitamin D is a fat-soluble vitamin and as such it can move into adipose tissue (46) which can lead to a drop in serum levels. This has also been associated with increased parathyroid hormone levels (47).

Vitamin D levels have a significant hereditable component suggesting a possible role for genetics in the etiology of insufficiency. Results from a genome-wide association study have confirmed that variants near genes involved in dihydrocholesterol metabolism, cholesterol synthesis, hydroxylation, and vitamin D transport can affect vitamin D status (48).

Demographic factors have also long been a source of interest in the epidemiology of vitamin D deficiency. Several reviews have shown significant differences in vitamin D levels with age (34, 49, 50). In the Middle East and Africa, children tend to have higher vitamin D levels than adults (51). This may reflect the greater amount of time they spend outside compared to other age groups. Recently, however, it has been shown that these differences are reducing which may be the result of a change in lifestyle in developed countries, with younger people spending a greater amount of time indoors (e.g. watching television and playing computer games) (52). The very elderly population has been found to be a group a particular risk of vitamin D deficiency. This is in part due to them producing less cholecalciferol with the same exposure to UVB light as younger adults but also to less time spent outside (53). The latter is particularly true of those institutionalized elderly (34, 42).

Women have often been found to have lower levels of 25(OH)D levels than men (42, 49, 50). Potential causes include differences in body fat composition, resulting in greater fat storage of vitamin D in women. Lower levels in women are a particular concern around the time of childbearing as the vitamin D status of a women during pregnancy is an important factor in the determination of the vitamin D status in her child (54).

At the population level the above factors can have significant effects on rates of vitamin D deficiency. For example, populations with greater numbers of older people will have an increased risk. At the individual level, genetic factors will also play a role. Many diseases reduce vitamin D levels, mainly by affecting absorption and metabolism. Malabsorption can be a primary intestinal syndrome, such as coeliac disease, Crohn's disease, Whipple's disease, or short bowel syndrome. Fat malabsorption is also problematic as vitamin D is a fat soluble vitamin. Hepatic and renal disease are well known to disrupt vitamin D metabolism and several drugs and inherited disorders have also been implicated. Independently, however, these conditions are relatively rare and are not known to have significant effects on the epidemiology of vitamin D deficiency at the population level.

In summary, vitamin D status is largely determined by the level of skin synthesis and dietary intake. Vitamin D synthesized in the skin is dependent on UVB exposure and therefore influenced by latitude, skin pigmentation, skin coverage, time spent outdoors, and use of sunscreen. Dietary vitamin D can be obtained throughs naturally occurring ergocalciferol or cholecalciferol in foodstuffs, dietary supplementation, or food fortification. A number of other factors such as adiposity, genetics, age, sex, and specific diseases also contribute to variation.

Geographical Variation in Vitamin D Levels

Vitamin D status has been assessed in numerous studies worldwide (table 1). However, data from Africa and Latin America are currently scarce. It should be noted that studies are not always directly comparable, since there are several different assays and inter-laboratory variation is still considerable. For the purposes of this review the threshold has been set at a serum level of 50nmol/l 25(OH)D and Vitamin D deficiency is described as a 25(OH)D level of less than 25nmol/l unless otherwise stated as these are the most commonly used definitions. In 2010 the Institute of Medicine report considered data from two large systematic reviews to access the relationship between vitamin D, PTH and calcium absorption. They developed a schematic representation of the relationship between vitamin D status as measured by serum 25OHD and integrated bone health outcomes and suggested that a serum 25OHD of 40nmol/L is sufficient to meet the vitamin D requirement for bone health in half the population, while 50nmol/L would be sufficient for 97.5% of the population. They

Table 1
Studies describing vitamin D levels and participant demographics

	Country	Age (years)	Sex	Number of Participants	Mean 25(OH) Vitamin D	Additional information
Europe						
Melhus (58)	Sweden	71	M	1194	68.7	
Chapuy (59)	France	35-65	M+F	1569	61	
Semba (60)	Italy	65+	M+F	1006	39.9	
Burnand (61)	Switzerland	25-74	M+F	3276	50	
Pilz (62)	Austria	70+	F	961	17.5	
Krieg (63)	Switzerland	70+	M+F	367	23.2	Female
					25.5	Male
Tolppanen (64)	UK	9.9	M+F	7565	60.7	
Das (66)	UK	14.7-16.6	F	37	14.8	Non-white
					37.3	White
Serhan (67)	UK	18+	M+F asian	98	16.5	
Van der Meer (68)	Netherlands	18-65	M+F	613	27*	Turkish
					30*	Moroccan
					38*	Other non Western
Van der Meer (69)	Netherlands	child bearing age	F pregnant	358	15.2*	Turkish
					20.1	Moroccan
					26.3	Other non Western
					52.7	Western
Middle East/Africa						
Alagol (71)	Turkey	14-44	F	48	56	Non-veiled
					31.9	Hands/face
					uncovered	
					9	Fully veiled
Ardawi (72)	Saudi Arabia	20-74	M	834	29	
Ardawi (73)	Saudi Arabia	20-79	F	1172	35.8	
Andiran (74)	Turkey	0-16	M+F	440	85	0-5 years
					51.2	5-10 years
					46.7	10-16 years
Mansour (75)	Saudi Arabia	4-15	M+F	510	32.6	
Aspray (76)	Gambia	25+	F	112	91.3	
Njemini (77)	Cameroon	60+	M+F	152	52.7	
Luxwolda (78)	Tanzania	>16	M+F	88	106.8	Non-pregnant
				139	138.5	Pregnant
Allali (79)	Morocco	24-77	F	415	42.4	
Meddeb (80)	Tunisia	20-60	F	261	40.3	
Asia						
Arya (81)	India	16-65	M+F	92	30	
Marwaha (82)	India	>16	F	541	23.2	Pregnant
Puri (83)	India	6-18	F	3127	31.9	
Sachan (84)	Northern India	>16	F	207	34.9	Pregnant
Harinarayan (85)	India	<18	M+F	117	21	
Agarwal (86)	India	9-24 months	M+F	34	30.9	High pollution
					67.6	Low pollution
Islam (87)	Bangledesh	16-40	F	189	36.7	Low socio-economic class
					43.5	High socio-economic class
Atiq (89)	Pakistan	6-11 months	F adult	62	39.8	Lower class nursing mother
					26.5	Higher class nursing mother
			M+F infant		52.3	Lower class breastfed infant
					22.5	Higher class breastfed infant
Ho Pham (90)	Vietnam	18-87	M+F	637	91.8	Men
					75.1	Women
Chailurkit (91)	Thailand	15-98	M+F	2641	64.8	Bangkok
					79.5	Central

					81.7	Northern
					78.3	Southern
Rahman (92)	Malaysia	50-65	F	101	44.4	Malay
					68.8	Chinese
Chen (94)	Central China	40-69	M+F	2018	31.7	
Foo (95)	China	15	F	301	34	
Lander (96)	Mongolia	6-36 months	M+F	98	24.1	
Suzuki (98)	Japan	65-92	M+F	2957	60.4	Women
					70.1	Men
North America						
Looker (99)	USA	all ages	M+F	20,289	76.4	1-5 years
					70	6-11 years
					63.9	12-19 years
					62	20-49 years
					59.2	50-60 years
					57.5	>70 years
Langlois (100)	Canada	6-79	M+F	5306	67.7	
Berger (101)	Canada	>25	F	1896	70.7	Women treated for osteoporosis
					69.9	Men treated for osteoporosis
South America						
Lips (102)	Mexico	>45	F	149	65.4	
	Brazil			151	81.3	
	Chile			115	75.4	
Oliveri (103)	Argentina	>65	M+F	389	35.4	South
					44.7	Mid
					51.7	North
Oceania						
Chen (104)	Australia	>60	M+F	1280	25.8	
Brock (105)	Australia	>18	M+F	377	44	Living at home
					36	Living in hostel
					33	Living in nursing home
Ding (106)	Tasmania		F	1002	52.8	
Rockell (107)	New Zealand	>15	M+F	3008	50	
Rockell (108)	New Zealand	5-14	M+F	1585	43	Maori

concluded that people are at risk of deficiency when serum 25OHD is < 30 nmol/L, that some people are potentially at risk of inadequacy when serum 25OHD is 30–50 nmol/L, and that over 50nmol/l is sufficient for almost all of the population (55).

Europe

The region in which the largest number of studies have been conducted is Europe. Within Europe there is high variation in serum 25(OH)D levels. One of the earliest reviews, the Euronut-Seneca study, compared the vitamin D status of 824 elderly people living in 11 European countries (56). Forty seven percent of the women and 36% of the men had serum levels <30nmol/l with vitamin D levels decreasing with age. Vitamin D concentrations were higher in the Northern European and Scandinavian countries compared to Southern Europe (56). As described above, this strong correlation between latitude and serum vitamin D was unexpected because ultraviolet irradiation is higher in southern Europe. A similar geographical correlation was observed between serum 25(OH)D and latitude in the MORE study which looked at the effect of raloxefene or placebo in osteoporotic women (57). The Uppsala Longitudinal Study of Adult Men in Sweden showed that despite no cutaneous synthesis of vitamin D during the winter months at this latitude only 5% had serum levels <40nmol/l (58). It is unclear whether this is due to increased dietary intake, such as cod liver oil consumption, or whether there is a genetic adaptation to ultraviolet light in this population. In France , the Suvimax study of 1529 men and women aged 35-65 years, showed a correlation between latitude and serum 25(OH)D, with mean levels lower (43nmol/l) in the north and higher (94nmol/l) in the south west (59). An Italian study based in Chianti, Tuscany studied 1006 men and women >65 years, 25% of their participants had a 25(OH)D <26nmol/l. Lower serum 25(OH)D was found in the more elderly, women, non smokers, those who were physically inactive or who had poorer health, and those with a lower level of education (60). A large Swiss study of 3276 men and women aged 25-74 years showed lower serum 25(OH)D levels was again associated with older age (>65years), less than 30 minutes outside daily, winter season and poor vitamin D nutritional intake, represented by absent margarine or butter intake and poor dairy consumption. Median levels in this population were 46nmol/l with only 6% having serum levels <20nmol/l (61).

A number of studies have confirmed that vitamin D deficiency is particularly common in the institutionalized elderly. A recent study in Austria showed that the median 25(OH)D serum level was 17.5(13.7-25.5) nmol/l. Only 6% of this population had a level >50nmol/l (62). Higher levels of mortality were associated with lower serum levels. This similarly compares to a Swiss study of 19 nursing homes in which 41.9% of the women and 31.4% of the men had a serum 25(OH)D level below 15.5nmol/l compared to 2.5% of the controls (63).

Vitamin D insufficiency is common amongst children. The ALSPAC birth cohort in the UK assessed 7560 children aged 9.9 years. 1.6% had serum 25(OH)D levels <25nmol/l, 29% had levels <45nmol/l and 75% had serum levels <75nmol/l(64). Less time spent outdoors, lower socioeconomic status, more advanced pubertal stage, non-white ethnicity and female gender were all associated with vitamin D deficiency (64). Similar results were seen in children referred to an orthopaedic clinic in Southampton, UK. 32% had vitamin D insufficiency with 25(OH)D levels <50 nmol/L and 8% had vitamin D deficiency (25(OH)D <25nmol/l) (65).

As expected, immigrants from Asian countries have a much higher risk for severe vitamin D deficiency. Serum 25(OH)D levels from a small healthy cohort of non-white, mainly south Asian girls in Manchester UK showed a mean serum 25(OH)D of 14.8nmol/l indicating severe vitamin D deficiency. 73% of the girls studied had levels <30nmol/l (66). Among the Indo-Asian population attending a rheumatology clinic in Wolverhampton UK, 78% had a 25(OH)D level <20nmol/l, compared to 58% of the control population (67). A study from the Netherlands looked at 613 adults over 18 years in general practice (68). The prevalence of vitamin D deficiency was higher in Turkish (41.3%), Moroccan (36.5%), Surinam South Asian (51.4%), Surinam Creole (45.3%), sub-Saharan African (19.3%) and other adults (29.1%) compared to the indigenous Dutch (5.9%). Modifiable determinants included consumption of fatty fish, use of vitamin D supplements, area of uncovered skin and preference for sun (68). A similar study of non western pregnant women within midwife practices in the Hague measured the vitamin D concentrations of 358 women. Mean serum 25(OH)D concentrations were 15.2nmol/l in the Turkish, 20.1 nmol/l in Moroccan and 52.7nmol/l in the Dutch. Overall more than 80% of the Moroccan and Turkish immigrants were deficient (25(OH)D <25nmol/l) compared to 6% of the Dutch with 22% of the Turkish women below detection point (69).

It can be concluded that vitamin D deficiency is common within Europe, specific at risk groups include non-western immigrants and the institutionalized elderly. The role of latitude in vitamin D status is not completely clear and higher serum levels in some Scandinavian studies may be due to diet or a genetic adaptation.

Middle East

Vitamin D deficiency is very common in this area of the world despite high levels of sunshine and UV radiation throughout the year. Studies in both Turkey and Jordan showed a strong relationship with clothing which in part may explain the low serum levels of 25(OH)D seen in these parts. A study of 22 men and 124 women in Jordan found that overall 59.9% of participants had a serum 25(OH)D level <30nmol/l. Serum 25(OH)D was highest in women wearing western clothing and levels decreased to be lowest in traditional women wearing hijab and completely veiled women wearing niqab. Only 4% of this study group had serum levels >50nmol/l, these were seen exclusively in men and the women wearing western clothing (70). A similar finding was seen in Turkish women, who wore three different dress types, serum 25(OH)D levels averaged 56nmol/l in the western dressed group, 31.9 nmol/l in the second group wearing a hijab with uncovered face and hands, and only 9nmol/l in the completed covered group suggesting that these women need supplementation due to lack of sunlight exposure (71). In a cross sectional study of 834 men living in the Jeddah region of Saudi Arabia, 87.8% had a serum 25(OH)D level <50nmol/l, with an overall mean 29nmol/l (72). A similar study of 1172 Saudi Arabian women from Jeddah found 80% had serum 25(OH)D levels <50nmol/l and about 10% were severely deficient with levels <12.5nmol/l. There was no significant difference in the serum levels seen between fully veiled women and those who exposed their face and hands. The main risk factors for vitamin D deficiency were obesity, poor sun exposure, inadequate vitamin D supplementation, high waist to hip ratio and age (73).

Studies in children show a varying incidence of vitamin D deficiency. In a recent study of 440 children aged 0-16 years attending a paediatric clinic in Ankara Turkey, 40% of the children had 25(OH)D levels <50nmol/l, of which 110 had levels <37.5nmol/l. Children with deficiency were significantly older than those with normal levels (mean age 10.3 vs 5.6 years) (74). These results are probably related to the introduction of vitamin D supplementation to all newborns since 2005 throughout infancy at no financial cost. In a Saudi Arabian study of 510 children aged 4-15 years, vitamin D deficiency was highly prevalent. The mean concentration of 25(OH)D was 32.6nmol/l, only 13.7% had a level >50nmol/l and 27.5% had severe deficiency (25(OH)D <17.5nmol/l). Within this study population, the Saudis and Yemenis had a higher incidence of deficiency than the Egyptians and other nationalities (75).

Africa

Whilst there is a plethora of vitamin D data from elsewhere in the world, the number of studies originating from Africa is limited. However, those that have been completed show much higher baseline levels of serum 25(OH)D compared to the rest of the world although there is significant variation within the continent (31). In a study of 113 Gambian women aged 45-80 years, the mean 25(OH)D level was 91.2nmol/l and there was no association with age(76). In Cameroon, a study found that in 152 men and women over 60 years the mean 25(OH)D concentration was 52.7nmol/l (77). A study assessing vitamin D status in the indigenous populations of Tanzania showed that the mean 25(OH)D was 106.8nmol/l in non-pregnant women and 138.5nmol/l in pregnant women. None of the subjects had levels below 25nmol/l. Women of Maasai and Hadzabe origin had higher 25(OH)D compared to women of Sengerema origin who cover all but their lower arms and faces (78). Thus, sunlight exposure rather than dietary intake appeared to be the principal determinant. There was a linear relationship between maternal and infant 25(OH)D (24). In a study of 200 black South Africans >65 years the mean serum 25(OH)D was 37nmol/l whilst 17% had a level <25nmol/l . Vitamin D levels appear to be slightly lower in North African countries. Investigators in Morocco studied 415 women aged 24-77 years. The mean serum 25(OH)D was 45.9nmol/l and 4% had a serum levels of <10nmol/l. Veiling, age and a lack of sun exposure all contributed to an increase risk of insufficiency (79). Lower serum 25(OH)D levels were seen in veiled women in Tunisia compared to the non veiled women (35.7vs 42.5). In this population overall, 47.6% of women had a serum 25(OH)D <37.5nmol/l. The incidence of vitamin D deficiency increased with age (80).

Asia

It has previously been noted that Asian immigrants to higher latitude countries have a high incidence of vitamin D deficiency. It was thought that this was in part due to their skin not being adapted to cope with low levels of UV radiation. However, studies across different parts of Asia show a widespread prevalence of vitamin D insufficiency within both sexes and all age groups.

In India low serum levels of 25(OH)D are commonly seen. A study of 92 staff in an urban North Indian hospital found the mean serum 25(OH)D levels was 30nmol/l and 19 of these subjects had serum levels <12.5nmol/l (81). In healthy pregnant women in Delhi the mean serum 25(OH)D was 23.2 nmol/l. Serum levels of 25(OH)D <50nmol/l were observed in 96.3% of the subjects (82). In healthy school children aged 6-18 years the mean serum 25(OH)D level was 31.9nmol/l with 29.9% having a level <22.4nmol/l. Lower serum levels were seen in children of higher socioeconomic class probably reflecting the increased BMI in this group (83). A study from northern Indian found low serum 25(OH)D (<55nmol/l) to be equally prevalent in rural (84.3)and urban(83.6)pregnant subjects, the mean level in his population was 34.9nmol/l (84). Some studies however found urban subjects more likely to be deficient (83, 85). Air pollution may play a role, in a study from Delhi infants aged 9-24 months had significantly lower serum 25 (OH)D in areas of high atmospheric pollution compared to infants from ales polluted part of the study (mean serum 25(OH)D 30.9nmol/l vs 67.6nmol/l). Haze scores were lower in the polluted area indicating less solar UVB reaching the ground (86).

In Bangladesh serum 25(OH)D <37.7nmol/l was seen in 50% of those in low income groups (median 36.7nmol/l) compared to 38% of high income groups (median (43.5nmol/L). Prevalence of low 25(OH)D increased in lactating women (87). Vitamin D insufficiency (<40nmol/l) was common (80%) regardless of age, lifestyle and clothing in study from Dhaka (88). Similar data is seen in Pakistan where in a study of healthy breastfed infants and their mothers vitamin D deficiency (25(OH)D <25nmol/L) was found in 55% of infants and 45% of mothers (89).

Vitamin D status in South East Asia is generally better. In a cross sectional study from Vietnam the mean 25(OH)D level was 91.8nmol/l in men and 75.1nmol/l in women (90). Across Thailand 2641 adults aged 15-98 years were selected from the Thai 4th National Health Examination Survey (2008-9) cohort. Subjects residing in Bangkok, had lower mean 25(OH)D levels than other parts of the country (Bangkok 64.8nmol/l, central 79.5nmol/l, northern 81.7nmol/l, north-eastern 82.2nmol/l and southern regions 78.3nmol/l) (91). Within each region subjects living in the more urban areas had lower circulating 25(OH)D (91), this may reflect less time spent outdoors or atmospheric pollution. In Malaysia, a country with similar latitude, levels of 25(OH)D were significantly lower in the Malay women (44.4nmol/L) compared to the Chinese women (68.8nmol/L). 71% of the Malay women had levels in the insufficient range (25-50nmol/l) compared to 11% of the Chinese women (92). Malay women commonly wear traditional dress with only face and hands exposed. They have less sun exposure compared to the Chinese population.

Vitamin D insufficiency is highly prevalent in China and Mongolia where rickets is still seen commonly (93). A study in Linxian, a semi-arid mountainous area in central China, showed a mean 25(OH)D of 31.7nmol and 25% of the population had a serum level <19.5nmol/l (94). In a study of 301 healthy adolescent girls from Beijing, 57.8% had vitamin D insufficiency (serum

25(OH)D <50nmol/l) , whilst 31.2% had levels <25nmol/l. Adequate vitamin D status was associated with higher bone mass and higher grip strength in these adolescents (95). In Mongolia, a study of children aged 6-36 months found 61% of then to be deficient (25(OH)D <25nmol/l) (96).

Vitamin D status in Japan is relatively better than other regions of Asia, this thought to be due to high levels of fish consumption (97). In a cross sectional study of the elderly (65-92 years) in Japan mean serum 25(OH)D levels were significantly lower in the women compared to men (60.4nmol/l vs. 71.1nmol/l) serum levels decreased with age in females but not the male population. Only 5% of men had levels in the insufficient range (<50nml/l) this compared to 17.7% in women (98).

North America

In the USA vitamin D status has been assessed using data from the National Health and Nutrition Examination Surveys (NHANES) which is a nationally representative, non-institutionalized sample of the population within the United States. In the 2000-2004 survey a representative sample was collected each year to give a total of 20,289 participants across all ages and ethnic groups (99). Mean levels of 25(OH)D were highest in the youngest group (children aged 1-5 years mean 76.4nmol/l) then fell in each subsequent age category (6-11 years ,70nmol/l; 12-19 years, 63.9nmol/l; 20-49, 62nmol/l; 50-60, 59.2nmol/l and >70, 57.5nmol/l). Serum levels <37.5nmol/l were present in only 3% of those aged 1-5 years and 19% of adults aged 20-49 years. Overall mean levels were slightly higher in men than women (62.9nmol/l vs. 61.5nmol/l). Non-Hispanic whites had the highest mean serum levels (66.9nmol/l) followed by non Hispanic blacks (53.9nmol/l) and Mexican Americans (40.1nmol/l). Serum levels were also higher in samples taken between the months of April-October. Compared to the previous NHANES survey in 1988-1994 age adjusted means were lower in men by between 5-9nmol/l. This can in part be attributed to BMI, milk intake (which is the US is fortified with 400IU per quart) and sun protection.

A nationally representative survey from Canada (Canadian Health Measures survey) collected data on 5306 individuals aged 6-79 years between 2007 and 2009. The mean concentration of 25(OH)D in this population was 67.7nmol/l. Mean concentrations were lowest among men aged 20-39 years (60.7nmol/l) and highest in boys aged 6-11 years (76.8nmol/l). An estimated 4.1% of the population had 25(OH)D levels <25nmol/l, and just over 10% had levels <37.5nmol/l. White racial background and frequent milk consumption were associated with higher concentrations (100). Over a period of 10 years the Canadian Multicentre Osteoporosis study, which analysed samples of 1896 women and 829 men, showed that serum 25(OH)D increased by 9.3nmol/l in women and by 3.5nmol/l in men. The percentage of participants with 25(OH)D levels <50 nmol/L was 29.7% at baseline and 19.8% at year 10 follow-up (101). This was in part due to increased use of supplements.

Latin America

Despite the large population of this area, only a few studies have assessed vitamin D status in the region. A multinational study of vitamin D status assessed individuals in Mexico, Brazil and Chile. Mean levels across the area were 73.8nmol/l. In the individual countries mean serum levels were 65.4nmol/ in Mexico, 81.3 in Brazil and 75.4nmol/l in Chile. The levels of vitamin D deficiency (<22.5nmol/l) were 1.3, 0.7 and 0% respectively, and insufficiency (<50nmol/l) 29.5, 15.2 and 19.1% respectively (102). A study in Argentina assessed the effect of latitude on vitamin D status. They found those living in the South had the lowest mean 25(OH)D levels (35.4nmol/l) compared to the mid region (44.7nmol/l) and North (51.7nmol/l) of the country (103).

Oceania

Vitamin D deficiency is seen in a number of at risk groups within Australia. A study of 1280 older men and women in residential care in Sydney found that the percentage of residents with vitamin D deficiency using cut off values of 25(OH)D at 30, 50 and 75nmol/l were 61.6%, 88.2% and 98.4% respectively (104). A study investigating at risk groups in the Sydney metropolitan area showed that serum 25(OH)D levels in the elderly population were higher in those living at home (44nmol/L) compared to individuals living in a hostel (36nmol/l) or nursing home (33nmol/l). Elderly participants of middle Eastern origin had the lowest mean level(21nmol/l) with 58% of this group having levels <25nmol/l (105). Other factors associated with vitamin D deficiency were mobility and sun exposure in people living in assisted care facilities, and low dietary vitamin D and calcium intake, reduced exercise and high BMI in the immigrant groups (51). A study from Tasmania found the mean serum 25(OH)D was 52.8nmol/l, with 56% of women in this cohort having a serum level<50nmol/l (106).

A national study of 3008 participants over 15 years (National nutritional study) in New Zealand showed that the mean level of 25(OH)D was 50nmol/l with levels marginally lower in women (48nmol/l). Pacific women had the lowest levels (34nmol/l). Women living on the South Island had a lower serum level compared to the North Island (43 vs 49nmol/l). The proportion of adults described as deficient (<17.5nmol/l) ranged from 0% in men aged 19-24 years to 10% in pacific women (107). In the National Children's Survey, a national sample of children aged 5-14 years, mean 25(OH)D levels were

43nmol/l in Maori, 36nmol/l in Pacific, and 53 in those of European decent (108). The prevalence of deficiency (<17.5nmol/l) was 5, 8 and 3% respectively, and insufficiency (<37.7nmol/l) was 41, 59 and 25% respectively. Lower levels were seen in girls and those with higher fat mass (108).

Conclusion

Vitamin D status has several important roles in bone and muscle health. Levels are determined by a combination of factors which influence synthesis in the skin, such as latitude and skin pigmentation, and dietary intake, such as food fortification and use of supplements. Level of adiposity may affect bioavailability, and demographic, genetic and disease factors can also play a role. It is clearly important to aim for a universal definition of what constitutes vitamin D deficiency to allow better comparability of studies. This will require collaboration and agreement across continents.

Regardless of the definition of vitamin D insufficiency it is apparent that sub optimal levels of 25(OH)D are a global problem with very few areas spared. Severe deficiency seems to be most common in the Middle East and South Asia. The high prevalence of rickets in these areas is of particular concern. Hypovitaminosis D is also particularly prevalent in immigrant populations to areas with less UV radiation. There are several areas, for example in Africa and Asia, where data are still not available on the prevalence of vitamin D deficiency. Future studies should focus on filling these knowledge gaps to provide a fuller picture of the global burden of this condition.

In terms of interventions, in regions such as Scandinavia, dietary supplements appear to have been effective in reducing the prevalence of deficiency. Furthermore, the food fortification used in North America has successfully increased the mean serum levels in the population. Both could be considered elsewhere in higher risk countries.

Conflicts of interest: Professor Cooper has received consultancy fees/honoraria from Servier; Eli Lilly; Merck; Amgen; Alliance; Novartis; Medtronic; GSK; Roche.

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