Impact of high latitude, urban living and ethnicity on 25-hydroxyvitamin D status: a need for multidisciplinary action?

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Word count- 4949 (excluding abstract, references)

Funding: This work was funded by a University of Surrey Urban Living Award (grant JV1214B).

Author Contributions: Writing and reviewing of manuscript MMM, ALD, KH, SM, RJM, SLN

Disclosures: SLN is Research Director of D3Tex Ltd, which holds the UK and Gulf Corporation Council (GCC) Patent for the use of UVB transparent material for vitamin D deficiency prevention.

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Derivatives License. Please cite this article in press as: Mendes MM et al. Impact of high latitude, urban living and ethnicity on 25-hydroxyvitamin D status: a need for multidisciplinary action? J Steroid Biochem Mol Biol (2019) (in press).

Link to publisher final version:

<https://www.sciencedirect.com/science/article/pii/S0960076018305417?via%3Dihub>

ABSTRACT

The effects of urban living on health are becoming increasingly important, due to an increasing global population residing in urban areas. Concomitantly, due to immigration, there is a growing number of ethnic minority individuals (African, Asian or Middle Eastern descent) living in westernised Higher Latitude Countries (HLC) (e.g. Europe, Canada, New Zealand). Of concern is the fact that there is already a clear vitamin D deficiency epidemic in HLC, a problem which is likely to grow as the ethnic minority population in these countries increases. This is because 25-hydroxyvitamin D (25(OH)D) status of ethnic groups is significantly lower compared to native populations.

Environmental factors contribute to a high prevalence of vitamin D deficiency in HLC, particularly during the winter months when there is no sunlight of appropriate wavelength for vitamin D synthesis via the skin. Also, climatic factors such as cloud cover may reduce vitamin D status even in the summer. This may be further worsened by factors related to urban living, including air pollution, which reduces UVB exposure to the skin, and less occupational sun exposure (may vary by individual HLC). Tall building height may reduce sun exposure by making areas more shaded. In addition, there are ethnicity-specific factors which further worsen vitamin D status in HLC urban dwellers, such as low dietary intake of vitamin D from foods, lower production of vitamin D in the skin due to increased melanin and reduced skin exposure to UVB due to cultural dress style and sun avoidance.

A multidisciplinary approach applying knowledge from engineering, skin photobiology, nutrition, town planning and social science is required to prevent vitamin D deficiency in urban areas. Such an approach could include reduction of air pollution, modification of sun exposure advice to emphasise spending time each day in non-shaded urban areas (e.g. parks, away from tall buildings), and advice to ethnic minority groups to increase sun exposure, take vitamin D supplements and/or increase consumption of vitamin D rich foods in a way that is safe and culturally acceptable. This review hopes to stimulate further research to assess the impact of high latitude, urban environment and ethnicity on the risk of vitamin D deficiency.

Keywords: Urban, rural, 25-hydroxyvitamin D, 25(OH)D, ethnicity, latitude

1. Introduction

Vitamin D deficiency is a global epidemic; the aetiology of which is tied to both the outdoor environment and availability of vitamin D from diet (foods in their natural state, fortified foods and supplements). Vitamin D deficiency has been associated with a wide variety of chronic diseases (e.g. heart disease, cancer, osteoporosis, diabetes, autoimmune and infectious disease) [1] and eradicating it is of clear public health importance.

In high latitude countries (HLC; defined in this review as latitude greater than 40 degrees N or S) season and climate are known to affect 25(OH)D status. Low 25-hydroxyvitamin D (25(OH)D) is particularly likely during the winter months, where there is no sunlight of appropriate wavelength for synthesis of pre-vitamin D in the skin. Climatic factors such as cloud cover may also lead to lower 25(OH)D status via lowering skin exposure to the sun.

Within urban areas, factors such as air pollution, indoor living and extensive shade due to tall building height and narrow roads may further worsen 25(OH)D status [2, 3]. Factors such as a higher number of indoor workers may also reduce 25(OH)D concentration, although this may vary by individual HLC concerned as some HLC countries have a higher proportion of outdoor workers in rural areas than do others. Latitude and urban related factors together may be of greater detriment to 25(OH)D status in darker skinned ethnic minority groups (e.g. African, Middle Eastern, South Asian), who are already at high risk of vitamin D deficiency due to skin pigmentation, clothing style, sun avoidance behaviour and genetics. These groups are known to be at higher risk of 25(OH)D deficiency in HLC compared to native populations [4-6].

As 25(OH)D deficiency is associated with higher risk of multiple chronic diseases, including osteoporosis, diabetes, cancer, cardiovascular disease and autoimmune disease [1], 25(OH)D deficiency may contribute to ethnic inequalities in health. Indeed, poorer health among ethnic groups in western countries, compared to their majority peers, has been widely documented [7, 8] and recent studies show that with increasing duration of residence in the new country, immigrants' health often worsens [9, 10]. Moreover, 25(OH)D deficiency may partly explain the higher risk of heart disease and

diabetes in African and South Asian groups [11] (albeit much of this association may be due to obesity) which is associated with vitamin D deficiency [12].

This Review will discuss vitamin D sources and metabolism, before discussing urban-rural differences in vitamin D status and specific factors related to latitude, urban living and ethnicity in HLC. It will then discuss multidisciplinary approaches to improve 25(OH)D status among HLC urban dwellers, including specific tailoring of approaches for ethnic minority groups.

2. Vitamin D sources, metabolism and optimal vitamin D status

Vitamin D is obtained from two sources, diet and UVB radiation of the skin. Vitamin D is the generic term for two different molecules, ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). Ergocalciferol is derived from UV radiation on ergosterol, which is largely distributed in plants and fungi, whereas cholecalciferol is formed from the action of UV rays in the skin in animals [13]. Therefore D₂ is found in some plant and fungi foods, and D₃ is found in animal foods.

Casual exposure of the skin to the UVB portion of sunlight (290-310nm) converts the molecule 7-dehydrocholesterol, naturally present in the epidermis, to pre-vitamin D. Pre-vitamin D is then metabolized to become vitamin D through a thermal isomerisation, which then binds to vitamin D binding protein in the blood and is transported to the liver, along with vitamin D from dietary sources. In the liver, these molecules first go through hydroxylation by the cytochrome P450 enzyme CYP2R1 (25-hydroxylase) to produce 25-hydroxyvitamin D (25OHD), the major circulating form and storage form of vitamin D in the body, as well as the usual serum measure used to assess vitamin D status. The molecule 25OHD undergoes a further hydroxylation in the kidney, made by the enzyme CYP27B1 (1 α -hydroxylase), resulting in the active form 1 α ,25OH₂D, which optimizes calcium and phosphate absorption from the intestine, as well as having direct effects on bone health [13-16].

Vitamin D is essential for the maintenance of bone health and the regulation of calcium and phosphorous absorption and homeostasis. Along with parathyroid hormone, it regulates calcium and phosphorous metabolism and enhances the absorption of calcium in the gut and the kidney.

Although the definition of vitamin D adequacy is still much debated and varies substantially amongst different agencies around the world, there is indeed a general consensus that serum levels of 25-hydroxyvitamin D (25OHD) should be above 25 nmol/l in order to prevent detrimental effects to bone health. However, the extent to which it should exceed 25nmol/L is widely debated. The UK Scientific Advisory Committee on Nutrition [17] has suggested over 25nmol/L for bone health but the US/Canadian Institute of Medicine [18] recommends over 50nmol/L [18]. It has been extensively argued that for non-skeletal health outcomes higher levels of 25(OH)D should be targeted, with recommendations ranging from 25 nmol/l up to 100 nmol/l. Indeed, the US Endocrine Society recommends over 75nmol/L for non-skeletal health [14].

Sufficient vitamin D is required from environmental sunlight exposure and the diet to ensure adequate 25(OH)D status. Factors that reduce sunlight exposure to the skin, or reduce the consumption of dietary vitamin D, will increase the risk of 25(OH)D deficiency. Research assessing differences in 25(OH)D between urban and rural settings, as well as latitude, urban and ethnic related factors associated with 25(OH)D status in HLC will now be discussed.

3. Vitamin D status in Urban vs. Rural settings

Vitamin D deficiency has been known for many years to be common in urban areas. For example, in the early 20th century, nutritional rickets due to vitamin D deficiency was common in the UK. This vitamin D deficiency was likely caused by lack of sunlight due to high levels of air pollution and shading from tall buildings in narrow streets, as well as long daily indoor working hours for children. Nutritional rickets continues to be a global Public Health problem today, and is on the increase[19]. In terms of HLC, nutritional rickets is relatively rare, for example in Denmark data shows an annual incidence of 2 in 100,000 children aged 0-2.9 years old [20]. It is most common in darker skinned ethnic groups, due to their higher risk of vitamin D deficiency. Urban living may increase the risk of rickets further via its effects on reducing vitamin D status. Increased rickets in urban areas in modern times is also likely due to the increased proportion of darker skinned ethnic minorities in urban areas compared with

rural areas, so may be a consequence of both the types of populations living in urban areas and the environmental or lifestyle factors reducing vitamin D status in urban spaces.

In terms of differences in 25(OH)D status between urban and rural areas, a lower 25(OH)D status in urban, as opposed to rural, settings has been proposed but there is a lack of studies, in either HLC or lower latitude countries, directly assessing this. In terms of HLC, in a Belgian study by Manicourt and Devogelaer (2008), urban women had higher levels of sun exposure, but also had a higher prevalence of 25(OH)D concentrations below 75 nmol/L than did rural women (84% vs. 38%). In Belgium, due to pollution rates, ozone levels are three times higher in the metropolitan capital, Brussels, than in the countryside [21] which could explain this study's result. In the same study, the urban dwelling women were found to require three times more sun exposure to gain the same concentration of 25(OH)D as those in the rural areas, even after adjusting for baseline 25(OH)D [21]. Similarly, a study of over 3000 German adults found that living in an urban area led to 1.4 times increased odds of 25(OH)D <25nmol/L (vitamin D deficiency) compared to living in a rural area [22]. The urban area studied was Augsburg, a small city of population circa 280,000 people, and the authors speculate the urban-rural difference would be larger if comparing the rural areas with a larger city [22].

Similar findings have been found in lower latitude countries. A study in Saudi women reported significantly lower 25OHD concentrations in those living in apartments than those in country houses or rural areas [23]. Saudi women have almost 100% coverage of the whole body when in public due to cultural clothing customs, and therefore would require a private courtyard or garden to allow them to expose their skin to the sun. Fonseca et al. (1984) suggest it might be easier for rural dwellers to obtain privacy (e.g. have a courtyard) [23]. We also speculate that rural women may spend more time outdoors (e.g. due to outdoor occupational work) and may therefore obtain some 25(OH)D via the small part of the face which is exposed.

Examination of data from the Korean National Health and Nutrition Examination Survey (2008) found higher 25(OH)D in adult rural dwellers than in adult urban dwellers, which the study authors suggested was due a more active lifestyle and lower

air pollution in rural areas [24]. Another Korean study [25] also found that rural dwellers had higher 25(OH)D, attributing this to nearly two-thirds of rural dwellers working outdoors in fishery, forestry or other agricultural industries, compared with almost no urban dwellers in these industries.

One study of over 1000 Mexican children found higher 25(OH)D in rural children, than in urban children, with 18% of urban children having 25(OH)D <50nmol/L (vitamin D insufficiency) compared with only 10% of rural children [26]. Finally, a study of Malaysian women found higher 25(OH)D in rural dwellers (median 70.7±18.3 nmol/L) than urban dwellers (median 45.7±15.5 nmol/L), with rural dwellers having 2.7 times more sun exposure per week due to increased outdoor working [27].

However, some studies have found no urban-rural difference in 25(OH)D status. A study in the US of over 9000 veterans, comparing large metropolitan, urban and rural residents, found a statistically significant, but not clinically meaningful difference in 25(OH)D status by area of residence [28]. Indeed, all areas had an average 25(OH)D concentration of 28-30nmol/L [28]. Similarly, in an Indian study [29] and a study in the United Kingdom (UK) [30], no difference in 25(OH)D concentrations between residents of urban or rural areas was identified. Sachan et al. (2005) suggest that the reasons for the lack of difference between Indian urban and rural areas, despite lower sun exposure in urban areas, is actually due to lower calcium intake in rural areas. They suggest that prolonged calcium deficiency leads to vitamin D deficiency, as has been seen in a rodent study [31]. Glass et al. (2009) do not speculate on the reasons for the lack of urban-rural difference in 25(OH)D status, but it could potentially be due to the fact that the majority of the UK rural dwellers are indoor workers, so sun exposure may actually be similar to urban dwellers.

Overall, further studies are needed to define the differences in the prevalence of vitamin D deficiency between urban and rural settings, particularly as only three of the above studies were from HLC, and urban-rural differences may differ by latitude and degree of westernisation. Moreover, we can speculate that the impact of outdoor working may be less relevant in HLC, whereby rural dwellers are less likely to be involved in outdoor manual working than is the case in lower latitude countries.

4. Latitude related factors

4.1 Season, time of day, altitude, cloud and ozone: influence on UVB availability

The cutaneous synthesis of vitamin D is dependent on the suitable UV photon reaching a 7-dehydrocholesterol molecule, which is influenced by the solar zenith angle according to latitude, season, local atmospheric conditions and time of the day. In latitudes higher than 40 degrees, there is no UV radiation of the appropriate wavelength (280nm-310nm) from the end of October to the end of March. For the remaining months of the year, 60% of the effective UV radiation occurs between 11.00am and 3.00pm [32, 33]. Moreover, 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 [15, 34]. Figure 1 shows mean circulating 25(OH)D levels in different populations according to geographic latitude, illustrating clearly that 25(OH)D declines with increasing distance from the equator. This suggests a lower 25(OH)D status in populations living in HLC.

Figure 1: Mean circulating 25-hydroxyvitamin D levels in children, adolescents, and adults according to geographic latitude (source: Zittermann et al. 2006[35]; reproduced with permission of Elsevier).

Altitude is another factor that affects dermal production of vitamin D. At higher altitudes, the atmosphere is thinner and filters less UVB radiation. Also, there may be differences in cloud cover by altitude. The literature on altitude and vitamin D production is limited, but it is known that altitude alters the length of the time period when vitamin D can be produced[36]. Few studies have directly assessed varying altitude and concurrent vitamin D production but one study [37], in November at 27° N, using ampoules of 7-dehydrocholesterol placed at varying altitudes between Agra (169m above sea level) and Everest Base Camp (5350m above sea level), showed a 4 times greater vitamin D production at higher altitudes. This is of course an extreme altitude, as people do not generally live at the equivalent of Everest Base Camp. However an increase in vitamin D production was also seen at intermediate altitudes, for example being 2 fold greater in Kathmandu (1400m) compared with Agra[38], so providing proof of principle that increased altitude is associated with higher vitamin D production, although the relative influence of different mediating factors responsible for this effect, for example changes in air pollution and cloud cover have not been elucidated.

Finally, excessive sunscreen use may also be a problem for 25(OH)D status in HLC. Regular use of high factor sunscreen, direct sun avoidance and “covering up” have been largely advised in sunny countries, especially in lower latitude countries, for cancer prevention purposes [39]. However, they have also been advised the same in HLC, and overzealous use of high factor sun screen, covering the body with clothing and sun avoidance on days where the risk of sunburn is low may adversely affect the ability of the skin to produce vitamin D.

5. Urban factors

5.1 Pollution

Urban areas are known to have much higher levels of air pollution than rural areas, due to pollutant emissions from industrial sites and transport. Urban areas also lack green vegetation which is known to reduce air pollution levels [40]. Air pollution may

also block UVB radiation, which could lead to lower 25(OH)D concentrations. Some research has supported an association between air pollution levels and 25(OH)D status, with higher 25(OH)D in those from less polluted areas of a city, compared with more polluted areas [2]. Even the air quality of the pregnant mother's living environment has been found to be associated with 25(OH)D concentration in the new-born infant [41].

Of course there are confounders that need to be considered in the relationship between air pollution and 25(OH)D status, including lower socioeconomic status of people living in areas with higher pollution levels [42], and lower socioeconomic status being associated with increased likelihood of being obese [43] which is associated with lower 25(OH)D concentration. More research is now needed in the area of 25(OH)D and air pollution, particularly to establish how much air pollution needs to be reduced to produce a meaningful improvement in 25(OH)D status and whether different types of pollutants are more detrimental to 25(OH)D production than others.

5.2 Built environment

In urban settings a large number of tall buildings with narrow roads, with little open space, will cause more shade, meaning less UVB radiation falling onto the skin. There is a lack of research on building height and 25(OH)D status, but recent modelling suggested significant reduction in UVB exposure when a high-rise urban environment was simulated, compared with an unobstructed environment [3] and this is a clear area where future research is needed.

5.2 Time spent outdoors

There is some data on time spent outdoors in HLC. For example, Diffey et al (2011) report data from studies in Denmark and England on outdoor exposure on weekends and weekdays in indoor adult workers. In Denmark [44] from April-October, weekend exposure from 12.00-15.00h was 30mins and from 07.00-19.00 was 1 hour 20 mins. Equivalent data for weekdays were 0 mins and 40 mins. On weekends, in England [45] in April and July, between 10.00 -15.00h outdoor exposure was 40 mins and between 11.00 - 13.00 it was 15 mins. Equivalent data for weekdays were 15 mins

and 6 mins. This suggests very little sunlight exposure in indoor workers on weekdays, but increased exposure at weekends. Of note, much of the exposure in the week may be at times of day when little or no vitamin D is produced in the skin (e.g. walking to work and back in the early morning and early evening). Another study analysing data from the Women's Health Initiative found that both recreational sun exposure and yard work were associated with increased 25(OH)D status in US postmenopausal women, but only in summer/autumn (fall), not winter/spring [46]. Finally, an Irish study found that recreational sun enjoyment was associated with higher 25(OH)D in older adults[47]. These studies suggest that although both adventitious and recreational sun exposure can improve vitamin D status, often the timing of adventitious exposure (e.g. on way to work) may not be optimal for dermal vitamin D production and that recreational sun exposure at weekends is likely to be of longer duration and at a more optimal time of day for vitamin D production (the hours nearest to noon), excluding a large proportion of the population who do not engage in this activity.

In terms of urban-rural differences, in urban areas it can be more difficult to get adequate exposure to sunlight than in rural areas, both due to factors of the built environment but also do to indoor lifestyles in cities. Recent work has started to define the amount of sun exposure required to maintain a sufficient vitamin D status in HLC and it is feasible and realistic for paler skinned urban dwellers to attain this. For example in the UK, Webb [48] estimated that 9 minutes per day between March and September, exposing the forearms, lower legs, hands and face (from June to August) and just the hands and face (March to May, September) was enough to keep individuals above 25nmol/L all year around. However, for South Asians, who typically have skin type V, a longer time period was required (24-40 minutes, with 35% of skin exposed to the sun), which is likely to be less feasible to achieve [49].

It is currently unknown what skin exposure would be required to produce sufficient vitamin D in Black skin year around, but is likely to be even longer than that for the South Asians and therefore even less feasible to achieve. These assumptions are based on exposing skin to full sunlight and not being in the shade, so urban dwellers would need to be away from tall buildings and shaded streets when getting their sun exposure, which gives an added inconvenience or barrier. Urban dwellers may have to make a large effort to move to a place where they can fully expose their skin (e.g. a city park, walking a few streets down) which is likely to be unrealistic in most cases.

In rural areas, with much higher availability of open space it will be much easier to attain full sunlight on the skin during this 9 minute period. Of course, if larger doses of vitamin D are recommended then the amount of sunlight required may still become unfeasible [50]. For example, if the skin was required to produce the equivalent of 4000IU dietary vitamin D then there would not be enough time available during a typical worker's lunch hour, during the months when vitamin D can be produced, without requiring unrealistic levels of skin exposure [50].

Changes in lifestyle choices and behaviours are likely driving changes in outdoor sun exposure. There is a clear trend over the last 30 years for urban children to spend less time outdoors and for increased screen time (combined television and computer use) to substitute for outdoor activity. Recent research from Canada suggests rural children spent more time outdoors (9.8% of day) compared with urban children (5.8% of day) [51], suggesting that living in an urban area means less outdoor activity for children. It is less clear as to whether overall leisure screen time varies between urban and rural areas, with one study finding that screen time was similar between urban and rural adolescents in Canada and the US, but the types of screen time varied by location and urban-rural status [52].

Increased screen time may impact on 25(OH)D status in two ways; first by increasing obesity (through concurrent eating, viewing adverts for unhealthy food, spending less time in physical activity and reducing sleep time) [53] and second through less times spent outdoors [54]. The impact of excessive screen time on obesity [55] and childhood mental wellbeing [56] have been well documented, but there is a lack of promotion of the potential negative impact of excessive screen time for 25(OH)D status. Although, one recent Dutch study found increased television viewing was a risk factor for increased risk of vitamin D deficiency [57] as did an analysis of US NHANES 2001-2004 data [58].

Also, outdoor manual work is usually less undertaken in urban than in rural areas. Although agricultural employment is generally on the decline in industrialised countries [59] some rural areas in HLC still have a significant proportion of agricultural workers, suggesting in that these counties occupational sun exposure is likely to be higher in rural areas compared to urban areas. However, the importance of this factor is likely

to vary by individual HLC. For example, Canada has a relatively large rural population who work outdoors in agricultural employment, which is not the case in the United Kingdom (UK). In countries with a lower percentage of rural workers in outdoor work we would expect less of an urban-rural divide in 25(OH)D status.

6. Ethnic factors

6.1 Skin pigmentation

Individuals with higher melanin content in their skin require more UV light exposure to synthesize the same amount of vitamin D₃ as individuals with less melanin [39, 60, 61] as cutaneous melanin pigment in human skin naturally competes for and absorbs the UVB photons responsible for the photolysis of 7-dihydrocholesterol to pre-vitamin D₃. This limitation was well observed in a study which found higher amounts of UVB were required to achieve a similar 25(OH)D concentration in Black than White adults [62]. However, another study found that baseline 25(OH)D concentration was more predictive of change in 25(OH)D after UVB exposure than was skin pigmentation, in UK dwelling White and South Asian women [63].

6.2 Behavioural and cultural factors

Clothing habits, due to cultural and religious preferences as well as prevalent environmental conditions, are also an important influencing factor that may contribute to a significant reduction in the synthesis of vitamin D [50, 64]. Ethnic minority groups with a formal requirement for a heavy, covered dress style are likely to have a reduced ability to synthesise vitamin D from UVB radiation, with concomitant impacts on their 25(OH)D status. Studies have confirmed lower 25(OH)D concentrations in Middle-Eastern women and girls who are veiled, compared with partly veiled, even within the same culture [65, 66]. This implies that veiled women in high latitude countries would also be at greater risk of a 25(OH)D deficit compared with non-veiled women. Urban living, darker skinned ethnic minority groups in HLC will be most affected by the lack of UVB availability for skin production of vitamin D, both due to time of day and season, but also as a consequence of living in areas shaded by taller buildings.

In terms of indoor behaviour in ethnic minority groups, there is little data on screen time, but one study found that pre-school age UK Pakistani children (12-36 months old) had increased television viewing time per day as compared with UK White children [67]. In US adults, African Americans (23%), but not Mexican Americans (8%), had a larger number of individuals watching >5 hours of television or computer use per day than did White Americans (13%) [68]. The above studies show that screen time usage may vary by specific ethnic group, so no general conclusion can be made that ethnic minority groups have a higher or lower screen time than non-minority groups.

In terms of outdoor sunlight exposure, a recent US study found similar number of minutes spent outdoors per week between Black and White adults [69]. However, research has suggested that western dwelling Asian populations [70, 71] may differ in their behaviours, and specifically are likely to practice sun avoidance, which would limit their outdoor activity in the summer. Again, it appears that differences in sunlight exposure are ethnic minority group specific, so we cannot make generalised judgements on the basis of solely belonging to any minority group.

6.3 Genetics

Inter-individual variability in 25(OH)D status can be partly explained by differences in the metabolism of vitamin D. The Vitamin D receptor gene plays an important role in vitamin D metabolism and polymorphisms in this gene can potentially affect Vitamin D expression [72, 73] as can polymorphisms in the hydroxylase enzymes controlling vitamin D metabolism, and in the vitamin D binding protein (DBP). Genetic variation could explain the considerable differences in vitamin D levels among populations seen independently of latitude and sunlight exposure [74, 75].

There is limited research into the genetics of vitamin D metabolism in darker skinned ethnic groups living in HLC, but some research suggests that some polymorphisms in GC and CYP2R1 genes (involved in vitamin D metabolism) are associated with 25(OH)D concentrations in Arabian [76] and South Asian [76, 77] groups. However, conversely one study found no association between vitamin D binding protein (DBP)

or vitamin D receptor (VDR) genotypes and 25(OH)D status in Australian dwelling Asians [78] albeit within a small sample (n=72) for a genetic analysis. Another study, in 989 Black Americans, found no associations between known polymorphisms in genes involved in vitamin D metabolism and 25(OH)D status [79].

In evolutionary terms, we can speculate that darker skinned immigrants to HLC have moved from a sunny area of the world, to which they are genetically adapted, with year round ability to produce vitamin D in the skin, to an area of the world where vitamin D can only be produced for part of the year, that they are not necessarily genetically adapted to. This suggests a potential genetic disadvantage in terms of being able to produce, and/or maintain adequate concentrations of vitamin D when living in a sun deprived environment. However, more research is required to provide evidence to test this hypothesis as current evidence concerning ethnicity, genetics and 25(OH)D status is limited.

7. Multidisciplinary approaches to improve 25(OH)D status HLC urban dwellers

This review has discussed urban-rural differences in 25(OH)D status. It has described the latitude related factors that affect 25(OH)D status in HLC (e.g. climate, lack of ability to synthesise vitamin D in the winter) as well as factors related to urban living that may detrimentally affect 25(OH)D status (e.g. air pollution, tall buildings causing excessive shade, indoor activity). It has also considered factors specific to urban dwellers from darker skinned ethnic groups living in HLC, who are at greater risk than native populations for vitamin D deficiency due to dietary, cultural, behavioural and genetic factors. Living in an urban area in a HLC is likely to further exacerbate 25(OH)D deficiency in these groups due to the above listed latitude and urban related factors. The review will now discuss possible multidisciplinary approaches to tackle vitamin D deficiency in HLC urban dwellers, including those from these ethnic minority groups.

7.1 Reducing air pollution

Countries globally are aiming to reduce levels of air pollution, and further reduction of this is likely to improve 25(OH)D status in their populations. The engineering of new

products to remove air pollutants, or to prevent their initial production (or release to the air) from industry and transport vehicles, will reduce air pollution levels and improve UVB radiation to the skin, which may improve vitamin D status. More research is now required to establish how much of a reduction in air pollution is required in order to achieve a meaningful increase in vitamin D status.

7.2 Recommendations for safe sunlight exposure

There is a dual dilemma concerning gaining adequate vitamin D from sunlight and also protecting the skin against skin cancer. The majority of vitamin D is made from exposure of skin to sunlight, and the production of vitamin D occurs before the skin burns, so burning is absolutely contraindicated for both skin health and achieving adequate vitamin D status. Recent research suggests that low dose summer sun exposure can lead to vitamin D sufficiency with only low level, non-accumulating damage to DNA [80].

However many skin experts suggest that all sun exposure is detrimental, even very short exposures, due to the cumulative effects of radiation exposure to the skin. One recent study suggested increased skin damage in children after exposing skin to the sun on holiday in Northern Europe [81], but this study has been criticised as the children were exposed to 6-7 hours of sun a day, which is far greater than that needed for adequate vitamin D synthesis, and use of sunscreen after an initial short period of unprotected skin exposure around noon would have reduced the skin damage but still have the benefit of producing vitamin D (commentary by Webb [82]. The subjects were also relatively vitamin D sufficient so would not be expected to make large gains in vitamin D status[82].

There is clearly a need for public health recommendations which consider the trade-off between protecting skin from sun damage and also allowing enough sunlight exposure to produce adequate vitamin D. In addition. current recommendations for sunlight exposure for optimal vitamin D levels should take into consideration not only individual but also environmental factors. Current recommendations, such as those in the UK, may account for latitude and time of day, e.g. encouraging adults to expose uncovered forearms, legs or hands to the sun for 10-15 minutes, between 11am and 3 pm per day, during March to October [83]. However, these do not consider whether

someone is living in an urban or rural environment, and as such do not recognise the potential influence of current ozone levels, cloud cover or air pollution levels.

Photobiologists and skin cancer specialists are required to guide the development of tailored messages for urban dwellers on safe sun exposure that still allows for dermal production of vitamin D. However, this risks making the overall sun exposure message too complicated for people to understand. Indeed, for this reason the UK NICE (2016) recommendation already ignores body position (e.g. laying down may irradiate more of the body than standing up). However, a caveat could be added to the recommendation to ensure that people are standing in full sunlight, particularly that urban dwellers move away from tall buildings (i.e. find a reasonably open space) when they aim to get their daily sunlight exposure. Psychologists and social scientists may be able to advise public health providers on ways to design messages to ensure they are effectively taken up by the target population.

Another possibility is for all new urban buildings to be built of a shorter height and for streets to be made wider. However, this is probably unlikely to occur, due to the pressures of providing enough occupational and residential space in cities, and a focus on moving people away from built-up shaded areas within sun guidance messages is more realistic. Indeed, town planners could design towns and cities with more open green spaces to enable sun exposure unshaded by buildings.

Of course, sun exposure messages are already problematic for some ethnic minority groups (e.g. Muslim women) who are not able to expose their arms, or in some cases their face or arms, in public. Interventions to improve sunlight exposure in this group may need to consider whether there is a private place (e.g. a garden) where exposure is acceptable. Of course this will be a particular problem for women who live in urban apartment blocks, who have no personal garden, or for whom gardens are overlooked by neighbours. Short sun exposures may not be enough to produce sufficient ($\geq 50\text{nmol/L}$) 25(OH)D status in UK South Asian women, as seen in the study by Rhodes et al. (2010) who exposed South Asian women to UVB 3 times a week for 6 weeks, giving the cumulative equivalent of 20 standard erythemal doses (SED) of sunlight [84]. Therefore, in addition to increasing safe sun exposure, other methods (e.g. dietary) will also be required for some ethnic minority groups. Psychologists and

social scientists, alongside nutritionists and dietitians, will be able to design culturally appropriate public health messages to improve vitamin D intake and to increase safe sun exposure for these groups.

Tackling the 'indoor culture' of excessive screen time, encouraging indoor urban workers to get some safe sun exposure during their work breaks and at the weekends, as well as encouraging more outdoor play in urban children is likely to be helpful for improving 25(OH)D status. However there are significant barriers to achieving this, not least the issue of time pressured working conditions, and for children a lack of availability of open spaces and the issue of perceived safety concerns of parents. This highlights the need for employers, community groups, local authorities and town planners to be involved in strategies to facilitate change, again using tailored messages informed by psychologists and social scientists.

7.3 Dietary Interventions

Nutritionists and dietitians, alongside psychologists and social scientists, can contribute to improving vitamin D intake in HLC urban dwellers, both directly by working with individuals and, perhaps more effectively, via public health campaigns and messages. It is worth noting that very few foods are natural sources of vitamin D (e.g. oily fish, eggs, meat, mushrooms) and even those have relatively small amounts per standard portion. The exception is oily fish, where a large portion (e.g. 100g) provides around 10 micrograms of vitamin D, depending on species and whether it is wild or farmed fish. However, oily fish is not regularly consumed in large amounts by most people in HLC. Moreover, many ethnic minority groups, for religious reasons, may consume little or no oily fish, meat and eggs (e.g. vegetarian and vegan Hindus) or don't consume a lot of oily fish in the traditional diet (e.g. Muslim Pakistanis, Middle Eastern groups). Even Bangladeshi populations, whose diet traditionally contains a lot of oily fish, do not eat necessarily large amount of oily fish when living in the UK, [85] the reason for which is unknown but could include cost of and availability of fish. Therefore, increasing dietary intake of vitamin D by recommending increased intake of natural vitamin D sources such as oily fish, eggs and meat may be challenging in some ethnic minority groups.

Due to the limited contribution of foods/diet to vitamin D status, vitamin D supplementation and/or food fortification have been increasingly proposed as an effective strategy of improving vitamin D status. Some HLC already have vitamin D fortified milk products (e.g. Canada and Finland) and these products have made an impact in improving vitamin D status in their populations as a whole. Indeed, the Finnish experience with food fortification is considered a land-mark example for fortification public policies. A voluntary food fortification policy was initiated in Finland in 2003 recommending the addition of 10 µg/100 g vitamin D to fat spreads and 0.5 µg/100 g to fluid milk products. A nationally representative survey of Finnish adults[86] reported that over a period of nearly 10 years, mean 25(OH)D concentrations increased from 47.6 nmol/L to 65.4 nmol/L and milk consumers had a 25(OH)D that was 20nmol/L higher than milk non-consumers. [86] Additionally, the prevalence of concentrations below 30 nmol/l went from 13% to 0.6%. Although the results are unquestionably very impressive, it is important to mention that the same survey reported that supplement intake increased from 11% to 41% [86]. Also, a recent systematic review and meta-analysis of randomised control trials assessing the impact of consuming vitamin D fortified foods on 25(OH)D status found that 11 micrograms per day led to a rise in 25(OH)D concentration of 19.4nmol/L [87]. However a number of the trials used milk based products which is an issue as many ethnic minority individuals are lactose intolerant, or are vegan, and so avoid milk products.

In Finland the implementation of a systematic national fortification programme was proven to be an effective approach to improving vitamin D status of the population. The challenge now comes when applying the Finnish protocol to other countries around the world, with different solar radiation, cultural habits, ethnic diversity and food accessibility. A new generation of fortified products, suitable for consumption by minority ethnic groups, are therefore urgently required in HLC. Fortification of biscuits or fruit juice are two possibilities, which would be suitable for all ethnic groups, with recent research suggesting both products are acceptable to consumers and effective in raising 25(OH)D levels [88]. In most HLC fortification of the national food supply is likely to benefit both urban and rural dwellers as the majority of both HLC populations likely consume food produced by the same companies. However, in some HLC (e.g. Northern Russia or Canada) there may be significant rural populations who eat mostly locally produced food and may not get access to the fortified foods. A food fortification

scheme is likely to be of more benefit all urban dwellers, albeit there may still be some restrictions to access such as availability and cost.

Vitamin D supplementation is another strategy, but relies on the motivation of each individual to comply with taking the supplements in the long term. Vitamin D2 may be more suitable for ethnic minority groups who are concerned about the use of animal products in the supplement (vitamin D3 is extracted from lanolin, found in sheep's wool). Although it has recently been shown to be only half as effective as vitamin D3 in raising 25(OH)D levels [88] it is more feasible for use in some ethnic minority groups (e.g. vegetarians, vegans, those who need a halal diet).

Tackling obesity through weight loss in adults, or improved weight for height in children, is also recommended. Although obesity is not strictly an urban-specific problem, it is common in urban areas and is known to be associated with reduced 25(OH)D status [12].

8. Conclusion

This review has presented evidence that living in urban areas in HLC exerts a variety of detrimental effects on vitamin D status. These factors may further exacerbate vitamin D deficiency in darker skinned ethnic minority groups. This review has highlighted the need to investigate the role of urban living in HLC, with a particular requirement to consider the increased risk profile of ethnic groups with regards to vitamin D deficiency. In particular, more research is needed into the impact of air pollution, indoor living and building height on 25(OH)D status, as well as robust studies of urban-rural differences in 25(OH)D status. The review proposes a multidisciplinary approach from engineers, town planners, photobiologists, nutritionists, dietitians, psychologists and social scientists to tackle vitamin D deficiency in the urban environment, with specific tailoring of approaches for ethnic minority groups.

References

- [1] M.F. Holick, Vitamin D deficiency, *N Engl J Med.* 357 (2007) 266-281.
- [2] K.S. Agarwal, M.Z. Mughal, P. Upadhyay, J.L. Berry, E.B. Mawer, J.M. Puliyl, The impact of atmospheric pollution on vitamin D status of infants and toddlers in Delhi, India, *Arch Dis Child.* 87 (2002) 111-113.
- [3] K.M. Wai, P.K.N. Yu, K.S. Lam, Reduction of Solar UV Radiation Due to Urban High-Rise Buildings - A Coupled Modelling Study, *Plos One.* 10 (2015).
- [4] A.L. Darling, K.H. Hart, H.M. Macdonald, K. Horton, A.R. Kang'ombe, J.L. Berry, S.A. Lanham-New, Vitamin D deficiency in UK South Asian Women of childbearing age: a comparative longitudinal investigation with UK Caucasian women, *Osteoporos Int.* 24 (2013) 477-488.
- [5] C. Henriksen, L. Brunvand, C. Stoltenberg, K. Trygg, E. Haug, J.I. Pedersen, Diet and Vitamin-D Status among Pregnant Pakistani Women in Oslo, *European Journal of Clinical Nutrition.* 49 (1995) 211-218.
- [6] J.A. Omand, P.B. Darling, P.C. Parkin, C.S. Birken, M. Khovratovich, K.E. Thorpe, S. Carsley, J. DeGroot, J.L. Maguire, T.K. Collaboration, Non-Western immigrant children have lower 25-hydroxyvitamin D than children from Western families, *Public Health Nutr.* 17 (2014) 1547-1554.
- [7] L.E. Egede, Race, ethnicity, culture, and disparities in health care, *J Gen Intern Med.* 21 (2006) 667-669.
- [8] D.R. Williams, V. Purdie-Vaughns, Needed Interventions to Reduce Racial/Ethnic Disparities in Health, *J Health Polit Policy Law.* 41 (2016) 627-651.
- [9] T.S. Leao, J. Sundquist, S.E. Johansson, K. Sundquist, The influence of age at migration and length of residence on self-rated health among Swedish immigrants: a cross-sectional study, *Ethnic Health.* 14 (2009) 93-105.
- [10] A. Ro, The Longer You Stay, the Worse Your Health? A Critical Review of the Negative Acculturation Theory among Asian Immigrants, *Int J Env Res Pub He.* 11 (2014) 8038-8057.
- [11] T. Tillin, A.D. Hughes, I.F. Godsland, P. Whincup, N.G. Forouhi, P. Welsh, N. Sattar, P.M. McKeigue, N. Chaturvedi, Insulin resistance and truncal obesity as important determinants of the greater incidence of diabetes in Indian Asians and African Caribbeans compared with Europeans: the Southall And Brent REvisited (SABRE) cohort, *Diabetes Care.* 36 (2013) 383-393.
- [12] A.R. Sousa-Santos, C. Afonso, A. Santos, N. Borges, P. Moreira, P. Padrao, I. Fonseca, T.F. Amaral, The association between 25(OH)D levels, frailty status and obesity indices in older adults, *PLoS One.* 13 (2018) e0198650.
- [13] H.F. DeLuca, Overview of general physiologic features and functions of vitamin D, *Am J Clin Nutr.* 80 (2004) 1689s-1696s.
- [14] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R.P. Heaney, M.H. Murad, C.M. Weaver, S. Endocrine, Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab.* 96 (2011) 1911-1930.
- [15] D.J. Raiten, M.F. Picciano, Vitamin D and health in the 21st century: bone and beyond. Executive summary, *Am J Clin Nutr.* 80 (2004) 1673S-1677S.
- [16] M.T. Kitson, S.K. Roberts, D-livering the message: the importance of vitamin D status in chronic liver disease, *J Hepatol.* 57 (2012) 897-909.
- [17] SCAN, Vitamin D and Health, Scientific Advisory Committee on Nutrition. (2016).
- [18] A.C. Ross, J.E. Manson, S.A. Abrams, J.F. Aloia, P.M. Brannon, S.K. Clinton, R.A. Durazo-Arvizu, J.C. Gallagher, R.L. Gallo, G. Jones, C.S. Kovacs, S.T. Mayne, C.J. Rosen, S.A. Shapses, The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know, *J Clin Endocrinol Metab.* 96 (2011) 53-58.
- [19] A. Prentice, Nutritional rickets around the world, *J Steroid Biochem.* 136 (2013) 201-206.
- [20] S.S. Beck-Nielsen, B. Brock-Jacobsen, J. Gram, K. Brixen, T.K. Jensen, Incidence and prevalence of nutritional and hereditary rickets in southern Denmark, *Eur J Endocrinol.* 160 (2009) 491-497.

- [21] D.H. Manicourt, J.P. Devogelaer, Urban tropospheric ozone increases the prevalence of vitamin D deficiency among Belgian postmenopausal women with outdoor activities during summer, *J Clin Endocr Metab.* 93 (2008) 3893-3899.
- [22] K. Richter, S. Breitner, A.R. Webb, C. Huth, B. Thorand, R. Kift, J. Linseisen, A. Schuh, J. Kratzsch, A. Mielck, S. Weidinger, A. Peters, A. Schneider, K.S. Grp, Influence of external, intrinsic and individual behaviour variables on serum 25(OH)D in a German survey, *J Photoch Photobio B.* 140 (2014) 120-129.
- [23] V. Fonseca, M. Elhazmi, R. Tongia, H. Abuaisha, Exposure to Sunlight and Vitamin-D Deficiency in Saudi-Arabian Women, *Postgrad Med J.* 60 (1984) 589-591.
- [24] E.Y. Choi, 25(OH)D status and demographic and lifestyle determinants of 25(OH)D among Korean adults, *Asia Pac J Clin Nutr.* 21 (2012) 526-535.
- [25] B.M. Song, Y. Rhee, C.O. Kim, Y. Youm, K.M. Kim, E.Y. Lee, J.M. Lee, Y.M. Yoon, H.C. Kim, Urban-Rural Differences Explain the Association between Serum 25-Hydroxyvitamin D Level and Insulin Resistance in Korea, *Nutrients.* 6 (2014) 5806-5818.
- [26] M. Flores, N. Macias, A. Lozada, L.M. Sanchez, E. Diaz, S. Barquera, Serum 25-hydroxyvitamin D levels among Mexican children ages 2 y to 12 y: A national survey, *Nutrition.* 29 (2013) 802-804.
- [27] M. Nurbazlin, W.S.S. Chee, P. Rokiah, A.T.B. Tan, Y.Y. Chew, A.S. Nusaibah, S.P. Chan, Effects of sun exposure on 25(OH) vitamin D concentration in urban and rural women in Malaysia, *Asia Pac J Clin Nutr.* 22 (2013) 391-399.
- [28] B.A. Bailey, T. Manning, A.N. Peiris, The Impact of Living in Rural and Urban Areas: Vitamin D and Medical Costs in Veterans, *J Rural Health.* 28 (2012) 356-363.
- [29] A. Sachan, R. Gupta, V. Das, A. Agarwal, P.K. Awasthi, V. Bhatia, High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India, *American Journal of Clinical Nutrition.* 81 (2005) 1060-1064.
- [30] D. Glass, M. Lens, R. Swaminathan, T.D. Spector, V. Bataille, Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK, *PLoS One.* 4 (2009) e6477.
- [31] M.R. Clements, L. Johnson, D.R. Fraser, A new mechanism for induced vitamin D deficiency in calcium deprivation, *Nature.* 325 (1987) 62-65.
- [32] D.o. Health, Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom, Report on Health and Social Subjects, 1991.
- [33] J. van Geffen, R. van der A, M. van Weele, M. Allaart, H. Eskes, Surface UV radiation monitoring based on GOME and SCIAMACHY Proceedings of the ENVISAT & ERS Symposium, 2004.
- [34] M.F. Holick, McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century, *Am J Clin Nutr.* 60 (1994) 619-630.
- [35] A. Zittermann, Vitamin D and disease prevention with special reference to cardiovascular disease, *Prog Biophys Mol Bio.* 92 (2006) 39-48.
- [36] O. Engelsen, M. Brustad, L. Aksnes, E. Lund, Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness, *Photochemistry and Photobiology.* 81 (2005) 1287-1290.
- [37] M.F. Holick, T.C. Chen, Z. Lu, E. Sauter, Vitamin D and skin physiology: A D-lightful story, *J Bone Miner Res.* 22 (2007) V28-V33.
- [38] M.F. Holick, Optimal vitamin D status for the prevention and treatment of osteoporosis, *Drugs Aging.* 24 (2007) 1017-1029.
- [39] A. Correia, S. Azevedo Mdo, F. Gondim, F. Bandeira, Ethnic aspects of vitamin D deficiency, *Arq Bras Endocrinol Metabol.* 58 (2014) 540-544.
- [40] K.V. Abhijith, P. Kumar, J. Gallagher, A. McNabola, R. Baldauf, F. Pilla, B. Broderick, S. Di Sabatino, B. Pulvirenti, Air pollution abatement performances of green infrastructure in open road and built-up street canyon environments - A review, *Atmos Environ.* 162 (2017) 71-86.

765 [41] N. Baiz, P. Dargent-Molina, J.D. Wark, J.C. Souberbielle, R. Slama, I. Annesi-Maesano, E.M.-C.C.S.
 766 Grp, Gestational Exposure to Urban Air Pollution Related to a Decrease in Cord Blood Vitamin D Levels,
 767 J Clin Endocr Metab. 97 (2012) 4087-4095.

768 [42] S.C. Gray, S.E. Edwards, M.L. Miranda, Race, socioeconomic status, and air pollution exposure in
 769 North Carolina, Environ Res. 126 (2013) 152-158.

770 [43] C.L. Ogden, M.M. Lamb, M.D. Carroll, K.M. Flegal, Obesity and socioeconomic status in children
 771 and adolescents: United States, 2005-2008, NCHS Data Brief. (2010) 1-8.

772 [44] E. Thieden, P.A. Philipsen, J. Heydenreich, H.C. Wulf, UV radiation exposure related to age, sex,
 773 occupation, and sun Behavior based on time-stamped personal dosimeter readings, Arch Dermatol.
 774 140 (2004) 197-203.

775 [45] A.R. Webb, R. Kift, M.T. Durkin, S.J. O'Brien, A. Vail, J.L. Berry, L.E. Rhodes, The role of sunlight
 776 exposure in determining the vitamin D status of the U.K. white adult population, Brit J Dermatol. 163
 777 (2010) 1050-1055.

778 [46] M.A. Kluczynski, M.J. Lamonte, J.A. Mares, J. Wactawski-Wende, A.W. Smith, C.D. Engelman, C.A.
 779 Andrews, L.G. Snetelaar, G.E. Sarto, A.E. Millen, Duration of Physical Activity and Serum 25-
 780 hydroxyvitamin D Status of Postmenopausal Women, Ann Epidemiol. 21 (2011) 440-449.

781 [47] F. O'Sullivan, E. Laird, D. Kelly, J. van Geffen, M. van Weele, H. McNulty, L. Hoey, M. Healy, K.
 782 McCarroll, C. Cunningham, M. Casey, M. Ward, J.J. Strain, A.M. Molloy, L. Zgaga, Ambient UVB Dose
 783 and Sun Enjoyment Are Important Predictors of Vitamin D Status in an Older Population, J Nutr. 147
 784 (2017) 858-868.

785 [48] A.R. Webb, A. Kazantzidis, R.C. Kift, M.D. Farrar, J. Wilkinson, L.E. Rhodes, Meeting Vitamin D
 786 Requirements in White Caucasians at UK Latitudes: Providing a Choice, Nutrients. 10 (2018).

787 [49] A.R. Webb, A. Kazantzidis, R.C. Kift, M.D. Farrar, J. Wilkinson, L.E. Rhodes, Colour Counts: Sunlight
 788 and Skin Type as Drivers of Vitamin D Deficiency at UK Latitudes, Nutrients. 10 (2018).

789 [50] A.R. Webb, O. Engelsen, Ultraviolet exposure scenarios: risk of erythema from recommendations
 790 on cutaneous vitamin D synthesis., Adv Exp Med Biol. 624 (2008) 72-85.

791 [51] C.J. Matz, D.M. Stieb, K. Davis, M. Egyed, A. Rose, B. Chou, O. Brion, Effects of Age, Season, Gender
 792 and Urban-Rural Status on Time-Activity: Canadian Human Activity Pattern Survey 2 (CHAPS 2), Int J
 793 Env Res Pub He. 11 (2014) 2108-2124.

794 [52] V. Carson, R.J. Iannotti, W. Pickett, I. Janssen, Urban and rural differences in sedentary behavior
 795 among American and Canadian youth, Health Place. 17 (2011) 920-928.

796 [53] T.N. Robinson, J.A. Banda, L. Hale, A.S. Lu, F. Fleming-Milici, S.L. Calvert, E. Wartella, Screen Media
 797 Exposure and Obesity in Children and Adolescents, Pediatrics. 140 (2017) S97-S101.

798 [54] H.J. Wilkie, M. Standage, F.B. Gillison, S.P. Cumming, P.T. Katzmarzyk, The home electronic media
 799 environment and parental safety concerns: relationships with outdoor time after school and over the
 800 weekend among 9-11 year old children, BMC Public Health. 18 (2018).

801 [55] E.A. Mitchell, A.W. Stewart, I. Braithwaite, R. Murphy, R.J. Hancox, C. Wall, R. Beasley, I.P.T.S. Grp,
 802 Factors associated with body mass index in children and adolescents: An international cross-sectional
 803 study, Plos One. 13 (2018).

804 [56] L.D. Rosen, A.F. Lim, J. Felt, L.M. Carrier, N.A. Cheever, J.M. Lara-Ruiz, J.S. Mendoza, J. Rokkum,
 805 Media and technology use predicts ill-being among children, preteens and teenagers independent of
 806 the negative health impacts of exercise and eating habits, Comput Hum Behav. 35 (2014) 364-375.

807 [57] T. Voortman, E.H. van den Hooven, A.C. Heijboer, A. Hofman, V.W.V. Jaddoe, O.H. Franco, Vitamin
 808 D Deficiency in School-Age Children Is Associated with Sociodemographic and Lifestyle Factors, J Nutr.
 809 145 (2015) 791-798.

810 [58] J. Kumar, P. Muntner, F.J. Kaskel, S.M. Hailpern, M.L. Melamed, Prevalence and Associations of
 811 25-Hydroxyvitamin D Deficiency in US Children: NHANES 2001-2004, Pediatrics. 124 (2009) E362-E370.

812 [59] J. Bryden, R. Bollman, Rural employment in industrialised countries, Agr Econ. 22 (2000) 185-197.

813 [60] C. Palacios, L. Gonzalez, Is vitamin D deficiency a major global public health problem?, J Steroid
 814 Biochem Mol Biol. 144 Pt A (2014) 138-145.

- [61] M. Shahriari, P.E. Kerr, K. Slade, J.E. Grant-Kels, Vitamin D and the skin, *Clin Dermatol.* 28 (2010) 663-668.
- [62] T.L. Clemens, S.L. Henderson, J.S. Adams, M.F. Holick, Increased Skin Pigment Reduces the Capacity of Skin to Synthesize Vitamin-D3, *Lancet.* 1 (1982) 74-76.
- [63] O.A. Hakim, K. Hart, P. McCabe, J. Berry, R. Francesca, L.E. Rhodes, N. Spyrou, A. Alfuraih, S. Lanham-New, Vitamin D production in UK Caucasian and South Asian women following UVR exposure, *J Steroid Biochem Mol Biol.* 164 (2016) 223-229.
- [64] L. Matsouka, L. Ide, J. Wortsman, J. MacLaughlin, M.F. Holick, Sunscreens suppress cutaneous vitamin D synthesis, *Journal of Clinical Endocrinology and Metabolism.* 64 (1987) 1165-1168.
- [65] M.A. Al-Ghamdi, S.A. Lanham-New, J.A. Kahn, Differences in vitamin D status and calcium metabolism in Saudi Arabian boys and girls aged 6 to 18 years: effects of age, gender, extent of veiling and physical activity with concomitant implications for bone health, *Public Health Nutr.* 15 (2012) 1845-1853.
- [66] K. Alyahya, W.T. Lee, Z. Al-Mazidi, J. Morgan, S. Lanham-New, Risk factors of low vitamin D status in adolescent females in Kuwait: implications for high peak bone mass attainment, *Arch Osteoporos.* 9 (2014) 178.
- [67] S.E. Barber, B. Kelly, P.J. Collings, L. Nagy, T. Bywater, J. Wright, Prevalence, trajectories, and determinants of television viewing time in an ethnically diverse sample of young children from the UK, *Int J Behav Nutr Phy.* 14 (2017).
- [68] E.S. Ford, Combined television viewing and computer use and mortality from all-causes and diseases of the circulatory system among adults in the United States, *Bmc Public Health.* 12 (2012).
- [69] D.M. Freedman, E.K. Cahoon, P. Rajaraman, J.M. Major, M.M. Doody, B.H. Alexander, R.W. Hoffbeck, M.G. Kimlin, B.I. Graubard, M.S. Linet, Sunlight and Other Determinants of Circulating 25-Hydroxyvitamin D Levels in Black and White Participants in a Nationwide US Study, *Am J Epidemiol.* 177 (2013) 180-192.
- [70] H. Jang, F.K. Koo, L. Ke, L. Clemson, R. Cant, D.R. Fraser, M.J. Seibel, M. Tseng, E. Mpofu, R.S. Mason, K. Brock, Culture and Sun Exposure in Immigrant East Asian Women Living in Australia, *Women Health.* 53 (2013) 504-518.
- [71] P.R. von Hurst, W. Stonehouse, J. Coad, Vitamin D status and attitudes towards sun exposure in South Asian women living in Auckland, New Zealand, *Public Health Nutr.* 13 (2010) 531-536.
- [72] D. Hunter, M. De Lange, H. Snieder, A.J. MacGregor, R. Swaminathan, R.V. Thakker, T.D. Spector, Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation, *J Bone Miner Res.* 16 (2001) 371-378.
- [73] L. Fu, F. Yun, M. Oczak, B.Y.L. Wong, R. Vieth, D.E.C. Cole, Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation, *Clin Biochem.* 42 (2009) 1174-1177.
- [74] J.M. Valdivielso, E. Fernandez, Vitamin D receptor polymorphisms and diseases, *Clin Chim Acta.* 371 (2006) 1-12.
- [75] T.C. Lins, R.G. Vieira, D. Grattapaglia, R.W. Pereira, Population analysis of vitamin D receptor polymorphisms and the role of genetic ancestry in an admixed population, *Genet Mol Biol.* 34 (2011) 377-385.
- [76] N. Elkum, F. Alkayal, F. Noronha, M.M. Ali, M. Melhem, M. Al-Arouj, A. Bennakhi, K. Behbehani, O. Alsmadi, J. Abubaker, Vitamin D insufficiency in Arabs and South Asians positively associates with polymorphisms in GC and CYP2R1 genes, *PLoS One.* 9 (2014) e113102.
- [77] B.R. Sapkota, R. Hopkins, A. Bjornnes, S. Ralhan, G.S. Wander, N.K. Mehra, J.R. Singh, P.R. Blackett, R. Saxena, D.K. Sanghera, Genome-wide association study of 25(OH) Vitamin D concentrations in Punjabi Sikhs: Results of the Asian Indian diabetic heart study, *J Steroid Biochem Mol Biol.* 158 (2016) 149-156.
- [78] N.H. Suaini, J.J. Koplin, J.A. Ellis, R.L. Peters, A.L. Ponsonby, S.C. Dharmage, M.C. Matheson, M. Wake, M. Panjari, H.T. Tan, P.E. Martin, A. Pezic, A.J. Lowe, D. Martino, L.C. Gurrin, P.J. Vuillermine, M.L.

Tang, K.J. Allen, I. HealthNuts Study, Environmental and genetic determinants of vitamin D insufficiency in 12-month-old infants, *J Steroid Biochem Mol Biol.* 144 Pt B (2014) 445-454.

[79] J.G. Hansen, W. Tang, K.C. Hootman, P.M. Brannon, D.K. Houston, S.B. Kritchevsky, T.B. Harris, M. Garcia, K. Lohman, Y. Liu, I.H. de Boer, B.R. Kestenbaum, C. Robinson-Cohen, D.S. Siscovick, P.A. Cassano, Genetic and environmental factors are associated with serum 25-hydroxyvitamin D concentrations in older African Americans, *J Nutr.* 145 (2015) 799-805.

[80] S.J. Felton, M.S. Cooke, R. Kift, J.L. Berry, A.R. Webb, P.M.W. Lam, F.R. de Gruijl, A. Vail, L.E. Rhodes, Concurrent beneficial (vitamin D production) and hazardous (cutaneous DNA damage) impact of repeated low-level summer sunlight exposures, *Brit J Dermatol.* 175 (2016) 1320-1328.

[81] J. Narbutt, P.A. Philipsen, A. Lesiak, T.S. Liljendahl, D. Segerback, J. Heydenreich, D. Chlebna-Sokol, P. Olsen, G.I. Harrison, A. Pearson, K. Baczynska, M. Rogowski-Tylman, H.C. Wulf, A.R. Young, Children sustain high levels of skin DNA photodamage, with a modest increase of serum 25-hydroxyvitamin D-3, after a summer holiday in Northern Europe, *Brit J Dermatol.* 179 (2018) 940-950.

[82] A.R. Webb, Assessing benefits and risks of holiday sun exposure in children, *Brit J Dermatol.* 179 (2018) 822-823.

[83] NICE, New NICE guidelines on sun exposure warn 'tanning is unsafe', 2016.

[84] M.D. Farrar, R. Kift, S.J. Felton, J.L. Berry, M.T. Durkin, D. Allan, A. Vail, A.R. Webb, L.E. Rhodes, Recommended summer sunlight exposure amounts fail to produce sufficient vitamin D status in UK adults of South Asian origin, *American Journal of Clinical Nutrition.* 94 (2011) 1219-1224.

[85] A.L. Darling, D.J. Blackbourn, K.R. Ahmadi, S.A. Lanham-New, Vitamin D supplement use and associated demographic, dietary and lifestyle factors in 8024 South Asians aged 40-69 years: analysis of the UK Biobank cohort, *Public Health Nutr.* (2018) 1-11.

[86] T. Jaaskelainen, S.T. Itkonen, A. Lundqvist, M. Erkkola, T. Koskela, K. Lakkala, K.G. Dowling, G.L. Hull, H. Kroger, J. Karppinen, E. Kyllonen, T. Harkanen, K.D. Cashman, S. Mannisto, C. Lamberg-Allardt, 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 (2017) 1512-1520.

[87] L.J. Black, K.M. Seamans, K.D. Cashman, M. Kiely, An Updated Systematic Review and Meta-Analysis of the Efficacy of Vitamin D Food Fortification, *J Nutr.* 142 (2012) 1102-1108.

[88] L. Tripkovic, L.R. Wilson, K. Hart, S. Johnsen, S. de Lusignan, C.P. Smith, G. Bucca, S. Penson, G. Chope, R. Elliott, E. Hypponen, J.L. Berry, S.A. Lanham-New, Daily supplementation with 15 μ g vitamin D-2 compared with vitamin D-3 to increase wintertime 25-hydroxyvitamin D status in healthy South Asian and white European women: a 12-wk randomized, placebo-controlled food-fortification trial, *American Journal of Clinical Nutrition.* 106 (2017) 481-490.