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## The risks and benefits of sun exposure 2016

David G. Hoel<sup>a</sup>, Marianne Berwick<sup>b</sup>, Frank R. de Gruijl<sup>c</sup>, and Michael F. Holick<sup>d</sup> 

<sup>a</sup>Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA; <sup>b</sup>Department of Internal Medicine and University of New Mexico Cancer Center, Division of Epidemiology and Biostatistics, University of New Mexico, Albuquerque, NM, USA; <sup>c</sup>Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands; <sup>d</sup>Section of Endocrinology, Diabetes and Nutrition, Department of Medicine, Boston University Medical Center, Boston, MA, USA

### ABSTRACT

Public health authorities in the United States are recommending that men, women and children reduce their exposure to sunlight, based on concerns that this exposure will promote skin cancer. On the other hand, data show that increasing numbers of Americans suffer from vitamin D deficiencies and serious health problems caused by insufficient sun exposure. The body of science concerning the benefits of moderate sun exposure is growing rapidly, and is causing a different perception of sun/UV as it relates to human health. Melanoma and its relationship to sun exposure and sunburn is not adequately addressed in most of the scientific literature. Reports of favorable health outcomes related to adequate serum 25(OH)D concentration or vitamin D supplementation have been inappropriately merged, so that benefits of sun exposure other than production of vitamin D are not adequately described. This review of recent studies and their analyses consider the risks and benefits of sun exposure which indicate that insufficient sun exposure is an emerging public health problem. This review considers the studies that have shown a wide range health benefits from sun/UV exposure. These benefits include among others various types of cancer, cardiovascular disease, Alzheimer disease/dementia, myopia and macular degeneration, diabetes and multiple sclerosis. The message of sun avoidance must be changed to acceptance of non-burning sun exposure sufficient to achieve serum 25(OH)D concentration of 30 ng/mL or higher in the sunny season and the general benefits of UV exposure beyond those of vitamin D.

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cancer; cardiovascular disease; melanoma; ultraviolet radiation; vitamin D; 25-hydroxyvitamin D

### Introduction

Public health authorities in the United States are currently advising that human sun exposure be reduced.<sup>1</sup> At the same time, NHANES data show that 32% of Americans suffer from vitamin D insufficiency.<sup>a</sup>

In this paper we review the current state of the science of the risks and benefits of sun exposure and suggest that public health advice be changed to recommend that all men, women and children accumulate sufficient non-burning sun exposure to maintain their serum 25hydroxyvitaminD [25(OH)D] levels at 30 ng/mL or more year-round.

### History

The first scientifically-established health benefit of sun exposure was the discovery in 1919 that sunlight cured rickets.<sup>4-5</sup> This was followed in 1924 up by the discovery

that an inactive lipid in the diet and skin could be converted by UV light into an antirachitic substance.<sup>6</sup> The identification of vitamin D occurred in 1931.<sup>7</sup> The association between sun exposure and reduced cancer mortality in North America was identified in the 1960s. In the 1980s, it was hypothesized that vitamin D was the protective factor. For most of the intervening years, instead of pursuing further benefits of sun exposure, scientific inquiry focused on the health risks of sun exposure, especially melanoma and other types of skin cancer.<sup>8</sup> Chemical sunscreens were developed in 1928.<sup>9</sup> Avoidance of intentional sun exposure and use of chemical sunscreens persisted as the standard advice of physicians and public health authorities for reducing the risk of melanoma and other forms of skin cancer.<sup>1,8</sup> The risks of inadequate sun exposure have been largely ignored. Recently, however, scientific inquiry has increasingly

**CONTACT** David G. Hoel  [dghoel@gmail.com](mailto:dghoel@gmail.com)  36 S. Battery, Charleston, SC 29401, USA.

<sup>a</sup>The 2010 Institute of Medicine vitamin D report defined vitamin D deficiency as serum 25(OH)D levels of less than 12ng/mL and vitamin D insufficiency as serum 25(OH)D levels of less than 20 ng/mL.<sup>2</sup> NHANES data for 2001–2006 show that 8% of Americans had 25(OH)D below 12 ng/mL and 32% had 25(OH)D below 20 ng/mL.<sup>3</sup>

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turned to the benefits of moderate sun exposure and the public health risks of inadequate sun exposure.<sup>10</sup>

## Risks of sun exposure

### Melanoma

The mechanism of melanoma is unknown, but is believed to be linked to genetic factors.<sup>11</sup> The principal identified non-genetic risk factor is ultraviolet radiation (UVR) exposure, and the relationship between melanoma and UVR is 2-sided: non-burning sun exposure is associated with a reduced risk of melanoma, while sunburns are associated with a doubling of the risk of melanoma.<sup>12</sup> It has long been observed that outdoor workers have a lower incidence of melanoma than indoor workers.<sup>13-19</sup> A 1997 meta-analysis found an OR of 0.86 (95% CI: 0.77-0.96) for occupational sun exposure.<sup>18</sup>

Biologically, UVB is known to induce DNA damage through the creation of pyrimidine dimers while UVA does so at orders of magnitude less efficiently.<sup>20</sup> Oxidative damage through the creation of free radicals (singlet oxygen and hydrogen peroxide) occurs at all UVR frequencies.<sup>20</sup> However, the human body has many defenses against such damage including DNA repair mechanisms, cell cycle and growth inhibitions, reduced proliferation, enhanced sensitivity to apoptosis, enhancement of cellular differentiation and anti-inflammatory effects; many of which are related to vitamin D produced by exposure to UVB.<sup>21-25</sup>

With respect to sunburns, melanocytes are not replicating cells, so once DNA damage has occurred, it is necessary for cellular replication to take place for the possibility of unrepaired or mis-repaired melanocytes to develop into malignant melanoma.<sup>20</sup> Sunburns correspond with rare occasions of cell divisions and ensuing vulnerability to mutations in otherwise indolent melanocytes.<sup>20</sup> With respect to chronic non-burning sun exposure, it is thought that protection against sunburn and development of melanoma derives from photo-adaptation (increased melanisation and epidermal thickening) or from the induction of higher levels of vitamin D, or possibly both.<sup>12,25-28</sup> Vitamin D produced by UVB exposure is converted to the active form of vitamin D by its sequential metabolism in the liver to form the major circulating form of vitamin D, 25-hydroxyvitamin D [25(OH)D] which is then converted in the kidneys to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D]. Evidence suggests that vitamin D that

is produced in the skin can also be converted in the skin to its active form 1,25(OH)<sub>2</sub>D<sup>25</sup>, thereby enhancing DNA repair<sup>29</sup> and lowering cancer risk.

The incidence of melanoma in the United States has increased dramatically from 1 per 100,000 people per year in 1935 to 23 per 100,000 per year in 2012. Various explanations for this phenomenon have been suggested, including diagnostic drift,<sup>30</sup> depletion of the ozone layer,<sup>31</sup> the widespread use of artificial UVR devices,<sup>32</sup> and the proliferation of large windows in office buildings.<sup>15</sup> None of these explanations is particularly satisfactory for the reason that none explains the steady increase in melanoma incidence since 1935. While sunburns have been associated with a doubling of melanoma risk,<sup>12</sup> chronic non-burning sun exposure and outdoor occupations have been associated with reduced risk of melanoma.<sup>12-19</sup> Indoor occupations such as professional, managerial, clerical, sales and service workers grew from 25% to 75% of total employment between 1910 and 2000.<sup>33</sup> 25% of Americans lived on farms in 1930 whereas only 2% do so today.<sup>34</sup> Indoor attractions such as air conditioning, television, computers and the internet probably have led to Americans spending more of their leisure time indoors, the prevalence of sunburns is high and has been increasing<sup>b</sup>, and serum 25(OH)D levels of the American public, a likely marker for sun exposure, are low and have been declining.<sup>c</sup> A more plausible explanation for the rise in melanoma incidence since 1935 may be the continually-increasing insufficient non-burning sun exposure and related increasing vitamin D deficiency/insufficiency, and the increasing sunburn prevalence experienced by the American public over the same time period<sup>d</sup>. Furthermore,

<sup>b</sup>According to the Centers for Disease Control and Prevention, the prevalence of sunburns increased from 32% of all adults in 1999 to 34% in 2004<sup>35</sup> and up to 50% in 2012.<sup>36</sup> Among adolescents aged 12-18 in 1999, 83% reported at least one sunburn in the previous summer and 36% reported three or more sunburns in the previous summer.<sup>37</sup>

<sup>c</sup>Data on temporal trends in vitamin D levels are contained in study by Ginde et al. 2009<sup>38</sup> who reported that NHANES data on serum 25(OH)D levels show that the prevalence of 25(OH)D of less than 10 ng/mL increased from 2% in 1988-1994 to 6% in 2001-2004 while over the same time period the prevalence of 25(OH)D of less than 20 ng/mL increased from 22% to 36%, and for 25(OH)D of less than 30 ng/mL increased from 55% to 77%.

<sup>d</sup>Such an explanation is not new. White et al. 1988<sup>39</sup> (published as Garland et al. 1990<sup>40</sup>) proposed that low levels of vitamin D (either locally available in skin or circulating in plasma) allow melanomas which were previously initiated by sunlight exposure to develop into clinically apparent disease in continually sunlight deprived individuals. This proposal was apparently ignored as precautions against melanoma focused on sun avoidance and liberal use of chemical sunscreens, with inadequate attention paid to the role of sunburns in melanomagenesis and to the role of vitamin D in inhibiting cancer. The first cancer cell line shown in 1980 to be inhibited in growth by 1,25(OH)<sub>2</sub>D was in fact a melanoma cell line. In 1989 Gallagher et al.<sup>41</sup> suggested that part of the increased incidence in melanoma could be attributed to the decline in outdoor workers.

epidemiological studies do not indicate any difference in melanoma risk based on the age at which UVR exposure occurs.<sup>12,17,18</sup> Sunburns appear to be equally risky at any age.<sup>17</sup> The public health messages of the past 50 y to avoid sun exposure and to use chemical sunscreens may have contributed to the rise in melanoma incidence.

We can find no consistent evidence that use of chemical sunscreens reduces the risk of melanoma. Green et al. 2011,<sup>42</sup> found in a prospective study that there may be an association between sunscreen use and reduced risk of melanoma. However, since the participants were told they were participants in a skin cancer prevention trial and were questioned periodically during the trial on their use of sunscreen, the likelihood that they were significantly more diligent in applying sunscreen in accordance with manufacturers' instructions than ordinary users of sunscreen cannot be discounted.<sup>6</sup> In addition, this study took place in a tropical environment, differing significantly from the environments of North America and Europe. Use of a placebo sunscreen was barred by ethical concerns.

Sunscreens do, however, reduce acclimatization to UVR and vitamin D production in the skin.<sup>46</sup> Since public health authorities recommend liberal use of sunscreens for good health, the labeling of sunscreens should contain a statement about the possibility of vitamin D deficiency that may result from excessive use of sunscreens. Labeling should also state that sunscreens have not been shown to be effective in reducing the risk of melanoma. Sunscreens have been shown in one study to be effective in reducing the risk of squamous cell, but not basal cell, skin cancer.<sup>47</sup>

### **Nonmelanoma skin cancer (NMSC)**

There are no official registries for basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), and estimates of the prevalence of these carcinomas vary widely. One group of investigators examined Medicare fee-for-service data, extrapolated to the entire United States population, and estimated that 2,152,500 persons were treated for 3,507,693 NMSCs in 2006.<sup>48</sup> Several of the same investigators estimated that 3,315,554 persons were treated for 5,434,193 NMSCs

in 2012 and revised the 2006 estimates to 2,463,567 persons and 4,013,890 NMSCs.<sup>49</sup> These latter estimates indicated a 14% increase in Medicare NMSCs over the 6-year period 2006–2012 and a 54% increase in non-Medicare NMSCs over the 6-year period. It is not clear in this analysis that all treatments for NMSCs were in fact treatments for malignancies rather than for non-cancerous lesions, and these investigators found the ratio of BCC to SCC to be 1 to 1 instead of the expected 4 to 1. Another recent study<sup>50</sup> which histologically confirmed all cases but studied only BCCs, calculated based on an analysis of a Kaiser Permanente BCC registry that approximately 2 million BCCs are treated annually in the United States in an undisclosed number of persons. Assuming a 4 to 1 ratio of BCC to SCC, this would indicate that 2.5 million NMSCs are treated annually. This study found that the incidence of BCC increased 17% during the 15-year period from 1998 to 2012.

As with melanoma, sunburns are associated with increased risk of SCC and BCC.<sup>16,17,51</sup> Cumulative sun exposure, which is associated with decreased risk of melanoma, is apparently associated with increased risk of SCC and BCC, although the relationship between cumulative sun exposure and NMSC is not entirely clear. Armstrong and Kricger 2001<sup>17</sup> found that only SCC, not BCC, is related to total sun exposure, and Rosso et al. 1998<sup>52</sup> found no association between cumulative lifetime sun exposure and BCC. Kennedy et al. 2003<sup>16</sup> found a positive association between increasing lifetime sun exposure and the development of SCC and BCC but statistical significance was not always reached after age adjustment. English et al. 1998<sup>53</sup> found that total time spent outdoors was only weakly associated with SCC. Gallagher et al. 1995a,b<sup>54,55</sup> found no association between cumulative lifetime sun exposure and risk of SCC or BCC, but Gallagher et al. 1995b<sup>55</sup> found that occupational sun exposure in the 10 y prior to diagnosis was associated with increased risk of SCC. Many studies have found increased risk of SCC and to a lesser extent BCC from occupational sun exposure.<sup>17,51,56,57</sup> Alam et al. 2001<sup>58</sup> found that the risk of SCC, but not BCC, is directly related to cumulative total dose of ionizing radiation from x-rays, that SCC may develop on sun-exposed areas in people with certain genodermatoses, such as oculocutaneous albinism, that chemical agents such as soot, arsenic and polycyclic hydrocarbons have historically been a major cause of SCC, and that

<sup>6</sup>Sunscreens are intended to prevent sunburn when used in thickness and frequency recommended by manufacturers or used in setting SPFs. However, studies have shown that the incidence of sunburn is higher or the same in people who almost always use sunscreens compared with those who rarely use sunscreens.<sup>43-45</sup>

human papillomavirus infection has been associated with SCC. The US Preventive Services Task Force, in its May 2012 Final Recommendation Statement on skin cancer counseling,<sup>59,60</sup> stated that studies that measured long-term or total sun exposure had found no association between cumulative sun exposure and either SCC or BCC.

## Benefits of sun exposure; Risks of inadequate sun exposure

### General

Scientific inquiry into the benefits of sun exposure languished for many decades following the observation in the 1920s that farmers in Europe developed non-melanoma skin cancer on their most sun-exposed areas - their ears, face, nose and backs of their hands.<sup>61</sup> Research on the benefits of sun exposure has accelerated in the past 15 y and particularly in the past 5 y.<sup>62</sup>

### Vitamin D

#### Biological plausibility

Vitamin D is a hormone and most cells and organs in the human body have a vitamin D receptor, which explains the wide variety of diseases and disorders that have been linked to vitamin D insufficiency in epidemiological studies.<sup>63</sup> The production of vitamin D by UV B radiation, the availability of vitamin D in food and supplements, and the biological plausibility of vitamin D as a mediator for a large variety of favorable health outcomes are well described in the literature.<sup>22-25,63-65</sup>

#### Recommended vitamin D status

There is considerable controversy within the scientific community regarding optimum 25(OH)D levels for human health. In 2010, the Institute of Medicine defined vitamin D deficiency as 25(OH)D of less than 12 ng/mL and vitamin D insufficiency as 25(OH)D of less than 20 ng/mL.<sup>2</sup> In 2011, The Endocrine Society defined vitamin D deficiency as 25(OH)D below 20 ng/mL and vitamin D insufficiency as 25(OH)D of 21–29 ng/mL.<sup>66</sup> Others have suggested even higher levels.<sup>22,67-69</sup> A letter signed by many respected vitamin D scientists and physicians recommends 40–60 ng/mL<sup>70</sup> which is in line with what the Endocrine Society recommended as the preferred range for health - i.e, a 25(OH)D of 40–60 ng/mL.<sup>66</sup> Most

reference laboratories have raised the lower boundary of the normal range to 30 ng/mL.<sup>68</sup>

#### Prevalence of vitamin D deficiency/insufficiency

Ginde et al. 2009<sup>38</sup> reported that NHANES data on serum 25(OH)D levels show that the prevalence of 25(OH)D of less than 10 ng/mL increased from 2% of the US population in NHANES III (1988–1994) to 6% in NHANES 2001–2004, and that over the same period the prevalence of 25(OH)D of less than 20 ng/mL increased from 22% of the US population to 36%.<sup>f</sup> The IOM report did not offer a solution to this problem since that was not its purpose; the IOM was charged with determining the DRI of vitamin D supplements and found that there was insufficient scientific evidence on the benefits of vitamin D supplementation to support raising the DRI of vitamin D supplements to more than 600 International Units (IUs) per day.<sup>8</sup> Using the Endocrine Society's definition of vitamin D sufficiency of 30 ng/mL, the level of vitamin D insufficiency increased from 55% of the US population in NHANES III to 77% in NHANES 2001–2004,<sup>38</sup> which indicates that the vast majority of Americans have an insufficient vitamin D status.

#### Mediators other than vitamin D

Several studies, discussed below, have found that mediators other than vitamin D are or may be involved in the beneficial effects of adequate sun exposure.

#### Benefits of vitamin D/sun exposure; Risks of vitamin D insufficiency/inadequate sun exposure

We next examined the health benefits associated with increasing levels of sun exposure and/or circulating serum 25(OH)D and the health risks associated with inadequate sun exposure and/or inadequate serum 25(OH)D, with particular emphasis on studies published since the 2010 IOM report.

<sup>f</sup> The differences between NHANES III and NHANES 2001–2004 may be attenuated by approximately 4 ng/mL after adjustment for improvements in the serum 25(OH)D assay performance from NHANES III to NHANES 2001–2004.<sup>71</sup>

<sup>g</sup> The Endocrine Society's 2012 review of the nonskeletal effects of vitamin D also found there was insufficient evidence to support a role of vitamin D supplementation in correcting vitamin D insufficiency.<sup>66</sup>

## All-cause mortality

Chowdhury et al. 2014<sup>72</sup> performed a meta-analysis of data from 73 cohort studies with 849,000 participants and 22 randomized controlled trials with 31,000 participants. This study found an inverse association of circulating 25(OH)D with risks of death due to cardiovascular diseases, cancer and other causes (RR 1.35, 95% CI 1.22–1.49 for all cause mortality, comparing the bottom third versus top 2-thirds of baseline circulating 25(OH)D distribution), but found that, with respect to possible benefits of vitamin D supplementation, further investigation is required before any widespread supplementation occurs. The prevalence of vitamin D insufficiency (defined as 25(OH)D less than 30 ng/mL) was found to be 69.5% for the United States and 86.4% for Europe. The authors further estimate that 9.4% of all deaths in Europe and 12.8% in the United States could be attributable to vitamin D insufficiency. Other meta analyses include Garland et al. 2014<sup>73</sup> who pooled the data from 32 studies (30 cohort studies and 2 nested case-control studies) that examined age-adjusted all-cause mortality and serum 25(OH)D levels and found that the overall age-adjusted hazard ratio for all-cause mortality comparing the lowest (0–9 ng/mL) group to the highest (greater than 50 ng/mL) was 1.9 (95% CI 1.6–2.2), indicating that individuals in the lowest group had nearly twice the age-adjusted death rate as those in the highest quantile. Schottker et al. 2014<sup>74</sup> conducted a meta-analysis of 8 cohort studies with 26,000 participants and found a 1.6-fold higher all-cause mortality in the bottom quintile (25(OH)D approximately <12 ng/mL) compared with the top quintile (25(OH)D approximately > 24 ng/mL) (RR 1.57, 95% CI 1.36–1.81).

Lindqvist et al. 2014<sup>75</sup> assessed the avoidance of sun exposure as a risk factor for all-cause mortality for 29,518 Swedish women in a prospective 20-year follow-up of the Melanoma In Southern Sweden cohort and found that the population attributable risk for all-cause mortality for those habitually avoiding sun exposure was 3%. As compared to the highest sun exposure group, the all-cause mortality rate was doubled (RR 2.0, 95% CI 1.6–2.5) among avoiders of sun exposure and increased by 40% (RR 1.4, 95% CI 1.1–1.7) in those with moderate exposure. The authors noted that Sweden has national guidelines providing restrictive advice on sun exposure habits in order to

lower the risk of skin cancer, and stated that these guidelines may be harmful in terms of overall health of the population. Lindqvist et al. 2016<sup>76</sup> found that women with active sun exposure habits were mainly at lower risk of cardiovascular disease mortality and other non-cancer mortality, and noted that avoidance of sun exposure is a risk factor for death of a similar magnitude as smoking. “Our finding that avoidance of sun exposure was a risk factor for all-cause death of the same magnitude as smoking is novel.”

Afzal et al. 2014<sup>77</sup> conducted a Mendelian randomization analysis showing that genetically low 25(OH)D levels were associated with increased all-cause mortality, but not with cardiovascular mortality. These results confirm that the measured low 25(OH)D levels in the general population associated with increased mortality as indicated in the above meta-analyses are related to vitamin D rather than simply a consequence of poor health or sequestration of vitamin D in adipose tissue, but indicate that some mediator other than vitamin D may be involved in cardiovascular mortality. Afzal et al. 2014<sup>77</sup> was the first study with sufficient sample size to investigate the association of genetically low 25(OH)D levels with increased mortality.

## Colorectal cancer

Rebel et al. 2014<sup>78</sup> showed for the first time the causality of the relationship between moderate UVR exposure and primary intestinal tumors in mice. The UVR-induced reduction in intestinal cancer in mice could at least in part be attributed to vitamin D. However, the investigators also found a reduced progression to malignancy as a result of UVR exposure which appeared not to be attributable to vitamin D. Three groups of hairless mice were compared: one on a low-vitamin D diet without vitamin D supplementation or UVR exposure, one on a low-vitamin D diet with vitamin D supplementation but without UVR exposure, and one on a low-vitamin D diet without vitamin D supplementation but with moderate UVR exposure. This permitted the comparison of effects of dietary vitamin D supplementation and UVR exposure. The tumor load (area) was similarly and significantly reduced in both the vitamin D supplementation group and the UVR exposure group, but only the UVR exposure group had a lower percentage of malignant adenocarcinomas. Thus the study provided the first

experimental evidence that physiologically relevant, moderate UVR exposure can reduce the load of primary intestinal tumors, which reduction can at least in part be explained by an increase in vitamin D status as a comparable reduction in tumor load was observed in the vitamin D supplementation group that had a similar increase in vitamin D status. However, a reduction in malignant progression and growth of adenocarcinomas could not be attributed to vitamin D as these effects were only observed with moderate UVR exposure and not with dietary vitamin D supplementation. Rebel et al. 2014<sup>78</sup> noted that prior studies had long shown that low exposure to solar UVR is significantly associated with increased risk of colon cancer, and that several recent studies showed that increased risk of colon cancer was significantly associated with prediagnostic low vitamin D status. The 2010 IOM report<sup>64</sup> acknowledged that epidemiological studies examining associations between vitamin D status and colorectal cancer incidence generally supported an inverse association, but declined to base vitamin D DRI's on colon cancer outcomes because of the paucity and conflicting findings of prospective randomized controlled trials involving vitamin D supplementation. Notably, the most recent, and only observational, study reviewed in the IOM report found no association of vitamin D supplementation with colon cancer risk, but found that patients in the highest quintile of prediagnostic circulating 25(OH)D concentration (more than 40 ng/mL) had a 42% reduced risk of colon cancer as compared to patients with the lowest quintile (less than 10 ng/mL).<sup>79</sup>

### Breast cancer incidence and mortality

Mohr et al. 2014<sup>80</sup> conducted a meta-analysis of data from 5 studies on the relationship between serum 25(OH)D levels at time of breast cancer diagnosis and breast cancer mortality which found that patients in the highest quintile of 25(OH)D (more than 32 ng/mL) had approximately half the death rate from breast cancer as those in the lowest quintile (less than 14 ng/mL) (HR 0.56; 95% CI: 0.4–0.7). The authors recommended that serum 25(OH)D levels in all breast cancer patients should be restored to the normal range, which the authors defined as 30–80 ng/mL.

Engel et al. 2010<sup>81</sup> found a 27% reduced risk of breast cancer incidence in women in the highest tertile of 25(OH)D (greater than 27ng/mL) as compared to

the lowest tertile (less than 19.8 ng/mL) in a nested case-control study (OR 0.73; 95% CI: 0.55–0.96). The authors noted that all 6 previous case-control studies on the subject have reported a significant inverse association between serum 25(OH)D levels and breast cancer and that an inverse effect between sun exposure and breast cancer has previously been observed. John et al. 1999<sup>82</sup> found that women with higher solar UVB exposure in NHANES III had only about half the incidence of breast cancer as those with lower solar exposure (RR 0.50; 95% CI: 0.33–0.80) and Knight et al 2007<sup>83</sup> found that increasing sun exposure from ages 10 to 19 reduced breast cancer risk by 35% (OR 0.65, 95% CI 0.50–0.85 for the highest quartile of outdoor activities vs. the lowest).

### Non-hodgkins lymphoma, colorectal, prostate and breast cancer, and multiple sclerosis

Van der Rhee et al. 2013<sup>84</sup> noted that the association between solar radiation and reduced cancer mortality in North America was identified more than 60 y ago<sup>85</sup> and that in 1980 it was hypothesized that vitamin D was the protective factor.<sup>40</sup> The authors conducted a systematic review to verify if epidemiological evidence is in line with the hypothesis that the possible preventive effect of sunlight on cancer is more than just the effect of vitamin D. Vitamin D intake studies were excluded from the review and the authors stated that their review presented the sum of epidemiological knowledge on the influence of sun exposure and circulating 25(OH)D levels on the risk of colorectal cancer, prostate cancer, breast cancer and non-Hodgkin's lymphoma (NHL). They concluded that: 1) there is an inverse association between sun exposure and both colorectal cancer risk and colorectal cancer mortality; 2) there is an inverse association between vitamin D status and both colorectal cancer risk and colorectal cancer mortality; 3) there is a negative association between sun exposure and prostate cancer risk and prostate cancer mortality but not between vitamin D status and prostate cancer risk or mortality; 4) there is an inverse correlation between sun exposure and breast cancer risk and breast cancer mortality, and possibly between 25(OH)D and breast cancer mortality, but studies on the association between 25(OH)D and breast cancer risk are inconclusive; 5) there is a negative association between sun exposure and NHL risk and NHL mortality but not between vitamin D

status and NHL risk or mortality; 6) there is a negative association between sun exposure and lymphoma risk, but no association between lymphoma risk and vitamin D intake or 25(OH)D levels; and, 7) for multiple sclerosis, both experimental and epidemiological studies show that the preventative role of sun exposure is independent of vitamin D production. The authors concluded that for colorectal cancer and breast cancer the benefit of sun exposure is mediated by high vitamin D levels produced by sun exposure, whereas for prostate cancer, NHL and multiple sclerosis the benefit of sun exposure is independent of vitamin D.<sup>84</sup>

### Bladder cancer

Zhao et al. 2016<sup>86</sup> found a 30% reduced risk of bladder cancer associated with 25(OH)D concentrations above 30 ng/mL compared to less than 15 ng/mL.

### Cardiovascular disease (CVD)

Liu et al. 2014<sup>87</sup> found that hypertension is reduced by UVR-induced nitric oxide independent of vitamin D. They showed that stores of nitrogen oxides in the human skin are mobilized to the systemic circulation by exposure of the body to UVA radiation, causing arterial vasodilation and a resultant decrease in blood pressure independent of vitamin D, confirming the hypothesis of Feilisch et al. 2010.<sup>88</sup> These results correlate with the findings of Afzal et al. 2014<sup>77</sup> that genetically low 25(OH)D levels were associated with increased all-cause mortality but not with cardiovascular mortality, indicating that a mediator other than vitamin D may be involved in cardiovascular mortality, and with the results of Tunstall-Pedoe et al. 2015<sup>89</sup> challenging vitamin D's alleged role in cardiovascular disease.

### Metabolic syndrome (MetS) and type 2 diabetes

Vitezova et al. 2015<sup>90</sup> found that higher 25(OH)D levels were associated with lower prevalence of metabolic syndrome (OR 0.61, 95% CI 0.49–0.77 for more than 30 ng/mL versus less than 20 ng/mL) in the elderly in an analysis of data from 3240 people (median age 71.2 years) imbedded in the Rotterdam Study, a prospective population-based cohort study of middle-aged and elderly adults. Importantly, after adjustment for body mass index (BMI), higher 25(OH)D levels were still significantly associated with lower odds of

MetS. Almost concurrent with Vitezova et al. 2015, Clemente-Postigo et al. 2015<sup>91</sup> showed that low 25(OH)D levels are associated with type 2 diabetes independently of BMI. These findings are important in light of the 2010 IOM report's discounting of the association studies linking low 25(OH)D levels to increased risk of type 2 diabetes on the ground that they may be confounded by obesity, which not only predispose individuals to type 2 diabetes but may also cause lower 25(OH)D levels as a result of sequestration of vitamin D in adipose tissue and possibly other mechanisms. Vitezova et al. 2015 noted that other recent studies had found an inverse association between vitamin D status and MetS in younger populations, but only one other study of older persons had found the association while another study of older persons had not. Neither Vitezova et al. 2015,<sup>125</sup> nor Clemente-Postigo et al. 2015<sup>91</sup> cited Geldenhuys et al. 2014,<sup>92</sup> which found that UVR exposure levels, not vitamin D supplements or 25(OH)D levels, reduced the risk of obesity and type 2 diabetes, indicating that 25(OH) levels may be to some extent a marker for UVR exposure in this regard.

Afzal et al. 2013<sup>93</sup> measured 25(OH)D levels in 9841 persons of whom 810 developed type 2 diabetes during 29 y of follow-up. The investigators observed an association of low 25(OH)D with increased risk of type 2 diabetes (HR 1.35, 95% CI 1.09–1.66 for lowest (less than 5 ng/mL) vs. highest (more than 20 ng/mL) quartile of 25(OH)D. This finding was substantiated by the authors' meta-analysis of 14 studies representing 16 cohorts with a total of 72,204 participants and 4,877 type 2 diabetes events (HR 1.50, 95% CI 1.33–1.70 for the bottom vs. top quartile of 25(OH)D). A prior 2011 meta-analysis [134 Mitri 2011<sup>94</sup>] had shown that individuals with 25(OH)D levels above 25 ng/mL had a 43% lower risk of developing type 2 diabetes (95% CI, 2457%–) compared with individuals with 25(OH)D levels below 14 ng/mL, and that vitamin D supplementation had no effect.

### Alzheimer disease and cognitive decline

Littlejohns et al. 2014<sup>95</sup> [135] studied a group of 1,658 Americans age 65 and older who were able to walk unaided and who were free of dementia. The participants were followed for 6 y to investigate who went on to develop Alzheimer disease and other forms of dementia. The investigators found that participants



with serum 25(OH)D levels below 10 ng/mL were more than twice as likely to develop Alzheimer disease than participants with serum 25(OH)D levels greater than 20 ng/mL (HR 2.22, 95% CI 1.02–4.83) and participants with serum 25(OH)D levels of 10 ng/mL to 20 ng/mL were 69% more likely to develop Alzheimer disease than participants with serum 25(OH)D levels greater than 20 ng/mL (HR 1.69, 95% CI 1.06–2.69). Similar results were obtained for all-cause dementia. According to the authors, this was the first large, prospective, population-based study incorporating a comprehensive adjudicated assessment of dementia and Alzheimer to examine their relationship with vitamin D concentrations. This study confirms other recent studies linking low vitamin D levels with cognitive decline.<sup>96-102</sup>

Keeney et al. 2013<sup>96</sup> manipulated vitamin D status in middle-age to old-age rats by dietary supplementation with low, moderate and high levels of vitamin D. The results suggested that dietary vitamin D deficiency contributes to significant nitrosative stress in the brain and may promote cognitive decline in middle-age and elderly humans.

Annweiler et al. 2013<sup>97</sup> was a systematic review and meta-analysis finding that 25(OH)D levels were lower in Alzheimer cases than in controls (summary random effect size 1.40, 95% CI 0.26–2.54), which means that the probability is about 140% that an individual without Alzheimer would have a higher 25(OH)D level than an individual with Alzheimer if both individuals were chosen at random from a population.

### **Multiple sclerosis (MS), type 1 diabetes, rheumatoid arthritis**

Wang et al. 2014<sup>103</sup> found that UVR suppressed experimental autoimmune encephalomyelitis (EAE - an animal model of MS), independent of vitamin D production, confirming the conclusions of van der Rhee et al. 2013<sup>84</sup> and the findings of Becklund et al. 2010.<sup>104</sup> The investigators showed that UVB irradiation did not suppress immune response in the periphery, but suppressed EAE by blocking selectively the infiltration and binding of inflammatory cells into the central nervous system. These findings support the long-held view that the incidence of MS is inversely related to UVR exposure.<sup>105-109</sup>

Baarnhielm et al. 2012<sup>110</sup> was an association study finding that persons with low UVR exposure had a significantly increased risk of MS compared with those who reported the highest exposure (OR 2.2, 95% CI 1.5–3.3), and that this association persisted after adjustment for vitamin D status. Wang et al. 2014<sup>103</sup> and Baarnhielm et al. 2012<sup>110</sup> confirmed the conclusions of van der Rhee et al. 2013<sup>83</sup> that sun exposure reduces the risk of MS through pathways independent of vitamin D.

Ponsonby et al. 2005<sup>108</sup> stated that genetic factors appear to be involved in MS, but the low concordance among identical twins for MS<sup>111</sup> and trends of increasing incidence of MS over time<sup>112</sup> suggest environmental factors are also important determinants, and that UVR exposure may be one factor that can attenuate MS through several mechanisms and that some the pathways are independent of vitamin D. Similar conclusions were made about 2 other autoimmune diseases, type 1 diabetes and rheumatoid arthritis. The authors concluded that it was critical to consider the benefits of sun exposure as well as the risks, and to provide information to the public on the minimum sun exposure required for beneficial health effects as well as the maximal sun exposure to avoid the adverse health effects associated with excessive sun exposure. Mokry et al. 2015<sup>113</sup> was a Mendelian randomization analysis showing that genetically low 25(OH)D levels were associated with increased risk of MS. Jalkanen et al. 2015<sup>114</sup> found a high level of vitamin D deficiency during pregnancy in MS patients.

Jacobsen et al. 2015<sup>115</sup> found that more sun exposure in the third gestational trimester was associated with lower risk of type 1 diabetes in male children. Sawah et al. 2016<sup>116</sup> found a high prevalence of vitamin D deficiency (25(OH)D levels less than 20 ng/mL) in children and adolescents with type 1 diabetes. Kostoglou-Athanassiou et al. 2012<sup>117</sup> found a high prevalence vitamin D deficiency in patients with rheumatoid arthritis.

### **Psoriasis**

Gisoni et al. 2012<sup>118</sup> found that the prevalence of 25(OH)D of less than 20 ng/mL was 57.8% in patients with psoriasis vs. 29.7% in healthy controls, and that in a logistic regression analysis, vitamin D deficiency was associated with psoriasis independently of other factors (OR 2.50, 95% CI 1.18–4.89).

The investigators noted that topical vitamin D derivatives and UVB radiation are used in the treatment of psoriasis. Vitamin D status was found to be unrelated to levels of self-reported sun exposure, but the measure used for sun exposure, which was minutes per day of sun exposure from March to September, may not have been appropriate for vitamin D production since it apparently did not include the time of day or the area of skin exposed.

### Liver disease

Gorman et al. 2015<sup>119</sup> in a review stated that a large number of studies in recent Years<sup>92,120,121</sup> have shown that exposure to UVR has the potential to curtail the development of non-alcoholic fatty liver disease (NAFLD) through vitamin D dependent and vitamin D independent mechanisms. The authors noted that most observational studies support an inverse association between serum 25(OH)D levels and NAFLD, but that vitamin D supplementation did not produce the same results. The authors further stated that circulating vitamin D levels may represent a proxy for bodily exposure to sunlight<sup>122</sup> explaining the observation that mediators induced by sun exposure other than vitamin D may play important roles in curtailing NAFLD.

### Statin intolerance and muscle pain, weakness

Khayznikov et al. 2015<sup>67</sup> found that statin intolerance because of myalgia, myositis, myopathy, or myonecrosis associated with serum 25(OH)D less than 23 ng/mL can be resolved with vitamin D supplementation raising serum 25(OH)D to 53 ng/mL. Aleksic et al. 2015<sup>123</sup> found that low vitamin D levels are a potentially significant and correctible risk factor for statin-related myopathy, especially in African-Americans.

### Macular degeneration

Millen et al. 2015<sup>124</sup> observed a 6.7-fold increased risk of age-related macular degeneration (AMD) among women with serum 25(OH)D levels less than 12 ng/mL who also had genetic risk for AMD, and noted that previous studies had found that decreased odds of AMD are associated with high compared to low concentrations of 25(OH)D.

### Dental caries in infants

Schroth et al. 2014<sup>125</sup> found that low prenatal 25(OH)D concentrations were associated with increased risk of dental caries among offspring in the first year of life.

### Reverse causation

Autier et al. 2014<sup>126</sup> suggested that low serum 25(OH)D levels may be the result rather than the cause of diseases associated with low serum 25(OH)D levels in observational studies (reverse causation). The authors offer little evidence to support such a hypothesis, and it is contraindicated by the prospective nature of many of the studies linking serum 25(OH)D levels with health outcomes, by Mendelian randomization studies<sup>77,113</sup> and by the body of knowledge concerning the bioactivity of vitamin D, particularly its cancer-inhibiting properties.

### Obesity

Geldenhuis et al. 2014<sup>92</sup> suggests that UVR exposure may be an effective means of suppressing the development of obesity and metabolic syndrome through mechanisms that are independent of vitamin D but dependent on other UVR-induced mediators such as nitric oxide. This study investigated whether UVR and/or vitamin D supplementation had an effect on the development of obesity and type 2 diabetes in mice fed a high-fat diet, and found that UVR significantly suppressed weight gain but vitamin D supplementation did not. These results indicate that low vitamin D status in obese persons may only be a marker for low UVR exposure or a result of sequestration of vitamin D in adipose tissue, and provide a new view of previous studies showing a consistent association between increasing body mass index and lower serum 25(OH)D levels.<sup>127</sup>

### Myopia

French et al. 2015<sup>128</sup> was a review stating that recent epidemiological evidence suggests that children who spend more time outdoors are less likely to be or to become myopic, irrespective of how much near work they do or whether their parents are myopic. The likely mechanism for this protective effect is visible light stimulating release of dopamine from the retina, which inhibits increased axial elongation, the structural basis of myopia.

The authors describe the effect of time outdoors on the risk of myopia as robust. The prevalence of myopia in the US in persons 12 to 54 y old increased 66% between 1971–1972 and 1999–2004, from 25.0% to 41.6%, according to the National Eye Institute of the National Institutes of Health.<sup>129,130</sup> For African Americans, the increase was 157.7%.<sup>130</sup> This high prevalence of myopia presents a major public health problem since, in addition to requiring corrective lenses, myopia poses substantially increased risk of retinal detachment, glaucoma, macular degeneration, amblyopia and cataracts.<sup>131,132</sup>

### Other benefits of sun exposure

Lambert et al. 2002<sup>133</sup> suggested that the prevailing amount of sunlight affects brain serotonergic activity. Deficiencies in serotonin and brain serotonergic activity have been linked to sudden infant death syndrome,<sup>134</sup> seasonal affective disorder,<sup>133</sup> depression,<sup>135</sup> schizophrenia,<sup>136</sup> Alzheimer disease,<sup>137</sup> and migraine headaches.<sup>138</sup> Beta-endorphin, a neuro-hormone that acts as an analgesic, has been known for many years to be released in the human body by exercise,<sup>139</sup> producing a feeling of wellbeing similar to the feeling of wellbeing induced by sun exposure. A recent study showed that UVR exposure significantly raised circulating plasma  $\beta$ -endorphin levels in a UV-exposure mouse model, leading to suggestions that UVR exposure is addictive.<sup>140</sup> Alternatively, the release of  $\beta$ -endorphins by sun exposure could be a natural reward mechanism encouraging sun exposure.

The benefits of serotonin and  $\beta$ -endorphin, as well as the effects of sun exposure on melatonin, photodegradation of folic acid, immunomodulation, photodaptation, and circadian clocks, are reviewed in van der Rhee et al. 2016.<sup>10</sup>

### Vitamin D supplements vs. sun exposure

In light of the studies discussed in this review that found health outcomes related to sun exposure independent of vitamin D, health outcomes dependent on serum 25(OH)D levels but not vitamin D supplementation, and health outcomes dependent on mediators other than vitamin D, it is apparent that vitamin D supplements are not an effective substitute for adequate sun exposure.

### Balancing the risks of moderate non-burning sun exposure against the risks of inadequate sun exposure

The only identified risk associated with the amount of non-burning sun exposure needed to achieve serum 25(OH)D levels of 30 ng/mL is some possible increased risk of nonmelanoma skin cancer. The amount of sun exposure required to produce this level of vitamin D varies among individuals and according to time of year, time of day and latitude. White people with Type II skins<sup>h</sup> at 40 degrees latitude can obtain their annual requirements of vitamin D by spending about 15 minutes in the sun with face, arms and legs exposed (half that time if in a bathing suit) 2 to 3 times a week between 11 a.m. and 3 p.m. during the months of May through October.<sup>141</sup> In comparison, nonmelanoma skin cancer is associated with many thousands or tens of thousands of cumulated hours of lifetime sun exposure.<sup>16,52,53</sup> Moreover, inadequate acclimatization to UVR in daily life carries the risk of sunburn and corresponding increased risk of both nonmelanoma skin cancer and melanoma.

The risks of inadequate non-burning sun exposure include increased risks of all-cause mortality, colorectal cancer, breast cancer, non-Hodgkins lymphoma, prostate cancer, pancreatic cancer, hypertension, cardiovascular disease, metabolic syndrome, type 2 diabetes, obesity, Alzheimer disease, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, psoriasis, non-alcoholic fatty liver disease, statin intolerance, macular degeneration and myopia.

People with darker skins require more time in the sun to produce their requirements of vitamin D but also have lower risks of nonmelanoma skin cancer, and people with Type I skins, who are unable to tan, require less time in the sun but have higher risks of nonmelanoma skin cancer. All persons should avoid sunburns, which are associated with substantial increased risk of melanoma and nonmelanoma skin cancer.

<sup>h</sup>There are 6 categories of skin on the Fitzpatrick Scale: Type I Very Fair White - always burns, never tans; Type II Fair White - usually burns, tans minimally; Type III Cream White - sometimes mild burn, gradually tans; Type IV Brown - rarely burns, tans with ease; Type V Dark Brown - very rarely burns, tans very easily; Type VI Black - never burns, tans very easily.

## Conclusions

Insufficient sun exposure has become a major public health problem, demanding an immediate change in the current sun-avoidance public health advice. The degree of change needed is small but critically important. The public must be advised to obtain enough sun exposure and vitamin D supplementation to maintain a serum 25(OH)D level of at least 30 ng/mL. The skin has a large capacity to produce vitamin D and a single whole body exposure to an amount of sunlight that is equal to 1 minimal erythemal dose is equivalent to ingesting approximately 15,000–20,000 IUs of vitamin D. Therefore to produce an equivalent of 4000 IUs of vitamin D a day would require that 50% of the body surface be exposed to 0.5 MEDs. To achieve a blood level of at least 30 ng/mL would require ingesting 2000 IUs of vitamin D daily which would be equivalent to 25% of the body surface exposed to 0.5 MEDs 2–3 times a week.<sup>24</sup> The amount of sun exposure required to achieve an MED depends on skin pigmentation, latitude, time of day and time of year. Warnings on the dangers of sunburn at any age should be emphasized. Periodic testing of serum 25(OH)D levels is also reasonable especially at the end of the summer which is when the blood level of 25(OH)D is at its highest level.<sup>141</sup>

## Abbreviations

5(OH)D	25-hydroxyvitamin D
BCC	basal cell carcinoma
CI	confidence interval
CVD	cardiovascular disease
HR	hazard ratio
IU	international units
MS	multiple sclerosis
NMSC	non-melanoma skin cancer
ng/mL	nanograms per milliliter
NHL	non-Hodgkins lymphoma
OR	odds ratio
RR	relative risk
SCC	squamous cell carcinoma
UVR	Ultraviolet Radiation (290–400 nm)
UVA	Ultraviolet-A (316–400 nm)
UVB	Ultraviolet-B (290–315 nm)

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## ORCID

Michael F. Holick  <http://orcid.org/0000-0001-6023-9062>

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