

# Estimating the global disease burden due to ultraviolet radiation exposure

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**Background** WHO's global burden of disease studies, undertaken since 1996, apportion the total global disease burden, measured in disability-adjusted life years (DALYs), to specific diseases and injuries. Recent assessments of the relative burden due to specific environmental risk factors, plus an understanding of the nature of the risk factor, may guide resource allocation in risk factor management. We report here the global disease burden due to ultraviolet radiation (UVR) exposure.

**Methods** A systematic literature review identified nine diseases with sufficient evidence of a causal relationship with UVR exposure and for which the population attributable fraction (PAF) for UVR could be estimated. For cutaneous malignant melanoma and cataract, the PAF was directly applied to disease burdens already calculated by WHO. For seven other diseases, we developed population-level exposure–disease relationships and used these to calculate disease incidence and mortality, and thence disease burden. We also estimated the disease burden from rickets, osteomalacia and osteoporosis that might result if global UVR exposure was reduced to very low levels.

**Results** UVR exposure is a minor contributor to the world's disease burden, causing an estimated annual loss of 1.6 million DALYs; i.e. 0.1% of the total global disease burden. A markedly larger annual disease burden, 3.3 billion DALYs, might result from reduction in global UVR exposure to very low levels.

**Conclusions** Sun protection messages are important to prevent diseases of UVR exposure. However, without high dietary (or supplemental) intake of vitamin D, some sun exposure is essential to avoid diseases of vitamin D insufficiency.

**Keywords** Ultraviolet rays, risk assessment, vitamin D, skin cancer, eye diseases, world health, environmental exposures

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## Background

Optimizing sun exposure for good health is currently the subject of considerable controversy. Past research has focused on understanding the adverse health effects of sun exposure, especially in relation to risks of skin cancer and the recent additional threat from stratospheric ozone depletion. Meanwhile, many diseases have now been linked, albeit some rather tenuously, with vitamin D deficiency—such that the protective effect of sun exposure might offset,

even outweigh, its adverse effects. Here we assess the disease burden attributable to ultraviolet radiation (UVR) at global and regional levels.

The World Health Organization's Global Burden of Disease (GBD) project<sup>1</sup> calculated the disease burden due to 107 major diseases and 10 risk factors at global and regional levels for the year 1990, combining mortality and morbidity into a single measure, the disability-adjusted life year (DALY).<sup>2</sup> With refined methods and more extensive data, the second GBD study (GBD 2000)<sup>3</sup> included a greater number of health outcomes and introduced a standardized 'comparative risk assessment' process to attribute fractions of the total cause-specific burden to 19 risk factors. That assessment assists an understanding of the relative gains in prevention consequent on specific risk factor reductions.

Since completion of GBD 2000, more detailed assessments of contributions to the total global disease burden of several environmental exposures have been made, for example for unsafe water, sanitation and hygiene,<sup>4</sup> indoor and outdoor air pollution<sup>5</sup> and occupational noise.<sup>6</sup> This paper is based on, and extends, the corresponding assessment that we carried out for ultraviolet radiation.<sup>7</sup>

### Exposure to ultraviolet radiation: a health hazard?

Living organisms on Earth evolved over many hundreds of millions of years under selection pressures that included differing levels of UVR. Skin pigmentation may have evolved under the competing pressures of protection of underlying cell structures from radiation damage and maximization of vitamin D production,<sup>8</sup> critical for bone health.

Solar UVR is ubiquitous during daylight hours. Ambient ground-level UVR comprises mainly UVA (400–315 nm) plus a small proportion (<10%, variable by time of day, season and location) of UVB (315–280 nm). Within-person and between-person UVR doses vary greatly, depending on location, time of day and season, clothing habits and behaviour and skin pigmentation.

Notably, UVR is one of few environmental exposures that may both cause and protect against disease: protecting against diseases of vitamin D insufficiency and causing skin cancers and eye diseases.

## Methods

A systematic review of the epidemiological literature identified nine diseases showing sufficient evidence of a causal association with UVR exposure (as judged by the Bradford Hill 'criteria').<sup>9</sup> Diseases of sporadic occurrence (e.g. photokeratitis and photoconjunctivitis, solar retinopathy) and the photodermatoses, which were considered to be caused by enhanced individual susceptibility rather than by over- or

under-exposure, were excluded from the assessment. A further three diseases were causally associated with insufficient UVR exposure, via vitamin D deficiency (Table 1).

For each included disease the population attributable fraction (PAF)<sup>10</sup> for UVR was calculated from published epidemiological literature [The PAF is that fraction of disease incidence that is attributable to exposure to the risk factor (and thus the fraction by which incidence could be reduced by elimination of exposure to that risk factor)]. Given the variations in published risk and exposure data, we estimated the upper and lower values of disease-specific PAF or, in one case, relied on a single 'best estimate' (Table 2). The UVR-attributable disease burdens were then calculated by applying the PAF to the estimated total burdens.<sup>6,11</sup>

For cutaneous malignant melanoma (CMM) and cortical cataract the estimated PAFs were directly applied to the disease burden calculated in the GBD 2000.

For other diseases, the disease-specific burden was calculated (in DALYs) from available evidence on the duration and disability weight (DW) for each disease stage and disease-specific incidence and mortality, as described below. Disease models were developed from available literature and by consultation with clinical experts, providing estimates of the proportions of incident or prevalent cases progressing through, and the duration of, each disease stage (Figure 1). DWs for each disease stage were derived from the GBD studies and Dutch<sup>12</sup> and Australian studies.<sup>13</sup>

### Non-melanoma skin cancers: squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)

Few population-based disease registries record these skin cancers, and therefore accurate global incidence and mortality statistics are not available.

Age-group and sex-specific incidence rates of SCC and BCC were derived from published population-based incidence studies and plotted against average daily ambient erythemal UVR (from satellite monitoring data)<sup>14</sup> for each study location and study year(s), e.g. Figure 2. The average daily ambient UVR for each country for the year 2000, weighted according to the within-country distribution of the population, was calculated by overlaying daily ambient erythemal UVR, estimated from satellite data<sup>14</sup> and averaged over 1997–2003, with the gridded world population, multiplying the layers for each cell in the grid, summing cells for each country and dividing by the total population of the country, using GIS software. Age-group and sex-specific incidence for each country in 14 WHO subregions was estimated by interpolation in the incidence-by-ambient UVR plots. Incidence studies generally involve fair-skinned populations. However, since skin pigmentation strongly modifies the effect of UVR exposure on skin cancer risk,

**Table 1** Candidate, and selected, health outcomes to be assessed for the burden of disease related to ultraviolet radiation

<b>Outcomes associated with UVR</b>	<b>Sufficient evidence of causality</b>	<b>Included in the Burden of Disease study</b>
<b>Immune effects</b>		
Acute		
Suppression of cell-mediated immunity	No	
Increased susceptibility to infection	No	
Impairment of prophylactic immunization	No	
Activation of latent virus infection—herpes labialis	Yes	Yes
Chronic		
Activation of latent virus infection—papilloma virus	No	
Rheumatoid arthritis*	No	
Type 1 diabetes mellitus*	No	
Multiple sclerosis*	No	
<b>Effects on the eyes</b>		
Acute		
Acute photokeratitis and conjunctivitis	Yes	No
Acute solar retinopathy	Yes	No
Chronic		
Climatic droplet keratopathy	No	
Pterygium	Yes	Yes
Pinguecula	No	
Squamous cell carcinoma of the cornea or conjunctiva	Yes	Yes
Cataract	Yes (cortical cataract)	Yes
Ocular melanoma	No	No
Macular degeneration	No	No
<b>Effects on the skin</b>		
Acute		
Sunburn	Yes	Yes
Photodermatoses	No	
Chronic		
Cutaneous malignant melanoma	Yes	Yes
Cancer of the lip	No	No
Basal cell carcinoma of the skin	Yes	Yes
Squamous cell carcinoma of the skin	Yes	Yes
Chronic sun damage/solar keratoses	Yes	Yes (solar keratoses)
<b>Other direct effects</b>		
Acute		
Medication reactions	Yes	No
Chronic		
Vitamin D insufficiency*		
–rickets, osteomalacia, osteoporosis	Yes	Yes
–tuberculosis	No	No
Cancers—prostate, Non-Hodgkins lymphoma, breast, colon*	No	No

Continued

**Table 1** Continued

Outcomes associated with UVR	Sufficient evidence of causality	Included in the Burden of Disease study
Hypertension*	No	No
Psychiatric disorders*		
–Seasonal affective disorder	No	No
–Schizophrenia	No	No
–General well-being	No	No
<b>Indirect effects</b>		
Effect on climate, food supply, disease vectors, atmospheric chemistry	No	No

Asterisk indicates possible beneficial effects of adequate UVR exposure. Adapted from.<sup>7</sup>

**Table 2** Population-attributable fractions (PAFs) for UVR-associated diseases

	Upper estimate	Lower estimate
Cutaneous malignant melanoma	0.9	0.5
Squamous cell carcinoma	0.7	0.5
Basal cell carcinoma	0.9	0.5
Solar keratoses	1.0	1.0
Sunburn	1.0	1.0
Cataracts	0.05 (best estimate)	0.05
Pterygium	0.74	0.42
Squamous cell carcinoma of the cornea and conjunctiva	0.7	0.5
Reactivation of herpes labialis	0.5	0.25

we derived adjustment factors for medium and deeply pigmented populations from the few available studies of skin cancer incidence in populations of different skin type.<sup>15,16</sup>

We derived age- and sex- specific incidence-to-mortality ratios from Australian data<sup>13</sup> and applied these globally, adjusting only for the higher reported case fatality rate in black populations (18.4%<sup>17</sup> compared with 0.7%<sup>18</sup> in white populations). While we were restricted to the use of Australian data due to lack of data availability for other countries, this is likely to underestimate non-melanoma skin cancer mortality in countries with less developed health care systems or where non-melanoma skin cancers are less common (and thus diagnosed and treated at a later disease stage). Incidence-to-mortality ratios were applied to the estimated incidence rates to provide age- and sex-specific mortality rates. Total deaths for each country were calculated and summed across WHO subregions. We used the WHO program DISMOD2 (software providing cohesive estimates of unknown disease parameters, e.g. case-fatality rate, given inputs of available data e.g. incidence,

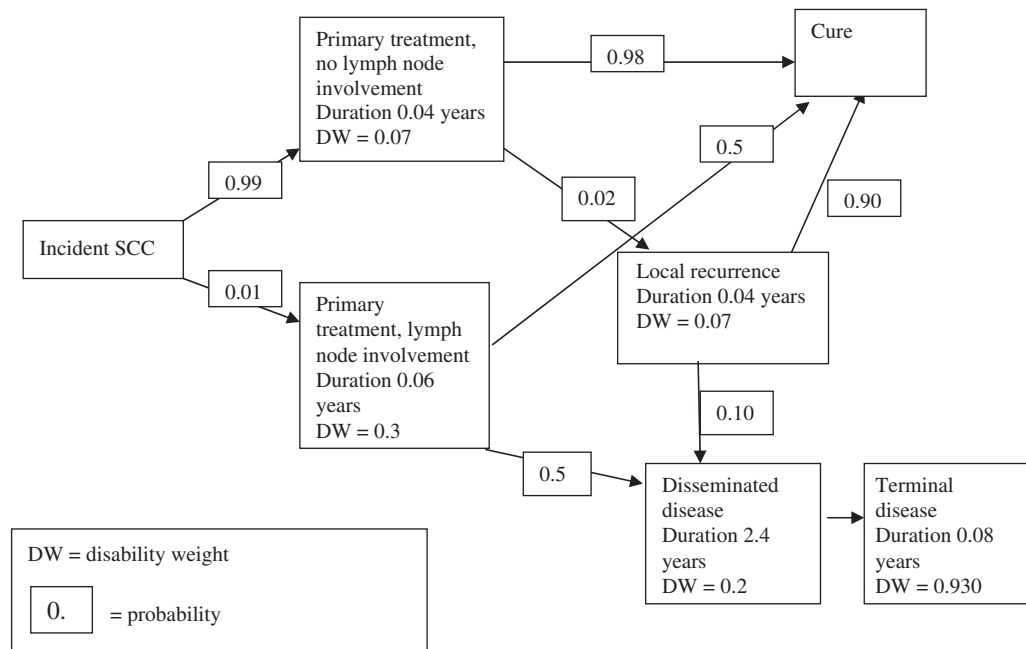
mortality, remission rate) to check that these estimates were consistent with published data on disease-specific case-fatality rates and to extrapolate estimates in GBD age categories where epidemiological data provided estimates in different age categories.

We developed disease models for SCC and BCC using the Australian Burden of Disease Study,<sup>13</sup> and consultation with clinical experts. DWs and duration of each disease stage (see Figure 1 for SCC) were derived from the Australian Burden of Disease Study<sup>13</sup> and the Dutch study of Disability Weights.<sup>12</sup> For BCC, we used a DW of 0.05, with duration of 2 weeks for removal of localized disease, with this being a curative treatment for 99.98% of incident cases. The remaining incident cases were assumed to develop disseminated disease, lasting 2.4 years with a DW of 0.2, progressing to a terminal phase of short duration (1 month) but high disability (DW=0.93, based on the Dutch study DWs for terminal disease).

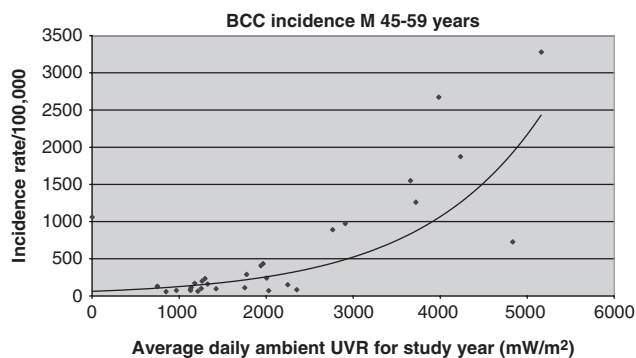
**Pterygium, solar keratoses, squamous cell carcinoma of the cornea and conjunctiva (SCCC)**

Accurate epidemiological or registry incidence or prevalence data for pterygium, solar keratoses and SCCC are available for some age groups only or for limited locations. Each of these diseases was assumed to have no associated mortality.

For solar keratoses, age- and sex-specific prevalence data from epidemiological studies were plotted in 10° latitude bands. Values for missing data were imputed in latitude band-prevalence plots by using age and sex patterns of disease prevalence, where age-specific data were incomplete within a latitudinal band, and latitudinal patterns of disease prevalence, where data were available for only some latitudinal bands. We assumed no disease burden from solar keratoses per se, but as the latter may be pre-malignant, their removal and possible progression to SCC are associated with a small disease burden. Based on epidemiological data, we assumed that 20% of solar keratoses remit per year;<sup>19,20</sup> 0.01% progress to SCC (DW and duration already described) and 5% are



**Figure 1** Disease model for SCC in WHO subregions with low adult mortality (A, B & C regions). Source: Lucas *et al.*<sup>7</sup>



**Figure 2** Incidence of basal cell carcinomas in males, aged 45–59 years at locations varying in average daily ambient UVR. For source papers, see supplementary reference list. Source: Lucas *et al.*<sup>7</sup>

removed, with a DW for removal of 0.02 (compared with 0.05 for localized BCC<sup>12</sup> and 0.01 for dental caries),<sup>1</sup> for a duration of one week.

Prevalence of pterygium generally increases with decreasing latitude.<sup>21,22</sup> However, there is little consistency in the age range of the denominator population in published prevalence studies. For example, the prevalence of pterygium was 6.9% in the Chinese population of Singapore aged 40 years or over,<sup>23</sup> 7.3% in New South Wales, Australia, in those over 49 years,<sup>24</sup> 44% in Australian Aboriginals in Northwestern Australia aged over 30 years<sup>25</sup> and 22.7% in a Mexican population sample aged 15–75 years.<sup>26</sup> To estimate the regional prevalence of pterygium by sex and WHO-specified age group,

prevalence data were first age-standardized for each location, from available data on age patterns of the disease and using imputed age-specific prevalence for any missing age groups. Within each 10° latitude band of study location, the summary data were averaged to provide a representative age-standardized prevalence. Using age and sex patterns for the disease, we then estimated age- and sex-specific prevalence for each latitude band. The disease burden from pterygium relates to surgical removal or to loss of vision if the pterygium remains and covers the cornea. We have assumed a 1% surgical removal rate in developed countries (WHO A, B and C regions).<sup>22,24,27</sup> Although pterygium surgery may account for a considerable proportion of all ocular surgery in developing countries<sup>28</sup> we assumed a lower removal rate of 0.5% of all pterygia in WHO D and E regions, and a low rate of pterygium-related visual loss (0.5%). Surgery was assumed to incur a DW of 0.298 (equivalent to ‘injury to the eyes’)<sup>1</sup> for a duration of 1 week (after consultation with clinical experts). Vision loss was assumed to incur a disability weight of 0.02 (mild vision loss)<sup>12</sup> for 5 years.

The age-standardized incidence rates of ‘eye cancers’ and the overall proportions that are histologically proven to be SCCC, are available for many countries.<sup>29</sup> Averaged age-standardized incidence rates were calculated for each WHO subregion. Using the available epidemiological literature,<sup>30–32</sup> age-specific incidence rates were estimated (using an Excel spreadsheet and repeated iterations of possible values, to achieve the set of age-specific incidence rates most compatible with both the age-standardized

rate and the population distribution of the disease in that region). We assumed no mortality caused by SCCC. Disease parameters were derived in consultation with clinical experts: 80% of incident cases would be treated by local resection, with an associated DW of 0.19 (similar to local resection of melanoma) lasting 4 weeks; 15% of incident cases would require more extensive resection, with an associated DW of 0.298 (injury to eyes, long term)<sup>13</sup> with disability lasting 2 months; 5% of incident cases would present with advanced disease requiring enucleation, associated with an initial DW of 0.43 (as for melanoma with extensive resection)<sup>12</sup> lasting 3 months, but ongoing disability for the rest of life (DW 0.2, derived from the GBD study<sup>1</sup> and lying between the values for an amputated arm and an amputated foot).

### Sunburn, reactivation of herpes labialis

For sunburn and reactivation of herpes labialis ('cold sores') few incidence data are available and the resulting estimates are thus highly uncertain.

For sunburn, some age-limited data are available for small regions,<sup>7,33–35</sup> mostly in fair-skinned populations living under high ambient UVR conditions. One-third of all incident sunburns are recorded as painful;<sup>36–38</sup> 3% of all sunburns are severe, with blistering.<sup>36,37</sup> Sunburns are very common, occur at all ages and are recurrent during 1 year. Sunburn per se was not considered to cause a disability; painful sunburn was assumed to have a DW of 0.01 (similar to acute tonsillitis)<sup>12</sup> and duration of 3 days; severe blistering sunburn was assumed to have a DW of 0.158 (based on the DW for a short-term burn of <20%)<sup>1</sup> and duration of 1 week.

A positive history of recurrent herpes labialis (RHL) may demonstrate a weak (negative) latitudinal gradient<sup>39–41</sup> and a peak of prevalence in late adolescence and early adulthood.<sup>40</sup> Recurrence rates over 1 year were averaged from published literature:<sup>39,40,42–44</sup> 48.6% of those with a history of recurrent herpes labialis had one recurrence; 35.1% had two recurrences and 16% have four or more recurrences in 1 year. We assumed a DW of 0.005 (less than acute nasopharyngitis<sup>13</sup> but >0) and duration of 5 days for one episode.

For both health outcomes, available data were used to derive incidence or prevalence, recorded by 10° latitude bands of location, WHO age group and sex. Missing data were imputed as for solar keratoses, above.

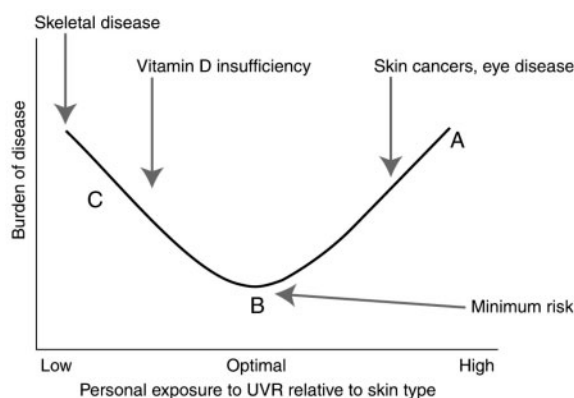
### A counterfactual of zero exposure is not appropriate for UVR

Cutaneous exposure to UVR is necessary for endogenous production of the hormone vitamin D, which is essential to bone health. Vitamin D deficiency unarguably causes rickets in infancy and osteomalacia and osteoporosis in adults.<sup>45</sup> While the potential

health consequences of vitamin D deficiency may be much wider than this (e.g. increased risk of multiple sclerosis, type 1 diabetes, a variety of cancers, cardiovascular disease), the evidence is not yet conclusive for any other conditions.<sup>46</sup>

Risk factor assessments typically examine disease burden in relation to a counterfactual exposure that incurs a minimum disease incidence. For most environmental risk factors this is zero exposure, e.g. zero exposure to air pollution is associated with a lower disease burden than exposure to any non-zero level of air pollution. However, since UVR confers both health risks and benefits, zero exposure does not entail the lowest disease risk (Figure 3).

To estimate the current disease burden averted by sufficient UVR exposure to avoid vitamin D deficiency, we consider a situation where the whole world population is exposed to the lowest observable levels of sun exposure. Most vitamin D derives from the action of UVB on steroid precursors in the skin, with subsequent hydroxylations in liver, kidney or target tissues, to produce the active hormone. Only a small proportion comes from dietary sources. This dietary proportion varies, however. Jablonski and Chaplin<sup>8</sup> describe three zones globally—in a low latitude band (30°N to 30°S), vitamin D supply is entirely dependent on sun exposure; in a high latitude band (>50° latitude) the traditional diet is high in vitamin D-rich foods; and in the mid-latitude region both diet and UVR exposure contribute.



**Figure 3** Schematic diagram of the relation between ultraviolet radiation (UVR) exposure and the burden of disease.<sup>91</sup> Points A and C represent inappropriate UVR exposure. Fair-skinned populations in Australia with high outdoor UVR exposure typify point A. Point C represents people with insufficient UVR exposure, whose dietary vitamin D intake will also be important in determining their vitamin D status. Point B represents optimal UVR exposure: a person with careful titration of correct UVR dose for skin type. Note that this is a schematic representation only, to demonstrate that there is a disease burden associated with both under- and over-UVR exposure. The curve could equally be J-shaped or reverse J-shaped. Source: Lucas RM *et al.*<sup>91</sup>

Vitamin D status reflects sun exposure over the preceding month or so. With very low sun exposure, populations would rapidly become vitamin D deficient. Those whose traditional diet lacks vitamin D would be most affected (equatorial regions). We calculated the burden of disease from rickets and other bone-related disease that could result from vitamin D deficiency due to very low levels of sun exposure.

To estimate the prevalence of vitamin D deficiency in each WHO subregion under this scenario we used the three abovementioned vitamin D 'zones' (latitudes  $\leq 30^\circ$ ,  $31^\circ$ – $50^\circ$ ,  $>50^\circ$ ) and sought epidemiological studies in which vitamin D levels had been measured in people who had little or no sun exposure—veiled women or institutionalized individuals. We used the prevalence of vitamin D deficiency in these studies to estimate prevalence of vitamin D deficiency, assuming very low UVR exposure.

In the low-latitude zone, populations probably have few dietary substitutes for sunlight-induced production of vitamin D.<sup>8</sup> However, coastal populations may have higher dietary intake of vitamin D (from oily fish) and thus be less affected by low levels of UVR.<sup>47</sup> We therefore estimated that 85% of the zone 3 population would have vitamin D deficiency under a scenario of very low UVR exposure.

In the highest latitude band, 20% of veiled ethnic Danish Moslem women had serum 25(OH)D levels below 10 nmol/l, a level likely to cause osteomalacia in adults and rickets in children.<sup>48</sup> Of note, veiled Arab women living in Denmark, consuming a traditional low-latitude diet, had lower 25(OH)D levels ( $7.1 \pm 1.1$  nmol/l) than ethnic Danish Moslems ( $17.5 \pm 2.3$  nmol/l), whose high dietary vitamin D ( $2.28 \mu\text{g/day}$  in ethnic Danish Moslems, compared with  $1.04 \mu\text{g/day}$  in Arab women) accords with Jablonski and Chaplin's estimates.<sup>8</sup> Thus we assumed 20% of the population in this zone would have vitamin D deficiency sufficient to produce rickets, osteomalacia or osteoporosis with very low UVR exposure.

In the mid-latitude band, 48% of a sunlight deprived elderly population in Baltimore ( $39^\circ$  N) had 25(OH)D levels  $<25$  nmol/l,<sup>49</sup> with an equal male-to-female ratio and no racial differences in levels (consistent with their vitamin D being primarily of dietary origin, since deeply pigmented skin makes vitamin D much more slowly than lightly pigmented skin).<sup>50</sup> In Lebanon ( $34^\circ$  N), 61.8% of veiled women had 25(OH)D levels below 5 ng/ml ( $12.5$  nmol/l).<sup>51</sup> The higher cut-point for vitamin D deficiency in the US study ( $<25$  nmol/l) and routine vitamin D supplementation of foods in the US, suggest that 48% may underestimate the prevalence of deficiency in populations at similar latitudes who do not have dietary vitamin D supplementation. Thus in this zone we assumed a prevalence of vitamin

D deficiency ( $<10$  nmol/l) of 62% under a scenario of very low UVR exposure, except in the USA, where we assumed 20% of the population would have vitamin D levels  $<10$  nmol/l under a scenario of very low UVR exposure (note that the 48% noted by Gloth *et al.*<sup>49</sup> referred to the proportion of the population with levels  $<25$  nmol/l—a much smaller fraction would be expected to have vitamin D deficiency sufficient to cause frank bone disease).

Rickets, osteomalacia and osteoporosis would become widespread with very low UVR exposure. To estimate the burden of disease that would result from a shift of population UVR exposure to very low levels, we assumed that all vitamin D-deficient people in each region would suffer the musculoskeletal consequences of this deficiency.

Childhood rickets carries a greatly increased risk of pneumonia, congestive heart failure and death<sup>52</sup> and rickets-induced bony deformities may cause life-long disability. We assumed a case fatality rate of 31% in WHO subregions with high child mortality (D and E subregions)<sup>52</sup> and 5% in other regions. Duration of rickets was assumed to be 6 months in children 0–4 years old, with disease onset at 12 months of age and a DW of 0.3. Vitamin D deficiency in older age groups also causes (less disabling) rickets in adolescents and osteomalacia in adults (DW 0.2, duration 0.5 years in the 5–59 age group). Muscle weakness and weakened bones due to vitamin D deficiency would cause considerable mortality and morbidity from falls and fractures in older adults. We assumed the occurrence of disability related to these musculoskeletal difficulties in those 60 years or older (DW = 0.1, duration 0.5 years) but not of mortality (due to lack of data linking vitamin D deficiency to mortality in this age bracket).

It is important to note that this exercise, estimating disease burden due to very low UVR exposure, is distinct from an assessment of the disease burden due to actual current levels of vitamin D deficiency. While vitamin D insufficiency is relatively common,<sup>53,54</sup> the clinical results of frank deficiency, e.g. rickets, are uncommon and generally confined to high-risk groups. Rather, this exercise draws attention to the harms that might attend health-motivated attempts to achieve very low levels of UVR exposure,<sup>55</sup> especially if unaccompanied by compensatory efforts to prevent vitamin D deficiency.

## Results

Estimates of the current global disease burden attributable to UVR exposure, based on the calculated disease burden of nine UV-induced diseases, are shown in Table 3, and elaborated below for each individual disease.

### Cutaneous malignant melanoma

Although ecological studies suggest a PAF for UVR exposure of  $\geq 0.9$ ,<sup>56</sup> the results from individual-level observational (case-control) studies indicate a PAF of 0.2–0.3. The latter, lower, PAF is probably an underestimate because of imprecision in the individual-level exposure measurement<sup>57</sup> (which necessarily biases risk estimates towards the null value) and difficulty in finding a truly non-exposed comparison group. Furthermore, ecological studies may overestimate the PAF because of failing to take account of positive confounding due to differences in exposure to some other contributory risk factor.<sup>56</sup> An upper (0.9) and lower estimate (0.5) were applied to the calculated melanoma disease burden in DALYs. Note however, that the calculated PAF derives principally from studies in fair-skinned populations. Melanoma is less common in more deeply pigmented populations and factors other than UVR exposure may be important in its pathogenesis.<sup>58</sup> Thus some fraction of the GBD 2000 CMM disease burden may be unrelated to UVR exposure and could be excluded from the attributable disease burden calculation if subgroup information were available.

Globally there were an estimated 211 921 incident cases of CMM, 65 161 deaths and a total melanoma disease burden of 690 000 DALYs.<sup>59</sup> We estimate that 345 000 (lower) to 621 000 (upper) of these DALYs were attributable to UVR exposure. As with other skin cancers, the disease burden (adjusted for population size) is disproportionately carried by fair-skinned populations, including those living in high ambient UVR locations, e.g. the Western Pacific Region.

### SCC of the skin

The PAF estimated from case-control studies was 0.35. Using the considerations outlined by Armstrong and Kricke,<sup>56</sup> ecological data suggest a PAF between 0.62 (migration studies),<sup>60</sup> 0.70 (high vs low ambient UVB)<sup>61</sup> and 0.83 (exposed vs unexposed skin sites).<sup>62</sup> We used an upper estimate of 0.7 and a lower estimate of 0.5 for fair-skinned populations. UVR may be less important for the development of SCC in intermediate and deeply pigmented populations (with SCC occurring on non-sun-exposed sites and within areas of chronic inflammation and scarring). Since the estimates of incidence (and mortality) were derived for each country, and adjusted for the broad pigmentary characteristics of each population, we were able to apply adjusted PAFs to these incidence data (intermediate pigmentation: 0.2 times the PAF in fair-skinned populations; deeply pigmented populations: 0.04 times the PAF in fair-skinned populations). Globally, we estimated that there were over 2 883 000 people with incident SCC in 2000 and 13 534 deaths. This resulted in the loss of 162 000 DALYs of which between 59 000 and 83 000 were attributable to UVR exposure.

**Table 3** Global disease burden attributable to UVR exposure, DALYs (000)

Disease	Upper estimate	Lower estimate
CMM	621.2	345.1
SCC of skin	82.7	59.1
BCC of skin	52.1	29.0
Photoageing	8.3	8.3
Sunburn	293.6	293.6
Cortical cataract	529.2	529.2
Pterygium	34.6	19.7
SCCC	1.7	1.2
RHL	68.3	34.1
Total	1691.9	1319.4

### BCC

Again the PAF estimated from case-control studies was considerably lower (PAF=0.25) than that estimated from ecological data (similar to melanoma,  $\geq 0.9$ ). In line with our CMM approach, we used a lower estimate of 0.5 and an upper estimate of 0.9 for fair-skinned populations. BCC is rare in African-Americans<sup>58</sup> and absent in a skin survey in the northern Solomon Islands—an area that has some of the most deeply pigmented people in the world.<sup>63</sup> However, unlike SCC, BCC in deeply pigmented persons usually occurs on sun-exposed areas, primarily the head and neck regions and appears to be mainly related to UVR exposure.<sup>64,65</sup> There are no available data to calculate PAF in those of medium and dark pigmentation, but we assumed BCC to have the same causal relationship with UVR exposure received by the target cells and thus the same PAF for all pigment groups. We estimated that globally, there were over 10 million people with new BCCs in 2000. Deaths from BCC are rare (estimated 3245 worldwide in 2000). Thus, despite the very high incidence, the total disease burden is relatively low: ~58 000 DALYs lost in 2000 and a UV-attributable disease burden of between 29 000 and 52 000 DALYs.

### Solar keratoses

Despite an estimated 532 million persons with solar keratoses in 2000, the disease burden due to these tumours (and imputing total attribution to UVR exposure) was estimated to be just 8000 DALYs (Table 3).

### Sunburn

Sunburn is entirely attributable to UVR exposure. Our estimates suggest that there are almost 2 billion incident sunburns in a single year, creating a global disease burden of almost 300 000 DALYs (Table 3).



The greatest disease burden is in the 15–29 years age group.

### Cortical cataract

Each of the major cataract types, cortical, posterior subcapsular and nuclear, shows some association with UVR exposure.<sup>66–69</sup> However, only cortical cataract displays strong and sufficient evidence of a causal association. Disability from cataract results from visual impairment, but cortical cataract appears less likely to be associated with visual loss than other cataract types,<sup>70,71</sup> has a weaker relationship with mortality and is less likely to result in cataract surgery.<sup>71,72</sup> Review of the epidemiological literature indicates that ~30% of all cataracts causing visual loss are cortical cataracts, and that the latter account for ~25% of the total disease burden.<sup>7</sup> The calculated PAF for cortical cataract with UVR exposure, based on the results of case-control studies, was 0.19, although this may be an underestimate due to the aforementioned inaccuracy in recalled exposure measurement. The GBD 2000 estimated that there were over 8 million incident cataracts in 2000,<sup>59</sup> causing the loss of over 10 million DALYs. Approximately 2.6 million of these are estimated to be cortical cataracts, with 529 000 DALYs attributable to UVR exposure (Table 3).

### Pterygium

The mean PAF calculated from case control studies was 0.42, with an upper estimate (using daily ocular dose as the exposure measure) of 0.74.<sup>73</sup> We estimate that there were over 200 million people with at least one pterygium in 2000, causing the loss of almost 47 000 DALYs, of which between 20 000 and 35 000 were attributable to UVR exposure (Table 3).

### SCCC

SCCC is a rare tumour of the eye. One study<sup>32</sup> reported links between SCC and UVR exposure similar to those between SCC of the eyelid and UVR. The PAF calculated from the single relevant study was 0.62.<sup>74</sup> We applied the same PAF as for SCC in fair-skinned populations (lower estimate 0.5, upper estimate 0.7) to all population groups. This presumes that the protective effect of pigmentation observed for SCC of the skin does not apply when considering disease of the cornea and conjunctiva. We estimate that there were almost 12 000 incident cases of SCCC globally in 2000, accumulating 2500 DALYs. The burden of disease attributable to UVR exposure (from SCCC) was between 1200 and 1700 DALYs (Table 3).

### Reactivation of herpes labialis

UVR exposure causes local immunosuppression and hence can reactivate some latent virus infections, such as herpes labialis (or cold sores). Around 25–50% of

cold sores are attributed, at least in part, to UVR exposure. Based on scanty data we estimated that there were over 1 billion new cases of reactivated herpes labialis in 2000, associated with 136 000 DALYs. The burden of this viral-reactivation disease attributable to UVR exposure was between 34 000 and 68 000 DALYs (Table 3).

### Potential disease burden caused by reduction of UVR exposure to very low levels

The burden of disease that might result from reduction of global UVR exposure to very low levels was estimated for the three vitamin D-deficiency bone diseases (rickets, osteomalacia and osteoporosis). Under this scenario, we could expect 4 billion cases of bone disease due to vitamin D deficiency with an associated disease burden of 3.3 billion DALYs.

## Discussion

Our estimates indicate there is a modest disease burden attributable to exposure to UVR—around 50 000 deaths and 1.6 million DALYs. This represents 0.1% of the total global disease burden in the year 2000. Of the nine outcomes for which UVR is at least partially causative, the greatest attributable disease burden arises from CMM (345 000–621 000 DALYs) and cortical cataracts of the eye (529 000 DALYs). Non-melanoma skin cancers, solar keratoses and pterygium, though common, are responsible for only a small disease burden (SCC: 59 000–83 000 DALYs; BCC: 29 000–52 000 DALYs; solar keratoses: 8000 DALYs; pterygium: 20 000–35 000 DALYs). While the estimate for the disease burden due to sunburn (290 000 DALYs) is relatively high compared with the other assessed diseases, this estimate is highly uncertain due to the lack of availability of suitable data inputs.

In addition, we have estimated a considerable potential disease burden (3.3 billion DALYs) if UVR exposure were reduced to levels that were insufficient to maintain the vitamin D levels needed to avoid the bone diseases, rickets, osteomalacia and osteoporosis.

This work was based on standardized methods,<sup>75</sup> allowing comparison with disease burdens due to other environmental risk factors. By assessing disease burden in DALYs, the work incorporates both mortality and morbidity—enabling proper evaluation of the disease burden due to non-fatal outcomes such as cataract. However, the data available for estimating incidence or prevalence were limited, particularly for some outcomes, e.g. sunburn, and more comprehensive data will be required for the refinement of estimates.

A further issue for resolution is the disparity between ecological and case-control study estimates of PAF. As noted, this disparity relates partly to the quality of the exposure assessment, probably leading

to an underestimate of the PAF in case-control studies. New methods of measuring 'past sun exposure', such as personal calendars where sun exposure experiences at particular ages are tied to memory aids such as place of residence, school attended or pets in the home, and objective measures of sun exposure such as silicone casts of skin on the back of the hand to measure cumulative actinic damage, may improve the accuracy of exposure measures. Ecological and individual-level studies also make comparisons across a different range of exposure disparity. Ecological studies typically compare populations experiencing the extremes of UVR exposure—e.g. US Whites vs Blacks; people born in Australia compared with migrants from low ambient UVR locations. Individual level studies may measure a narrower range of varying exposure experience under common levels of ambient UVR. The 'unexposed' reference group is 'less-exposed' not unexposed, with corresponding diminution of the measure of association and of the PAF.

Ecological studies may overestimate PAF by failing to allow for differences in the underlying risk function across the set of compared populations. This possibility is well illustrated by the U-shaped relationship between latitude and melanoma risk in Europe,<sup>76</sup> probably reflecting confounding of the latitudinal UV gradient with a latitude gradient in skin pigmentation. Nevertheless, ecological estimates, comparing across whole populations rather than between individuals, may provide more accurate estimates of PAF, since those estimates are less influenced by the 'genetic noise' arising from within-population inter-individual genotypic variation. Improved understanding of the role of genetic factors in disease risk may allow refinement of ecological estimates by comparing populations of similar genetic composition but with varying exposure experience.

Many other smaller issues need attention if current estimates are to be extended or improved. How should incidence estimates based on ambient UVR take account of behavioural differences in sun exposure between different populations that alter actual UVR exposure? Most incidence estimates derive from research in lightly pigmented populations, often in situations where there is already widespread concern about sun exposure practices: how transferable are these data to other populations? How should the estimates be refined to take account of the common situation of multiple skin cancers or solar keratoses in one individual? And there remain various disease-specific issues. For example, can we quantify the likelihood of loss of vision or death, for cortical vs other cataract types? Are skin cancers UV-related in deeply pigmented persons? Resolution of these questions and critical evaluation of new evidence for a causal role of UVR exposure in diseases listed in Table 1 but omitted from this evaluation,

e.g. ocular melanoma, is required to refine the current estimates.

The global disease burden attributable to UVR exposure is relatively small compared with burdens attributable to major lifestyle (such as smoking, alcohol, overweight) or other environmental risk factors. Indeed, direct environmental exposures account for a relatively small proportion of the total global disease burden<sup>77</sup>: unsafe water, sanitation and hygiene (3.7% of GBD), indoor smoke from household use of solid fuels (2.7%), urban air pollution (0.8%), lead exposure (0.9%), climate change (0.4%) and UVR (0.1%). However, many environmental risk factors contribute in complex and possibly interactive ways that are not yet included in the burden of disease analyses. For example, UVR-induced immunosuppression may enhance susceptibility to infection, so that a portion of that disease burden currently caused by a variety of infections might be attributable to UVR exposure.<sup>78</sup>

The first GBD study<sup>1</sup> viewed 'environment' as comprising those exposures that are unnaturally imposed (air pollution, tobacco, water-borne infections) on human populations. The second GBD study and its associated risk factor assessments have extended that scope to include exposures to natural components of the environment—climatic conditions, UVR, cosmic radiation and naturally-occurring fluoride. In this extended 'environmental exposure' domain, a general assumption of dose-dependent adverse risk to health, as typically occurs with exposure to unnatural toxicological agents, is not appropriate. Humans evolved under assorted environmental pressures from each of these natural environmental exposures, and maintenance of good health may require a balance between the risks and benefits of exposure. This balance may lead to J-shaped rather than simple linear relationships between exposure and net harm: an initial fall in net harm as exposure increases from zero to an optimum exposure (where harm is minimum), then an increase in harm with increasing exposure thereafter. Thus, we must consider possible beneficial (e.g. vitamin D sufficiency) as well as adverse effects (e.g. skin cancers) of these exposures within the natural environment.

We used a counterfactual approach to estimate the potential harm that would result from global reduction of UVR exposure to very low levels, i.e. comparing disease burden under a scenario of very low UVR exposure, to that where everyone has sufficient exposure to avoid vitamin D deficiency bone diseases. That is, we did not seek to quantify the 'current' disease burden incurred by people who have vitamin D deficiency sufficient to cause bone disease. Better prevalence data that include clinical as well as subclinical disease, or widespread measurement of 25(OH)D using standardized methods, and clarification of the levels of 25(OH)D

that denote sufficiency, insufficiency and deficiency<sup>79</sup> would be required for that assessment.

The potential disease burden due to very low UVR exposure serves to highlight the important public health benefits of maintaining vitamin D levels through adequate UVR exposure or through vitamin D supplementation if such exposure is contraindicated. In addition to the bone diseases of vitamin D deficiency, there are a number of other diseases for which there is increasing, but not yet sufficient, evidence of a causal protective role for adequate UVR exposure, e.g. a range of cancers,<sup>80,81</sup> including breast,<sup>82</sup> colon,<sup>83</sup> prostate<sup>84</sup> and non-Hodgkin lymphoma<sup>85</sup> and autoimmune disorders such as multiple sclerosis<sup>86</sup> and type 1 diabetes.<sup>87</sup> These diseases accounted for 9.4% of the total global disease burden in 2000 and may have UVR PAFs ranging from 0.06 to 0.65.<sup>88</sup> If future research shows them to be causally associated with UVR exposure, they will contribute further to the disease burden that might result from very low UVR exposure.

Data on the relationship between vitamin D levels and ambient UVR levels, across a variety of skin types and age groups, are currently limited. Such data are needed to verify the assumptions necessarily made in this assessment, which were based on a very small number of studies. This work, and better documentation of the regional prevalence of the various vitamin D states, will improve the accuracy of the disease burden estimates.

In summary, this first comprehensive study of the global disease burden caused by exposure to ultraviolet radiation reveals a modest burden due to UVR exposure and probably a larger disease burden avoidable by sufficient UVR to maintain vitamin D at levels required to avoid vitamin D deficiency bone diseases. For allocation of health resources, the unit of measure of disease burden must be suited to the question being asked. In terms of mortality and DALYs, UVR exposure is a relatively minor player, but in terms of health costs, the huge number of skin cancers is a preventable burden on health systems, particularly in fair-skinned sun-seeking populations.<sup>89</sup>

Similarly, however, we must recognize that some sun exposure is essential to avoid diseases of UVR under-exposure. Here we have examined only avoided vitamin D deficiency bone diseases, but there may be a large burden of preventable disease, such as some cancers and autoimmune diseases, at least partly caused by vitamin D insufficiency. More research and analysis are required before we will know how best to draw a balance in public policy and action between the harmful and beneficial effects of sun exposure.<sup>88,90</sup>

## Supplementary Data

Supplementary data are available at *IJE* online.

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**Conflict of interest:** None declared.

### KEY MESSAGES

- Inappropriate sun exposure is an avoidable environmental risk factor for human disease, causing skin cancers, eye diseases and immune suppression.
- Ultraviolet radiation exposure caused the loss of 1.6 million DALYs in 2000 (0.1% of the total global disease burden).
- Sufficient sun exposure to prevent vitamin D deficiency probably avoids a large potential disease burden.
- Sun exposure should be tailored to the level of ambient UVR and personal skin type.
- More research is needed to adequately evaluate the balance of benefits and harms from exposure to the sun in different environments.

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## Commentary: The complexities of minimizing risks due to UV exposures

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For many years, the public health message about solar ultraviolet radiation (UV) focused nearly exclusively on its toxicity. Sunlight was a risk to be avoided. Yet, as has been increasingly emphasized in the scientific literature and lay press, UV is an agent that poses both harms and benefits to health. Solar UV exposure presents established risks to the skin and eyes, as well as initiating the predominant source of vitamin D, with recognized contributions to bone health and other possible health benefits. Understanding both sides of the UV and human health ledger is crucial to developing public health policy that will minimize the net burdens associated with UV.

Lucas *et al.*<sup>1</sup> address the complexities of UV exposure by estimating with a single metric [disability-adjusted

life years (DALYs)] both the international burden of disease resulting from actual exposures to UV and the health burdens that would follow if very low world UV exposures were achieved. The comparison is limited to established health risks of UV, principally melanoma, other skin cancers, sunburn and certain types of cataracts, and the established health benefits of vitamin D in preventing rickets, osteoporosis and osteomalacia. In examining the potential trade-off between UV damage and inadequate vitamin D, the study assumes existing patterns of vitamin D exposure from non-UV sources, such as diet (natural and fortified foods) and oral supplementation. Although, readers may question or challenge the myriad assumptions that underlie such an exercise, the study dramatizes how much may be at stake if public health policy addresses the risks of UV without being mindful of its impact on vitamin D status.

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