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Human health in relation to exposure to solar ultraviolet radiation under changing stratospheric ozone and climate†

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The Montreal Protocol has limited increases in the UV-B (280–315 nm) radiation reaching the Earth's surface as a result of depletion of stratospheric ozone. Nevertheless, the incidence of skin cancers continues to increase in most light-skinned populations, probably due mainly to risky sun exposure behaviour. In locations with strong sun protection programs of long duration, incidence is now reducing in younger age groups. Changes in the epidemiology of UV-induced eye diseases are less clear, due to a lack of data. Exposure to UV radiation plays a role in the development of cataracts, pterygium and possibly age-related macular degeneration; these are major causes of visual impairment world-wide. Photodermatoses and phototoxic reactions to drugs are not uncommon; management of the latter includes recognition of the risks by the prescribing physician. Exposure to UV radiation has benefits for health through the production of vitamin D in the skin and modulation of immune function. The latter has benefits for skin diseases such as psoriasis and possibly for systemic autoimmune diseases such as multiple sclerosis. The health risks of sun exposure can be mitigated through appropriate sun protection, such as clothing with both good UV-blocking characteristics and adequate skin coverage, sunglasses, shade, and sunscreen. New sunscreen preparations provide protection against a broader spectrum of solar radiation, but it is not clear that this has benefits for health. Gaps in knowledge make it difficult to derive evidence-based sun protection advice that balances the risks and benefits of sun exposure.

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1. Introduction

Recognition of and action on depletion of stratospheric ozone occurred against a background of rapidly increasing incidence of skin cancer in light-skinned populations. These increases pre-dated ozone depletion, and resulted from changes in sociocultural norms for clothing and the perceived value of tanned rather than pale skin as a sign of health and affluence.[1–3] Because of actions taken under the Montreal Protocol and its amendments to limit release of ozone depleting substances (ODSs) to the atmosphere, there have not been large increases in UV-B radiation over populated areas of the Earth's surface (reviewed in ref. 4). Nevertheless, it remains important to recognise the very large potential risks to human health that could be caused by stratospheric ozone depletion. Several analyses of the 'world avoided' by the Montreal Protocol,[5,6] or predictions of skin cancer incidence under scenarios of runaway ozone depletion,[7–9] show the scale of these risks.

Future projections, assuming continuing compliance with the Montreal Protocol and its amendments, and dependent on global climate change, are that, by the end of the 21st century,

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there is likely to be 'super recovery' of the global ozone column compared to 1980 levels, and lower ambient UV-B radiation particularly at higher latitudes, due to increased cloud cover. Levels of UV-B radiation may increase in the tropics (depending on the emission scenario modelled), particularly over currently highly polluted areas, as air pollution diminishes.[4] Here we assess the evidence, primarily published since our 2014 assessment,[10] of the risks and benefits to human health of exposure to UV radiation. Fig. 1 provides a conceptual overview of the paper. Biologically relevant exposure to UV radiation (or the dose) depends on behaviour (time in the sun and the amount of skin exposed) as well as the intensity of ambient UV radiation. To date, increases in exposure have occurred largely due to changes in behaviour, but these provide an indication of the consequences for human health of exposure to higher (and, in the future, lower) levels of UV radiation because of depletion of stratospheric ozone and future recovery.

Recognition of the risks to health from increasing exposure to UV radiation has generated new industries in sun protection. We thus also assess recent progress on sun protection aimed at reducing the effects of exposure to UV radiation to the skin and eyes. The unintended environmental consequences of sun protection, such as sunscreen washing into surface waters, are addressed in ref. 11. The potential adverse and beneficial effects for health of exposure to chemicals that are transformed into more or less toxic compounds following absorption of UV radiation, *e.g.*, photosensitisation, are discussed in ref. 12. The potential risks to health from ozone-depleting chemicals and their replacements, and the health burden caused by UV-induced changes in air quality, are discussed in ref. 13. Other indirect effects on human health are the result of changes in food quality and quantity, and ecosystem services, such as disinfection of surface waters used for drinking and the UV-induced degradation of pollutants. These are addressed in ref. 11, 12 and 14, as are the interactive impacts of climate change for such services.

In this paper, we first present the evidence on the importance of behaviour as a major modifier of the personal received dose of UV radiation, compared to the available ambient UV radiation. We then briefly describe the damage to DNA and modulation of immune function that occurs following exposure to UV radiation and drives both adverse and beneficial effects. This is followed by an assessment of recent research on the adverse effects of exposure to solar UV radiation, beginning with effects on the skin, particularly skin cancers and photodermatoses, and followed by effects on the eyes, and then emerging evidence on other health risks. The evidence for beneficial effects of UV radiation, including through vitamin D and non-vitamin D pathways, is then assessed, followed by a brief consideration of the balance of risks and benefits of sun exposure for health. In the next sections we consider sun protection tools and messaging. We finish with an assessment of recent evidence on possible

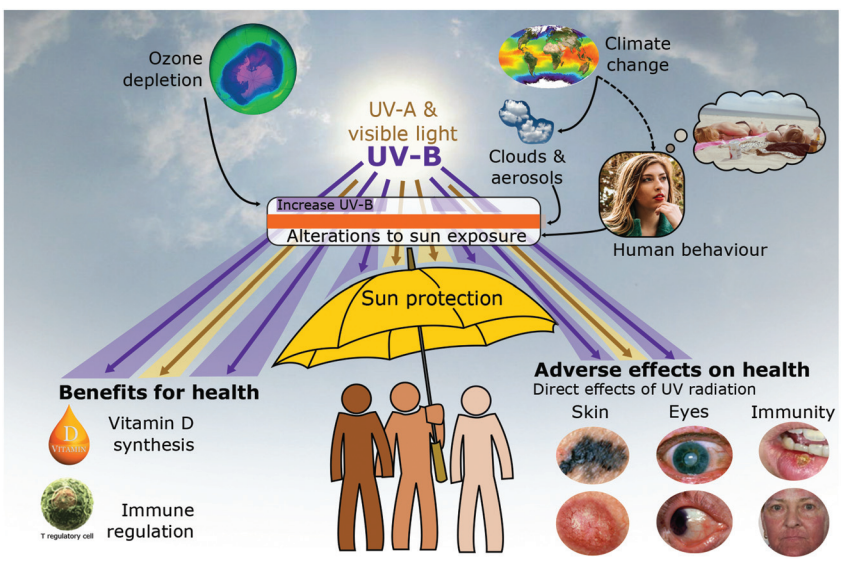

Fig. 1 Conceptual diagram. Depletion of stratospheric ozone causes an increase in UV-B radiation at the Earth's surface; in the future, recovery of the ozone layer will lead to a reduction in clear-sky UV-B radiation. Climate change will alter cloud cover and tropospheric air quality (aerosols) that will, in turn, affect solar radiation at the Earth's surface across all wavelengths. Human behaviour is a major modulator of the received dose of UV radiation. These factors thus work together to determine human exposure to UV radiation; the dose of UV radiation reaching sensitive tissues depends, in turn, on skin pigmentation and the use of sun protection including physical protections like sun umbrellas, as well as clothing, hats, sunscreen and shade. Adverse effects on health include skin cancers and photosensitivity disorders (photodermatoses), cataracts and other eye diseases, and immune suppression that leads to the reactivation of latent virus infections. Benefits include synthesis of vitamin D in the skin, regulation of immune function that may reduce the severity of some skin diseases and possibly systemic autoimmune diseases. Climate change will alter these risks and benefits to health through changing behaviour in relation to sun exposure, *e.g.*, due to changes in ambient temperature and precipitation. The photograph of the thinking woman was adapted from an image by Tyler Nix on Unsplash; the photograph of the sunbathers was adapted from an image by Maciej Serafinowicz on Unsplash (https://unsplash.com/collections).

future effects, including those that may be influenced by climate change (or where changes in UV radiation could influence the health impacts of climate change), and identify some gaps in our knowledge to guide future research.

2. The role of behaviour in determining exposure to UV radiation

Almost 90% of the world's population lives at a location where the peak annual UV Index (UVI) reaches more than 10;[15] thus, the potential for exposure to UV radiation is high. However, the actual personal dose received depends on behaviour. In most locations that have been studied, the mean daily exposure to UV radiation for both adults and children is around 4–5% of the available ambient dose of UV radiation for the day.[16,17] There is, however, considerable variability,[4] with a range from one-tenth to ten times the mean,[18] highlighting the important role of behaviour. Achieving accurate and personalised measurement of exposure to UV radiation is thus important in individual-level studies of health risks and benefits. Most studies have been undertaken in Caucasian populations and the findings may not be applicable to other ethnic groups.[19] Understanding how exposure to UV radiation may affect health is challenging because there is no definition of an "optimal" exposure. Indeed, it is likely that optimal exposure will be highly variable, according to individual sensitivity, for example, based on genetic factors including skin type, and possibly other factors such as age.

2.1. Changing behaviour in relation to sun exposure under concurrent global environmental changes

There are very few data on the effect of warmer temperatures on patterns of sun exposure. An older study showed that people were more likely to spend at least 15 minutes outdoors on warmer compared to cooler days, but this pattern reversed when outdoor temperatures were >28 °C.[20] More recently, it was found that people living in cooler (but not hotter) climates increased their time outdoors in warmer weather.[21] These data suggest that a simple correlation between rising temperatures and time outdoors is unlikely. It will be important to also consider the effects of urbanisation, including the urban 'heat island' effect, with evidence showing reduced exposure to UV radiation in the man-made canyons typical of cities,[4] as well as changes in cloud and precipitation that reduce the amount of ambient UV radiation, or the time spent outdoors, respectively.

3. Biological pathways underpinning the effects of exposure to UV radiation on health

UV radiation striking the skin is absorbed by molecules – chromophores – in the epidermis (most superficial layer of the skin) and dermis (below the epidermis). The most energetic, short wavelength UV-B photons penetrate only into the epidermis and upper dermis, while UV-A photons can reach the deeper dermis. Exposure to UV radiation results in natural adaptation to provide protection through tanning and thickening of the epidermis (epidermal hyperplasia).[22] Darker skin pigmentation is the result of a greater melanin content in the epidermis; this modifies the dose of UV radiation received by epidermal and dermal chromophores (reviewed in ref. 23; see also section 7.4).

3.1. The importance of DNA photodamage

DNA is a major epidermal chromophore for UV-B radiation (see Fig. 2). The cyclobutane pyrimidine dimer (CPD) is the most frequent DNA photoproduct.[24] CPD formation can lead

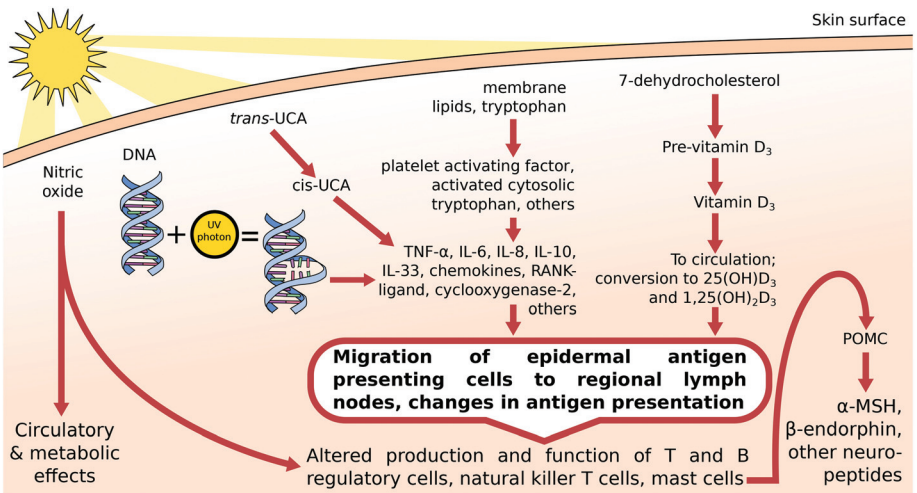

Fig. 2 Cascading consequences of UV irradiation of human skin. UV photons are absorbed by a range of chromophores, including DNA, membrane lipids, urocanic acid (UCA), and 7-dehydrocholesterol, with subsequent effects on immune cells and secretion of neuropeptides, including α-melanocyte stimulating hormone (MSH). POMC: pro-opiomelanocortin; IL: interleukin; TNF: tumour necrosis factor; RANK: receptor activator of nuclear factor kappa-B.

to characteristic mutations – 'UV signature' mutations (C to T, CC to TT) – that are found in cutaneous malignant melanomas (CMMs), keratinocyte cancers (KCs, formerly called non-melanoma skin cancers, and including squamous cell and basal cell carcinoma (SCC and BCC, respectively)), and actinic keratoses (scaly growths on the skin that may be a premalignant stage of SCC). In addition, recent work shows that sun-exposed, but normal-appearing, skin has thousands of clones of abnormal cells, with a high proportion containing cancer-causing mutations.[25] These mutated epidermal cells are actively eliminated by non-mutated cells to restore the normal skin architecture.[26] Skin cancers occur when repair and/or control mechanisms are overwhelmed; skin cancers have more mutations than any other cancer.[27] UV-B and UV-A radiation also cause oxidative damage to DNA and other biomolecules[24] that may contribute to skin cancer genesis.

3.2. UV-induced modulation of immune function

The human immune system has innate and adaptive (or acquired) components, with considerable communication between them. Innate immune responses are typically rapid,[28] while, for those of the adaptive immune system, there is a lag of hours or days between exposure to a pathogen or antigen and the maximal immune response. Both innate and adaptive responses have immunological 'memory'. The 'trained immunity' of the innate system is non-specific but provides short-term (days to months) protection against secondary infection with related or unrelated pathogens.[29,30] In contrast, immunological memory in the adaptive system is pathogen- or antigen-specific and lasts for years; a subsequent exposure to the same pathogen results in a more immediate, targeted, immune attack.

Exposure of the skin or eyes to UV radiation causes modulation of immune function through pathways that are both vitamin D-dependent and independent. In simple terms, innate immune function is upregulated and adaptive immune function downregulated. Fig. 2 provides an overview of events occurring in the epidermis and dermis following UV irradiation that have consequences for immune function. Additional information is provided in the ESI.†

3.2.1. Upregulation of innate immunity. Exposure of the skin to UV radiation results in the release of pro-inflammatory cytokines (signalling molecules regulating immunity), chemokines (molecules inducing directed chemotaxis), and antimicrobial peptides (AMPs; for a review of AMPs, see ref. 31). The AMPs can be directly cytotoxic to pathogens and/or facilitate the cytotoxicity of natural killer cells and other cells of the innate immune system.[32]

3.2.2. Suppression of adaptive immunity. UV photons are absorbed by chromophores in the skin. These include DNA, RNA, *trans*-urocanic acid (UCA), and membrane lipids, including 7-dehydrocholesterol, the precursor of vitamin D. Through a range of pathways, this results in upregulation of regulatory T (T_{reg}) and B (B_{reg}) cells, and dampening of cell-mediated immune processes.[33]

4. Adverse effects on human health from exposure to UV radiation

Adverse effects on health from exposure to UV radiation arise from UV-induced immune suppression and damage to the skin and eyes that is beyond the repair capabilities of the body.

4.1. Adverse effects of UV-induced immune modulation

Suppression of immune responses provides a permissive environment for the activation of viral infections and possibly for new bacterial and protozoal infections, impairment of vaccination, the development of skin cancers (see section 4.2.1), and the expression of some photodermatoses (see section 4.2.2).

4.1.1. Activation of viral infections. Several recent studies show an increased risk of reactivation of latent herpes virus infections following exposure to high doses of solar UV radiation. For example, there was a three-fold greater risk of recurrent infection of the eye with herpes simplex virus in association with spending eight or more hours per week outdoors when the UVI was >4 compared to less time outdoors with UVI < 4.[34] Studies from South Korea,[35] Taiwan,[36] and Australia,[37] show that shingles, caused by the reactivation of herpes zoster virus, is more common when ambient levels of UV radiation are higher (*e.g.*, 10% higher in summer than winter in South Korea[35]).

The human herpes virus HHV8 is a necessary, but not sufficient, cause of Kaposi sarcoma, a cutaneous malignancy.[38] A study in the USA has shown that in male veterans infected with human immunodeficiency virus (HIV), the risk of Kaposi sarcoma was increased in men who lived in locations with high ambient UV radiation or who had KC prior to the development of Kaposi sarcoma.[39] Other studies describe both positive[40] and inverse[41] associations between levels of ambient UV radiation and the incidence of oral, pharyngeal, and cervical cancers. The positive association was hypothesised to be due to the increased risk of infection with human papillomavirus (HPV, see section 4.2.1 and ESI†) because of higher exposure to UV radiation. A possible protective effect of vitamin D (see section 5.1) was suggested to explain the inverse association.

4.1.2. Vaccination. The evidence suggesting that exposure to solar UV radiation reduces the efficacy of vaccines, including those against poliovirus, influenza, tuberculosis, measles, and hepatitis B virus, was reviewed in 2011.[42] Since then, few investigations in this important area have been carried out. In a systematic review of 24 randomised trials, the effectiveness of the Bacille Calmette Guerin (BCG) vaccine against tuberculosis (TB) was progressively higher with increasing distance from the Equator,[43] possibly due to lower UV-induced suppression of immune function at higher latitudes.

4.1.3. Intracellular bacterial and protozoal infections. The lesions of post kala-azar leishmaniasis, a long-term outcome of visceral leishmaniasis, which is caused by a protozoal infection spread by sandflies, occur on sun-exposed body surfaces, suggesting that UV-induced immune suppression may play a key role.[44]

There is conflicting evidence on whether exposure to UV radiation is beneficial or harmful for TB. In a study in Birmingham, UK, notifications for TB were 24% higher in summer than winter,[45] consistent with UV-induced immune suppression. However, a global ecological study reported that the incidence of TB over the period 2004–2013 was 78% lower in countries in the highest quartile of solar UV-B radiation compared to those in the lowest quartile (after adjustment for average pigmentation of skin, degree of urbanisation, consumption of fish, prevalence of type-2 diabetes, and index ranking of human development).[46] In this model, variation in UV-B radiation accounted for 6.3% of the global variation in the incidence of TB. A similar finding of an inverse association between levels of solar radiation and incidence, hospital admissions, and mortality for TB has been recently reported in Chile.[47] The protective effect of higher UV-B or solar radiation was ascribed to higher vitamin D status in sunnier locations as well as upregulation of innate immunity. However, recent studies confirm previous reports that randomised controlled trials of vitamin D supplementation in people with TB are not effective in reducing signs of infection (sputum smear or culture positivity).[48,49] The explanation for the inconsistent findings in relation to higher ambient UV radiation is not clear.

4.2. Adverse effects of higher exposure to UV radiation on skin

Exposure to UV radiation that is inappropriately high for the individual's skin type causes sunburn. This ranges from a short-lived mild reddening of the skin to painful blistering that lasts several days. Other inflammatory reactions of the skin (photodermatoses) occur in people who are abnormally sensitive to UV radiation (see section 4.2.2). Long-term exposure to UV radiation damages the structural proteins in the dermis (*e.g.*, elastin and collagens), causing wrinkling and the typical appearance of photoageing, and is the major environmental risk factor for several types of skin cancer.

4.2.1. UV-induced skin cancers. Skin cancers occur as a result of repeated DNA damage following exposure to UV radiation, incomplete or deficient DNA repair, and UV-induced suppression of acquired immunity. Skin cancer is the most common cancer in populations of predominantly light-skinned people. For example, in New Zealand there are *ca.* 3000 new cases of colorectal cancer per year, compared to over 90 000 new cases of skin cancer predicted for 2018.[50] The incidence has been increasing steadily through much of the 20th and 21st centuries. This increase reflects changes in the prevalence of risk factors (*e.g.*, increased leisure time in sunny locations, migration of fair-skinned populations to regions with high ambient UV radiation, changing fashions in clothing, and use of sunbeds), coupled with increased surveillance, early detection, and improvements in tools and criteria for diagnosis.

The two main types of skin cancer, CMM and KC, arise from epidermal melanocytes and keratinocytes, respectively. Merkel cell carcinoma is a much less common skin cancer, which may also be etiologically linked to exposure to UV radiation.

Cutaneous malignant melanoma. Exposure to solar UV radiation is the most important known environmental cause of CMM,[51] typically on a background of phenotypic susceptibility, including lightly pigmented skin, and red or light-coloured hair. A recent study from Canada found that increases of one standard deviation in summer ambient UV radiation were associated with a statistically significant 22% greater risk (hazard ratio = 1.22, 95% CI 1.19–1.25) for CMM.[52] Approximately 5–10% of CMMs occur in those with a family history of CMM.[53]

Aetiology: environmental risk factors. In light-skinned populations, estimates of the proportion of risk of CMM that can be attributed to exposure to UV radiation vary from 60%[51] to 96%.[54] A recent assessment of the global burden of CMM attributable to UV radiation estimated that 168 000 new CMMs in 2012 were attributable to 'excess' UV radiation (that is, in comparison with an historic population with minimal exposure to UV radiation), as a result of population changes in lifestyle, from sun avoidance to sun-seeking behaviour.[54] The divergent (dual) pathways hypothesis[55] posits that CMMs can be separated into those that are associated with a high number of naevi (moles), and occur in younger people and on typically sun-protected skin, such as the trunk; and those developing on chronically sun-exposed skin, for example the head and neck, in typically older people with an average number of naevi. Epidemiological evidence strongly supports an increased risk of CMM in association with high-dose intermittent sun exposure (*e.g.*, leading to sunburn) in naevus-prone individuals, as well as a role for chronic sun exposure for some types of CMM, *e.g.*, lentigo maligna melanoma.[56]

Occupational exposure to UV radiation can increase the risk of CMM. A study estimated that, in Britain, there were 241 new CMMs in 2011 and 48 deaths from CMM (95% CI 33–64) in 2012 that could be attributed to occupational exposure to solar radiation (particularly in construction, agriculture, defence, and land transport).[57] From 2005 to 2014, CMM was the most frequently diagnosed cancer in active members of the USA military (excluding KC). Incidence rates increased with each additional year of service; for infantry, the incidence at 20 years of service was more than 44 times greater than in the first three years of service (5.34 in year 20 compared to 0.12 average over years one to three, per 10 000 people per year).[58] The equivalent increase for healthcare workers (*i.e.*, primarily indoor occupations) was from 0.50 to 2.82 per 10 000, a 5-fold increase.

High-dose sun exposure at any time during life increases the risk of CMM, but exposure occurring in childhood, and associated with the development of naevi, may be particularly important.[59] A previous report that higher sun exposure prior to diagnosis of CMM was associated with a reduction in subsequent mortality[60] was not confirmed in a more recent study with a rigorous study design and focus on this specific question.[61]

Aetiology: phenotypic risk factors. Having a skin phenotype of higher susceptibility to sunburn (lighter skin or eye colour) was associated with increased risk of invasive CMM among

both White and non-White (excluding African American) population groups in the USA Multi-ethnic Cohort Study.[62] The effect was stronger within the non-White than the White group. Incidence of CMM is higher in women than men in the pubescent and reproductive ages in both White and non-White populations.[63] Whether this is the result of a preference for a tan, hormonal influences, or other factors, requires further investigation.

A melanoma risk prediction model incorporating only age, gender, and host phenotypic risk factors (hair, eye, and skin colour, freckling, number of moles) predicted the risk of CMM with 72% accuracy; adding hours of tanning (but not total sunburns), and *MC1R* genotype (see below) improved this only slightly to 74%.[64] In another model, the strongest predictors of invasive CMM in adults aged 40–69 years were age, sex, tanning ability, number of naevi at age 21 years, and number of prior skin lesions treated destructively.[65]

A range of non-UV-related risk factors have been recently described. In a Danish study, the risk of CMM was increased in association with higher birth weight, and being tall in both childhood and adolescence, but not in relation to body mass index or body surface area.[66] The birth weight finding is consistent with some,[67,68] although not all,[69] previous studies; if this is a real finding it may indicate that an increased risk of CMM originates early in life, potentially driven by processes that regulate childhood height and/or birth weight. An inverse association between risk of CMM and a history of atopy (a genetic tendency to develop allergic diseases such as hay fever, asthma, and eczema) may reflect heightened immune surveillance in the skin of people with a history of atopic (allergic) dermatitis.[70]

Aetiology: genetic risk factors. High-risk genes for CMM include those involved in skin pigmentation, tumour suppressor pathways (*e.g.*, the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) found in 20% of familial CMM cases), immune suppression, and telomere maintenance.[53] The *MC1R* gene is well recognised as an important regulator of skin pigmentation. The R (null) alleles of *MC1R* are strongly linked to red hair, freckling, and sun sensitivity, and to inefficient DNA repair and reduced apoptosis (controlled cell death) of melanocytes. In white participants with a histopathologically confirmed CMM, the presence of an R allele was associated with a 42% (95% CI 15–76%) higher UV-signature mutation load compared to not having an R allele. This approximately equates to the higher mutation load associated with an additional 21 years of age.[71] New gene polymorphisms associated with increased susceptibility to CMM are being identified;[72] these may improve understanding of mechanistic pathways and provide potential opportunities for the development of novel therapeutic agents. Additional detail of recent research on the pathogenesis of CMM is provided in the ESI.†

Incidence of CMM around the world. The incidence of CMM is highest in light-skinned populations, particularly those living in locations with high ambient UV radiation, *e.g.*, Australasia, but also some countries with low annual UV radiation, *e.g.*, Norway, Denmark, and the Netherlands.[73] The incidence increases with increasing age.[74,75] Globally, the increasing incidence of CMM from 2005 to 2015 (56%) was exceeded only by that of prostate (66%) and thyroid (99%) cancers.[76]

Temporal trends in the incidence of CMM are variable by country or region (see Table 1). That is, while the age-standardised incidence rate (ASIR) continues to increase in some countries, it appears to have peaked in others, and the incidence in younger age groups is decreasing in several countries and/or regions, for example in the USA,[77] Australia,[78,79] and New Zealand,[78] possibly as a result of strong sun protection programs beginning in the 1980s. In Denmark, the increases in incidence have been particularly steep in the elderly (70 years and older).[80]

Table 1 Incidence of cutaneous malignant melanoma and changes over time in recently released data and publications

		Age standardised incidence rate (ASIR)[a] per 100 000		Change in incidence (average annual % change, AAPC)	
Location[Ref.]	Year	Male	Female	Male	Female
[a]United Kingdom[74]	2000	13.7	14.3		
	2010	24.3	22.0	+7.7%	+5.4%
	2014	28.0	24.1	+3.8%	+2.4%
[b]USA (whites)[81]	2000	28.5	19.1		
	2010	36.2	24.8	+2.7%	+3.0%
	2014	38.8	26.1	+1.8%	+1.3%
[d]Canada[82]	1992	9.8	8.9		
	2010	17.2	14.5	+4.2%	+3.5%
[a]Denmark[80]	1989–2003	14.9	17.3		
	2004–2011	23.5	27.8	+5.2%	+5.5%
[a]Denmark[83]	1985–1987	7.3	8.7		
	2008–2012	21.6	24.7	+4.5%	+4.3%
[a]Iceland[84]	1990–1999	5.9	10.9		
	2000–2009	10.2	16.5	+7.3%	+5.1%
[a]Netherlands	1994–1997	4.9	8.8		
(thin melanoma, <1 mm)[85]	2006–2010	9.1	15.0	5.0%	4.3%
[c]Estonia[86]	1995	~4.1	~5.5		
	2013	8.6	11.3	+4.4%	+3.8%
[a]South Tyrol, Italy[87]	1998–2002	12.2	13.3		
	2008–2012	23.1	23.1	+8.9%	+7.4%
[a]Catalonia, Spain[88]	2000	5.1	6.1		
	2007	6.3	6.5	+3.4%	+0.9%
[c]Australia[89]	2000	42.8	31.9		
	2010	45.3	30.9	+0.6%	−0.3%
	2014	46.1	32.5	+0.4%	+1.3%
[c]New Zealand[90]	2000	37.5	35.4		
	2013	39.4	35.8	+0.4%	+0.1%
Israel[a91]	2006	19			
	2010	16		−3.9%	
[c]Iran[92]	1996	0.48	0.42		
	2000	0.50	0.55	+1.0%	+7.7%
[c]Africa (total)[93]	2004	5.1	3.9		
	2013	4.9	2.9	−0.4%	−2.8%
[c]South Africa	2004	20.5	16.1		
(whites only)[93]	2013	19.7	13.8	−0.4%	−1.6%
[c]Costa Rica[94]	1985–1989	1.3	0.9		
	2003–2007	2.5	2.2	+5.1%	+8.0%

[a] European Standard Population. [b] US Standard Population 2000. [c] World Standard Population. [d] Crude incidence. Note that the reference population for standardisation varies across studies, limiting comparability across studies.

Data from the USA, UK and Australia showed that the age-specific incidence of CMM increased over 17 sequential 5-year birth cohorts from 1895–1899 to 1975–1979, but the slope of the increase was decreasing.[95] These changes are likely to be due to both external factors that affect all age groups equally (*e.g.*, changes in diagnostic criteria) and cohort effects that are specific to the unique experience of a particular age group as they move through time (*e.g.*, preference for a tan, sun protection education in childhood).[95]

The importance of factors other than ambient UV radiation is exemplified by the rapid increase in CMM incidence in Estonia that began following that country's transition to an open market economy in the 1990s. This was possibly driven by increased use of tanning beds and holidays in sunny locations,[86] although part of the increase could have been due to earlier and more accurate detection of CMM. The importance of cultural differences (for example, clothing habits) and probably degree of skin pigmentation was shown in a study comparing the incidence of CMM in five Iranian provinces (1996–2000) with locations in the USA matched on levels of ambient UV radiation. Despite the similarity in ambient UV radiation, the age-standardised incidence rates were 38-fold higher for men and 36-fold higher for women in the USA compared to Iran.[96]

Changing patterns in CMM mortality. Melanoma was the cause of nearly 60 000 deaths globally in 2015.[73] Age-standardised mortality rates due to CMM have stabilised in some countries, probably due to a combination of prevention through sun protection programs, earlier detection, and improvements in treatment. For example, in the USA, the mortality rate of 2.7 per 100 000 persons in 2011 was the same as in 1982,[75] and in Australia, mortality was stable at around 6.0 per 100 000 from 2004 to 2012.[89] In light-skinned people globally, the peak birth years for CMM mortality were 1936–1940 in Oceania, 1937–1943 in North America, 1945–1953 in the UK and Ireland, and 1957 in Central Europe. For people born later than these years in each location, the lifetime risk of death from CMM decreased and, for those born in 1990–1995, the risk level was similar to that for people born before 1900–1905.[97]

Incidence of CMM in people of different ethnicities. The incidence of CMM is lower in people with darker skin; for example, in the USA (2010–2014) it was 31.6 per 100 000 population in non-Hispanic whites *vs.* 4.7 in Hispanics and 1.1 in African Americans.[81] In addition, incidence is stable in Hispanics and African Americans but increasing in non-Hispanic whites. When CMM does occur in people with dark skin, it is typically found on the sole of the foot, under the fingernail (collectively referred to as acral lentiginous melanoma), or on other sites that are not highly sun-exposed. Medical care is often sought at an advanced stage with a consequent poorer prognosis.[98] Differences in incidence of CMM are not only due to protection arising from greater levels of melanin in the skin. Hispanics who adopt the behaviours and norms of a USA lifestyle (*e.g.*, preference for a tan, not using sun protection), and Hispanics who are born in the USA, have a higher risk of sunburn and CMM compared to those who retain their traditional lifestyles.[99]

Keratinocyte cancers. The KCs are the most common cancers in many light-skinned (predominantly Caucasian) populations. Although they are less likely to be lethal than CMM or internal cancers, they incur high costs and can be a source of considerable disability due to disfigurement from either the cancer or the treatment.

Aetiology: environmental risk factors. The primary cause of KC is exposure to solar UV radiation. It has been estimated that essentially all KCs that occur in Australia are attributable to high exposure to solar UV radiation, and that 10% of SCCs that would otherwise have occurred in 2010 were avoided due to regular sunscreen use.[51]

The patterns and timing of sun exposure (*i.e.*, intermittent *vs.* continuous; early life *vs.* cumulative) in relation to the different types of KC remain somewhat unclear. While SCC is clearly associated with cumulative exposure to the sun, the patterns that underpin risks of BCC are more complex. This is best exemplified by the body site distribution of the two cancer types. Whereas SCC occurs almost universally on body sites that are frequently exposed to the sun (*i.e.*, face, head, forearms, hands, and lower legs), a significant proportion of BCCs occur on the trunk,[100] suggesting a role for intermittent sun exposure. This hypothesis is supported by the findings of a recent study among French women where recreational sun exposure was more strongly related to BCC, and total and residential sun exposure were more strongly related to SCC.[101] The use of sunscreen with a high sun protection factor (SPF) prior to the age of 25 was associated with reduced risk of BCC, but use after that age was associated with increased risk of both BCC and SCC, possibly due to higher sun exposure in sunscreen-users during adulthood.[101] Similarly, in an Australian study, higher ambient UV radiation at the location of residence during early life (birth and up to 20 years) was associated with an increased risk of BCC but not SCC, and the risk of SCC but not BCC was associated with long-term cumulative sun exposure assessed by self-reported work outdoors.[102] BCC is the most common of the KCs, so this emphasises the need to focus on protection from sun exposure early in life.

Aetiology: phenotypic risk factors. Several phenotypic factors are associated with risk of KC, primarily because they influence the dose of UV radiation that reaches the target cells of the skin. A recent study from Australia found that self-reported skin colour, tanning tendency, and freckling all contributed significantly to predicting the risk of KC.[103]

Aetiology: genetic risk factors. Multiple genome-wide association studies (GWASs) (for example, ref. 104 and 105) have identified germline genetic variants that alter the risk of BCC. The BCC susceptibility loci identified in the most recent GWAS clustered into five functional categories: telomere biology, immune regulation, epidermal differentiation, non-coding RNA, and pigmentation.[105] These are mostly consistent with previous findings. An analysis of variants in vitamin D receptor binding sites identified several that were associated with BCC risk, supporting a potential role for vitamin D in BCC carcinogenesis.[106]

Most germline variants associated with SCC risk are pigmentation loci.[107,108] GWASs have also identified other

variants, including in genes involved in tumour interaction with the immune system, anti-apoptotic pathways, and cellular proliferation. Larger effect sizes are seen in younger age groups, highlighting the greater impact of environmental factors in SCCs that arise at older ages.

Several rare inherited genetic disorders influence the risk of KC and help to elucidate possible mechanisms underpinning their aetiology. For example, the genetic disorder xeroderma pigmentosum (which also increases risk of CMM, and see section 4.2.2) is caused by mutations in genes in the nucleotide excision repair pathway. The function of the gene products in this pathway is to repair UV-induced photoproducts. Mutation in these genes results in a very high frequency of KC at a young age; overall, the incidence is 150 times higher than in the general population, and in patients under 20 years the incidence is 5000 times higher.[109]

A possible role of HPV in the aetiology of SCC was identified by studying patients with epidermodysplasia verruciformis. These patients have increased susceptibility to infection with some HPV subtypes, resulting in widespread hyperproliferative lesions that develop into SCCs in up to 60% of patients.[110] The hypothesis that HPV may influence risk of SCC in people without epidermodysplasia verruciformis is not yet confirmed, but a new rodent model supports the view that HPV and UV radiation act synergistically to increase risk of SCC.[111] These findings provide impetus for further exploration of the interaction between UV radiation and HPV in the aetiology of cutaneous SCC in humans, and perhaps indicate that vaccination against some HPV subtypes may have a role to play in prevention of SCC in the future. More detailed information on the pathogenesis of KC and the role of HPV is given in the ESI.†

Incidence around the world. In some locations, the incidence of KCs outnumbers that of the major internal cancers by a factor of 40.[112] BCC outnumbers SCC, although the ratio depends on age and sex; a study in Australia reported that, in women and men aged 40–44 years, the ratios were 12 : 1 and 8 : 1 respectively, but in people aged 65–74 years the ratio was approximately 2 : 1 in both sexes.[113] Similarly, in a USA northern Californian population, the ratio of BCC to SCC in 31 to 45-year-olds was 5 : 1, but those aged over 60 years had approximately the same number of BCCs and SCCs.[114]

Although death from KC is uncommon, morbidity is significant, with a large economic impact (see section below). However, accurately measuring incidence rates and monitoring trends over time is difficult, because many lesions are treated destructively without prior biopsy, and KCs are generally not recorded in cancer registries because of the large numbers of both lesions and people affected.

The highest incidence of KC occurs in Australia. Individuals often present with multiple KCs, so it is important to consider both person-based and lesion-based incidence (with the latter always higher than the former). A recent report based on data from Australia's universal health insurance scheme (Medicare) estimated that the person-based incidence (2011–2014) for KC excisions was 1531 per 100 000 people per year. The ASIRs for BCC and SCC were estimated as 770 and 271 per 100 000 people per year, respectively.[113] Almost half (47%) of those treated during the study period had two or more KCs excised. Thus, the lesion-based incidence rate for excisions was 3154 per 100 000 people per year and, if destructive treatments were included, this increased to 4458 per 100 000 people per year. Recently reported incidence rates from other countries with Caucasian populations are considerably lower, as seen in Table 2.

Incidence of KC in people of different ethnicities. There are limited recent data on the incidence of KC in countries without predominantly Caucasian populations, but reported rates are at least an order of magnitude lower (Table 2).

Table 2 Incidence of keratinocyte cancers worldwide

		Incidence rate per 100 000 per annum		
Incidence[a]	Year	All keratinocyte cancer	SCC only	BCC only
Australia[113 b]	2011–2014			
Person-based		1531	271	770
Lesion-based		3154		
[b]Auckland (New Zealand)[112]	2008			
Lesion-based		1906	522	1385
[c]North Rhine-Westphalia (Germany)[115]	2015	188 (Men) 149 (Women)		
[d]Nordic countries[116]	2011–2015	18 (Men) 12 (Women)		
[c]United Kingdom[116]	2002–2006	99	23	76
[e]Minnesota (United States)[117]	2000–2010		163	321
[d]Lesser Antilles[118]	2000–2010		15	
[d]South Korea[119]	2011–2014		1	2
[f]South Africa (Black Africans)[120]	2000–2004		3 (Men) 2 (Women)	3 (Men) 2 (Women)

[a] Person-based incidence is reported unless otherwise specified. [b] Age-standardised to the Australian (2001) population. [c] Age-standardised to the European standard population. [d] Age-standardised to the world standard population. [e] Age-standardised to the United States (2010) population. [f] Population used for age standardisation not reported.

Table 3 Trends in keratinocyte cancer incidence in recent publications

		Change in incidence (average annual % change, AAPC)					
		BCC		SCC		KC	
Location[ref.]	Years	Male	Female	Male	Female	Male	Female
South Korea[119]	1999–2014	+8.0%	+9.0%	+3.3%	+6.8%		
Spain (Girona)[121]	1994–2012	+1.0%	+2.0%	+1.6%	+1.4%		
Germany[122]							
Schleswig-Holstein	1999–2012					+2.3%	+3.3%
Saarland	1999–2012					+6.0%	+6.3%
Nordic countries[116]	2006–2015					+3.1%	+3.9%

Trends in KC incidence. In almost every location where trends have been monitored, there is evidence of a substantial increase in incidence of KC over time (see Table 3).

Despite the increasing burden of KC around the world, there is evidence of a decrease in younger populations in some locations. In Australia, the excision rates for KC declined significantly in people younger than 45 years between 2000 and 2011 (Fig. 3), and a similar decrease was also observed for lesions treated using destructive methods, *e.g.* cryotherapy (freezing).[123] The incidence rate in younger groups also decreased in British Columbia in Canada[124] and was stable in northern California.[125]

Merkel cell carcinoma. Merkel cell carcinoma (MCC) is a rare, highly aggressive, skin cancer mainly affecting the elderly and the immunosuppressed; for example, there is an increased risk following solid organ transplantation. Tumours are typically solitary and found on sun-exposed areas of the skin. They are commonly located in the dermis, arising from epithelial stem cells or early stage B-lymphocytes, rather than the neuroendocrine Merkel cells as was originally thought.[126]

MCC can be 'virus-positive' or 'virus-negative' depending on the presence or absence of the Merkel cell polyomavirus.

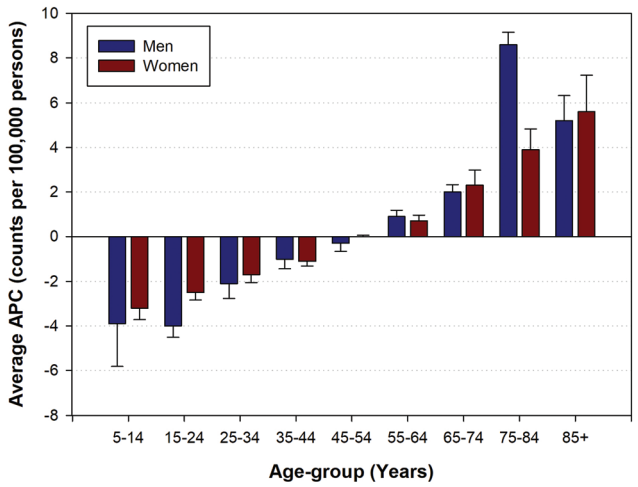

Fig. 3 Average annual percentage change (AAPC) with 95% confidence interval of excision rates for keratinocyte cancer in Australia in 2000–2011 by age-group (from ref. 123, reproduced with permission).

Exposure to UV radiation is thought to be important to disease pathogenesis in both virus-positive and virus-negative MCC.[127] In the northern hemisphere, most cases of MCC are virus-positive (>80%),[128] whereas in regions with high levels of ambient UV radiation, virus-negative tumours predominate. Virus-negative tumours have a particularly high load of UV-signature mutations.[129]

The incidence of MCC is increasing in light-skinned populations but is highly variable across the world. The highest rates are in Australia and New Zealand, with the latter reporting an incidence of 17.6 per 100 000 between 2002 and 2011 in those aged >85 years.[130] Incidence appears to be higher in men than women. MCCs typically metastasize early and have a poor prognosis.

Populations at particularly high-risk for UV-induced skin cancers. Immunosuppression following solid organ or stem cell transplantation greatly increases the risk of all forms of skin cancer, particularly SCC. The occurrence of these tumours on sun-exposed skin points to UV radiation acting synergistically with immune suppression.[131]

A recent review found standardised incidence ratios (SIRs) (comparing the incidence in transplant recipients with that in the general population) for SCC in kidney transplant recipients ranging from 81 in Denmark to 121 in Sweden.[132] SIRs were even higher in people who had received heart transplants: 113 and 198 in Denmark and Sweden, respectively. However, risks are declining with newer, more individualised immunosuppressive regimens and better advice about personal protection against sun exposure. A study in more than 8000 transplant recipients in Norway found that the SIR for SCC in those receiving transplants between 1983 and 1987 was 103; this had declined to 22 in people who received their transplant between 2003 and 2007.[133]

The incidence of CMM is also increased following organ transplantation (*e.g.*, a two-fold increase following heart transplantation[134]), hematopoietic stem cell transplantation,[135,136] and in other immunosuppressed states, *e.g.*, HIV infection.[137]

Health costs of skin cancers. A recent economic analysis from Australia that included costs of diagnosis and treatment of CMM, as well as management of lesions subsequently found to be benign, estimated the cost of CMM to be *ca.* AUD 272 million per year.[138] In the USA, the annual cost of treating newly diagnosed CMM is estimated to increase from USD 457 million in 2011 to USD 1.6 billion in 2030.[139]

The high incidence of KC poses a substantial economic burden. KC accounted for 8.1% of all health system spending on cancer (excluding screening) in Australia in 2008–2009.[140] The total cost of treatment in 2010 was *ca.* AUD 512 million.[141] KC accounted for 5% of total cancer healthcare expenditure in the USA in 2007–2011 (total cost USD 4.8 billion).[139] Even in countries where the incidence is lower, the costs of healthcare are substantial. For example: Sweden (2011), *ca.* 39 million EUR;[142] UK (2008), GBP 106–112 million (depending on the method used to calculate costs);[143] South Africa (2014–2015), USD 13.8 million.[144] A systematic review found that, relative to population size, the costs of treating KC were highest in Australia, with a cost to population ratio of 16 (2013 EUR per person), followed by New Zealand (ratio ~6), and Sweden (ratio ~4).[145]

A systematic review suggests that sun protection campaigns are cost-effective.[145] An analysis of the benefits of mass-media campaigns in New South Wales, Australia, found that for every dollar invested there was a return of AUD 3.85.[146] A modelling study for Australia found that for an additional investment in skin cancer prevention of AUD 0.16 per capita, 140 000 cases of skin cancer would be prevented from 2011 to 2030.[147]

Interaction with increasing ambient temperature. A study from 10 years ago suggested that higher temperatures may amplify the induction of human KC by UV radiation.[148] More recent results provide only limited support for such an effect.[149] The incidence of BCC increased in association with greater lifetime residential ambient UV radiation ($P < 0.0001$); there was also an increase in incidence with higher residential ambient temperature, but this was not statistically significant ($P = 0.09$). In analyses stratified by quintile of ambient UV radiation, the incidence of BCC increased with increasing ambient temperature, but this was statistically significant only in the third quintile of ambient erythemally weighted UV radiation ($P = 0.03$; 184–196 J m^{-2}). The finding of a significant effect only in the third quintile (and not the 4th or 5th) suggests that this may be due to chance.

Interaction with air pollution. Particulate matter (PM) and polycyclic aromatic hydrocarbons (PAHs) cause skin carcinogenesis in animal models (reviewed in ref. 150). The mechanism may be through the production of reactive oxygen species (ROS), generated mainly by UV-A wavelengths, and subsequent DNA damage.[151] There is little specific evidence in human studies, although the combination of sun exposure and cigarette smoking increases the risk of SCC and malignant lesions of the lip,[152,153] most likely because of direct deposition of tar on the lips from the combustion of tobacco. Because the major route of exposure of humans to particulate air-pollutants is *via* the respiratory system (see ref. 13), this interaction is unlikely in humans.

4.2.2. Photodermatoses. Photodermatoses are inflammatory skin disorders induced or exacerbated by exposure to UV radiation, and in some cases visible radiation.[154]

Pathogenesis. The photodermatoses fall into five groups based on their underlying aetiology; a brief overview and some examples are listed below.

(i) Dysregulated immune responses to UV and/or visible radiation. Examples include: polymorphic light eruption, which may be caused by a UV-induced reaction involving specific inflammatory proteins (interleukins, IL) of the IL-1 and/or IL-36 family;[155] chronic actinic dermatitis, which may be a delayed-type hypersensitivity reaction to UV radiation;[156] solar urticaria, which is a rapid onset immune disorder mediated by mast cells, possibly due to photo-induced allergens that bind to immunoglobulin E.[157]

(ii) DNA repair disorders; for example, xeroderma pigmentosum (see section 4.2.1). Most patients with xeroderma pigmentosum have abnormal erythemal sensitivity to sunlight,[158] and a marked increase in risk of CMM and KC.[159]

(iii) Intrinsic biochemical defects (metabolic disorders), such as the rare disorders erythropoietic protoporphyria‡ and X-linked protoporphyria, which are caused by mutations leading to defects in the synthesis pathway for haem, a component of the red pigment (haemoglobin) in red blood cells.[160,161] Absorption of photons (maximal activation ~405 nm) by excess accumulated porphyrins (specific to the disease) results in the formation of reactive oxygen species (ROS) that can activate cutaneous pain sensors. This may be the origin of the severe skin pain experienced in erythropoietic protoporphyria.

(iv) Phototoxic and photoallergic reactions to drugs and exogenous chemicals. Many drugs and chemicals cause phototoxic and/or photoallergic reactions, triggered by the UV-absorbing properties of the agent or its metabolites.[162] Phototoxicity can occur through damage by ROS,[163,164] or drug binding to DNA, as with psoralens (used with UV-A phototherapy to treat psoriasis).[165] Included is the systemic photosensitivity occurring with many medications (for example, antihypertensive drugs such as thiazides,[166] and non-steroidal anti-inflammatory drugs),[167] and the photocontact reactions occurring with sunscreen filters, topical non-steroidal anti-inflammatory drugs,[168] and sap from some plants.[169] The photosensitivity is largely induced by UV-A but also UV-B radiation.[170] The factors that influence personal susceptibility to this photosensitivity are poorly understood.[167] Increasing evidence also suggests long-term exposure to certain photosensitising drugs, *e.g.*, voriconazole, can increase the risk of CMM or KC.[171,172]

(v) Photoaggravation of existing disorders. Photosensitivity occurs in a proportion of patients who have disorders with an underlying immune pathogenesis. For example, a high percentage of people with systemic and cutaneous lupus erythematosus are photosensitive,[173] and exposure to UV radiation can induce flare-ups of disease activity.[174] The skin disorders psoriasis and atopic dermatitis are most commonly ameliorated by exposure to UV radiation. However, a subset of patients with psoriasis have severely photosensitive psoriasis,[175] and approximately 5% of patients with atopic dermatitis develop

‡ The porphyrias are a group of conditions in which chemicals (porphyrins) are abnormally increased in the body.

photoaggravated atopic dermatitis. The reason for this switch from a UV-responsive to a UV-aggravated disorder is unclear.[176]

Incidence of photodermatoses. While large epidemiological studies are scarce, certain photodermatoses are highly prevalent. In a multicentre survey of 6995 indoor workers, polymorphic light eruption was found to affect approximately 18% of the European population.[177] Drug photosensitivity occurs in 4% of patients under investigation for photosensitivity.[170] Several conditions are rare diseases, including chronic actinic dermatitis and solar urticaria; the prevalence in Scotland, UK, is estimated at 16.5 and 3.9 per 100 000, respectively.[178]

Incidence in different skin types/ethnicities. Polymorphic light eruption is reportedly less common in India (0.6% of attendees at a skin outpatient clinic)[179] and China (0.7% of a population sample).[180] Examination of 631 primary patient visits to a HIV dermatology clinic found HIV-related photosensitivity in 7.3% of African American patients (*versus* 5.4% of all patients).[181] While individual photodermatoses show differing prevalence and demographics, overall they remain common in people of darker skin.[182,183]

Morbidity due to photodermatoses. Clinical features of photodermatoses depend on the disorder and include severe phototoxic pain, burning erythema and itching, blistering, eye involvement (including conjunctivitis and pterygium), and incapacitating systemic symptoms. Photodermatoses cause major negative impacts on patients;[184] both their clinical manifestations and the need for light avoidance have consequences for schooling, employment, family and social activities,[185] and mental health.[186]

Possible future effects of changes in UV radiation and climate on photodermatoses. Photodermatoses are triggered by exposure to UV radiation, often with demonstrable UV dose-thresholds for their provocation. Many conditions show a seasonal pattern, with their expression most pronounced in, or even restricted to, the spring and summer months. Accordingly, the impact of polymorphic light eruption was shown to follow the variation in level of ambient UV radiation across seasons in several locations in Europe.[187] Changes in UV radiation as a result of recovery of stratospheric ozone depletion, and changes in exposure as a result of global climate change may consequently alter the incidence and severity of a range of photodermatoses, including drug-induced photosensitivity.

4.3. Adverse effects on the eye as a result of exposure to UV radiation

Exposure to sunlight is a known or suspected risk factor for several eye diseases that can cause moderate or severe visual impairment; for example, cataract and age-related macular degeneration (see section 4.3.2).[188] Despite the high disease burden, there is a lack of awareness about sun protection for the eyes. For example, in a cross-sectional study of university students in northern China (n = 386), over 90% were aware of the effects of UV radiation on sunburn and skin cancer, but only 28% were aware of increased risk of cataracts, and 3% of risk of pterygium. Protection of the eyes during sun exposure was uncommon.[189]

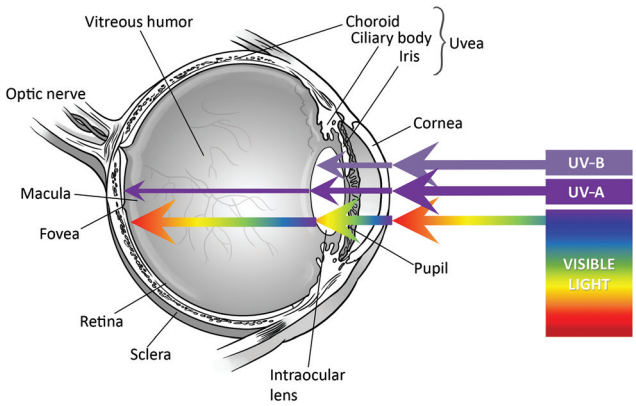

Fig. 4 Schematic of the anatomy of the eye, showing the penetration of solar UV and visible radiation of different wavelengths in the healthy adult eye.

When sunlight impinges on a normal healthy eye, it passes through the cornea, the intraocular lens, and the vitreous humour to reach the retina (Fig. 4). Radiation with wavelengths <300 nm is largely absorbed by the cornea. In young children (up until around 10 years of age), UV radiation of wavelength around 320 nm can be transmitted by the lens.[190] The wavelength of peak absorption by the lens increases with age, from around 365 nm at age 8 years to ~400 nm in adulthood and ~450 nm at age 65 years, although there are considerable differences between individuals.[190] Thus, UV radiation may reach the retina in the child, but not in the healthy adult eye.[191]

4.3.1. Effects on the superficial layers of the eye. Exposure of the cornea or the conjunctiva to high-intensity UV radiation causes photokeratitis or photoconjunctivitis, respectively. Prolonged exposure of these superficial structures, such as through sun exposure over the lifetime, can result in pterygium,[192] pinguecula, ocular surface squamous neoplasia,[193] and, probably, melanoma of the conjunctiva.[194]

Pterygium. This is a wedge-shaped growth on the conjunctiva or cornea. It is not malignant (although it can contain premalignant cells) but if it extends over the cornea it can impair vision. Treatment is by surgery to remove the pterygium; however, this may not be universally available and often needs to be repeated for recurrences.

The prevalence of pterygium increases with age, and is often higher in men, those with outdoor occupations, and in populations living at high altitude. The highest prevalence is between latitudes 40°N and 40°S, an area known as the 'pterygium belt'.[195] For example, 39% of adults aged 20 years and over had a pterygium in Gondar (altitude 2133 m), northwest Ethiopia (within the pterygium belt), with the prevalence nearly four-fold higher in outdoor, compared to indoor, workers.[196] In a hospital-based study in Cambodia, the majority of patients diagnosed with pterygium lived in rural areas (80.3%) and had always worked outdoors (61.2%).[197] A

meta-analysis of risk factors for pterygium showed a linear reduction in the pooled prevalence of pterygium with increasing latitude band.[198] The incidence of pterygium decreased from 3.0 to 1.3 per 1000 person-years between 2004 and 2013 in South Korea, possibly due to improved awareness of the importance of eye protection and a reduction in outdoor occupations, such as farming, fishing, and forestry, over time.[199]

Heat, dust, and low humidity are thought to also contribute to the genesis of pterygium. In a study from Pakistan, 87% of people with pterygium lived in hot, dry conditions.[200] In a large study from western Rajasthan, India (n = 5012), people with a pterygium had a three-fold greater risk of also having spheroidal degeneration of the cornea, for which the risk factors are thought to be low humidity, strong winds, and small injuries from sand particles.[201]

Pinguecula. Commonly associated with UV radiation and ageing, pinguecula is characterised by the development of benign, yellowish, slightly raised nodules on the nasal side of the conjunctiva, in a similar location to pterygia. These lesions are most often asymptomatic but can be unsightly, become inflamed, or cause dry eye syndrome. Pinguecula can be very common. For example, in a population-based study in rural eastern China (126°E, 31°N), pinguecula was identified in 76% of the population aged ≥50 years. Older age and outdoor occupation were strongly associated with higher prevalence of pinguecula.[202]

Ocular surface squamous neoplasia. Ocular surface squamous neoplasia (OSSN) refers to malignant lesions on the cornea and conjunctiva that may occur over a pinguecula or be apparent within excised pterygia.[203] Chronic exposure to UV-B radiation (especially in people with lighter skin type), HIV/AIDS, and infection with HPV are major risk factors for the development of OSSN. The incidence of OSSN is relatively high in African countries because it is more common for multiple risk factors to co-occur.[204] For example, ASIRs of 3.4 and 3.0 cases per 100 000 population per year were found for men and women respectively in Zimbabwe,[205] compared to the USA (<1 per 100 000).[206]

Exposure to UV radiation may initiate the development of OSSN through some combination of DNA damage, local and systemic immunosuppression, and reactivation of latent HPV infection.[207] In a study from Kenya, greater time spent in sunlight, less use of hats, having more outdoor occupations, and lower education were associated with higher prevalence of OSSN.[208]

Conjunctival melanoma. Melanomas of the eye are rare, and conjunctival melanoma accounts for only *ca.* 5% of these.[209] In Denmark, the annual incidence rate of conjunctival melanoma increased from 0.36 per million per year in 1960–1969 to 0.87 per million per year from 2000–2009,[210] in parallel with rising incidence of CMM (see Table 1), supporting exposure to UV radiation as a common risk factor. Findings of a strong UV-mutational signature in tumour samples[194] lends further weight to a role for exposure to UV radiation.

4.3.2. Effects on the deeper structures of the eye. Absorption of UV radiation by the lens, and penetration beyond the lens, depends on the wavelength (Fig. 4), and varies according to age and the transparency of the lens.

Cataract of the lens. Cataract occurs when the lens, a small transparent disc-shaped tissue in the eye, develops cloudy patches. Over time, these patches increase in size and number, and cause blurry vision and blindness. Cataract is the leading cause of blindness worldwide (12.6 million people blind and 52.6 million people with vision impairment due to cataract in 2015).[188] Due to the wide accessibility of surgery to replace the opaque natural lens with an artificial one, cataract-related vision loss is uncommon in developed countries. However, poor access to effective surgery as a consequence of lower socioeconomic status and/or lack of proximity to appropriate medical facilities can result in cataract-associated loss of vision in both developed and developing countries.[211]

Long-term exposure to UV radiation is a major cause of cataract, particularly those of the cortex and, perhaps, those located at the back of the lens, just under the capsule of the lens (posterior sub-capsular).[212] These cataract types commonly make up over 50% of all cataracts, although this varies with age and location. A high prevalence of cataract, especially cortical[213] and posterior sub-capsular, with a younger age of onset, was found to be a major contributor to age-related visual disability in a high altitude region of China (higher UV-B radiation), compared to a low altitude region.[208] Another study estimated that an increase in the daily ambient erythemal UV radiation of 1000 J m^{-2} was associated with the cataract-related loss of an additional 92 disability-adjusted life years (DALYs) per 100 000 population.[214] The burden of disease (in DALYs per 100 000) was much higher in the elderly (<65 years old: 34; 65–74 years: 607; ≥75 years old: 1342) and in an agricultural population compared to a non-agricultural population (177 *vs.* 81).[214]

Age-related macular degeneration. In adults, longer wavelength UV-A, visible, and infrared radiation reach the retina and may cause degeneration of retinal tissue.[215] UV-B radiation can reach the retina in young children. Higher exposure of the eye to solar radiation is thus a plausible risk factor for age-related macular degeneration (AMD), a leading cause of blindness worldwide.[216]

AMD develops when the part of the eye responsible for central vision (the macula) loses function. The underlying mechanisms of AMD are not yet clear, but probably include oxidative stress, mitochondrial dysfunction, and inflammation.[217] There are two main types of AMD. Dry AMD occurs when the macula is damaged by the build-up of lipid deposits. This is the least severe, but most common form of AMD (90% of all cases), and results in gradual loss of central vision occurring over many years. Dry AMD may progress to the more severe wet, also called neovascular, AMD. Here, there is leakage from abnormal blood vessels that have grown from the choroid into the macula, or there is a build-up of fluid/blood exerting a physical force on the macula. If untreated, central vision deteriorates within days or weeks.[218] Clinically, AMD is often defined as early, intermediate or late stage, based on the size and the number of lipid deposits under the retina. The

disease burden of AMD is increasing; globally the age-standardised loss of DALYs due to AMD increased from 5.3 to 6.3 per 100 000 between 1990 and 2016,[219] with vision impairment due to AMD affecting 8.4 million people.[188]

The association between stage of AMD and exposure to the sun remains unclear. In a case-control study of 3701 Europeans, past sunlight exposure (≥ 8 hours outside daily) was associated with increased risk of early (odds ratio (OR) 5.54, 95% CI 1.25, 24.58) and late (OR 2.77, 95% CI 1.25, 6.16) AMD after adjustment for age, sex and smoking behaviour.[220] Working outdoors was associated with late (OR 2.57, 95% CI 1.89, 3.48) but not early (OR 1.20, 95% CI 0.85, 1.71) AMD in the same study.[220] However, in a study in Bordeaux, France (n = 963 residents aged 73 years and over), both low and high lifetime ambient UV radiation (compared to intermediate) were associated with increased risk of early, but not late, AMD.[221] It is not clear what the biological pathways could be to support this apparent U-shaped association. The inconsistency in the findings across various studies may relate, at least in part, to the challenges of accurately measuring sun exposure to the eye over a lifetime, and failure to account for possible confounding factors. Nevertheless, these indications of a link with sun exposure, for a disease as serious as AMD, support public health measures recommending that the eye be protected from excessive exposure to solar radiation.

Uveal melanoma. Uveal melanoma (UM) involves the iris, ciliary body, or choroid (collectively known as the uvea). It is rare (incidence of 5.1 cases per million per year in the USA from 1973–2008[222]) but has high mortality; only 69% of patients will survive beyond 5 years.[223] There is little direct evidence of an association between UM and exposure to UV radiation, but people with markers of a sun-sensitive phenotype are at increased risk. For more information, see ESI.†

Pseudoexfoliation syndrome and glaucoma. Pseudoexfoliation syndrome (PXF) is an uncommon age-related disorder characterised by accumulation of protein in the drainage system of the eye. It can cause glaucoma, the second most frequent cause of blindness.[224] Recent evidence suggests that the risk of PXF increases with greater time outdoors and a history of work over water or snow, and is reduced with the use of sunglasses.[225] However, the evidence is not consistent. Long-term protracted sun exposure (≥5 hours per day) was associated with a non-significant 3-fold increase in risk of PXF (OR 2.76, 95% CI 0.96, 7.96, P = 0.06) based on 16 cases (prevalence 0.12%) in a population-based study in South Korea;[226] however, there was no evidence of an association in older residents (≥50 years) of an isolated island in Korea.[227]

4.3.3. Future predictions taking account of changing UV radiation and interactions with climate change. There are not yet any quantitative projections of UV-induced eye diseases that consider the effects of global climate change. Based on our knowledge of risk factors, reduction in snow and ice cover because of global warming, as well as lower UV radiation at high northern latitudes in the future, should result in a reduction in the risk of UV-induced eye diseases, because of the reduced dose from both direct, and more importantly, reflected radiation. On the other hand, drought and wildfires, with loss of vegetation, will result in increased reflected and diffuse UV radiation (particularly important for exposure of the eye), and release of particulate matter into the troposphere. This is a 'perfect storm' for pterygium – low humidity, high heat, high dose of UV radiation, dust and other particulate matter. The risks will not be evenly spread; at high latitude (typically high-income countries), risk will be decreased and good access to surgery for cataract and pterygium reduces the risk of visual impairment. Rural and poor populations, and populations in drought areas, may have reduced access to surgery, and thus suffer the dual burdens of visual impairment and loss of livelihood.

4.4. Other health risks linked to exposure to solar radiation

We have previously reported[228] on emerging evidence of links between greater exposure to UV radiation and an increased risk of several other disorders, including goitre and thyroid cancer,[229] Parkinson's disease,[230,231] and mania.[232] The supporting evidence remains sparse.

In France, the incidence of B-cell acute lymphoblastic leukaemia in children aged less than five years was higher with higher levels of erythemal UV radiation at the location of residence, above a threshold of 100 J m^{-2} (daily average UV radiation dose over the period 1988–2007).[233] Further studies are required to substantiate this association.

5. Beneficial effects on human health from exposure to UV radiation

The best-known beneficial effect of exposure to UV radiation is the cutaneous synthesis of vitamin D. Immune suppression due to exposure to UV radiation, occurring through vitamin D and non-vitamin D pathways, has both benefits and adverse effects on health.[234] The adverse effects of UV-induced immune suppression are described above; evidence for benefits is considered below, along with benefits of exposure to UV radiation for vision and other health outcomes.

The commonly accepted marker of vitamin D status is the concentration of 25-hydroxyvitamin D (25(OH)D) in serum or plasma. Exposure to solar UV radiation within the preceding 1–2 months is a major determinant of 25(OH)D concentration.[235] Thus, while the concentration of 25(OH)D in serum or plasma is the accepted marker of vitamin D status, it is also an estimate of recent exposure to solar UV radiation. "Sufficient" recent sun exposure could be construed as that which results in "sufficient" 25(OH)D (see below). Randomised placebo-controlled trials of vitamin D supplementation test the health benefits of vitamin D alone, separate from UV-induced production of vitamin D that may have benefits unrelated to vitamin D, as discussed below.

5.1. Vitamin D

Vitamin D is produced in the skin following exposure to UV-B radiation. There is a small number of substantive food

sources, such as oily fish and certain types of mushrooms, and vitamin D is also available as a supplement. Irrespective of the source, vitamin D is hydroxylated in the liver to 25(OH)D and in the kidney to the active form, 1,25-dihydroxyvitamin D (1,25$(OH)_2$D). The active form of vitamin D can also be produced from 25(OH)D by a wide range of cell types that have the requisite enzymes, allowing autocrine (effects on the cell producing the 1,25$(OH)_2$D), paracrine (effects on nearby cells), as well as endocrine (effects on distant cells through changes in blood levels) signalling.[236]

There is a lack of consensus on the criteria (in terms of concentration of 25(OH)D) that define the categories of vitamin D status – deficiency, insufficiency, sufficiency. In 2011, after a comprehensive systematic review of the literature, the National Academy of Medicine (USA) concluded that a concentration of 25(OH)D in serum or plasma of 50 nmol L^{-1} is sufficient to optimise the bone health of most people.[237] The 2016 report of the Scientific Advisory Committee on Nutrition (SACN) in the UK recommended that the serum 25(OH)D concentration should not fall below 25 nmol L^{-1} at any time of the year.[238] A recent study showed that a 25(OH)D concentration of ~30 nmol L^{-1} was sufficient to optimise bone mineral density and a range of markers of muscle strength and function in middle-aged women.[239] Possible mechanisms of action of active 1,25$(OH)_2$D for multiple health outcomes are described briefly in the ESI.†

5.1.1. Prevalence of vitamin D deficiency. The lack of consensus over the definition of deficiency, combined with historic challenges in measuring the concentration of 25(OH)D, make it difficult to document the international prevalence of vitamin D deficiency and any temporal trends. However, there are now standardised measurement protocols and rigorous quality assurance schemes resulting in more comparable measurements across studies and over time. The importance of this is highlighted in a study from Germany in which the results of three national health surveys conducted from 1998 to 2011 were retrospectively standardised. In all studies, the mean 25(OH)D after standardisation was higher than in the original study.[240]

Studies using standardised methods indicate that low vitamin D status is common in many parts of the world. For example, across a range of northern European countries the annual mean prevalence of 25(OH)D concentration of <50 nmol L^{-1} was found to be 40%, with 13% having a 25(OH)D concentration of <30 nmol L^{-1}.[241] Dark-skinned ethnic subgroups were much more likely to have 25(OH)D levels <30 nmol L^{-1} than light-skinned groups (three times higher in the UK and 71 times higher in a Finnish immigrant population).

A high prevalence of vitamin D deficiency in northern Europe is not surprising, since modelling shows that there is not enough ambient UV-B radiation to produce sufficient vitamin D for at least 4 months over winter in Germany, Ireland, the UK, Denmark, Finland, and Iceland.[242] In light of this, the UK SACN recently recommended routine supplementation of 400 IU per day to maintain 25(OH)D levels >25 nmol L^{-1}.[238] Fortification of food may also be an effective way of mitigating the risk of vitamin D deficiency. In Finland, for example, fortifying liquid milk products resulted in a decrease in the prevalence of severe deficiency (25(OH)D < 30 nmol L^{-1}) among people not using supplements from 13% to less than 1%.[243]

In the USA, the National Health and Nutritional Examination Surveys (NHANES) found no change in the mean 25(OH)D concentration (after assay standardisation) from 1988 to 2006 (~62 nmol L^{-1}), but an increase of 5 nmol L^{-1} from 2007 to 2010, partly due to supplementation. The prevalence of vitamin D insufficiency (25(OH)D < 50 nmol L^{-1}) was ~30% from 1988 to 2006 and 26% in 2009–2010. Less than 7% of the study population had a 25(OH)D concentration of <30 nmol L^{-1}.[244] Data from the Australian National Health Survey show that *ca.* 23% of the population had low vitamin D status (<50 nmol L^{-1}), with 6% <30 nmol L^{-1}.[245]

There are limited data on the prevalence of vitamin D deficiency in low- and middle-income countries. A recent systematic review found that two-thirds of low- and middle-income countries had virtually no data that could be used to determine the prevalence of vitamin D deficiency.[246] Among the 29 countries with data available, at least 20% of the population, or of an at-risk population subgroup (infants, children, women of child-bearing age, pregnant women), were vitamin D deficient (<25 to 30 nmol L^{-1}) in five countries (Afghanistan, Pakistan, India, Tunisia and Mongolia). This suggests a public health issue warranting mitigation.

5.1.2. Vitamin D and health. The role of vitamin D in health remains controversial, apart from the established association between vitamin D and musculoskeletal health. Low concentrations of 25(OH)D have been linked to increased risk of a broad range of health conditions. However, it is not clear whether the low 25(OH)D level causes the health condition or is an effect of it (called reverse causation). In addition, issues in the study design or analysis of the data (*e.g.*, selection or measurement bias, or uncontrolled confounding factors) may account for the associations described.

Vitamin D plays a critical role in calcium homeostasis and vitamin D supplementation is widely recommended in older people to avoid osteoporotic fractures. A recent meta-analysis of cohort or nested case-control studies found that low serum 25(OH)D concentration (defined as <50 nmol L^{-1} in most included studies) was associated with significantly increased risk of total fractures and hip fractures,[247] but the results did not enable a criterion for 'sufficiency' to be derived. Meta-analyses of randomised trials of the effect of vitamin D supplementation on bone mineral density[248] or fracture[249] do not suggest that supplementation is of benefit in community-dwelling (*i.e.*, not institutionalised) adults. This conclusion is supported by Mendelian randomisation studies§ (see footnote

§ Mendelian randomisation is a method used to control for reverse causation and confounding factors. It uses genetic polymorphisms known to affect 25(OH)D concentration as an instrumental variable to test, in large populations, a causal association with a disease outcome.

for explanation), which found no association between genetically determined 25(OH)D concentration and bone mineral density, bone metabolism markers, or fracture.[250,251]

A recent review of meta-analyses and randomised controlled trials concluded that there is limited evidence that supplementation with vitamin D has any effect on health other than musculoskeletal conditions.[252] However, two meta-analyses, one using individual patient data, found evidence that vitamin D supplementation caused a modest reduction in upper respiratory tract infections,[253,254] mainly confined to those who had low vitamin D status.[255] A Cochrane review¶ and meta-analysis found some evidence that supplementation can reduce all-cause and cancer mortality in middle-aged and older people, but could not exclude that the results may be due to chance.[256]

Despite observational studies suggesting inverse associations between concentration of 25(OH)D and risk of cardiovascular disease, supplementation trials have failed to find effects on endothelial function,[257] arterial stiffness,[258,259] or hypertension.[260] Mendelian randomisation studies are inconclusive, with one of the two published studies finding that higher genetically-determined 25(OH)D concentration was associated with reduced systolic and diastolic blood pressure and reduced odds of hypertension,[261] but the other finding no association.[262]

There is considerable and consistent support for an association between higher concentration of 25(OH)D and reduced risk of the autoimmune disease multiple sclerosis (MS),[263] including from a Mendelian randomisation study.[264] Indeed, vitamin D deficiency is commonly considered an established risk factor for the disease.[265] Lower 25(OH)D concentration at birth[266] and during adulthood[267] may both be important. However, vitamin D supplementation trials in people with MS have thus far failed to demonstrate a clinical benefit.[268]

Observational studies consistently show associations between low 25(OH)D concentration and increased risk of colorectal cancer.[269] However, to date, trials have found no benefit of vitamin D supplementation, and two Mendelian randomisation studies suggest there is no causal link between 25(OH)D concentration and colorectal or other cancers.[270,271]

The role of vitamin D in maternal or foetal outcomes during pregnancy is controversial. Observational studies show a link between low concentrations of maternal 25(OH)D and increased risk of pre-term birth,[272] but a high quality meta-analysis found no beneficial effect of vitamin D supplementation.[273] Two meta-analyses found that vitamin D supplementation during pregnancy was associated with reduced risk of the baby being small for gestational age,[273,274] but a study published since then found that supplementing pregnant women in Bangladesh, where vitamin D deficiency is common, had no effect on infant length-for-age scores at 1 year of age.[275]

¶Cochrane reviews are systematic reviews of primary research in human health care and health policy; they are recognised internationally as the highest standard in evidence-based health care.

5.2. Beneficial effects on immune function

Defence against microbial attack of the skin rests on the integrity of the surface, the innate immune response, and the adaptive immune response. UV irradiation damages the skin surface but upregulates innate immune responses, while also modulating (largely suppressing) adaptive immune responses (see section 3.2). UV-induced local suppression of cellular immunity may have benefits for skin disorders such as psoriasis and atopic dermatitis, while systemic suppression may be beneficial for disorders such as autoimmune disease and allergy. These are discussed in the sections below.

Recent publications focus on the balance, following exposure to UV radiation and upregulation of vitamin D synthesis, of immune suppression and upregulation, and innate *vs.* adaptive immunity, for effects on the skin microbiome,[32] the development of childhood food allergy,[276] and the seasonality and outcomes of infectious diseases.[277] Much work remains to be done to understand these effects, including the impact of the exposure dose and the time course of exposure on the direction and magnitude of any effects.

5.2.1. Beneficial effects of UV radiation on immune-related skin disorders. The beneficial effects of exposure to UV radiation on skin disorders are wide ranging, including enhanced skin barrier function, reduced epidermal cell turnover, epidermal and dermal cell apoptosis, in addition to many further anti-inflammatory effects, and the modulation of innate and adaptive immune responses.[33] Exposure to UV radiation, as used therapeutically in phototherapy, ameliorates a number of immune-mediated skin diseases, including psoriasis, atopic dermatitis, polymorphic light eruption, and vitiligo.[278] Suppression of psoriasis can be prolonged, which may be attributable to restoration of T_{reg} cell numbers.[279] A discussion of the mechanisms of phototherapy and effects on these disorders is included in the ESI.†

5.2.2. Systemic suppression of adaptive immunity. Several studies have reported an association between higher levels of sun exposure or ambient UV radiation and reduction in (autoimmune) inflammatory bowel disease (IBD): risk of Crohn's disease (hazard ratio (HR) = 0.49, 95% CI 0.23, 1.01 for the third *vs.* the first tertile of ambient UV radiation, P for trend = 0.04),[280] paediatric Crohn's disease (increase in incidence of 0.23 per 100 000 population for each 10° increase in latitude),[281] and hospitalisation (reduction of 0.44 cases per increment of UV radiation in MJ m^{-2} per day, 95% CI −0.82, −0.05, P = 0.03),[282] and need for bowel surgery for both ulcerative colitis and Crohn's disease (Crohn's disease: relative risk (RR) = 1.24, 95% CI 1.16, 1.32; ulcerative colitis: RR = 1.21, 95% CI 1.09, 1.33), for low UVI (0–2) compared to high UVI (≥8).[283] However, findings from cross-sectional and case-control studies of lower 25(OH)D levels in people with IBD than in those who do not have the disease[284] may be due to reverse causality. There is some support from animal models that exposure to UV radiation is important in reducing risk or activity in inflammatory bowel disease through both vitamin D and non-vitamin D pathways.[285]

Low concentrations of 25(OH)D in early childhood were associated with an increased risk of wheeze in one study ($P < 0.005$ for adjusted OR of wheeze at 10 years of age in association with number of follow-up visits where the child had low 25(OH)D levels)[286] and, in a meta-analysis, low maternal 25(OH)D levels were associated with an increased risk of persistent asthma in the offspring (pooled OR = 0.84, 95% CI 0.70, 1.01, $P = 0.06$, comparing the highest with the lowest category reported in each study).[287] Whether these effects are causal, vitamin D- or non-vitamin D-mediated, is not yet clear.

Higher levels of sun exposure over the lifetime are associated with reduced risk of developing MS (for example, adjusted OR = 0.70, 95% CI 0.53, 0.94 for each increment in lifetime UV dose of 1000 KJ m^{-2})[234,288–290] through plausible biological pathways.[234] Further support for these findings comes from a recent multi-ethnic case-control study in the USA, where higher levels of lifetime exposure to UV radiation were associated with reduced risk of early MS consistently across whites, Hispanics, and African Americans (adjusted OR = 0.53, 95% CI 0.31, 0.83, $P = 0.007$ in African Americans; adjusted OR = 0.68, 95% CI 0.48, 0.94, $P = 0.02$ in whites; adjusted OR = 0.66, 95% CI 0.42, 1.04, $P = 0.07$ in Hispanics).[291] This is in contrast to the increased risk in association with low levels of 25(OH)D, which was apparent only in whites.

The lack of effect of supplementation with vitamin D on clinical relapse in people with MS has been noted above. There is, however, some evidence of benefit from UV radiation. For example, there is a well-described seasonal variation in disease relapses in people with MS, and this demonstrates latitudinal variation, with a shorter gap between relapses in people living at higher latitude (lower levels of UV radiation).[292] In a longitudinal cohort study, conversion to MS (in people who had had a first, isolated, demyelinating event (FDE), the most common precursor of MS) and relapse activity were lower in those with higher lifetime sun exposure (with no association with 25(OH)D concentration at initial participation in the study following the FDE).[293] Furthermore, participants who increased their sun exposure after a FDE had a significantly reduced risk of conversion to MS and subsequent relapse. Finally, a recent clinical trial showed that people with an FDE who were randomised to receive an 8-week course of phototherapy had a 30% lower risk of developing MS within 12 months.[294] However, the results were not statistically significant, probably because of the small sample size ($n = 10$ in phototherapy and control groups).

Admissions to hospital for anaphylaxis (a severe allergic reaction) increased with increasing latitude (>34° S) and lower levels of ambient solar UV radiation in children in Chile.[295] This is consistent with a previously described latitudinal gradient in anaphylaxis described in Australia.[296]

5.3. Benefits for eye health and vision

There is accumulating evidence that lack of sun exposure in childhood increases the risk of myopia (short-sightedness). Myopia occurs when the eye is too long, or the lens or cornea focus light too strongly; incoming light thus focuses in front of the retina (rather than on the retina), resulting in blurry vision. Although myopia can be corrected with spectacles, contact lenses and/or surgery, severe myopia may lead to blinding eye diseases (cataract, glaucoma, retinal detachment, and myopic maculopathy) in later life.[297]

The prevalence of myopia is increasing rapidly in many countries. Around 80% of 20-year-olds in many East and Southeast Asian countries[298] and 38% of young adults (aged 18–24 years) in the USA are myopic.[299] Intense study during school years and less time spent outdoors are two major factors thought to account for this rapid increase.[300]

In an elderly European population (mean age 72 years), an increase of one standard deviation in exposure to UV-B radiation (determined using self-reported sun exposure and meteorological data) during teenage years and in early adulthood was associated with a 20–30% reduction in risk of being myopic.[301] In two large trials in China, interventions to increase time outdoors during and after school hours in schoolchildren reduced the incidence of myopia by 9% over a 3-year intervention in 6-year-olds, and by *ca.* 5% in a one-year intervention in 6–11-year-olds.[302,303] However, it remains unclear what element of 'time outdoors', *i.e.*, whether it is the strength of the irradiance outdoors or the need to focus on objects at a variety of distances, provides this protective effect.

The evidence for a role of vitamin D deficiency in risk of myopia is mixed, with some studies showing an association,[304–306] but no evidence of effect in others, including studies using the Mendelian randomisation approach.[297,301,307] The contrasting findings could reflect differences in study designs, reverse causality (whereby individuals with myopia spend less time outdoors), or that the 25(OH)D level is simply a proxy for time outdoors, with some other element of 'time outdoors' being the causal factor. For example, exposure to UV radiation or the higher intensity of shorter wavelength (blue) visible light encountered outdoors compared to indoors may protect against the development of myopia by slowing elongation of the eyeball.[308,309]

5.4. Additional health benefits

High blood pressure is the risk factor responsible for the second greatest loss of DALYs globally (89.9 million in 2016).[310] Observational studies and a single intervention study support a possible benefit of sun exposure for high blood pressure, potentially through UV-A-mediated release of nitric oxide stores in the skin that cause arterial vasodilation and reduction in blood pressure.[311] Furthermore, exposure to UV-B radiation may inhibit the development and progression of atherosclerosis through modulation of inflammation.[312]

In a prospective study in southern Sweden, adults with high intentional sun exposure had a lower risk of cardiovascular disease (CVD), and death due to a cause unrelated to cancer or CVD, than those who avoided sun exposure.[313] Avoidance of high-dose sun exposure was a risk factor for death of similar magnitude to smoking in this study.[313] Several studies also support this association of low sun exposure with higher rates of all-cause mortality, mainly through increased risk of death

from CVD and other non-cancer diseases (reviewed in ref. 314). Whether these associations are vitamin D-related, attributable to exposure to UV radiation *per se*, or working through other pathways, such as exercise, is unclear.

Higher sun exposure is associated with reduced risk of some cancers, but it is difficult to determine whether this is causal. Lower incidence of colon cancer in Finnish fishermen and women could be due to higher exposure to UV radiation (reflected in the higher incidence of lip cancer in this population), or presumed higher consumption of fish.[315] It is particularly hard to interpret ecological studies showing lower incidence of cancers (for example, non-Hodgkin lymphoma[316] and multiple myeloma[317]) at lower latitude or where there is higher UV-B irradiance, as it is difficult to adequately adjust for possible confounding factors.

6. Risk *vs.* benefit of exposure to solar and/or UV radiation

The balance between risk and benefit of sun exposure depends on the size of the effect, the proportion that can be attributed to high or low exposure, and the total health burden of the outcome. There is convincing evidence (reviewed above) that exposure to UV radiation is a risk factor for a number of adverse health effects; the proportion of those diseases that is attributable to exposure to UV radiation has been quantified.[51] However, there is not yet conclusive evidence that low sun exposure causes disease, or, if it does, the size of the disease burden incurred.

We have previously reported on the balance between DNA damage and synthesis of vitamin D.[228] Short-term, high-dose sun exposure increased levels of 25(OH)D, at the expense of accompanying DNA damage (assessed using a urinary biomarker).[318] In contrast, low-dose regular irradiation with solar-simulated UV radiation (3 times weekly for 6 weeks) increased 25(OH)D concentration while producing DNA damage (CPDs on skin biopsy) that was partially repaired at 24 hours post-exposure.[319] Importantly, the damage did not accumulate over the course of UV irradiation, indicating adequate repair between exposures. Both the pattern and the dose of exposure appear to be important, as is the time post-exposure that the damage to DNA is measured. A study in children on holiday by the Baltic Sea showed that exposure to UV radiation that resulted in borderline erythema was accompanied by a 25% increase in concentration of 25(OH)D, but also a large increase in DNA damage (assessed using a urinary biomarker 24 hours after the last exposure to the sun).[320]

A recent study assessed the balance of increasing 25(OH)D levels *vs.* whole epidermal CPDs in people across the full range of skin types (I–VI) for different sub-erythemal doses (20%, 40%, 60% and 80% of their personal minimum erythemal dose (MED)) of solar-simulated UV radiation.[321] Levels of both whole-epidermis CPDs and serum 25(OH)D increased according to the MED dose fraction (*i.e.*, UV dose adjusted for skin type); even the lowest dose of UV radiation (0.2 MED) resulted in a gain in 25(OH)D but also induced CPDs, across all skin types. There was, however, a marked difference across different skin types for CPDs in the basal cells where the carcinogenic risk is highest: from undetectable in dark skin types (IV–VI) even at the highest MED dose, to significantly increased in light skin types (I–III) even at the lowest MED dose.[321] Thus, skin type is important in framing sun protection messages: lighter skin is very sensitive to DNA damage,[322] but vitamin D production is similar across skin type groups for similar MED dose fractions of UV radiation. Notably, at 48 hours post-irradiation, there had been DNA repair and there was no difference in CPD levels in skin between exposed and unexposed controls, for any skin type.

For high-burden diseases, such as hypertension,[311] possible beneficial effects of sun exposure that only minimally increase adverse effects (*e.g.*, skin cancer) may greatly alter the balance of risks and benefits of sun exposure.

Future projections for ambient UV radiation[4] are that UV-B radiation will be lower in 2075–2095 compared to 1955–1975 at high latitudes, with particularly marked reductions in the winter months. UV-B radiation is likely to be higher in the tropics, and over cities that are currently heavily polluted, with regulation of air pollution leading to clearer skies. These future projections have important implications for the balance of risk and benefits of exposure to UV radiation. That is, in high northern hemisphere locations where low vitamin D status is already common, there may be an increased risk of vitamin D deficiency, although this may be offset by warmer temperatures that encourage people to spend more time outdoors with more skin exposed. In the tropics, the risks of adverse effects may be increased, particularly if these populations also adopt Western preferences for tanning and sunny holidays.

7. Protection from the health risks of sun exposure

The health risks of sun exposure can be mitigated through appropriate sun protection behaviours, but the degree of protection required depends on individual susceptibility to damage from exposure to UV radiation. The photoprotection needs, and the balance of risks and benefits, of people with dark skin differ from those with light skin.[321,322]

Weather forecasts and several apps for mobile phones provide information on the UVI to guide whether sun protection is required. Recommendations are that when the UVI is 3 or higher protection should be used.[323] Protection of the skin and eyes involves a suite of options, best used in combination. Staying out of the sun, and wearing clothing, hats, and sunglasses are of primary importance. Sunscreen is typically a second line of defence, particularly useful for body surfaces that cannot be covered by clothing, such as the face and hands. Nevertheless, sunscreen was the most frequently nominated sun protection strategy in a large sample (n = 4217) of people living in Western Australia, particularly amongst adolescents and women.[324]

7.1. Hats and clothing

Hats protect the scalp and provide shade to different parts of the face, depending on the hat type and the elevation of the sun. A wide-brimmed hat offers the best cover, with a typical protection factor of 5 to the nose and ears, and 2–3 to the cheeks, while baseball caps provide good protection to the nose but leave ears, cheeks and neck unprotected. Legionnaire style hats have a flap of fabric covering the neck and ears, making them particularly effective at protecting these sites.[325]

Clothing provides good photoprotection, depending on the weave, colour and fabric type (*e.g.*, natural or synthetic). The UV protection factor (UPF) for fabric is comparable to the sunscreen protection factor (SPF) used for sunscreen. Shirts with a loose weave, such as linen, have a lower UPF (ranging from 5 for white to 15 for black materials), whereas tightly woven cotton t-shirts have a UPF of ≥40.[326] However, clothes with a high UPF fabric may have limited coverage. Thus, a garment protection factor (GPF) has been proposed as a new metric that takes account not only of the UPF of the fabric but also the body surface area covered.[327] There are three nominal categories of sun protection: 0 to <3 (minimal), 3 to <6 (good), and ≥6 (excellent).

7.2. Sunglasses

Recommendations for sun protection typically include the use of UV-certified sunglasses (for example, Sun Smart Australia,[328] and the World Health Organization[323]).

Both spectacles and contact lenses provide partial eye protection from UV radiation. Regular plastic spectacle lenses achieve higher protection against UV radiation than glass lenses; however, both need to have a UV-protection coating for full safety.[329] Other lens materials including polycarbonate, most high refractive-index plastics, and photochromic lenses inherently block 100% of UV radiation without a special coating. Commercially available soft contact lenses block *ca.* 90% of UV radiation and limit the light reaching the cornea.[330] In a recent study, the use of contact lenses and spectacles was associated with a reduction in UV-induced damage (as measured by conjunctival autofluorescence) on the nasal side but not the outer side of the eye.[331] This was unexpected, as UV-induced eye disorders (see section 4.3.1) are typically more pronounced on the nasal side.

Sunglasses provide excellent protection from UV radiation provided they have a wrap-around style; however, a large proportion of sunglasses purchased from unauthorised dealers in developing countries and distributed to developed countries do not conform with international standards for protection from UV radiation.[332] Often, the same sunglasses are kept and used for many years, although both the protection from UV radiation and the impact resistance of the lenses deteriorate over time. New research suggests that the current standard stress test (for ageing of sunglasses) is not adequate to assure safe use for two years (the average time a person keeps a pair of sunglasses) by users who wear them for a maximum of 2 hours a day.[333] A more appropriate test protocol has been proposed (including exposure to a solar-simulator for 67.7 hours at a distance of 50 mm from the lamp bulb). However, there is concern that the temperature rise in this experimental setup may adversely affect the optical properties of the lens.[333]

7.3. Shade structures

Shade provides broad-spectrum photoprotection and its provision is especially important in school playgrounds[334] and other play areas; it should be an architectural/landscaping consideration at the design stage of new buildings and/or parks, where it can provide photoprotection at no cost to the user. The efficacy of shade can be graded by its protection factor (PF), which is the ratio of the biologically effective UV (UV_{BE}) irradiance on a horizontal plane in full sun to the UV_{BE} under the shade structure.[335] The PF should be at least 15 for effective shade, although PFs of 30 or 35 are recommended.[335] The PF takes account of the UPF, which is a measure of the attenuation of erythemal UV radiation by the material providing the shade, as well as the coverage in terms of both sky-view and UV radiation reflected from surrounding material.[335] Optimal shade includes having ground structures with low albedo (*e.g.*, grass rather than concrete), cloth canopies with a UPF ≥ 20, and protection from both diffuse and direct UV radiation. A recent study showed that a beach umbrella alone does not provide sufficient protection for extended time in the sun.[336] Shade from trees or artificial structures reduces the direct incident UV radiation, but may not be effective in limiting exposure from indirect, *e.g.*, reflected UV, depending on the angle of the sun and the surrounding surfaces.[337]

People may use shade to keep out of the heat, and thus serendipitously improve their sun protection. A recent trial of shade provision in parks in Denver (USA) and Melbourne (Australia) showed that people were more likely to use passive recreation areas (*i.e.*, areas used for activities, such as sitting or standing while socialising, or watching sports) if shade structures were provided.[338] The authors concluded that public investment in shade provision was warranted for reducing the risk of skin cancer.

7.4. Sunscreens

Sunscreens are formulations of chemicals that are applied to the skin to attenuate solar UV radiation. Their active ingredients absorb and may scatter UV photons. The index of sun protection is the sun protection factor (SPF), which is the MED with sunscreen divided by the MED without sunscreen. SPF is primarily a measure of protection from UV-B radiation. It is determined under stringent prescribed laboratory conditions, including application of sunscreen at 2 mg cm^{-2} to human skin and exposure to solar-simulated UV radiation. While the determination of SPF is largely harmonised internationally,[339] UV-A protection and the labelling of sun protection products can vary according to the regulatory domain (*e.g.*, EU *vs.* USA). There remains considerable inter-laboratory variability in testing SPF, with coefficients of variation that exceed 50% in some cases,[340] although the new international standard for

in vivo testing (ISO 24444) should improve standardisation.[341] In addition, new *in vitro* methods for SPF measurement are being developed.[342]

Reduction in the dose of UV-B radiation delivered to the skin due to sunscreen application in theory reduces vitamin D synthesis but, in practice, this may not be important because vitamin D synthesis occurs at sub-erythemal doses;[321] methods of sunscreen application are also imperfect (Fig. 5).

The MED of a light-skinned person is 2–3 standard erythemal doses (SEDs; 1 SED = 100 J m^{-1} of erythemally weighted UV radiation).[343] Under idealised conditions, exposure of the skin to 45 SED through a sunscreen of SPF 15 transmits three SEDs to skin cells. This reduction in dose can be expected to reduce the risk of sunburn, as well as mutagenic DNA photodamage.[344–346] However, although sunscreens are UV-protective, it is not yet confirmed that the degree of protection against sunburn (*i.e.*, SPF) equates to that against DNA photodamage (*i.e.*, DNA-PF).

Regular use of sunscreen is associated with fewer naevi, a marker of CMM risk, in children.[347] A randomised controlled trial has shown that daily sunscreen use reduced the risk of SCC and CMM, but not BCC,[348,349] although limitations of the study suggest that the conclusions should be viewed with caution.[350] Two other studies[351,352] have reported that regular use of sunscreen was associated with reduced risk of CMM, *i.e.*, regular use of sunscreen with SPF $\geq$ 15 was associated with an 18% reduction in the risk of CMM in women aged 40–75 years,[352] and that greater use of sunscreen in childhood was associated with a 40% reduction in CMM before age 40 years.[351]

Dark skin pigmentation has been thought to provide a DNA-PF of ~6 compared with light skin. However, a recent comparison of white (phototype I/II) and black skin (phototype VI) shows DNA-PFs of 59.0 (95% CI 24–110), 16.5 (95% CI 11–27), and 5.5 (95% CI 4.5–5.5) for the basal, middle and upper epidermis, respectively.[322] The high DNA-PFs for the lower layers of the epidermis are more consistent with observed differences in incidence of CMM (*ca.* 30-fold higher in white *vs.* black Americans, see section 4.2.1) than the overall DNA-PF. The high DNA-PF for the basal layer of the epidermis suggests that in black populations, sunscreen is not required.

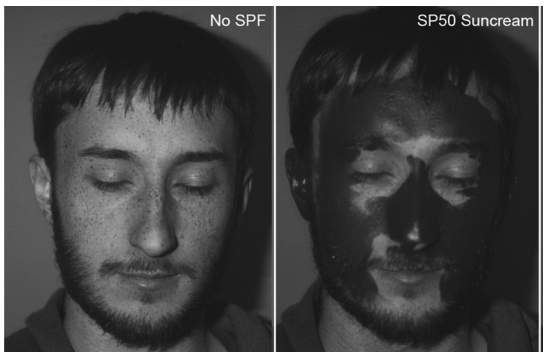

Fig. 5 Left shows a UV image with no sunscreen. Right shows an image with SPF 50 sunscreen coverage in black. Note lack of application in the region around the eyes (from ref. 356). SPF, sun protection factor.

A "typical" woman (body surface area 1.6 m^2) on a beach holiday needs ~100 g of sunscreen per day for three whole body applications under SPF test conditions, and a 'typical' man (body surface area 1.9 m^2) needs 114 g. The "teaspoon rule" is a good rule of thumb guide for sunscreen application at 2 mg cm^{-2}.[353] This advises just over half a teaspoonful for each arm, and the head and neck area, and just over a teaspoonful for each leg, and the anterior and posterior torso. Numerous studies have shown that people apply much less and therefore do not achieve the labelled SPF.[354] In surveys of people on a beach in Denmark, the percentage of women reporting having used sunscreen on a given day increased from 45% in 1997 to 78% in 2016; in men it rose from 39% to 49%.[355] Although the estimated quantity of sunscreen applied increased from 0.48 mg cm^{-2} in 1992 to 0.57 mg cm^{-2} in 2016, it remained too low for adequate protection.[355]

Poor application of sunscreen can also mean that some areas are not protected at all, including the eyelid and periorbital regions (Fig. 5 [356]); sunglasses may be a better option for this area.

A laboratory study showed a linear relationship between time spent on sunscreen application and the thickness of the sunscreen.[357] Furthermore, when participants applied sunscreen a second time, twenty minutes after the end of the first application, the mean thickness increased from 0.71 to 1.27 mg cm^{-2}. Thus, encouraging people to spend more time on sunscreen application and/or applying sunscreen twice, may result in better photoprotection.

A field study compared the effectiveness in preventing sunburn of sunscreens with SPFs of 50+ (application 1.1 ± 1.3 mg cm^{-2}) and 100+ (application 1.0 ± 0.98 mg cm^{-2}), using a randomised double-blind split-face design (n = 199) in natural sunlight at a ski resort.[358] Mean time outdoors was 6.1 ± 1.3 hours. Over half (55.3%) of the participants had more sunburn on the 50+ side and only 5% had more sunburn on the 100+ side, showing that even amongst high SPF sunscreens, there is better protection from 100+ compared to 50+.

7.4.1. Risks and potential risks of sunscreen use. Contact and photocontact allergy can occur with use of sunscreen products, the latter involving the absorption of UV radiation by a sunscreen filter; both conditions manifest clinically as acute dermatitis. Multi-centre studies show that contact and photocontact allergy may be more common than previously thought. For example, in a European study, 9.2% of 1031 patients with exposed-site dermatitis had photocontact allergy, and ~4% had contact allergy, to organic sunscreens.[168] The prevalence of contact allergy to a sunscreen agent was similar in a UK study (5.5%), but there was a lower prevalence of photocontact allergy (4.4%).[359] Identification of the culprit agent enables its avoidance, with selection of a different sunscreen required for photoprotection.

Exposure of the skin to UV radiation results in natural adaptation, through tanning and epidermal hyperplasia.[22] It is plausible that use of sunscreen nullifies this natural adap-

tation, potentially increasing the risks of the adverse effects of UV radiation when the skin is unprotected.[360] However, sunscreen use is safer than topical skin bleaching agents for those who favour a lighter skin complexion.[361]

In a study of 100 Latina teenagers in rural California, self-reported use of sunscreen was associated with 58% higher urinary concentration of the UV-filter, benzophenone-3.[362] This filter has also been detected in human milk and urine.[363] However, no health effects in humans have so far been described.

Increasing concern about the environmental risks of sunscreens (described in ref. 11) has triggered interest in alternative molecules, such as mycosporine-like amino acids (MAA) that act as a 'sunscreen' in marine organisms.[364,365] These have not yet been tested in humans.

7.5. Interventions to reduce harmful exposure to UV radiation

There is good evidence that multi-component, community-wide interventions can be effective in improving sun-protective behaviours, particularly sunscreen use, amongst children and adults.[366] These interventions use a combination of integrated strategies including mass media campaigns, environmental interventions (such as installation of shade structures) and policy changes implemented across multiple settings within the community. Interventions targeted to specific settings, including child-care centres, schools, and outdoor recreational and tourism settings, and outdoor workers, can be effective in reducing the overall exposure to UV radiation of those who engage with these settings.

In Australia there has been a long history of multicomponent community-wide interventions,[367] supported by policies such as not applying sales tax to sunscreens with a high SPF and legislation requiring employers to protect their employees from the harms associated with outdoor work. The falling skin cancer rates in younger cohorts in Australia[78] are likely to be at least partially attributable to these population-wide intervention efforts. Similar trends have not been seen in the USA[78] and the UK[74] where intervention efforts have been sporadic[368] and generally underfunded to achieve the desired population-wide effect.[369]

7.5.1. Sun protection behaviour. There is continuing evidence of risky behaviour with regard to sun exposure in light-skinned populations.[10] Even where there are strong programs for protection against sun exposure, sunburn on at least one occasion in the previous year is common (*e.g.*, 37% of adults in the 2010 USA National Health Interview Survey[370]), particularly in young adults (18–29 years, 52%), and those with light skin type (44%). Deliberate sun exposure also remains common (*e.g.*, 78% of respondents in a telephone interview in France[371]). Australian adolescents desire a tan despite being aware of the long-term health risks.[372] In Hungary, 74% of 12–19-year olds had experienced at least one episode of serious sunburn, 5% purposely sunbathed daily, and 10% did not use any form of sun protection.[373] In Ireland, with the highest incidence of CMM in Europe, nearly 50% of a sample of Cork university students reported deliberate tanning in the previous summer.[374] Thus, despite health promotion programs to increase knowledge about the risks associated with sun exposure, risky behaviour continues.

A personal or family history of CMM does not reduce risky behaviour with respect to the sun, despite evidence that ongoing exposure of CMMs to UV radiation may promote metastasis.[375] A systematic review showed that a substantial proportion of people diagnosed with CMM reported subsequent sunbathing (up to two-thirds at least once since diagnosis), sunburns (60% at least once in a 3-year period) and indoor tanning (up to a quarter of survivors), and many did not practice skin self-examination.[376] Similarly, children of people who have survived CMM had higher sun exposure and sunburn than average-risk populations in a study from California.[377]

Exposure to the sun in childhood may be particularly important to risk of CMM and BCC in later life in light-skinned populations. In Australia, a 2011–2012 national survey found that 77% of primary schools had a written sun protection policy, and 75% of those without one were planning to develop one in the next 12 months.[378] Nevertheless, in a study from tropical north Queensland, Australia, fewer than 50% of schools had policies that shade should be provided during outdoor events, and even fewer that events should be scheduled to avoid the peak sunlight hours.[379] In a nationally representative sample of schools in the USA, sun safety practices and policies were uncommon.[380] For example, only 12% of high schools, 18% of middle schools and 15% of elementary schools scheduled outdoor activities to avoid times when the sun was at peak intensity.[378,379] The trends of decreasing incidence of skin cancers in younger age groups[78,123] could be reversed unless sun protection programs targeting exposure in childhood, adolescence, and in high-risk groups are continued.

7.5.2. The UV Index – is it still fit for purpose?. The UVI provides a measure of the erythemally weighted UV irradiance at the Earth's surface. It can be measured or calculated, and is often provided as a UV forecast, in the form of a whole number that is the maximum UV irradiance expected for the day. Current messaging for sun protection uses five categories of exposure: "low" (1, 2), "moderate" (3, 4, 5); "high" (6, 7), "very high" (8, 9, 10), and "extreme" (11 or higher); sun protection is recommended when the UVI is ≥ 3. For the biological effects of UV radiation, the dose (rather than the irradiance) is important; that is, consideration needs to be taken of both the UVI and the duration of exposure.[381] A recent study has shown that sunburn can occur at a UVI < 3 if there is sufficient duration of exposure,[381] and thus sun protection may be required even at low UVI. It has been recommended that messages about sun protection that use the UVI should be locally appropriate, *e.g.*, extending the graphical representation to higher values in locations where the UVI reaches very high levels, or changing category criteria where the population is predominantly dark skinned.[382] A counter-argument is that messaging regarding sun protection should be globally consistent to

enhance understanding and uptake. The UVI remains a useful tool for public communication on requirements for sun protection,[382] although there may be a need to provide more nuanced messaging incorporating duration of time in the sun.

7.5.3. New developments for sun protection. New tools are becoming available for monitoring personal sun exposure, such as electronic dosimeters and smartphone apps. These are reviewed in ref. 4.

8. Future effects: changing stratospheric ozone, ambient UV radiation, and climate change

Predicted reductions in ambient UV radiation by 2100 as a result of recovery of the stratospheric ozone layer, and changes in cloud cover,[4] particularly at high latitudes, together with climate-induced changes in sun exposure behaviour,[21] will change the balance of risks and benefits for human health in any location. In addition to direct effects, through the pathways described above, these pressures will have a range of indirect effects. Food security will be affected as a result of alterations in terrestrial[14] and aquatic[11] ecosystems, as well as air pollutants such as tropospheric ozone.[13] This will be an important determinant of human health, both directly and as a driver of conflict and climate change-induced migration. The interactive effects of climate change and UV radiation are changing the growing seasons of plants (see ref. 14), including extending the duration of allergen production.[383] This has knock-on effects for human allergic disorders, increasing the risks and duration of hay fever and asthma. The interactive effects on ecosystem services such as disinfection of surface waters, including following extreme weather events, are discussed in ref. 11. The potential impacts of changing stratospheric ozone (through changing ambient UV radiation) on the health effects that have been linked to climate change, and the potential impacts of climate change on the health effects of exposure to UV radiation, are summarised in Table 4.

Several occupations associated with renewable energy technologies are amongst the most rapidly growing in the USA,[384] but also incur a high risk of increased exposure to UV radiation, such as work associated with installation and repair of wind turbines and solar panels. Outdoor workers, such as farmers, may be particularly at risk from the combination of high levels of UV radiation and an increasing number of hot days.[385] Changes in behaviour, such as not working outdoors through the middle of the day, may be required.

UV radiation may adversely affect the physiology and insecticide tolerance of mosquitoes, and this effect may be accentuated by environmental pollution.[386] The tiger mosquito (*Aedes albopictus*) is a vector for dengue fever. The female mosquito lays eggs in water-holding containers (for example, discarded tyres). A recent study showed that UV-B irradiation at levels to mimic full sun caused reduced survival compared to shade or no-sun conditions.[387] The importance of sun exposure and UV-B radiation received, in conjunction with global climate change, for the spread and geographic range of dengue and other mosquito-borne diseases is not clear.

9. Knowledge gaps

Our assessment of the recent evidence has highlighted several knowledge gaps that limit our understanding and assessment of the risks and benefits of exposure to UV radiation, and use of sun protection.

9.1. Vitamin D

Production of vitamin D occurs rapidly following UV irradiation of the skin; exposure to even low doses of solar-simulated UV radiation, *e.g.*, 0.2 MED, increases 25(OH)D levels[321] (this dose is achievable for a light-skinned person (skin type II) in ~10 min at a UVI of 3). If the pre-vitamin D action spectrum is as suggested by recent work (reviewed in ref. 4), exposure to UV-A radiation may cause a net loss of vitamin D synthesised in skin.[388] At low UVIs, it is possible to achieve considerable exposure to UV-A wavelengths, with potential adverse effects on health.[389] This raises further questions about the appropriateness of current messages that no sun protection is required when the UVI is less than 3.[381] Further work to better define the pre-vitamin D action spectrum is required.

Considerable uncertainty remains about the health effects of vitamin D beyond musculoskeletal health and the mechanistic pathways, including the possible risks of over-enthusiastic, population-wide use of vitamin D supplements.[390]

9.2. Photodermatoses

More information is required on the possible risks to human health from exposure to higher levels of UV radiation with respect to photodermatoses, including immune-mediated conditions, drug photosensitivity, and photoaggravated conditions. It is important that due attention is paid to this area in view of their high prevalence and morbidity.

9.3. Possible skin cancer risks associated with chemical bleaching of skin

Skin lightening or bleaching of melanin by mercurials, corticosteroids, and other compounds, often in unregulated formulations, is a global problem because it is associated with side effects such as dyschromia of skin, diabetes, and hypertension.[361,391] Loss of melanin is likely to lead to loss of photoprotection as noted in a report of cases of SCC in Senegal associated with cosmetic skin lightening.[392] There is a need for further research into the photobiological consequences of depigmentation, including in vitiligo.

9.4. Risks *vs.* benefits of sun exposure

It remains impossible to make even qualitative assessments of the balance of risks and benefits, for populations or individuals, for several reasons. First, the totality of possible benefits

Table 4 Summary of potential health effects of changing levels of stratospheric ozone (*via* changes in ambient UV radiation) and of climate change, and possible interactions. Red arrows show potential effects of climate change on UV-related health outcomes; purple arrows show potential effects of UV radiation on climate change-induced health risks

Health-related effects of stratospheric ozone depletion through changes in UV radiation		Impacts of climate change and associated factors on UV-induced health effects
Skin cancers and photodermatoses: risk is increased with increased exposure to UV radiation	←	Warmer temperatures lead to increased time outdoors in cool locations, and less time outdoors where it is already hot. Warmer temperatures and air pollution may promote skin carcinogenesis.
Eye conditions: the risk of a range of acute and chronic eye diseases is increased with higher levels of UV radiation, but also other factors, such as particulates	←	Hotter, dryer conditions may increase the risk of pterygium; dehydration events (because of hotter, drier conditions) may increase the risk of cataract. Loss of snow and ice cover may reduce some eye disorders.
Immunosuppression, including reducing risk of autoimmune conditions, such as multiple sclerosis	←	Warmer ambient temperatures worsen the symptoms of multiple sclerosis.
Synthesis of vitamin D in skin and other potential benefits of UV irradiation of skin and eyes	←	Warmer ambient temperatures may change behaviour (as above) to increase or decrease time outdoors and covering clothing; warmer temperatures may increase the rate of chemical reactions in the skin, *e.g.*, production of vitamin D. Higher precipitation may reduce time outdoors at high latitudes where vitamin D production is already marginal. Urbanisation, urban heat islands, and urban "canyons" may reduce exposure to UV radiation.
Health protection – sunscreens, hats, covering clothing, umbrellas	←	Warmer temperatures may make it less comfortable to wear hats, sunscreens and covering clothing, but make shade preferable.
Impacts of changes in UV radiation on health risks of climate change		**Health effects of climate change and associated factors**
UV radiation is potentially insecticidal; lower levels because of recovery of the ozone layer may enhance climate change effects to increase risks of infection.	→	Changing range of vector-borne, *e.g.*, malaria, and water-borne diseases
Use of sun protection, *e.g.*, clothing, hats, and sunscreen, may exacerbate effects of increasing heat, leading to greater risk of heat stroke.	→	Increase in risk of heat stroke and heat stress because of increase in hotter days, warmer ambient temperature, and extreme heat events
UV radiation has an important role as a disinfectant of surface waters. Lower UV radiation because of recovery of stratospheric ozone (and clouds) may reduce this effect, and increase the health risks following extreme weather events.	→	Increased injury, death, and contamination of freshwater supplies, because of an increase in extreme weather events
UV radiation has an important role as a disinfectant of surface waters.	→	Increased risk of water-borne infectious diseases due to reduced availability of clean drinking water
Changes in food quality and quantity due to changes in UV radiation will positively or inversely interact with climate change effects.	→	Challenges to food security (conflict)
Predicted reduction in UV radiation at higher latitudes will increase the risks of vitamin D deficiency and the loss of benefits of higher sun exposure, *e.g.*, for blood pressure and autoimmune diseases.	→	Climate change-induced migration of dark-skinned migrants, often from lower to higher latitude regions

is unclear, although mechanistic pathways are being elucidated. Second, there is little quantification of benefits for typical, 'real-life' patterns and amounts of sun exposure. Third, there is a range of complicating factors, such as skin type, genetics, and cultural habits for clothing and sun exposure, which make the balance highly variable, and therefore challenging to assess.

9.5. Uncertainties in sun protection

There has been a global trend, driven by consumer demand and industry marketing, to have higher protection from UV-A radiation in sunscreens, at the expense of UV-B protection for a given SPF. It is not established if this has an overall benefit or not. We need better understanding of the action spectra for the beneficial and adverse effects of UV radiation and their interactions. Better understanding is also required of the relationship between a sunscreen's SPF, *i.e.*, the protection from erythema, and its DNA protection factor (DNA-PF), *i.e.*, its ability to prevent DNA photodamage. While it is assumed that one provides a good measure of the other, this has not been confirmed experimentally.

There is recent interest in whether the action spectrum for erythema extends into the visible radiation wavelength range.[393] These wavelengths are not included in the laboratory assessment of SPF (which uses solar-simulated UV radiation); the actual SPF under natural conditions is not clear. Moreover, wavelengths from UV-B to UV-A and visible radiation can provoke photodermatoses, yet sunscreen protection factors for these conditions are not established.

While there has been a considerable increase in smartphone apps and devices for monitoring UV radiation, the impact on behaviour with respect to sun exposure has not been well assessed. This includes perseverance with the use of such devices, as well as long-term effects on behaviour.

9.6. Climate change-related unknowns

The size of the health effects of interactions between climate change and ozone depletion and recovery, *e.g.*, for food security, allergy, climate change-induced migration leading to changes in the skin type distribution (and thus the balance of risks and benefits) of populations, and disinfection of surface waters by solar UV radiation, remains unclear. It is important to appreciate the full range of potential effects on human health, as input to imperatives to act on climate change. However, quantifying these effects is very challenging.

9.7. Interactive effects of exposure to UV radiation and air pollution

UV radiation initiates the chemical processes that lead to the production of photochemical smog (see ref. 13). On the other hand, heavy air pollution blocks UV radiation from reaching the Earth's surface. Perhaps the most striking of the future predictions for levels of ambient UV radiation at the Earth's surface are for large increases over currently heavily polluted areas,[4] as the pollution becomes reduced by regulation and advances in technology.

9.8. Health risks of UV-related breakdown of environmental pollutants

UV radiation is a major source of breakdown of waste material (*e.g.*, plastics and microplastics[394]) and chemical pollutants (*e.g.*, pesticides and pharmaceuticals[12]) in the environment. The possible risks to health from the degradation products in the environment that may accumulate up the food chain are not yet clear.

10. Conclusions

Projections of ambient UV radiation under the combined effects of recovery of stratospheric ozone, current and future climate change, and climate change-induced changes in cloud cover suggest lower levels in most regions not currently affected by high levels of air pollution (depending on the assumptions included in the climate change models used). Because of depletion of stratospheric ozone, there has been a strong focus on understanding the health risks of exposure to excessive UV radiation. There now needs to be improved understanding of possible benefits of having some exposure to UV radiation, and how this will be affected by the recovery of stratospheric ozone, in conjunction with the effects of climate change. In a predicted future with lower levels of UV radiation, lack of sun exposure may increase health risks, *i.e.*, no longer receiving current benefits. At the same time, and for some years to come, we will continue to see the consequences of high past sun exposure, such as high skin cancer incidence, due to the lag between exposure and the occurrence of adverse effects.

Projections also show marked increases in UV radiation in specific regions because of clearer skies, *e.g.*, over China. Increasing ambient UV radiation could be accompanied by higher incidence of skin cancer if there are accompanying changes in behaviour with respect to sun exposure, *e.g.*, cultural changes toward sun-seeking behaviour because of adoption of more 'Western' habits.

The Montreal Protocol stimulated intense research into the health risks of higher levels of UV-B radiation at the Earth's surface, particularly skin cancer. This has greatly improved our understanding of the disease burden and mechanistic pathways, leading in turn to better diagnosis and treatment. Additional research is now required to better understand the disease burden, mechanistic pathways, and personal susceptibility factors for other adverse effects of exposure to UV radiation (*e.g.*, photodermatoses) as well as the broad range of potential beneficial effects.

In the future, there will be many interactions with factors related to stratospheric ozone and to global climate change – chemically in the stratosphere, but also through changing levels of ambient UV radiation and tropospheric air quality. The consequences of global climate change will affect whole populations, for example, through forced migration because of rising sea levels, in ways that alter usual exposures to UV radiation. At the individual level, climate change may alter beha-

viours to receive more, or less, UV radiation, depending on acclimatisation to warmer temperatures. At this stage, we can only qualitatively note that such changes may occur and speculate on the possible or likely risks to human health.

Conflicts of interest

There are no conflicts to declare.

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