Sunlight: Time for a Rethink?

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UVR is a skin carcinogen, yet no studies link sun exposure to increased all-cause mortality. Epidemiological studies from the United Kingdom and Sweden link sun exposure with reduced all-cause, cardiovascular, and cancer mortality. Vitamin D synthesis is dependent on UVB exposure. Individuals with higher serum levels of vitamin D are healthier in many ways, yet multiple trials of oral vitamin D supplementation show little benefit. Growing evidence shows that sunlight has health benefits through vitamin D–independent pathways, such as photomobilization of nitric oxide from cutaneous stores with reduction in cardiovascular morbidity. Sunlight has important systemic health benefit as well as risks.

Keywords: Environment and public health, Health status, Mortality, Nitric oxide, UVR

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INTRODUCTION

Medical attitudes to sunlight have changed in the last century. We have moved from an era of fashionable suntans and sanatoria delivering heliotherapy to one in which dermatology advice is firmly opposed to unprotected sun exposure. Although well-intentioned, the current dermatology approach to sunlight only considers skin health, in particular, risks of skin cancers and photoaging, and fails to take into account systemic health benefits and modern research on mechanisms through which sunlight affects overall health. I hope that this paper will help colleagues reconsider.

HISTORY OF UV ADVICE RELATED TO SKIN CANCER

UVR is an established environmental carcinogen, as confirmed by epidemiological, mechanistic, and clinical trial data (De Gruijl, 1999; Green et al, 1999). Keratinocyte cancers and melanoma are both more prevalent in white-skinned populations in very sunny countries such as Australia and South Africa than in the United Kingdom (UK), although the epidemiological nature of the relationship between sunlight exposure and melanoma is less clear than for keratinocyte cancers (Pfeifer, 2020).

Public health advice on UV exposure for much of the last century has focussed on these adverse effects. Unna (1894) first identified the link between UV exposure and skin cancer in sailors in 1894 with his description of Seemans Haut. Proof that UV was indeed the causative carcinogen was provided by Findlay (1928), when he showed that irradiation of mice with a mercury vapor lamp induced epithelial malignancies. Building on these data, the succeeding century has seen the development of improved sun protection, initially with behavioral changes and clothing, and, since the 1940s, a continually evolving range of increasingly efficacious UV filters (Ma and Yoo, 2021). Sunscreens prevent sunburn, skin aging, and squamous cell skin cancer (Green et al, 1999) in white-skinned individuals. What is missing however is any evidence that higher sunlight exposure increases all-cause mortality or that sun avoidance extends lifespan.

EVOLUTION OF SKIN COLOR

Homo sapiens evolved in Africa around 150,000 years ago. The divergence of our hominid ancestors from their primate ancestors involved the loss of body hair and development of extensive sweat glands. Profuse sweat glands on terminal hair-free skin enables evaporative heat loss (Baker, 2019), which fitted genus *Homo* well for sustained activity needed to run down nutritious prey species (Carrier et al, 1984; Jablonski and Chaplin, 2010). However, with this loss of hair, our naked epidermis was directly exposed to UV. Within African human populations, tight constraints on eumelanin coding *MC1R* alleles show that dark skin was the favored evolutionary adaptation to this environment (Harding et al, 2000; Rogers et al, 2004). On dispersing from Africa to lower-light environments, these constraints were lost, and a number of pale skin variants developed, not only of *MC1R* but also in other genes, notably *KITLG* in East Asia and *SLC24A5* and *SLC45A2* in Europe (reviewed in Jablonski [2021]). This repeated and independent evolution of pale skin in populations living at high latitudes with lower ambient UV underlines the importance of sun exposure for health, although it tells us little of the mechanisms driving this gain of evolutionary fitness. Some clues may be found by looking at when and where these occurred. Modern humans have been present in Europe for around 40,000 years (Hublin, 2015) and East Asia for around 60,000 years (Shi et al, 2008), yet pale skin genotypes are much more recent. Selective sweeps of Eurasian populations with pale skin variants occur from 30,000 years before present. Strong selective pressures for pale skin variants have only been present within European populations for the last 5000 years (Wilde et al, 2014), during which time light skin variants in *SLC24A5* and *SLC45A2* have become fixed (Rocha, 2020). The marked strengthening of selection for pale skin variants (2–10 % per

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Abbreviations: BP, blood pressure; CI, confidence interval; MS, multiple sclerosis; NO, nitric oxide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2DM, type 2 diabetes mellitus; UCA, urocanic acid; UK, United Kingdom

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generation) is equivalent in effect size to genetic variants coding for lactase persistence and malaria resistance (Lucock, 2023). This powerful selection occurs in Europe after the development of farming that occurred with the domestication of sheep, cattle (Pitt et al, 2019), and goats in the fertile crescent around 10,000 years before present and of wheat 9000 years before present (Peng et al, 2011). There are fewer data on the timing of the shift to pale skin phenotypes in East Asia, but millet (Lu et al, 2009; Yang et al, 2012) and pig (Xiang et al, 2017) farming are first identified in Northern China around 10,000 to 11,000 years before present as pale skin phenotypes become prevalent. Farming has developed independently in numerous locations through history, yet only when the Neolithic farming transition occurs in high-latitude locations does pale skin become favored. The shift from foraging to farming lifestyles is marked by a reduction in quality and diversity of diet and by the advent of infectious disease as a selective force, as populations cease to be dispersed foragers and become farmers living in settlements prone to zoonotic disease (Larsen, 2023). Pale skin facilitates vitamin D formation in a low-light environment and has been considered as the primary selective force (Jablonski, 2021), although recent analyses suggest that other mechanisms than pale skin could account for vitamin D sufficiency in European populations (Hanel and Carlberg, 2020). Despite lower serum 25-hydroxyvitamin D levels (the vitamin D measured by most assays), bone mineral density and 1,25 dihydroxyvitamin D are higher in Black than in White populations in the same UV environment (Qiu et al, 2023). The lack of a direct relationship between sunlight exposure, skin color, and bone health is not consistent with the idea that bone health drove the development of pale skin at high latitudes. Vaccination, antibiotics, and public health measures have largely negated infectious disease as a selective pressure in the modern era, but data discussed later in relation to the COVID-19 pandemic suggests that UV-driven processes reducing infectious disease may have offered survival benefits to pale-skinned individuals in lower-light environments in evolutionary time scales.

SUNLIGHT AND ALL-CAUSE MORTALITY

Weighing of risk–benefit ratios is a central skill of medicine and practiced consciously or subconsciously in all our patient interactions. When we prescribe a treatment, we consider the indication (benefit) and the side-effect profile (risk). Epidemiologically, all-cause mortality represents an accurate summation of risks and benefits of any exposure and should guide public health advice in the same way. Accurately quantified increases in all-cause mortality confirm the harmful effects of hypertension, smoking, lack of exercise, poor diet, airborne pollution, poverty, high cholesterol, obesity, inadequate childhood nutrition, and many other factors on health (Lim et al, 2012). The diseases consequent on these risk factors are varied, but public health measures to mitigate them are all based on a robust evidence base intended to extend healthy lifespan. No such data linking increased all-cause mortality with sunlight exposure exist, despite the known carcinogenic effects of UV on skin. Two large prospective cohort studies from northern Europe link increased sun exposure with reduced all-cause mortality. In the Melanoma in Southern Sweden study, 30,000 Swedish women were followed for 25 years, with sun seeking behavior and relevant confounders recorded at baseline. Twenty-five years after enrolment, sun seeking behavior was inversely correlated with all-cause mortality, despite a higher incidence of cases of melanoma in those with more sun exposure (Lindqvist et al, 2014). The reduction in all-cause mortality was particularly related to lower rates of cardiovascular death (Lindqvist et al, 2016). We have analyzed the much larger UK Biobank cohort studying the relationship between sunlight exposure and all-cause mortality in around 377,000 white-skinned participants (in review [Stevenson et al, 2023[1]]). Two independent measures of sunlight exposure were used—latitude of residence and use of sunbeds—and their accuracy as a measure of sun exposure was confirmed by their association with increased measured vitamin D levels. The direction of confounders was different for each measure of UV exposure, yet in both cases, increased sun exposure correlates with reduced all-cause mortality, which was particularly related to reduced cardiovascular mortality but also cancer mortality (including skin cancer). All-cause mortality was reduced with a hazard ratio of 0.94 (95% confidence interval [CI] = 0.92–0.96) for each 300 km of domicile further south (and thus increased sun exposure) after correcting for demographic, socioeconomic, behavioral, and clinical confounders. This equates to an increased lifespan of 16 days for each 300 km lower latitude. Data from these 2 independent studies confirm that for white-skinned inhabitants of North European countries, the benefits of sunlight exposure outweigh the risks (Alfredsson et al, 2020).

Skin color determines our biological response to UV and is central to any consideration of risk–benefit ratio. There is no epidemiological evidence that UV-induced skin cancer occurs in black skin (Lopes et al, 2021), yet UV-driven reductions in blood pressure (BP) (Weller et al, 2020) and in vitamin D synthesis Clemens et al, 1982; Farrar et al, 2013) are blunted in Black compared with that in White individuals. Crude associations between all-cause mortality in groups with different skin colors in the same country are difficult to make because of confounding by social factors. This can be avoided by comparing white-skinned redheads (the most photosensitive phenotype) with white nonredheads. In low-light environments, white redheads have lower all-cause mortality than white nonredheads, but this survival advantage is lost with higher UV exposure (Lindqvist et al, 2020).

MECHANISMS, VITAMIN D, CORRELATION BUT NOT CAUSATION (UNLESS YOU HAVE RICKETS)

Epidemiological and evolutionary evidence suggests significant benefits from sun exposure but do not reveal mechanism(s). Vitamin D formation is the best studied UV-dependent biomolecule. UVB radiation is required for the epidermal formation of cholecalciferol, the precursor for active vitamin D3, 1,25 dihydroxycholecalciferol. Measured

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vitamin D status (which is generally of the intermediate singly hydroxylated 25, hydroxycholecalciferol) serves as a useful biomarker for UVB sunlight exposure as demonstrated by the seasonal variations in vitamin D with a nadir in the winter months. Calcium and phosphate metabolisms are dependent on vitamin D, and low vitamin D levels due to inadequate diet or sun exposure cause rickets in children and osteomalacia in adults. The effective allied naval blockade of Germany during the First World War led to widespread civilian malnutrition and rickets in children (Cox, 2015). In 1919, the German physician Kurt Huldschinsky (1919) showed that UV irradiation of children with rickets with a mercury vapor lamp cured rickets. Three years later, McCollum identified an active agent in cod liver oil, which he named vitamin D, which was equally effective at preventing and treating rickets (Holick, 2023). In 1940, when Great Britain in its turn was blockaded by German U boats and concern over possible malnutrition of the population was high, cod liver oil supplementation was introduced by government decree for all children (Gomberg, 1944) and successfully prevented rickets. This storied history and the clear benefits of cod liver oil being equally efficacious as UVR in preventing and treating rickets has had a powerful effect on public attitudes to vitamin D. Numerous diseases, including hypertension, cardiovascular disease, cerebrovascular disease, metabolic disease, multiple sclerosis (MS), and cancer, are all associated with low measured vitamin D levels, and the vitamin D health supplement industry globally is worth around $1.5 billion per annum (Mordor Intelligence, 2023). A total of 30% of all Americans aged >60 years take vitamin D supplements (Cummings and Rosen, 2022). However, correlation is not proof of causation. Meta-analyses of multiple randomized controlled clinical trials of oral vitamin D supplementation fail to show any benefit in reducing cardiovascular disease, hypertension, cerebrovascular disease, type 2 diabetes mellitus (T2DM), chronic kidney disease, or MS (Lucas and Wolf, 2019). The 2 largest ever randomized placebo controlled trials of vitamin D supplementation—the VITAL study (www.vitalstudy.org; >25,000 participants) and ViDA study (>5000 participants)—have concluded. The primary endpoints were of incident cardiovascular disease and of incident cancer. Both endpoints were negative (Manson et al, 2020; Scragg et al, 2017), as were secondary endpoints of depression reduction (Okereke et al, 2020), incident falls (Scragg, 2019) and fractures (LeBoff et al, 2022), frailty (Orkaby et al, 2022), atrial fibrillation (Albert et al, 2021), and stroke outcome (Rist et al, 2021). A possible reduction in cancer mortality for those with a prevalent cancer diagnosis and reduction in progression to T2DM in patients with prediabetes were seen in the VITAL study (Barbarawi et al, 2020). The strong observational relationship between higher observed vitamin D levels and better health in all these domains stands in contrast to the large body of negative intervention trials and Mendelian randomization studies (Bouillon et al, 2022). A *New England Journal of Medicine* editorial in 2022 concluded that "in view of this wealth of data, the general population should stop taking Vitamin D supplements" (Cummings and Rosen, 2022). Nonetheless, dermatology advice is for rigorous sunlight avoidance, with oral vitamin D supplementation presumed to make up for detriments in health that occur with low measured vitamin D levels in sun avoiders (American Academy of Dermatology, 2023). This advice is outdated in an era where the overwhelming body of evidence shows that vitamin D supplementation is only of benefit to narrowly defined subgroups of the population and a limited number of conditions.

MECHANISMS, NITRIC OXIDE, AND CARDIOVASCULAR DISEASE

Hypertension is the leading cause of disability-adjusted life years worldwide and is responsible for 18% of all deaths globally (Murray et al, 2012). Population BP correlates directly with latitude, such that around 25% of variance in BP can be accounted for by latitude in the pre-antihypertensive treatment era (Weller et al, 2021). Season also has a strong effect on BP. In the UK, summer-to-winter variation in population BP is 5.6 (95% CI = 7.1−4.0)/3.3 (95% CI = 4.0−2.7) mmHg (Kollias et al, 2019). These data suggest a sunlight-related mechanism. Measured vitamin D levels correlate inversely with BP, such that those with vitamin D levels in the upper quartile are half as likely to have a diagnosis of hypertension as those in the lower quartile (Zhang et al, 2020). However, oral supplements with vitamin D have no effect on BP (Bolland et al, 2014), so a vitamin D−independent effect must be responsible.

I and collaborators have identified an alternative mechanism through which sunlight lowers BP. The skin contains large stores of nitrogen oxides, largely as nitrate, nitrite, and S-nitrosothiols (Mowbray et al, 2009). The discovery by Feelisch et al (2010) that nitrate could be photoreduced by UV in the presence of thiols (Dejam et al, 2003) raised the possibility that these cutaneous nitrogen oxides might account for the well-established seasonal and latitudinal variation in population BP. The Weller group and the Suschek group then independently demonstrated that UVA irradiation of human volunteers mobilizes nitric oxide (NO) from cutaneous stores to the circulation where it lowers BP (Opländer et al, 2009) through arterial dilatation, independently of temperature (Liu et al, 2014). UVA was used because it does not synthesize vitamin D, and the vitamin D−independent nature of UV-induced BP reduction could thus be demonstrated. The UV energy of natural sunlight required to mobilize NO from keratinocytes is below that which leads to detectable DNA damage (Hazell et al, 2023). In an epidemiological study of over 340,000 American patients undergoing dialysis who have their BP measured thrice weekly and are treated at over 2000 different dialysis centres dispersed across the contiguous United States and followed for over 2 years, we were able to investigate the relationship between UV and BP, correcting for temperature and studying the effects of wavelength and skin color on this relationship. We confirm that independently of temperature, UV exposure correlates inversely with BP and that beneficial hypotensive effect of UV is more marked in White than in Black Americans and greater for UVB than for UVA (Weller et al, 2020).

BP reduction correlates linearly with reduction in cardiovascular events (Ettehad et al, 2016), which themselves are the leading cause of global mortality (World Health Organization, 2020). The relative risk reduction is independent of age and pretreatment BP (Blood Pressure Lowering

Treatment Trialists' Collaboration, 2021), although the absolute risk reduction is greater for older cohorts and those with higher pretreatment values. Hypertension is not a disease but a classification, and at population level, reductions in BP reduce population cardiovascular events and mortality. Reflecting this, the American Heart Association changed the definition of hypertension in 2017 from a clinic BP >140/90 mmHg to >130/80 (Whelton et al, 2018), and the European Societies of Hypertension and of Cardiology made a similar reclassification in 2018 (Williams et al, 2018). Seasonal variation in mortality is consistent across countries at higher latitude and largely driven by variation in cardiovascular mortality (Marti-Soler et al, 2014). It matches the same seasonal variation in BP and is not seen in countries closer to the equator. Temperature plays some part in the seasonal BP variation, but we have shown that it accounts for only around half (Weller et al, 2020). The tight relationship between BP and consequent cardiovascular events means that the 6 mmHg higher systolic BP in winter than in summer (Kollias et al, 2019) can be causally linked to the 23% higher cardiovascular mortality (Stewart et al, 2017). Inadequate UV exposure in winter months thus underlies much of the regular winter rise in all-cause mortality.

OTHER MECHANISMS OF ACTION OF UV ON SYSTEMIC HEALTH

UV-driven vitamin D formation accounts for some of sunlight's benefits, in particular, those related to bone health. UV-driven NO release probably accounts for much of the cardiovascular effects. Other mechanisms throughout which UV might affect systemic health exist but have been as yet little studied in man. Stratifying gene transcription in PBMCs and adipocytes by the season in which they were analyzed shows that 30% of protein-coding genes show seasonal variation (Dopico et al, 2015). Broadly speaking, proinflammatory genes are upregulated in winter, matched by a rise in protein markers of inflammation such as IL-6 receptor and CRP. The authors suggest that these circannual rhythms prepare the body for the rise in prevalence of infectious disease in winter, at the cost of increasing the risk of cardiometabolic diseases related to inflammation.

The normal racemic mix of *trans*– and *cis*–urocanic acid (UCA) in the epidermis is altered to predominantly *cis*-UCA by UV exposure (Hart and Norval, 2021). This isomerization gives photoprotective effects, with UCA-deficient mice showing 40% more photodimers formed after UVB irradiation than wild-type mice (Barresi et al, 2011). Photoisomerized *cis*-UCA has immunomodulatory effects on the skin, which on the one hand control inflammation and on the other may promote skin cancer by reducing cell-mediated immunity. *cis*-UCA may also reduce systemic inflammation (Hart and Norval, 2021). UV irradiation of mice leads to an increase in circulating blood levels of UCA, followed by an increase in neuronal UCA. This in turn leads to an increase in the excitatory neurotransmitter glutamate by supplying UCA as a substrate to an intraneuronal glutamate biosynthetic pathway, resulting in enhanced memory and learning (Zhu et al, 2018). This may not be directly analogous to man, where UV exposure changes the racemic mixture of UCA in the epidermis and circulation rather than the total amount of UCA, and the intraneuronal UCA–glutamate pathways have not been demonstrated, yet learning disability in Scottish schoolchildren is linked, dose dependently, to reduced maternal UVB exposure in utero (Hastie et al, 2019).

MYOPIA AND THE DEVELOPMENT OF OPHTHALMOLOGICAL GUIDANCE ON MINIMUM TIME OUTDOORS

The incidence of myopia is increasing worldwide. Three generations ago, around 20–30% of East Asian children had myopia (Morgan et al, 2021), but now, 80–90% are affected (Chen et al, 2018). Myopia is a risk factor for retinal detachment, glaucoma, and cataracts and is on course to become the leading cause of severe vision impairment and preventable blindness in Europe and globally (Németh et al, 2021). Myopia is strongly associated with reduced time spent outdoors (Xiong et al, 2017), but the association with near work independently of this remains uncertain (Gajjar and Ostrin, 2022; Ip et al, 2008; Saw et al, 2000), and the International Myopia Institute now considers that the relationship between reduced outdoor time and myopia is stronger than the association with near work (Morgan et al, 2021). Clinical trial data show that increasing the time children spend outside reduces the risks of developing myopia and reduces the increase in refractive error (He et al, 2015). The mechanism through which time spent outdoors leads to myopia remains uncertain, but the epidemiological and trial data are robust enough for the American Academy of Ophthalmology (Gifford et al, 2019; Jacobs et al, 2023) and the international Task Force on Myopia to now recommend that children spend a minimum of 8–15 hours per week outside to reduce the risk of developing myopia (Taskforces - Myopia Institute). Dermatology advice in the UK that people avoid sunlight and seek shade between 11 AM and 3 PM (https://www.nice.org.uk/guidance/ng34/chapter/supporting-information-for-practitioners) stands in contrast to this.

MS AND OTHER CONDITIONS SUGGESTED BY THE SUNLIGHT QUARTET

Clinical trial evidence on disease-specific benefits of sunlight exposure is limited, but a quartet of indirect measures can suggest those conditions where UV is important. Because skin color determines response to UV, this must be considered in analyzing epidemiological measures. UV-influenced, vitamin D–independent disease can be hypothesized where there is a latitudinal gradient, seasonal variation, and a correlation with measured vitamin D levels, yet no benefit in clinical trials from vitamin D supplementation or Mendelian randomization proxy measures for this (Table 1). In diseases where sunlight's beneficial mechanism of action is through vitamin D, supplementation will alleviate disease, but this is only robustly demonstrated for prevention or treatment of rickets. Diseases matching these 4 criteria are shown in Table 1. The paradigmatic disease is MS, which is the classic sunlight deficiency disease and has now had the first controlled pilot trial of UVB phototherapy in the treatment of clinically isolated syndrome, an early form of MS. In the phototherapy arm, a trend to reduced relapse was shown (Hart et al, 2018), but performing the study in Australia inevitably meant that the unirradiated control group would

Table 1. Sunlight Quartet of Conditions in which There Is an Epidemiological Suggestion of Vitamin D–Independent Health Benefits from Sunlight Exposure

Condition	Latitude Relationship	Seasonal Relationship	Vitamin D Correlation	Vitamin D Supplementation Effect
Multiple sclerosis	Population prevalence increases by 5.27 per 100,000 per degree higher latitude (Simpson et al, 2019)	MS relapses peak in late winter/early spring and trough in late summer/early autumn. At higher latitudes, the peak and trough times move earlier (closer to minimum/maximum UV times) (Spelman et al, 2014)	Seasonally adjusted risk of relapse of MS HR = 0.90 (95% CI = 0.83–0.98) per 10 nmol/l increase in measure vitamin D ($P = .016$) (Simpson et al, 2010)	Cochrane systematic review of placebo controlled clinical trials of vitamin D supplementation shows no reduction in clinical or MRI measures of relapse (Jagannath et al, 2018)
BP/hypertension	Population BP correlates with latitude ($R^2 = 0.26$) in pre-antihypertensive medication era (Weller, 2016)	Daytime winter to summer home BP difference is −6.05 (−7.04 to −5.06) mmHg systolic/−3.05 (−3.53 to −2.56) mmHg diastolic (Kollias et al, 2019)	Circulating vitamin D levels correlate inversely with relative risk of hypertension diagnosis (Zhang et al, 2020)	Oral vitamin D has no effect on BP (Autier et al, 2017; Bouillon et al, 2022; Rostand et al, 2016)
Ischaemic heart disease	IHD deaths correlate with latitude in Europe ($R^2 = 0.25$) (Zittermann et al, 2005). Carotid atherosclerosis correlates with latitude (Baldassarre et al, 2010)	Cardiovascular events are 10–30% higher in winter than in summer in temperate latitudes (Gemmell et al, 2000; Mackay et al, 2019; Scragg, 1981; Stewart et al, 2017)	Low vitamin D levels associated with incident cardiovascular disease (Wang et al, 2008)	Vitamin D supplementation has no effect on incident cardiovascular disease (Barbarawi et al, 2019; Manson et al, 2019)
T2DM		Fasting glucose and HbA1c nadirs in summer (Gikas et al, 2009; Higgins et al, 2009; Tseng et al, 2005)	Baseline serum vitamin D correlates inversely with probability of developing T2DM (Gagnon et al, 2012; Lips et al, 2017)	Vitamin D supplementation does not lower the risk of T2DM in subjects unselected for vitamin D insufficiency (Pittas et al, 2019)
COVID-19	COVID-19–specific mortality correlates inversely with local UV environment (Cherrie et al, 2021)	COVID-19 infection rate increases Autumn → Winter and decreases Spring → Summer (Carleton et al, 2021)	Severe COVID-19 (hospitalization or death) more prevalent with vitamin D insufficiency (Pereira et al, 2022)	Oral vitamin D (Jolliffe et al, 2022) or cod liver oil (Brunvoll et al, 2022) have no effect on COVID-19 infection/mortality
All-cause mortality	Latitude effects of sunlight confounded by skin color	Overall mortality peaks in winter and nadirs in summer in temperate countries but not in low-latitude countries (Marti-Soler et al, 2014). Seasonal mortality variation relates to latitude and thus day length variation (Douglas and Rawles, 1999)	Low-serum vitamin D levels nonlinearly associated with increased mortality (Fan et al, 2020)	No effect of vitamin D supplementation on mortality (Zhang et al, 2019). Mendelian randomization study results inconsistent (Afzal et al, 2014; Sutherland et al, 2022; Trummer et al, 2013)

Abbreviations: BP, blood pressure; CI, confidence interval; HBA1c, hemoglobin A1c; HR, hazard ratio; IHD, ischemic heart disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; T2DM, type 2 diabetes mellitus.

have received a relatively high environmental amount of UV, reducing the power to detect a difference. Nonetheless, in addition to the clinical trend to reduced disease progress, a significant normalization of markers of immune dysfunction was shown (Trend et al, 2020), and this has been repeated by other investigators (Breuer et al, 2014; Ostkamp et al, 2021). A larger formal clinical trial of UVB phototherapy to treat MS is now needed.

The COVID-19 pandemic, where initially we lacked prophylactic vaccines or targeted therapies, made it possible to study the effects of environmental factors such as sunshine on the risks of transmission and disease severity of a prototypic infectious disease. As outlined in the previous section on the evolution of skin color, the strong selective pressure for pale skin phenotypes occurs in the last 5000 years in Europe, after the development of farming, when infectious disease would have become a significant selective pressure (Larsen, 2023). There is no evidence for pale skin genotypes in the upper Paleolithic and Mesolithic hunter gatherers who inhabited Europe for the preceding 40,000 years, and as recently as 5300 years before present, we can see the dark skin genotypes in northern Europe (Jensen et al, 2019; Wang et al, 2023). COVID-19 mortality is latitude/environmental UV dependent (Cherrie et al, 2021) and shows strong seasonality, with lower growth rates correlating to increased UV and unrelated to changes in temperature or humidity (Carleton et al, 2021). Infection risk is significantly higher in those with low-serum vitamin D level (Teshome et al, 2021), as is development of severe disease (Pereira et al, 2022), yet oral supplementation with either cod liver oil (Brunvoll et al, 2022) or vitamin D (Jolliffe et al, 2022) has no effect on infection rates or disease severity (Mariani et al, 2022; Murai et al, 2021). UV inactivates severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in aerosol and may thus reduce transmission in an indirect way, but a randomized, controlled, double-blinded pilot study of narrow-band UVB phototherapy for treatment of patients hospitalized with COVID-19 showed direct benefit, with a reduction in COVID-19 mortality (2 of 15 in UVB group vs 5 of 15 in control group) (Lau et al, 2022). COVID-19 mortality in Europe and the United States was higher in dark-skinned than light-skinned populations, and this is only partly accounted for by social factors and comorbidities (Batty et al, 2022). Attenuation by skin color is a marker of UV-driven disease processes, and COVID-19 morbidity fits this pattern. The mechanisms throughout which UV might reduce COVID-19 morbidity are unclear, although UV has pleiotropic effects on immunity, including activation of the innate immune system (Bernard et al, 2019). More specifically, NO is released from cutaneous stores (Liu et al, 2014) and can

block the myristoylation of the spike protein on SARS-CoV-2 required for binding to the angiotensin-converting enzyme 2 receptor (Akaberi et al, 2020). This effect is common to other coronaviruses (Åkerström et al, 2009, 2005).

SUMMARY

Multiple strands of evidence point to the importance of sunlight on health, but research in this field has been limited by the focus of the dermatology community almost exclusively on harmful effects (American Academy of Dermatology, 2022; National Health Service, 2022) and the absence of involvement of nondermatologists in considering wider health outcomes related to sun exposure. I would like to conclude by highlighting 2 areas.

All-cause mortality is markedly higher in winter than in summer. A Scot is 30% more likely to die during a week in January than during a week in July (Gemmell et al, 2000), and the same marked variation in mortality with a winter peak and summer nadir is seen for cardiovascular and non-cardiovascular/noncancer mortality in all higher-latitude countries (Marti-Soler et al, 2014) but not in equatorial countries. Hippocrates writing in the 5th century before Christ described this seasonal variation in disease. The regular rise in cardiovascular and respiratory infectious mortality every winter is so predictable that hospital staffing levels, doctors holiday dates, and even government policy on the timing of lifting of COVID-19 restrictions are planned to avoid times when the National Health Service will be under maximum winter stress (Sample and Grover, 2021). We have lived with this regular annual pandemic for millennia and are so normalized to it that little thought is given to why it should occur. Associations with changes in temperature or humidity or indoor living are made but with minimal proof that these factors are causally related. The evidence outlined earlier for UV being important is at least as robust as existing largely anecdotal explanations.

Any advice on sun exposure must take skin color into account. A mismatch between skin color adapted to an ancestral UV environment and current residence is harmful, thus, for example, the high rates of skin cancer in people of White European heritage in Australia or the southern United States compared with those in Europe (Leiter et al, 2020), which are not seen in Aboriginal Australians (Condon et al, 2003). Looking at the beneficial effects of UV, we see that in the United States Black Americans have a prevalence rate of hypertension 2.24 (1.97−2.56) times as high as that in White Americans (Aggarwal et al, 2021). However, West Africans have a prevalence of hypertension that is half that of Black Americans (hypertension prevalence of 16% in West Africans, 26% in Black Caribbean, and 33% in African Americans [Cooper et al, 1997]).

Dermatologists and skin researchers have made great progress in understanding some aspects of the interaction between UV and our skin, but we need to stand back and take a more holistic view of UV exposure and human health. The United Nations Environmental Effects Assessment panel (Neale et al, 2023) and an Australian panel endorsed by the Cancer Council of Australia and Australasian College of Dermatologists (Neale et al, 2024) have both just produced position statements recognizing that sunlight has beneficial effects that should be considered in formulating policy on sunlight exposure and highlighting the necessity of carrying out further research into these beneficial effects. We should take note.

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CONFLICT OF INTEREST

RBW is founder of Dr Weller Limited, a company developing nitric oxide−releasing sunscreens.

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