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Risks and Benefits of UV Radiation

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Abstract

While UV radiation is a skin carcinogen, this should not obscure the growing evidence that sunlight has significant health benefits, including impacts on cardiovascular and metabolic health. Epidemiological and mechanistic evidences for the importance of different wavelengths of sunlight, including blue light and UV radiation, are presented.

Introduction

The health risks associated with excess exposure to UV radiation are well known and have been central to most public health advice on sun exposure. Suspicions that UV radiation might be carcinogenic were raised as early as the 19th century by dermatologists such as Unna who described Seemanshaut [1, 2], the tendency for occupationally sun exposed seamen to develop skin photoageing and cutaneous cancers. Proof that UV radiation was indeed carcinogenic was then confirmed by Findlay in 1928, where, using a mouse model, he was able to demonstrate that UV radiation induced skin cancers [3]. The evidence for carcinogenicity of UV radiation has grown since then with an evolution of understanding of the mechanisms by which UV radiation can predispose people to keratinocyte skin cancers and the more worrying malignant melanoma [4]. However, despite a century of work, there are no data showing that sunlight shortens lifespan.

Broadly, there are two patterns of sun exposure leading to skin cancers. Chronic sun exposure is a risk factor for skin photoageing, squamous cell skin cancer and lentigo malignant melanoma. Unfortunately, it has not been possible to provide a dose-response curve for this relationship other than to say that outdoor workers are at increased risk of squamous cell skin cancer on sun-exposed sites, such as the head and neck, compared with indoor workers [5, 6]. This is in sharp contrast to other causes of disease such as hypertension [7] and smoking [8] in which very precise dose-dependent effects on mortality can be calculated. Intermittent

sun exposure, particularly burning exposure (sunburn) and exposure in childhood, is a risk factor for superficial spreading and nodular melanoma [9]. Paradoxically chronic sun exposure in adulthood, as marked by having an outdoor occupation and being tanned, appears protective [9, 10]. While the incidence of melanoma is rising in Europe and America, possibly as a result of the rise in short intense periods of sun exposure on sunny holidays, the mortality is changing little [11], reflecting the fact that most melanomas are diagnosed when classified as thin and thus with a good prognosis. Acral melanoma is not related to sun exposure [12]. While superficial spreading and nodular melanoma are largely diseases of white-skinned populations, acral melanoma has a similar, but low, incidence in white- and black-skinned people [13] at different latitudes, reflecting its UV-independent aetiology. Thus, while UV radiation is the major environmental risk factor for superficial spreading and nodular melanoma, it is the nature of exposure rather than the total amount that determines this.

Homo sapiens arose around 200 millennia ago in Africa, and the ancestors of non-African humans left that continent around 80,000 years ago [14]. Until the industrial revolution in the mid-19th century, the entire history of our species has been lived predominantly outdoors, whether as hunter-gatherers or farmers. Chronic sun exposure is thus the environmental norm for us, and human skin colouration has evolved to adapt us to local environmental UV radiation levels [15]. DNA analysis from west European stone age hunter-gatherer skeletons, the direct ancestors of current pale-skinned British [16] and Scandinavians [17], show that as recently as 4,700 BC we had dark skin colouration. The rapidity with which high-latitude humans have evolved paler skin – only a few hundred generations – suggests a strong adaptive drive to pale skin to maximise health benefits from sunlight exposure and enhance evolutionary fitness.

As our evolutionary history suggests, sunlight is a normal and indeed essential part of our environment. Sunlight and UV exposure were considered important clinical and health modalities in the early 20th century, particularly for treatment of tuberculosis. It was not until later that century that medical opinion shifted towards using sunblock and limiting UV exposure to prevent skin cancers and eye diseases [18, 19]. With the discovery that vitamin D could prevent rickets and bone diseases previously linked with inadequate sun exposure, clinicians and public health agencies began prescribing dietary vitamin D and recommending sun avoidance. However, as described below, new observations suggest that sun exposure has many health benefits, including those we have described for cardiovascular and metabolic health. We are rediscovering forgotten knowledge that sun exposure is beneficial for alertness and cognition, thermal comfort, mood and well-being [20–24]. Furthermore, many health benefits of sun exposure may not simply be replaced by dietary vitamin D. A more balanced approach towards sun and light exposure is now emerging as an important worldwide public health issue.

Vitamin D: Correlation but Not Causation

UVB wavelengths (290–315 nm) of sun radiation induce dermal synthesis of vitamin D, essential to human bone health. Observational studies report inverse relationships between serum 25-hydroxyvitamin D (25(OH)D) levels for all-cause mortality and many chronic health conditions, including hypertension, cardiovascular disease (CVD) and diabetes [25]. However, meta-analyses of numerous well-conducted interventional studies show limited effects of oral vitamin D supplements on all-cause mortality and numerous chronic diseases and major contributing risk factors, including adiposity, CVD and hypertension, diabetes and glucose metabolism disorders, metabolic syndrome, multiple sclerosis, mood disorders, chronic pain and systemic inflammation [25–28]. Thus, while high 25(OH)D levels are associated with increased incidence of chronic disease and markers thereof, interventions to

raise levels with oral supplements do not help (much). Vitamin D status is more likely to be a marker for exposure to sunlight, which acts through other mediators to prevent the development of chronic ill health [29], and is also a marker itself of good health and thus time spent outdoors (reverse causation).

Concerningly, health supplement claims around vitamin D are not subjected to the same scientific and regulatory scrutiny as pharmaceutical products. Indeed, the vitamin D industry is worth around 1 billion dollars per year [30]. The desire for a simple solution – oral vitamin D supplementation – to solve multiple health problems is understandable, but the first lesson of epidemiology is that correlation is not causation. There is unfortunately a history of undeclared conflicts of interest in the promotion of vitamin D [30], and a sometimes obsessive fixation on the molecule has had the unintended consequence of preventing exploration of alterative mechanisms by which sunlight yields health benefits. The National Institutes of Health Office of Dietary Supplements concluded that "it is … not possible to specify a relationship between vitamin D and health outcomes other than bone health" [31]. Some common themes can be identified in diseases where the ameliorative or preventative effects of sun exposure should be considered. These are the existence of latitude incidence/prevalence gradient(s) and/or seasonality in disease incidence/prevalence and an inverse relationship with measured serum 25(OH)D levels. If oral vitamin D supplementation reduces disease incidence/prevalence, this is indicative of a vitamin D-mediated mechanism, but in many/most cases [25, 26, 32, 33] this is not seen, thus pointing towards UV-mediated but vitamin D-independent processes.

Exciting findings from our research teams and others (see below) are providing new evidence that low, non-burning levels of sun exposure may curb the development (and burden) of chronic health conditions, particularly CVD, obesity and metabolic dysfunction.

Latitude and Season Correlate Strongly with Blood Pressure, CVD and All-Cause Mortality

Incident UV radiation from the sun increases in intensity during summer and with decreasing latitude (distance from the equator). Seasonal variation in systolic blood pressure in temperate countries such as the United Kingdom is ~5–6 mmHg, while systolic blood pressure (Fig. 1), hypertension prevalence and incidence of acute coronary syndrome increase with rising latitudes [34–36]. Within Europe, carotid artery intima-media thickness, a marker for atherosclerosis, correlates more closely with latitude than with any other risk factor [37]. There is seasonal variation in Australia for hypertensive disorders of pregnancy, which peak for births in late winter [38].

Seasonal change in the United Kingdom and Australia likely contribute significantly towards CVD with reduced cervical artery dissection rates (associated with stroke) in summer in both countries [39]. Further afield, we observed in 340,000 dialysis patients that increased sun exposure correlated with reduced blood pressure, with ~40% of this correlation due to UV radiation, independently of temperature [40]. (See Table 1 for three measurements taken per week for 3 years at >2,000 sites in the United States). Consistent with this, UVA exposure inversely correlated with incident myocardial infarction in Scotland [41], and sunshine duration – rather than simple day-length – correlated with shifts in ST-elevation myocardial infarction occurrences from day-time to night-time in summer [42].

COVID-19 and Sun Exposure

COVID-19 has become a pandemic since the start of 2020. CVD is a predisposing factor for COVID-19-specific mortality with increased mortality seen, after adjustment for age, at higher latitudes [43]. However, rapid reviews of the evidence by

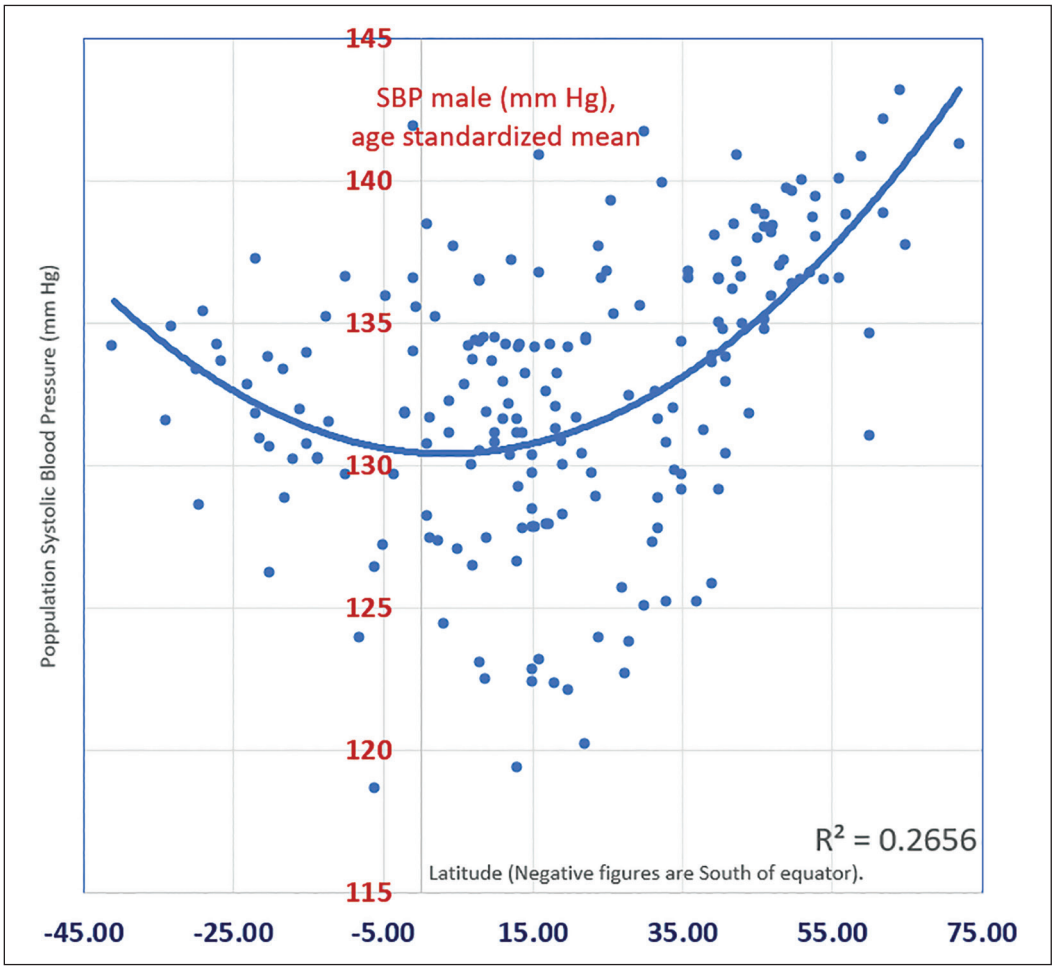

Fig. 1. Population systolic blood pressure as a function of latitude. Male systolic blood pressure in 1980 (before modern effective anti-hypertensive agents became available) is plotted against midpoint latitude for all 198 countries in the world.

Table 1. Units for UV and temperature are 100 × mmHg/(W × m^{-2}), where a unit of 1.0 represents a change of population BP of 1 mmHg for a change of incident UV radiation of 100 W/m^2

Self-declared skin colour		White (n = 218,549)		Black (n = 123,908)	
		SBP change per unit UV (95% CI)		SBP change per unit UV (95% CI)	
Corrected for co-variates	UVA	−0.75	(−0.78 to −0.72)	−0.63	(−0.66 to −0.59)
	UVB	−12.73	(−13.22 to −12.23)	−10.49	(−11.07 to −9.91)
Corrected for co-variates and temp	UVA	−0.32	(−0.37 to −0.27)	−0.23	(−0.29 to −0.16)
	UVB	−5.63	(−6.48 to −4.78)	−4.17	(−5.26 to −3.08)

Adapted from Weller et al. [40].

both the Royal Society and National Health Service Institute for Clinical Excellence have found the evidence for any benefit of vitamin D supplementation in reducing COVID-19 mortality to be insufficient [44]. COVID-19 mortality in the United States inversely correlated with non-vitamin D forming environmental UVA after correcting for extensive confounders. This effect is replicated in independent datasets from Italy and England, suggesting that sunlight via non-vitamin D pathways may reduce the burden of COVID-19 disease [45].

Sun Exposure May Reduce All-Cause Mortality

A range of human studies – all initially designed to quantify the risk of skin cancer – shows surprising reductions in all-cause mortality with increased sun exposure. In 40,000 individuals tracked for 20 years in Sweden, increased sun exposure was dose-dependently associated with reduced all-cause mortality even after correcting for major known confounders (smoking, alcohol, occupation, income, BMI and exercise) [46]. Similarly, in a randomised, controlled, intervention study of 1,700 residents of far-north Queensland (Australia), there was a non-significant trend to higher all-cause deaths for those in the sunblock intervention (21/812, 2.6%) than the control group (12/809, 1.5%) [47]. Together, these findings suggest that sun exposure promotes longevity.

Our Human Experiments Demonstrate That UV Radiation Reduces Blood Pressure

Liu et al. [48] and Oplander et al. [49] have shown that controlled UV exposure reduces blood pressure via release of nitric oxide (NO) from skin stores. NO is a free radical with signal modifying abilities that play a role in multiple physiological and pathological pathways. Due to its short half-life and tendency to react with other molecules, NO itself cannot be effectively stored but is rapidly oxidised to nitrite (NO^{2-}) and then to the more stable nitrate (NO^{3-}). There are two generally different mechanisms in the production of NO: One is through the NO synthase pathway, and the other is the chemical reduction in the nitrate-nitrite-NO pathway [50]. We have previously found quantities of nitrate, nitrite and nitrosothiols stored in the skin, at concentrations significantly higher than that in the circulation [51]. UV radiation in the presence of thiols can photoreduce nitrate to nitrite and thence NO [52], leading us to speculate that UV radiation might directly mobilise NO from the skin to the systemic circulation and produce cardiovascular benefits [53]. We then experimentally confirmed this in a randomised cross-over study, in which whole-body exposure of young male adults to 20 J/cm^2 UVA for 10 min reduced blood pressure by ~3 mmHg more than sham irradiation [48]. This correlated with a rise in circulating nitrite (the stable oxidation product of NO) and fall in nitrate. Hypertension is a risk factor for myocardial infarction, and analysis of all myocardial infarctions in Scotland in the first decade of this century shows that incident inversely correlates with UVA levels independently of temperature and UVB [41].

Sun Exposure May Reduce Metabolic Dysfunction

We have also demonstrated that low, non-burning doses of UV radiation reduce weight gain and metabolic dysfunction in mice fed a high-fat diet [54]. For example, UV prevented glucose intolerance (Fig. 2a) and reduced liver lipid levels (Fig. 2b). These effects were linked to UV-induced NO [55]. In adults the incidence of type 2 diabetes and fasting glucose are lowest in summer (reviewed in [56]). Seasonal differences in fasting

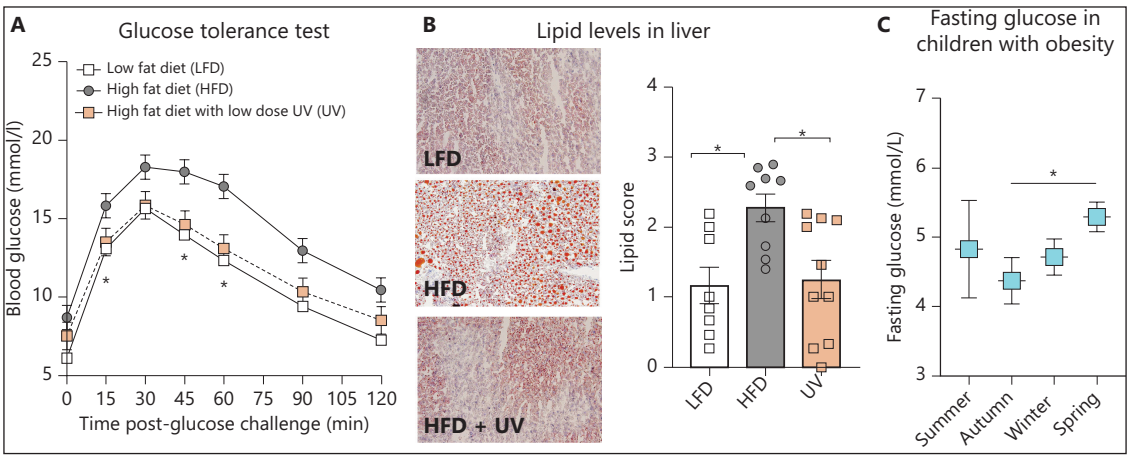

Fig. 2. Metabolic dysfunction is reduced by UV light. Twice a week exposure to low dose UV light suppressed: **(a)** blood glucose measured during a glucose tolerance test and **(b)** liver lipid (fat) levels (red staining; oil red) in mice fed a high fat diet (HFD). Data from (a and b) are shown as mean ± SEM (* $p < 0.05$, comparing LFD [low fat diet] control treatment, or UVR, to HFD, one-way ANOVA) and are reproduced from that reported in Dhamrait et al. [54]. In **(c)** seasonal changes in fasting glucose occurred in children with obesity living in Perth (mean ± SD, * $p < 0.05$, one-way ANOVA), in whom a strong inverse relationship ($r = -0.67$, $p = 0.002$) for fasting glucose, and daily terrestrial UVR levels measured in the previous 6 months were observed. Data from (c) are reproduced from that reported in Clarke et al. [57].

glucose levels have been observed in children with obesity in Perth, Australia (Fig. 2c) [57]. Other large epidemiological studies suggest that the risk of type 2 diabetes is reduced in women with "active sun exposure habits" even after accounting for confounding physical activity [58].

Other Bioactive Molecules Induced by Sun Exposure

A suite of bioactive molecules, in addition to vitamin D and NO, is induced by sun exposure, which have various independent and interacting effects on health and well-being. These include dopamine, serotonin, beta-endorphin, urocanic acid, glutamate and others yet-to-be discovered. Insufficiencies in these molecules may contribute to all-cause mortality and the development of many chronic conditions, including those mentioned above (for vitamin D), and others such as internal cancers (e.g., breast and colon), myopia, autism, Alzheimer's disease, learning disabilities and asthma [59]. Space limitations prevent more extensive discussion here but to remind readers that there is more to sunlight than just vitamin D, a couple of interesting examples are worth highlighting.

Cognitive function, Alzheimer's disease and dementia are more prevalent in individuals with low measured serum vitamin D levels [60, 61], but with no evidence for benefit from oral supplementation. This probably in part reflects poor cardiovascular health for which low vitamin D levels are a (non-causally related) marker [33]. In a superb series of experiments, researchers

from China have identified a fascinating alternative pathway starting with mobilisation of urocanic acid by UV radiation in the skin, feeding into an intraneuronal pathway for glutamate biosynthesis leading to enhanced learning in a rodent model [62].

UV radiation affects gene regulation independently of vitamin D [63]. Remarkably, around 30% of the human transcriptome has a seasonal cycle with, broadly speaking, anti-inflammatory genes being upregulated in summer and pro-inflammatory genes in winter [64]. These variations are also seen in serum protein markers of inflammation and may represent an evolutionarily driven "turning-up" of pro-inflammatory pathways to fight infectious diseases more prevalent in winter months [64]. However, this pro-inflammatory milieu (occurring when UV radiation levels are lower) may be linked to increased prevalence of metabolic/cardiovascular/cerebrovascular disease observed in winter.

Blue Light, Circadian Rhythm and Health Effects

Blue light (λ~450–490 nm) is emitted as part of the spectrum of sunlight and by modern electric devices (e.g., computers, LED screens and electric lighting technologies). There are known and well-characterised benefits of blue light exposure, when received at the right time of day, for the maintenance of day-to-night rhythmic patterns of sleep and other physiological activities that exhibit a circadian rhythm, including blood pressure and blood glucose. Blue light is a critical environmental modulator of human circadian rhythms, acting through photoreceptive cells in the retina of the eye to signal to the brain to regulate the production of the hormone melatonin and keep central and peripheral body clocks in sync. Disruption of circadian rhythm may increase risk for chronic diseases such as obesity, depression, internal cancers, neurodegenerative diseases, metabolic disorders and inflammation [65]. Exposure to electrically generated (blue-containing) light at the wrong time of day (i.e., night) may cause circadian disruption. This is hypothesised to be an important driver of chronic diseases and is presumed to be mediated by increased use of computers, tablets and mobile phones [66] and the increased brightness of commercially available screens, some with peak luminance of 1,000 cd/m^2 [67]. While there is currently much concern about light from these electric devices suppressing the production of melatonin and disrupting circadian rhythms, research has also shown that insufficient exposure to blue-rich light early in the day can also lead to circadian disruption [68, 69].

Summary

Sun exposure is the environmental norm for *Homo sapiens*. While excess UV radiation, particularly sunburn, is a major risk factor for the development of skin cancer, a growing number of health benefits are being identified. Unsurprisingly, for an exposure which has been with us throughout our evolutionary history, several mediators and gene regulatory mechanisms account for this, in addition to vitamin D. Good medicine involves the study of benefits as well as risks linked to any behaviour, and advice on "healthy sun" has to take these benefits into consideration to give a properly balanced message.

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Conflict of Interest Statement

Dr Weller owns shares in Dr Weller Ltd.

Author Contributions

RBW had the idea for the paper. MM produced the first draft. This was revised by RW (particularly cardiovascular and COVID section), SG (particularly metabolic section) and WD (blue light section). All authors fulfil the ICMJE criteria for authorship.

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