PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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Phil. Trans. R. Soc. B 2012 **367**, 785-792
doi: 10.1098/rstb.2011.0308

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doi:10.1098/rstb.2011.0308

Research

Human skin pigmentation, migration and disease susceptibility

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Human skin pigmentation evolved as a compromise between the conflicting physiological demands of protection against the deleterious effects of ultraviolet radiation (UVR) and photosynthesis of UVB-dependent vitamin D_3. Living under high UVR near the equator, ancestral *Homo sapiens* had skin rich in protective eumelanin. Dispersals outside of the tropics were associated with positive selection for depigmentation to maximize cutaneous biosynthesis of pre-vitamin D_3 under low and highly seasonal UVB conditions. In recent centuries, migrations and high-speed transportation have brought many people into UVR regimes different from those experienced by their ancestors and, accordingly, exposed them to new disease risks. These have been increased by urbanization and changes in diet and lifestyle. Three examples—nutritional rickets, multiple sclerosis (MS) and cutaneous malignant melanoma (CMM)—are chosen to illustrate the serious health effects of mismatches between skin pigmentation and UVR. The aetiology of MS in particular provides insight into complex and contingent interactions of genetic and environmental factors necessary to trigger lethal disease states. Low UVB levels and vitamin D deficiencies produced by changes in location and lifestyle pose some of the most serious disease risks of the twenty-first century.

Keywords: UVB; melanin; vitamin D; cutaneous malignant melanoma; rickets; multiple sclerosis

1. INTRODUCTION

Skin pigmentation in humans is correlated most strongly with ultraviolet radiation (UVR), among all environmental factors measured [1,2]. As the most important factor regulating the penetration of UVR into the skin, pigmentation has wide-ranging effects on health [1,2]. Some of the diseases associated with extremes of UVR exposure such as skin cancer and rickets have been known for a long time, but those associated with chronic low-UVR exposure and vitamin D deficiency have been appreciated only recently.

Early members of the genus *Homo* and ancestral *Homo sapiens* evolved darkly pigmented skin, rich in the natural sunscreen eumelanin, as protection against the manifold negative effects of intense UVR on the skin and body [2,3]. Eumelanin absorbs and scatters ultraviolet and visible light, and prevents the formation of reactive oxygen species formed when UVR reacts with cellular contents in the skin [4,5]. The dark-skinned phenotype was established in the *Homo* lineage by about 1.2 Ma and has been maintained by strict stabilizing selection at the melanocortin 1 receptor (*MC1R*) locus in African hominins ever since [6–8]. Dispersal outside of the tropics brought hominins into environments with less intense and more highly seasonal UVR, especially the medium wave form, UVB (280–315 nm), necessary for the production of pre-vitamin D_3 in the skin [2,3]. Dispersals into environments of generally low and highly seasonal UVB were associated with positive selection for maintenance of the capacity for cutaneous synthesis of pre-vitamin D_3 through loss of permanent constitutive pigmentation [2,3,9]. This has been proved by genetic evidence for selective sweeps having established depigmented integumental phenotypes independently in the ancestors of western Europeans and eastern Asians [10,11] and probably also in *Homo neanderthalensis* [12]. Dispersal of human populations into latitudes between about 23° and 46° was accompanied by the evolution of partially depigmented phenotypes capable of tanning [3]. Many such populations probably represent repigmented descendants of previously depigmented peoples—such as in the case of the indigenous peoples of the New World—but identification of candidate loci associated with evolution of secondary dark pigmentation is still in its early stages [13]. The range of skin pigmentation in modern humans is the product of two reciprocal clines working to promote the UVB-induced photosynthesis of pre-vitamin D_3 in the skin on the one hand and prevent the multifarious damage caused by UVR on the other hand [3,9]. Genes controlling skin pigmentation are among the most strongly scrutinized by natural selection because of the skin's role in regulating UVR penetration into the body. In recent human history, however, culture and genes have worked in concert to produce adaptations that are contingent on maintenance of particular behaviours and environmental conditions.

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One contribution of 14 to a Discussion Meeting Issue 'Immunity, infection, migration and human evolution'.

In roughly the last 5000 years, people have moved faster and over longer distances than ever before because of innovations in land, sea and air transportation. Many now live in places distant from their ancestral homelands and follow lifestyles dramatically different from those of their forebears. Because of one or both of these factors, the majority of the world's people now experience solar regimes unlike those under which their ancestors evolved. The health-related penalties associated with these remarkable changes in location and lifestyle are generally poorly understood and under-appreciated. Here, we briefly review the current state of knowledge on the relationship between skin pigmentation, UVR exposure, migration history, lifestyle and disease risk. We illustrate the discussion of the effects on disease prevalence of changes in location, lifestyle or both with examples of two types of diseases. The first is associated with insufficient UVB to maintain adequate vitamin D levels and is exemplified by rickets and multiple sclerosis (MS). These diseases are exacerbated by dark skin pigmentation, urban lifestyles or other factors leading to low UVB exposure, or both. The second is associated with high levels of UVR relative to skin pigmentation and is exemplified by cutaneous malignant melanoma (CMM).

2. HUMAN EXPOSURE TO ULTRAVIOLET RADIATION

Many factors determine the amount of UVR to which a person is exposed, beginning with the amount reaching the Earth's surface at a particular place and time of day. This depends on the angle at which solar radiation passes through the atmosphere (the solar zenith angle or SZA), the mass of air through which the Sun's rays must pass (the path length) and the presence of clouds and pollution in the lower atmosphere [14–16]. The shorter the wavelength, the more likely it is that radiation will be absorbed or scattered by the atmosphere. Outside of tropical latitudes, large SZAs and increased path lengths result in increased absorption and scattering of the UVB wavelengths responsible for pre-vitamin D_3 production in the skin [17–21]. The presence or absence of sunlight is not a good guide to the presence or absence of UVB [22], and for much of the year outside of the tropics there is little or no UVB in sunlight, except at very high altitudes [3]. At the equator, by contrast, UVB irradiance is high throughout the year and exhibits peaks at the two equinoxes and nadirs at the two solstices [3]. This results in an annual range of variation of about 20 per cent at the equator in vitamin D_3-inducing wavelengths of UVB. In contrast, at 50° N, there is a difference of 250 per cent in vitamin D_3-inducing wavelengths of UVB over the course of the year, with the nadir in the solar winter from November to February exhibiting no effective vitamin D_3-inducing wavelengths of UVB [9].

Actual human exposure to UVR depends not only on geographical position, but also on the time of day, posture, clothing and behaviour [14,23]. Clothes and shade-seeking behaviours reduce effective solar exposure markedly when people are outside [24], but for over half of the world's population who are city dwellers, the potential for UVR exposure is primarily regulated by the urban built environment [25]. Studies of the time budgets of modern urban dwellers indicate that 80–90% of time is spent indoors or in vehicles [26], greatly limiting the potential for vitamin D production. A typical office worker taking lunch on a sunny day, for example, receives only 5–25% of the UVR that would fall on a flat open surface during the same period because of the blocking effect of tall buildings against the open sky [25]. The potential for pre-vitamin D_3 production is reduced further still by dark skin pigmentation. Other things being equal, the higher the eumelanin content, the lower the rate of pre-vitamin D_3 production in the skin [2,20,21,27–38]. When the zones of cutaneous pre-vitamin D_3 production potential are mapped following a previously established protocol [2], it is evident that lightly pigmented people inhabiting the zone near the equator can experience enough UVB through casual sun exposure on unprotected skin to produce physiologically adequate amounts of vitamin D. In the subtropical zone, there is at least one month during which there is insufficient UVB to catalyse pre-vitamin D_3 production for people with lightly pigmented skin, and during which they must rely on stored vitamin D (as 25-hydroxyvitamin D; 25(OH)D) to satisfy their physiological needs. For people with darkly pigmented skin, these 'vitamin D safe zones' are smaller and shifted towards the equator because of the efficacious sunscreening action of eumelanin. Beyond the subtropical areas in the warm temperate, cool temperate and polar regions, there is insufficient UVB averaged over the year to produce pre-vitamin D sufficient to satisfy their body's requirements. The threshold begins at around 42° latitude. People living at higher latitudes than 42° must supplement their diets with vitamin D_3-rich foods, such as oily fish, in order to prevent vitamin D deficiency and its disease sequelae. Long-term occupation would have been very difficult or impossible for darkly pigmented people at these latitudes unless they subsisted primarily on vitamin D_3-rich foods (table 1) [2,3,9].

The distribution of human populations today reflects the effects of over 500 years of voluntary and involuntary long-distance migrations and increasing urbanization. When population concentrations are examined relative to the potential for making pre-vitamin D_3 in the skin (figure 1 and table 1) [2], a large fraction of the world's population occupies regions, mostly in the Northern Hemisphere (NH), that receive insufficient UVB to catalyse cutaneous pre-vitamin D_3 production for at least one month per year. In the NH, a large proportion of people occupying these regions are moderately or darkly pigmented descendants of immigrants, including many in North America who are descendants of African slaves and many in Europe who are descendants of South Asian and East Asian immigrants.

3. DISEASES RELATED TO UVB EXPOSURE INSUFFICIENT TO MAINTAIN ADEQUATE LEVELS OF VITAMIN D

Vitamin D, while classified as a vitamin, is a secosteroid hormone produced following exposure to UVB. It is best known for its roles in calcium absorption and the development and maintenance of healthy bones.

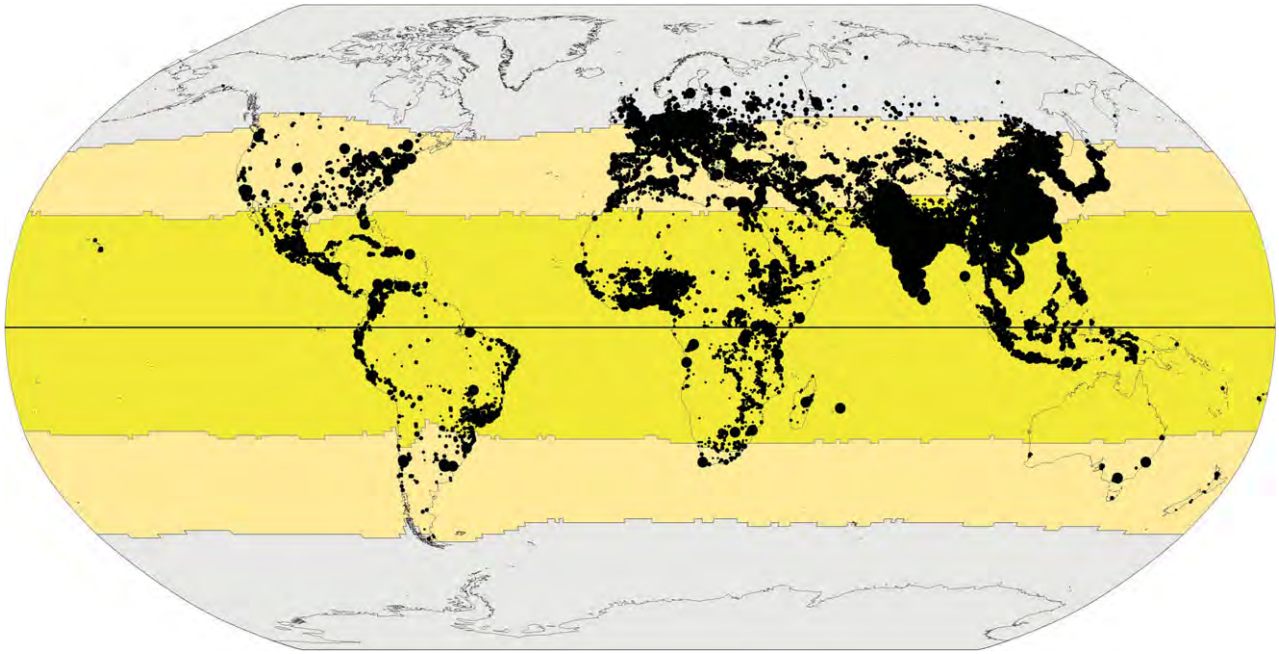

Figure 1. Global population plotted relative to zones of cutaneous pre-vitamin D_3 production potential for lightly pigmented skin. People inhabiting the yellow zone near the equator can experience enough UVB through casual sun exposure on unprotected skin to produce physiologically adequate amounts of pre-vitamin D_3. Those inhabiting the tan zone will experience at least one month during which there is insufficient UVB to catalyse pre-vitamin D_3 production in the skin, during which they must rely on stored vitamin D (as $25(OH)_2D$) to satisfy their physiological needs. For people in the grey zone, there is insufficient UVB averaged over the year to produce pre-vitamin D_3 sufficient to satisfy their body's requirements. These people must supplement their diets with vitamin D_3-rich foods such as oily fish in order to prevent vitamin D deficiency and its sequelae. For people with darkly pigmented skin, the size of the yellow and tan 'vitamin D safe' zones is smaller and shifted towards the equator because of the efficacious sunscreening action of eumelanin, and the grey zone is concomitantly expanded. World Robinson projection; global population estimates from Global Population 2000 Basin DataSet delivered via ArcOnLine, accessed 2010.

Table 1. The distribution of world population according to vitamin D synthesis zones for lightly pigmented skin, as illustrated in figure 1. Over half of the world's population lives in the equatorial zone shown in yellow in figure 1, which is vitamin D safe for people with lightly pigmented skin receiving casual UVB exposure. The Northern Hemisphere (NH) is much more densely populated than the Southern Hemisphere (SH), and a larger fraction of people live in regions that receive low and highly seasonal UVB, resulting in reduced pre-vitamin D3 synthesis potential.

region (and colour zone in figure 1)	population (in millions)	percentage of world population	percentage of land area
SH cold temperate–polar zone (grey)	0.36	0.006	3.6
SH subtropical and warm temperate zone (tan)	95	1.6	16.5
equatorial zone (yellow)	3198	52.7	40.7
NH subtropical and warm temperate zone (tan)	2392	39.4	15.2
NH cold temperate–polar zone (grey)	386	6.3	24.0

Studies in recent years have demonstrated many non-classical roles for vitamin D in the immune, cardiovascular, muscular, reproductive and integumentary systems, as well as in cancer prevention [39–43]. Its best-characterized target organs are the intestine, kidney and the bone, but nuclear receptors for the hormone have been identified for 36 tissues. Vitamin D exerts paracrine functions in 10 organs, and performs essential regulation of B and T lymphocytes, the adaptive and innate immune systems, pancreas, brain and heart [39]. The critical roles played by vitamin D in improving the barrier function of the skin and in maintaining the integrity of the epithelium in the skin, gut and respiratory and urinary tracts have now been recognized [44]. The first step in the cutaneous production of vitamin D is initiation of the conversion of 7-dehydrocholesterol (7-DHC) to pre-vitamin D_3 by UVB, a process that occurs optimally at 297 nm, but up to 310–315 nm. Pre-vitamin D_3 is transformed in the skin into vitamin D_3 within hours [29,45] and then exits the skin into the circulation bound to vitamin D-binding protein before being converted into its biologically active form, $1,25(OH)_2D_3$ (also known as calcitriol or 1,25-dihydroxyvitamin D_3) [39,46]. The hydroxylation steps necessary to convert vitamin D_3 into $1,25(OH)_2D_3$ occur successively not only in the liver and kidney but also in several other tissues, including the bone, placenta and granulomatous lymph nodes [39,47]. It is significant with respect to disease susceptibility that the immune system has the potential to synthesize $1,25(OH)_2D_3$ and to elicit autocrine or paracrine functions from immune cells

expressing the vitamin D receptor [48]. However, this can occur only when sufficient levels of serum 25(OH)D are circulating. The levels of 25(OH)D necessary to maintain maximal performance of the immune system have not been established, but are probably considerably higher than previously recognized [44]. Vitamin D status is measured by the serum 25(OH)D clinical assay. The ascertainment of vitamin D deficiency or insufficiency on the basis of serum 25(OH)D levels is still debated, but 30 ng ml^{-1} is widely recognized as indicating optimal vitamin status. The global high prevalence of vitamin D insufficiency and deficiency is related mostly to insufficient UVB exposure to maintain adequate 25(OH)D levels.

The importance of vitamin D was first recognized because of its association with bone health and the development of rickets in children. Nutritional rickets is a short-latency disease that results from impaired bone mineralization in children because of calcium malabsorption arising from vitamin D deficiency or, less frequently, from calcium or phosphate deficiency [49,50]. Rickets became more common after industrialization led to increases in UVB-quenching pollutants [51,52], but is not a disease of industrialization. It has been recognized from Neolithic skeletal materials at the rate of 1–2.7% [51–54], was recorded in Greek, Roman and Chinese literature dating from 900 BC, and was described in a medical treatise by Francis Glisson in 1650, before industrialization [49,54,55].

Rickets is the most common bone disease in children worldwide, but data on prevalence are few [56,57]. The disease often afflicts immigrants, including children with dark pigmentation living in low-UVB environments and those living in poverty in cities with little access to recreational sunshine. The development of rickets is promoted by coarse, high-fibre diets of legumes, which contain calcium-chelating phytates that both prevent the dietary calcium from being absorbed [58] and lower the half-life of 25(OH)D [59]. Although the recovery from rickets can occur quickly after restoration of adequate vitamin D and calcium, children afflicted by rickets often have lower peak bone mass and lower bone density as adults [56,60], and these attributes are predisposing to osteomalacia and osteoporosis. Continued low exposure to UVB as a result of indoor living and the wearing of concealing clothing further increases the likelihood that these long-latency diseases will develop. The predicted global disease burden caused by very low UVB levels and associated low 25(OH)D levels has been estimated at four billion cases or 3.3 billion disability-adjusted life years, based on morbidity estimates of bone diseases (rickets, osteomalacia and osteoporosis) alone [61]. This far exceeds the disease burden connected with high UVR exposure [62].

The effects of vitamin D deficiency on regulatory functions of B and T lymphocytes and the adaptive and innate immune systems [39] have focused attention on the role played by inadequate levels of vitamin D in the aetiology of infectious diseases, cancer and autoimmune diseases. Low vitamin D levels have been connected to epidemics of influenza [63]. Vitamin D plays an important part in cancer prevention [40,64], but the results of controlled clinical trials are needed to establish the extent of its protective action relative to, or in addition to, genetically based risk. Vitamin D has regulatory effects on inflammatory markers and autoimmune diseases, such as diabetes and MS [44,65]. Here, we focus on recent studies that have implicated low UVB and inadequate vitamin D with increased risk of MS.

MS is one of the most common neurological disorders and causes of disability in young adults. It is an inflammatory and degenerative disease of the central nervous system characterized by demyelination and axonal loss. A pronounced latitudinal gradient in MS prevalence starting at about 42° of latitude implicates solar wavelengths in the UVB range [66–68] (figure 2). This is also indicated by a month-of-birth effect, and changes in the timing of the month-of-birth effect according to the strength of UVB. These effects suggest that UVB conditions during the third trimester of pregnancy, when myelin production is greatest, may be more important. The cascade of causality involved in the development of MS is complex and involves the interaction of genetically based risk factors with environmental factors at particular times during pre- and post-natal development and adulthood [71,72]. Inherited risk owing to variations at immune-related disease loci so far identified accounts for about 50 per cent of this risk, but the influence of gene interactions, rare genetic variants and epigenetic factors is still poorly understood [73]. Case–control ratios by US state and MS prevalence by North American region exhibit a strong negative (inverse) correlation with UVR levels, supporting the role of low UVB and inadequate vitamin D in MS aetiology [74].

The high and rising incidence of MS in Scotland [75,76] has precipitated a search for environmental factors that might be implicated in disease aetiology. Low UVB and inadequate vitamin D in association with genetically based risk have been implicated, but the reasons for increasing incidence must be sought through reference to the archaeological record, demographic history and changes in lifestyle. Year-round habitation of Scotland after the Last Pleistocene glaciation about 14 000 yr BP was made possible by a biocultural adaptive complex involving both skin pigmentation and diet. Because of Scotland's extremely low UVB conditions (especially in the cloudy west), maximally depigmented skin alone was insufficient to ensure adequate amounts of vitamin D throughout the year (figure 1). Late Pleistocene and Holocene inhabitants of Scotland survived primarily in coastal settings where they pursued lifestyles emphasizing the gathering and hunting of vitamin D_3-rich foods [77,78]. Changes in human subsistence and diet began with the introduction of agriculture and grazing about 5000 yr BP, and have accelerated greatly under the influences of industrialization and urbanization in the last 200 years. Resulting changes in the physical location of human domiciles, patterns of daily activity and behaviour, and diet have led to reduced exposure to UVB and reduced consumption of vitamin D_3-rich foods. This has perturbed the 'vitamin D compromise' that was central to the biocultural adaptive complex established in Scotland during prehistoric times. The 'imperfect storm' thus created has been intensified by further erosion of vitamin D status owing to decreased oily fish consumption resulting from reduced fish availability.

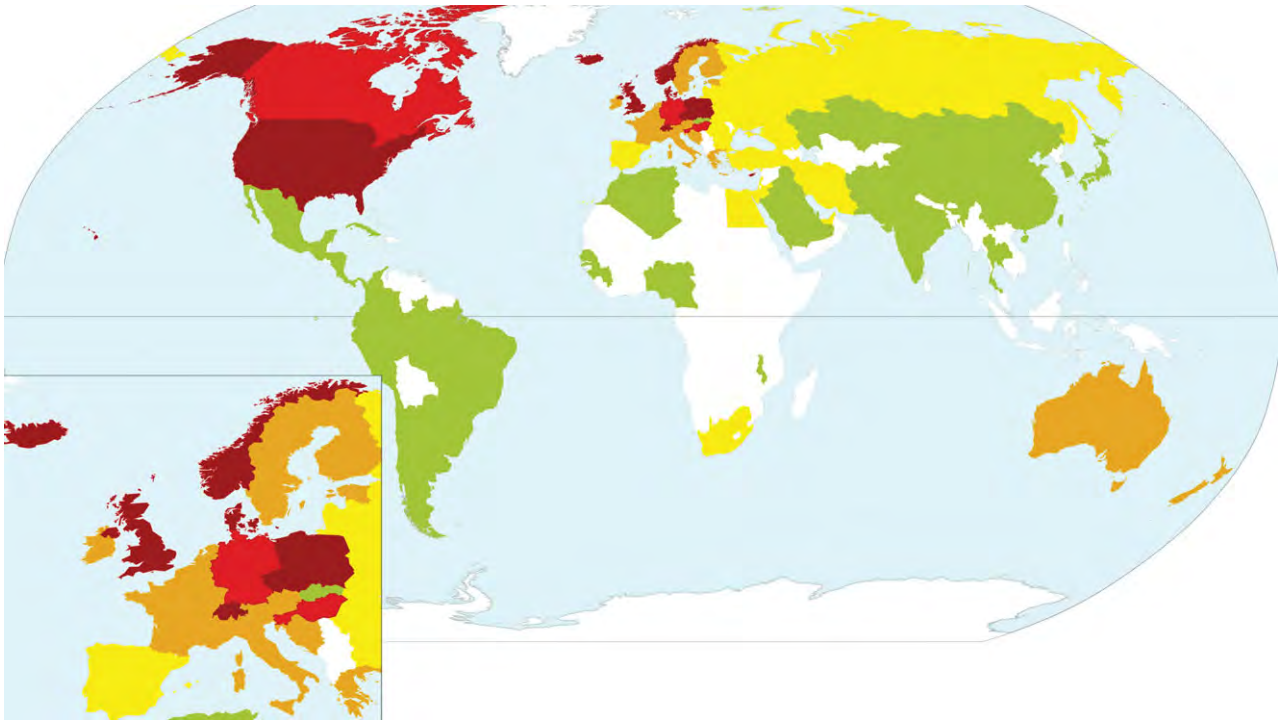

Figure 2. Prevalence of MS per 100 000 population. The bright red areas represent regions of extremely elevated risk (greater than 2 s.d.); the dark-red, moderately elevated risk (greater than 1.3 s.d.); orange, elevated risk (greater than 0.5 s.d.); yellow, normal risk (−0.5 to 0.5 s.d.) and green, lower than normal risk (less than −0.5 s.d.), each from the mean. Standard deviations were computed from data for 2007 and 2008 based on data from the Multiple Sclerosis International Federation (MSIF; www.atlas-ofms.org). The latitudinal gradient of MS prevalence beginning at a threshold latitude of approximately 42° N is evident on the inset map despite the coarseness of the data. The elevated risk of MS in Australia and New Zealand can be attributed mainly to the genetically elevated risk of its European settler populations [69,70]. World Robinson projection.

Prevalence of MS across England varies with latitude and UVB, but the results of a recent study conducted by a team including one of us (G.C.) have shown that the distribution of MS across England is explained both by UVB exposure and the prevalence of infectious mononucleosis caused by Epstein–Barr virus (EBV) [66]. This suggests that the development of MS is contingent upon the realization of a series of influences directed by trigger-point switches rather than a simple dose response to low UVB and insufficient vitamin D. The pleiotropic roles of vitamin D on the immune system may lead to an abnormal or variant response of the immune system when an individual has vitamin D deficiency [66]. The strong association between low UVB, EBV prevalence and MS suggests the operation of conditional gene–environment–virus interactions in an additive and nonlinear progression based on critical thresholds at particular points in development.

4. DISEASES RELATED TO HIGHER LEVELS OF UVR EXPOSURE RELATIVE TO SKIN PIGMENTATION

The effects of UVR on biological systems are wide-ranging, multifarious and mostly destructive [79,15]. Darkly pigmented, eumelanin-rich skin protects against considerable damage to DNA caused by UVR [80], and is associated with much lower rates of skin cancer than lightly pigmented skin [81–84]. The protective effects of eumelanin on DNA structure were established by an experimental study showing that heavily pigmented melanocytes resumed proliferation faster after UVB irradiation than can lightly pigmented ones, and that DNA from lightly pigmented melanocytes was more badly damaged than DNA from heavily pigmented melanocytes after irradiation with increasing doses of UVB [81,85]. In contrast, the production and presence of yellow-red-coloured pheomelanin in lightly pigmented skin appears to increase the risk of oxidation stress in melanocytes. This, combined with the limited ability of pheomelanin to absorb UVR, predisposes to an elevated skin cancer risk among light-skinned individuals [86]. The damaging effects of UVR on DNA structure are widely recognized [81,85,87–89], but are associated with the initiation of skin cancers that mostly affect people towards the end or after their reproductive careers [2,90]. CMM is the only type with a high incidence rate among people of reproductive age, but overall incidence and mortality rates for melanoma prior to the mid-twentieth century were very low (less than five per 100 000) [91]. The increasing incidence and prevalence of CMM is related to acute, irregular exposure to high levels of UVR from sunlight and artificial sources early in life by people with lightly pigmented skin [92–94]. Exposure to high UVR has been caused both by migration of populations from low-UVR to high-UVR environments, such as in the translocation of large numbers of people from Great Britain to Australia in the early twentieth century, and by a dramatic increase in the popularity of recreational sun-tanning over most of the last century [95,96]. The 'vacation effect' now contributes substantially to UVR-related CMM morbidity and mortality

[14,25,97]. These conditions cannot be considered typical of our species prior to the twentieth century. For most of the history of our species, humans have moved relatively little during their lifetimes because they lacked the means of transportation to do so.

5. CONCLUSIONS

Migrations, followed by changes in diet and lifestyle, have made evident a high rate of mismatch between skin pigmentation and the solar environment affecting many people. Long-distance migration of people with differentially selected and adapted skin colours makes people more obvious within their host populations. Skin colour is the most noticeable physical characteristic of people and is often incorrectly used to predict group identities and reinforce inclusionary prejudices. These adverse effects lead to high levels of stress and sociocultural pathologies that are manifest as physical disease, mental illnesses and social maladies.

In the last 500 years, large numbers of people have undertaken voluntary or forced migrations from low- to high-UVR environments, and vice versa. These have resulted in two major categories of adverse health outcomes, those related to insufficient UVR exposure to maintain adequate vitamin D status such as rickets and MS, and those such as CMM related to higher levels of UVR exposure than are appropriate for the level of skin pigmentation. The risk of both of these major types of diseases is elevated by urbanization, indoor lifestyles and the calendar of modern life's activities. Diseases associated with vitamin D deficiency—including several types of cancer, and autoimmune and infectious diseases—are ultimately attributable to changes in location in lifestyle. These will be a major source of morbidity and mortality in the twenty-first century.

We thank Danny Altmann, François Balloux and Rosemary Boyton for inviting us to participate in the Royal Society Discussion Meeting, 'Human evolution, migration and history revealed by genetics, immunity and infection'; the final manuscript benefited from the papers and discussions that occurred at the meeting. We are grateful to George Ebers and Sreeram Ramagopalanat the Wellcome Trust Centre for Human Genetics at the University of Oxford for continuing discussions about the nature and magnitude of environmental influences on the development of MS.

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