RCE-30

Ultraviolet Radiation, Vitamin D and Health

Report of the independent Advisory Group on Non-ionising Radiation

March 2017

This report from the independent Advisory Group on Non-ionising Radiation reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.

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ACKNOWLEDGEMENT

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Executive Summary

Vitamin D is a fat-soluble vitamin that is essential for bone health and may play a part in other aspects of health and disease. Levels in man are derived from two sources, intake in the diet, and synthesis in the skin. Skin synthesis is initiated by cutaneous absorption of ultraviolet radiation (UVR), typically from the sun but also from artificial sources.

Circulating 25-hydroxyvitamin D (25(OH)D) levels are the currently accepted best indicator of vitamin D status. The levels in individuals reflect their diet (rich sources are oily fish and fortified foods), supplement intake, behavioural and environmental factors that affect their cutaneous UVR exposure, and endogenous factors affecting the effectiveness of this UVR, including skin colour and age. The environmental factors affecting solar UVR exposure include latitude, season, cloud cover, air pollution, time of day and length of day. The behavioural factors include clothing, sunscreen use, and whether a person is outdoors and whether under shade.

In general for white people in the UK, the majority of vitamin D derives from cutaneous synthesis and a lesser amount from diet. The proportions vary between individuals and are unclear in non-whites. Vitamin D has a half-life in the blood of a few weeks, and possibly can be stored in tissues for months. In experimental situations in humans, an approximately linear dose-response has been found between cumulative UVR dose and plasma 25(OH)D level, although this may reach a point at which a plateau is reached. Experimentally, whole body narrowband UV-B exposure has been found to have similar or greater efficacy than vitamin D supplements in raising 25(OH)D levels. The efficacy of a given UVR dose appears greater in whites than non-whites, including South Asians.

Plasma 25(OH)D levels in the UK population are generally greater in summer than winter (lowest at winter end), in whites than non-whites, in the non-obese than the obese, and at younger ages than in the very elderly or those living in institutions. The seasonality and pigmentation differences reflect primarily differences in cutaneous synthesis rather than diet. Levels also tend to be low in people with photosensitivity and in recipients of organ transplants, who deliberately avoid sun exposure, and in people with gastrointestinal conditions causing fat malabsorption.

The plasma 25(OH)D level needed for health is a controversial topic because several potential health effects of vitamin D have been posited, most of which have not been established. Certain effects on bone are well established: by influencing calcium absorption and bone mineralisation vitamin D prevents rickets (in children) and osteomalacia (in adults and children). The plasma level of 25(OH)D required to prevent these diseases is about 25 nmol L^{-1}. About 15-25% of the white working age adult population in the UK in winter, and 4% in the UK in summer have levels below 25 nmol L^{-1}. In UK South Asian adults, about 90% exhibit 25(OH)D <25 nmol L^{-1} in winter and 58% in summer, and among photosensitive patients about one third are <25 nmol L^{-1} in the UK winter, and 9% in summer. Levels <25 nmol L^{-1} are present in only a few percent of infants and young children in the population overall, at least in summer, but in far more South Asian children, and in the majority of South Asian adolescents in the UK. About 10-15% of over 65s in private households but 30% living in institutions have levels <25 nmol L^{-1}.

It has been hypothesised that vitamin D can also prevent certain cancers; the strongest evidence is for colorectal cancer, but the evidence for this is incomplete and the hypothesis remains unproven. It has been suggested that higher 25(OH)D levels might be needed to reduce cancer risks than are needed for bone health. Risks of several other conditions, including fractures, multiple sclerosis, type 2 diabetes and cardiovascular disease have been hypothesised to be increased by low vitamin D status, but the evidence is limited and inconclusive.

Vitamin D status in the UK population could be increased by changes in UVR exposure or diet, fortification of foodstuffs, or use of supplements. The UK Scientific Advisory Committee on Nutrition recommends that infants (0-1 year old) have a dietary intake of 8.5-10 µg day^{-1} and everyone aged 1 year and over should have a dietary intake of 10 µg day^{-1}. There is no mandatory fortification of foodstuffs in the UK other than for infant milk formula.

Excessive oral vitamin D intake can lead to vitamin D toxicity, with hypercalcaemia and ill-effects such as renal impairment. In practice, Vitamin D toxicity does not occur from UVR exposures.

Consideration of measures to reach a particular vitamin D status in the population needs to take account of both oral intake and UVR exposure, for different population groups.

About 15 minutes per day UK summer sunlight exposure during the middle of the day while wearing light summer clothing to reveal about a third of skin surface area achieves >50 nmol L^{-1} 25(OH)D in the majority of whites, while under the same conditions about 20-25 minutes per day is needed for brown-skinned South Asians to achieve >25 nmol L^{-1}. Information is lacking, and is needed, on 25(OH)D levels in black people in the UK.

While alterations, and possibly increases, in UVR exposure of individuals could be used to raise their Vitamin D status, several adverse effects of UVR exposure are also known, primarily increased risk of skin cancer, most seriously cutaneous melanoma. Skin cancer risk is highest in whites. Risk of melanoma appears to be particularly increased by intermittent exposure of unexposed skin, as occurs in sunbathing, but chronic cumulative exposures affect risks of non-melanoma skin cancer and probably also at least some types of melanoma.

Consideration of potential methods to increase vitamin D status by changes to UVR exposure patterns would therefore need to take account of both potential adverse and beneficial effects, and would need to be conducted separately, and reach separate conclusions, differentially by skin colour and age.

1. Introduction

1.1 AGNIR and its remit

Public Health England (PHE) has, amongst its functions, the responsibility for advising the UK governments and agencies on standards of protection for exposure to non-ionising radiation. The Advisory Group on Non-ionising Radiation (AGNIR) was set up in 1990, reporting to the Director of the former NRPB and more recently to the Health Protection Agency and PHE with the terms of reference: to review work on the biological effects of non-ionising radiation relevant to human health and to advise on research priorities.

The AGNIR was reconstituted in 1999 as an independent advisory group and now reports through the Centre for Radiation, Chemical and Environmental Hazards to the Director of Health Protection of Public Health England.

AGNIR has issued 15 major reports in the Documents of the NRPB/Health Protection Agency: Radiation, Chemical and Environmental Hazards (HPA, CRCE) series and a number of statements that are listed at the end of this Introduction. The Group's publications have reviewed experimental and epidemiological studies, together with exposure data, relevant to assessing possible health effects from exposures to electromagnetic fields (EMFs), ultraviolet radiation (UVR) static magnetic fields and ultrasound. They have been a valuable input to inform advice from PHE and its predecessor organisations and have been used in the development of exposure guidelines, as well as being widely circulated and used by Government and the devolved administrations. AGNIR last published a review of the health effects of UVR in 2002.

This AGNIR review, like its predecessors, reflects the consensus view of the AGNIR members.

AGNIR is a scientific review body and does not advocate policy actions or recommend what should be done practically. This is particularly important for this review because there are a number of policy-related questions, for example the extent to which people should go out in the sun or should take vitamin D supplements. However, AGNIR advises what future research should be undertaken to improve the evidence base.

Where policy-related actions seem to be indicated because of AGNIR conclusions, it will be a matter for PHE to develop any advice necessary.

1.2 UVR, exposures in the UK

Ultraviolet radiation (UVR) arises from both natural and artificial sources. It is the component of the non-ionising part of the electromagnetic spectrum within the wavelength range 100-400 nm. UVR is normally classified into three regions as follows: UV-A (315-400 nm), UV-B (280-315 nm) and UV-C (100-280 nm).

For most people the main source of UVR exposure is the sun, modified by altitude, cloud cover and sun elevation. However, artificial sources of UVR may provide a substantial proportion of the exposure received by specific groups, for example people who use artificial tanning facilities (sunbeds) and people who have UVR medical treatments. Occupational exposure to artificial UVR occurs in a range of professional and industrial applications, where exposures are limited by regulation. Climate change may affect ambient levels of ultraviolet radiation (UVR) into the future. Lifestyle and behaviour factors also have important influences on human exposure.

1.3 Health effects of UV radiation

There are both health benefits and detriments of UVR exposure, which vary between people with different genetic backgrounds, places of residence and lifestyles. This makes it complex to develop straightforward, evidence-based health promotion advice that allows individuals to balance the detriments and benefits of UVR exposure and protect themselves appropriately from adverse effects.

UVR has well recognised acute and chronic adverse health effects which are mainly confined to the skin and the eyes and are dependent on individual sensitivity. The rapid increase in the incidence of cutaneous melanoma in the UK has been attributed to greater recreational exposure to UVR, including the trend to take holidays in sunnier countries nearer the equator.

Solar UVR has long been recognised as having a role in maintaining adequate vitamin D status, as measured by the plasma concentration of 25-hydroxyvitamin D, 25(OH)D. Vitamin D is essential for skeletal health. However skin type may have a major effect on the beneficial effect of cutaneous production of vitamin D. Exposure to sunlight is sometimes a by-product of health promoting activities such as outdoor exercise. Cultural differences can also affect the amount of time spent outdoors and the clothing people wear.

1.4 The need for a review of UVR and vitamin D

AGNIR has published a number of reports and statements about the health effects of UVR, including its use for cosmetic tanning (AGNIR 1995, AGNIR 1999 a,b, AGNIR 2002). Since the last report in 2002, the role of UVR in maintaining adequate vitamin D status (plasma 25(OH)D), and indeed how adequate vitamin D status should be defined, has been controversial. Since 2002 there have been more studies published on the potential non-skeletal benefits of higher vitamin D status including hypotheses about a cancer-protective effect of vitamin D. This has led to debate about the appropriate health advice to give about UVR exposure (Jenkins and Holick 2005). It therefore appears timely to review the effects of UVR on vitamin D status, and the consequences of this for health. This information can inform public health protection policies in the future to maximise public health.

AGNIR has expertise in UVR metrology and health effects but does not have specialist expertise in nutrition: there are other expert scientific committees in the UK that have that role. The Government Scientific Advisory Committee on Nutrition (SACN) has recently completed an in-depth review “to review the Dietary Reference Values for vitamin D intake and make recommendations” (SACN 2016) and there is cross-membership between AGNIR and the SACN Vitamin D Working Group. Both groups are supported by Public Health England, but began their work under previous organisational configurations.

1.5 Purpose and scope of this review

This review aims to provide the scientific evidence to underpin public health protection advice about UVR exposures and vitamin D. AGNIR is aware that there are a wide range of cultural, behavioural, dietary as well as geographical and meteorological factors that alter people’s exposure to UVR from the sun and intake of vitamin D such that the balance of effects will vary greatly by geography. Therefore unlike previous AGNIR reports, some of the scientific literature considered in this report is deliberately limited geo-culturally. Thus the conclusions of the report are addressed mainly to the UK.

This review summarises the existing scientific knowledge on the effects of UVR on human health and vitamin D metabolism. Vitamin D status is a concept used in the document and is measured by the widely-used serum marker 25(OH)D, despite some uncertainties about other factors, eg binding proteins that may alter tissue availability of the active hormone. The review explains what is known about the plasma 25(OH)D levels needed for health and the relative contributions of sunlight and diet

to vitamin D status in the UK. The review also summarises briefly dietary aspects of vitamin D status in the UK.

The scientific evidence about the adverse effects of UVR is only summarised: more detail can be found in AGNIR (2002). There remains controversy about whether there are potential non-skeletal positive health effects of different plasma concentrations of vitamin D. SACN reports provide comprehensive reviews of the evidence about the health effects of Vitamin D.

This review is more focussed on human studies than has been the case in AGNIR reports on other types of non-ionising radiation exposure. This is in part because there is no need to repeat the biological basis of UVR-related harm that was covered at length in the 2002 AGNIR report. It is also because many aspects of diet, UVR exposure and their impact on vitamin D status have behavioural aspects that are not amenable to cellular or animal research.

The scientific papers reviewed here have been carefully examined to determine what weight to give to individual findings. This includes consideration of scientific quality as well as expert judgement about each study and how it fits with the existing canon of work. Consistency with the existing body of evidence is an important criterion, as are the well-described issues with different study designs.

1.6 Structure of the review

The executive summary summarises the report and its conclusions and recommendations.

Chapter 2 provides an overview of the potential sources of UVR exposure to people, the response functions used to assess exposure and how the metrics may relate to radiant exposures that people may receive in practice. Throughout the document, skin colour is referred to as white, brown or black without reference to phototype or ethnic origin unless more precisely defined in the study by reference to the Fitzpatrick classification. Some studies only allow a white/non-white classification.

Chapter 3 considers the cutaneous synthesis and metabolism of vitamin D, dietary and supplemental sources, vitamin D status of the UK population and effects of vitamin D on skeletal health. It explains the analytical techniques for assessing vitamin D status and the limitations of interpreting studies that have used different analytical techniques. It considers the variations in vitamin D status in the UK population, demonstrating the complexities afforded by the UK's diverse ethnicity and lifestyles.

Chapter 4 considers the photobiological aspects of vitamin D. It covers the action spectrum of pre-vitamin D synthesis and the influence of spectral emission on vitamin D. It also considers the effects of external factors and personal and lifestyle attributes on UVR-induced vitamin D status including skin colour, age, surface area, sunscreen, genetics and obesity. It explains the effects of photoprotection and sun avoidance strategies on vitamin D status and the relative contributions of sunlight and diet to vitamin D status. It describes population subgroups that may have a different risk-benefit ratio for UVR exposure.

Chapter 5 covers the health impacts of vitamin D including impacts on skeletal health and potentially on other health outcomes including cancer and other systemic diseases. A distinction is drawn between established health effects and hypotheses with varying scientific support.

A summary of the report is given in Chapter 6.

Recommendations for further research are given in Chapter 7.

The report concludes with a number of appendices and a Glossary. Appendix A summarises the known adverse health effects of UVR, largely by reference to previous reviews of this field. Appendix B summarises the UK and international recommendations on serum 25(OH)D levels and dietary intakes. Appendix C lists publications of the Advisory Group on Non-ionising Radiation.

1.7 References

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2. Sources of ultraviolet radiation exposure

2.1 Introduction

The main source of ultraviolet radiation (UVR) contributing to personal exposure is the sun. Levels of solar UVR are generally at their highest during clear days in summer at and around solar noon, and unprotected exposure to UVR from the sun during such times contributes most to personal dose. The levels of solar UVR have been measured, albeit spasmodically, from two main standpoints. The first relates to obtaining baseline data on solar UVR at different geographical locations and the second relates to assessing the environmental impacts of stratospheric ozone depletion.

For some individuals, UVR from artificial sources could also contribute materially to their total exposure. Such sources of exposure include sunbeds used for cosmetic tanning and high intensity sources used in industry, including welding arcs, and those used in medical therapy. For occupational exposure, regulations limit the radiant exposure per working day. These exposure limits represent conditions under which it is expected that nearly all individuals may be repeatedly exposed without short-term adverse effects.

This chapter provides an overview of the potential sources of exposure to people from UVR, the response functions used to assess exposure and how the metrics may relate to weighted radiant exposures that people may receive in practice.

UVR forms the part of the electromagnetic spectrum with wavelengths from about 100 nm to 400 nm, as shown in Figure 2.1. However, wavelengths below about 180 nm are very strongly absorbed in air, so have no health implications from practical sources of exposure.

The International Commission on Illumination (CIE, from its French title Commission Internationale de l´Eclairage) has defined sub-regions of the UVR spectrum (CIE, 2011), which take account of the transmission of the UVR in human tissue and potential health effects, as follows.

UV-A (315 – 400 nm)
UV-B (280 – 315 nm)
UV-C (100 – 280 nm)

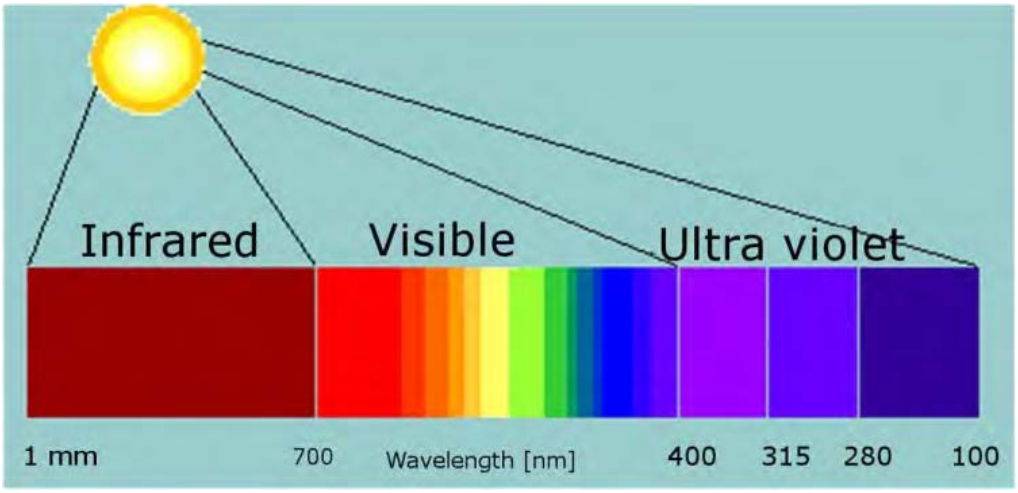

Figure 2.1: Optical radiation part of the electromagnetic spectrum

It should be noted that the visible optical radiation band (380 to 780 nm) overlaps with UV-A. Wavelengths down to 360 nm may be optically perceived, depending on the observer and the source radiance.

2.2 Exposures from the sun

The sun is the main source of UVR. The broad spectrum and intensity of the UVR emitted from the sun are due to its high surface temperature (approximately 5800 K). The quantity and spectral distribution of solar radiation at the Earth's surface depend on the power output of the sun, the path of the radiation through the Earth's atmosphere, and the transmission properties of the atmosphere. Solar UVR undergoes absorption and scattering as it passes first through the outer layers of the atmosphere, and then the stratosphere and the troposphere before reaching the Earth's surface (Figure 2.2).

The most important of these processes are absorption by molecular oxygen (O_2) and absorption by ozone (O_3). The boundary between the troposphere and the stratosphere is at approximately 10 km from the Earth's surface. The stratospheric ozone layer, formed between 10 and 40 km above the Earth's surface, prevents almost all UVR of wavelengths less than 290 nm and a substantial proportion (70%–90%) of UV-B radiation from reaching the Earth. Therefore, the ground level component of the solar UVR spectrum consists of wavelengths in the range from about 290 to 400 nm. Ground-level UVR consists of two major components, namely radiation received directly from the sun and radiation that has been scattered by the atmosphere. The ratio of the scattered to direct radiation varies with wavelength and with solar zenith angle (at 0° the sun is directly overhead and at 90° it is on the horizon from a horizontal viewpoint). The ratio increases as the wavelength decreases and the solar zenith angle increases: UV-B is scattered more than UV-A and the amount of scattering increases as the sun moves from overhead towards the horizon.

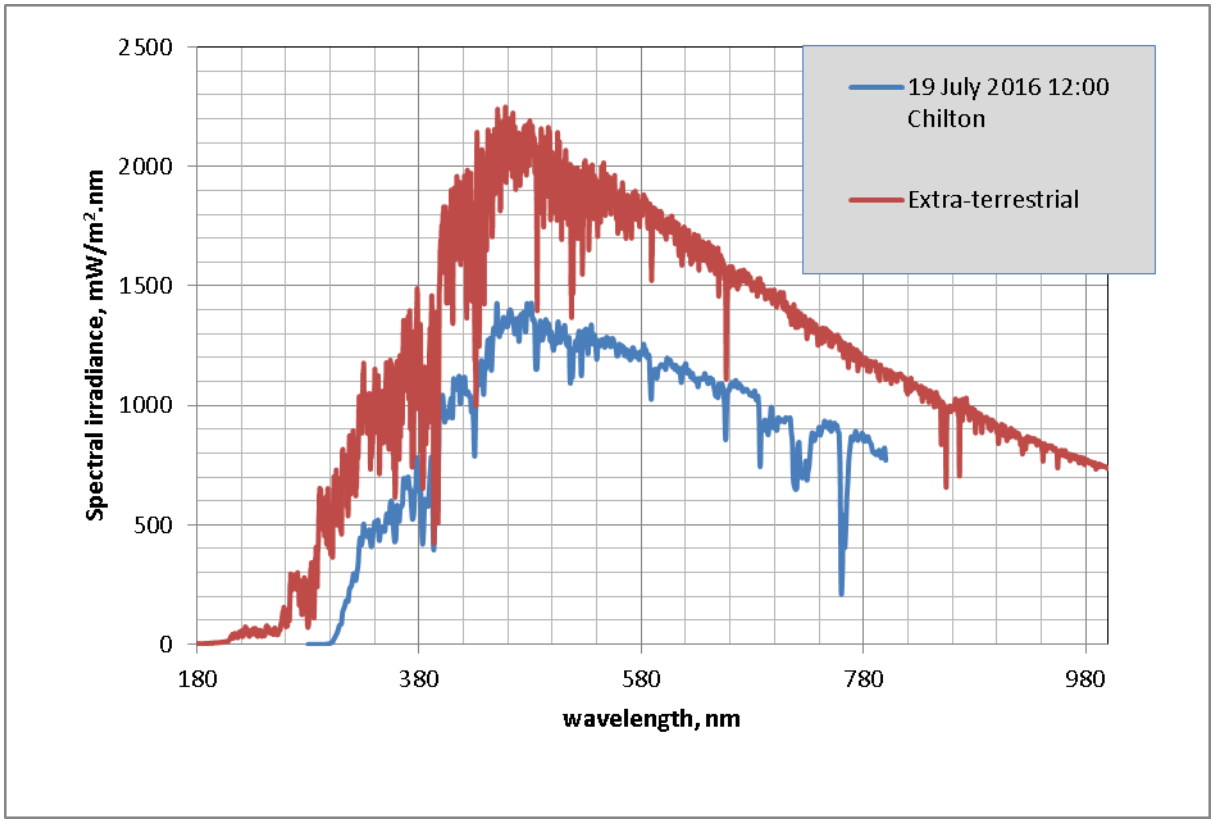

Figure 2.2: Solar radiation spectrum above the atmosphere and at ground level

The sea level spectral distribution in Figure 2.2 results from scattering of the incident radiation and absorption by specific molecules. The latter occurs at specific wavelengths of the incident radiation, producing narrow bands of high attenuation.

Stratospheric ozone depletion and the predicted associated increase in solar UVR reaching the Earth's surface have become major environmental issues. Although it is of value to investigate, monitor and model stratospheric ozone depletion and atmospheric changes, it is also important to assess the impact of atmospheric changes by measuring the levels of solar UVR at the Earth's surface. It is the amount of solar UVR at ground level rather than the status of stratospheric ozone *per se* that will determine the effects (positive and negative) on human health. Even when stratospheric ozone depletion is indicated over a region of the Earth's surface, it will not necessarily result in increased amounts of solar UVR at ground level. This is due to other atmospheric absorption and scattering processes, localised atmospheric pollution including, in particular, ozone in the troposphere, and cloud cover (Madronich et al., 1998). In terms of public health, of particular concern is an increase of solar UVR at times of the year when people have not been exposed to solar UVR for several months, such as in the Spring. Gies et al. (2013) and O'Hagan et al. (2013) have reported the impact of such events in Australia and the UK, respectively.

2.2.1 External factors

Human exposure to solar UVR depends on geographical location, altitude, time of day, time of year and cloud cover, and behavioural protective factors (Bergmanson and Sheldon, 1997). El Paso, which is at the same latitude (around 33°N) as Atlanta, Georgia, receives 38% more UVR, because of its greater altitude. Hawaii (around 20°N) receives ten times more UVR exposure than Alaska (greater than 55°N) because it is closer to the equator (Scotto, 1996). The highest reported level of surface UVR was on the Chatnantor Plateau in Chile (5100 m altitude, 23°S, 68°W) and was 0.5 W m^{-2} (Cordero et al., 2014).

In the UK, the spectral UVR irradiance (at a wavelength of 300 nm) is theoretically at a maximum at solar noon (GMT), when the solar zenith angle is at its lowest. This is of the order of ten times higher than that over the period before 09:00 GMT or after 15:00 GMT. Seventy per cent of the global UVR exposure (the integrated total exposure dose of biologically weighted UVR falling on a horizontal surface) is delivered during the four hours centred around solar midday. It should be noted, too, that spectral irradiance varies with wavelength, and increases more than 1000-fold between 290 and 310 nm.

2.2.1.2 Stratospheric Ozone

Ozone is present in the stratosphere in concentrations of about three molecules per 10^6 air molecules. The amount of ozone is specified in terms of a column of gas and is quantified by the Dobson Unit (DU). One DU is a 10 µm thick layer of ozone molecules under standard temperature and pressure or 2.69×10^{20} molecules per square metre in the column above that square meter. The ozone levels vary throughout the year, but are around a mean value of 320 DU in the UK.

2.3 Exposures from artificial sources

Artificial sources of optical radiation that emit UVR are commonplace. They include artificial tanning devices, security ink/paint illuminators, ink/dye/resin curing lamps, lamps for electrical insect killers, fluorescent lights, UV-A lamps in the entertainment industry and from welding arcs. UVR may be emitted from a source, either adventitiously or deliberately, for any one of many applications. There are few artificial sources that result in human exposure to UVR greater than that from solar radiation. However, exceptions are those used for medical therapy and diagnosis, cosmetic tanning and a few industrial sources, generally effectively enclosed, but where accidental exposure may occur. Worker exposure is subject to legislation in Europe (EC, 2006). A review of potential artificial sources of UVR is given in AGNIR (2002).

2.3.1 Sunbeds

Probably the highest personal exposure to artificial UVR for the public is from the use of artificial tanning equipment – sunbeds (horizontal) or sun cabins (vertical), which will be generically termed sunbeds here. The lamps used in sunbeds tend to fall into two main categories: those that are primarily UV-A emitters and those that emit a mixture of UV-A and UV-B (Figure 2.3). Sunbed B contains an older type of lamp, which emits UV-B in approximately the same proportion of UV-A as from a solar spectrum. Sunbed A is a refurbished installation with lamps primarily emitting UV-A.

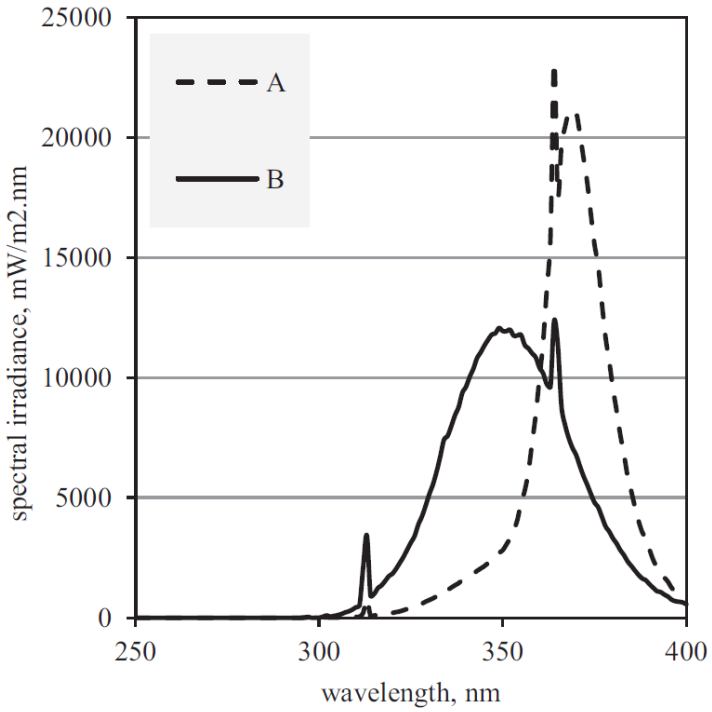

Figure 2.3: Spectral irradiance of sunbeds A and B: sunbed A had been retro-fitted with low UV-B lamps (from Khazova et al., 2015)

2.4 Skin types in relation to UVR exposure

Human skin varies greatly in response to UVR (see Appendix A). In general, there is a more damaging response in individuals who have very fair, genetically non-pigmented skin with relatively little ability to synthesise melanin after exposure to UVR from the sun. Tanning ability and burning after UVR exposure are inversely correlated. Table 2.1 shows the six skin phototypes commonly referred to in the literature.

Table 2.1: Summary of main characteristics of different skin types, based on Fitzpatrick (1988).

Skin type	Skin colour (Sun protected site)	Susceptibility to sunburn	1 MED (as SED)	Tanning ability	Susceptibility to skin cancer
I	White (very fair), often with freckles	Very readily	2 – 3	Never	Very high
II	White (fair)	Readily	3 - 4	Minimal	Very high
III	White	Moderately	4 - 5	Good	High
IV	Olive	Occasionally	5 - 6	Very good	Moderate
V	Brown	Rarely	8 -12	Excellent	Low
VI	Black/dark brown	Never/rarely	16 – 24	Excellent	Low

The terms standard erythemal dose (SED) and minimum erythemal dose (MED) are defined in the Glossary. Note that one SED is 100 J m^{-2} of UVR biologically weighted with the CIE action spectrum for erythema (section 2.5) and that there is considerable overlap of MED with different skin types.

Data for skin types I-IV in Table 2.1 are taken from Harrison and Young (2002). Data for skin types V and VI are estimated from Shih et al (2015). This study also showed that the imaging technique it was based on was more sensitive than visual determination of MED, especially for skin types V and VI. Note that there is considerable variation of published MED values for skin types V and VI.

2.5 Action spectra

The effectiveness of UVR at producing effects in people (and indeed other organisms) may vary with wavelength. Action spectra have been developed so that the UVR spectral irradiance incident on a person can be weighted and then summed. The summed value is then compared with a metric for benefit or harm. Three action spectra are relevant to this report: erythema (CIE, 1998), non-melanoma skin cancer (NMSC) (CIE, 2006a) and pre-vitamin D_3 production in the skin (CIE, 2006b). These are shown in Figure 2.4.

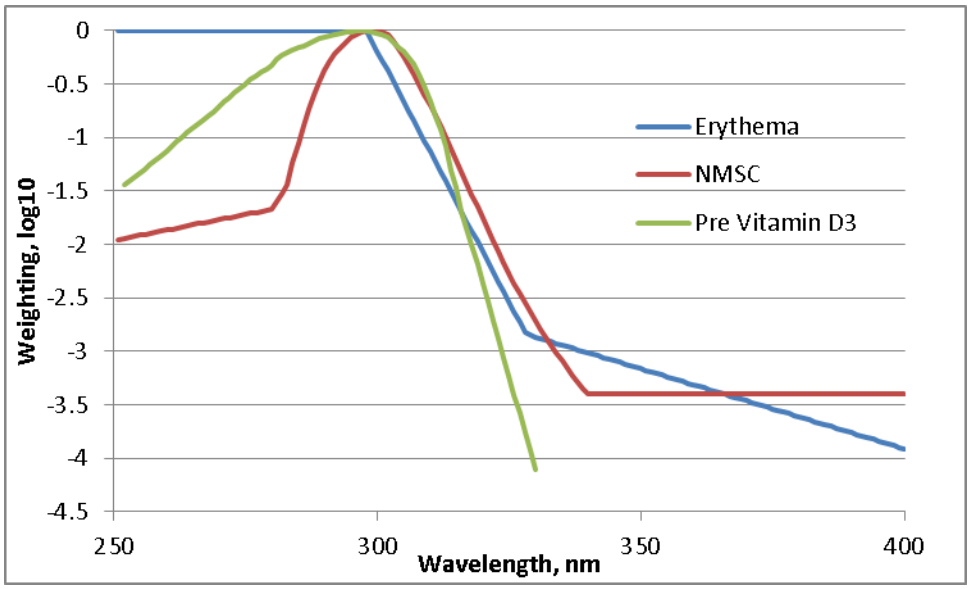

Figure 2.4: UVR action spectra for Erythema, Non-melanoma skin cancer (NMSC) and pre Vitamin D_3 production

2.6 Measurement of UVR, including personal exposures

Measurements of solar UVR have been made worldwide for many years. In the UK, both spectral and broadband ground-based solar UVR measurements are undertaken routinely. Spectral measurements are made at Reading (around 51.5°N), Chilton and Manchester, whilst broadband measurements are made across the UK. Trend data has been published (Smedley et al., 2011). The daily values of ozone vertical columns for Reading and the values of erythemally weighted UVR (UVR_{eff}) (which is affected by ozone depletion) to UV-A (320–400 nm) (which is relatively unaffected by ozone depletion) for Chilton are plotted in Figure 2.5.

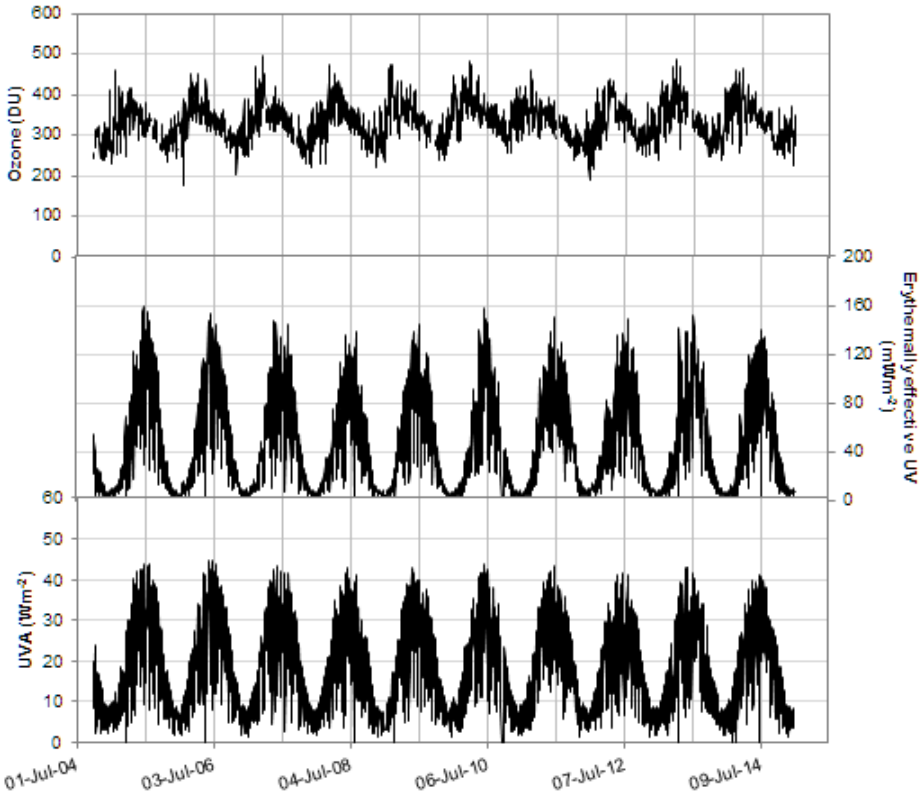

Figure 2.5: Total column ozone (Reading), erythemally effective UV and UV-A (Chilton)

Hooke et al. (2012) analysed the UV-B to UV-A ratio from spectral data measured at PHE Chilton from 2004 to 2008. The UV-B and UV-A spectral irradiances were weighted with the erythemal action spectrum before the ratios were calculated. Figure 2.6 shows the variation in peak ratio across a calendar year for each year from 2004 to 2008 and the average of these years.

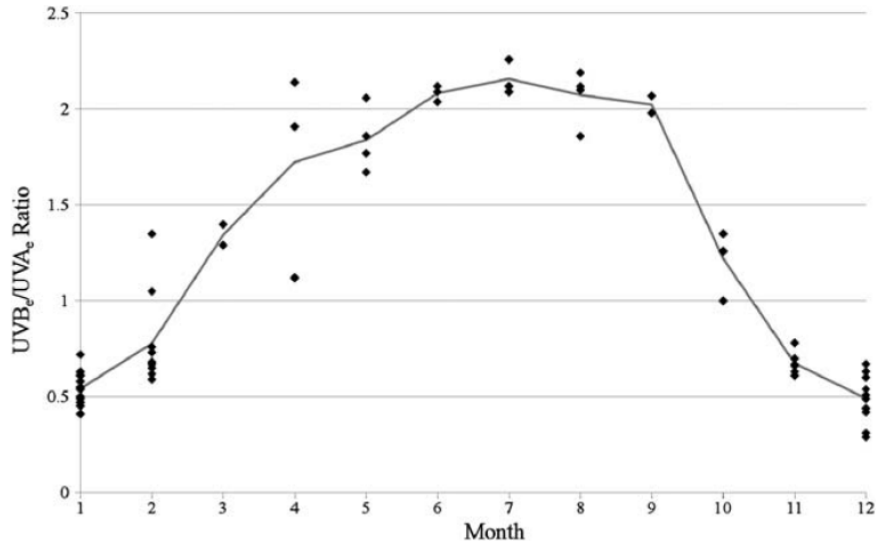

Figure 2.6: Peak UV-B/UV-A (erythemally weighted) on clear days from 2004 to 2008. Line indicates average monthly values

Broadband measurements (Hunter et al., 2011) of erythemally weighted UVR (UVR_{eff}) at PHE measurement sites across the UK from 1989 to 2008 show a statistically significant

upward trend in the annual UVR_{eff} of 1.68% per year and 1.36% per year for UV-A. The mean annual UVR_{eff} (SED, or standard erythema dose) (CIE, 1998) as a function of latitude across the UK is shown in Figure 2.7 for six measurement sites.

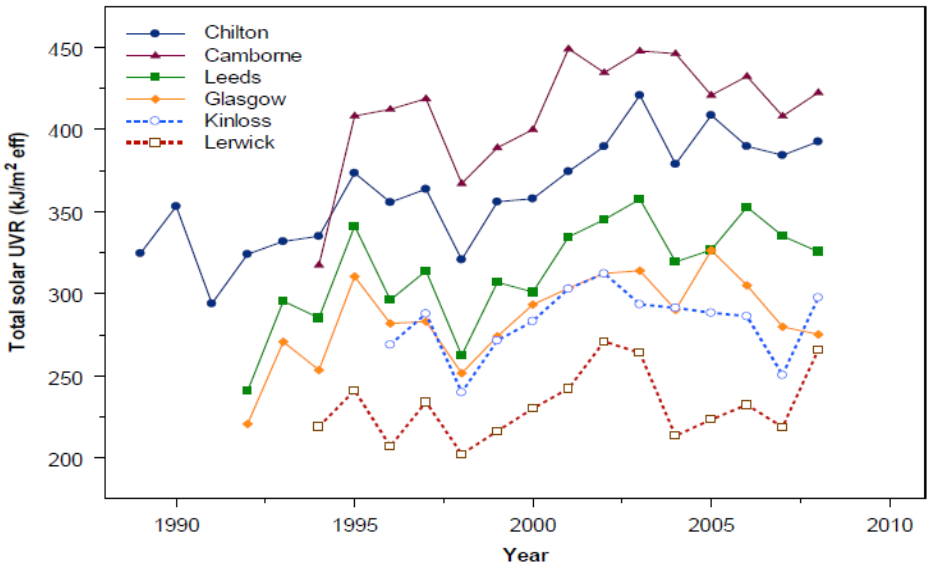

Figure 2.7: Total yearly erythemal UVR_{eff} data for six UK sites. Chilton (1989-2008), Glasgow (1992-2008), Leeds (1992-2008), Camborne (1994-2008) and Kinloss (1996-2008)

Erythemally weighted UVR levels can be expressed in terms of the UVR index (ICNIRP, 1995), which numerically equals 40 times the time-weighted average effective UVR irradiance (W m^{-2} eff).

Most studies of terrestrial UVR assess the UVR incident on a horizontal surface and weight the irradiance with the erythemal action spectrum. These assessments are only totally relevant to a person lying horizontal and apply to the skin that is exposed. Relating the horizontal irradiance to the actual radiant exposure received by a person is complex, due to the angle of exposure (to direct and scattered UVR) as a function of time, any protection measures applied and the proportion of skin exposed.

Spectral irradiance data for Chilton, UK (January and July), Izaña, Tenerife and Melbourne, Australia are shown for measurements close to solar noon in Figure 2.8.

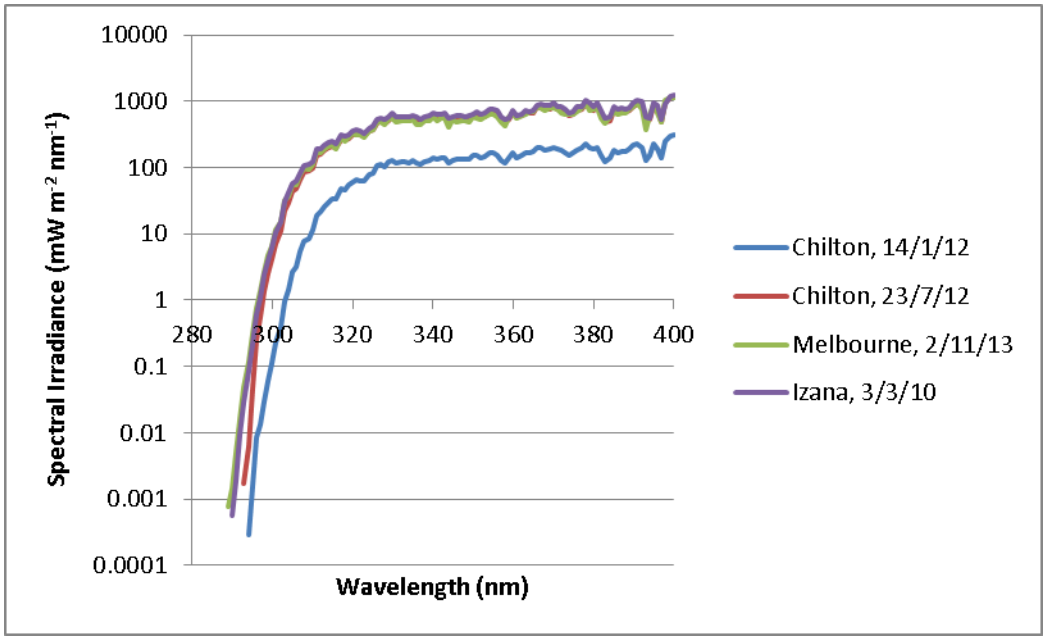

Figure 2.8: Solar spectral irradiance at Chilton (summer and winter), Melbourne (late spring) and Izaña (spring)

The lower wavelength edges of the spectra in Figure 2.8 are critically dependent on the path of the UVR through the stratospheric ozone layer, which itself is dependent on solar zenith angle, altitude and season. The data can be weighted for erythema – Figure 2.9 – or pre-vitamin D_3 – Figure 2.10.

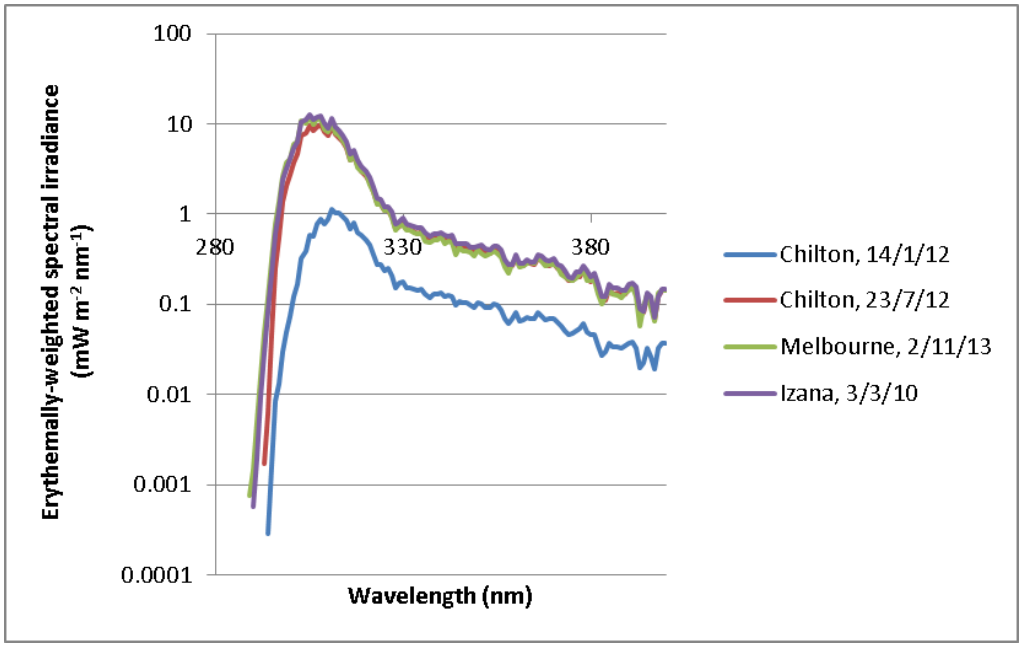

Figure 2.9: Spectral irradiance data from Figure 2.6 weighted for the erythema action spectrum shown in Figure 2.3

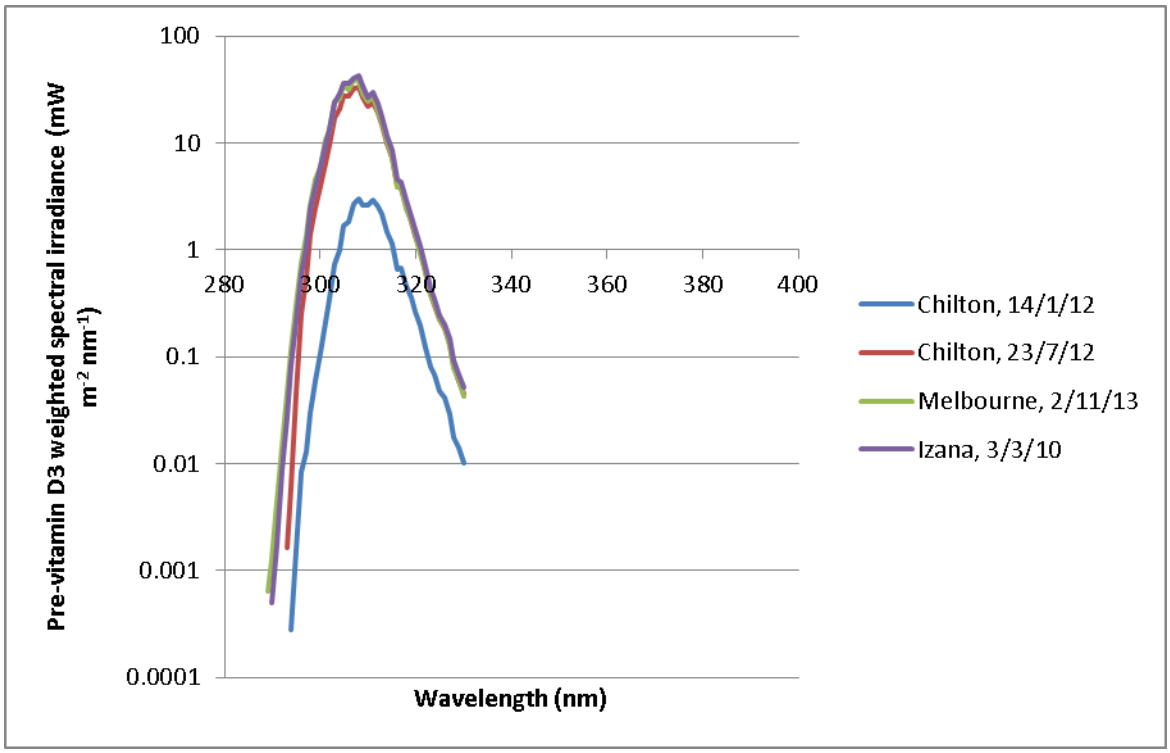

Figure 2.10: Spectral irradiance data from Figure 2.6 weighted for the pre-vitamin D_3 action spectrum shown in Figure 2.3.

The action spectrum for pre-vitamin D_3 is only currently defined up to 330 nm, which explains the cut-off in Figure 2.10. The weighted spectral irradiance values can be summed for comparison and the ratio of pre-vitamin D_3 to erythema weighted irradiance can be calculated (Table 2.2). It can be seen that the reduction in pre-vitamin D_3 weighted irradiance is greater from summer to winter than for erythemal weighting due to the pre-vitamin D_3 not taking account of UV-A.

UK citizens travelling to ski resorts or to hot countries will be exposed to solar radiation spectra that may be both greater in spectral irradiance, but also include wavelengths below those normally experienced in the UK, even in the peak of summer. Figure 2.11 shows a comparison of spectral irradiance measured on the island of La Reunion in the Indian Ocean (RU) with Izaña, Tenerife (IZ) in winter, an Austrian ski resort at the summit (Grafenberg) and in the valley below, with the UK (Chilton) in the summer and winter.

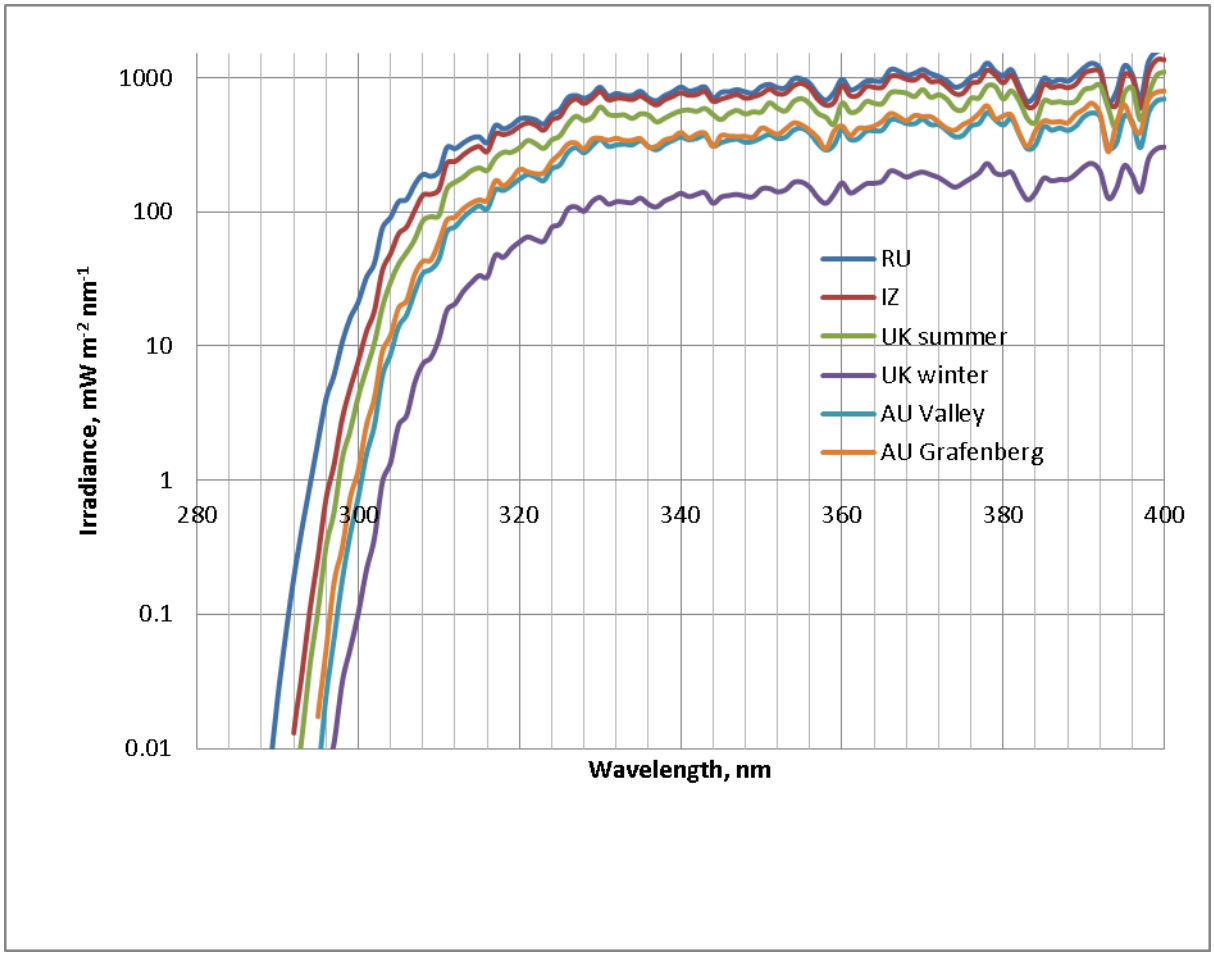

Figure 2.11: Spectral irradiance measured in the UK, La Reunion, Tenerife and Austria

The spectral irradiance values shown in Figure 2.11 can be weighted for erythema (Figure 2.12) and pre-vitamin D_3 production (Figure 2.13).

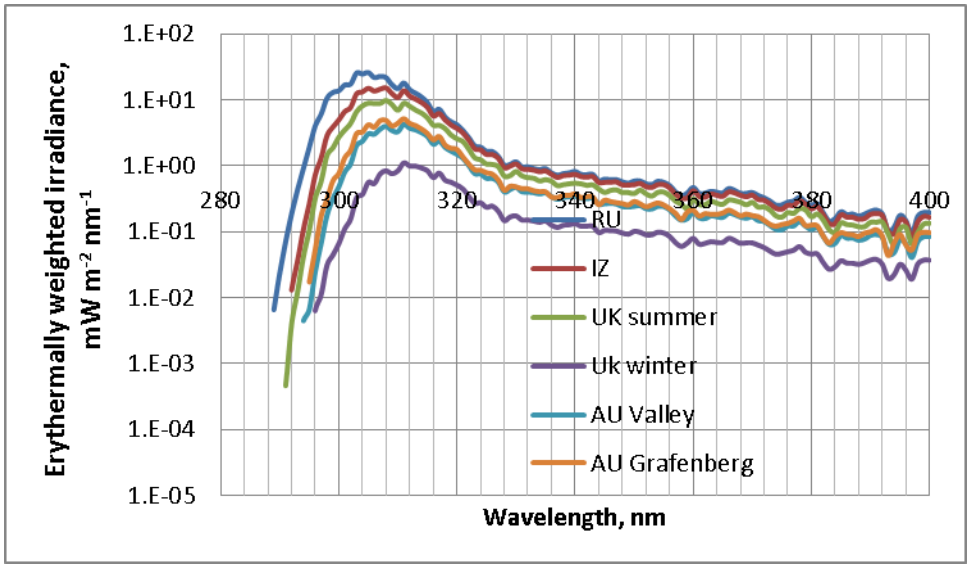

Figure 2.12: Erythemally weighted spectral irradiance from data in Figure 2.11

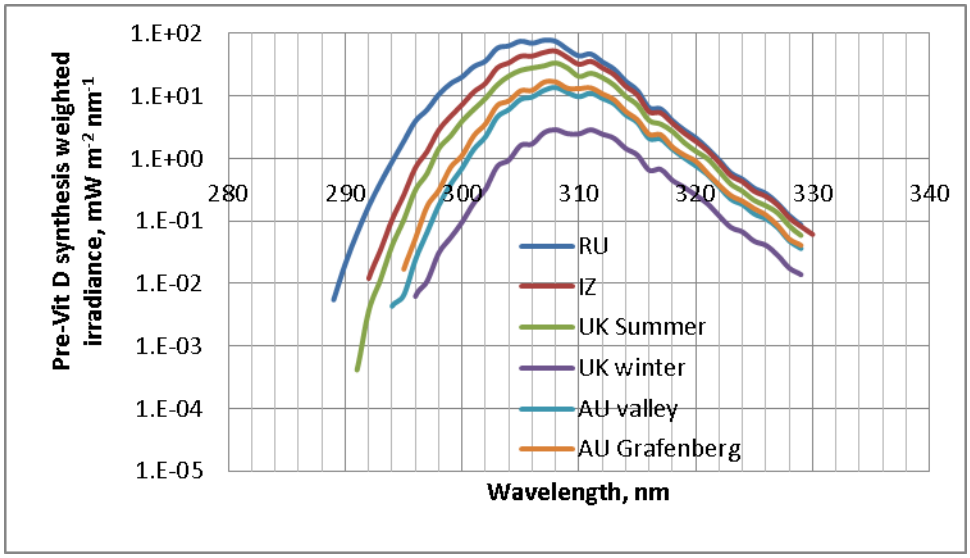

Figure 2.13: Pre-vitamin D_3 weighted spectral irradiance of data in Figure 2.11

Table 2.2: Weighted irradiances from figures 2.9, 2.10, 2.12 and 2.13

Site	Pre-vitamin D_3 weighted irradiance (mW m^{-2})	Erythemally weighted irradiance (mW m^{-2})	Ratio of Pre-vitamin D_3 to Erythemally weighted irradiance
Chilton (14/1/12)	30.2	21.5	1.40
Chilton (23/7/12)	232.0	169.8	1.90
Melbourne (2/11/13)	384.2	195.8	1.96
Izana (3/3/10)	415.5	212.7	1.95
La Reunion	812.7	402.3	2.02
Grafenberg peak	161.8	90.0	1.78
Grafenberg valley	127.3	74.9	1.70

The spectral irradiance from the sunbed measurements (Figure 2.3) can also be weighted with the erythemal and pre-vitamin D_3 action spectra. This is shown in figures 2.14 and 2.15, respectively.

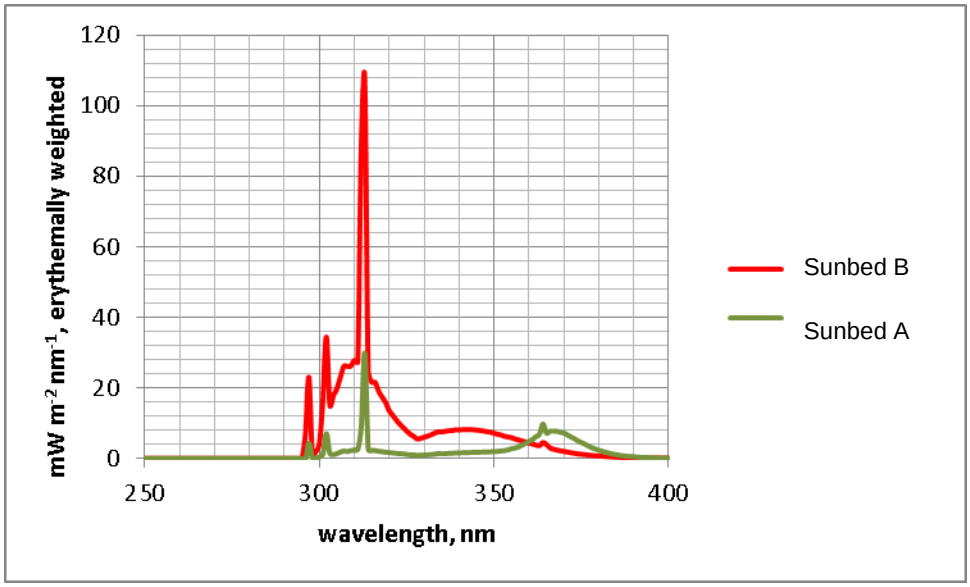

Figure 2.14: Sunbed lamp spectral irradiance, erythemally weighted

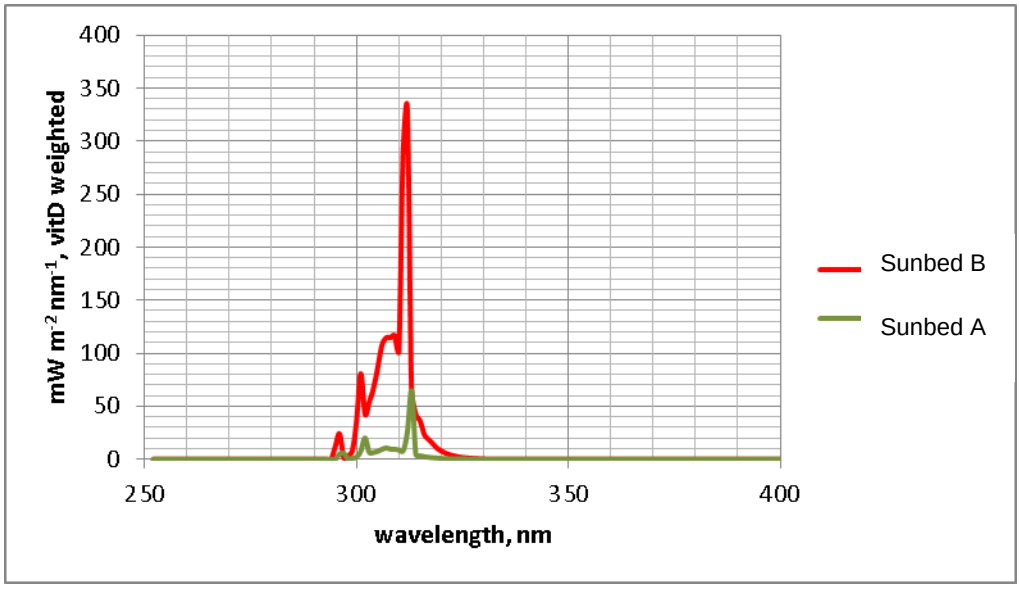

Figure 2.15: Sunbed lamp spectral irradiance, pre-vitamin D_3 weighted

Table 2.3: Analysis of weighted irradiances from figures 2.14 and 2.15

Site	Pre-vitamin D_3 weighted irradiance (mW m^{-2})	Erythemally weighted irradiance (mW m^{-2})	Ratio of Pre-vitamin D_3 to Erythemally weighted irradiance
Sunbed A	226	313	0.72
Sunbed B	1829	991	1.84

Table 2.3 shows that sunbed B has a similar pre-vitamin D_3 to erythemally weighted irradiance ratio to a solar spectrum. However, sunbed A, which is primarily a source of UV-A, is less effective for pre-vitamin D_3 production.

UVR assessment by installed active measurement systems tends to be carried out with the detector oriented in a particular plane – usually horizontal for solar UVR and perpendicular to the lamp plane for sunbeds. Detectors will ideally have a cosine response function with incident angle to mimic the transmission of UVR in the skin. However, personal exposure is rarely under the same conditions as these active measurement systems. For example, people move about and any exposed skin can be irradiated from a range of incident angles. People may also be wearing clothing, with a range of UVR (as a function of wavelength) transmission factors, sunscreen and hats or they may seek shade. Therefore, assessing the actual radiant exposure for a given period of time is complex.

Personal dosemeters are available for assessing erythemally weighted radiant exposure as a proxy for skin exposure. These may be integrating or may log the radiant exposure for specified integration periods over time intervals. These erythemally-weighted dosemeters may be used as an indicator for pre-vitamin D_3 production, assuming that the spectrum of the UVR is known.

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3. Overview of vitamin D and metabolism

3.1 Introduction

The cutaneous synthesis of vitamin D is the only proven beneficial biological effect arising from exposure to UVR. Vitamin D has an established role in calcium metabolism and skeletal health. Vitamin D can prevent and cure rickets – the classical childhood disease of vitamin D deficiency – and osteomalacia in children and adults. Other potential benefits of vitamin D have been hypothesised, including the possibility of protection against a range of cancers. Both the more and less established relationships are considered in this chapter. A schematic of vitamin D metabolism is included in section 3.3. Adverse effects of exposure to UVR are summarised in Appendix A.

Vitamin D takes two forms: ergocalciferol, also called vitamin D_2, and cholecalciferol, also called vitamin D_3. Both forms of vitamin D are equally effective in maintaining calcium metabolism, although not until converted to their active metabolites. Vitamin D_2 is synthesised in plants and fungi by irradiation of ergosterol. Vitamin D_3.is synthesised by UV irradiation of 7-dehydrocholesterol in the skin of humans and animals.

Generally, unless specifically identified, no distinction is made between vitamin D_2 and vitamin D_3 in the following discussion and the term vitamin D refers to either form (or both). Any vitamin D originating from endogenous cutaneous synthesis is vitamin D_3, whilst dietary sources of vitamin D, including supplements and fortification may be either vitamin D_2 or vitamin D_3.

Vitamin D is converted by vitamin D 25-hydroxylase in the liver to 25-hydroxyvitamin D (25(OH)D) (Wilkins et al., 2016). 25(OH)D is the circulating metabolite that is most commonly used as the marker of vitamin D status. 25(OH)D is converted by 25 vitamin D 1α hydroxylase in the proximal convoluted tubule of the kidney or by monocyte-macrophages and by other tissues to the active metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The enzyme that catalyses the conversion of 25(OH)D into $1,25(OH)_2D$ is stimulated by parathyroid hormone – the principal control hormone of plasma calcium secreted in response to a fall in serum calcium.

$1,25(OH)_2D$ acts at nuclear receptors to regulate transcription over a timescale of hours. In the small intestine it increases calcium ion uptake by increasing enterocyte synthesis of calbindin (a calcium shuttling protein) and both apical and basolateral calcium pumps, exchangers and channels (Ca^{2+} ATPase, Na^{+}-Ca^{2+} exchanger, epithelial Ca^{2+} channels). $1,25(OH)_2D$ acts in a similar way to increase Ca^{2+} and phosphate conservation in the distal tubules of the kidney. $1,25(OH)_2D$ action is necessary for the action of parathyroid hormone on bone. It acts to inhibit collagen synthesis by osteoblasts and induce differentiation and action of osteoclasts to increase Ca^{2+} loss into the circulation.

Serum Ca^{2+} can be within the normal range even when levels of 25(OH)D are very low. In children vitamin D deficiency can lead to rickets, renal rickets and vitamin D resistant rickets. In adults and children deficiency can cause osteomalacia. Very large intakes of vitamin D can cause vitamin D toxicity which can lead to symptoms of hypercalcaemia eg renal stones.

3.2 Analytical techniques for vitamin D measurements

Measurement of serum 25-hydroxyvitamin D (25(OH)D) concentration is considered to be the best and most reliable clinical indicator of vitamin D status because it has a long half-life in the circulation (about 2-3 weeks) and is not subject to tight homeostatic control. Two forms of 25(OH)D exist in the circulation. $25(OH)D_3$ (cholecalciferol) is derived from the action of sunlight on the skin and conversion of the vitamin D_3 in the liver, although small amounts can be obtained from the diet (eg oily fish) and from supplements. $25(OH)D_2$ (ergocalciferol) is derived from plant sources and is mainly obtained from supplements. 'Total' serum 25(OH)D (ie comprising the sum of $25(OH)D_2$ and $25(OH)D_3$) is used diagnostically and clinically, as well as in the derivation of dietary reference values for vitamin D. In population studies, particularly national nutrition and health surveys, it may be useful to know the serum concentrations of these two metabolites separately; however, some immuno-assays do not detect 100% of $25(OH)D_2$.

The hormonally active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), circulates at 1000-fold (pmol L^{-1}) lower concentration than 25(OH)D, has a short half-life and is very tightly regulated (Fraser and Milan, 2013). Assays for $1,25(OH)_2D$ are specialised, technically difficult and should not be used to assess vitamin D sufficiency. $1,25(OH)_2D$ assays may be useful in connection with hyper- or hypo-parathyroidism, renal disease or sarcoidosis.

Several techniques are currently used to measure 25(OH)D, each with advantages and disadvantages (Carter, 2012; Granado Lorencio et al., 2013). These can be divided into two groups: immunochemical methods, based on radioactive, enzymatic or chemiluminescence detection, and which can be manual or automated; and chromatographic/physical detection methods, High Performance Liquid Chromatography (HPLC), LC-Mass Spectrometry (MS) and LC tandem MS (LC-MS/MS).

Modern immunoassays (IA) have the advantage of being simple to use, quick and have a high throughput, which has made them extremely popular. The majority of the data collected over the past 20 to 30 years has been from antibody-based assays. However, automated immunoassays may be affected by lot-to-lot variation and, as they are non-extraction assays, are subject to serum matrix effects that can lead to wide discrepancies in individual samples. These immunoassays measure total 25(OH)D; however not all antibodies cross-react equally with $25(OH)D_2$ compared to $25(OH)D_3$, which can lead to underestimation of total 25(OH)D. Immunoassays may also be affected by the vitamin D binding protein concentration (Heijboer et al., 2012) and other cross-reacting metabolites (eg 24,25-dihydroxyvitamin D), which can contribute to a positive bias in serum 25(OH)D concentrations relative to chromatographic methods.

The preferred methods for measurement of 25(OH)D are chromatographic methods, These employ sample extraction, chromatography and correction for procedural losses. They have the advantage of being able to measure $25(OH)D_2$ and $25(OH)D_3$ separately and are not subject to matrix effects. LC-based assays which use a tandem mass spectrometer (LC-MS/MS) allow discrimination between $25(OH)D_2$ and $25(OH)D_3$ and most other compounds by their unique molecular masses and mass fragments (Makin et al., 2010). However not all laboratory MS methods resolve 3-epi-25(OH)D (not detected by IAs) from $25(OH)D_3$ (Heijboer et al., 2012) [which is present in most paediatric samples and samples from some adults] nor other potentially interfering isomers that may co-elute with $25(OH)D_3$ (Shah et al., 2011) leading to overestimation of $25(OH)D_3$. Most recent methods employ short LC retention times, and in some cases automated robotic extraction and LC separation steps with computerised MS systems, and thus can be made relatively operator-free and provide high throughput. Their potential advantages include high specificity, high sensitivity, and better reproducibility (<10%). The consensus among analysts is that LC-MS/MS assays will become the 'gold standard' for assay performance in the future (de la Hunty et al., 2010; IOM, 2011).

A major concern with all these assays has been the reliability and comparability of the different techniques (Carter et al., 2004). Analytical uncertainties in published 25(OH)D measurements have made it very difficult to compare data across countries or combine datasets. However the role of standard reference materials and inter-laboratory collaboration and quality assurance schemes is an important aspect of overcoming the challenges that the different assay methodologies present.

The wide variation in measurements of serum 25(OH)D concentrations, made using different methods and in different laboratories, should be taken into account in the interpretation of studies that have examined the relationship between serum 25(OH)D concentration and health outcomes. If data from different studies are to be combined and interpreted with confidence, it is important that the assays used measure the same metabolite(s) and deliver comparable results.

The Vitamin D External Quality Assurance Scheme or DEQAS (Charing Cross Hospital, London, UK) established in 1989 now includes approximately 980 laboratories worldwide (Carter et al., 2010). It serves as a quarterly monitor of performance of both analysts and 25(OH)D analytical methods. Since it was established there has been a gradual improvement in the inter-laboratory comparability and imprecision although some method biases in terms of accuracy and precision as well as variability remain as high as 15-20%. However, some skilled analysts can perform better than this with a coefficient of variation less than 10%.

The introduction of the National Institute of Standards and Technology (NIST) reference standards, calibrated using a 'validated' LC-MS/MS method (Phinney, 2009) suggests that the variability of all methods will be improved in the future and that an improvement is already occurring (Carter and Jones, 2009). From 1st January 2015 manuscripts reporting sex steroid assays as important end points in the Journal of Clinical Endocrinology and Metabolism must use MS-based assays and it is likely that, in the near future, this requirement will extend to other journals and to vitamin D metabolites (Handelsman et al., 2013).

The issue of international standardisation of serum 25(OH)D measurement is also being progressed by the Vitamin D Standardization Program, a collaborative initiative between the Office of Dietary Supplements of the National Institutes of Health, the Centers for Disease Control and Prevention, the NIST and a number of the national health surveys around the world (VDSP, Federal Register, 2011; Sempos and Binkley, 2014). The International quality assurance/collaboration schemes, such as DEQAS and VDSP as well as existing and next generation standard reference materials for 25(OH)D, will further help limit inter-laboratory assay-specific differences in this status marker.

3.3 Cutaneous synthesis/metabolism of vitamin D

Human skin has two main layers: the inner thicker dermis that is mostly extracellular matrix (eg collagen) that gives skin its mechanical properties and the outer thinner cellular epidermis of which keratinocytes are the main cell type. The epidermis (see Figure 3.1) can be sub-divided into five strata from the inner to the outer; stratum basale, stratum spinosum, stratum granulosum, stratum lucidum and the stratum corneum. Overall, this has a thickness of about 10 cell layers and typically <100 μm. New keratinocytes are formed from stem cells in the stratum basale and undergo progressive terminal differentiation until they are shed (desquamation) from the dead compacted stratum corneum. The epidermis also contains a few other types of cells. Melanocytes are melanin producing dendritic cells located in the stratum basale. Their dendrites transfer melanin to keratinocytes. Skin colour depends on the degree of melanocyte activity (melanogenesis).

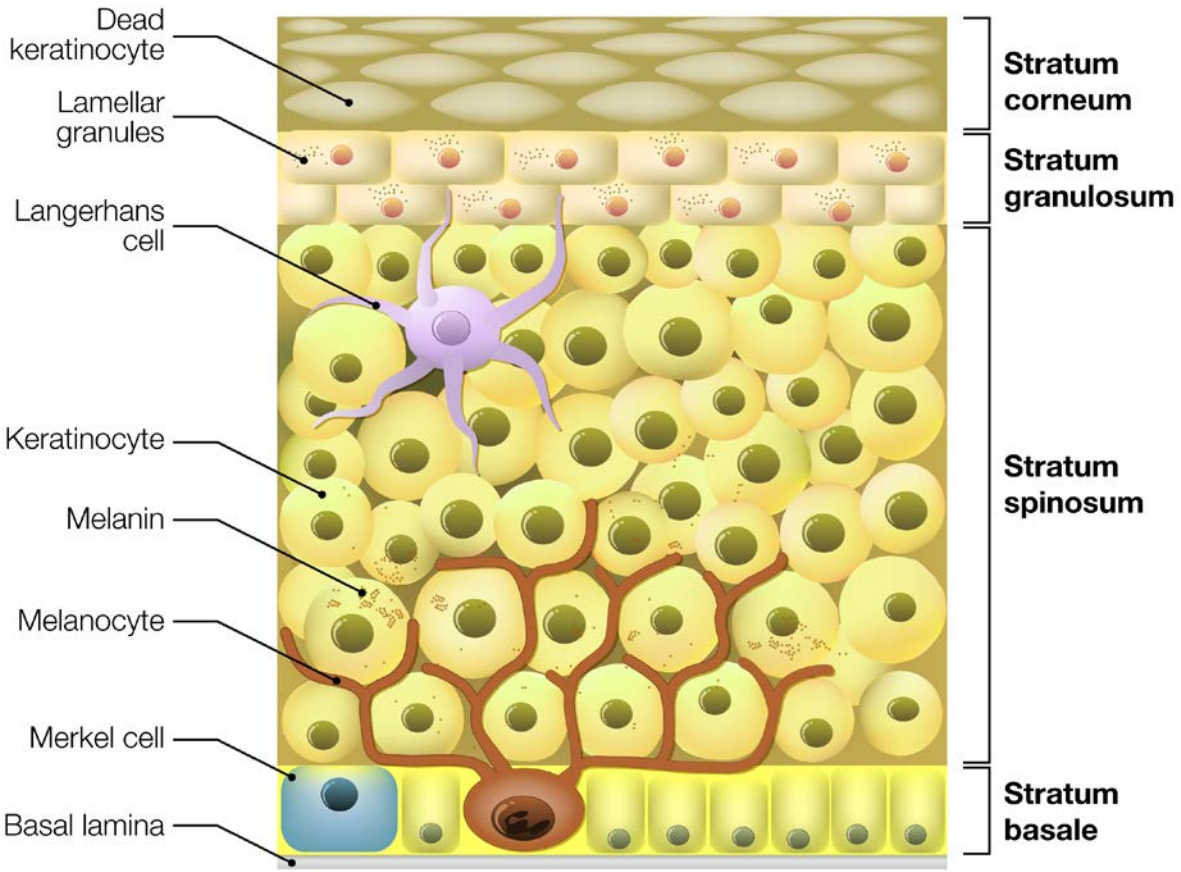

Figure 3.1: Cross section through the skin showing structural elements including those relevant to vitamin D synthesis and metabolism. NB: stratum lucidum not shown.

Photobiological processes are initiated by the absorption of optical radiation by skin chromophores (Young, 1997) that have characteristic UV and/or visible radiation absorption spectra. Whereas UVR has several adverse effects on health (Appendix A), initiation of cutaneous vitamin D synthesis is the established health benefit. A summary of the vitamin D_3 (hereafter referred to as vitamin D) synthesis pathway is shown in Figure 3.2. The chromophore for the production of vitamin D in the skin is 7-dehydrocholesterol (7-DHC), found primarily in the epidermis. 7-DHC, found in high concentration in cell membranes, is a metabolite in the biosynthetic pathway for cholesterol, the synthesis of which occurs *de novo* from acetyl-CoA in keratinocytes (Glossmann, 2010). 7-DHC is also known as pro-vitamin D. Absorption of UV-B (280-315 nm) by 7-DHC results in its photoconversion to pre-vitamin D.

Body heat induces the conversion of pre-vitamin D to vitamin D, which takes about three days. (Holick et al., 1980). Vitamin D passes via the dermis into the circulation carried by vitamin D binding protein (VDP). It becomes biologically active, as a steroid hormone, after two hydroxylation steps; the first in the liver (regulated by D-25 hydroxylase (25-OHase)) and the second in the kidneys (regulated by 25(OH)D-1α hydroxylase (1α-OHase), as shown in Figure 3.2. This second step is under homeostatic regulation by parathyroid hormone (PTH) released from the parathyroid glands. However, both enzymatic steps also occur in other tissues. For example, epidermal keratinocytes can metabolize pre-vitamin D via D-25 hydroxylase and 25(OH)D-1α hydroxylase to form the active metabolite 1α,25$(OH)_2$D which plays an important role in keratinocyte differentiation. The keratinocyte enzymes are the same as those found in the liver (CYP27 gene) and kidney (CYP27B1 gene) (Bikle, 2004). Recent studies suggest that 1α,25$(OH)_2$D enhances the repair of DNA photodamage in cultured keratinocytes (Gordon-Thomson et al., 2012).

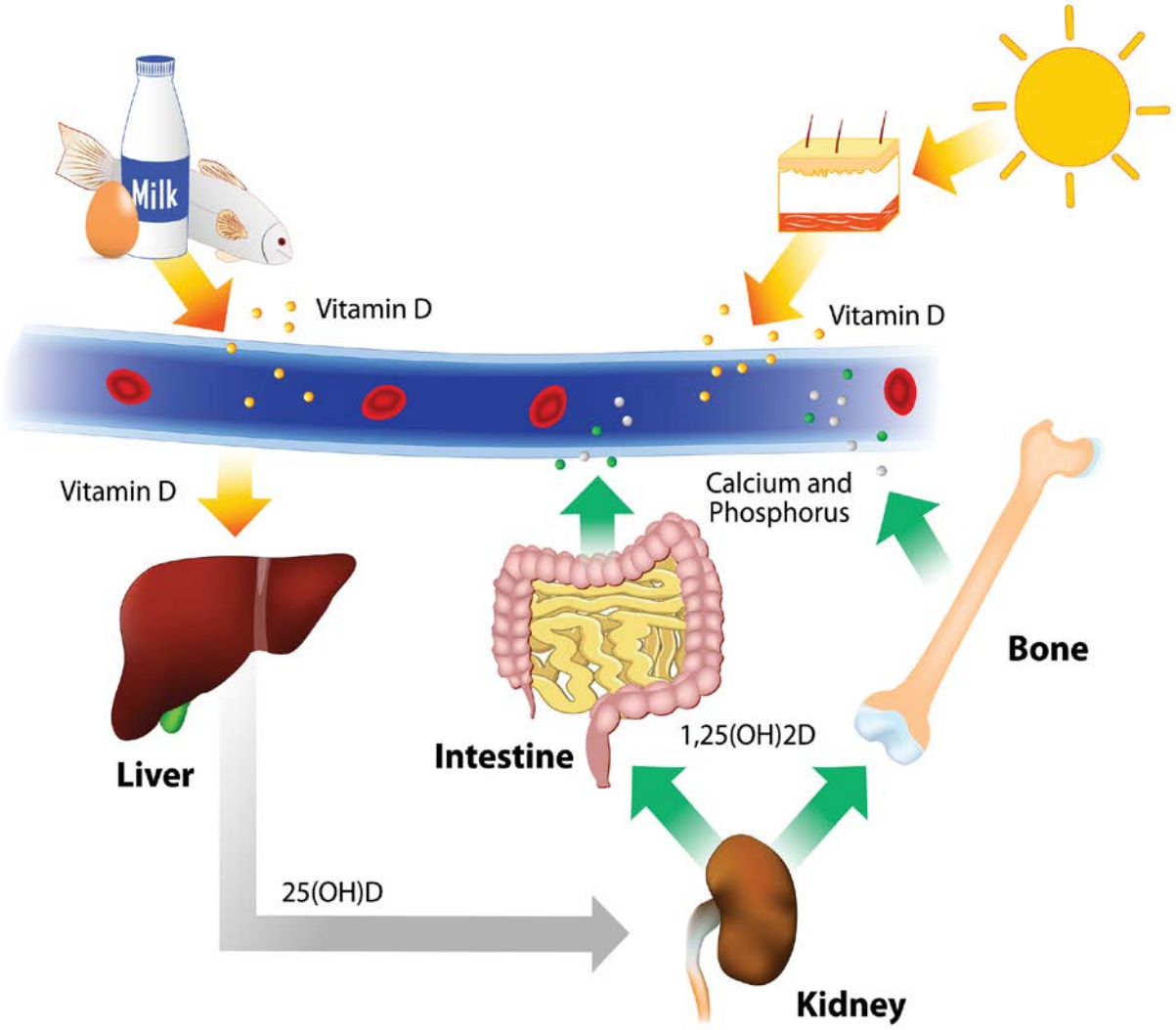

Figure 3.2: Summary of the vitamin D_3 synthesis pathway

There are few studies on the location of 7-DHC within the skin. The highest concentrations of 7-DHC are reported to be in the stratum basale (303 ng cm^{-2}) and stratum spinosum (393 ng cm^{-2}) (Holick et al., 1980) where most of the synthesis of pre-vitamin D takes place, with a much smaller amount in the strata corneum and granulosum combined (58 ng cm^{-2}). However, a small amount of 7-DHC has also been reported in the dermis, which can be photo-converted into pre-vitamin D *in vitro* (MacLaughlin and Holick, 1985). The concentration of 7-DHC in the overall epidermis and in the stratum basale (other strata not measured) declines steeply with age, along with the ability to photosynthesize pre-vitamin D. In contrast, age has been reported to have little effect on 7-DHC in the dermis (MacLaughlin and Holick, 1985). Other factors that modify vitamin D synthesis are discussed in section 4.6.

Other vitamin D related photochemical reactions occur in the skin in addition to 7-DHC → pre-vitamin D, which can be reversed by UV-B (Galkin and Terenetskaya, 1999; Norval et al., 2010). Pre-vitamin D can be converted to lumisterol, tachysterol and toxisterols and *vice versa* by UV-A and UV-B and vitamin D can be photoconverted to suprasterol I and II and 56-transvitamin D. The biological functions of these reaction products are not known. It has been argued that the photodegradation of vitamin D is a homeostatic process to regulate vitamin D (Webb et al., 1989). This may explain why vitamin D toxicity from solar UVR does not occur.

The relationship between vitamin D intake and plasma / serum 25(OH)D concentration has been described in many randomised controlled trials (see for example Cranney et al., 2007; Seamans and Cashman, 2009; Aloia et al., 2008; IOM, 2011; Gallagher et al., 2013; Gallagher et al., 2014; Heaney et al., 2003; Ng et al., 2014) and is summarised in the Scientific Advisory Committee on Nutrition's report on vitamin D and health (2016).

3.4 UK population vitamin D status

Data on the vitamin D status of the general population in the UK were obtained from the National Diet and Nutrition Survey (NDNS) rolling programme, a continuous survey of diet and nutrition in adults and children aged 18 months upwards (results from 2008/09-2011/12 combined Bates et al., 2014), the Health Survey for England (HSE, Craig et al., 2005) and the Scottish Health Survey (SHS, Bromley et al., 2011).

Data on infants and young children (aged 4-18 months) were obtained from the 2011 UK Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (Lennox et al., 2013).

The ethnic profile of the sample in the DNSIYC was very close to that of the population of infants and children in the UK, with 82% of children classed as white, 8% Asian, 3% black and 7% mixed race or other. No information was available on the ethnic profile of the samples in the NDNS, the HSE or the SHS.

Nationally representative data are not available for pregnant or lactating women; therefore data from UK based cohort studies are reported below.

In the UK the Committee on Medical Aspects of Food Policy (COMA) in its 1991 report defined low vitamin D status as a plasma 25(OH)D concentration below 25 nmol L^{-1}. This was endorsed by the Scientific Advisory Committee on Nutrition (SACN) in its 2007 report. As a result, surveys frequently report the proportion of the population with plasma/serum 25(OH)D levels below 25 nmol L^{-1}.

3.4.1 Infants and young children

In the DNSIYC, the mean plasma 25(OH)D concentration for infants and young children aged 5-18 months was 66.5 nmol L^{-1}, with 6% of infants aged 5-11 months, and 2% of infants aged 12-18 months having a plasma 25(OH)D concentration below 25 nmol L^{-1} (Lennox et al., 2013).

Plasma 25(OH)D concentration was not analysed for seasonal variability in the DNSIYC; however it has previously been reported to be dependent on season in children aged 1.5-4.5 years in the UK (Davis et al., 1999).

A population survey of 2 year old children of Bangladeshi, Indian, or Pakistani origin living in England (n=618), found that 20-34% had serum 25(OH)D concentrations below 25 nmol L^{-1} (measured during October to November 1996) (Lawson and Thomas, 1999). This compared with 1% of children aged 1.5-4.5 years (measured October to December) in the NDNS sample in which the children were predominantly white (Gregory et al., 1995).

3.4.2 Older children

In the NDNS, the mean plasma 25(OH)D concentration in 4-10 year olds was 52.3 nmol L^{-1} for boys and 48.0 nmol L^{-1} for girls with around 14% of 4-10 year olds having a 25(OH)D concentration below 25 nmol L^{-1} (Bates et al., 2014).

For 11-18 year olds, the mean plasma 25(OH)D concentration was 44.9 nmol L^{-1} for boys and 41.1 nmol L^{-1} for girls, with around 22% of 11-18 year olds having a 25(OH)D concentration below 25 nmol L^{-1} (Bates et al., 2014) (Table 3.1).

A study of adolescent girls aged 14.7-16.6 years living in Manchester (n=51) found that 73% had a plasma 25(OH)D concentration below 30 nmol L^{-1} and 17% had a concentration below 12.4 nmol L^{-1} (Das et al., 2006).

3.4.3 Pregnant and lactating women

A study in North West London analysed serum 25(OH)D concentrations of pregnant women by season (n=346; mixed ethnicity) (McAree et al., 2013). Thirty six percent of women had a serum 25(OH)D concentration below 25 nmol L^{-1}, 45% had a concentration between 25-75 nmol L^{-1} and 18% had a concentration above 75 nmol L^{-1} on their first antenatal appointment. Mean concentrations were 38 nmol L^{-1} in summer (July-September), 38 nmol L^{-1} in autumn (October-December), 26 nmol L^{-1} in winter (January-March) and 32 nmol L^{-1} in spring (April-June). The percentage with serum 25(OH)D concentration below 25 nmol L^{-1} ranged from 29% in the summer to 49% in the winter.

When analysed according to Body Mass Index (BMI), women with a BMI of more than 30 kg m^{-2} had significantly lower serum 25(OH)D concentrations than women with a BMI below 30 kg m^{-2}.

25(OH)D concentration was also analysed according to skin colour. Women with dark skin colour (listed as of African, Afro Caribbean and Asian ethnicity) had significantly lower serum 25(OH)D concentrations (8% 25(OH)D >75 nmol L^{-1}) compared with women with light skin colour (listed as of White British, Irish and White European ethnicity) (43% 25(OH)D >75 nmol L^{-1}).

In the Southampton Women's Survey, blood samples of pregnant women (n=977; predominantly white) were taken at 35 weeks gestation. The median serum 25(OH)D concentration was 62 nmol L^{-1}, and 35% had a serum 25(OH)D concentration below 50 nmol L^{-1} (Crozier et al., 2012).

Blood samples (taken throughout the year) were also available for pregnant women (n=369; predominantly white) taking part in the ALSPAC study 1991/1992 (Lawlor et al., 2013). Median serum 25(OH)D concentrations were 55.1, 60.1 and 67.4 nmol L^{-1} in the first, second and third trimesters respectively. In the third trimester, 34% of women had a serum 25(OH)D concentration below 50 nmol L^{-1} and 6% below 27.5 nmol L^{-1}.

3.4.4 Adults aged 19-64 years

In the NDNS, mean plasma 25(OH)D concentration was 43.5 nmol L^{-1} for men and 47.3 nmol L^{-1} for women 19-64 years, with around 23% of the adult population having a plasma 25(OH)D concentration below 25 nmol L^{-1} (Bates et al., 2014) (Table 3.1).

The percentage of the population aged 19-64 years with a plasma 25(OH)D concentration below 25 nmol L^{-1} in July to September was 8.4% rising to 39.3% in January to March (Bates et al., 2014) (Table 3.2).

A regional difference in the percentage of the adult population with a plasma 25(OH)D below 25 nmol L^{-1} concentration was found in the HSE and the SHS. The percentage of the population with a plasma 25(OH)D concentration below 25 nmol L^{-1} ranged from 15.1% in the South west of England to 34.8% and 33.0% in London and Scotland respectively (Table 3.3).

A study in Surrey (Latitude 51°N) of premenopausal women (n=140) compared serum 25(OH)D concentrations in South Asian women with concentrations in Caucasian women (Darling et al., 2014). South Asian women had lower serum 25(OH)D concentrations than Caucasian women in every season, with 95 to 96% of South Asian women having a serum 25(OH)D concentration below 50 nmol L^{-1} throughout the whole year.

3.4.5 Adults over 65 years

In the NDNS, mean plasma 25(OH)D concentration was 47.0 nmol L^{-1} for men and 42.5 nmol L^{-1} for women aged 65 years and older, with about 21% having a plasma 25(OH)D concentration below 25 nmol L^{-1} (Bates et al., 2014) (Table 3.1).

Serum 25(OH)D concentration was measured in the over 65s living in private households and institutions in the 2000 HSE. The mean serum 25(OH)D concentrations for men and women in institutions were 38.1 nmol L^{-1} and 36.7 nmol L^{-1} respectively, compared with 56.2 nmol L^{-1} and 48.4 nmol L^{-1} for men and women living in private households (Hirani and Primatesta, 2005).

For those living in institutions, the prevalence of serum 25(OH)D concentration below 25 nmol L^{-1} was 30.2% for men and 32.5% for women compared with 9.6% of men and 15.0% of women living in private households (Hirani and Primatesta, 2005).

3.4.6 Serum 25(OH)D concentration by Body Mass Index (BMI)

Vitamin D is fat soluble and is stored in body tissues. Adipose tissue was seen to be the major site of accumulation of injected radioactive vitamin D in human tissues (Mawer et al., 1972). A number of studies have reported adiposity and body mass index to be inversely related to serum 25(OH)D concentrations (Parikh et al., 2004; Snijder et al., 2005; Arunabh et al., 2003; Liel et al., 1988) suggesting that vitamin D is not readily available from adipose tissue and that because of its lipophilic nature, it is sequestered rather than stored. This is supported by some studies that reported increases in serum 25(OH)D concentrations with weight reduction in obese individuals (Zitterman et al., 2009; Tzotzas et al., 2010).

Details about accumulation and mobilisation of vitamin D stores from adipose tissue and other tissues such as muscle are not clear at this time (IOM, 2011).

In the SHS, the mean 25(OH)D concentration was 41 nmol L^{-1} for those with a BMI of less than 25 kg m^{-2}, 38.5 nmol L^{-1} for those with a BMI of 25 kg m^{-2} to less than 30 kg m^{-2} and 33.3 nmol L^{-1} for those with a BMI of 30 kg m^{-2} or more (Table 3.4). More people with a BMI of 30 kg m^{-2} or more had a 25(OH)D concentration below 25 nmol L^{-1} (38%) compared with those with a BMI of 25-29 kg m^{-2} (28%) and those with a BMI of less than 25 kg m^{-2} (33%).

3.4.7 Genetic influences on vitamin D

Twin and family studies suggest a genetic component to the inter-individual variability in serum 25(OH)D concentrations. Rates of heritability have been estimated to range from 29 to 80% (Shea et al., 2009; Hunter et al., 2001).

Rare mutations in genes involved in vitamin D metabolism lead to functional vitamin D deficiency. For example, mutations in the genes coding for CYP27B1 and VDR cause vitamin D dependent rickets type I (VDDR I) (Fu et al., 1997) and vitamin D dependent rickets type II (VDDR II) (Malloy et al., 1999) respectively. Rare mutations in the DHCR7 gene cause Smith-Lemli-Opitz syndrome, characterised by reduced activity of 7-DHC reductase, accumulation of 7-DHC, low cholesterol and many congenital abnormalities (Tint et al., 1994).

A number of polymorphisms, genetic variants that occur at a frequency of at least 1% in the population, in genes encoding proteins involved in vitamin D metabolism have been identified. Two meta-analyses of genome-wide association studies (Ahn et al., 2010; Wang et al., 2010) examined the influence of single nucleotide polymorphisms in such genes on serum 25(OH)D concentrations. Ahn et al. (2010) included 9 cohort studies from the United States and Finland (discovery sample, n = 4501; replication sample, n = 2221). Genome-wide significant associations with serum 25(OH)D concentration were found for single nucleotide polymorphisms identified in the genes encoding DSP (rs228769, rs7041,

rs115563), CYP2R1 (rs206079) and at the NADSYN1/DHCR79 locus (rs3829251). Wang et al. (2010) included 15 cohort studies from the United States, Canada and Europe (discovery sample, n = 16125; replication sample, n = 17744. Single nucleotide polymorphisms at three loci reached genome-wide significance for an association with serum 25(OH)D concentration: rs2282679 in the DBP gene, rs12785878 near DHCR77 and rs10741657 near the CYP2R1 gene.

These findings suggest that common polymorphisms in genes involved in vitamin D metabolism might combine with behavioural and environment factors to influence serum 25(OH)D concentrations. The functional relevance of these polymorphisms is not clear.

3.5 Reasons for variation in vitamin D status within the UK population

Variations in vitamin D status within the UK population are largely attributable to different amounts of vitamin D acquired through the cutaneous route following sunlight exposure, with lesser contributions from differences in dietary and supplementation practices, and potentially from metabolic/genetic differences (Figure 3.3).

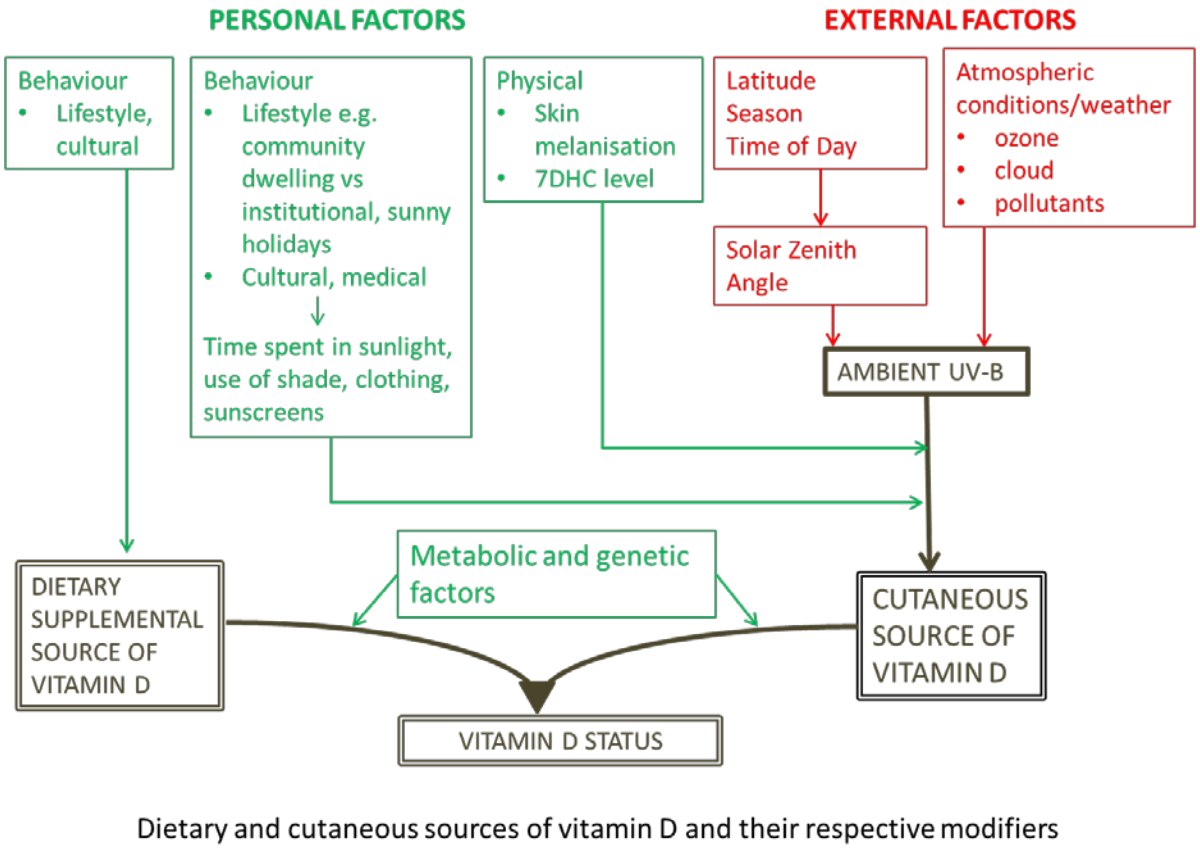

Figure 3.3: Dietary and cutaneous sources of vitamin D and their respective modifiers

Studies are consistent in showing the average daily dietary vitamin D intake in the UK is below 5 µg (section 4.1). However, variations in dietary vitamin D intake can affect vitamin D status, such that those who consume vitamin D supplements and oily fish have higher status (Hyponnen and Power, 2007) while vegetarians have lower status (Crowe et al., 2011). Studies performed year-round in Greater Manchester (53.5°N) reported low intake (median 3.3 µg) in white adults and even lower (median 1.3 µg) in South Asian adults, and little seasonal variation in these values (Webb et al., 2010; Kift et al., 2013). Findings consistent with the above are reported from population samples in Aberdeen (57°N) and Surrey (51°N) (Ashwell et al., 2010; Macdonald et al., 2011).

The acquisition of vitamin D through the cutaneous route is governed by external and personal factors. Key external factors are latitude, season, time of day and weather, all of which determine the amount of ambient UV-B available for photochemical conversion of pro-vitamin D (7-DHC) to pre-vitamin D within the skin. The UK population shows a predictable seasonal pattern in vitamin D status, with highest level at summer-end and lowest at winter-end, reflecting the negligible UV-B available across November-February at UK latitudes (Hyponnen and Power, 2007; Webb et al., 2010). The UK also shows a latitudinal pattern, with highest vitamin D status in (sunnier) S. England and lowest in N. Scotland, as in the nationwide study of 7437 white British adults aged 45 years (Hyponnen and Power, 2007).

Personal factors influencing cutaneous acquisition of vitamin D comprise firstly physical parameters, including skin melanisation, which reduces the amount of UV-B available to the chromophore 7-DHC, and older age, which is associated with reduced amounts of 7-DHC in skin cells. Secondly, lifestyle, cultural and medical requirements influence sunlight exposure behaviour, including time spent outdoors, use of shade, clothing and sunscreens.

Higher prevalence of low vitamin D status occurs population-wide in winter. The degree of prevalence is dependent on where cut-offs are drawn for vitamin D deficiency and sufficiency. Approximately half (46.6%) of a sample of 7437 of white people from the national 1958 birth cohort studied at age 45 years had winter/ spring 25(OH)D levels <40 nmol L^{-1}, with 15.5% participants showing <25 nmol L^{-1}, the levels designated in this study as insufficient and deficient, respectively (Hypponen and Power, 2007). This is similar to the NDNS findings in British adults 19-64 years (see section 3.4). However, the vast majority of ambulant white non-elderly adults have 25(OH)D regarded by the authors as sufficient (>40 or >50 nmol L^{-1}) in summertime (Hyponnen and Power, 2007; Webb et al., 2010).

In contrast, several UK population subgroups have high risk of year-round low vitamin D status, which can include very low 25(OH)D levels (<12.5 or <25 nmol L^{-1}). These include those institutionalised with little outdoor exposure (Webb et al., 1990), those who extensively cover their skin/practice sun-avoidance for cultural (Kift et al., 2013) or medical (Rhodes et al., 2014) reasons, and at different stages of the age-span. Ethnicity is an important determinant of vitamin D status in the UK, with studies showing that people with more melanised skins have high prevalence of low status compared with whites at the same latitude (Darling et al., 2013; Kift et al., 2013; Macdonald et al., 2011; Mavroeidi et al., 2010). A study in Birmingham showed low levels (<15 nmol L^{-1}) in 42.2% of those of South Asian origin and 12.5% of black people of African-Caribbean origin (Patel et al., 2013).

Further information on personal and external factors influencing vitamin D status is provided in other sections of this document (including 3.5 and 4.2.4 to 4.2.6).

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Table 3.1: Plasma 25(OH)D, by sex and age, in the UK from the NDNS for years 2008/09-2011/12

Aged 1.5 years and over

Plasma 25(OH)D	Sex and age group (years)												
	Male				Female				Total				
	4-10	11-18	19-64	65+	4-10	11-18	19-64	65+	1.5-3	4-10	11-18	19-64	65+
Plasma 25(OH)D (nmol L^{-1})													
Mean	52.3	44.9	43.5	47.0	48.0	41.1	47.3	42.5	[58.1]	50.2	43.0	45.4	44.5
Median	51.7	42.8	39.0	45.5	49.1	38.3	44.5	41.4	[51.0]	50.4	40.7	41.8	43.1
sd	23.96	23.75	23.87	22.47	22.21	21.08	25.61	20.18	[26.75]	23.16	22.51	24.84	21.29
2.5^{th} percentile	16.1	10.4	7.1	12.3	14.3	7.1	10.2	11.8	[17.4]	14.3	7.1	7.1	12.1
97.5^{th} percentile	106.0	100.0	92.4	94.8	108.0	87.5	106.0	87.1	[105.0]	106.0	96.3	104.0	94.8
% below 25 nmol L^{-1} [a]	12.3	19.7	24.0	16.9	15.6	24.4	21.7	24.1	[7.5]	13.9	22.0	22.8	21.0
Number of subjects	129	273	551	140	108	250	770	198	[42]	237	523	1321	338

[a] Department of Health (1998) Nutrition and Bone Health with Particular Reference to Calcium and Vitamin D. Report on Health and Social Subjects no. 49. London: The Stationery office.

Table 3.2: Plasma 25(OH)D by month blood sample was taken, by age, in the UK from the NDNS for years 2008/09-2011/12

Aged 1.5 years and over

Plasma 25(OH)D	Age group (years)				
	Total				
	1.5-3[a]	4-10	11-18	19-64	65+
Plasma 25(OH)D (nmol L^{-1}) January-March[1,b]					
Mean		37.2	31.5	34.8	40.5
Median		32.9	28.1	29.4	36.7
sd		17.56	18.77	22.91	22.91
% below 25 nmol L^{-1} [c]		31.4	40.0	39.3	29.3
Plasma 25(OH)D (nmol L^{-1}) April-June[2,b]					
Mean		[47.2]	43.5	44.2	44.9
Median		[48.9]	41.2	40.4	38.2
sd		[18.60]	19.27	24.39	21.89
% below 25 nmol L^{-1} [c]		[8.2]	12.7	24.4	21.3
Plasma 25(OH)D (nmol L^{-1}) July-September[3,b]					
Mean		66.0	52.3	57.5	50.5
Median		60.8	50.3	56.3	48.7
sd		22.66	21.39	23.42	18.31
% below 25 nmol L^{-1} [c]		1.7	13.4	8.4	3.6
Plasma 25(OH)D (nmol L^{-1}) October-December[4,b]					
Mean		50.2	44.3	45.6	43.7
Median		52.9	37.3	41.0	42.6
sd		23.14	26.62	22.73	19.94
% below 25 nmol L^{-1} [c]		11.7	24.3	16.9	25.7
Number of subjects					
[1] Plasma 25(OH)D (nmol L^{-1}) January-March	[12]	68	125	345	106
[2] Plasma 25(OH)D (nmol L^{-1}) April-June	[8]	[48]	152	369	85
[3] Plasma 25(OH)D (nmol L^{-1}) July-September	[8]	59	136	341	75
[4] Plasma 25(OH)D (nmol L^{-1}) October-December	[14]	62	110	266	72

[a] Due to cell sizes for those aged 1.5 to 3 years being below 30, data have not been presented for children aged 1.5 to 3 years.
[b] Due to limited cell sizes, the 2.5th and 97.5th percentiles have not been presented.
[c] Department of Health (1998) Nutrition and Bone Health with Particular Reference to Calcium and Vitamin D. Report on Health and Social Subjects no. 49. London: The Stationery office.

Table 3.3: Vitamin D status by region - adults 16 years and over in England and Scotland

Aged 16 years and over

Health Survey for England 2010; Scottish Health Survey 2010-2011

	Region										
	South West	**East of England**	**South East**	**London**	**East Midlands**	**West Midlands**	**Yorkshire and Humber**	**North East**	**North West**	**All England**	**Scotland**
% below 25 nmol L^{-1}	15.1	18.7	20.8	34.8	23.2	30.1	26.7	28.1	24.8	24.1	33.0
Number of subjects	431	417	648	348	397	382	389	360	451	3,823	1,453

Table 3.4: Vitamin D status in Scotland by Body Mass Index

Aged 16 and over

		Scottish Health Survey 2010-2011 combined		
Plasma 25(OH)D		**BMI**		
		Less than 25	25 to less than 30	30 and over
Mean Vitamin D	nmol L^{-1}	41	38.5	33.3
SE of mean	nmol L^{-1}	1.8	1.1	1.1
Standard deviation	nmol L^{-1}	25.7	21.7	18.4
% below 25 nmol L^{-1}	%	33	28	38
95% C.I.	%	(27-40)	(24-33)	(32-44)
Number of subjects		412	515	400

4. Dietary and photobiological aspects of vitamin D

4.1 Dietary and supplemental sources of vitamin D in the UK

A detailed description of dietary sources of vitamin D and of dietary vitamin D intakes in various population groups is provided in SACN's 2016 report on Vitamin D and Health (SACN 2016). A brief overview is provided here.

There are few food sources of naturally occurring vitamin D. The main dietary sources are foods of animal origin, fortified foods and supplements. Rich food sources include oily fish, eggs, fortified fat spreads[1] and fortified breakfast cereals (Table 4.1).

Table 4.1: Vitamin D content (µg/100g) of main dietary sources in the UK

Food	Vitamin D (µg/100g)
Oily fish	3-16
Egg yolk	~12
Red meat	~1
Fat spreads	~7
Breakfast cereals	~4

4.1.1 Vitamin D intake: contribution from different sources

Information on the diet, nutrient intake and nutritional status of the UK population is provided in the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (Lennox et al., 2011) for infants and young children aged 4 to 18 months and in the National Diet and Nutrition Survey (NDNS) rolling programme (results from 2008/2009 – 2011/2012 combined) (Bates et al., 2014) for the general population aged 1.5 years and over.

For adults aged 19-64 years, food sources make a larger contribution to dietary intake of vitamin D than food supplements: mean daily intake of vitamin D from food sources is 2.8 µg while Vitamin D supplements increase mean daily intakes to 3.9 µg in men and 3.4 µg in women. The mean daily vitamin D intake from food sources in older adults (65 years and over) is 3.3 µg. Dietary supplements containing vitamin D make a larger contribution to intakes in this age group than in the 19-64 years age group, increasing daily mean intakes to 5.1 µg in men and 5.2 µg in women (Table 4.2).

[1] Colloquially known as 'margarines'.

Mean intakes for non-breast fed infants aged 4-18 months were above the RNI except at 12-18 months, where mean intakes were 55% of the Reference Nutrient Intake (RNI)[2] from all sources. For breast fed infants, intakes of vitamin D from all sources (excluding breast milk) were below the RNI at 41% (4-6 months), 52% (7-9 months), 54% (10-11 months) and 37% (12-18 months) (Table 4.4). Mean vitamin D intake from all sources was 32% of the RNI for children aged 1.5-3 years. The mean intake for adults aged 65 years and over was 51% of the RNI (Table 4.3).

The mean daily vitamin D intake for children aged 4-10 years was 2 µg from dietary sources and 2.7 µg from all sources (including supplements). In adolescents aged 11-18 years the mean daily vitamin D intake was 2.1 µg from dietary sources and 2.4 µg from all sources (including supplements) (Table 4.2). The Committee on Medical Aspects of Food (COMA) did not set an RNI for ages 4-65 years and therefore their intakes were not compared to an RNI.

4.2 Photobiological aspects of vitamin D

4.2.1 Introduction

All photobiological responses in the skin are initiated by the absorption of UV or visible radiation energy by molecules known as chromophores (see Section 3.3). This results in an 'excited' molecular state that may lead to structural changes or interactions with other molecules. The skin, especially the epidermis, is rich in chromophores.

An action spectrum (wavelength dependence) is a measure of efficacy of different wavelengths, and typically has a peak in a given spectral region. The absorption spectrum of a given chromophore determines the action spectrum of a given photobiological reaction.

Action spectra are determined by exposing the test sample (cells or tissue) to different UVR spectra, which ideally should be monochromatic. Typically a dose-response is generated for each wavelength and parameters based on the dose-response curves (eg slope) are used to generate the action spectrum.

Under ideal conditions, the action spectrum of a given photobiological outcome should match the absorption spectrum of its chromophore. This is the case with the action spectrum for photosynthesis and the absorption spectrum of chlorophyll. The situation is more complex in skin because competing chromophores (Young, 1997) may attenuate UVR so that the UVR dose measured on the skin surface may be higher than that received by the target chromophore. For example, DNA has an absorption maximum at 260 nm (UV-C) in solution that matches the maximum for the action spectrum for the formation of cyclobutane pyrimidine dimers (CPD) *in vitro*. However, the action spectrum for CPD in human epidermis *in vivo* shows a red-shift of about 40 nm with a peak at 300 nm because of epidermal attenuation of shorter wavelengths (Young et al., 1998). Furthermore, at wavelengths <300 nm the action spectrum for CPD varies with epidermal layer, demonstrating the influence of competing chromophores at shorter wavelengths that have little or no relevance for terrestrial solar UVR (~295 – 400 nm).

[2] In this section, the RNIs referred to are those that were in place at the time of the NDNS survey 2008/09-2011/12.

4.2.2 Action spectrum of pre-vitamin D synthesis and influence of spectral emission on vitamin D

The most widely used action spectrum for the production of pre-vitamin D is that published by the Commission Internationale de l'Eclairage (CIE) (Bouillon et al., 2006) as shown in Figure 2.4 along with the CIE action spectrum for human erythema (sunburn) (CIE, 1998) . This figure shows that UV-B is much more effective than UV-A for both endpoints, although the spectral range for erythema is much greater. The erythema spectrum is based on several human *in vivo* studies, which have been generally validated by other researchers (Young et al., 1998), whereas the CIE pre-vitamin D spectrum is based on a single study (MacLaughlin et al., 1982) using *ex vivo* skin. The validity of this CIE spectrum has been questioned in some detail (Norval et al., 2010). For example, the original results were lost and scanning a published figure and extrapolation between data points was done to generate the CIE spectrum. Furthermore, many of the experimental details are lacking.

The absorption spectrum of 7-DHC in solution shows three maxima (Galkin and Terenetskaya, 1999; Norval et al., 2010) at about 272, 282 and 292 nm. There is low efficacy for the formation of pre-vitamin D *ex vivo* at 272 and 282 nm (MacLaughlin et al., 1982) which suggests considerable attenuation at these wavelengths by other skin chromophores such as DNA and stratum corneum urocanic acid. However, these peaks are not relevant for terrestrial UVR. The peak of the CIE action spectrum, at 297 nm, for pre-vitamin D is about 5 nm red-shifted compared with absorption of the third 292 nm peak of 7-DHC in solution (Norval et al., 2010). This also suggests some attenuation by skin chromophores in this spectral region, the tail of which overlaps with terrestrial UVR.

An action spectrum can serve different purposes, but its main value in the case of pre-vitamin D is its use as a biological weighting function for the efficacy of a given solar UVR spectrum (see section 4.2.1) to synthesize vitamin D. It should be noted that pre-vitamin D and serum 25(OH)D are different endpoints and that the action spectrum for the former may not necessarily predict that of the latter.

4.2.2.1 Use of action spectra in risk benefit calculation

The weighting of a UVR emission spectrum with an action spectrum results in an efficacy spectrum which is the product of a given action spectrum and a given emission spectrum. A typical noon summer solar UK spectrum has about 5% UV-B, but when this spectrum is weighted with the CIE action spectrum for erythema, the small UV-B component is responsible for about 85% of erythemal efficacy. The net conclusion from this is that it is not possible to draw any photobiological conclusions about any spectral region of terrestrial UVR or visible radiation without an action spectrum for the endpoint in question.

The biological weighting of solar UVR spectra with the CIE pre-vitamin D action spectrum (Bouillon et al., 2006) has been used to predict the ability to synthesize vitamin D with variations in latitude, season and time of day (Kimlin et al., 2007; Webb and Engelsen, 2006; Webb and Engelsen, 2008). This has also been used to predict the vitamin D synthesis efficacy of various tanning lamps (Sayre et al., 2010) and assess the effect of clouds on vitamin D production (Feister et al., 2011; Parisi et al., 2012).The weighting of solar UVR with action spectra for erythema and pre-vitamin D provides risk benefit evaluations for given spectral conditions, including sunbed use. Most public health advice advocates avoiding midday UVR, yet it has been argued that noon is the best time to obtain vitamin D because the benefit is greater than the risk of sunburn for a given exposure (Sayre and Dowdy, 2007; Webb and Engelsen, 2006).

The validity of calculations like those above totally rests on the reliability of the action spectra in question. Small inaccuracies can have a major impact, especially where there are steep declines in efficacy over a short spectral region as is the case for erythema and vitamin D in the solar UV-B region. Furthermore, the use of an action spectrum as a biological weighting

function for a broad UVR emission spectrum, such as solar UVR, is only valid if there is no spectral interaction; for example, if one part of the solar UVR spectrum degrades pre-vitamin D or vitamin D, which is known to occur (Norval et al., 2010). Some *in vitro* studies have suggested that UV-B and shorter wavelength UV-A, known as UVA-II (315 – 340 nm), degrade vitamin D (Webb et al., 1989), but a recent *in vivo* study suggests that UV-A has very little influence on vitamin D status *in vivo* (Sallander et al., 2013). However, the validity of this study has been questioned (Norval and de Gruijl, 2014).

4.2.3 Relationship between UVR dose and changes in vitamin D status

The traditional exposure unit in photobiological studies was the minimal erythema dose (MED), which is a measure of individual UVR sensitivity. However, this can make study group comparisons difficult because there is considerable interpersonal variation when MED is expressed as a physical dose (J m^{-2}) (Harrison and Young, 2002). More recently, the trend has been to use the standard erythema dose (SED), which is independent of personal UVR sensitivity. One SED is defined as 100 J m^{-2} of erythemally effective UVR (Diffey et al., 1997). In effect, this is obtained by weighting the emission spectrum of the source with the CIE spectrum. An MED on white buttock skin is typically 2-3 SED (Harrison and Young, 2002).

It is relatively easy to show a vitamin D status dose response for an increase in UVR in laboratory studies where conditions are tightly controlled and are typically done with repeated UVR exposures. Different authors have taken different approaches in study design. In some cases UVR doses have been based on fractions of individual MEDs and, sometimes, doses have been increased as the study progressed. This approach has been used in some studies designed to replicate tanning protocols using sunbeds (Moan et al., 2009; Porojnicu et al., 2008; Thieden et al., 2008). It should be noted that some of these studies have been directly funded by the sunbed industry, with potential for conflict of interest. In other studies, the dose per exposure has been fixed and expressed as a fixed fraction of SED. The latter approach has fewer variables, which makes it easier to study the relationship between dose and outcome.

Sampling approaches have also varied between studies. In some cases different study groups have been assigned different doses and in other studies there has been serial sampling during the course of the study. Other factors that have varied between studies include body surface area exposed and UVR emission spectrum.

A dose response has been shown between different study groups receiving different (0.75 – 3.0 SED) UVR doses (Bogh et al., 2011a; Bogh et al., 2011b) and in general, the response fits a linear model when the total number of exposures was at least four. A study that assessed the effects of dose (0.375 – 3.0 SED) and dose-rate (20-fold range) on 24% of the body surface showed that dose was the critical factor irrespective of dose- rate (Bogh et al., 2011b).

In one study 120 volunteers (skin types I-IV) were exposed to 1.3 SED of fluorescent solar simulating radiation 3 times a week for 6 weeks over ~35% body surface area (Rhodes et al., 2010). There was a fairly linear increase in serum 25(OH)D over the first 3-4 weeks approaching a plateau between weeks 5-6. Overall, the increase was from 44 ± 19 (SD) to 70 ± 16 nmol L^{-1}. Others have also observed a linear UVR dose response in a “sunbed study” followed by a plateau in a study over 4 weeks with 10 exposures (Porojnicu et al., 2008). In another study, with 15 exposures over a longer period, the same authors (Moan et al., 2009) showed no evidence of a plateau with a group of subjects who started with a baseline level of <50 nmol L^{-1}. However, a plateau was evident when the baseline was >50 nmol L^{-1}. This is supported by another study that showed that UVR- induction of vitamin D synthesis was inversely related to the level of 25(OH)D at the start of the study (Bogh et al., 2010).

Vitamin D status is seasonal (Webb et al., 2010), which is an overall reflection of ambient UVR exposure dose, and probably body surface area exposed. However, it is much more difficult to determine dose responses in field conditions, because this requires the measurement of personal UVR exposure. This has been done in one-week holiday studies in which personal UVR exposure was measured with electronic dosimeters. Serum 25(OH)D was measured in March before and after either a week's sun holiday in the Canary Islands or skiing in Austria. A UV-B dose dependent increase in serum 25(OH)D was observed when body surface area exposed was taken into account (Petersen et al., 2014). This study also showed a significant association between increased 25(OH)D and biomarkers of skin DNA photodamage (CPD). The CPD, primarily caused by solar UV-B, can result in mutations that lead to skin cancer. This suggests that UV-B-enhanced vitamin D status from intentional holiday exposure is accompanied by adverse molecular changes with carcinogenic potential.

In vitro dose-response studies on the conversion of 7-DHC to pre-vitamin D show non-linear relationships, with declining conversion at higher doses (Olds et al., 2008). This suggests that increasing UVR exposure dose *in vivo* beyond a certain level may have diminishing returns along with the risk of sunburn and other potentially harmful effects either by single exposures or repeated sub-erythemal exposure, especially in fair skin types (Young et al., 2007). This is supported by a human laboratory study in which increasing the exposure dose by a factor of 12 increased serum 25(OH)D by about 1.7 times (Bogh et al., 2011a).

4.2.4 Effect of external factors on solar UVR-induced vitamin D status (time of day, season, latitude, weather etc)

4.2.4.1 Effect of external factors on solar UVR-induced vitamin D production

Detailed information on the physics of ultraviolet radiation, including potential sources of exposure to people from UVR, the response functions used to assess exposure and how the metrics may relate to weighted radiant exposures that people may receive in practice, is provided earlier (Chapter 2). In brief, the external factors governing how much UV-B is available for cutaneous vitamin D synthesis can be divided into the predictable, ie the latitude, season and time of day, and the less predictable, ie the weather, or state of the atmosphere (Webb, 2006).

Latitude, season and time of day determine the Solar Zenith Angle (SZA), ie the angle between the local perpendicular and the sun's location in the sky. The SZA in turn governs the amount of UV-B reaching the earth's surface, by determining the path-length of radiation through the atmosphere (and hence its attenuation) and the angle at which radiation strikes the surface (and thus the surface area over which the incident energy is spread). Vitamin D production is maximal with small SZA, when the sun is high in the sky, ie at low latitudes, in the summer and around solar noon. An increased SZA, as occurs with increasing latitude, in autumn and winter, and outside noon hours, results in reduced surface UV-B, and thus very little cutaneous vitamin D production occurs in the UK during the winter months (Webb and Engelsen, 2006).

The atmospheric variables of ozone, cloud and pollution affect the amount and wavelengths of UVR reaching the earth's surface (Webb and Engelsen, 2006). Stratospheric ozone shows global, seasonal, year-year and day-day patterns, and is a strong absorber in the UV-B wavelengths. Cloud generally decreases all wavelengths of radiation, although this varies dependent on cloud type, depth and sky cover. While cumulus clouds may have little effect, a thick layer of covering stratus cloud has a major impact on UVR reaching the earth's surface. Some aerosol pollutants (suspended particles) absorb at particular wavelengths, though in general there is overall attenuation of UVR.

The state of the earth's surface can also influence the UV-B radiation incident on the skin surface through its reflectivity, ie albedo. In particular, snow reflects a high proportion of UVR to the atmosphere, with back-scattering causing a proportion to return to the surface.

How much of the ambient UV-B then reaches the skin surface and is potentially available for cutaneous vitamin D synthesis is dependent on the local environment, eg whether shaded by tall buildings in cities or in open areas such as parks and beaches, and behavioural factors.

4.2.4.2 Human studies examining relationships between UK sunlight exposures and vitamin D

A prospective cohort study in Greater Manchester (53.5°N) employing UV dosimeter badges in 125 healthy ambulant white (skin type I-IV) adults aged 20-60 years showed they were exposed to ~2% of the ambient UVR (Webb et al., 2010). They received median solar UVR exposures of 3.7 SED/week in spring/summer compared with only 0.1 SED in winter. This produced a clear seasonal 25(OH)D pattern, monthly measurements revealing the peak level (mean 71, SD 26 nmol L^{-1}) to occur in September with a fall to the trough level (45.8, SD21.8) in February (Webb et al., 2010). In contrast, dietary vitamin D remained low in all seasons (median 3.27 µg day^{-1}, range 2.76-4.14). Sun exposure diaries indicated that during peak ambient UV-B times (11:00 to 13:00), subjects spent a mean daily time outdoors in spring/summer of 9 (SD13) minutes on weekdays, doubling to 18 (SD23) at weekends (total 81 minutes per week). The time for the longer period of 10:00 to 15:00 was 22 (26) minutes during weekdays and 49 (47) during weekends. Thus in these real-life conditions, relatively short frequent exposures to sunlight in the midday hours were seen to increase the vitamin D status of the population. Multifactorial regression of February 25(OH)D level on the summer level indicated that the trough level could be retained above 50 nmol L^{-1} with a late summer level of 76 (95%CI 64-88) in women and 87.3 (70-104.8) in men. This applied to 28% of the population, with 72% falling below 50 nmol L^{-1} in winter.

A similar group of white adults (skin type I-IV, 20-60 years) in Greater Manchester were given a simulated summer's sunlight exposures in an a well-characterised irradiation cabinet in order to define closely the UVR dosimetry parameters and conditions. Thus in this UVR intervention study, 120 adult volunteers received sub-erythemal exposures of 1.3 SED (equivalent to 1.1 SED in sunlight) x3 weekly using fluorescent lamps with an emission spectrum close to Manchester June midday sunlight (Rhodes et al., 2010). A 6-week course was given as this is the length of the peak summer holiday period, and the course was completed within January-February to avoid confounding by ambient UV-B. Volunteers wore casual clothing (T-shirt and shorts) to reveal commonly exposed skin sites, totalling ~35% skin surface area. In the first 4 weeks the sunlight equivalent of 3.3 SED per week produced an average rise in 25(OH)D of ~6 nmol L^{-1} per week, while there was evidence of a plateau developing in weeks 5-6, with an average rise of ~1.5 nmol L^{-1} per week, the latter potentially attributable to photo-adaptation. At the start of the course 62.5% (95%CI 55.2-69.4) of the group had 25(OH)D <50 nmol L^{-1} whereas at completion the vast majority, ie 90% (84.9-93.7) had 25(OH)D >50 nmol L^{-1}.

In real-life, exposure of the dorsal and ventral surfaces would need to occur sequentially rather than simultaneously, as in the above simulated summer sunlight intervention, and people adopt postures ranging from horizontal to the vertical randomly orientated to the sun. Thus it is estimated that the equivalent time in sunlight to achieve the above 25(OH)D levels ranges from 13 minutes (horizontal) to 17 minutes (vertical), on the basis of 6x exposures per week, with unshaded skin exposure to cloudless midday summer sunlight (Webb et al., 2011).

Field studies performed to the same protocols as above in other sectors of the Greater Manchester population are described in further sections of this report: for South Asian adults (section 4.2.5.2), white adolescents (section 4.2.5.3), South Asian adolescents (section 4.2.5.3) and patients who avoid sun-exposure (section 4.2.6.3). The impact of simulated summer sunlight exposures in South Asian adults, including UVR-25(OH)D dose-response, is also described (section 4.2.5.2).

4.2.5 Effect of personal attributes on UVR induced vitamin D status (includes skin colour, age group, volume, groups with low levels)

4.2.5.1 Skin colour

A wide range of epidemiological studies in different parts of the world, including the UK, have shown that people with pigmented skin have lower vitamin D status than those with white skin living at the same location (Harris and Dawson-Hughes, 1998; Mavroeidi et al., 2010; Renzaho et al., 2011; Kift et al., 2013), and this is usually attributed to the photoprotective effects of melanin. Indeed, it has been argued that loss of pigment as early humans migrated North from Africa was driven by the need for vitamin D photosynthesis in less sunny climates (Yuen and Jablonski, 2010).

There have been relatively few experimental studies to evaluate the impact of melanin skin pigmentation on vitamin D synthesis, and these have given conflicting results (Farrar et al., 2011; Libon et al., 2013; Springbett et al., 2010). For example, a study of n=7 people with black skin compared with n=13 with white skin given the same absolute doses of total body sub-erythemal UV-B 2×weekly for 6 weeks showed similar gain in 25(OH)D (Brazerol et al., 1988). Bogh et al. (2010) gave 4 exposures with 3 SED of UV-B to skin of the torso (24% body surface area) in n=9 pigmented/white pairs of people matched for baseline 25(OH)D, and found constitutive skin pigmentation did not influence 25(OH)D production, while baseline vitamin D status did. This study used non-solar UV-B, highly effective at vitamin D production, that may induce pre-vitamin D above the most melanised layers of the epidermis.

In contrast, other studies report less effective vitamin D production in people with pigmented skin when given identical UVR doses and protocols to people with white skin. This includes a study in n=6 South Asians which indicated they had the same capacity to synthesise vitamin D as white subjects if UVR doses related to their minimal erythemal dose (MED), ie higher absolute doses, were given (Lo et al., 1986). A study of n=72 subjects of various skin tones given near-total-skin UV-B 3xweekly for 4 weeks also found the 25(OH)D response was pigmentation dependent (Armas et al., 2007). A recent study has compared responses of white people with South Asians to simulated UK summer sunlight exposures to commonly photoexposed skin sites (Farrar et al., 2011). The study was performed in the winter months to avoid confounding by ambient UVR (protocol and results in sections 4.2.4 and 4.2.5). These data suggest that melanin does inhibit vitamin D production. A recent systematic review found that on balance skin pigmentation reduces vitamin D synthesis (Xiang et al., 2015).

Overall, the role of melanin is not completely resolved and this may be situational. UVR wavelength-dependent penetration, and the relative locations of melanin and 7-DHC in the skin are likely to influence effects of skin type on the formation of vitamin D. Thus possible reasons for differences between studies include differences in position/amounts of melanin and 7-DHC molecules competing for the UV-B photons, differences in constitutive and facultative melanisation, and differences in UV dose and emission spectrum (Bjorn, 2010).

A ~six-fold difference of epidermal melanin content between skin types I/II and V/VI has been reported using photoacoustic and reflectance techniques (Viator et al., 2004). Epidermal melanin absorbs and scatters UV-B, reducing the amount available to be absorbed by 7-DHC. This can explain why it is that while people with darker skin are seen to synthesise vitamin D effectively, they appear in general to require higher UV-B doses than those with paler skin. Lifestyle differences, including clothing coverage, time spent in the sun, and diet, can also contribute to their lower observed vitamin D status (Kift et al., 2013).

A recent study confirming black Americans had lower levels of 25(OH)D also indicated they had lower vitamin D binding protein levels than white Americans (Powe et al., 2013). However, it is currently unclear whether this impacts on bioavailable 25(OH)D (Bahn et al., 2012; Powe et al., 2011).

4.2.5.2 UK residents with brown skin (skin type V)

A recent intervention study simulated a UK summer's sunlight exposures and examined vitamin D status outcomes in brown skinned South Asians (skin type V, n=15) compared with 20-60 year old white people (skin type I-IV, n=120) living in Greater Manchester, UK (Farrar et al., 2011). Performed with identical UV dose (1.3 SED) and exposure protocols (as described in section 4.4.2, paragraph 2) to ~35% area of commonly photoexposed skin sites in winter-time, this enabled examination of biological differences in UVR-25(OH)D response under conditions designed to mimic natural UK exposure. A notable difference in response of the groups was seen, with a significantly lower 25(OH)D rise of 10.8 nmol L^{-1} in the South Asians versus 26.3 nmol L^{-1} in the white group ($p<0.0001$).

Further, a UVR-25(OH)D dose-response study was conducted in South Asians (brown skin, skin type V, total n=60) in Greater Manchester employing the same conditions as above but with 6 UV dose-groups ranging from 0.65-3.9 SED (Farrar et al., 2013). At baseline, 90% of these brown skinned subjects had 25(OH)D <25 nmol L^{-1}. It was found that a final 25(OH)D level ≥50 nmol L^{-1} could be reached in only a minority of subjects receiving the higher doses. However, in those receiving ≥1.95 SED, 25(OH)D was raised above 25 nmol L^{-1} in nearly all (94%) volunteers, with a mean final level of 37.5 nmol L^{-1} (SD12.5), and mean rise of 21.8 nmol L^{-1} (SD14.4; 95%CI: 17-26.5). Taking into account that in real life the dorsal and ventral surfaces are not exposed simultaneously to sunlight, and that people adopt postures ranging from horizontal to the vertical randomly orientated to the sun (Webb et al., 2011), this equates to exposures of ≥19.5 mins (horizontal) to 25.5 mins (vertical) ie ≥22.5 minutes ×6 weekly, when wearing casual clothes to expose ~35% skin surface area, in unshaded midday summer sunlight. This demonstrates that brown skinned South Asians can potentially enhance their vitamin D status through modest sun exposure practice in the UK.

Prospective cohort studies were performed to compare year-round vitamin D status, sunlight exposure and other contributors in adults 20-60 years of South Asian (skin type V, n=125) and white Caucasian (skin type I-IV, n=125) ethnicity at the same UK latitude, ie 53.5°N (Kift et al., 2013). Both behavioural and biological factors are at play in such field studies. South Asians had year-round 25(OH)D approximately only one-third the level of the white group, with median 22.5 nmol L^{-1} (IQR 16.8-34.3) in summer, falling to 14.5 (10-20.3) in winter. In summer, 58% of South Asians had 25(OH)D <25 nmol L^{-1}, rising to 90% in winter. The study found a range of lifestyle differences may contribute, with lower daily dietary vitamin D (median 1.3 µg day^{-1}), compounded by virtually no use of vitamin D supplements, and lower personal UV exposure as recorded by dosimeters (~1% ambient UV vs >2% in the white group). Diaries recorded similar times spent outdoors, implying greater use of shade than in white adults, and lower surface area exposed. Vitamin D status was similarly low in 35 Asian women in Surrey (51°N), with a median 25(OH)D of 24 nmol L^{-1} in summer, 16.9 in winter (Macdonald et al., 2011).

Genetic differences may also influence vitamin D status, including possibly through increased 25(OH)D-24-hydroxylase activity, which catabolises 25(OH)D and $1,25(OH)_2D$ to inactive metabolites, in South Asians (Awumey 1998; Shaw and Pal 2002; Farrar et al., 2012).

4.2.5.3 Age-group

Vitamin D has a critical role in calcium homeostasis and is essential for healthy bones through the lifespan, as discussed in section 5.1. The current sub-section examines specific contributors to vitamin D status in the UK at different life-stages, while further information on life-stage vitamin D status is presented in section 3.4. Stages of life where there may be increased risk of inadequate vitamin D status are during pregnancy/breast-feeding/infancy (see section 5.1.11) and early childhood (increased requirements), adolescence (bone growth spurt), and older age (reduced capacity of the skin to synthesise vitamin D; potentially less sunlight exposure) (AGNIR 2002).

While there is no formal national registry, there are reports of an increase in clinical cases of vitamin D deficiency in the UK in the past few years, particularly in South Asian children, with infants presenting with symptomatic hypocalcaemia including seizures, as well as the bone-deficiency disorder of rickets (Shaw and Pal 2002; Goldacre et al., 2014).

The NDNS (Bates et al., 2014) showed higher 25(OH)D levels in 4-10 year olds than 11-18 year olds (Section 3.4). Absoud et al., (2011) reported higher risk of 25(OH)D <50 nmol L^{-1} in adolescents (14-18 years) compared with younger children (4-8 years) (odds ratio, OR3.6), in non-white children (OR37.0), samples taken in the winter season (OR6.5), and in children not taking vitamin D supplements (OR3.7).

Adolescents are reported to have lower sunlight exposure levels than younger children (Diffey et al., 1996). A longitudinal study in Greater Manchester, UK, reported on the year-round vitamin D status of 131 white adolescents aged 12-15 years (Farrar et al., 2016). It was found that 16% of the adolescents had 25(OH)D <25 nmol L^{-1} and 79% had <50 nmol L^{-1} in at least one season. Dietary vitamin D intake was low year-round, whereas personal sun exposure was seasonal and occurred predominantly across the school week. Holidays accounted for a 17% variation in peak 25(OH)D ($P < .001$). Those with 25(OH)D <25 nmol L^{-1} were shown to have low femoral neck bone mineral apparent density compared with matched reference data ($P = .0002$). A similar longitudinal study has recently been completed examining seasonal vitamin D status in South Asian adolescents aged 12-15 years in Greater Manchester. [Reference eg Rhodes, pers comm].

Vitamin D is important for maintenance of musculoskeletal health in older people (section 5.1). Vitamin D status at these ages may be influenced by both intrinsic (physiological) and extrinsic (environmental and behavioural) factors, as follows.

It is considered that older people have reduced capacity to synthesise vitamin D in view of lower cutaneous 7-DHC levels (MacLaughlin and Holick, 1985; see next paragraph), and as only ~15% of available 7-DHC can be converted to pre-vitamin D on one UVR exposure (MacLaughlin et al., 1982). Nevertheless, their skin can mount a vitamin D response to artificial UVR sources (Corless et al., 1978).

An inverse correlation was found for 7-DHC content with age, in skin obtained from ~26 surgical donors aged 8-92 years, involving a range of skin sites and surgical indications (MacLaughlin and Holick, 1985). Skin samples from 5 of the donors selected from the larger pool involving a range of skin sites were UVR-exposed *ex vivo*; in the oldest patients the consequent pre-vitamin D content was approximately only half that in the young individuals (MacLaughlin and Holick, 1985).

Reduced mobility and outdoor access reduce sunlight exposure of the skin, conferring high risk of vitamin D deficiency, as seen in the institutionalised elderly (Webb et al., 1990). A cross-sectional study of 1766 ≥65 year-olds performed as part of the Health Survey for England 2000, also indicated little effective intervention, ie of taking supplements in line with DH recommendations, on vitamin D replacement (DH 1991, 1998). Studies performed in the 1970-80s supported the thesis that the UK elderly population had lower 25(OH)D status than younger adults, with less seasonal variation. For example Corless et al. (1975) found lower status in those aged 64-100 years (median 86 years) than 17-58 years (median 30 years), and Lester et al. (1977) reported community-dwelling people aged 70-88 years (mean 75 years) to have lower status and show less seasonal variation than younger groups reported in the literature, for example those aged 18-37 years as reported by Stamp and Round (1974). A fall in plasma 25(OH)D was reported with age in females aged 25-95 years (Nordin, 1980).

Seasonal characteristics of vitamin D status, and responses to and contributions of sunlight, are unclear in the UK's growing population of ambulant retirees.

4.2.6 Effect of photoprotection and sun avoidance measures

Photoprotection depends on clothing and sunscreens, but also on pigmentation, which has been discussed in section 4.2.5.

4.2.6.1 Clothing and skin surface area exposed

Clothing modifies the skin surface area exposed to solar UVR. It offers good protection against sunburn that is dependent on fabric properties such as colour, weave, wetness, etc. The level of protection is expressed by the ultraviolet protection factor (UVP) (Gambichler et al., 2006). The transmission of vitamin D effective UVR (ie weighted with the pre-vitamin D action spectrum) through clothing has been measured (Parisi and Wilson, 2005) on different body sites on manikins exposed to 3 hours (09:30 – 12:30) of Australian summer sun. There was a considerable (often > 100-fold) attenuation of vitamin D effective UVR that varied with body site and was dependent on fabric type and whether fit was tight or loose.

The interactions between UVR dose, with a UV-B phototherapy source rich in non-solar UVR (<295 nm) that is highly effective in the formation of pre-vitamin D (see Figure 2.4), and surface area exposed has been studied (Bogh et al., 2011a). Increasing the surface area exposed from 6 to 24% had a significant effect on vitamin D status when exposures were 0.75 SED (4 exposures). However, a comparable increase in body surface area had no effect on vitamin D status with exposures of 1.5 and 3 SED. Increasing exposure dose had a significant effect on vitamin D status when exposed body surface area was 6% (half back) or 12% (full back), but had no effect when surface area was 24% (back and chest).

The studies described above do not provide any information on the effect of surface area exposed to solar UV-B radiation (>295 nm) on vitamin D levels. It is possible to make theoretical estimates for this based on the CIE action spectrum for the synthesis of pre-vitamin D. One such calculation (Dowdy et al., 2010) suggests that Boston (42.4°N) noon March sunlight is about 30% more effective per SED than a UV-B phototherapy source. However, the opposite conclusion was reached in a study in Copenhagen (56°N) in which the authors state that a UV-B phototherapy source was eight times more effective than solar UVR when only hand and face were exposed (Datta et al., 2012). It is clear that more field studies of solar UVR exposures, at different latitudes, are required to determine the effect of surface area exposed on vitamin D status.

Poor vitamin D status is common in the Middle East and North Africa, especially in women (Bassil et al., 2013). One reason for this is the wearing of full body clothing for religious or cultural reasons (Hatun et al., 2005). There is also evidence that being fully covered in Western countries has a detrimental effect on vitamin D status (Ojah and Welch, 2012). The effect of long sleeves or wearing a hat on vitamin D status was assessed in 5,920 adults (Linos et al., 2012). Hats had no effect (p for trend = 0.65), whereas long sleeves impaired vitamin D status (p for trend = 0.02).

Overall, it can be stated that clothing can be very effective at inhibiting vitamin D production.

4.2.6.2 Sunscreens

Sunscreens are designed and tested for their ability to inhibit erythema and their efficacy is expressed by their sun protection factors (SPF). The erythema action spectrum (Figure 2.4) shows that effective sunscreens must contain good UV-B protection, although regulatory bodies also require some UV-A protection. Sunscreen use is also widely advocated for the prevention of skin cancer and this advice is supported by long-term prospective studies in Queensland, Australia. These have shown that daily sunscreen use reduces the incidence of squamous cell carcinoma (SCC) (van der Pols et al., 2006) with some evidence of reduction of malignant melanoma (MM) (Green et al., 2011). In addition, such use also reduces skin photoageing (Hughes et al., 2013).

There has been concern about the effect of sunscreen use on vitamin D synthesis; given the similarity of the action spectra for erythema and pre-vitamin D. One theoretical study, based on solar emission, action and absorption spectra indicated that an SPF = 15 would be more effective at preventing vitamin D synthesis than at preventing erythema (Sayre and Dowdy, 2007).

Studies done to address the effect of sunscreen use on vitamin D status have been reviewed (Norval and Wulf, 2009; Springbett et al., 2010). Overall, the conclusions from these reviews were that sunscreen use in practice was unlikely to have much impact on vitamin D synthesis because people do not apply sunscreens at the thickness (2 mg cm^{-2}) that is used for SPF testing. For example, a recent study (Petersen et al., 2013) reported that Northern Europeans on holiday in Egypt applied their sunscreens at 0.79 mg cm^{-2}. The mean labelled SPF was 15 but the effective SPF would have been about 3. The tendency for sunscreen use to be sub-optimal in practice is supported by a US study on 5,920 adults, which reported that sunscreen use (low, moderate or high) had no significant effect (p for trend = 0.42) on vitamin D status (Linos et al., 2012). In contrast, a similar analysis for shade seeking had a significant (p for trend = 0.001) negative impact on vitamin D status.

Overall, people are probably getting much less protection from sunburn than they intended when they use sunscreens, especially if their intention is to prolong UVR exposure.

4.2.6.3 Population subgroups: photosensitive people, organ transplant recipients and vegetarians.

4.2.6.3.1 Photosensitive people

The photosensitivity disorders comprise a range of conditions affecting children and adults characterised by abnormal skin reactions to UV and/or visible radiation in sunlight; they are mostly chronic in nature and have high overall prevalence (AGNIR, 2002; Appendix A). They include: immune-mediated conditions including the common polymorphic light eruption (Rhodes et al., 2010) and rarer conditions such as solar urticaria and forms of lupus erythematosus; biochemical and genetic disorders including cutaneous porphyrias and DNA repair disorders; and drug-induced photosensitivities (that can occur with >3000 drugs in use, for example thiazide diuretics and non-steroidal anti-inflammatory drugs).

Photosensitive people restrict their sun exposure to avoid precipitating their condition. Whilst specific treatments for photosensitivity conditions depend on their underlying pathogenesis, central to their management is medical advice to minimise sun exposure and employ photoprotective measures.

The Department of Health has recommended that groups at-risk of vitamin D deficiency should take vitamin D supplements 10 µg (400 IU) day^{-1}, but photosensitive individuals are not specifically mentioned in the UK guidance (DH, 1991, 1998). Congruent with this, patients appear unaware of this recommendation. A recently reported questionnaire survey of UK photosensitive adults under dermatologist care showed they spend less time outdoors during summer and sunny holidays than healthy adults, yet are no more likely to take vitamin D supplements (Stafford et al., 2010).

In the UK, substantial proportions of patients were reported to have 25(OH)D levels below the 50 nmol L^{-1} and 25 nmol L^{-1} cut-offs in a retrospective study of a range of photosensitivity conditions presenting to the Dundee, UK, photoinvestigation unit (Reid et al., 2012) and in a cross-sectional study of erythropoietic protoporphyria patients (Holme, 2008). Blood levels taken at random times, without inclusion of healthy comparator samples, can be difficult to interpret in view of 25(OH)D seasonality and widespread reports of low levels in healthy populations.

A prospective study has examined year-round vitamin D status in a sample of photosensitive patients under dermatologist care (n=59) in comparison with concurrently-assessed healthy individuals (n=109) at the same UK location (53.5°N) (Rhodes, 2014). Patients had seasonal 25(OH)D variation, but 50 and 25 nmol L^{-1} cut-offs weren't reached at summer-end in 47% and 9% of patients respectively, rising further to 73% and 32% at winter-trough. After adjustment for demographic factors, values for patients were lower than for healthy volunteers by 18% (95% CI 4 to 29%) and 25% (7 to 39%) in summer and winter, respectively. Behavioural factors explained 25(OH)D differences between the two groups. Patients demonstrated significantly lower weekend UV-B doses, smaller skin surface-area exposure and greater sunscreen use. Photosensitive patients are at high risk of year-round low vitamin D status, contrasting with seasonal lows in healthy adults; this might potentially confer greater health risk. An estimation was made of the average supplement dose required to maintain 25(OH)D >50 nmol L^{-1};. a 1 µg day^{-1} increment in vitamin D supplement was estimated to raise summer and winter 25(OH)D by 5% (95% CI 3 to 7%) and 9% (5 to 12%) respectively. At a mean winter 25(OH)D of 29.3 nmol L^{-1} for a non-supplementing, white, photosensitive patient, an average supplement dose of 7 µg day^{-1} (95% CI 3 to 10) was suggested to maintain 25(OH)D >50 nmol L^{-1} year-round.

4.2.6.3.2 Organ transplant recipients and other patients at high risk of skin cancer

Skin cancer shows higher incidence rates in organ transplant recipients (OTR). There is a particularly high risk of SCC (up to 250-fold) and these additionally display aggressive behaviour and higher rates of metastasis in OTR, while BCC are increased ~10-fold and melanoma 2-8-fold (Euvrard et al., 2003; Reichrath, 2010). Ultimately, there is a substantial mortality in OTR related to complications of skin cancer. Risk factors contributing to their risk of NMSC are those seen in the general population, such as Fitzpatrick skin type I/II, age, and extent of exposure to UVR, and those specific to OTR, such as type and dosage of immunosuppressive treatment. The highest risk overall is seen in OTR who have been treated for many years with immunosuppressive therapy (Reichrath, 2010).

Some studies show little awareness by OTR of the measures to reduce skin cancer risks. However, OTR are increasingly educated in sun avoidance/protection practice, and these rigorous sun avoidance programmes could potentially lead to lowered 25(OH)D (Surber et al., 2012). A study in Germany found that serum 25(OH)D levels examined at winter-end in renal transplant patients with adequate renal function and practising solar protection showed a significantly lower geometric mean, of 27 nmol L^{-1}, than the 50 nmol L^{-1} in age- and sex-matched controls (Querings et al., 2006). Low vitamin D status reported in organ transplant candidates and OTR may also relate to a number of disease-specific factors (Stein and Shane, 2011).

The particularly vigilant photoprotective measures that can be advised to OTR, other immune-compromised patients, and others at high risk of skin cancer including those genetically predisposed (such as patients with basal cell naevus syndrome), potentially impact on their vitamin D gain from sunlight. Thus they may have a higher oral vitamin D requirement and assessment of their vitamin D status is indicated.

Associations between 25(OH)D levels and risk of skin cancer have been examined in several studies (Reddy, 2013), with conflicting results both for NMSC and melanoma. Sun exposure habits are a likely confounding factor. Both potentially skin cancer protective (including pro-differentiation, anti-proliferative) and promoting (immune-suppressive) actions of vitamin D have been described in skin.

4.2.6.3.3 Vegetarians and vegans

A cross-sectional study of 2107 white adults aged 20-76 years from the European Prospective Investigation into Cancer and Nutrition (EPIC) -Oxford cohort revealed that oral vitamin D intake was lower in vegetarians and vegans than in meat and fish eaters, meat eaters showing the highest mean intake of 3.1 µg day^{-1}, fish-eaters 2.2 µg day^{-1}, vegetarians

1.2 µg day^{-1} and vegans the lowest at 0.7 µg day^{-1} (Crowe et al., 2011). Their mean 25(OH)D levels were 76.4 nmol L^{-1}, 74.3 nmol L^{-1}, 66.9 nmol L^{-1} and 55.9 nmol L^{-1}, respectively, with vegans showing levels 20% (summer) to 38% (winter) lower than meat eaters.

4.2.7 Relative contributions of sunlight and diet to vitamin D status, and comparison of artificial UVR sources and supplementation in increasing 25(OH)D levels

4.2.7.1 Contributions of sunlight and diet to vitamin D status

Cutaneous synthesis of vitamin D following exposure to UV-B in sunlight is well-established as the major source of vitamin D in most situations in the UK, and it is estimated that sunlight provides 80-90% of the vitamin D source in white adults (Ashwell et al., 2010; AGNIR, 2002). Clearly, the exact contributions of sunlight and diet to vitamin D status will vary according to a range of external and personal factors (section 3.5).

Diet provides a low average amount of vitamin D (usually ~3 µg day^{-1}) in the UK, and this varies little across the seasons (Webb et al., 2010). Variations in dietary practice can influence vitamin D status, with those consuming higher amounts through vitamin D supplements (≥200 IU) and oily fish having higher status (Hyponnen and Power, 2007) and lower intake in vegetarians and vegans associating with lower 25(OH)D levels (section 4.2.6).

A seasonal 25(OH)D cycle is evident in white residents at UK latitude, 51-57°N, reflecting the ambient UV-B available to initiate cutaneous vitamin D synthesis. Year-round measurements show highest 25(OH)D levels at summer-end and lowest at winter-end, with negligible UV-B exposure in the UK winter (Macdonald et al., 2011; Webb et al., 2010). In contrast, UK residents of South Asian origin show no or minimal seasonal change in 25(OH)D, indicating a lower contribution from sunlight (Mavroeidi et al., 2010; Kift et al., 2013). Winter holidays abroad at sunny locations substantially elevate the vitamin D status of UK residents (Mavroeidi et al., 2013).

Winter vitamin D status in the UK is essentially gained from dietary intake and from stored vitamin D acquired through the skin by end of summer/autumn. However the tissue storage of vitamin D is poorly understood. A range of half-lives for circulating 25(OH)D are reported, though these are relatively short, of the order of 3-4 weeks. Observational studies including in the UK and in submariners suggest there is, however, tissue storage for several months (Ashwell et al., 2010; Macdonald et al., 2010; Webb et al., 2010).

4.2.7.2 Comparisons of UVR sources and supplementation in increasing 25(OH)D levels

The relationship between amounts of vitamin D acquired through sun-exposure and orally has been explored by Holick, who estimated (“Holick’s Rule”) that the equivalent of 1000 IU orally could be achieved through sun exposure of 0.25 total skin surface by 0.25 of an individual’s MED (1 MED being roughly 2-4 SED in white skin) (Dowdy et al., 2010). This was based on an experiment involving one exposure of the near-total body surface to 1 MED from a UV-B-rich phototherapy source including non-solar wavelengths <295 nm (Adams et al., 1982) that are very effective at production of pre-vitamin D. Recent comparison of the action spectra for erythema production and pre-vitamin D formation of this source against those for sunlight suggested that the sunlight exposure equivalent is over-estimated by about one-third (Dowdy et al., 2010). It should be noted that the estimate also involves assumptions that vitamin D production is uniform across skin sites and proportionate to area exposed and UV-dose.

Recently, studies have directly compared regimens of oral vitamin D supplements with whole body exposure to dermatology treatment lamps emitting ~311 nm (narrowband UV-B). Bogh et al. (2012a) in Sweden employed a 6-week course of UV-B (3×weekly) or 1600 IU vitamin

D plus 1000 mg calcium daily in deficient subjects (25(OH)D <25 nmol L^{-1}), while Ala-Houhala et al. (2012) in Finland utilised 4 weeks of UV-B (3×weekly, total 48.4 SED) or 800 IU of vitamin D daily in subjects with average baseline 25(OH)D >50 nmol L^{-1}. Substantially higher efficiency of narrowband UV-B was seen in raising 25(OH)D levels in both studies.

A small cross-over study in Norway found vitamin D supplements 2000 IU daily for 30 days produced a similar rise in 25(OH)D to 10× total body sunbed exposures over 35 days (total 23.8 SED); they were also equally effective in maintaining the elevated 25(OH)D levels (Lagunova et al., 2013).

Findings in individual studies may be influenced by baseline 25(OH)D level, reflecting differences in oral vitamin D intake in different countries, for example in countries, including those in Scandinavia, where there is a higher intake of oily fish.

4.2.7.3 Amounts of UVR and oral supplements for maintenance of vitamin D status during winter

Supplements: From RCTs of vitamin D supplements performed in Ireland, it was estimated that to maintain winter 25(OH)D >25 nmol L^{-1} in 97.5% of the adult population requires oral vitamin D ~7–12 µg day^{-1} (the range encompasses those who seek and those who avoid sun exposure), and to maintain 25(OH)D >50 nmol L^{-1}, an intake of ~25 µg day^{-1} (Ashwell et al., 2010; Cashman et al., 2008).

UVR lamps: An RCT aimed to examine the frequency of artificial UV exposure required to maintain 25(OH)D levels ≥50 nmol L^{-1} over winter (Bogh et al., 2012b). A once fortnightly near-total body exposure to low level broadband UV-B maintained 25(OH)D through the winter in white adults, while levels rose with weekly exposures and fell with monthly exposures.

British summer: An intervention study in Manchester (53.5°N) designed to simulate UK casual low-level summer exposures found that low dose, sub-erythemal UVR (1.3 SED[3] 3×weekly for 6 weeks, total 23.4 SED) from UV lamps to informally dressed white adults (n=120) exposing ~35% surface area produced a mean final 25(OH)D of 70(SD16) nmol L^{-1}, with 90% subjects ≥50 nmol L^{-1} (Rhodes et al., 2010) and 26% reaching ≥80 nmol L^{-1}. The findings coincide with a longitudinal observational study across the seasons in similar subjects (n=125) at the same location, where polysulphone badges showed ~3.4 SED per week attained from summer sunlight; mean end-summer 25(OH)D level was 71(SD26) nmol L^{-1}, with ≥50 nmol L^{-1} and ≥80 nmol L^{-1} reached in 82% and 24%, respectively. Regression analysis indicated a 25(OH)D level of ~80 nmol L^{-1} (76 nmol L^{-1} in women; 87 nmol L^{-1} in men) at summer-end was required to maintain ≥50 nmol L^{-1} at winter-trough (62% variance, $p<0.001$) (Webb et al., 2010).

It is possible, but untested, that more of the population could reach a higher end-summer level, if required, through modest adjustment of low level, sub-erythemal sun exposures such as with a wider skin area uncovered; alternatively vitamin D status could be enhanced orally. Increased sun-exposure could potentially assist avoidance of deficient levels in people with pigmented skins, who have low skin cancer risk, and where sun exposure is limited as in the institutionalised (section 4.2.4).

[3] 1.3 SED is equivalent to ~13 minutes of unshaded June midday sunlight exposure to a flat surface (Manchester, UK, 53.5°N). In the cabinet, ventral (front) and dorsal (back) body surfaces are exposed simultaneously; in sunlight this would be achieved by lying for ~13 minutes each on the front and back surfaces.

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Table 4.2: Vitamin D intake (µg day^{-1}) by age and sex, in the UK

Aged 1.5 years and over **National Diet and Nutrition Survey year 1, 2, 3 & 4 combined (2008/09 - 2011/12)**

Vitamin D	**Sex and age group (years)**														
	Boys			**Men**		**Girls**			**Women**		**Total**				
	4-10	11-18	Total boys	19-64	65+	4-10	11-18	Total girls	19-64	65+	1.5-3	4-10	11-18	19-64	65+
Intake from food sources															
Vitamin D µg															
Mean	2.0	2.4	2.2	3.1	3.9	1.9	1.9	1.9	2.6	2.9	1.9	2.0	2.1	2.8	3.3
Median	1.9	2.1	2.0	2.5	3.2	1.7	1.6	1.7	2.1	2.5	1.4	1.8	1.8	2.3	2.7
sd	1.0	1.3	1.2	2.3	2.7	1.1	1.2	1.2	1.9	1.9	2.0	1.1	1.3	2.1	2.3
Upper 2.5 percentile	4.5	5.7	5.4	9.2	11.9	4.2	4.9	4.6	7.5	7.7	8.5	4.4	5.4	8.5	9.2
Lower 2.5 percentile	0.5	0.4	0.5	0.5	0.9	0.4	0.3	0.4	0.4	0.5	0.3	0.4	0.4	0.5	0.7
Intake from all sources[a]															
Vitamin D µg															
Mean	2.7	2.6	2.7	3.9	5.1	2.6	2.1	2.3	3.4	5.2	2.3	2.7	2.4	3.6	5.1
Median	2.1	2.2	2.2	2.7	3.7	1.9	1.7	1.8	2.5	3.5	1.5	2.0	1.9	2.6	3.6
sd	2.1	1.9	2.0	4.5	4.0	4.5	1.6	3.2	3.0	4.8	2.4	3.5	1.8	3.8	4.5
Upper 2.5 percentile	8.0	7.7	7.7	12.3	16.8	7.3	6.4	6.9	11.8	20.2	10.6	7.5	6.9	12.0	19.2
Lower 2.5 percentile	0.6	0.4	0.5	0.6	0.9	0.4	0.3	0.4	0.5	0.7	0.3	0.5	0.4	0.6	0.8
No. of people	665	744	1409	1126	317	612	753	1365	1571	436	604	1277	1497	2697	753

[a] All sources include the contribution from dietary supplements containing vitamin D

Table 4.3: Average daily intake of vitamin D as a percentage of Reference Nutrient Intake (RNI), by age and sex, in the UK

Aged 1.5 years and over		**National Diet and Nutrition Survey year 1-4 combined (2008/09 - 2011/12)**			
Vitamin D		**Sex and age group (years)[b]**			
		Total	**Men**	**Women**	**Total**
		1.5-3	65+	65+	65+
		%	%	%	%
Food sources only					
Vitamin D	Mean	27	39	29	33
	Median	20	32	25	27
	sd	29	27	19	23
All sources[a]					
Vitamin D	Mean	32	51	52	51
	Median	21	37	35	36
	sd	34	40	48	45
No. of people		604	317	436	753

[a] All sources includes the contribution from dietary supplements containing vitamin D

[b] At the time of the NDNS survey 2008/09-2011/12, there were no RNIs set for people between the ages of four and 64 years; therefore % RNI is only expressed for those aged 1.5 to three years and 65 years and over.

Table 4.4: Average daily intake of vitamins as a percentage of Reference Nutrient Intake (RNI)[c], by age, in the UK

Diet and Nutrition Survey of Infants and Young Children aged 4-18 months					
Vitamin D		**Age group (months)**			
		4-6	**7-9**	**10-11**	**12-18**
		%	%	%	%
All sources					
Vitamin D non-breastfed[a]	Mean	117	127	111	55
	Median	115	126	111	27
	sd	34	44	50	55
Vitamin D breastfed excluding breast milk[b]	Mean	41	52	54	37
	Median	27	44	45	21
	sd	44	39	51	40
Food sources					
Vitamin D non-breastfed[a]	Mean	115	125	108	50
	Median	113	124	108	24
	sd	32	41	49	50
Vitamin D breastfed excluding breast milk[b]	Mean	35	46	38	26
	Median	18	37	31	17
	sd	41	37	33	24
No. of people		329	630	449	1275

[a] Vitamin D intake does not include values for breastfed children as the vitamin D content of breast milk is not known. The numbers of people are: 240 for 4-6M, 489 for 7-9M, 381 for 10-11M and 1177 for 12-18M. Breastfeeding status is defined by whether it was recorded in the four-day diary.

[b] Vitamin D intake includes values for breastfed children excluding the contribution from breast milk (therefore excluding any exclusively breastfed children (n=2)) as the vitamin D content of breast milk is not known. The numbers of people are 89 for 4-6M, 141 for 7-9M, 68 for 10-11M and 98 for 12-18M. Breastfeeding status is defined by whether it was recorded in the four-day diary.

[c] The RNIs referred to are those that were in place at the time of the NDNS survey 2008/09-2011/12.

5. Vitamin D and health

5.1 Impact of vitamin D on skeletal health

Although abnormal plasma/serum 25(OH)D concentrations have been posited to affect the risks of a range of human disease the strongest evidence is for certain skeletal diseases.

5.1.1 Introduction

Bone health is dependent on calcium metabolism and vitamin D plays an established key role in calcium homeostasis through its influence on calcium absorption and bone mineralisation. The skeletal system undergoes several distinct life stages spanning bone accretion in utero, childhood and adolescence followed by bone maintenance in early adult life and bone loss during late adulthood. There is a substantial literature of both observational studies and randomised controlled trials (RCT) in these areas, but methodological issues often limit interpretation. Several extensive and detailed reviews (SACN, 2007; SACN, 2016; AHRQ, 2007 [Cranney A et al.]; AHRQ, 2009 [Chung M et al.]; IOM, 2011; NORDIC, 2013 [Lamberg-Allardt et al.]) addressing the relationship between vitamin D and skeletal health have been completed in recent years and with more recent trial and study data, form the basis for this section.

5.1.2 Other factors influencing skeletal health

Many other factors apart from vitamin D are known to influence bone health including dietary calcium and phosphorus, age, body mass index, physical exercise, and hormonal status. These additional factors are often difficult to evaluate accurately and control for in large scale studies which has frequently complicated their interpretation.

5.1.3 Bone Health Biomarkers: BMD and BMC

Bone mineral density (BMD) and Bone Mineral Content (BMC) are bone mass biomarkers most commonly derived from non-invasive DEXA (Dual Energy X-ray Absorptiometry) measurements obtained at specific skeletal locations. BMD is typically estimated from a 2D cross sectional BMC measurement where 32% of the mineral detected in bone is assumed to be calcium. More accurate measures of BMD can be obtained using 3D or volumetric measurements, typically obtained with a dual energy CT system. BMC measurements alone are more widely used in children where rapid bone growth may influence the BMD estimate.

5.1.4 Rickets

Rickets is a childhood disease with characteristic deformities (bowing of the long bones), fractures and stunting of the developing skeleton. These and other features of rickets were described in the 17th century by Glisson (Dunn, 1998) who correctly identified that the condition was neither inherited nor contagious. The causal relationship between rickets, lack of sunlight and vitamin D deficiency was not discovered until the late 19th and early 20th century (Rajakumar, 2003), a time when the disease was widespread amongst children in poor communities in Europe and North America. The relationship between geographical latitude and the incidence of rickets was demonstrated by Palm who correctly associated this with sunlight exposure (Palm, 1890). Animal experiments by Mellanby published in 1919 clearly established that rickets could be treated by dietary intervention although the exact

nature of the anti-rachitic factor was not discovered until 1922 following further experimentation by McCollum and colleagues (McCollum, 1957). The linkage between sunlight exposure, serum 25(OH)D levels and rickets was made in a series of classic studies on human infants in 1922 (Chick, 1976). Following these discoveries many governments intervened in the first half of the 20th century to add vitamin D to foods (milk, margarine) and the incidence of rickets declined rapidly. The role of vitamin D supplementation is being reconsidered given the overall improvements in nutrition and environment as well as the persistence of rickets in some UK population groups.

The AHRQ review (Cranney A et al., 2007) reported there was reasonable evidence for an association between serum 25(OH)D levels and rickets but that evidence was too limited and inconsistent to set a threshold above which rickets does not occur. Mean serum 25(OH)D levels of 30 nmol L^{-1} were reported in several studies in children with confirmed rickets but other studies reported higher mean levels up to 50 nmol L^{-1}. The IOM review (IOM, 2011) considered that these differences most likely related to variations in dietary calcium intake and that studies from developing countries with low calcium intakes were more likely to have rickets at higher mean serum 25(OH)D levels. It was noted that a minimum dietary calcium intake to prevent rickets has not been determined.

In the UK there is evidence that at the same latitude (Birmingham, 52.5°N) adult populations of South Asian origin have relatively lower levels of serum 25(OH)D and that children of South Asian origin have a higher incidence of rickets than white children (SACN, 2007). In the USA populations of African American origin with increased skin pigmentation also have lower vitamin D levels than otherwise similar Caucasian populations. However there is evidence they have a higher mean bone mass during their life cycles, and are less prone to developing osteoporosis related fractures in old age (IOM, 2011). This apparent paradox is unresolved and the IOM considered that the available evidence was not sufficient to influence policy and that further research is required.

5.1.5 Osteomalacia

Osteomalacia, is characterised by low serum phosphate, elevated parathyroid hormone levels and inadequate bone mineralisation leading to bone deformities and insufficiency fractures in the mature skeleton. This was recognised during the 20th century as the effect of vitamin D deficiency in adults and mature (ie fused growth plates) bones in children. Vitamin D deficiency associated with osteomalacia may arise from malabsorption, chronic anti-convulsant therapy, coeliac disease, systemic malignancy, and renal tubular acidosis or from inherited defects of vitamin D and phosphorus metabolism. A confident diagnosis of osteomalacia often requires histopathological confirmation on a bone biopsy sample, an invasive procedure; this, it has been argued, may lead to underdiagnosis (IOM, 2011).

5.1.6 Osteoporosis

Osteoporosis is characterised by a decrease in bone mass and density, but with typically normal serum calcium and phosphate levels (unlike rickets and osteomalacia). It is more common in the elderly and predisposes to fractures particularly involving the hip and spine. It is commoner in women than men and in women is more frequent following the menopause. Several factors including hormone imbalances, chronic illness and drug treatment have been causally implicated. A causal role for vitamin D has not been established (IOM, 2011). Osteoporosis is associated with high morbidity and an increasing societal health care burden owing to treatment costs, related complications and disability (Strom et al., 2011).

5.1.7 Fracture risk in the elderly

BMD is strongly associated with fracture risk in the elderly population (particularly hip, vertebrae and forearm), (IOM, 2011). BMD is also reduced in both osteoporosis and osteomalacia. Although hip fracture in the elderly is most commonly associated with

osteoporosis there is post-mortem and other evidence that osteomalacia co-exists with osteoporosis in up to 40% of elderly patients at the time of their first hip fracture (IOM, 2011).

The IOM reported that associations between plasma/serum 25(OH)D concentrations and fracture risk were not consistent (IOM, 2011). AHRQ Ottawa concluded that supplementation of vitamin D with calcium reduced risk of fracture in institutionalised elderly over 71 years of age. The evidence from cohort studies and randomised controlled trials published subsequent to the above systematic reviews is inconsistent. Meta-analyses of studies using vitamin D supplements with fracture risk as outcome suggest a protective effect of vitamin D (Bischoff-Ferrari et al., 2009, 2012) but these studies have limitations and have been the target of substantive criticism, including by IOM (2011). Overall the data in this area remain discordant.

5.1.8 Stress fracture risk

Stress fractures typically occur following prolonged exercise in the physically active, typically during adolescence and early adult life, and are not usually the result of direct trauma. Several studies in military recruits have given conflicting results regarding an association between serum 25(OH)D concentrations and stress fractures (Givon, 2000; Välimäki, 2005; Ruohola, 2006).

Moran et al. (2012) demonstrated an association between dietary intake of vitamin D and stress fracture incidence. Lappe et al. (2008) demonstrated a reduction in stress fracture incidence in female Navy recruits receiving vitamin D and calcium supplements; however this study failed to control for BMD, hormonal status and dietary calcium intake. Overall the evidence for a relationship between stress fracture incidence and serum 25(OH)D levels is inconclusive.

5.1.9 Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative disease that involves the loss of articular cartilage with associated changes involving adjacent subchondral bone. Several observational studies have found a positive association between serum 25(OH)D concentrations and the severity and rate of progression of osteoarthritis but the IOM review (IOM, 2011) concluded there was insufficient evidence overall to confirm this association.

5.1.10 Muscle function

Muscle weakness and pain are recognised characteristics of rickets and osteomalacia (IOM, 2011). There is evidence from animal and human studies for a role of serum 25(OH)D in muscle function (Ceglia, 2013).

Observational studies conducted in young people and adults have produced mixed evidence for an association between vitamin D status and muscle function (Ward et al., 2009; Ceglia et al., 2011; Stockton et al., 2011). Only a few intervention RCTs and cohort studies of supplementation in these two age groups have been performed. These reported significant improvements in some but not all measured muscle parameters in groups with baseline serum OHD levels of <50 nmol L^{-1} (Ward, 2010; Wyon, 2013; Gupta, 2010).

There have been more cohort studies and RCTs both of baseline 25(OH)D levels and interventions with supplementation related to muscle performance in adults >50 yrs (Beaudart et al., 2014). These have given inconsistent results with some studies demonstrating significant performance improvements, typically in narrowly defined patient groups (eg institutionalised stroke patients), but others demonstrating no effect.

Overall there is limited evidence of a small beneficial effect of Vitamin D supplementation on several muscle performance parameters in those with serum OHD levels <50 nmol L^{-1}. Further research and larger randomised controlled trials are required to confirm these findings.

5.1.11 Falls in the elderly

Meta-analyses of vitamin D supplementation and risk of falling suggest that vitamin D supplementation may reduce the risk of falling in elderly people with low serum 25(OH)D concentrations (Bischoff-Ferrarri et al., 2009; Murad et al., 2011). However, there is considerable heterogeneity in the literature reporting studies of vitamin D and risk of falling, and some controversy regarding both study methodology and interpretation of the published results.

Paradoxically, there is also some evidence that high dose vitamin D supplementation might increase the risk of falls (Sanders et al., 2010; IOM, 2011). This has been an inconsistent finding but has given rise to concern that high dose vitamin D supplementation in the elderly may not be without hazard.

5.1.12 Pregnancy, lactation and infancy

During pregnancy mineralisation of the fetal skeleton is relatively limited, as the majority of development is cartilaginous, but mineralisation increases substantially after delivery and during the first three years of life. During lactation there is definite evidence of maternal BMD loss of up to 15% but published studies in normal populations demonstrate that this loss is corrected when lactation ends. There is good evidence that vitamin D supplementation during pregnancy increases maternal serum 25(OH)D concentrations in a range of different ethnicity study populations (SACN, 2007). However the IOM review (IOM, 2011) concluded there was no evidence that maternal serum 25(OH)D concentrations influenced materno-fetal calcium transfer and no evidence of an increased maternal requirement for vitamin D or calcium during pregnancy. The IOM review concluded there was no evidence that vitamin D supplementation during pregnancy or lactation influenced the fetal, infant, or maternal skeletal health outcomes.

In the UK in 2003 the National Institute for Clinical Excellence (NICE) determined that there was insufficient evidence of benefit to recommend vitamin D supplementation in pregnancy. However in 2008 NICE (NICE public health guidance 11) revised this position, which concurred with the position statement of SACN in 2007, that vitamin D supplementation is recommended for pregnant and lactating women (particularly those with reduced UV-B exposure) and for exclusively breast fed infants during the first five years of life.

In the North American setting the IOM (2011) review did not recommend routine supplementation during pregnancy. There are several important differences between the UK and USA study contexts, which may partly explain the different recommendations in the two regions. Milk in the USA is fortified with vitamin D whereas it is not in the UK (and most of Europe) where flour and margarine are typically fortified. Additionally there are differences in latitude, sun exposure behaviour, and study population ethnicity. North American dietary surveys indicate overall higher mean serum 25(OH)D concentrations when compared with the UK.

5.1.13 Hypervitaminosis D

Multiple case reports of the effects of accidental or intentional overdosing with oral or parenteral Vitamin D have been published since it became possible to synthesise vitamin D (IOM, 2011; DeLuca, 1974). These document hypercalcaemia, increased bone sclerosis on X-ray and eventual soft tissue calcification with related cardiac and renal impairment. These cases have usually involved abnormally large doses of vitamin D being given experimentally

or inadvertently. The Committee on Toxicity of the Food Standards Agency has recently reviewed the evidence for adverse effects of vitamin D supplementation and have endorsed the tolerable upper levels proposed by the European Food Standards Agency of 100 µg day^{-1} for adults and children aged 11-17 (COT, 2014). They identified that these levels may be inappropriately high for individuals with diseases that predispose to hypercalcaemia such as sarcoidosis and tuberculosis.

5.2 Other potential health impacts of vitamin D (adverse and beneficial)

5.2.1 Introduction

While the effect of vitamin D (and calcium) on bone health is established, numerous studies have also been performed on non-musculoskeletal health outcomes, mostly hypothesizing a beneficial effect of vitamin D, but more recent data indicating also a possibility of an adverse effect on some outcomes. Research on extra-skeletal effects of vitamin D has been stimulated by ecological studies of disease incidence in relation to latitude or levels of solar radiation in different countries or regions (Garland and Garland, 1980; Simpson et al., 2011), as well as the discovery of the vitamin D receptor (VDR) in tissues that are not associated with calcium homeostasis, such as skin, breast, prostate, pancreas and colon cancer cells (Christakos and DeLuca, 2011). Studied outcomes are for example cancer, cardiovascular disease, metabolic syndrome, diabetes, asthma, multiple sclerosis, rheumatoid arthritis and other autoimmune diseases, tuberculosis, neuropsychological functioning such as autism, and pregnancy outcomes.

This section reviews the scientific evidence from studies in humans. A comprehensive review of the epidemiological evidence on vitamin D and health can be found in the recent report from the UK Scientific Advisory Committee on Nutrition (SACN, 2016). Extra-skeletal effects of vitamin D have been studied extensively also in experimental animals; reviews of this evidence can be found for example in the report by the US Institute of Medicine (IOM) (IOM, 2011), and in a review by Christakos and Deluca (Christakos and DeLuca, 2011).

This chapter is limited to health outcomes where evidence is available from several prospective observational studies and randomised clinical trials, ie the study designs that provide the most valid information in this field, as discussed below. Thus, it does not cover all outcomes listed above. In addition, this chapter is not intended to be a comprehensive review of all individual original scientific studies, but rather a summary of the scientific evidence based primarily on the most up-to-date systematic reviews.

Epidemiological studies of health effects related to vitamin D face several challenges. Exposure to vitamin D can be by dietary intake or synthesis in the skin on exposure to UV. Estimates of serum concentration of 25(OH)D are used as an indicator of vitamin D status, and are considered to reflect the contribution from the diet and cutaneous synthesis (see Chapter 4). The relationship between the concentration of 25(OH)D and vitamin D intake has been characterised in many RCTs. Despite its acceptance as a biomarker of vitamin D status the use of serum concentration of 25(OH)D in epidemiological studies has limitations. Blood samples are usually only collected at one point in time, and may be affected by season of blood draw because cutaneous synthesis of vitamin D is limited during the winter. The serum concentration of 25(OH)D may also be affected by the disease itself or its treatment; thus, blood samples must be taken prospectively, making cross-sectional studies and traditional case-control studies with blood sampling after disease occurrence sensitive to reverse causality and therefore less informative.

Some epidemiological studies have assessed vitamin D status by prediction from questionnaire information, with varying degree of detail, eg based on a number of factors

assumed to affect 25(OH)D levels, or simply based on questionnaire information on dietary vitamin D intake. Estimates of dietary intake of vitamin D are subject to the same limitations known to exist for other nutrients when self-reported methods are used, as is assessment of other factors of importance such as exposure to UV radiation.

Confounding from characteristics that affect serum 25(OH)D concentration, which are also used to estimate 25(OH)D levels from questionnaire information, such as geographic location, skin pigmentation, dietary vitamin D intake, supplements, adiposity, and leisure time physical activity (as a surrogate for sunlight exposure), may be insufficiently controlled in observational studies, both in studies using blood samples to estimate serum 25(OH)D concentration and the much less precise estimates from questionnaire responses. The degree of potential confounding is dependent on the aetiology of the studied disease.

The ideal study design to address the question about the effect of vitamin D on various health outcomes is a randomised controlled trial, which through the randomization takes care of potential confounding, and the controlled exposure takes care of reverse causality. Such studies need, however, to be large enough and have sufficiently long treatment and follow-up periods to estimate adequately potential effects on rare outcomes, and outcomes with long latency periods, such as the incidence of specific cancer subtypes. Notwithstanding these challenges many informative studies have been conducted, some of which suggest an association between vitamin D status and/or intake and some health outcomes.

Numerous scientific studies have been performed on the potential effects of vitamin D on various chronic diseases, which have been summarized in systematic reviews including a report by the US IOM on dietary reference intakes 2011 (IOM, 2011), a review for the fifth version of the Nordic nutritional recommendations (NNR5) 2013 (Lamberg-Allardt et al., 2013), and some more recent systematic reviews published in the scientific literature (Autier et al., 2014b).

5.2.2 Cancer

Epidemiological research in this area has increased considerably over recent years, and has been systematically reviewed by expert groups commissioned by for example the International Agency for Research on Cancer (IARC, 2008), the US Agency for Healthcare Research and Quality, referred to as AHRQ in the remainder of this report (Chung et al., 2009; Cranney et al., 2007), the US IOM (IOM, 2011), and the Nordic NNR5 (Lamberg-Allardt et al., 2013). These expert groups have taken slightly different approaches, with more formal quality assessments performed by AHRQ, IOM and NNR5, while the IARC report reviewed observational studies on sun exposure, intake of vitamin D, and serum 25(OH)D, and conducted a meta-analysis of observational studies of vitamin D levels and some specific cancer types. The most recent systematic review, which included only RCTs and prospective cohort and nested case-control studies with measured serum 25(OH)D, was published in 2014 by Autier and colleagues (Autier et al., 2014b).

IARC concluded in 2008 that the evidence from the observational epidemiological studies on the incidence of colorectal cancer and sporadic colorectal adenoma was “consistent and persuasive” for an inverse association with serum 25(OH)D levels, whereas the IOM expert group (2011), incorporating also the AHRQ review, found the evidence from observational studies on colorectal cancer inconsistent, based on one prospective cohort study that reported an inverse association while most nested case-control studies found no effects. This was also the conclusion of the NNR5 review (Lamberg-Allardt et al., 2013). The recent systematic review by Autier and colleagues included a larger number of observational studies than the IOM report, with the latest published in 2013. An inverse association with plasma 25(OH)D concentration was observed for colorectal cancer based on 10 observational studies, with the cut-point for the lowest quantile varying between 10 and 20 nmol L^{-1} and the cut-point for the highest quantile between 19 and 42 nmol L^{-1}. Thus, there is some support from prospective observational studies for a reduced incidence of

colorectal cancer related to higher 25(OH)D concentrations, but confounding or reverse causation cannot be ruled out with reasonable confidence.

All three expert groups, as well as Autier and colleagues, concluded that the evidence from randomised controlled trials of vitamin D supplementation did not support an effect of 25(OH)D levels on colorectal cancer risk, but noted that only few randomised trial data are available. So far, only the Women's Health Initiative Investigation has studied the effect of vitamin D supplementation on colorectal cancer risk (Brunner et al., 2011; Wactawski-Wende et al., 2006), including 36,282 participants, with a mean follow-up of 7 years in the latest publication. Participants in the treatment group received a daily dose of 400 IU vitamin D_3 (10 µg). Personal use of vitamin D supplements was, however, common in both the treatment and placebo group and increased during the follow-up to reach about 52% in both groups at year 6, which may have diluted the exposure contrasts between the groups. At least 70% of the participants in each group took at least 50% of their study medication through year 6. Although this RCT is large, it is possible that the treatment and follow-up period is insufficient to detect an effect on cancer risk.

For breast cancer, IARC stated that some studies suggested an inverse association with 25(OH)D levels, but with large differences between studies, and when case-control studies were excluded from the meta-analysis the evidence was only weak. The IOM and the Nordic expert groups reached similar conclusions, based on a larger set of studies. Results from the large RCT based on the Women's Health Initiative did not suggest any effect on breast cancer development from vitamin D supplementation, nor any effect on benign proliferative breast disease (Rohan et al., 2009). For prostate cancer, all three expert groups conclude that the findings suggest no effect of 25(OH)D levels (15 studies were reviewed by the IOM expert group), although no RCTs had been conducted.

For other tumours the evidence was insufficient for an evaluation at the time of the IARC review. The more recent systematic review by Autier and colleagues summarizes evidence from cohort and nested case-control studies with measured serum 25(OH)D and RCTs for a number of other cancer outcomes; no consistent effects were observed on the incidence of oesophageal and gastric cancer (9 studies), ovarian cancer (7 studies), endometrial cancer (7 studies), non-Hodgkin lymphoma (10 studies), bladder and kidney cancer (9 studies), or skin cancer (3 studies). For pancreatic cancer a significantly increased risk was observed at high 25(OH)D concentrations (≥100 nmol L^{-1}), based on a pooling of 8 cohort studies (Stolzenberg-Solomon et al., 2010), but no effect on pancreatic cancer risk was found in the Women's Health Initiative RCT. IARC found no indications of adverse effects from long-term maintenance of high levels of 25(OH)D.

5.2.3 Type 2 diabetes and metabolic syndrome

Cross-sectional studies have reported lower levels of 25(OH)D among persons with prevalent diabetes, metabolic syndrome or hyperglycaemia, but the study design does not allow determination of the temporality of events, which prevents conclusions about causality. The IOM review concluded that prospective studies supported an inverse association between serum 25(OH)D levels and type 2 diabetes, but limitations in study design prevented firm conclusions (IOM, 2011). Confounding from overweight and obesity were mentioned as potential sources of bias. Evidence from RCTs did not support a protective effect of vitamin D supplementation on type 2 diabetes. The Nordic evaluation reached the same conclusions (Lamberg-Allardt et al., 2013).

The systematic review by Autier et al., (2014b) identified prospective observational studies that included in total well over 70,000 participants, and found consistent inverse associations between serum 25(OH)D and the incidence of type 2 diabetes. Another systematic review and meta-analysis of the observational studies reported a 40% reduced risk of type 2 diabetes in the category with the highest 25(OH)D concentration compared with the category with the lowest concentration (Song et al., 2013), corresponding to a 4% lower risk of type 2

diabetes with each 10 nmol L^{-1} increment in 25(OH)D levels in a linear trend analysis. Whether the association reflects a causal effect is unclear: reverse causation or confounding from lifestyle including physical activity have been suggested as potential explanations. Randomised clinical trials have not provided support for a causal effect; a meta-analysis of 35 short-term RCTs (follow-up ranged from 4 weeks to 7 years) did not find an effect of vitamin D supplementation on the risk of type 2 diabetes (Seida et al., 2014). Furthermore, no association was found with other indicators of glucose homeostasis including insulin resistance (Seida et al., 2014). Similarly, the systematic review by Autier and colleagues (Autier et al., 2014b) did not find support for an effect in any of several RCTs of diabetes incidence or other indicators of glucose metabolism disorders. With the exception of the Women's Health Initiative study, the RCTs were quite small.

Mendelian randomization studies have also been used to address causality. The results of the most recent and most comprehensive of these did not provide support for a causal association between circulating 25(OH)D levels and type 2 diabetes (Ye et al., 2015). This study is based on >100,000 individuals (28,000 patients with type 2 diabetes) of European descent, four genetic variants as instruments and uses several indicators of glucose metabolism as outcome (fasting insulin levels and Hba1c) besides type 2 diabetes.

Taken together, the current literature does not support that vitamin D supplementation can be used for prevention of type 2 diabetes nor that it improves glucose homeostasis, but results from long-term randomised trials are still lacking.

5.2.4 Multiple sclerosis

Observations of a latitude gradient in the prevalence of multiple sclerosis (MS) has been reported (Simpson et al., 2011), and vitamin D deficiency in populations living in geographical areas at high latitudes has been hypothesised as a possible explanation. There may, however, also be other differences between geographical regions, eg in climate and in the completeness of national MS registers, which could be alternative explanations of such ecological observations.

Observational studies of MS that have measured serum 25(OH)D were reviewed by the IOM expert group, which concluded that they did not provide consistent evidence that serum 25(OH)D is associated with a reduced risk of MS, but findings varied considerably. No RCT was available at the time of the IOM report. The NNR5 report did not identify any systematic reviews of MS, nor any RCTs (Lamberg-Allardt et al., 2013), while the most recent systematic review (Autier et al., 2014b) identified three prospective observational studies of which two found an inverse association and one found no effect of serum 25(OH)D levels on MS. Six recent RCTs of clinical endpoints related to MS (relapse, disability) found no effect of vitamin D supplementation on the clinical course of MS (Autier et al., 2014b).

Differences in MS occurrence according to month of birth have also been reported (Dobson et al., 2013), with a higher risk of MS among those born in April and May in studies from the northern hemisphere, and a reduced risk among those born in October and November, which has been interpreted as indirect evidence of a pre-natal effect of vitamin D on MS occurrence. This was, however, not confirmed in a Swedish nested case-control study where measurements were made of the 25(OH)D concentration in neonatal blood spots from MS patients and healthy controls (Ueda et al., 2014).

5.2.5 Cardiovascular outcomes

Most of the available large prospective cohort studies found inverse associations between serum 25(OH)D levels and CVD outcomes (IOM, 2011), while some of the earlier studies reviewed in the AHRQ report indicated a U-shaped association (Chung et al., 2009), with increased risk of CVD both at low and at high levels of 25(OH)D. None of the RCTs found effects of vitamin D supplementation on CVD risk (IOM, 2011; Lamberg-Allardt et al., 2013).

The most recent systematic review (Autier et al., 2014b) identified 4 meta-analyses with prospective observational studies of multiple CVD outcomes, including together around 20 studies and more than 70,000 participants, and 14 additional observational studies not included in any meta-analysis. All meta-analyses and the majority of the newer observational studies found an inverse association between serum 25(OH)D levels and CVD outcomes such as myocardial infarction, stroke and hypertension, as well as broader disease categories like 'cardiovascular disease'. In contrast, results from a large number of RCTs indicated no effects of vitamin D supplementation on a large number of outcomes studied in relation to cardiovascular health, with a few exceptions (Autier et al., 2014b). Another recent meta-analysis of 21 randomised clinical trials of vitamin D supplementation and cardiovascular disease found no effect on the risk of myocardial infarction or stroke (Ford et al., 2014).

5.2.6 All-cause mortality

For all-cause mortality, some observational studies have indicated a U-shaped or reverse-J-shaped dose response pattern (IOM, 2011; Chung et al., 2009). Other studies simply reported higher mortality at low serum 25(OH)D concentrations (IOM, 2011). Results from trials with vitamin D supplementation reviewed by the IOM indicated a slightly lower mortality in the treatment group, although non-significant. The Nordic report identified only one systematic review of observational studies (Lamberg-Allardt et al., 2013), which found no association between 25(OH)D concentration and mortality in four cohort studies, and an inverse trend in one study. Results from RCTs indicated a reduced mortality particularly when vitamin D was administered together with calcium. The most recent systematic review (Autier et al., 2014b) reported an inverse association in two meta-analyses of prospective studies, the largest based on over 60,000 individuals, and a large number of additional observational studies not included in the meta-analyses, comprising altogether over 200,000 persons. The results from the observational studies consistently showed inverse associations between serum 25(OH)D concentrations and all-cause mortality. Also the RCTs identified reported a lower mortality in the vitamin D treatment groups. The authors noted that trials often included elderly women and a large proportion of persons living in institutions (Autier et al., 2014b).

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6. Conclusions

6.1 Sources of ultraviolet radiation exposure

For most people the major source of UVR exposure is the sun. However, for some individuals, for at least some of the time, UVR from artificial sources may be a major contributor to their total exposure. Such sources include those used for medical therapy, cosmetic tanning and a few industrial sources.

Ground-level measurements of solar UVR have been made worldwide for many years. They provide only a limited database for assessing personal exposure to solar UVR, primarily due to the challenges of converting from measurements made on the horizontal plane to actual radiant exposures received by people in practice.

UVR from the sun can contribute to erythema risk and to pre-vitamin D_3. The relative efficiency for each is dependent on the UVR spectrum. Solar radiation data, expressed as solar UV Index, which is weighted with the erythema action spectrum, are readily available. Weighting data for pre-vitamin D production are not so available.

Occupational exposure considerations for artificial UVR are likely to be dominated by the risk of erythema and exposure should be minimised in accordance with legal requirements.

6.2 Vitamin D and metabolism

Vitamin D takes two forms. Vitamin D_3 comes from endogenous cutaneous synthesis. Dietary and supplementary vitamin D can be either vitamin D_2 or vitamin D_3. The generic term vitamin D refers to either form (or both). Vitamin D is metabolised in the liver and then the kidney and other tissues. The liver metabolite, 25(OH)D, is most commonly used as the marker of vitamin D status. Vitamin D has an established role in calcium metabolism and skeletal health. Serum Ca^{2+} can be within the normal range even when levels of 25(OH)D are very low.

Measurement of serum 25(OH)D concentration is accepted as the best, most reliable indicator of vitamin D status in view of its long circulating half-life and absence of tight homeostatic control. Two forms, $25(OH)D_2$ and $25(OH)D_3$, together make the total circulating 25(OH)D. It can be measured by two groups of techniques, ie immunochemical or chromatographic/physical detection methods, with Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS) likely to become the “gold standard” for assay performance in the future.

There is wide variation in measurement of 25(OH)D concentrations, made using different methods and in different laboratories, making it challenging to compare or combine datasets. While the Vitamin D External Quality Assurance Scheme (DEQAS) monitors the performance of analysts and 25(OH)D analytical methods, the introduction of the National Institute of Standards and Technology (NIST) reference standards is assisting improvement in the variability of methods. International standardisation of serum 25(OH)D measurement is also being progressed by the Vitamin D Standardization Program (VDSP).

The synthesis of vitamin D is initiated by the absorption of UV-B radiation by 7-dehydrocholesterol in the skin, which gives rise to pre-vitamin D that thermally converts to

vitamin D. Biologically active vitamin D requires two hydroxylation steps, primarily in the liver and kidney respectively. However, many tissues have the enzymes to complete both steps.

Information on the vitamin D status of the UK general population is taken from national surveys (DNSIYC, NDNS, HSE, SHS). In the UK, low vitamin D status has been considered by the Scientific Advisory Committee on Nutrition (SACN) as a plasma 25(OH)D concentration below 25 nmol L^{-1} and hence nutrition surveys have frequently reported the proportion of the population with concentrations below this.

National surveys indicate that 6% of infants aged 5-11 months, 2% of infants aged 12-18 months, 14% of children aged 4-10 years; 22% of adolescents aged 11-18 years; 23% adults aged 19-64 years; and 21% adults aged 65 years and over have plasma 25(OH)D concentrations below 25 nmol L^{-1}.

Vitamin D status varies according to season, broadly speaking, the proportion of people with a 25(OH)D concentration below 25 nmol L^{-1} at the end of winter (March) is greater than the proportion with low status at the end of summer (September), Vitamin D status varies with location in the UK. It also varies with Body Mass Index (BMI) and skin colour, with lower plasma levels generally found in people with higher BMI and in those with darker skin.

Variation in vitamin D status is attributable primarily to variation in the amount of vitamin D synthesised in the skin following exposure to UV-B in sunlight, with generally low, constant amounts obtained from dietary sources. External conditions ie latitude, season, time of day, atmospheric conditions and weather, personal conditions including skin melanisation and metabolic factors, and lifestyle and sun-exposure behaviour as well as diet, all contribute to variation in vitamin D status within the UK.

6.3 Diet and photobiology

6.3.1 Dietary and supplemental sources of vitamin D in the UK

The main dietary sources of vitamin D are foods of animal origin, fortified foods and food supplements. In national surveys, mean intakes for non-breast fed infants aged 4-18 months were above the Reference Nutrient Intake (RNI)[4] except at 12-18 months, when the mean intake was 55% of the RNI. Mean intakes for breast fed infants were below the RNI at all stages of infancy. The mean intake for children aged 1.5-3 years was 32% of the RNI and for adults aged 65 years and over was 51% of the RNI.

There are no RNIs set for people aged 4-65 years. The mean intake for children aged 4-10 years was 2.7 µg day^{-1}, for adolescents aged 11-18 years was 2.4 µg; and for adults aged 19-64 years was 2.8 µg.

6.3.2 Action spectrum of pre-vitamin D synthesis and the relationship between UVR dose and changes in vitamin D status

Action spectroscopy provides information on the relative efficacy of given wavelengths to induce a given photobiological outcome. An action spectrum can be used as a weighting function for solar, or other, UVR emission spectra. The action spectra for pre-vitamin D and

[4] RNIs referred to are those in place at the time of the surveys reported in Lennox et al., 2011 and Bates et al., 2014.

erythema, which overlap in the UV-B region, have been used to make risk benefit assessments of solar UVR under given conditions. Changes in vitamin D status are UV-B dose dependent but baseline status and body surface area exposed are also determining factors.

6.3.3 Effect of external factors on solar UVR-induced vitamin D status (time of day, season, latitude, weather, etc)

External factors influencing the amount of ambient UV-B available for cutaneous vitamin D synthesis can be divided into the predictable, ie latitude, season and time of day, with the highest amounts seen at lower latitudes, during the summer season and hours around noon, and the less predictable, ie the weather, or state of the atmosphere. Reflectivity of the earth's surface also influences the amount of UV-B incident at the skin surface, with augmentation by snow and water. Structures in the local environment, eg tall buildings, are a further external modifier.

Ambulant white 20-60 year old adults at mid-UK latitude are exposed to a median of 3.7 SED of UVR/week from spring/summer sunlight and 0.1 SED in winter, producing a clear seasonal pattern in 25(OH)D level with peak in September and trough in February. Brief (approximately 15 minutes) noon-hour exposures to UK summer sunlight several times per week while casually dressed lead to 25(OH)D >50 nmol L^{-1} in the majority (90%) of white adults. With this regimen, a plateau in 25(OH)D appears from 5 weeks, which may reflect skin photoadaptation.

6.3.4 Effect of personal attributes on UVR induced vitamin D status (including skin colour, age group, volume, groups with low levels)

People with pigmented skin have lower vitamin D status than those with white skin living at the same location, and the absorption and scattering of incident UV-B by melanin may play a substantial role in this. Comparative UVR intervention studies in people of different colour have shown conflicting results, some, including one mimicking the conditions of exposure during a UK summer, exhibiting significantly reduced vitamin D response to UVR in persons with more-pigmented skin, while others suggest surprisingly little impact of melanin. The reasons for the differences between studies are unclear.

UK adults of South Asian ethnicity (brown skin, skin type V) have year-round 25(OH)D approximately one-third that of white adults. Both biological (including skin melanisation) and behavioural factors (including lower levels of dietary vitamin D, vitamin D supplement use and personal UV exposure) may contribute. Contrary to general assumptions, people with brown skin (South Asians, skin type V) can achieve an increase in vitamin D status following exposure to UK summer sunlight; regular noon-hour exposures of 22 minutes while casually dressed can place their 25(OH)D level above 25 nmol L^{-1}.

Stages of life where there may be increased risk of inadequate vitamin D status are during pregnancy, breast-feeding, infancy and early childhood, and adolescence (increased requirements) and older age.

Non-white children (4-18 years) have much higher risk of 25(OH)D levels <50 nmol L^{-1} than white children (odds ratio 37.0), and adolescents 14-18 years have higher risk of 25(OH)D <50 nmol L^{-1} than children 4-8 years (odds ratio 3.6).

Elderly adults may have reduced capacity of the skin to synthesise vitamin D due to lower levels of the cutaneous precursor 7-DHC. Reduced mobility and outdoor access reduce sunlight exposure, as illustrated by a high risk of 25(OH)D <25 nmol L^{-1} in the institutionalised elderly.

6.3.5 Effect of photoprotection and sun avoidance measures

Photoprotection strategies such as sun avoidance, clothing and sunscreen use may have a negative effect on vitamin D status.

Central to the management of photosensitivity disorders is minimisation of sun exposure and use of photoprotection. This puts patients at high risk of year-round vitamin D deficiency; a recent longitudinal UK study shows that while seasonal 25(OH)D variation occurs, the 50 and 25 nmol L^{-1} cut-offs were not reached at summer-end in 47% and 9% of patients respectively, rising to 73% and 32% at winter-trough.

Photosensitive individuals are not specifically mentioned in current UK guidance on vitamin D supplements, and there appears a lack of awareness regarding this: a questionnaire survey of photosensitive adults under dermatologist care showing they are no more likely to take vitamin D supplements than healthy adults.

Organ transplant recipients are increasingly employing intensive photoprotective measures on medical instruction in view of their high incidence of skin cancer and substantial skin cancer-related mortality. This can result in lower 25(OH)D levels, to which disease-specific factors may also contribute.

Cross-sectional study shows lower dietary vitamin D intake in vegetarians and vegans than in meat and fish eaters, and this is reflected in their circulating 25(OH)D, with vegans showing levels 20% (summer) to 38% (winter) lower than meat eaters.

6.3.6 Relative contributions of sunlight and diet to vitamin D status, and comparison of artificial UVR sources and supplementation in increasing 25(OH)D levels

Cutaneous synthesis of vitamin D following exposure to UV-B in sunlight is well-established as the major source of vitamin D in most situations in the UK (estimated at 80-90% in white adults), although the exact contributions of sunlight and diet to vitamin D status will vary according to a range of external and personal factors. For example, while a seasonal 25(OH)D cycle is evident in white residents at UK latitude (51-57°N), residents of South Asian origin show minimal seasonal change in 25(OH)D, implying a lower contribution from sunlight.

While winter vitamin D status in the UK is largely gained from stored vitamin D acquired through the skin by end of summer/autumn and from dietary intake, the tissue storage of vitamin D is in general poorly understood. Winter holidays abroad at sunny locations substantially elevate vitamin D status.

Estimates of equivalent doses of UVR and oral vitamin D supplements in raising 25(OH)D levels are approximate as cutaneous synthesis may be influenced by several factors including UV emission spectrum, skin surface area exposed, involvement of photoexposed versus protected sites, UV exposure protocol, baseline vitamin D status, and skin type.

Studies of courses of near-total body exposure to narrowband UV-B treatment lamps (~311 nm) compared with different oral vitamin D supplement doses, in healthy human samples differing in baseline vitamin D status, showed higher efficacy of the lamps in raising status.

In the UK, 25(OH)D level falls from an end-summer peak (September) to a winter-trough (February). It is estimated that an end-summer level of ~80 nmol L^{-1} (76 nmol L^{-1} in women; 87 nmol L^{-1} in men) is required to maintain ≥50 nmol L^{-1} at winter-trough (62% variance, $p<0.001$).

A once fortnightly near-total body exposure to low level broadband UV-B has been shown to maintain 25(OH)D ≥50 nmol L^{-1} through the winter in white adults.

6.4 Vitamin D and health

6.4.1 Skeletal health

Vitamin D plays an established role in calcium homeostasis through its influence on dietary calcium absorption and bone mineralisation. Whilst there is some uncertainty regarding optimal serum 25(OH)D there is good evidence for adverse health effects of vitamin D deficiency on bone health and a causal relationship with rickets and osteomalacia. There is reasonable evidence and a degree of consensus that a serum 25(OH)D concentration of less than 25 nmol L^{-1} is associated with an increased risk of rickets and osteomalacia although there is little agreement on what concentration is considered sufficient to avoid these risks. An adequate dietary intake of calcium remains important and there is evidence that this mitigates the effect of lower serum 25(OH)D concentrations.

The relationship between serum 25(OH)D concentrations alone and fracture risk remains unclear. There is moderate evidence that combined vitamin D and calcium supplementation improves BMD and reduces fracture risk in institutionalised elderly white populations. There is some evidence, although not conclusive, that vitamin D supplementation may have beneficial effects on muscle health in the elderly. Conflicting evidence exists regarding a relationship between vitamin D status and osteoporosis, osteoarthritis, stress fractures and muscle function.

Adverse health effects related to excessive administration of vitamin D have been described in case reports. There is inconsistent evidence that high dose supplementation of vitamin D may increase the risk of falls in the elderly.

6.4.2 Other potential health impacts

Many prospective observational studies have found inverse associations between serum 25(OH)D concentration and various non-skeletal health outcomes, notably colorectal cancer (but not other cancer types), diabetes, some cardiovascular outcomes, and to some extent MS, and recent observational studies have generally supported initial findings. An increased risk of pancreatic cancer associated with high 25(OH)D concentrations has been observed. However, the findings from the observational studies have generally not been supported by evidence from randomised controlled trials. An exception to this pattern is all-cause mortality where both observational and intervention studies indicate an inverse association. Whether this is valid outside of populations studied in the RCTs, ie elderly in institutions who are likely to have low serum 25(OH)D levels at baseline, needs to be further investigated.

Various reasons for the discrepancy between observational and intervention studies have been discussed. Several non-nutritional factors influence serum 25(OH)D concentrations (Kuhn et al., 2014), and these may confound the associations in observational studies. Even though many studies attempt to control for confounding from these characteristics, residual confounding is a possibility.

Observational studies may also be subject to reverse causation, ie the disease causes low serum 25(OH)D concentrations, or alternatively that characteristics associated with other risk factors for the disease affect 25(OH)D concentration. If this is the case, supplementation with vitamin D will not affect disease risk. The systematic reviews and meta-analyses discussed above have, however, considered only prospective cohort and nested case-control studies, where blood samples for measurement of the serum 25(OH)D concentration were taken many years before end of follow-up. In the observational studies of colorectal cancer, for which the most suggestive evidence is available, the mean follow-up time varied between 8

and 17 years. Autier and colleagues have pointed to the influence of inflammatory processes on both serum 25(OH)D concentration and the risk or severity of various diseases (Autier et al., 2014b). Such processes may influence serum 25(OH)D levels long before manifest disease, which could also potentially introduce reverse causation or confounding in prospective studies, unless serum 25(OH)D levels are measured very long before diagnosis. Autier and colleagues report that for example for colorectal cancer, the protective effect is diminished with longer follow-up periods (Autier et al., 2014a), but these findings are based on few observations.

Alternative explanations for the lack of effects in RCTs have also been proposed, eg by Christakos et al. (2013) and Giovannucci (2014). Treatment and observation periods may have been too short to provide relevant evidence and administered doses may not have been optimal for a beneficial effect to occur. In addition, widespread personal use of vitamin D supplements in both the treatment and placebo groups may have diluted contrasts between the groups. Several RCT reports were not analyses of the primary outcome for which the RCT was originally designed, but secondary analyses.

Evidence from RCTs is usually given stronger weight than observational epidemiological studies in evaluations of scientific evidence, because RCTs minimize the potential for bias. For outcomes with long induction and latency periods, such as colon cancer, it may, however, not be possible simply to dismiss the findings from the prospective cohort studies, despite the potential limitations inherent in the observational design. It remains possible that null findings in the available RCTs simply reflect too short treatment and/or follow-up periods, that treatments are given too late in life, or that the extensive self-medication with vitamin D supplements in both the treatment and control groups may have made contrasts between groups too small.

Despite the large number of epidemiological studies and systematic reviews and meta-analyses conducted, the existing scientific evidence is not sufficient to draw firm conclusions about the effect of vitamin D on health outcomes other than skeletal health.

7. Research recommendations

Research should be carried out to verify the action spectrum for pre-vitamin D, which has been questioned.

Any biological functions of pre-vitamin D photoproducts such as lumisterol should be determined.

Standardisation of assay methods for 25(OH) is ongoing, and vital for research and clinical applications.

National surveys of vitamin D status need to include and publish sufficiently large samples of white and in particular of non-white groups to give stable estimates of levels in these groups by age.

Functional biomarkers, such as systemic immunoregulatory molecules, should be compared when vitamin D status is comparably improved by UV-B radiation and dietary supplementation. Differences in the profiles of such molecules, with different intervention strategies, may help to explain the lack of evidence for health benefits with supplementation studies that have been attributed to vitamin D from epidemiological studies.

Research examining the relationship between sunlight exposure and vitamin D status gain in UK resident black people, specifically skin type VI, is required to address an information gap in this group that is both little-studied and potentially at high risk of vitamin D deficiency, and where current data are conflicting.

Research to identify doses and patterns of sun-exposure that provide minimal risk for skin cancer while gaining sunlight's vitamin D benefit, including biomarker assessments as intermediate health outcomes, is needed to provide a more robust evidence base for sun-exposure advice. Such research needs to be specific by skin type and age. This is particularly needed for the rapidly growing population of ambulant >65 year-olds, since concepts regarding sunlight-vitamin D relationship in the elderly are based on scarce, historical data.

Vitamin D is unusual for a nutrient in that it is obtained from sun exposure in addition to oral ingestion. National recommendations on vitamin D acquisition focus on oral ingestion and omit the solar source because the amount of UVR that would bring 97.5% population above adequacy cannot be specified. Yet in practice the public continue to sun expose. Hence multidisciplinary methodological research is required, bringing together expertise from photobiology and oral nutrition fields, to evaluate the equivalence and combined effects of supplementation, diet and UVR on vitamin D status, in order to enable recommendations on the combined vitamin D sources.

Studies are required that identify acceptable public sunlight exposure behaviours, and hence could underpin the construction of public health messages, for different population subgroups in the UK (eg for South Asians), taking account of beliefs, attitudes, and customs. The needs of people who have been medically advised to limit sun exposure may also need to be considered.

Carefully controlled research is needed regarding the relationships between 25(OH)D levels, and osteoporosis, osteoarthritis, muscle function and stress fractures. The effect of dietary supplementation on falls and fractures in at risk populations is another key area for further

carefully controlled trials addressing the weaknesses identified in current studies and meta-analyses.

Despite the large number of epidemiological studies and systematic reviews and meta-analyses conducted, the existing scientific evidence is not sufficient to draw firm conclusions about the effect of vitamin D on health outcomes other than bone health. Further evidence is needed from large, well-designed randomised controlled trials with sufficiently long treatment and follow-up periods, and from prospective observational studies with measurements of 25(OH)D taken many years before diagnosis, and with careful control of relevant confounding factors. Pooling of original data from prospective cohort and nested case-control studies may be an efficient way to advance knowledge beyond what meta-analysis of published results can accomplish, as it would allow construction of comparable definitions and categorizations of exposure and confounding factors, as well as investigation of adequate induction and latency periods, with better statistical power.

Appendix A: Adverse impacts of UVR on health

A1 Introduction

The sun is the main source of ultraviolet radiation (UVR) exposure for most of the population. However, artificial sources of UVR may provide a significant proportion of the exposure received by specific groups, including those who use artificial tanning facilities and those who receive UVR medical treatment. Although occupational exposure to UVR from artificial sources is possible in a range of applications, including arc welding, modern work practices and legislation tend to limit such exposure. However, the adverse health impact of legacy UVR exposures remain for some exposed individuals.

One of the main challenges with the link between UVR exposure and adverse health effects is personal dosimetry, whether from solar or artificial sources. Whilst it is relatively straightforward to determine ambient levels of UVR, the actual exposure of any one person is more difficult to assess.

Reviewing the adverse health effects of exposure to UVR is not the main objective of this report and the evidence on that topic has therefore not been approached comprehensively. However, a brief overview is provided here. A detailed review was carried out by the Advisory Group on Non-ionising Radiation, published by the former National Radiological Protection Board in 2002 (AGNIR, 2002).

The main body tissues at risk following exposure to UVR are the skin and the eyes. However, the impact of UVR exposure on the immune response of humans is also discussed.

A2 The skin

The adverse effects on the skin are divided into acute and chronic effects, as summarised in Table A1. Generally, these occur on the area of skin exposed to UVR.

A2.1 Erythema (sunburn)

Erythema is a reddening of the skin, which occurs as a result of excessive UVR exposure, and is commonly known as sunburn.

An action spectrum (as a function of UVR wavelength) for erythema is well developed and has been published in an international standard (BSI, 1999). The action spectrum has also been adopted in European law (EC, 2006) on the basis that managing the risk of erythema also manages the risk of other acute adverse health effects. However, the exposure limit values under this legislation only apply to workers.

Two quantities are used for erythema risk. The standard erythema dose (SED) is a fixed physical quantity, which is equal to 100 J m^{-2}. The amount of UVR to produce a just-measureable degree of erythema in people depends on skin type, degree of adaptation to sun exposure (ie time of year and behaviour), and possibly age. Therefore, each person has their own minimal erythema dose (MED) at a given time. An MED will generally be a

multiple of SEDs. For example, for a person with skin type II (white Caucasian skin), 1 MED is approximately 3 SEDs. Note that Chapter 2 includes a table of skin types and their respective susceptibility to erythema.

Acute molecular/cellular effects
DNA photodamage (and its repair) leading to mutation
Melanogenesis
Reactive oxygen species (ROS) that damage cellular macromolecules and organelles
Epidermal cell death (apoptosis)
Langerhans cell (antigen presenting) depletion that alters immune function
Changes in gene and protein expression that mediate UVR effects
Vitamin D photosynthesis

Clinical and sub-clinical effects	
Acute	Chronic
Erythema	Skin cancer
Tanning	Photoageing and associated reduction of skin function
Suppression of acquired immunity	
Enhancement of innate immunity	
Reduction of blood pressure – UV-A via nitric oxide (NO)	
Photosensitivity conditions	

Table A1 Summary of the main effects of UVR, including from the sun, on human skin

A2.2 Photoageing

Photoageing tends to occur in chronically sun-exposed skin. Photoageing is usually seen on the face, neck and dorsa of hands. Clinical features include wrinkles, actinic lentigines or ‘age spots’, mottled hyperpigmentation, a yellow appearance – elastosis, leatheriness – the skin is thickened, with surface roughness, telangiectasia and actinic keratoses. The clinical features are related to skin type.

Both UV-A and UV-B are implicated in photoageing. However, there are a number of reports of photoageing on one side of the body of professional drivers of vehicles in sunny climates implicating UV-A transmission through window glass.

There are no quantitative data on the UVR exposure required to produce photoageing.

A2.3 Pre-malignant damage

Chronic UVR exposure is associated with the development of actinic keratoses. These are small scaly, erythematous lesions which are seen on sites of habitual sun exposure. Some of these lesions progress to squamous cell carcinoma (SCC), but there is also some evidence for regression of the lesions with sun avoidance.

Other less common conditions associated with chronic UVR exposure include actinic porokeratosis and actinic granuloma.

The UVR action spectra for these conditions have not been developed, nor has a dose-response function.

A2.4 Non-melanoma skin cancer

Skin cancer is the commonest cancer in white people, with a rising secular incidence mainly attributed to increased sun-exposure. UVR is a complete carcinogen, both initiating the skin cell DNA damage that can lead to mutagenesis, and also promoting carcinogenesis. Commonest are the non-melanoma skin cancers (NMSC), comprising predominantly basal cell carcinomas (BCC) and SCC, while melanomas are less common but have high risk of mortality.

NMSC is much more common in white than in non-white populations. Data from case-control and cohort studies within white populations have shown a raised risk in individuals with light coloured eyes, pale skin and red or blond hair, and in those who burn easily and do not tan in the sun.

UVR is not the only risk factor for SCC and BCC. Patients who are immunosuppressed following, for example, organ transplants are at greater risk.

Since the mortality for NMSC is low, and death certificates are often incorrectly coded, there is likely to be a degree of underreporting of incidence and mortality.

A2.4.1 Squamous cell carcinomas

Squamous cell carcinoma appear as persistent, red crusted, lesions on the exposed skin, most commonly on the face and scalp, but also on the neck and hands. SCC can also occur on the lip (see A2.5). It is occasionally fatal due to metastasis. The epidemiological evidence linking cumulative lifetime exposure to UVR from the sun is strong in white skinned people.

Bowen's disease is an early form of cancer affecting the squamous cells and is sometimes called SCC in situ. It is often seen on the legs of older women, although also at other photoexposed sites.

A2.4.2 Basal cell carcinomas

Basal Cell Carcinoma is about four times more common than SCC, but the probability of metastases is extremely low. A typical BCC is a raised translucent nodule which develops slowly over a period of months or years on the face and often around the eye. BCCs can be nodular, superficial or morpheoic in nature. If not detected and removed early, they can spread locally and cause tissue destruction, including to skin, cartilage and bone.

Although exposure to UVR is implicated for BCC risk, the link with cumulative lifetime exposure is less clear. There is some evidence from British immigrants to Australia for a link with early-life exposure to UVR.

A2.5 Cancer of the lip

SCC of the lip almost exclusively involves the lower lip. It is predominantly a male disease, possibly due to a synergistic link between pipe tobacco smoking and UVR exposure. The incidence rate is falling, which could be linked to a decline in pipe smoking.

A2.6 Melanoma

Although melanoma is a relatively rare form of skin cancer, it is responsible for about 80% of skin-cancer deaths. The risk of melanoma is associated with excessive exposure to UVR, but the relationship appears to be complex. Short bursts of exposure to UVR levels above those normally received by the individual, especially at younger ages, probably resulting in sunburn, seem to be implicated. However, it is possible that cumulative exposure to UVR may also contribute to the risk in some circumstances, but reduce the risk in others.

There are four main clinical pathological types of melanoma:

- superficial spreading
- nodular
- lentigo melanoma
- acral (or acral/lentiginous) melanomas, including subungual lesions

The most common type of melanoma is superficial spreading. They are small brown or black lesions characterised by an irregular lateral edge, and three or more central shades of brown, black, red/blue or even white. They tend to occur on the leg in females and on the back of males.

Nodular melanomas occur on any site of the body, but are commonest on the trunk. They are usually densely black raised nodules, frequently with a history of bleeding.

Lentigo melanomas tend to occur on the sun-exposed skin of the elderly. They have a slow initial growth pattern over months or years, with initially a flat, irregular brown lesion, which over time develops a central raised nodule.

Acral melanomas are found on the palms and soles of the feet. They are usually brown or black, flat or raised lesions, with an irregular outline and several colours in the central region of the lesion.

The likelihood of survival after treatment of primary melanoma is directly related to the thickness of the tumour. Therefore, early detection and treatment is critical for survival rates.

Cancer Research UK have analysed the melanoma incidence data from the relevant UK databases (CRUK, 2012a) and the data for the period 1975 to 2010 are shown in Figure 1. There has been a four-fold rise in incidence rate over this period.

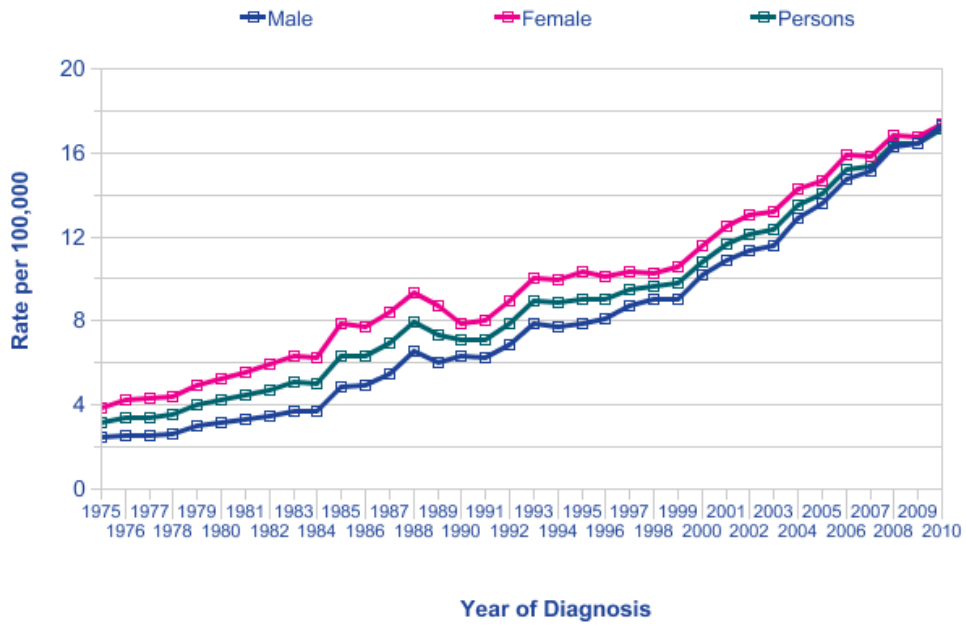

Figure 1: European Age-Standardised Melanoma Incidence Rates per 100,000 Population, by Sex, UK[a].

The mortality rates from 1971 to 2010 are shown in Figure 2 (CRUK, 2012b).

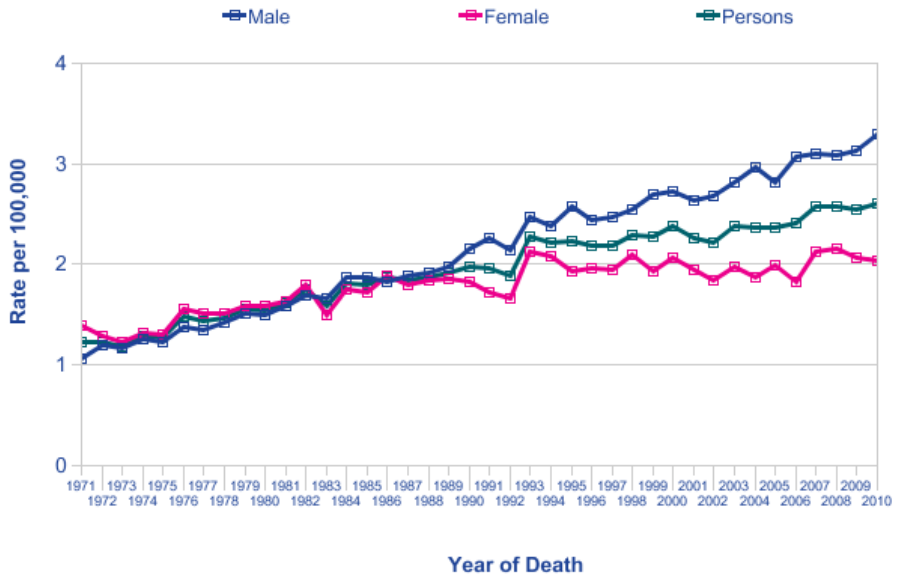

Figure 2: European Age-Standardised Melanoma Mortality Rates per 100,000 Population, UK[a]. .

The increase in melanoma rates in white populations has generally followed a birth cohort pattern, ie in each succeeding generation rates have been higher through life than were the rates in the preceding generation. This implies that either the major aetiological factors act at an early age to affect lifetime risk, or behaviours are acquired early in life that are perpetuated and hence affect continuing risk.

The most plausible explanation hypothesised for the rise in melanoma incidence has been that it is due to a rise in intermittent recreational exposure to UVR from the sun. This is supported by data suggesting that the risk of melanoma overall has been found greater for people with indoor occupations than those with outdoor occupations.

Several case-control studies have investigated melanoma risk in relation to history of sunburn. Interpretation is not easy because the likelihood of sunburn depends on both skin sensitivity and sun-exposure behaviour, and it is difficult to distinguish the separate effects of these. Even if there is a relation to sunburn rather than to the skin type susceptible to sunburn, it would remain an open question whether this represented an aetiological effect of the sunburn itself or whether the sunburn was simply a marker of intense, intermittent exposure. Furthermore, there is considerable potential for recall bias in histories of sunburn, particularly when the histories relate to childhood episodes occurring several decades before the interview.

A2.7 Photosensitivity disorders

The photodermatoses occur in children and adults and comprise a wide range of disorders exhibiting abnormal skin reactions on exposure to UV and/or visible radiation. They comprise immunological disorders, such as chronic actinic dermatitis, solar urticaria (SU) and polymorphic light eruption (PLE), metabolic disorders including erythropoietic protoporphyria (EPP), chemical and drug-induced conditions including phototoxic and photoallergic dermatitis, genodermatoses such as xeroderma pigmentosum, and photoaggravated conditions such as lupus erythematosus.

In total, photodermatoses affect a very large number of people. While some conditions are rare, such as EPP (0.5-1.33 per 100,000) (Lecha et al., 2009; Wahlin et al., 2011), others occur commonly, particularly PLE which mildly affects a high proportion of the European population (18,000 per 100,000) (Rhodes et al., 2010). Sunlight exposure produces a range of clinical features depending on specific condition, including pain, itching, erythema, eczema, blistering, scarring, and in certain cases skin cancer, of photoexposed sites.

Photosensitivity disorders can be disabling, for example with symptoms occurring within a few minutes of sun exposure in EPP, SU and drug-induced phototoxicity, those affected can be unable to spend even brief periods outdoors. A very large impact on life quality is seen in many of those affected (Jong et al., 2008; Stafford et al., 2010).

A3 The eyes

The human eye is partially protected from overhead exposure to solar UVR by its location and the action of the eyelids. Actual exposure depends on the latitude, time of day, season, weather and reflective surfaces in the field of view.

The International Commission on Illumination has recently published a report that summarises the transmission characteristics of the eye as a function of wavelength, the components of the eye and age (CIE, 2012).

A3.1 Cornea and conjunctiva

The peak sensitivity for photokeratitis is at 270 nm, and reduces at lower and higher wavelengths. At 270 nm, the threshold is approximately 40 J m^{-2}. At sea level and in the absence of a stratospheric ozone hole, the shortest UVR wavelength normally experienced is about 280 nm. Therefore, photokeratitis usually occurs from artificial sources of UVR (such as from arc welding, termed arc-eye, or accidental exposure to UV-C from germicidal lamps) or from ocular exposure at altitude (snow blindness). The condition is very painful, usually compared with sand being rubbed into the eye, has a latency period of about 24 hours and resolves after a further 24 hours.

Photoconjunctivitis has a similar action spectrum to photokeratitis, but with a lower threshold of 30 J m^{-2} at 270 nm.

In contrast to the skin, the cornea becomes more sensitive with repeated exposure to UVR.

Chronic injury is considered to be due to scattering of UVR from the environment. Pterygium arises as a wing-shaped overgrowth of the conjunctiva, which spreads onto the nasal cornea. UV-B is strongly implicated with chronic exposure to highly reflective surfaces, for example in desert areas, of people with a predominantly outdoor existence.

Pingueculae are small, bilateral fleshy elevations of the nasal temporal, interpalpebral conjunctiva, accompanied by elastotic degeneration. An association with UVR exposure has been reported, but the evidence is less convincing than for pterygium.

Climatic droplet keratopathy is more common in men, increases in severity with age and is found in locations where the solar UVR is high. Outdoor work, with high ambient reflectivity for UVR, is a risk factor.

A3.2 Lens and cataract

UVR in the wavelength range 305 to 400 nm penetrates the cornea and is strongly absorbed in the lens, although the degree of absorption is dependent on age. Norval et al. (2011) reported that there is considerable evidence that UVR is a risk factor for the development of cortical cataract, with less evidence to support a relationship with nuclear cataract. The evidence for an association with posterior subcapsular cataract is weak.

A3.3 Retina

Neonates, infants and aphakes are at greater risk of photic retinal damage than non-aphakic adults, due to the increased transmission of UV-A to the retina. However, a major risk to the retina may be from blue optical radiation.

Age-related macula-degeneration was not linked to UVR exposure. However, blue light may be implicated.

A3.4 Ocular melanoma

There is limited evidence for a link between UV-B and ocular melanoma (Norval et al., 2011). These melanomas include both external (eyelid and conjunctiva) and intraocular (iris, ciliary body and choroid) tumours, but epidemiological data suggests that UVR may only be implicated for external tumours.

A4 Immune response

Exposure to UVR results in suppression of immune response, with links to herpes simplex infection and skin cancer as potential health outcomes. The chain of events leading to the immunomodulation is known to be complex. It is initiated by chromophores in the skin such as DNA and trans-UCA which, on absorption of UVR, change their properties and trigger the production of various mediators, particularly cytokines, both locally and systemically. There are associated changes in the populations of antigen presenting cells in the skin and in their function. The final step is the induction of T cells capable of down regulating immunity and in a probable imbalance in T cell subsets with promotion of those synthesising Th2 factors, such as IL-4 and IL-10, and concomitant abrogation of those synthesising Th1 factors, such as IFN-γ.

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Appendix B: Recommendations on serum levels and intake

This appendix contains a synopsis of the recommendations by review bodies in the UK and abroad. No endorsement of any set of recommendations by AGNIR is implied.

B1 United Kingdom (UK)

In the UK, the Scientific Advisory Committee on Nutrition (SACN) published new advice on vitamin D in July 2016 (SACN 2016). SACN recommended a reference nutrient intake (RNI) for vitamin D of 10 µg day^{-1}, throughout the year, for everyone in the general UK population aged 4 years and above.

The Reference Nutrient Intake (RNI) represents the daily intake of a nutrient considered sufficient to meet the needs of nearly all the population (97.5%).

The RNI of 10 µg day^{-1} for the general UK population includes pregnant and lactating women and population groups at increased risk of vitamin D deficiency. Groups at increased risk of deficiency are those with minimal sunshine exposure as a result of not spending time outdoors (eg, frail and institutionalised people); those who habitually wear clothing that covers most of the skin while outdoors; and those from minority ethnic groups with dark skin.

Since there were insufficient data to set RNIs for children aged under 4 years, SACN recommended Safe Intakes[5] for this age group: 8.5-10 µg day^{-1} for all infants from birth up to the age of 1 year, including those who are exclusively breastfed and partially breast fed infants, and 10 µg day^{-1} for children aged 1 up to 4 years.

The RNI/Safe Intakes were developed to ensure that the majority of the UK population has a satisfactory vitamin D status (as measured in the blood) throughout the year, in order to protect musculoskeletal health. SACN was not able to quantify and take account of sunlight exposure in setting these recommendations because of the number of factors that affect endogenous vitamin D synthesis.

B2 United States/Canada

In the United States and Canada, Dietary Reference Intakes (DRI's) and recommended serum concentrations for vitamin D were published in the Institute of Medicine's (IOM) 2011 report (IOM, 2011). IOM selected bone health as the basis for setting an estimated average requirement (EAR) and a recommended dietary allowance (RDA) for vitamin D for all life stage groups, except infants where an adequate intake (AI) was specified. These reference values were set assuming minimal sunlight exposure. The RDA represents the intake likely to meet the needs of about 97.5% of the population.

[5] Safe Intakes were set by SACN's predecessor committee (the Committee on Medical Aspects of Food and Nutrition Policy) if there were insufficient reliable data to set DRVs.

The IOM set the RDA for pregnant and lactating women, and children and adults 1-70 years old at 15 µg day^{-1}, and at 20 µg day^{-1} for adults over 70 years of age.

Due to insufficient evidence the IOM were unable to develop an RDA for vitamin D for infants 0-12 months. An Adequate Intake (AI), a level assumed to ensure nutritional adequacy, of 10 µg day^{-1} was set for this group.

There is considerable discussion regarding the serum 25(OH)D concentration associated with deficiency, adequacy for bone health, and optimal overall health. The cut-offs for serum 25(OH)D concentration set by the IOM are described in Table B1.

Table B1: Cut-offs for serum 25(OH)D concentration

nmol L^{-1}	**Health status**
<30	Associated with Vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30-50	Generally considered inadequate for bone and overall health in healthy individuals
≥50	Generally considered adequate for bone and overall health in healthy individuals
>125	Emerging evidence links potential adverse effects to such high levels, particularly >150

B3 European Food Safety Authority (EFSA)

EFSA recommended an AI of 10 µg day^{-1} for infants aged 7-11 months and an AI of 15 µg day^{-1} for all other groups in the population of the European Union aged one year and more (including pregnant/lactating women) in its 2016 report (EFSA, 2016). EFSA considered that a serum 25(OH)D concentration of 50 nmol L^{-1} was a suitable target value for all population groups on which to base the setting of adequate intakes.

An AI is the average observed daily level of intake by a population group (or groups) of apparently healthy people that is assumed to be adequate.

B4 World Health Organization (WHO)/Food and Agriculture Organization (FAO)

Recommended Nutrient Intakes (RNI's) for vitamin D were published by the WHO and FAO in their 2004 report (WHO/FAO, 2004). They recommended that vitamin D requirements could be met most efficiently by exposure to sunlight, with approximately 30 minutes of exposure on the arms and face (without sunscreen) meeting all daily vitamin D needs.

It was recognised that latitude, season, the ageing process, skin pigmentation, clothing and use of sunscreen negatively influence endogenous synthesis of vitamin D and that not all of these factors can be resolved. The WHO/FAO set RNI's for those not synthesising vitamin D.

The RNI's set by WHO/FAO are the intakes which meet the needs of almost all healthy individuals (97.5% of the population) and are reported to be equivalent to the RDAs set by the IOM.

The WHO/FAO set the RNI for 0-50 year olds and pregnant and breast feeding women at 5 µg day^{-1}. The RNI was increased to 10 µg day^{-1} for those aged 51-65 years and to 15 µg day^{-1} for those aged 65 years plus.

Plasma 25(OH)D concentration cut-off points are not stipulated by WHO; however, a plasma 25(OH)D concentration above 27 nmol L^{-1} is noted as necessary for normal bone health (WHO/FAO, 2004).

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Glossary

Physical terms

Absorption (atmospheric): the reduction in the intensity of any form of radiated power resulting from power or energy conversion in an absorbing medium, such as the atmosphere.

Artificial UVR sources: UVR sources, other than the sun, eg arcs, discharge tubes and tungsten halogen lamps.

Atmospheric pollution: pollution of the atmosphere by processes, usually industrial, used by human beings. Pollutants include hydrocarbon compounds, carbon monoxide and oxides of nitrogen and sulphur (see tropospheric ozone).

Berger meter: a UVR detector designed to measure erythemally weighted UVR.

Biological action spectrum: represents the effectiveness of a particular biological effect as a function of wavelength. It is the relative plot of the reciprocal of the dose required to produce the effect against wavelength normalised at one chosen wavelength (normally the most efficacious).

Broadband measurements (detectors): integrated measurements over a range of wavelengths, often inherently incorporating a weighting function representative of a biological action spectrum.

Blue light: light in the wavelength range between about 400 and 500 nm.

Cathode ray tube: an electronic tube in which a controllable beam of electrons is produced and directed on to a surface resulting in the emission of optical radiation.

Cloud cover: the effectiveness of cloudiness on the solar irradiation of a horizontal plane can be approximated by the expression F = 1 – 0.056C, where C is the cloudiness factor, usually quoted in tenths of sky covered from 0 to 10 (10 being complete sky cover). Thus, for complete cloud cover, the terrestrial UVR intensity would decrease to 44% and for half cloud cover to 72%. This expression does not account for cloud quality.

Electromagnetic radiation: radiation considered as a wave of electric and magnetic energy travelling through a medium.

Erythemally weighted UVR: integrated UVR that has been multiplied (as a function of wavelength) with a function representative of the action spectrum for the biological effect of erythema.

Illuminance: the areal density of luminous flux incident at a point on a surface (unit = the lux, ie lumen per square metre, or, practically for solar light, the kilolux where 1 klux) = 10^3 lux).

Integrated (function): either time integrated (eg dose) or wavelength integrated (eg erythemally weighted UVR) functions summed over all relevant time or wavelength intervals.

Irradiance: the areal density of radiant flux incident at a point on a surface (unit = watt per square metre (W m^{-2}), or mW m^{-2}).

Liquid crystal (display): a display based on changes in reflectivity of a liquid crystal cell when an electric field is applied.

Minimum erythemal dose (MED): the UVR dose that produces a just perceptible erythema on previously unexposed skin. The MED is a measure of personal UVR sensitivity

Network: a coordinated collection of measurement sites.

Optical radiation: electromagnetic radiation comprising UVR, visible and/or infrared radiation.

Ozone: O_3 produced photochemically by the action of solar UVR at wavelengths below 242 nm on oxygen molecules and located in a layer between 20 and 30 km above the earth's surface.

Photometric quantities/units: a system of quantities/units used to quantify the amount, rate and spatial and spectral distributions of visible radiation relative to the response of the human eye.

Photon (energy): a quantum of electromagnetic radiation equal to a constant (Planck's Constant) times the frequency of the radiation (unit = the hertz).

Photopic (response): response of the human eye under normal conditions of illumination.

Radiant exposure: the time-integrated irradiance falling on a surface (unit = joule per square metre ($J\ m^{-2}$)).

Radiometric quantities/units: a system of absolute quantities/units used to quantify the amount, rate and spatial and spectral distributions of electromagnetic radiation; they do not depend on the response of any detector.

SED (Standard Erythema Dose): is a measure of erythemal UVR equivalent to an erythemal effective radiant exposure of 100 $J\ m^{-2}$. The SED is independent of personal UVR sensitivity.

Scattering (atmospheric): irregular reflection or dispersal of electromagnetic radiation by particles, water droplets and pollutants in the atmosphere.

Scotopic: response of the human eye under conditions of low illumination.

Spectral measurements: measurements made at small wavelength intervals (often 1 nm) to which any suitable biological action spectrum can be subsequently fitted.

Stratosphere: the Earth's atmosphere above the troposphere, extending from about 8 km and 16 km above the Earth at the poles and equator, respectively, to about 50 km.

Stratospheric ozone depletion: reduction in the ozone content in the stratosphere by the action of certain chemicals such as chlorofluorocarbons (CFCs) and halons.

Sun Protection Factor (SPF): is the ratio of the least amount of ultraviolet energy required to produce a minimal erythema on sunscreen-protected skin to the amount of energy required to produce the same erythema on unprotected skin.

Terrestrial solar UVR: UVR from the sun in the wavelength range from about 290 to 400 nm which penetrates to the Earth's surface.

Tropospheric ozone: generated by the action of UVR on molecules of nitrogen dioxide (NO_2), the formation of which is accelerated by solar UVR acting on atmospheric pollutants, particularly NO_2 emissions from transport and industry and hydrocarbon emissions from car exhausts.

Ultraviolet radiation (UVR): electromagnetic radiation in the wavelength range 100 to 400 nm.
UV-A (ultraviolet A) UVR in the wavelength range 315 to 400 nm.
UV-B (ultraviolet B) UVR in the wavelength range 280 to 315 nm.
UV-C (ultraviolet C) UVR in the wavelength range 100 to 280 nm.

UVR (biologically) effective: UVR at a particular wavelength which has been multiplied by a factor indicating the efficacy of a given biological effect at that wavelength; each weighted component is then summed over a wavelength interval (unit W m^{-2} effective).

Visible radiation: electromagnetic radiation in the wavelength range 380/400 to 760/780 nm.

Wavelength: the distance between two similar and successive points on an alternating wave (unit for optical radiation = the nanometre (nm) or 10^{-9} m).

Weighting function: represents the relative effectiveness of a particular effect normalised at a given point (generally the most efficacious) (see biological action spectrum).

Clinical and biological terms

Acral lentiginous melanoma (ALM): an uncommon type of melanoma, but the most common type seen in non-white individuals, occurring chiefly on the palms and soles, especially on the distal phalanges of the fingers and toes, often on the tip of the digit or nail fold or bed, and sometimes involving mucosal surfaces, such as the vulva or vagina.

Actinic keratosis (AK): a keratinised plaque having aberrant cell differentiation and proliferation, which can spontaneously regress or may develop into invasive malignancy.

Actinic damage: tissue damage caused principally by ultraviolet radiation, but possibly also by visible radiation.

Antigen: a molecular structure that the immune system recognises as foreign (non-self); an antigenic determinant is the part of the structure, which is recognised.

Antigen presenting cell: specialised cell which processes and transports antigens to T lymphocytes to stimulate an immune response.

Aphakic: an eye lacking a crystalline lens.

Basal cell: a cell in lowest layer of the epidermis.

Basal cell carcinoma (BCC): epithelial tumour of the skin originating from basal cells – typically occurs as pearly nodule or a plaque with a central depression.

Carcinogen: an agent that induces cancer.

Carcinogenesis: production and development of cancer.

Cataract: a partial or complete opacity in the lens of the eye that may impair vision and, if dense, cause blindness.

Chromophore: a molecule that absorbs ultraviolet or visible radiation, such as DNA.

Collagen: insoluble extracellular fibrous protein that forms the major part of the dermis.

Conjunctiva: the membrane that lines the eyelids and covers the exposed surface of the sclera (white of the eye).

Conjunctivitis: inflammation of the conjunctiva.

Connective tissue: supporting tissue that consists of large amounts of extracellular material. The dermis is the connective tissue of the skin.

Contact hypersensitivity reaction: cell mediated allergic response caused by direct skin contact with certain chemicals.

Cornea: the transparent structure forming the front part of the eye.

Dermis: the deeper mainly extracellular compartment of the skin, ie situated beneath the epidermis.

Elastin: protein that forms elastic fibres in the dermis.

Endothelium: epithelium that lines blood vessels and internal body surfaces.

Epidermis: the upper compartment of the skin.

Epithelioma: malignant growth derived from epithelium.

Epithelium: arrangement of cells covering a free surface.

Erythema: a redness of the skin.

Eumelanin: dark-brown or black form of melanin.

Fibroblast: a specialised cell that synthesises and secretes the fibrous components (eg collagen) of connective tissue.

Immunosuppression: suppression of an immune response.

Keratin: a protein with structural and barrier functions. Present in skin, hair and nails.

Keratinisation: intracellular deposition of keratin.

Keratinocyte: a skin cell that synthesises keratin.

Keratitis: inflammation of the cornea and iris.

Keratoacanthoma (KA): firm skin nodule with a centre of keratotic material.

Langerhans cells (LC): major epidermal antigen presenting cells.

Lentigo (plural lentigines): a brownish or yellowish macule on the skin, most often on hands, arms or face.

Lentigo maligna melanoma (LMM): a cutaneous malignant melanoma (cancer) found most often on the sun-exposed area of skin.

Leucocyte: white blood cell; protects against infection.

Lupus erythematosus: a group of connective tissue (autoimmune) disorders primarily affecting women aged 20 to 40 years.

Lymphocyte: type of leucocyte found in the lymph glands and spleen; major component of the immune system.

Macrophage: large migratory white blood cell that ingests invading organisms and scavenges damaged cells.

Malignant melanoma: a malignant cancer of melanocytes that is the most serious type of skin cancer.

Melanin: group of black, dark-brown, or reddish pigments present in the skin. Produced in melanocytes and stored in melanosomes.

Melanocyte: dendritic clear cell of the epidermis that synthesises the pigment melanin.

Melanoma: tumour arising from the melanocyte system of the skin and other organs. When used alone refers to malignant melanoma.

Metastasis: process in which cells detach from a tumour and spread around the body (verb: metastasise).

Neoplastic transformation: the conversion of normal cells into tumour cells.

Nodular melanoma: a type of malignant melanoma that is in the form of swelling, usually but not always darkly pigmented, most often occurring on the head, neck and trunk.

Non-melanoma skin cancer (NMSC): cancers that are not derived from melanocytes and most often have keratinocyte origin, ie squamous cell and basal cell carcinomas.

Oedema: swelling of skin due to build up of intercellular fluid.

Optical axis of the lens: the hypothetical straight line that passes through the centres of curvature of the front and back surfaces of the lens of the eye.

Phaeomelanin: reddish-brown melanin.

Phakic: crystalline lens of eye is present.

Porphyria : a disease of porphyrin metabolism, characterised biochemically by marked increase in formation and excretion of porphyrins or their precursors and clinically by various neurologic and cutaneous manifestations.

Solar: pertaining to the sun.

Squamous cell carcinoma (SCC): scaly or raised malignant tumour.

Stratum corneum: keratinised layer of exfoliating epidermis; outer layer of the skin.

Stroma: a supporting framework of connective tissue.

Superficial spreading melanoma: most common type of malignant melanoma, characterised by a period of radial growth of atypical of melanocytes in the epidermis, usually associated with a lymphocytic cellular host response that is sometimes accompanied by partial or complete regression.

Xeroderma pigmentosum (XP): a rare genetic disease that results from a deficiency of one of the enzymes necessary for the nucleotide excision repair of UVR-damaged DNA. Problems start in infancy or early childhood with erythema and vesicles and progresses to freckle-like pigmentation/telangectasia with further superficial ulceration, warty-growths and areas of atrophy – epithelial cancers are very likely.

Epidemiological terms

Bias: a systematic tendency to overestimate or underestimate a parameter of interest because of a deficiency in the design or execution of an epidemiological study.

Case-control study: an epidemiological study in which people who have developed a health outcome (cases) are identified, and their earlier exposure to putative causes is compared with that of controls who have not developed the health outcome.

Cohort (Cohort study): an epidemiological study in which people who differ in their exposure to putative determinants of a health outcome are followed up and the subsequent occurrence of the health outcome is compared according to exposure. Cohort studies may be conducted prospectively or retrospectively.

Confidence interval (CI): an interval calculated from data when making inferences about an unknown parameter. In hypothetical repetitions of the study, the interval will include the parameter in question on a specified percentage of occasions (eg 95% for a 95% confidence interval).

Confounding: a tendency to overestimate or underestimate the strength of a causal association in an epidemiological study because the putative cause that is under investigation is associated with another variable that independently determines the risk of the health outcome. Confounding can lead to a false conclusion about whether or not there is a causal relationship between exposure and disease.

Cross-sectional study: an epidemiological study in which the prevalence of one or more health outcomes and/or their determinants is assessed in a population at a point in time or over a relatively short period.

Odds ratio (OR): the ratio of the odds of a health outcome in people exposed to a risk factor to that in people who are unexposed or exposed at a different level. The odds of a health outcome are defined as P/(1-P) where P is the probability of the outcome.

One-sided test: a test for a difference in only one direction (eg a test for an increased – but not a decreased – risk in an exposed group relative to a comparison group).

Prevalence ratio: ratio of the prevalence rates for the disease or symptoms under investigation in the study and comparison groups.

Proportional mortality ratio (PMR): the ratio (often expressed as a percentage) of the number of deaths in a study group from a specified cause to the number that would have been expected if, for each combination of sex, age and/or other potential confounding variables, the proportion of all deaths that were from that cause was the same as in a specified standard population (often the national population).

Proportional registration ratio (PRR): analogous to the proportional mortality ratio (PMR) but based on cancer registrations rather than deaths.

Prospective study: an epidemiological study in which data on health outcomes are collected as they occur, unlike a retrospective study (see below).

Probability value: probability that a test statistic would be as extreme as or more extreme than observed if the null hypothesis were true. The letter p, followed by the abbreviation ns (not significant) or by the symbol < (less than) and a decimal notation such as 0.01 or 0.05, is a statement of the probability that the difference observed could have occurred by chance under the null hypothesis.

Relative risk (RR): the ratio of the risk (probability) of a health outcome in people exposed to a risk factor to that in people who are unexposed or exposed at a different level. Relative risks may be estimated with or without adjustment for possible confounding factors, such as age. For rare health outcomes, the relative risk is numerically similar to the odds ratio (see above).

Retrospective study: an epidemiological study in which data are collected on health outcomes that occurred before the study began.

Risk: probability or likelihood of injury, harm or damage occurring.

Significance level: probability of obtaining a result at least as extreme as that observed in the absence of a raised risk. A result that would arise less than 1 in 20 times in the absence of an underlying effect is often referred to as being ‘statistically significant’.

Standardised incidence ratio (SIR): the ratio (often expressed as a percentage) of the number of incident cases of a disease in a study group to the number that would have been expected if, for each combination of sex, age, and/or other potential confounding variables) the group had experienced the same incidence as that in a specified standard population (often the national population. An SIR greater than 100 (expressed as a percentage) signifies risk raised in the study group compared with the standard population, and an SIR of less than 100 signifies a reduced risk.

Standardised mortality ratio (SMR): defined in the same way as an SIR, but with death from a specified cause, rather than incidence of a disease, as the health outcome.

Statistical power: the probability that, with a specified degree of statistical confidence, an underlying effect of a given magnitude will be detected in a study. A study with low power might easily fail to detect an important effect, simply by chance.

Statistically significant result: a finding in a study that deviates from a stated (or assumed) null hypothesis to an extent that would rarely occur (usually meaning with a probability of less than 5%, ie $p < 0.05$) simply by chance if the null hypothesis were true.