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Esposizione alla radiazione solare e vitamina D

A cura di R. Pozzi, S. Morelli, M.C. Gauzzi

TECNOLOGIE E SALUTE

HIGHER INSTITUTE OF HEALTH

Exposure to solar radiation and vitamin D

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2025, 73 p. ISTISAN Reports 25/10

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Keywords: Vitamin D; Solar UV radiation; Mobile applications

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Key words: Vitamin D; Solar UV radiation; Smartphone App

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INTRODUCTION

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Natural ultraviolet radiation and vitamin D synthesis are the common threads of the topics covered in this report, to which experts with interdisciplinary expertise have contributed.

During skin exposure to the sun, the ultraviolet B (UVB) component can cause both beneficial effects such as the synthesis of vitamin D, and harmful effects in the form of sunburn and
erythema in the case of short-term exposure, or in the form of skin cancer in the case of prolonged exposure.

Public attention to adverse health effects prevails even over evidence of beneficial effects. The scientific community is engaged not only in studying the molecular mechanisms underlying health effects, both beneficial and harmful, but also plays an active role in communicating the health risks posed by ultraviolet radiation.

The topics covered in this report have been proposed following a path that starts from the most general scientific issues and arrives at the applicative aspects of new technologies.

The chapter "Exposure to Solar Radiation: Only Harmful Effects?" addresses some general aspects that apply to all contributions, such as the description of the dual action of solar ultraviolet radiation, which promotes both beneficial effects such as the skin synthesis of vitamin D, but also harmful effects on health such as erythema and skin and eye cancers. Both environmental and personal factors that can contribute to this effect are also described.

negatively interfere with the skin's synthesis of vitamin D and influence its deficiency in the body. The concept of the perception of the potential health risks of excessive sun exposure was also introduced, along with the measures implemented to inform and raise awareness among an ever-increasing number of people. This was done with the aim of introducing the use of indicators such as *the UV Index* (UVI), including through dedicated apps, and exploring the potential use of these tools for vitamin D as well.

In the chapter "Vitamin D and COVID-19: Data and Controversies," we attempted to clarify the role of vitamin D in SARS-CoV-2 infection and COVID-19 disease. In particular, we illustrated how the hypothesis of a role for vitamin D arose—based on pre-pandemic knowledge.
protective effect of vitamin D on this disease and the experimental evidence available to date on the subject was reviewed, from basic and preclinical research to epidemiological and clinical studies.

The following chapter, "Vitamin D and Multiple Sclerosis," illustrates the role of vitamin D in this neurodegenerative disease, the etiology of which is influenced by both genetic and environmental factors. Vitamin D deficiency and Epstein-Barr virus infection are currently recognized as the main environmental (and therefore potentially modifiable) risk factors. Particular attention was paid to the possible molecular interactions between the vitamin D receptor, viral proteins, and genetic risk factors in defining the pathogenesis of the disease.

The chapter "Strategies for Controlling Exposure to Solar Ultraviolet Radiation in Outdoor Work" focuses primarily on the harmful effects of sun exposure in the workplace. Technical standards and regulatory aspects at the national and international levels for risk assessment and the implementation of effective prevention and protection measures for workers are illustrated.

The chapter "Measurement of Solar Ultraviolet Radiation and Vitamin D" provides instructions on how to measure solar UV radiation received by the skin and, based on the current state of the art and regulations on this topic, how to calculate how much vitamin D can be synthesized as a result of this exposure. Furthermore, the discussion highlights the challenges associated with these procedures and the operational limitations encountered. A case study is also used to illustrate and discuss the results obtained by applying the procedure to a real-world setting.

The chapter "Sun Protection and Vitamin D with Apps: Opportunities and Challenges" provides a first look at the world of technologies and sensors capable of measuring the UVI index (solar ultraviolet radiation index), which can be used to calculate the amount of vitamin D synthesized through sun exposure. It was felt necessary to explore the market and relevant literature to evaluate the reliability and simplicity/usability of the proposed solutions, in the form of apps. The goal is to identify and/or propose, with appropriate future studies, the best possible solutions for different user groups.

The chapter “Apps supporting vitamin D synthesis from solar radiation: the experience of the British NHS” describes the Sun4Health App, based on a patented technology *(HappySun®)* that uses real-time satellite data and AI-based algorithms to automatically and accurately detect sun exposure and simultaneously monitor the effective dose of solar radiation accumulated across the entire body surface, taking into account both the erythemal reaction of the skin and vitamin D synthesis. The use of the App in a specific clinical study and the results achieved are also described.

The set of topics covered offers new insights and provides added value to individual exposures, also reaffirming an ancient but still valid message: the importance of "conscious and informed" sun exposure, which can make a difference, improving the well-being not only of muscles and bones, but also of many pathologies involving vitamin D.

We hope that reading this report will help provide the reader with useful tools
to achieve greater awareness regarding sun exposure.

EXPOSURE TO SOLAR RADIATION: ONLY HARMFUL EFFECTS?

Roberta Pozzi
National Center for Radiation Protection and Computational Physics, Istituto Superiore di Sanità, Rome

Ultraviolet radiation

Ultraviolet (UV) radiation – both natural, as a component of solar radiation reaching the ground, and artificial, emitted by sources and equipment used in industry, medicine, and research – has been classified and included by the International Agency for Research on Cancer (IARC) in Group 1 among the physical, chemical, and biological agents known to be carcinogenic to humans.

IARC classifications are based on scientific evidence obtained from epidemiological studies, preclinical studies conducted on animals or *in vitro* studies available at the time of writing. The classifications may be periodically updated based on the availability of new data and new scientific evidence. The classification of solar ultraviolet radiation in Group 1 was assigned on the basis of epidemiological studies that have established the causal link in populations of Caucasian origin between exposure to solar radiation and the onset of the most common skin cancers such as basal cell carcinoma *(BCC),* squamous cell carcinoma *(SCC)* and melanoma (1). This classification for solar radiation was confirmed in the 2012 monograph (2), in which the classification of artificial UV radiation in Group 1 was also proposed following evaluations of the carcinogenicity induced in humans exposed to artificial tanning devices. The onset of cutaneous and ocular melanoma and the onset of SCC have been associated with this type of exposure.

Both artificial and natural UV radiation is conventionally divided into three ranges: UVC (180-280 nm), UVB (280-320 nm), and UVA (320-400 nm). These wavelengths also have an associated energy, which is higher at shorter wavelengths and tends to decrease with increasing wavelength. UV radiation can be transmitted, reflected, scattered, or absorbed by the chromophores present in the skin and eyes, the most external and exposed organs of the body.

UVC radiation is potentially the most damaging to biological tissue, but solar UVC is almost completely blocked by the presence of the ozone layer in the stratosphere, which prevents radiation from reaching the ground. Human exposure to UVC may be due to emissions from artificial radiation sources in the workplace.

The UVB component reaches the ground in a percentage varying between 5-10%, managing to partially pass through the ozone layer. This type of radiation is capable of directly modifying the bases of DNA. Understanding the molecular and cellular mechanisms between exposure to UVB and the onset of carcinogenesis constitutes one of the major *focuses* of scientific research (2).

UVA radiation accounts for 95% of the UV radiation that reaches the earth's surface. UVA can interact indirectly with DNA, but it can penetrate the dermis where it interacts directly with lipids and proteins, causing premature skin aging.

At physiological levels, UV radiation stimulates cell growth and differentiation, the formation of melanin in the melanocytes of the epidermis and the stimulation, by UVB, of vitamin D synthesis at the skin level (Figure 1). Excessive exposure to ultraviolet radiation can promote the onset of acute responses such as erythema and sunburn and promote skin hyperplasia or, in the case of chronic exposure, it can promote the onset of tumoral pathologies (3).

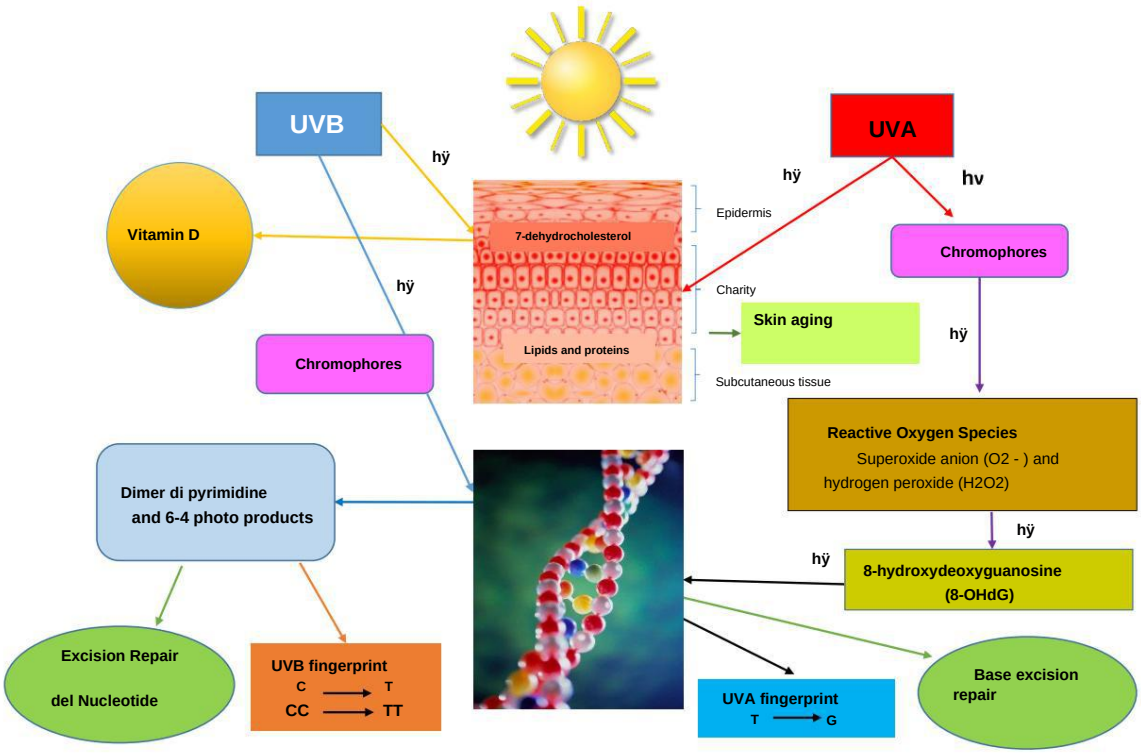


Figure 1. Main effects induced by UVB and UVA on skin and DNA

UVB radiation induces direct and specific DNA damage such as pyrimidine dimers and 6-4-photoadducts. Some damage can be repaired by a mechanism called *Nucleotide Excision* Repair (NER). If this mechanism fails, mutations can be transmitted through cell division and are identified as UVB genetic fingerprints *of* the CÿT and CCÿTT types.

UVA radiation does not act directly on DNA but indirectly with the formation of reactive oxygen species *(ROS)* or *reactive nitrogen species (RNS)* which are able to transfer the energy of UVA generating mutagenic oxidative forms such as 8-hydroxydeoxyguanosine (8-OHdG). Also for UVA the typical mutation is also defined as a genetic fingerprint *but* of the TÿG type and also for UVA some mutations can be repaired, in this case through *Base Excision Repair* (BER) (4) as shown in Figure 1.

The effects just described at the molecular level can translate into skin and eye diseases both among the general population who are exposed to the sun on an occasional basis, but above all for many categories of workers who may be exposed for professional reasons. to solar UV radiation (outdoor workers) and other categories of workers who may be exposed to artificial UV sources. Some international scientific commissions have

proposed guidelines or technical documents that analyse the types of work exposure and propose indications/recommendations both for the specific professional training to be provided to the worker but also regarding the obligations and responsibilities of the employer regarding the prevention measures to be undertaken and the solutions to be adopted for the protection of the health of workers in these work environments (5, 6).

Vitamin D

The beneficial and harmful effects of sun exposure have one element in common: UVB radiation. The photochemical reaction for the cutaneous synthesis of vitamin D begins through the interaction of UVB radiation photons with 7-dehydrocholesterol (7-DHC, a precursor to cholesterol) present in the skin's keratinocytes (Figure 2).

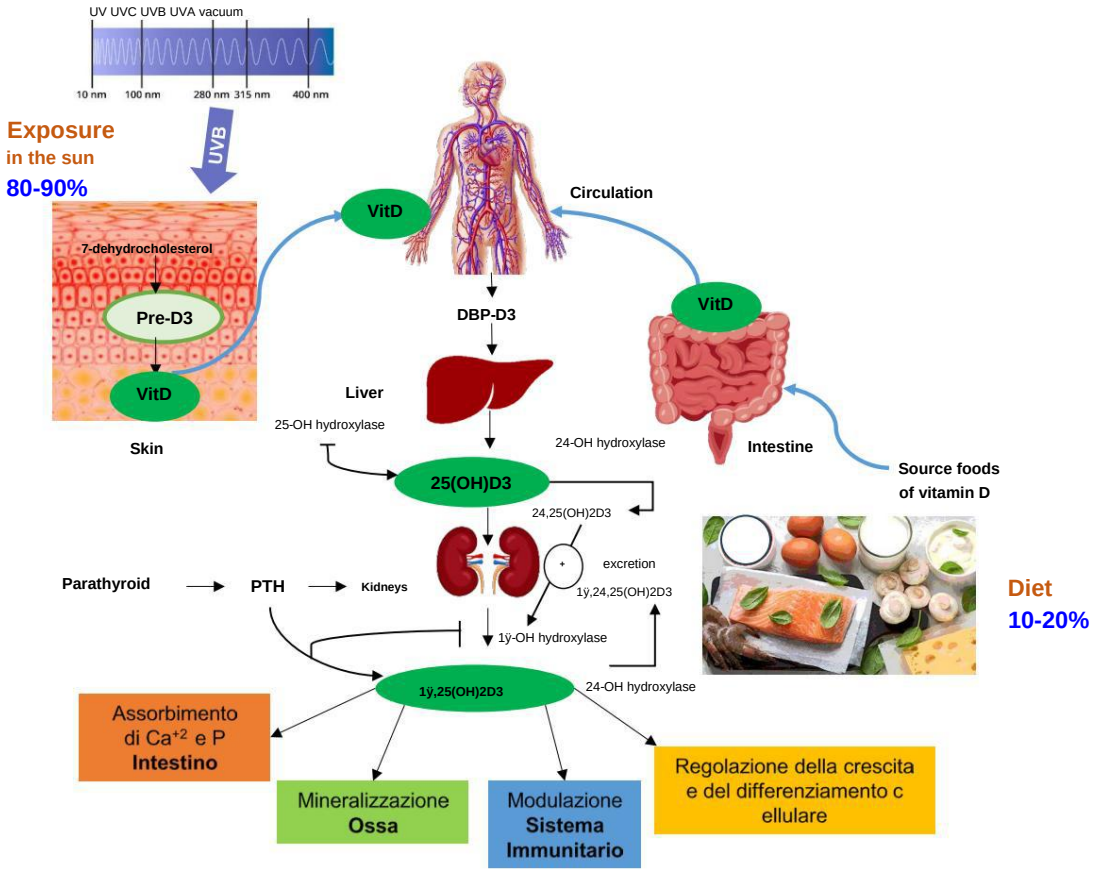


Figure 2. Major biochemical pathways of vitamin D synthesis

The interaction of UVB photons stimulates the conversion of 7-DHC, also known as pro-vitamin D3, into pre-vitamin D3. During prolonged exposure to the sun, not all skin 7-DHC is converted into pre-vitamin D3 , but it has been estimated that approximately 10-15% is transformed. The conversion from pre-vitamin D3 to vitamin D3 is a rapid, temperature-regulated reaction that also leads to the formation of inactive photoproducts that, through a photoregulatory mechanism, prevent overexposure to the sun from causing an over-vitamin D3.

production of vitamin D, the levels of which could be toxic to the body (7). Vitamin D3 , once it leaves the keratinocytes, is transported by the vitamin *D-Binding Protein* (DBP) and reaches the liver through the bloodstream where, in the hepatocytes, it undergoes a first hydroxylation reaction with the formation of 25(OH)D *(see* Figure 2). This intermediate in turn is transported by DBP through the blood to the kidneys where it undergoes a second hydroxylation reaction which leads to the formation of 1,25-dihydroxyvitamin D (1ÿ,25(OH)2D3), the “active” form of the hormone (8).

Vitamin D is essential in the metabolism of calcium and phosphorus and in the correct Mineralization of bones and skeleton. It is important in the prevention and treatment of rickets in children, osteomalacia (adult rickets), and osteoporosis in the elderly. About 80% of the body's vitamin D requirement is met by skin synthesis and only about 20% by diet. Food sources of vitamin D include milk, meat, butter, egg yolk, salmon, anchovies, mackerel, tuna, liver, and mushrooms. Cod liver oil is also a well-known source of vitamin D. In some countries, to support adequate vitamin D intake, foods such as orange juice and milk are fortified with vitamin D.

Vitamin D synthesized by the skin and that obtained from diet and supplementation follow different metabolic pathways described in Figure 3.

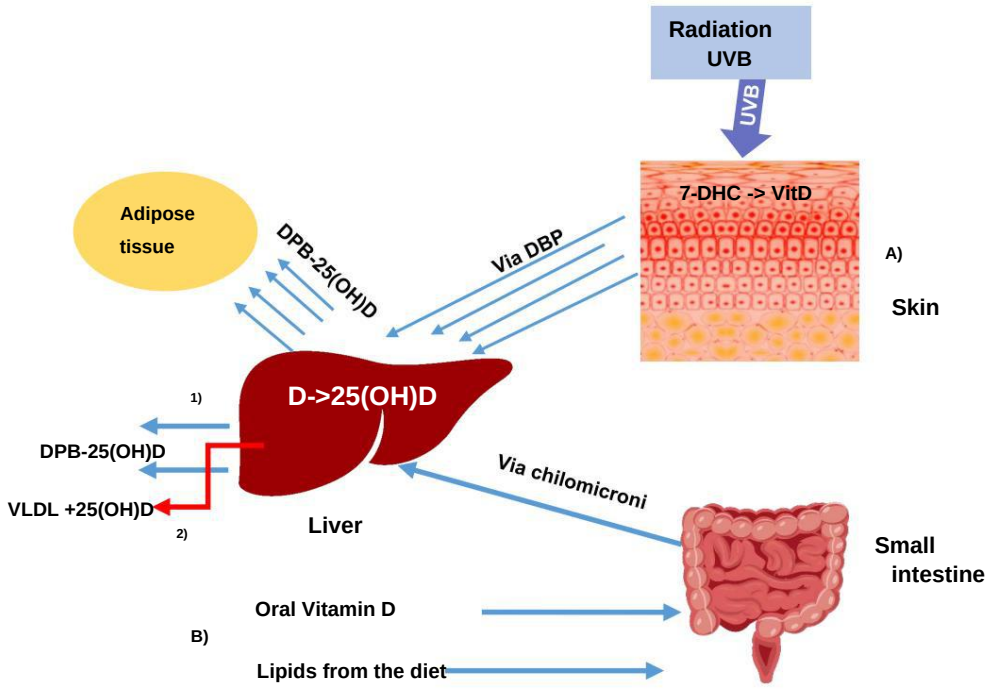


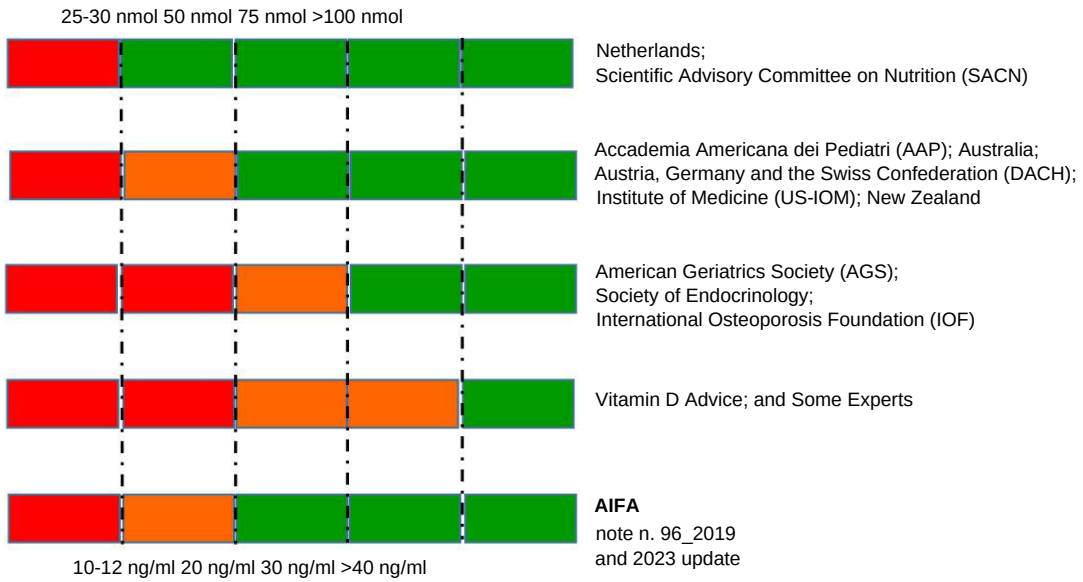
Figure 3. Differences in vitamin D metabolism following oral intake or supplementation

Vitamin D formed during cutaneous synthesis follows a metabolic pathway characterized by slow and continuous transport mediated by DBP, from the skin to the liver where it is transformed into 25(OH)D.

Vitamin D, taken through supplementation and diet, is rapidly absorbed in the small intestine. Its transport to the liver is mediated by chylomicrons and the 25(OH)D produced by hepatic metabolism is released into the bloodstream both through DBP and, to a lesser extent, by very low density lipoproteins (VLDL) which can deposit it in the arterial walls. This latter mode of transport could explain a particular form of vitamin D toxicity found in experimental animals, in the absence of hypercalcemia and calcification of soft tissues (9). It is also important to remember that 25(OH)D is a lipophilic compound and a part of that produced by the body is stored in adipose tissue and made bioavailable in the winter months (7) during which the cutaneous synthesis of vitamin D is strongly limited by the reduced exposure to sunlight.

The half-life of 25(OH)D is approximately two weeks in the bloodstream and its concentration is in the order of nanograms/mL while the half-life of 1-ÿ25(OH)2D3, the active form of the vitamin, is estimated to be several hours and its concentration is in the order of picograms/mL.
Therefore, blood determination of 25(OH)D is preferable to obtain information regarding the *status,* i.e. the levels, of vitamin D in the body (10). Both cutaneous synthesis and dietary intake contribute to vitamin D *status* . Dietary intake is generally low, consisting of approximately 10-20% of the total intake, and to this can be added personal choices (vegetarian, vegan diets) which further penalise the consumption of foods which naturally contain vitamin D. Exposure to the sun, which could lead to good levels of vitamin D through cutaneous synthesis, can be influenced by both environmental factors and factors linked to lifestyle habits. What levels of serum vitamin D are useful for maintaining good body function is the subject of open scientific debate.

Specific government agencies or scientific committees provide indications regarding the recommended vitamin D levels for the population (Figure 4), in order to maintain the right levels of serum 25(OH)D concentration in the body based on age, gender and particular moments of life characterised by specific vitamin D needs (pregnancy, elderly people or those at risk of osteoporosis) (11).



Red: severe deficiency; **Orange:** mild deficiency; **Green:** sufficiency

Figure 4. Serum 25(OH)D levels according to some international agencies and scientific expert committees

Environmental and personal factors influencing cutaneous vitamin D synthesis

Cutaneous vitamin D synthesis is strongly influenced by environmental and personal factors (Figure 5) which interfere, to varying degrees, with the availability of UV radiation from the sun (12).

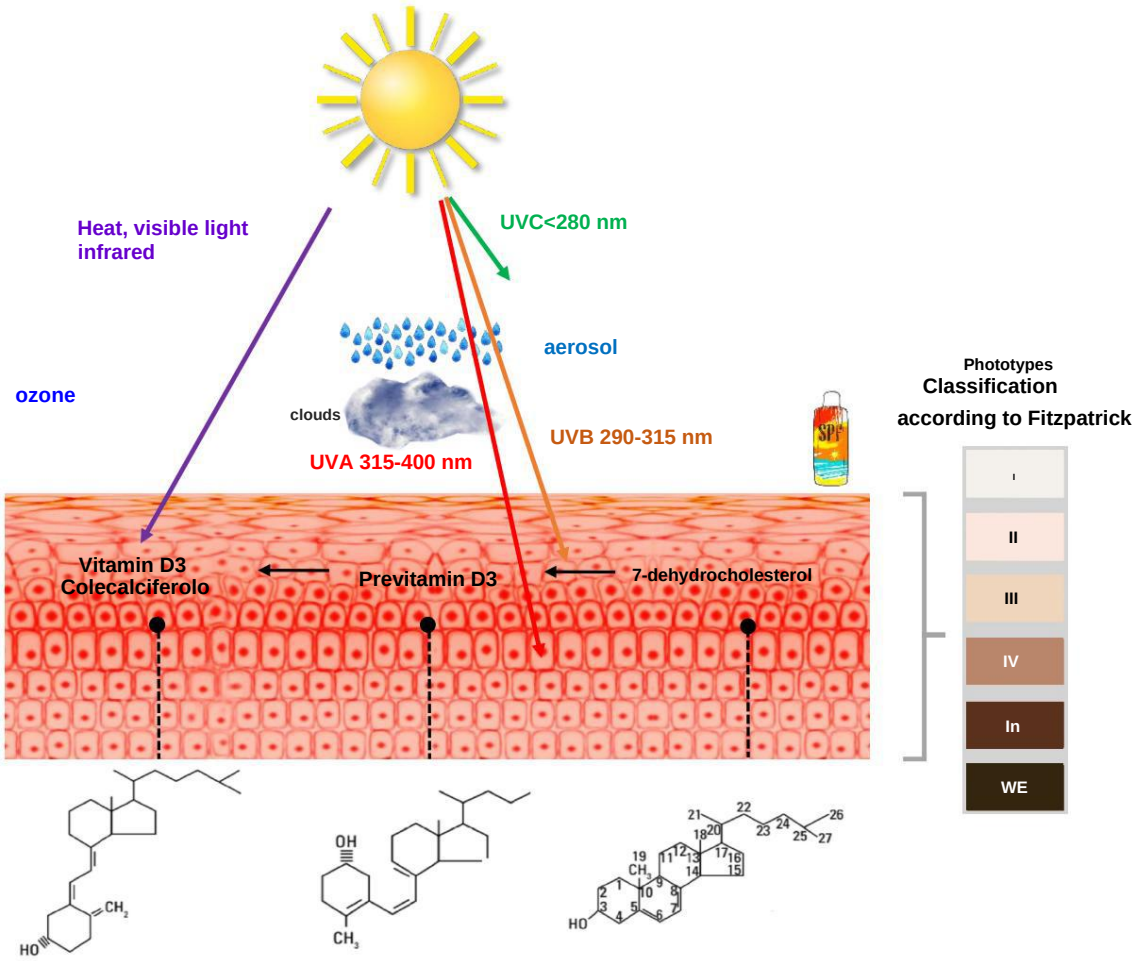


Figure 5. Environmental and personal factors relevant to cutaneous vitamin D synthesis

Among the environmental factors it is important to remember:

ÿ *Latitude*

In many locations the availability of solar UV radiation, sufficient for skin synthesis, is drastically limited to a few months a year by latitude as reported by some authors for locations at northern latitudes (13), but also for cities at southern latitudes (14). This data, in fact, may play a significant role in the widespread vitamin D deficiency among the population.

ÿ *Changing of the seasons*

There is a greater chance of skin synthesis of vitamin D in summer than in winter.
In the summer season, people generally spend or do more outdoor activities.

ÿ *Time of day*

UVB radiation is responsible for the skin's synthesis of vitamin D. The combined action of UVB and UVA, however, can lead to the onset of skin redness and erythema.
Both types of radiation are at their maximum intensity during the central hours of the day.

ÿ *Altitude* The

intensity of radiation reaching the ground in the mountains is higher than that at sea level, therefore it is important to take appropriate precautions to avoid adverse health effects.

ÿ *Presence of the ozone layer*

This presence is crucial in blocking UVC radiation in the upper atmosphere, allowing (on a typical summer day) approximately 5% of UVB and approximately 95% of UVA radiation to reach the earth. The ozone layer in the stratosphere is sensitive to changes caused by human activities in the form of gases and emissions, to the point that its integrity is partially compromised in some areas of the earth (near the poles). Eliminating the use of some specific propellants for aerosol products is slowly reversing this process.

ÿ *Angle with which solar radiation reaches the ground* Also known

as *Solar Zenith Angle* (SZA) is the angle formed between the vertical of the place (Zenith) and the line between the observer and the sun. Smaller angles, which occur when the sun is high in the sky (midday), correspond to more intense UV radiation; in the case of larger angles, the radiation must pass through a larger portion of the atmosphere to reach a certain place, losing part of its intensity. The combination of time of day, time of year (alternation of the seasons) and latitude contribute to defining a specific SZA for location and time (7).

Vitamin D synthesis can also be influenced by personal factors:

ÿ *Phototype*

Regarding vitamin D synthesis, light skin types synthesize it most easily, but at the same time, they can be exposed to the harmful effects of UV radiation. Dark skin types have a high melanin content in their skin, which makes them naturally protected or melanocompetitive from the harmful effects of UV radiation, but require longer exposure times to synthesize adequate levels of vitamin D.

ÿ *Age*

For a long time it was believed that progressive skin aging, with consequent thickening and reduction in the quantity of 7-DHC, could constitute an obstacle to the cutaneous synthesis of vitamin D, especially in the elderly. Recent works in scientific literature have explored this issue in depth, arriving at the conclusion that even in the elderly there is the capacity for good cutaneous synthesis of vitamin D (15).

ÿ *Weight (obesity) :*

Vitamin D, as previously mentioned, is a lipophilic substance, and this affinity means that part of the vitamin D circulating in the body is stored in adipose tissue and released from there during the winter months when skin synthesis is low or completely absent. In obese individuals, however, the vitamin D stored in adipose tissue is at risk of being sequestered and not made bioavailable for the body's needs. For this reason, obese individuals may be vitamin D deficient.

ÿ *Height* An

individual's height contributes to the calculation of the surface area of our largest organ: the skin. It is easy to understand that a tall person will have a greater usable surface area of skin to expose, and cutaneous vitamin D synthesis is directly proportional to the percentage of exposed surface area. It is not necessary to be entirely exposed to obtain adequate vitamin D levels. The percentages of skin surface area indicated in the literature generally vary between 25% and 35% (16,17).

ÿ *Use of creams with sun protection factor*

Creams with *Sun Protection Factor* (SPF) are useful for preventing the harmful effects due to exposure to solar UV radiation. Some scientific studies have highlighted that their diffusion and use could negatively interfere with the normal cutaneous synthesis of vitamin D in subjects who used this type of protection with a reduction in synthesis estimated up to 98% less than in non-users of SPF creams (18). A recent study (19) has reduced the negative impact on the cutaneous synthesis of vitamin D among users of SPF creams taking into account that in the current formulations of the creams there are filters for protection from both UVA and not only for UVB and that the majority of people do not follow the indications regarding the frequency and optimal quantities of application of the products recommended by the manufacturers, managing to synthesise vitamin D despite the application of protective creams.

ÿ *Cultural and religious habits*

Wearing very covering clothing can interfere with the skin's synthesis of vitamin D.

ÿ *Chronic pathologies and vitamin D deficiency*

Certain physiological conditions can interfere with either the proper synthesis of vitamin D (chronic liver and kidney diseases) or its absorption (e.g., certain digestive diseases, use of certain medications). All of these factors can contribute to the widespread vitamin D deficiency in the population, which has been associated with numerous pathologies (Figure 6).

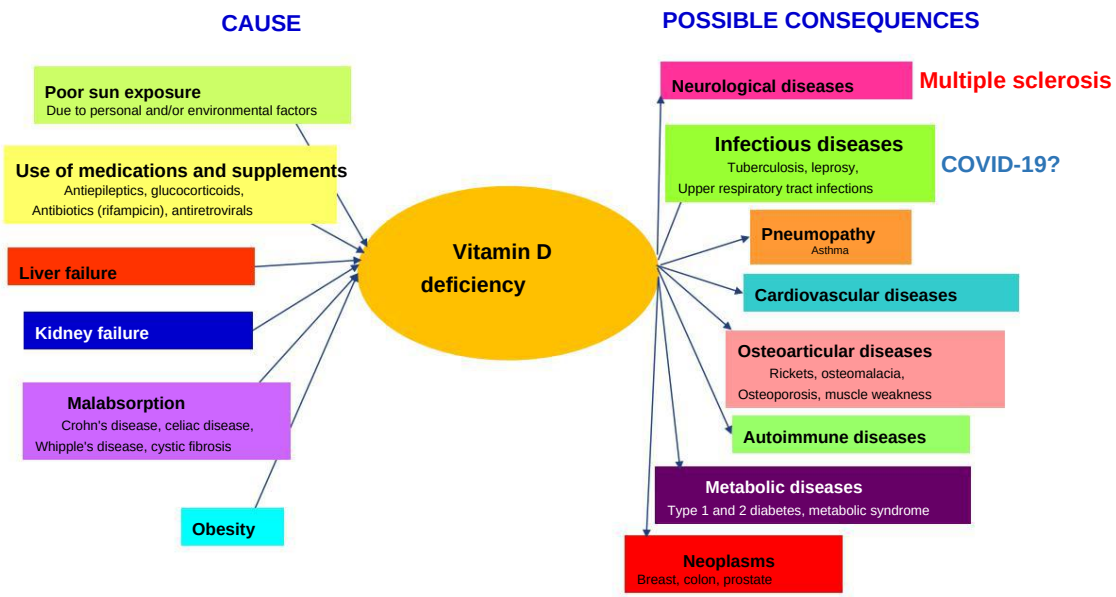


Figure 6. Causes and possible consequences of vitamin D deficiency

UVI, vitamin D and App

In response to an increase in the incidence of skin cancers due to sun exposure, in 2002 an international group of experts drafted for the World Health Organization (WHO) the publication “Global solar UV Index: a practical guide” (20) with the aim of providing a useful tool, the UVI, to national and local authorities to develop integrated approaches for effective communication for the prevention and protection from damage due to sun exposure.

WHO has defined and standardized UVI as:

$$= \ddot{y} \quad \overset{400}{250} \quad \times ( ) \qquad [1]$$

Where

IUV is the
UVI, ker is a constant equal to 40 m2 /W,
Eÿ is the solar spectral irradiance (W/m2 nm) at wavelength ÿ,
Ser is the reference spectrum of action for erythema

The UVI calculated using the formula [1] is a scalar number obtained by multiplying the solar spectral irradiance, detected with a spectroradiometer, by the erythemal action spectrum. Erythema in this case is the specific physiological effect caused by the physical agent being studied (solar UV radiation) in its interaction with the target tissue, the skin.

Figure 7 shows the graphic associated with UVI which consists of a scale of numbers from 1 to 11+ with colours from green to purple to indicate an increasing situation of potential danger due to excessive exposure to the sun (20). Operational messages are also associated, to protect oneself by means of individual protection devices such as a wide-brimmed hat which is important because it also allows protection of the nape of the neck and ears, the use of sunglasses, preferably wrap-around ones which allow protection of the eyes from excessive direct and diffused light; the use of clothing as they constitute a physical barrier to protect the skin and cream with a sun protection factor intended as a prevention/protection tool and not as a possibility to prolong the time of exposure to the sun.

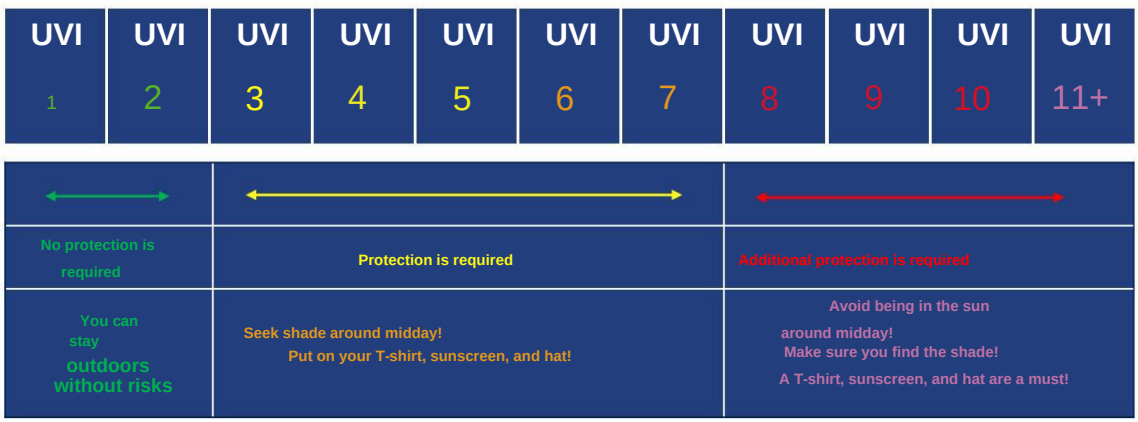


Figure 7. UVI with operational indications for correct sun exposure according to WHO (20)

The WHO document of 2002 (20) proposed solutions to communicate and make the scientific contents of the document understood by the widest possible audience through

press releases, interviews given by experts, meetings open to the public, publication of brochures, in other words through the most widely used and widespread mass media of that period.

UVI has been used by many international scientific organizations to conduct public health awareness campaigns among their respective countries. The experience implemented by the Australian Cancer Council Victoria is certainly one that has achieved positive results by focusing on changing the sun exposure habits of its citizens.1

In June 2022, the WHO launched a *press release* inviting users to download a specific UVI app called *Sunsmart.* This app retains the name of the Cancer Council Victoria Australian communications campaign, but updates the communication tool to reflect the current situation. The app is available on both Android and iOS platforms and provides simple tips for protecting yourself from excessive sun exposure, both at work and during your free time.

UVI and vitamin D app

Cutaneous synthesis of vitamin D from exposure to solar UV radiation covers approximately 80% of our body's needs. On the other hand, excessive exposure to the sun can cause an increase in harmful effects on the skin and eyes, which are the most exposed organs in the body. The damage associated with solar UV radiation, thanks to the formalisation of UVI, has recently been the subject of extensive media communication, including through dedicated Apps. In this context, the development of a scientifically validated App that reports both information, with the possibility of wide diffusion among the population, could be an effective and simple tool to use: it would provide information on UVI, with specific indications on how and when to protect oneself from excessive exposure to ultraviolet radiation, but also information on vitamin D, allowing one to acquire useful indications on the most appropriate times of the day to expose oneself to the sun and benefit from vitamin D synthesis. This challenge is *in progress* and it is clear that further studies and in-depth analyses are necessary (21). A recent web search identified a few apps that provide information on both UVI and vitamin D in terms of exposure times or synthesized doses at the user's geo-referenced location. Further aspects of the apps will be explored in specific contributions to this report.

Conclusions and future perspectives

In recent decades, numerous international education and communication campaigns have been conducted regarding the risks of excessive exposure to solar radiation. Their aim is to encourage changes in the population's habits and teach the most appropriate measures to prevent adverse health effects such as sunburn and erythema, or skin and eye cancers.

This focus remains valid, as recently reiterated in a *Position Statement*
Australian (22), both for the population and for those who work outdoors. Attention has been paid to the different phototypes that constitute the Australian population and to their different capacity for cutaneous synthesis of vitamin D. It is also important to bring to general attention a concept

[1] https://www.cancervic.org.au/cancer-information/preventing-cancer/be-sunsmart

which should by now be acquired and become part of everyone's personal cultural background: exposure to the sun is important for the cutaneous synthesis of vitamin D.

After years spent understanding how to protect ourselves from excessive sun exposure, reclaiming the basic concept that informed and conscious sun exposure promotes good health is not a given, even in some scientific circles. It is relatively complex to understand that a physical agent like ultraviolet radiation can be both a carcinogen and beneficial for health. However, it is precisely this challenge that allows us to study and implement tools, including apps, that, if based on scientifically sound and validated criteria, can increasingly serve the public health sector.

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COVID-19 VITAMIN: DATA AND CONTROVERSIES

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General concepts

Since the beginning of the COVID-19 pandemic, vitamin D has received considerable attention from the medical and scientific community for its potential role in preventing or treating the disease. After more than four years and over 2,000 scientific publications on the topic, the topic remains controversial. This chapter provides a brief introduction to COVID-19 and the pre-pandemic knowledge that led to the hypothesis of a protective role for vitamin D in this disease. It then summarizes the current state of the art on the topic, highlighting the issues on which there is consensus in the scientific community and those that remain open or controversial.

Clinical manifestations and risk factors of COVID-19

The emergence of a new beta coronavirus, called SARS-CoV-2 *(Severe Acute Respiratory Syndrome Coronavirus* 2), in late 2019 triggered the COVID-19 pandemic, which – as we all know – has had a catastrophic global impact, causing nearly 7.1 million deaths worldwide to date (https://data.who.int/dashboards/covid19/deaths; last accessed 28/05/2025).

SARS-CoV-2 infects primarily (but not exclusively) cells of the respiratory tract and can cause a broad spectrum of clinical manifestations. Infection may be asymptomatic or characterized by mild or moderate symptoms, the most common of which include fever, cough, shortness of breath, fatigue, myalgia, nausea, vomiting, diarrhea, headache, weakness, anosmia, and ageusia. In some cases, however, the infection manifests as a severe disease, with a wide range of complications including pneumonia, acute respiratory distress syndrome *(ARDS),* thromboembolism, and multiorgan failure that can have life-threatening consequences. fatal (1, 2). Among the main risk factors for the onset of severe disease, advanced age, obesity, concomitant chronic diseases (such as diabetes), ethnicity, male sex and latitude were immediately recognized. All these factors were also known as risk factors for vitamin D deficiency (3).

Pathogenesis of COVID-19 and the biological plausibility of the protective function of vitamin D

The pathogenesis of COVID-19 is generally described in two phases: an initial phase in which viral replication is the main driver of any symptoms, and a subsequent phase caused primarily by an uncontrolled immune response (also called the cytokine storm phase). Viral load peaks in the first week of SARS-CoV-2 infection and then gradually declines as the immune response increases. At the same time, in the first few days, the infection can range from asymptomatic to mildly symptomatic in most patients, with upper respiratory symptoms and/or a flu-like systemic illness. Severe COVID-19, on the other hand, usually develops at least after

one week after the onset of the disease, when a dysregulation of the immune response can occur, with blockage of the *interferon* response and hyper-inflammation culminating in the so-called cytokine storm (1, 2, 4) (Figures 1 and 2).

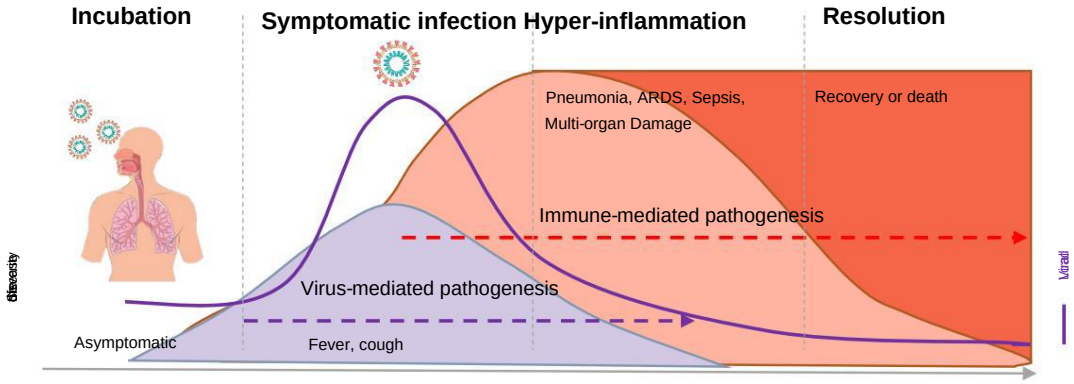

Figure 1. Pathophysiology of COVID-19 (4)

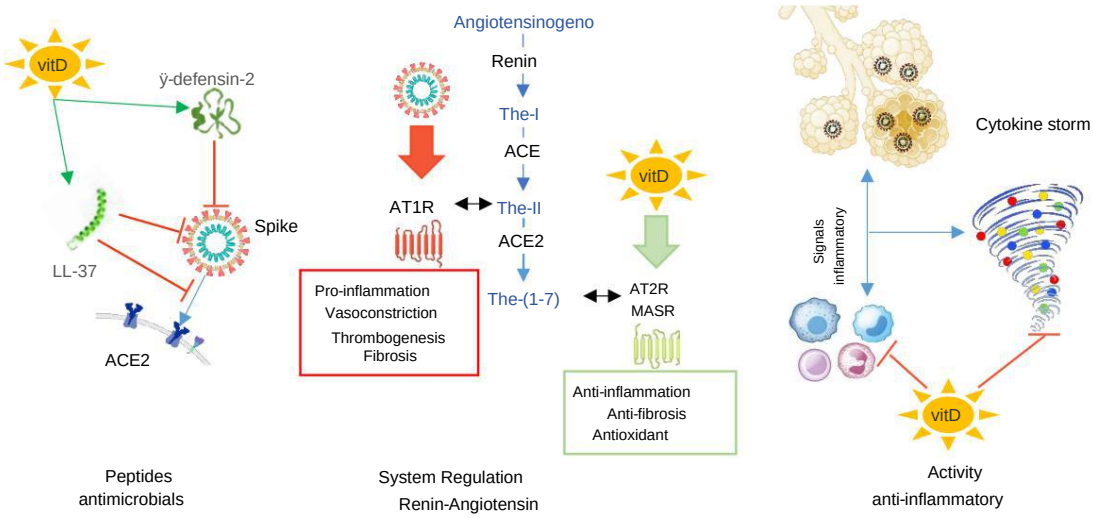

Figure 2. Possible mechanisms of action of vitamin D during SARS-CoV-2 infection (some images adapted from Davian Ho for Innovative Genomics Institute) and from Smart Servier medical art https://smart.servier.com)

Based on pre-pandemic studies, there was a strong biological rationale for hypothesizing a protective function of vitamin D, both in the initial viremic phase and in the subsequent phase characterized by an excessive inflammatory response. Studies conducted in the context of other infections had documented its ability to induce the production of antimicrobial peptides, such as cathelicidin and defensins, which can have a direct antiviral effect (virion destruction) or sterically inhibit the virus's binding to ACE-2, as well as the ability to regulate the expression of ACE2, the cellular receptor of SARS-CoV-2, which is also an important component of the renin-angiotensin system, whose dysregulation contributes to the severity of the disease. Vitamin D also modulates the immune response, attenuating the production of pro-inflammatory cytokines and chemokines and increasing the expression of anti-inflammatory ones, and targeting T cells.

toward a regulatory response. In this way, vitamin D contributes to the resolution of inflammation, which is necessary for the elimination of the virus but harmful to tissues if excessive, and could counteract the "cytokine storm" in the more advanced stages of the disease (Figure 2).
Other proposed molecular mechanisms for the protective activity of vitamin D include: i) maintenance of epithelial barrier integrity in the respiratory tract through regulation of tight and adherens junctions; ii) induction of autophagy, a defense mechanism against intracellular pathogens, such as viruses, which isolates microorganisms in intracellular vesicles where they are then destroyed; iii) cooperation with type I interferon, one of the most potent mediators of the body's innate antiviral response (5-7).

Vitamin D in the prevention of acute respiratory infections

One of the strongest arguments supporting the hypothesis of a protective role of vitamin D in COVID-19 came from a systematic *review* of 25 randomized controlled clinical trials in which vitamin D had been prescribed for the prevention of acute respiratory infections, published in 2017 (8). The meta-analysis of individual data from almost 11,000 participants in the clinical trials indicated that vitamin D supplementation reduced the risk of contracting an acute respiratory tract infection (in 1 out of 33 treated patients). Through subgroup analysis, the authors also reported that the benefit was greater in those who received daily or weekly doses of vitamin D compared to those who received high doses (the so-called “bolus”) in a single or multiple administrations (the number of patients needed to treat to obtain a benefit dropped to 20) and in those who had initial blood 25-hydroxyvitamin D [25(OH)D] levels ÿ 25 nmol/L (the number of patients needed to treat to obtain a benefit dropped to 8 – even 4 in the “non-bolus” treatment subgroup and initial level of 25(OH)D ÿ 25 nmol/L).

The study was updated in 2021 (9) to include 18 new clinical trials and the meta-analysis of a total of 48,488 patients, and confirmed the protective effect in the total population analyzed and in the subgroup of patients treated with daily doses (but not the reduction in the subgroup with initial 25(OHD) levels ÿ 25 nmol/L). A protective effect was also observed in the subgroup of young people aged 1 to 16 years.

This pre-pandemic body of knowledge generated great anticipation in the medical and scientific community and led to a veritable flood of publications—primarily observational studies (as well as a large number of *reviews,* commentaries, and letters, which almost exceeded the number of original papers)—with unfortunately often contradictory results.

Vitamin D Status and COVID-19: epidemiological and observational studies

A large number of epidemiological and observational studies have highlighted the presence of an inverse relationship between blood vitamin D levels (or, more precisely, 25(OH)D, the main circulating metabolite) and the risk of both infection and disease severity. There is general consensus on this association, but there could be several possible explanations underlying it: i) *causality:* vitamin D deficiency may increase susceptibility to severe disease due to the attenuation of antiviral and anti-inflammatory responses to the virus; ii) *reverse causality:* severe COVID-19 reduces the amount of circulating 25(OH)D by increasing catabolism or reducing the concentration of the plasma transport protein; iii) *confounding factors:* the same factors may be independently associated with both increased susceptibility to COVID-19 and vitamin D insufficiency and this may introduce biases *in* the statistical analysis (5) (Figure 3).

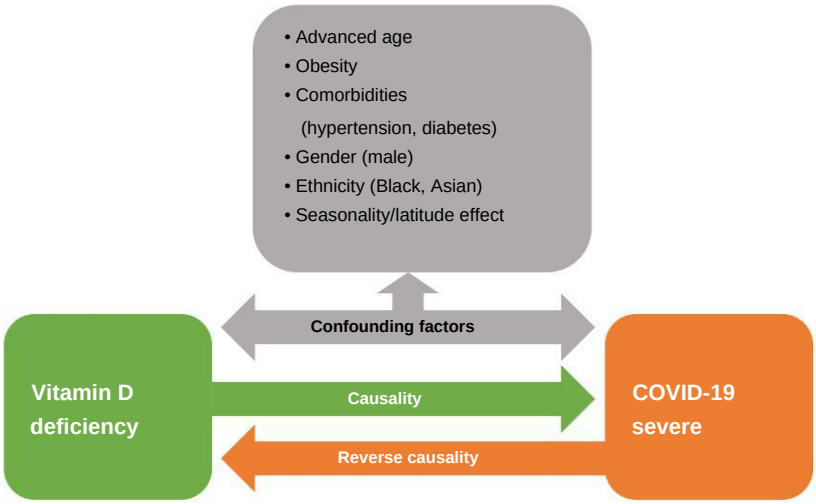

Figure 3. Possible interpretations of the association between vitamin D deficiency and COVID-19 severity

A type of observational study not subject to this type of *bias* is Mendelian Randomization *(MR)* (10). MR studies allow us to analyze the cause-effect relationship between a modifiable factor – for example, vitamin D levels in the blood – and the consequences of its variations on a phenomenon or disease of interest, in this case COVID-19. They are based on Mendel's laws of inheritance and can be applied in all cases in which the modifiable factor under study is associated with genetic variations in one or more genes. This is the case of vitamin D levels, for which several variants (or, in technical terms, single nucleotide polymorphisms) of genes implicated mainly in the synthesis and catabolism of 1,25-dihydroxy vitamin D [1,25(OH)2D], but also in lipid metabolism with tissue-specific expression in the skin associated with genetically "low" vitamin D levels have been identified (11). MR studies are often considered natural randomized controlled trials, in which randomization is due to the random distribution of alleles, according to Mendel's laws. However, all studies conducted to date report the absence of an association between genetically determined low vitamin D levels and the risk of infection or severe disease (12).
However, these studies also have limitations: a) serum 25(OH)D levels are largely a reflection of environmental factors; the heritability of serum 25(OH)D levels has been estimated to be less than 10%; b) MR is a useful tool for assessing the potential impact of long-term (lifelong) exposure to low levels of vitamin D (e.g., multiple sclerosis). This approach may be less relevant for acute respiratory infections, where even transient changes in serum 25(OH)D can have a biological effect.

Vitamin D administration for therapeutic or preventive purposes for COVID-19: clinical studies

The *gold standard* for establishing a cause-and-effect relationship and evaluating the prophylactic or therapeutic potential of a molecule is randomized controlled clinical trials. To date, the results of approximately 20 clinical trials on the effects of vitamin D administration for therapeutic or preventive purposes in COVID-19 have been published. These studies are difficult to compare.

because they are very different from each other in terms of numerous parameters, such as the study design, the sample size (from a few dozen to several hundred participants), the nature of the intervention – administered vitamin D metabolite (vitamin D, 25(OH)D3, 1,25(OH)2D3) and dose/frequency of administration (from 500,000 IU, the so-called bolus, to 200 IU; single dose *vs.* repeated doses) –, and the primary outcomes analyzed (mortality, length of hospital stay, need for intensive care, resolution of symptoms and viral *clearance).*

The results are in fact very heterogeneous, as are the conclusions of various systematic reviews and meta-analyses of these studies. It has been reported that vitamin D supplementation reduced mortality (13), hospital stay, but not mortality (14), and admission to intensive care (15-17). Other meta-analyses, however, report contradictory data and the absence of significant effects of vitamin D supplementation (18, 19). Even the observed favourable effects are however – although statistically significant –
of minor importance.

The available studies on the administration of vitamin D for preventive purposes are fewer, but two clinical studies in particular (20, 21) published jointly in the *British Medical Journal,* did not find any preventive effect of vitamin D supplementation.
Despite this, the editorial accompanying their publication suggested that, although both were large and well-designed studies, the possibility of a positive effect of vitamin D, which is difficult to measure experimentally, still remained open (22).

Unlike studies with traditional drugs, those on vitamin D have a series of important critical issues to consider when interpreting the results:

- ÿ In vitamin D studies, participants in the control group are also exposed to some extent to the agent being studied: exposure can arise from exposure to UVB radiation, from diet, or from supplements that are also permitted in the placebo group for ethical reasons.

- ÿ The “ideal” study would enroll people with known vitamin D deficiencies and then ask them to be randomized to receive vitamin supplements or a placebo, but this is unethical since anyone with a vitamin D deficiency should receive regular supplements. As a result, many studies do not test baseline blood 25(OH)D levels.

- ÿ For the same reasons, most studies are conducted on samples that include people with sufficient vitamin D levels, for whom the further increase resulting from supplementation is unlikely to have a benefit.

- ÿ Identifying optimal blood concentrations and dosing strategy for vitamin D supplements is an unsolved problem. One concept that seems to emerge clearly from different studies, even in the context of other diseases, is the importance of the vitamin D dose (low/moderate *vs.* high) and the administration method (daily, repeated or a single administration). In particular, it seems that single administration and/or very high doses are less effective than daily or repeated administration of lower doses. As evidence of this, a recent randomized controlled clinical trial on vitamin D administered as a bolus (100,000 IU every 3 months) to prevent rickets in children reported negative results, despite the key role of vitamin D in the onset of rickets being undisputed (23). There are several plausible biological explanations why bolus and/or high doses of vitamin D may not be effective: (i) transiently elevated 25(OH)D levels induce the inhibitory and catabolic enzyme vitamin D-24-hydroxylase CYP24A1, which may persist for several weeks after 25(OH)D has dropped; (ii) it is also likely that transiently elevated 25(OH)D levels

induce FGF23, which can then suppress the activating enzyme 1ÿ-hydroxylase in both renal and extrarenal tissues.

ÿ Finally, in the interpretation of null results, one must also take into account the concomitant vaccination campaign with a highly effective vaccine.

Basic and preclinical research

Several *in vitro* and *ex vivo* cellular as well as animal models play a fundamental role in understanding the biology of SARS-CoV-2 and in screening potential therapeutic agents (24-26) (Figure 4). Among these, the most widely used include: (i) conventional cell cultures (Vero cells, a monkey renal epithelial cell line widely used to isolate, propagate and study SARS-CoV-2; Calu-3 or Caco-2, cells from the respiratory or intestinal epithelium, respectively, that express ACE-2 and TMPRSS2 and have replaced Vero cells as a cell culture model for SARS-CoV-2); (ii) airway epithelial cells (primary or lineages) differentiated at the air-liquid interface (ALI), an experimental condition that simulates the environment in which these cells naturally occur, and allows for the production of a pseudostratified ciliated and columnar epithelium that mimics the physiology of the upper (nasal cells) and lower (bronchial cells) airways; (iii) respiratory organoids, which contain functional respiratory tract cell types and provide a physiologically relevant platform with which to study the pathophysiology of SARS-CoV-2 or the mechanism of drug action. In particular, organoids and primary cultures can be derived from donors with diverse genetic or pathological backgrounds and thus provide a model for examining the impact of such backgrounds on SARS-CoV-2 infection. Finally, several animal models have been developed for the *in vivo* analysis of SARS-CoV-2, including transgenic mice expressing human ACE2, Syrian golden hamsters, ferrets, and some non-human primates, susceptible to SARS-CoV-2 infection and/or disease.

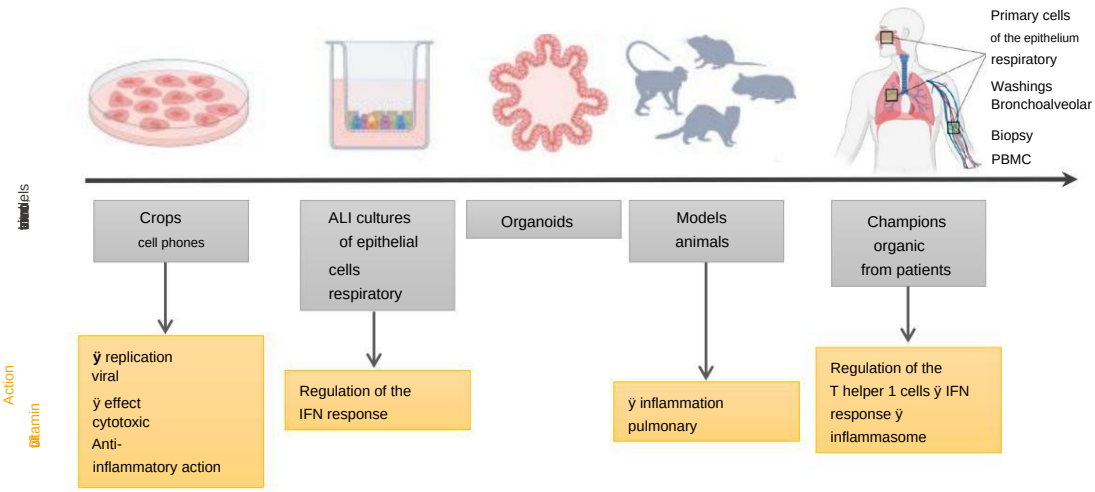

Figure 4. In vitro, in vivo and ex vivo models for the study of SARS-COV-2 and main results obtained in works on vitamin D and SARS-CoV-2

Basic research and preclinical studies on vitamin D and SARS-CoV-2 infection are surprisingly few, but they nevertheless appear to confirm some of the hypothesized mechanisms of action for a protective effect of vitamin D during SARS-CoV-2 infection.

Indeed, a direct antiviral action of calcitriol has been observed, capable of inhibiting viral replication and the cytotoxic effect in different cell types, including Vero cells (27) and Calu-3 cells (28). Among the possible mechanisms underlying the antiviral activity there could be the regulation of the *interferon response,* observed in ALI cell cultures infected in vitro with SARS-CoV-2 (29), and in blood and saliva samples obtained from patients (30). A decrease in the production of pro-inflammatory cytokines/an anti-inflammatory activity of vitamin D3 has also been observed in primary epithelial cells exposed to the N protein of SARS-CoV-2 (31) and in the mouse animal model, but not in the hamster model (32). Finally, it was observed that T cells isolated from bronchoalveolar lavages of COVID-19 patients were unbalanced towards the pro-inflammatory TH1 phenotype and showed a dysregulation of vitamin D target genes (33).

It is important to underline that vitamin D activities in *in vitro* experimental models are generally studied in the context of acute, relatively short treatments (a few hours/days) with supraphysiological doses of 1,25(OH)2D. This context is far from the physiological situation, in which tissues are exposed mainly to the blood precursor 25(OH)D, which can be locally converted to 1,25(OH)2D by cells – such as macrophages – expressing the CYP27B1 enzyme. Thanks to the support of the European Isidore network (https://isidore-project.eu/), we have therefore recently started a project aimed at developing a more "physiological" *in vitro* model to define whether and how the cellular response to SARS-CoV-2 is affected by long-term exposure to physiological doses of 25(OH)D, the vitamin D metabolite in blood that best defines individual vitamin D status (Figure 5).

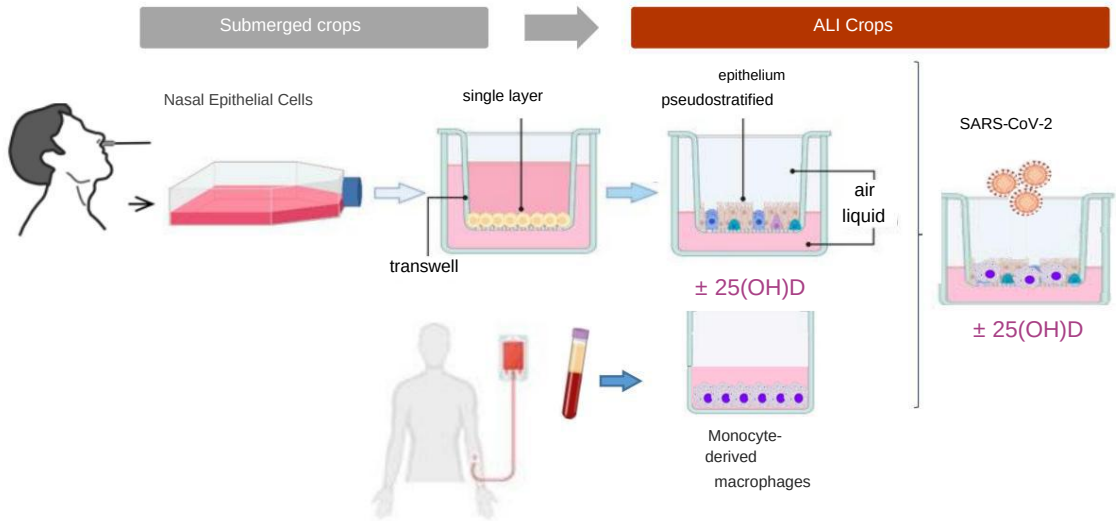

Figure 5. In vitro model for studying the effect of long-term exposure to 25(OH)D on SARS-CoV-2 infection (model extendable to other pathogens that primarily target respiratory cells)

The project is based on the hypothesis that adequate levels of vitamin D in the body strengthen the innate antiviral response to SARS-CoV-2. As part of this project (in collaboration with M. Alves of the Institute of Virology and Immunology, University of Bern, Switzerland), we have already developed a culture model of primary epithelial cells at the air/liquid interface.

nasal differentiated into a polarized epithelium that recapitulates the characteristics of the *in vivo* epithelium and exposed to 25(OH)D for up to 4 weeks.

The model will be implemented with the addition of primary macrophages and used to study possible actions of 25(OH)D on the early response to SARS-CoV-2 infection *(see*
Figure 5). Once developed, the model could also be used to study other respiratory pathogens, thus contributing to the enrichment of preclinical research on the mechanisms of action of vitamin D with further useful tools.

Conclusions and future perspectives

The impact of vitamin D deficiency on the risk of COVID-19 infection and disease severity remains plausible, although unproven. Despite the significant body of literature on vitamin D and COVID-19, several important open questions remain:

ÿ There is a lack of basic and preclinical research on vitamin D and COVID-19.

Observational and epidemiological studies show an association between low blood vitamin D levels and the risk of SARS-CoV-2 infection and severe disease, but the causal relationship has not yet been established. Vitamin D deficiency should still be avoided, even with safe sun exposure.

ÿ Clinical studies on the administration of vitamin D for preventive or therapeutic purposes have not yet confirmed a protective effect against COVID-19.

ÿ Future clinical studies should carefully consider the dose and formulation of vitamin D, and be conducted especially in at-risk populations.

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MULTIPLE SCLEROSIS VITAMIN

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Introduction

Multiple Sclerosis (MS) is a degenerative disease of the central nervous system, with an autoimmune component, which manifests itself with a progressive loss of motor and cognitive abilities (1). It mainly affects young adults, although recent studies have highlighted an increase in cases with onset in pediatric age (2) and in people over 50 years of age (3).

There are several clinical forms of MS, each with distinctive characteristics. The disease typically manifests with an initial demyelinating episode *(Clinically Isolated Syndrome,* CIS) followed by partial or complete recovery of function. When this is followed by other episodes,
The most common form of the disease, relapsing-remitting MS (RRMS), develops after the onset of these pathological manifestations. This form manifests with acute episodes of neurological deterioration followed by periods of partial or complete recovery. RRMS accounts for approximately 85% of cases at onset. Another significant form is secondary progressive MS (SPMS), which often evolves from RRMS. In SPMS, after an initial period of relapses and remissions, a continuous progression of neurological deficit is observed without periods of significant remission. This phase is characterized by further progressive degeneration and accumulation of disability. Primary progressive MS (PPMS) is characterized by a continuous progression of symptoms from the onset, without distinct episodes of relapses and remissions. This type of MS is less common, representing approximately 10-15% of cases, and generally involves a gradual progression of neurological disability. Finally, there is the relapsing progressive form (PRMS), which combines features of continuous progression with acute relapses. In this form, patients experience a progressive deterioration of symptoms with the addition of episodes of acute worsening (4). There is also a very rare form called Radiologically Isolated Syndrome *(RIS)* which is only evident through magnetic resonance imaging and is usually diagnosed following an incidental finding (5).

It is estimated that approximately 2.8 million people worldwide are currently affected by MS with an incidence of 0.1% and a prevalence that increases with latitude (6) and with a prevalence double in females compared to males (7-11).

In recent years, significant improvements have been achieved in the healthcare landscape for people with MS, particularly in the ability to make diagnoses (12) and in the development of new therapeutic approaches, thus allowing for the preparation of early treatments capable of delaying the progression of the disease over time.

The therapies currently available are based on the knowledge acquired so far on the pathogenic mechanisms and mainly target the immune system (13). Since the causes of the disease are not yet known, it is not possible to develop etiological therapeutic approaches that are able to cure MS.

Etiology of multiple sclerosis

Genetic factors

Epidemiological studies have highlighted that the factors contributing to the onset of the disease are both environmental and genetic (14, 15). More than 200 genetic factors predisposing to the disease are known to date and have been identified thanks to genetic association studies conducted by analyzing large regions of the human genome *(Genome-Wide Association Study,* GWAS). Thanks to the work of international consortia, up to 47,429 blood samples from people with RRMS and more than 68,000 samples from control populations matched for age, sex and geographical origin have been analyzed (16, 17, 18, 19).

Specifically, mostly single nucleotide polymorphisms *(SNPs)* have been identified: 32 in the regions coding for the major histocompatibility complex *(MHC)* which are also the most polymorphic regions of the human genome (20), 200 susceptibility variants outside the MHC regions and 1 variant on the X chromosome. These variants, although associated with an increased risk of developing the disease, are very rare in the general population and also in the population of people with MS and are not able to explain the onset of the disease by themselves.

Environmental factors

Environmental factors include childhood obesity, smoking, exposure to chemical agents, but those supported by the greatest experimental evidence are infection with the Epstein-Barr virus (EBV) and reduced levels of vitamin D in the blood (14).

Infection with the Epstein-Barr virus

EBV is a gamma-herpesvirus that infects almost the entire adult population and has recently been identified as a factor that precedes the onset of the disease. In a population of approximately 10 million soldiers of the United States Army, subjected to blood sampling for diagnostic purposes during their years of service, approximately 1000 were found to have developed MS and of these only one was negative for anti-EBV antibodies. Furthermore, the onset of the disease occurred only after the development of antibodies against the virus (21), demonstrating that infection with EBV is a necessary element for the onset of MS.

The EBV virus perpetuates itself, within a few infected B lymphocytes, throughout the individual's life, in a form of latency that inhibits the expression of viral proteins and prevents the immune system from recognizing and eliminating infected cells.

The association between the virus and the disease has been based over the years on epidemiological evidence showing a high antibody titer in patients compared to healthy subjects (22, 23), the identification of the presence of the virus in autopsy brain tissues of people with MS, but not in controls (24) and in the observation of viral reactivation phenomena both in the peripheral blood circulation and in the central nervous system, due to an altered immune response to the virus (25, 26). Furthermore, the genetics of the virus also seems to be important in defining the interaction between the virus and the host (27, 28) and would help to explain the apparent paradox of the association between a disease
relatively rare and a ubiquitous infection. By studying a region of the viral genomic DNA that encodes the protein *Epstein-Barr Nuclear Antigen 2* (EBNA2), a latency phase protein of the virus, we identified a viral DNA allele, called 1.2, which is associated with an increased risk of developing MS (27, 28). The EBNA2 protein is an activator

transcriptional capable of modifying the expression levels of both viral and cellular genes by modifying the chromatin structure (30) through the formation of phase separation foci (31). The viral protein does not have DNA binding sites, but exerts its function as a transcriptional activator through binding to cellular transcription factors. Among these, the one most associated with the functionality of the viral protein is the *Recombination signal Binding Protein for immunoglobulin kappa J region* (RBPJ) (32). It is conceivable that the genetic variants of the virus, in combination with the human ones, may contribute to altering, towards a disease phenotype, the interaction between virus and host (27, 29), promoting an altered gene transcription.

UVB exposure and vitamin D levels

As previously mentioned, the prevalence of MS increases with increasing latitude (33), in direct proportion to the decrease in irradiation by UVB rays, which are responsible, in addition to intake through food, for vitamin D levels in the blood.

Epidemiological studies have highlighted the role of vitamin D in MS since the 1980s, when it was observed that the risk of MS decreased in people migrating from higher to lower latitudes (34), that the age of migration influenced the risk of developing MS, while the second generation of migrants assumed the risk of the host country. These observations confirm that the environment and in particular exposure to the sun are important factors in MS. Subsequent studies have then allowed us to evaluate the association between vitamin D intake, through diet or supplements, and the risk of developing MS (35). Using data from two cohorts called *Nurse's Health Study*
(NHS)-I and NHS-II, composed respectively of 121,700 nurses aged 30 to 55 and 116,671 aged 25 to 42, it was seen that those who reported a higher intake of vitamin D, through diet and use of supplements, had a lower risk than those who consumed less vitamin D. Furthermore, in general higher levels of 25(OH)D, regardless of the intake route, were associated with a reduced risk of developing the disease, suggesting a protective role for vitamin D.

The protective role seems to have an effect on the offspring as well, in fact the *Finnish Maternity Cohort* comprising more than 800,000 women with more than 1.5 million serum samples, was used to examine the association between vitamin D levels and the risk of MS in the offspring, observing that there is an increased risk in the offspring of women who had lower vitamin D levels during pregnancy (36). Using data from the Danish National MS Registry and the Danish Newborn Screening Biobank *(DNSB)* it was also possible to observe that children born with low 25(OH)D levels (<30 nmol/L) had an elevated risk of developing the disease (37). Vitamin D levels are relevant not only with respect to the risk of disease, but also for its severity and progression (38). This evidence had led to the hypothesis that vitamin D supplementation in the diet of people with MS could have some therapeutic effect on disability and relapse rate. In this perspective, over the years several studies have been conducted in which vitamin D has been administered as a supplement alone or in combination with disease-modifying therapies. The results obtained so far are not able to unequivocally demonstrate a therapeutic role for vitamin D, due to the small number of samples analysed, the different administration methods and concentrations and the various combinations with pharmacological therapies (39). However, these studies suggest that treatment with vitamin D may exert an immunomodulatory effect thanks to its pleiotropic role capable of promoting innate immunity, modulating the activity of adaptive immunity and favouring the production of anti-inflammatory cytokines such as IL-10 and TGF-ÿ (40, 41).

The levels and bioavailability of vitamin D and its metabolites are strictly related to the proteins that transport them in the blood. Being hydrophobic compounds, they are transported through binding to some proteins, including the *vitamin D Binding Protein* (DBP) which transports approximately 85% of the active form. Some studies have tried to understand whether the concentration of this protein in the blood was correlated with the alterations in vitamin D levels observed in MS, obtaining conflicting results in some cases (42). In particular, the study conducted on an Italian population (43) highlighted an increased level of DBP in the blood of people with MS compared to controls, confirming what had already been observed in a pediatric population (44), and hypothesizing that an increase in DBP could reflect an increase in the vitamin D bound to it and a lower bioavailability for entry into cells. On the contrary, an increase in DBP could reflect a compensatory mechanism to increase the transport of vitamin D and its bioavailability in a condition of deficiency.

Once inside the cell, vitamin D exerts its action by binding to the *Vitamin D Receptor* (VDR) which acts as a transcription factor regulating gene transcription through binding to specific DNA sequences called *Vitamin D Response Elements* (VDRE) which are found in correspondence with promoters and regulatory regions (45). Through this binding, vitamin D is able to regulate, within the cell, calcium metabolism, cell growth and processes linked to inflammation. In correspondence with the regions bound by the VDR, genetic polymorphisms have been identified which are able to alter the binding affinity of the transcription factor with DNA. Furthermore, these variants are significantly enriched in the genetic intervals associated with autoimmune diseases including MS (46). Specifically, two variants, rs2881514 and rs2531804, have been identified as relevant in influencing the binding between VDR and DNA, contributing to defining the susceptibility to MS (47). Other genetic polymorphisms have been identified in correspondence with enzymatic activities that participate in the metabolic processes of vitamin D by influencing them (48), but no associations with MS have been observed.

Interaction between genetic factors, vitamin D receptor and viral proteins

Although we have a wealth of information on the causal role of various genetic and environmental factors associated with the onset of MS, we still lack a complete picture of their interactions in defining the disease phenotype. In an attempt to better understand this aspect, we conducted a bioinformatics study to evaluate whether the regulator

viral transcriptional signaling, EBNA2, as already seen in the case of VDR (46), was able to interact with disease-predisposing genes. To do this, we took into consideration the approximately 200 known MS-associated variants and identified a 50 kb region upstream and downstream of each SNP, identifying a genomic region in which to evaluate the possible presence of EBNA2 binding. To this end, data on the localization of the viral protein on the human genome available in the literature were used (49). This analysis was conducted for MS and for other autoimmune diseases such as rheumatoid arthritis and lupus, which have EBV as a risk factor in common with MS. We found that EBNA2 is located within susceptibility sites more than would be expected by chance (observed versus expected overlap factor [O/E] = 5.392 $p < 2.0e-05$) and this occurs via the cellular factor RBPJ in genomic regions associated with MS, rheumatoid arthritis, and lupus, but not in other inflammatory diseases. We then asked whether this observation was significant in itself or should be considered in the context of other disease-relevant gene-environment interactions, such as those attributable to vitamin D. We therefore tested for overlap between EBNA2 genomic occupancy and VDR binding sites.

EBNA2 shows complete overlap with VDR binding sites (O/E = 96.16, $p < 2.0e-05$), even after normalizing for chromatin accessibility state ($p < 0.001$).

This occurs only in MS and not in other autoimmune diseases associated with EBV infection (50). The propensity of EBNA2 and VDR to have an overlapping genomic localization allows for two possible functional interpretations (Figure 1a-b):

1. EBNA2 and VDR may compete for binding to the same genomic regions characterized by the presence of MS-associated genetic polymorphisms (Figure 1a);
2. EBNA2 and VDR can interact with each other at the same binding sites (Figure 1b), hypothesizing that VDR may represent one of the cellular factors through which EBV, via EBNA2 and EBNA3 as already shown by (51), can direct gene transcription in the genomic regions associated with MS.

These data suggest that non-heritable risk factors may work synergistically with each other and with genetic factors to determine alterations in immune system cells that may predispose to disease.

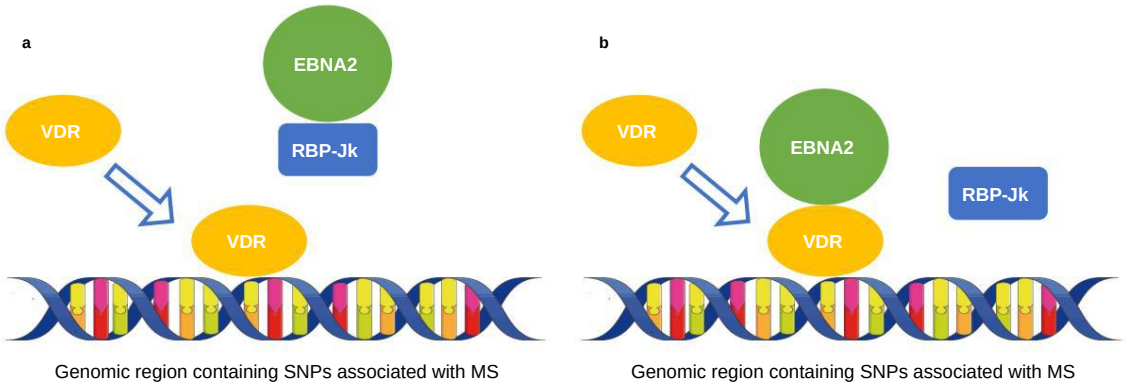

Figure 1. Hypothetical binding model of EBNA2 and VDR to MS-associated genomic regions: (a) model of competition between the EBNA2/RBPJ complex and VDR; (b) interaction model between VDR and EBNA2

Conclusions

Overall, epidemiological studies have identified low vitamin D levels as a significant predisposing factor for MS, which appears early in the body's life. However, it is still unclear how this deficiency may play a causal role in the onset of the disease.

Proteins that transport the hormone in the blood may play an important role, but it is unclear whether the reduced levels of these proteins observed in people with MS are a consequence of reduced availability of vitamin D and metabolites in the bloodstream.

A significant role can also be attributed to genetic polymorphisms that alter the binding capacity of the VDR to target DNA, altering vitamin D-dependent gene transcription mechanisms. Although there is considerable evidence suggesting a causal role for these polymorphisms, their distribution in the MS population cannot fully explain the onset of the disease. Furthermore, the VDR, which functions as a transcription factor, can interact or compete with viral transcription factors (e.g., EBNA2 and EBNA3), altering gene transcription mechanisms.

Further studies will be useful to further investigate the role of vitamin D in MS and its interaction with other transmissible and non-transmissible factors that predispose to the disease.

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CONTROL STRATEGIES OF EXPOSURE TO ULTRAVIOLET RADIATION SOLAR IN OUTDOOR WORK

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Introduction

Nearly 20 years after the entry into force of Legislative Decree no. 81 of 9 April 2008, attention to prevention and safety in the workplace has developed and grown to the point that it is very difficult today to find work activities for which a Risk Assessment Document (DVR) has not been drawn up, compliant with the indications provided in a Title of the Decree itself.

This Consolidated Law on Workplace Safety, however, while representing a fundamental tool in the assessment process, obviously cannot be exhaustive but leaves the employer with the task of "evaluating, calculating and/or measuring" the specific risk factors for workplace safety purposes to be considered in drafting the DVR, regardless of whether these risk factors are more or less defined within the Decree itself.

It is in fact possible that no indication regarding specific occupational risks can be found within Legislative Decree 81/2008: this is the case, for example, of Microclimate or Hyperbaric Atmospheres which are mentioned in Title VIII Physical Agents but which are not specifically addressed therein.

In particular, if we consider that the risk of occupational exposure defined in Chapter V of Title VIII concerns only Artificial Optical Radiation (AOR), it means that the legislator wanted to purposely exclude the Sun from the regulatory treatment, the only non-artificial optical source but of significant protectionist importance which therefore would seem to be excluded from the physical agents to be taken into account in the risk assessment. It is true that art. 28 of the Decree would oblige the employer to evaluate all risks especially when, as in the case of solar radiation, the latter is included in the Group 1 carcinogens of the classification (1) *of the International Agency for Research on Cancer* (IARC) but, in reality, it happens that finding in the company DVR of activities carried out outdoors a section dedicated to the evaluation of the risk of exposure to solar radiation is, even today, more of an exception than the rule. This is despite the fact that the ultraviolet (UV) component of solar radiation has historically been classified as a carcinogen by the National Institute for Insurance against Accidents at Work (INAIL) for its long-term effects. Recent news events remind us that solar radiation, across the entire spectrum, is sadly capable of increasing the number of accidental deaths at work due to its potential acute effects, manifesting primarily as heat stroke and dehydration, which can lead to cardiovascular problems, or dizziness and loss of balance. In some jobs, such as construction sites, this could result in fatal falls from heights.

Exposure to solar radiation, and in particular to its UV component, represents, also due to the number of workers potentially exposed, one of the most widespread and important, yet at the same time most overlooked, occupational risk factors among physical agents.

The quantity used to measure the extent of exposure in the context of UV prevention is the spectral irradiance E(ÿ), or the power flux incident on a surface expressed in W/m2 ; the effectiveness of UV radiation in producing adverse biological effects on the skin and the eye is however highly variable as a function of the wavelength and therefore, through a specific spectral weighting function S(ÿ) (2), reported in the graph below (Figure 1), the UV spectral irradiance becomes an effective irradiance Eeff from which to derive the effective radiant exposure Heff, or the dose experienced by the worker in the exposure time, to be compared with the limits set out in Annex XXXVII to Legislative Decree 81/2008 if referring to UV radiation originating from artificial sources.

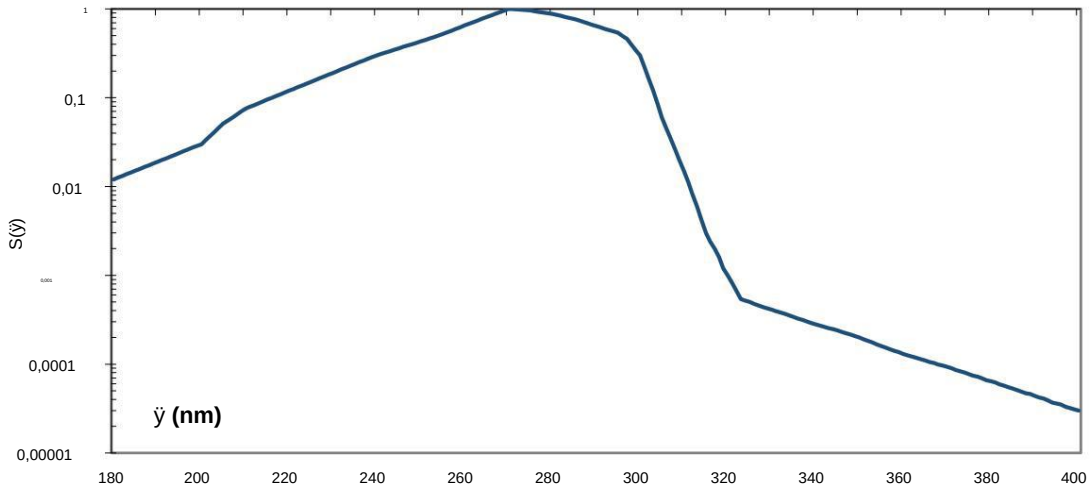

Figure.1 International Commission on Non-Ionizing Radiation Protection (ICNIRP) spectrum of action for UV radiation erythema

Conversely, in the case of solar radiation, given the particularity of the source and the fact that no specific limit value is explicitly provided to refer to, a different approach to the assessment of occupational exposure is necessary.

To meet the need for a synthetic indicator capable of providing an estimate of the risk from UV exposure applicable to the general population (3,4), thanks to a collaboration between the World Health Organization *(WHO),* the United Nations Environment Programme *(UNEP),* the World *Meteorological Organization (WMO)* and *the International Commission on Non-Ionizing Radiation Protection* (ICNIRP) the definition of the UV *Index* (UVI) has been reached :

$$I_{\mathrm{UV}} = \mathrm{k}_{\mathrm{er}} \cdot \int_{250\,nm}^{400\,nm} E_{\lambda}(\lambda) \cdot s_{\mathrm{er}}(\lambda)\, \mathrm{d}\lambda$$

where the constant *ker* represents a normalization coefficient of the effective irradiance Eeff, integrated across all solar UV, thus defining a standard for measuring exposure to UV radiation that describes the relative exposure risk in an extremely direct and easily understandable way.

UVI values vary as irradiance increases: 1-2 (low), 3-5 (medium), 6-7 (high), 8-10 (very high), and 11+ (extremely high); the higher the UVI value, the greater the potential for damage to skin and eyes and the shorter the exposure time required for such damage to occur. The UVI represents an estimate of the risk due to solar irradiance and was designed to raise awareness of the risks of excessive exposure to solar radiation. Starting from a score of 3 (moderate risk), the use of sunscreen is recommended. In general, the UVI value can be obtained through measurements or calculation models.

A sufficiently precise and reproducible estimate of exposure is the quantity defined as *Minimal Erythemal Dose* (MED), which represents the minimum dose of UV irradiation capable of inducing perceptible erythema in the irradiated area, within 8-24 hours of exposure.

Since UV sensitivity is highly variable depending on various factors, such as the spectral composition of the radiation, individual sensitivity and adaptation, the dose of a given radiation required to induce a perceptible erythema, i.e. the MED, also varies significantly depending on the same factors; therefore, for protectionist purposes, it was necessary to define a standardized unit, the *Standard Erythemal Dose* (SED) where 1 SED is equivalent to an exposure of 100 J/m2.

One hour of exposure to a UVI of 1 is equivalent to approximately 1 SED.
Both the MED and the SED are standardized units of measurement under *the International Standard Organization* (ISO) and the *Commission Internationale d'Eclairage* (CIE) (5).

Workers who are certainly exposed to high levels of solar radiation mainly work in the agriculture, fishing, and construction sectors, although we must not overlook all those public and private sectors that regularly use their employees outdoors for a significant portion of their working hours, from services to transportation and public order.

The results of some studies allow us to define more precisely the main groups of workers with a high exposure to solar radiation: those employed in agriculture, gardening, forestry, fishing and maritime activities, and in

construction, shipbuilding and road construction sites, open-cast quarries, law enforcement officers and other work activities, including sporting activities, mainly outdoors.

The construction sector is certainly one of the sectors that can lead to the highest exposure to solar UV radiation. Although not many studies have specifically measured individual occupational exposure in the construction industry, almost all of them have detected levels exceeding the limit of 30 J/m2 proposed by the ICNIRP, equivalent to 0.3 SED and used as the Exposure Limit Value (LV) for Effective Radiant Exposure in Legislative Decree 81/2008.

An Australian study conducted on 493 outdoor workers, of which approximately 50% were employed in the construction industry, measured UV exposure exceeding the VL in over 90% of the subjects. The jobs found to be at greatest risk were those of roofer and asphalt layer, whose average SED was 9.98 and 7.6 respectively, corresponding to an effective radiant exposure exceeding the limit for artificial UV radiation by approximately 30 times (6). A Swiss study in 2007 followed 20 construction workers from July to September, monitored with individual dosimeters applied to various parts of the body. In all cases, the VL was exceeded, with an average daily exposure of between 11.9 and 28.6 SED depending on the altitude of the construction site. These doses exceed the VL applied to ROA by a factor of between 30 and 40 times (7).

As with construction, there are few studies that have measured UV exposure in workers.
to agriculture. Exposures exceeding the limit for artificial optical radiation have been detected in a group of horticultural workers followed for a working week in New Zealand (8) and similar results have been obtained in Australia (9). In Europe, lower exposures have been measured for a group of gardeners in Ireland and Denmark while in Tuscany, a survey conducted in April on about twenty farmers measured an average dose of irradiance

effective on the back of subjects of 18.7 SED; more recently, still in Tuscany, an exceeding of the exposure limit value for ROA was observed in all 32 winemakers monitored in the study (10).

Regarding other categories of outdoor workers in 2008 in Valencia, Spain, personal dosimeter monitoring of 4 gardeners and 5 lifeguards revealed a mean effective irradiance dose of 4.13 and 11.4 SED respectively, again well above the limits (11).

A 2009 Australian study found mean daily exposures ranging from 6.9 to 1.7 SED in 168 lifeguards, nearly 70% of whom had exposures above permitted limits (12).

Solar radiation and outdoor work: underestimated risk

The official INAIL data available on deaths at work show a clear downward trend from 2008, the year of publication of Legislative Decree 81/2008, to 2017, going from 1,624 reports of fatal accidents to only 1,029 cases in 2017 (13) and then rising drastically from 2018 onwards, reaching the unfortunate figure of 1,731 deaths in 2020, also due to the recent COVID-19 pandemic, to slowly start to decline again (Figure 2).

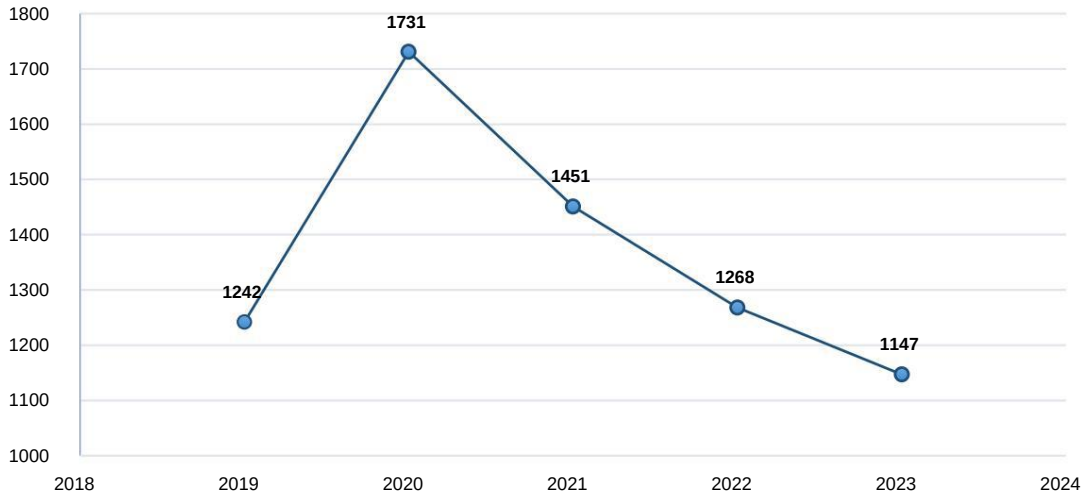

Figure 2. Reports of fatal accidents. Years 2019-2023

However, the trend in occupational disease reports has remained stable in recent years, ranging between 560,000 and 700,000 cases, as reported in the 2023 INAIL Annual Report. For both accidents and occupational disease reports, we should actually apply correction factors to the official statistics that take into account undeclared work and illegal work. In fact, INAIL statistics only consider cases, including *commuting accidents,* involving an insured person, i.e., a worker with a regular employment contract.

INAIL databases therefore do not include undeclared, irregular or black market workers who, depending on the economic macro-sector, can represent up to 20% of employed workers (14), as in the case of Construction or Agriculture, Forestry and Fishing where the seasonality itself favours irregular employment relationships. Obviously, it is not possible to take this reality into account in an exhaustive manner and probably, if real data were available, it would show very different numbers from those that are made official. Limiting the subsequent analysis to the risk of exposure of outdoor workers to solar UV radiation, we observe that the official INAIL statistics for 2018 (15) report 111 reports of occupational diseases in Agriculture due to solar radiation out of a total of 11,499 reports; the overall number of reports in Agriculture in 2023 is practically identical with 11,487 reports, as reported in the INAIL 2023 Annual Report (13), even if there is no updated statistical data for the type of occupational disease which we can, at this point, consider similar to the 2018 data explained below. Solar radiation, therefore, represents one of the main causes of occupational disease reported in the agricultural sector (with approximately 1.0% of reports) after noise-induced hearing loss (2.2%), lumbar disc herniation (8.1%), biomechanical overload of the upper limbs (20.8%) and non-listed diseases (66.5%), the latter of which are largely destined not to be recognised. Table 1 shows the data relating to the overall reports of occupational disease presented in 2018 for the Agriculture macro-sector. The data for all the reports of occupational disease are present.

submitted, the generic ones having solar radiation as their cause and those presented as Skin tumors; for each of these, the number of applications that were positively defined (accepted) and the ratio with the total number of applications is reported.

In Italy, skin epitheliomas of photo-exposed sites or *Non-Melanoma Skin Cancer* (NMSC) due to UV exposure are included in the Tables of Occupational Diseases, both for Industry (item 84) and for Agriculture (item 19), as well as being included in group 6 of List I of Diseases for which doctors are required to report.

Table 1. Reports of occupational diseases to INAIL registered in 2018 for the Agriculture sector

Complaints	Total	Definite positive	Positive/ Total Ratio
All occupational diseases	11499	5077	44,1%
Diseases caused by solar radiation	111	95	85,6%
Melanoma and other malignant skin tumors	75	58	73,3%

In general, workers regularly exposed to solar UV for more than 75% of their working time in Italy are more than 700,000 (16); this number rises to more than 2,500,000 workers if more limited exposures are considered during the day but with daily doses, however, higher than the limit for UV from artificial sources. Although NMSC are recognized occupational pathologies in Italy, in recent years less than 40 cases of UV-induced skin epitheliomas have been reported to INAIL per year, cases which became 75 in 2018, against an expected incidence (17) in outdoor workers, taking only the first of the two figures of employed people reported above, of approximately 1,000 cases per year (of which approximately 800 *Basal Cell Carcinoma-BCC* and 200 *Squamous Cell Carcinoma-SCC;* this estimate is consistent with the expected frequency of NMSC in the population, equal to approximately 10% of the population itself.

UV-induced occupational skin cancers are therefore largely under-reported in Italy (18), as INAIL itself has recognised in a recent publication edited by
Central Health Superintendency (19) and there is reason to believe that if a

: If there were a systematic reporting process for cases considered to be of occupational origin, these pathologies would certainly be among the most frequent occupational diseases, as recently occurred in Germany, where reports of NMSC attributable to occupational UV exposure are in the order of several thousand cases per year (17). The reasons for this tendency to not report occupational skin cancers may be multiple and complex: the onset of the pathologies at a late age, often after the interruption of work activity, a clinical diagnosis which often does not include a sufficient and adequate work history, a lack of knowledge on the possible occupational origin of the pathology both on the part of the treating physicians and on the part of the patients/workers (20). An additional problem for NMSC is their treatment which often takes place in a semi-ambulatory regime, with very heterogeneous annotation practices in the Tumor Registries across the national territory with a consequent failure by patients to recognize the severity and neoplastic nature of the pathology (21).

Even when skin cancers occur during working life in individuals undergoing health surveillance, it should be remembered that, since solar radiation is not included among the specific physical risks under Title VIII, it is often difficult to have its origin in professional activity and its subsequent insurance management accepted.

Finally, we recall that actinic keratoses in *outdoor* workers are also classified as occupational diseases (L57.0) with a two-year compensation period. The estimated frequency of these diseases, for which there is still no consensus in the scientific community on their classification as pre-malignant skin lesions or squamous cell carcinomas *in situ,* is still higher than that of NMSC.

Although underestimated, the risk of outdoor workers' exposure to solar UV radiation is nevertheless linked to the onset, even late, of *long-term* occupational diseases such as NMSC, malignant melanoma (MM), and actinic keratosis. However, solar radiation across the entire spectrum (in addition to the UV component, which accounts for 5% of the radiation, it should be remembered that the remaining 95% of solar radiation reaching the Earth's surface is made up of visible and infrared radiation) is certainly responsible for a high number of fatal accidents, even if they are often not immediately attributable to it.

The summer cases of workers dying from exhaustion, heat, or falling from heights due to illness caused by increasingly extreme weather conditions, even in our latitudes, while working in the fields or outdoors under the scorching sun, demonstrate a broader range of possible effects due to a lack of or inadequate risk assessment.

According to INAIL statistics, the cases reported with fatal outcome in 2017 in Agriculture (22)
They accounted for approximately 15% of all workplace deaths, with 155 official events; the Green Deaths Observatory of ASAPS (Association of Supporters and Friends of the Highway Police) reported 178 agricultural fatalities in 2017, of which 146 were crushed by their own tractors (82% of the total).
Again according to INAIL statistics, in 2022 there were 137 fatal accidents in agriculture (23), of which 48 were attributable to the use of a means of transport.

A similar number of victims characterizes the construction sector which sees in the same year 2017 115 fatal accidents (of which approximately a third are statistically falls from heights) (24).

How many of these drivers and workers, whose apparent cause of death was being crushed by their vehicle or falling from a height, lost even for a moment control, balance, or grip due to dizziness, fainting, or slowed reflexes caused by the heat, dehydration, or glare, perhaps after hours of working under the sun without a break to cool down and rehydrate?

Unfortunately, it is a question that no one will ever be able to give a precise answer to but it leaves to glimpse a truth that is not only that described by official statistics.

A possible truth is that the lack of an adequate Risk Assessment of exposure to solar radiation in all those working environments in which the latter represents an agent

Significant physical exposure can no longer be tolerated, both with regard to the long-term effects due to the UV component which is at the origin of occupational skin diseases, and the short-term effects, where the sun determines working climatic conditions which are often extreme and objectively difficult to evaluate but whose outcome, if not evaluated, can prove fatal.

Solar radiation and outdoor work: technical standards and mitigation strategies

In light of the above, the need—which is actually an obligation for the Employer pursuant to Article 28 of Legislative Decree 81/2008—to conduct an exposure risk assessment for all activities involving a significant portion of working time outdoors should be evident and aimed at managing all prevention strategies useful for minimizing doses to workers, also considering the fact that, unlike many other situations and risk agents, for solar radiation it is evidently not possible to work directly on the source.

Although the potential health risks for workers exposed to solar radiation are not specifically addressed in Legislative Decree 81/2008, Article 181, paragraph 1, explicitly refers to the need to resort, as an alternative, to the use of technical standards applicable to the specific risk agents being assessed.

For the measurement and evaluation of personal exposure to UV radiation emitted by the sun, the UNI EN 14255-3 (25) standard has been available and in force since 2008 and applies to the general population and to workers who carry out their activities outdoors.

This technical standard describes how a risk assessment can be carried out using the previously mentioned UVI but also the method called Skin Exposure Factor *(fSE).*

This approach is based on the determination of the fSE factor:

$$f_{SE} = f_1 \times f_2 \times f_3 \times f_4 \times f_5 \times f_6$$

obtained as a product of a series of factors fn (with 0 ÿ fn ÿ 1) that quantitatively influence the extent of skin and eye exposure in the external environment and dependent on: f1 latitude and season, f2 cloud cover, f3 duration of exposure, f4 ground albedo, f5 clothing, f6 presence of shade.

The fSE value thus determined represents an index whose value, as in the case of UVI, can be associated with an increasing exposure risk and a series of indications for protection from exposure as reported in Table 2.

Table 2. Skin exposure factor (fSE) from UNI EN 14255-3:2008

Skin exposure factor	Skin protection required
fSE < 1	None
1 < fSE < 3	T-shirt, wide-brimmed hat
3 < fSE < 5	Long-sleeved shirt, trousers, wide-brimmed hat, SPF 15+ sunscreen
fSE > 5	Change your work environment and practices. Try providing some shade. Wear a long-sleeved shirt, pants, a wide-brimmed hat, and SPF 15+ sunscreen.

This *FSE* -based solar radiation exposure risk assessment procedure has been included in the Physical Agents Portal (https://www.portaleagentifisici.it), a web service developed by the Public Health Laboratory of the South East Tuscany Local Health Authority (USL Toscana Sud Est) in collaboration with INAIL (National Institute for Accident and Emergency Work) and the Modena Local Health Authority (USL). The aim is to provide an information tool that guides company safety managers and prevention operators towards the correct response for the prevention and protection from physical agents in all work environments.

The *Sole Sicuro* app for calculating UVI is also available on the Physical Agents Portal as a risk assessment tool . This app uses weather forecasts, geographic location (by entering the municipality where the outdoor activity takes place), surface type, and type of work performed, to provide specific and highly accurate prevention recommendations.

In the Risk Assessment process, in addition to the indications provided by UNI EN 14255-3, it is also possible to consider the possibility of adopting administrative procedures, including training and scheduling of work activities in order to minimize exposure during daytime hours with the highest UV Index values.

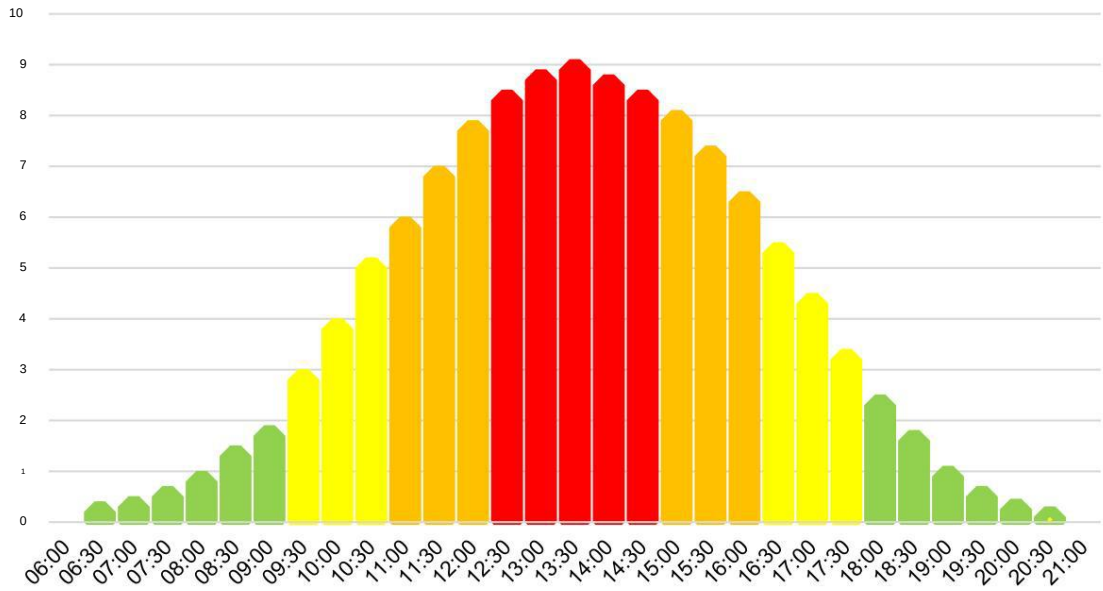

Figure 3. Daily UVI trend with clear skies in Rome in the month of July (the colors correspond to the color code used for UVI)

In fact, approximately two-thirds of the daily UV dose is received in the two hours before and after solar midday, and in any case, more than a third of the dose (36%) is reached in the two hours around solar midday; planning an adequate lunch break indoors during this time slot is an administrative procedural measure that alone reduces daily exposure to UV radiation by more than 20%.

For workers who spend a significant portion of their day in motor vehicles and generally in the cabins of the vehicles used, laminated windshields and clear or tinted windows and glass can dramatically reduce the amount of UV rays entering.

in the vehicle; these are also technical measures that can significantly mitigate the UV dose experienced at the end of the shift.

Furthermore, it is important to consider the possibility of planning and using all the Personal Protective Equipment (PPE) capable of minimizing the dose: clothing, hats and visors, sunglasses, and sunscreen.

When it comes to clothing, numerous factors influence the degree of protection provided by fabrics:

– *Weft tension (one of the most important parameters)*
If images can be observed through the fabric held in front of a lamp, the protective effect is very low; if only light filters through the fabric, the protective effect is modest; if no light filters through, the protective effect is excellent.

– *Fabric color*
Darker colors absorb more strongly than lighter colors but must not negatively impact the ability to regulate temperature in high temperatures.

– *Wet fabrics*
When fabrics get wet, they generally transmit more UV rays, especially cotton, which shows a greater transmission capacity.

– *Fabrics certified with ultraviolet protection factors*
Ultraviolet Protection Factor 30 (UPF 30) means that skin covered by this fabric is protected 30 times more than exposed skin without protection.

Wearing appropriately designed hats is very important, for example, to ensure a high level of protection for the face, neck, and back of the head; legionary-style hats and helmets with neck protection are certainly the most effective for protecting these areas of the body.

Sunglasses and eyeglasses provide excellent eye protection from solar UV exposure, but the amount of protection provided, however, may depend more on the design and how they are worn than on the transmission properties of the lenses. The design that offers the best protection is the wraparound style of sunglasses, and all glasses should be worn so that the frame is snug and flat against the wearer's forehead to eliminate leakage around the lenses.

A final PPE that is extremely widely used in recreational settings but much less so in occupational settings is sunscreen; sunscreens provide a high level of protection in both the UVB and UVA regions, and their actual effectiveness as sunscreens is determined by many factors, including the following:

– *Application thickness*
Most people apply between a quarter and half the recommended amount of product and therefore achieve a level of protection between 20% and 50% of what is expected.

– *Inappropriate application*
Most people do not apply sunscreen evenly and therefore do not provide protection to large parts of their body, especially the ears, neck, feet, and legs.

– *Type of sun protection*
Many sunscreens contain inorganic chemicals like titanium oxide, which make the creams harder to apply and therefore result in reduced coverage.

– *Re-application time*
It is unlikely that many people will reapply sunscreen as regularly as required.

Sunscreens, as mentioned, are now widely used in recreational settings: on the beach and on ski slopes, they're now a common sight; however, this is not the case in the workplace, where many factors, from clothing to the dust present in many work environments, make this PPE highly unwelcome.

To protect outdoor workers from exposure to solar radiation, there are many factors to consider when drafting the risk assessment report, all of which can and do make the assessment complex and incomplete. However, what is truly important and essential for those involved in workplace health and safety to understand is that any assessment, no matter how incomplete and incomplete, is always better than an unjustifiable lack of a risk assessment document for outdoor workers.

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MEASUREMENT OF SOLAR RADIATION ULTRAVIOLET AND VITAMIN D

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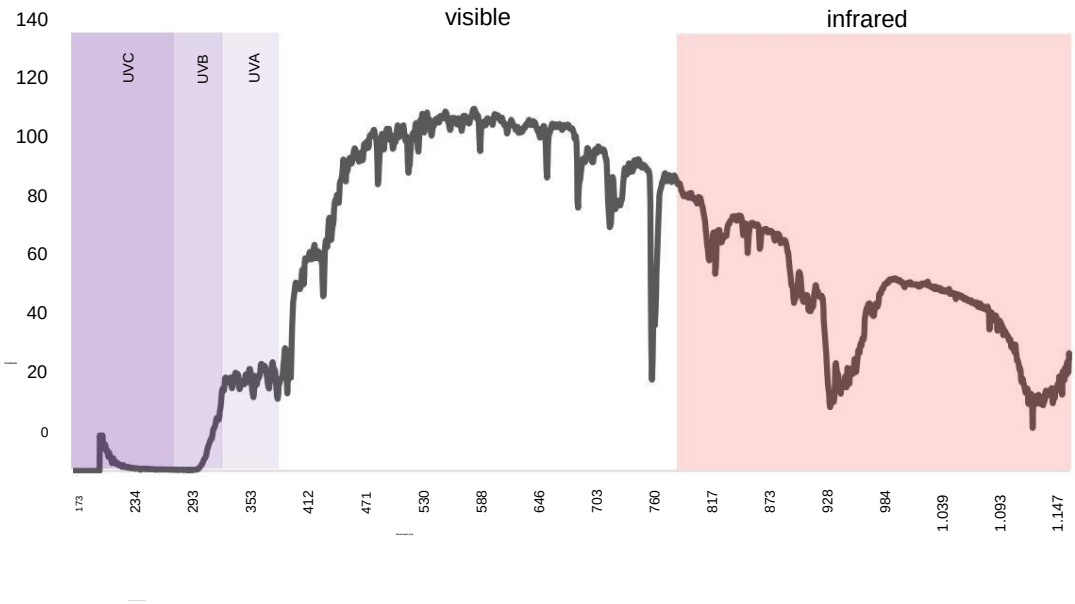
Introduction

Solar radiation is composed of electromagnetic waves with wavelengths between 100 and 4000 nm and varying intensities. The solar spectrum is divided into emission bands, characterized by wavelength ranges, which correspond to specific effects on humans: ultraviolet (100-380 nm), visible (380-780 nm), and infrared (780-4000 nm). Ultraviolet (UV) radiation has the highest energy content but is emitted in the smallest quantities: it represents only about 10% of all solar radiation and can be subdivided into UVC (100-280 nm), UVB (280-315 nm), and UVA (315-380 nm). Thanks to the presence of ozone in the atmosphere, which almost completely absorbs the UVC band, only UVA and some UVB rays reach the ground. Figure 1 shows the solar spectrum measured on the ground in the range 170-

1150 nm.



Exposure to solar UV radiation allows the human body to synthesize vitamin D, but prolonged exposure can cause short- or long-term damage to the skin and eyes.
On the contrary, too short exposure to solar UV radiation does not allow the production of vitamin D which the human body needs. Following numerous studies, vitamin D deficiency

Vitamin D has been associated with various diseases, including diabetes, cancer, multiple sclerosis, autoimmune, cardiovascular and respiratory diseases (1-6).

The daily requirement of vitamin D varies from individual to individual and depends on multiple factors, including age and health status. According to the indications provided by the Istituto Superiore di Sanità on the ISSalute portal (https://www.issalute.it/index.php/la-salute-dalla-a-alla-z-menu/v/vitamina-d#fabbisogno-giornaliero), in line with the requirements of the European Food Safety *Authority (EFSA)* (7), the minimum daily amount of vitamin D indicated for healthy individuals is 400 International Units *(IU).*

IU) for children aged 7 to 12 years and 600 IU for adults; these amounts increase during pregnancy and breastfeeding, in cases of diseases such as obesity and osteoporosis, or if the patient takes medications that interfere with vitamin D metabolism.

The amount of vitamin D the human body can produce as a result of exposure to solar radiation depends on several factors: since the amount of solar UV radiation received by the skin is the main factor determining the activation of the vitamin D production mechanism, the time of day, season, and latitude of exposure are all factors that influence the level of vitamin D synthesized by the body. The latter increases as solar radiation hits the skin: during the central hours of the day, a greater amount of vitamin D can be produced than during the hours when the sun is lower toward the horizon, as well as in the summer season compared to other seasons, especially winter. Furthermore, in Nordic countries, where the sun's arc is lower and cloud cover is frequent, the amount of vitamin D synthesized is lower than in countries at Mediterranean latitudes. At the same time, the exposed body surface as well as the duration of exposure are factors that influence the amount of vitamin D produced by the body: the latter increases with the increase of both the area of skin exposed to solar UV rays and the time during which it is exposed. Furthermore, skin type is a factor that determines the sensitivity of the human body to solar UV radiation (8): light phototypes are extremely (type I) and very sensitive (type II) to the sun and, in case of exposure, burn easily, but are able to synthesize a greater quantity of vitamin D than dark phototypes, which are little (type V) and minimally (type VI) sensitive to the sun.

In addition to being a consequence of exposure to solar UV radiation, vitamin D can be ingested through food such as fatty fish, liver, egg yolk and mushrooms which naturally contain vitamin D; some foods can be artificially fortified with vitamin D, such as milk or breakfast cereals, but do not contain it naturally; furthermore, there are also numerous vitamin D supplements on the market, but they are not substitutes for an adequate diet. Pharmacological supplementation is only recommended in case of confirmed vitamin D deficiency and upon medical prescription: in a 2019 Note (9), the Italian Medicines Agency (AIFA) indicates that vitamin D supplementation is justified in the healthy adult population when the blood concentration of its precursor, calcidiol 25(OH)D, falls below 20 ng/mL; in fact, it is indicated as desirable to maintain the concentration of 25(OH)D within values between 20 and 40 ng/mL.

The daily requirement of vitamin D could also be synthesized as a consequence of exposure to artificial radiation, since the production mechanism of vitamin D is triggered by UVB radiation, regardless of the source from which it comes. The use of artificial radiation would have the advantage of being able to precisely dose the quantity of UV radiation administered to humans, both in terms of irradiation and duration. Some scientific studies, supporting this possibility, propose the installation of lamps that emit UVB radiation in offices (10). However, due to the danger of UVB radiation for human health (11), it is not possible to use lamps with UV emission, except for health purposes.

or scientific, which go beyond general lighting; the European legislation on photobiological safety of lamps classifies their dangerousness based on their emission (12).

In this article, we provide guidance on how to measure solar UV radiation received by the skin and calculate the amount of vitamin D synthesized as a result of this exposure, based on the current state of the art and legislation on this topic.

This discussion will highlight the challenges associated with these operations and the operational limitations encountered. A case study will be used as an example to demonstrate and discuss the results obtained by applying the procedure to a real-world setting.

Sizes

Irradiance is the quantity that expresses the power emitted by the sun (or another radiative source) incident on a unit surface. Irradiance can be total, if we consider the entire radiation emitted by the source, or limited to a single electromagnetic band or a defined interval; when we consider the irradiance of each individual wavelength, we speak of spectral irradiance. In all cases, the unit of measurement is W/m2 .

The effect produced by each single wavelength on the human body is defined by action spectra, i.e. weighting curves that transform physical radiation into effective radiation; the International Commission on Illumination (CIE) has defined various action spectra, among others that of vitamin D. In the CIE Technical Report 209/2014 the criteria for harmonising the nomenclature of the erythemal and vitamin D action spectra are analysed (13). As can be seen in Figure 2, which shows the erythemal and vitamin D action spectra, the effect of UV radiation on the skin varies as a function of the wavelength: the synthesis of vitamin D is stimulated by UVB radiation, while the harmful effects on the skin and eyes are due to all three UV bands to a different extent.

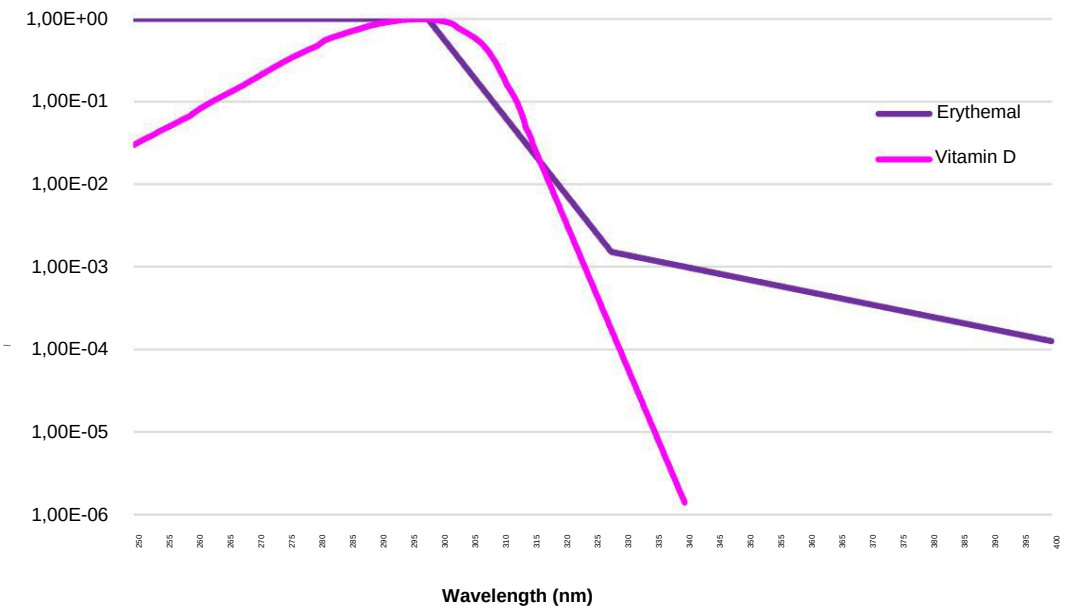


Figure 2. CIE standardized erythemal and vitamin D action spectra

By integrating the product of the UV spectral irradiance and the corresponding action spectrum, the provitamin D production-weighted irradiance EVitD (W/m2) and the erythemal-weighted irradiance Eer (W/m2) are obtained, respectively.

The estimation of vitamin D dose (EVDD) and erythemal dose are similar, but the estimation of VDD has peculiarities that increase its uncertainty. Like the erythemal dose, the vitamin D dose can be calculated by multiplying EVitD by the exposure time t (s) as follows:

$$= \times \ddot{y} \quad \begin{matrix} 330 \\ 252 \end{matrix} \qquad [1]$$

where Eÿ is the spectral irradiance and Dÿ is the action spectrum of vitamin D.

The action spectrum Dÿ to be inserted in the previous equation is the one standardized by the CIE, which was defined starting from the studies of MacLaughlin *et al.,* published in 1982 (14).
However, the accuracy of this curve has been questioned (15, 16) and recently the scientific literature has proposed a revision of it (17, 18).

Furthermore, in Technical Report 209/2014 (13), the CIE defines the quantities for vitamin D in analogy with the erythemal quantities. The Minimum Dose of vitamin D (MDD) is defined as the minimum dose to maintain adequate vitamin D levels based on body exposure equivalent to a daily oral intake of 1000 IU. Unlike the corresponding erythemal quantity, the MED, the MDD value is not indicated for each phototype: in fact, the quantity of vitamin D synthesised by the human body varies not only according to the skin type, but also according to some personal parameters, such as, for example, the exposed body surface, the weight and the age of the person. Due to these peculiarities inherent in the estimation of vitamin D, the MDD appears to be of little practical use.

In order to have universal quantities applicable independently of the phototype and other variables, the standard erythemal dose (SED) and the standard dose of vitamin D have been defined.
(SDD), which correspond to an effective radiant exposure weighted with the respective CIE action spectrum equal to 100 J/m2 The safety limit for erythemal effects following sun exposure has been established in the literature at 1.0 – 1.3 SED, similar to that for artificial optical radiation (19). On the contrary, the minimum SDD threshold that allows the human body to synthesize the optimal daily amount of vitamin D has not been established.

The World Health Organization (WHO) has defined the UV Index (UVI) (20), an index referring to the erythemal effects that is easy to understand and use, intended for the general public and aimed at protecting the population from the damage caused by exposure to solar UV radiation. The UVI assumes a variable value between 1 and 11+, which is defined on the basis of the erythemal weighted irradiance with the CIE Ser action spectrum:

$$= \ddot{y} \quad \begin{matrix} 400 \\ 250 \end{matrix} \quad ( ) \qquad [2]$$

where Eÿ is the spectral UV irradiance of the sun (W/m2) and ker is the erythemal constant equal to 40 m2 /W.

For each UVI value, the level of risk of skin damage is defined and the protective elements to be adopted in case of exposure are indicated. A similar index for vitamin D does not exist, but in some works the UVI is applied to calculate the level of vitamin D synthesized by the human body (21, 22).

Measurement of solar UV radiation

To know the correct exposure time that allows the synthesis of the optimal daily quantity of vitamin D (IU) without incurring negative erythemal effects, it is necessary to calculate the effective exposure (Eeff, in J/m2), otherwise defined as dose, starting from the spectral measurement of solar UV radiation.

Spectral irradiance can be measured with a spectroradiometer, a scientific instrument capable of measuring the intensity of radiation received on the sensor for each wavelength, within a band and with a step that can be defined by the operator based on the sensitivity and resolution of the instrument *(see* Figure 1). Some spectroradiometer models are equipped with erythemal and vitamin D weighting curves and allow the display of erythemal irradiance Eer and weighted irradiance EVitD in addition to physical irradiance E. Alternatively, to obtain the same values, the operator must perform a data analysis process in which the measured spectral irradiance is multiplied by the erythemal or vitamin D action spectrum, and then integrated over all the wavelengths considered. In any case, to calculate the dose, the weighted irradiance value must be multiplied by the exposure time, applying equation 1).

The spectroradiometer is an instrument that measures radiation on a single plane, making it unsuitable for characterizing the exposure of a complex body like the human, which is composed of curved surfaces. While accepting the level of inaccuracy that results from approximating body regions to flat surfaces, spectral measurements should be performed on multiple planes and in various directions. To overcome these problems, dosimeters have been developed. These are generally small, wearable devices that measure the level of erythemal irradiance (Eer) with a time interval defined by the operator.

Polysulfone dosimeters, for example, are made of thin films of thermoplastic material that undergoes a photodegradation process when exposed to solar radiation, producing a spectral response similar to the erythemal action spectrum Ser. However, this type of dosimeter has some disadvantages: they must be calibrated with the spectroradiometer before use by simultaneously exposing the two instruments to the same irradiance condition, to determine the dosimeters' response at the wavelength of maximum sensitivity (330 nm); furthermore, polysulfone dosimeters have the further disadvantage of saturating beyond a certain cumulative dose. Electronic dosimeters are easier to use: they are small, wearable radiometers that directly apply erythemal weighting to the measured physical irradiance, providing the erythemal irradiance Eer.

Whatever type of dosimeter is used, the measured data must still be extracted and processed to obtain the erythemal dose.

Dosimeters only calculate erythemal dose; there are no similar tools for calculating VDD. However, all the tools described above are expensive and require expert intervention for use and subsequent data analysis; these difficulties make them unsuitable for large-scale use for estimating VDD.

Vitamin D calculation

The calculation of the amount of vitamin D (IU) synthesized as a consequence of an exposure dose VDD (J/m2) does not have a regulatory definition, nor are there any guidelines indicating the method, since a certain relationship between VDD and IU of vitamin D has not yet been defined. In the literature, two relationships have been proposed that link the synthesized vitamin D and the VDD.

first it is based on the so-called Holick rule, named after the scientist who formulated it (23): solar exposure of ¼ of the body surface at ¼ of MED produces vitamin D equivalent to an intake of 1000 IU of vitamin D. This rule is expressed by the following relationship:

$$= 21120 \quad \frac{\times}{\quad} \qquad [3]$$

where C is the percentage of body surface exposed.

The second relationship was proposed by Salomo *et al.* in 2021 (21): it exploits the UVI, which, as is a quantity referring to erythemal exposure, but which is easily available because its value is provided by numerous sites and applications:

$$= 21120 \quad \frac{\times \times}{\times} \qquad [4]$$

where t is the exposure time in seconds and Ker is a constant corresponding to 40 (m2 /W).

Both relationships adopt quantities referring to erythemal exposure, highlighting a deficiency in the quantities defined for the estimation of vitamin D.

The two previous relationships have been applied in a preliminary study (24), the result of the collaboration between the Istituto Superiore di Sanità, Sapienza University of Rome and the National Research Council. As part of the study, solar radiation measurements were carried out in Rome on 12 April 2024 from 11:00 to 14:00 in clear sky conditions; the solar spectral irradiance in the UV band between 150 and 400 nm was measured using an Avantes AvaSpec 204B spectroradiometer, with a sampling interval of 15 minutes.

Subsequently, the measured spectral data were exported and processed to calculate VDD with formula [1], UVI with formula [2], and vitamin D with formulas [3] and [4].

Table 1 reports the vitamin D values in IU calculated and referred to ¼ sun exposure. of body surface area of a person 1.70 m tall, of phototype II, for 15 minutes.

Table 1. Vitamin D levels calculated with the Holick and Salomo formulas in IU

Exhibition time	vitamin D (Holick)	vitamin D (Solomon)
11:45-12:00	4463 IU	5702 IU
12:45-13:00	4990 IU	6177 IU
13:30-13:45	5170 IU	6177 IU

It was not possible to determine which of the two relationships allowed for the most accurate calculation of values, because the study did not perform blood measurements on humans that would have allowed for the calculation of the amount of vitamin D synthesized in response to sun exposure. However, it is noted that the values obtained with the Holick rule are more variable than those calculated using the UVI, due to how this index is defined. In fact, the UVI values used to calculate vitamin D levels varied by only two units between 11:45 AM and 1:45 PM on the day of measurement.

Conclusions

From the above considerations it emerges that in-depth *in vivo* studies are desirable in order to produce greater certainties on the relationship between exposure to solar UV radiation and the quantity

of vitamin D synthesized by the human body. In particular, it would be useful to define the DCS value for each skin type.

Furthermore, tools that can be easily used by the population are needed, capable of indicating on any day and at any time the time of exposure to the sun necessary to synthesize the optimal daily quantity of vitamin D.

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SUN PROTECTION AND VITAMIN D WITH APPS:

OPPORTUNITIES AND CHALLENGES

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Introduction

Given the problems caused by vitamin D deficiency and the usefulness of obtaining some vitamin D from the sun, it was decided to explore the world of technologies and sensors capable of easily measuring the solar ultraviolet (UV) radiation index, from which the amount of vitamin D synthesized with sun exposure could be calculated.

There is therefore a need for reliable tools capable of determining the amount of vitamin D synthesized in a fraction of the time and under specific conditions of location and exposure of a person.

For this reason, it was felt necessary to explore the market and the relevant literature, in order to evaluate the reliability and simplicity/usability of the proposed solutions, in the form of Apps, with the aim of indicating and/or proposing the best possible solutions for different user groups.

These solutions can be tailored to any individual who might expose themselves to the sun on a daily basis, balancing the risks of exposure (photoaging, erythema, skin cancer, etc.) with the benefits (a given amount of solar radiation acquired in a defined time period that allows for the synthesis of a given amount of vitamin D). Any target user to whom the proposed solutions are addressed can be categorized by age group, skin phototype, type of job (user who works indoors or outdoors), lifestyle and clothing style, and type of health problems and/or pathologies.

Some dedicated apps

Various types of sensors for calculating the UV index *(UltraViolet Index,* UVI) have been proposed and studied in the literature , either incorporated into *stand-alone* devices or supported by dedicated *smartphone* applications (1-4). On the other hand, in recent years there has been a proliferation of *smartphone* apps that provide UVI measurement in a given location, but only some of these apps also provide an estimate of the amount of vitamin D synthesized at a given time of exposure. Most apps are free and available for both Android and iOS systems and obtain the UV index measurement from meteorological databases; among these, only a few apps rely on satellite data to obtain the UVI measurement. The reflection that emerges from the analysis of the scientific literature is twofold: sensor-based devices are more reliable, but are less easy to use and do not achieve the goal of continuous and large-scale use.

Given the current proliferation of *smartphones,* ubiquitous devices in our daily lives, apps could be used on a large scale and, if properly programmed and evaluated, could prove to be the best solution for reaching a wide range of users. While these apps put sun protection at your fingertips, their reliability and usability must also be considered.

UVI app

The literature reports works describing many apps that measure UVI, many of which were developed specifically for specific studies; in App *stores* you can find countless apps that measure UVI, and which generally also provide indications of weather conditions.
and some atmospheric parameters. Among the many apps available online, one app is worth noting.
which has also been recommended by the *World Health Organization* (WHO), and which will be described below.

App SunSmart

In 2002, the WHO introduced the definition of UVI: it is a measure of the intensity of UV radiation at the Earth's surface that is relevant to the effects on human skin; the index values range from zero and up (the higher the value, the greater the potential for damage to skin and eyes and the shorter the time required for damage to occur) and are generally expressed as whole numbers, which are grouped by category of exposure to solar radiation (low: UVI < 2; moderate: UVI 3 to 5; high: UVI 6 to 7; very high: UVI 8 to 10; high: UVI = 11+).

Therefore the UVI becomes a useful tool to inform and warn the public of the potential
health risk associated with high levels of solar UV radiation.

In 2010, Cancer Council Victoria (Australia) and other partners developed and sponsored a freely downloadable mobile app (SunSmart *App) to provide Australian users with information on the risks of sun exposure, in order to prevent excessive exposure and provide protection recommendations,* using UVI. In 2018, the app's effectiveness in contributing to a change in user habits was tested through a randomized controlled trial. The primary purpose of the trial was to test the feedback received from the app on the effect of UV radiation.
SunSmart or a dosimetric device, on sun exposure behaviors and sun protection habits in young adults (Australia): the group that had used the App
reduced the time of exposure without protection (5).

From June 2021, the *SunSmart* App goes global: the new *SunSmart Global UV* App (https://www.sunsmart.com.au/resources/sunsmart-app), for a given geographic location, provides local information on UV radiation levels; weather and UVI forecasts up to five days, and highlights the time slots in which sun protection is recommended.

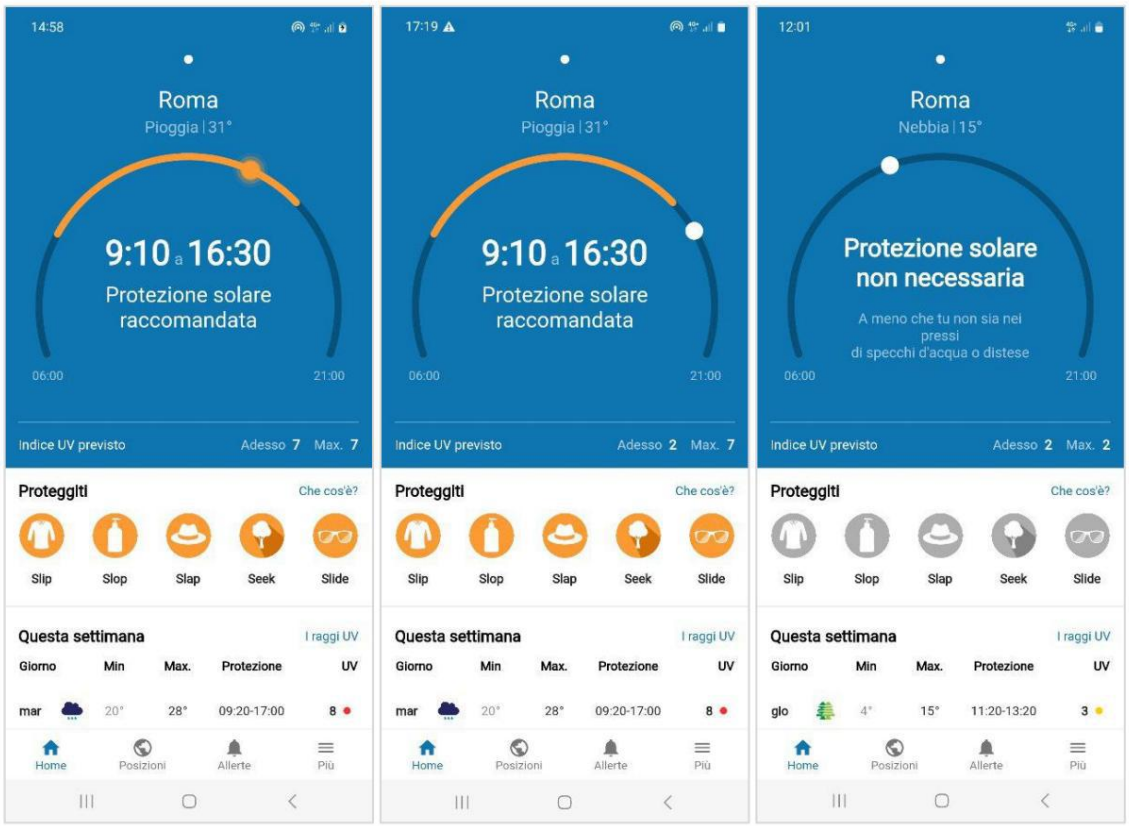
In a statement dated 21 June 2022 on its website (https://www.who.int/news/item/21-06-2022-sunsmart-global-uv-app-helps-protect-you-from-the-dangers-of-the-sun-and-promotes-public-health), the WHO “encourages” anyone to download this App to prevent negative effects resulting from overexposure to the sun during work and leisure time (6), reporting a comment by the Secretary General of the World Meteorological Organization
(World Meteorological Organization, WMO) of the United Nations, Professor Petteri Taalas:

> “This app combines meteorological, environmental and health expertise to help protect people from the sun both at work and in their leisure. It is unique because it uses data from country-level weather and UV measuring stations to provide accurate and location-specific UV Index readings. It is a great example of science serving society”.

Today, in commercial *stores ,* there are many Apps available, downloadable for free, which provide UVI values for each location, together with weather information and atmospheric parameters, as well as information and advice on exposure risks and good protection practices, as well as the time slots in which exposure is not recommended.

Figure 1 shows some screenshots taken from Android *smartphones* during the operation of the *SunSmart Global UV App:* the App reports the current UVI values for the identified location (Rome) and some weather parameters, and, when necessary, in addition to indicating a

In the series of suggestions for protection from solar radiation (bottom of the screens), the App indicates the time slot in which sun protection is recommended (Figure 1a and Figure 1b); however, when it is not necessary, such as in the case of low UVI, the time slot in which protection is required is not identified (Figure 1c).



a b c

Figure 1. Screenshots of the SunSmart Global UV App taken in Rome: on July 1, 2024 at 2.58 pm (a) and 5.19 pm (b) – given the high UVI value (max expected 7) the App displays the message "sun protection recommended" between 9:10 and 16:30; and on 6 March 2024 at 12:01 (c) – given the low UVI value (max expected 2) the App displays the message "sun protection not necessary"

Vitamin D App from Sun Exposure

In the same June 21, 2022, press release recommending the *SunSmart Global UV App,* the WHO also emphasizes that everyone needs sun exposure, especially for the production of vitamin D, which helps prevent bone diseases such as rickets, osteomalacia, and osteoporosis.

So the question arises: how long should we expose ourselves to the sun to produce vitamin D? How can we reconcile the potential harmful health risks associated with overexposure with the benefits of vitamin D production? Is it desirable to have apps that combine these aspects? To address these issues, a survey was conducted of apps available in the literature and on the market (Google Play and Apple Store) that estimate vitamin D synthesis from sun exposure. They found: 1) two free downloadable apps, *dminder* and *Sun Index,* intended for a

a broad, non-specialized audience; 2) a commercial App, *Sun4Health®,* available only upon request; 3) other non-commercial Apps created for specific studies.

Before describing in detail the two Apps found in the *stores,* a mention is made of the other Apps that were found in the search:

– *App Sun4Health®*

Developed by siHealth Ltd (UK), this App provides UVI values and vitamin D levels derived from sun exposure; it is based on satellite data acquired and processed in real time and works without a sensor (Figure 2). This App is CE certified as a Class I medical device and the technology is protected by an international patent. The validity of the App for sun protection and vitamin D health has been tested in different contexts (7).

Figure 2. Sun4Health® App: Example of a screenshot taken from the manufacturer's website https://www.sihealth.co.uk/our-solutions/sun4health/ (image reproduced courtesy of siHealth Ltd)

– *Non-commercial apps for studies*

Two studies by Park *et al.* from 2019 (3, 4) describe a portable device based on a UVI sensor to measure UV light irradiance *(Erythemally weighted UVB,* EUVB), from which vitamin D intake resulting from exposure can be calculated. In the first study (3) the developed application that interfaces with the portable device is presented and provides the user with the current EUVB and UVI, as well as the estimated amount of vitamin D synthesized in IU *(International Units)* and the exposure time (Figure 3). In the second study (4) a UVB LED lighting system is presented that provides the individual daily dose of UV both outdoors and indoors; the system can also calculate the user's daily vitamin D intake (4) (Figure 4).

Figure 3. Screenshots of the App presented in the study by Park et al. (3): on the left the information relating to EUVB and UVI; on the right the amount of vitamin D synthesis and the necessary exposure time.

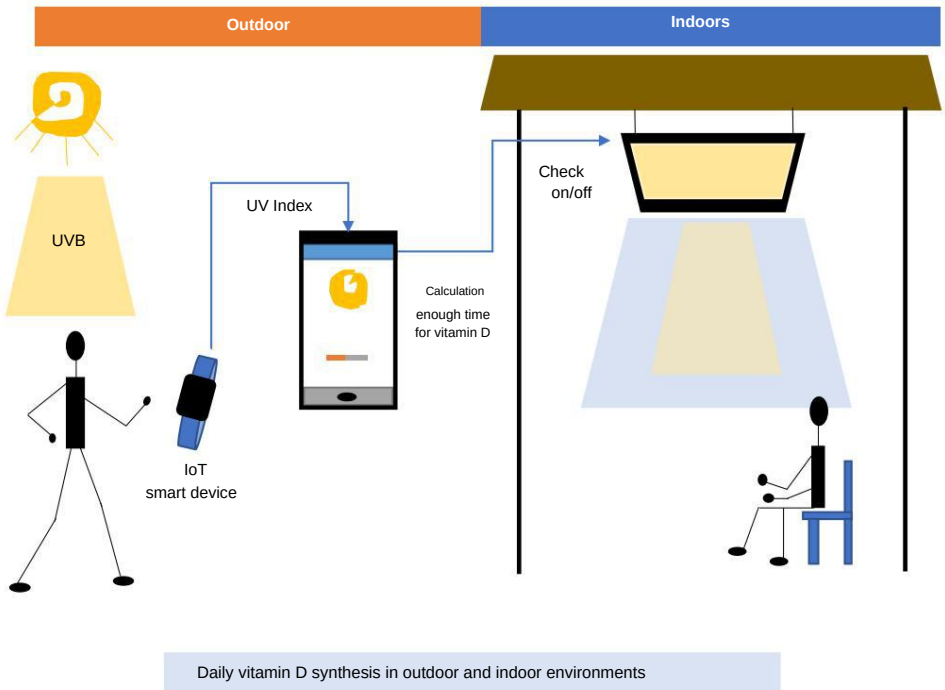


Figure 4. System proposed in the study by Park et al. (4) consisting of: an IoT (Internet of Things) device that measures UVB dose both outdoors and indoors; a general UVB LED lighting that can safely deliver UVB dose indoors; and a smartphone application that provides information on cumulative UVB dose and estimated vitamin D intake.

The main information provided by apps available in the *stores* is: UVI at the current geographic location; some meteorological information and atmospheric parameters (sun elevation, declination, solar noon, ozone layer height); recommendations and warnings on sunscreen use; skin cancer risk; and estimated vitamin D synthesis.

Given the dependence of skin vitamin D synthesis on sun exposure, environmental factors, and personal characteristics, these apps allow the input of personal parameters such as height, weight, age, skin phototype, and percentage of exposed body surface area. As vitamin D-related output, these apps provide the amount of vitamin D "obtained from the sun" (the amount of vitamin D that can be synthesized) in a given time interval, expressed in IU, or the time required to reach a predetermined IU vitamin D goal.

Below is a brief description of the main features of the two Apps commercial apps called *dminder* and *Sun Index.* Their main features, taken from the English-language websites of the *stores* explored, are shown in Table 1. Both apps are available for Android and iOS systems in the “Health & Fitness” category.

Table 1. Main features of dminder and Sun Index, both available on systems Android and iOS, and belonging to the “Health & Fitness” category

General characteristics	App Name – Version			
Name	dminder v. 4.4.0	dminder v. 9.29.3	Sun Index version 1.9.47	Sun Index version 1.9.47
Producer (Village)	Ontometrics (USA)	Ontometrics (USA)	Comfable Inc. (Canada)	Comfable Inc. (Canada)
Operating system	Android	iOS	Android	iOS
Release date	29/5//2014	1st version 9.6.0 16/9/2020	30/5/2016	1st version 1.8.73 6/19/2019
Age rating (classification by age)	3	12+	3	4+
User rating (5-stars rating)	3.6	4.1	4.4	4.6
Number of downloads	100K+		100K+	
Last updated	16/5/2023	17/6/2023	22/3/2023	22/3/2023

Both apps are available in a free basic version and a paid version with advanced features.

App dminder

The *dminder* App uses the *smartphone* 's GPS to geolocate the person and indicate the useful time interval of the day for exposure that allows obtaining the required level of vitamin D. Figure 5 shows two screens of the App's *homepage.*
in execution mode on an Android *smartphone ,* in Rome, on March 6, 2024, at two different times: the screens present different information and commands for operating the App. On the left screen, you can see that the useful time interval for exposure that allows the synthesis of vitamin D is indicated by “D from 9:37 to 3:05 PM”; at the time point that is outside the useful range, only two commands are displayed on the *homepage :* “Add supplemental dose” and “Add previous sun session”.
The right screen in Figure 5 shows the additional commands if you are within the range

Helpful for vitamin D: “Sunscreen Reminder” and “Start Sunbathing.” The “Start Sunbathing” command starts counting the amount of vitamin D you’re synthesized.

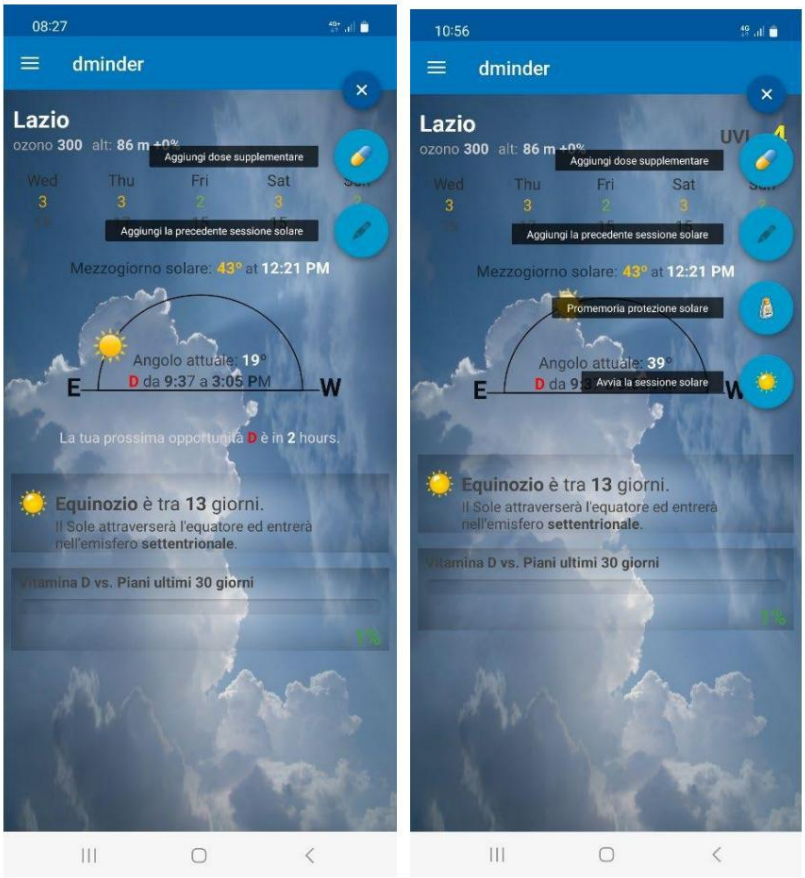
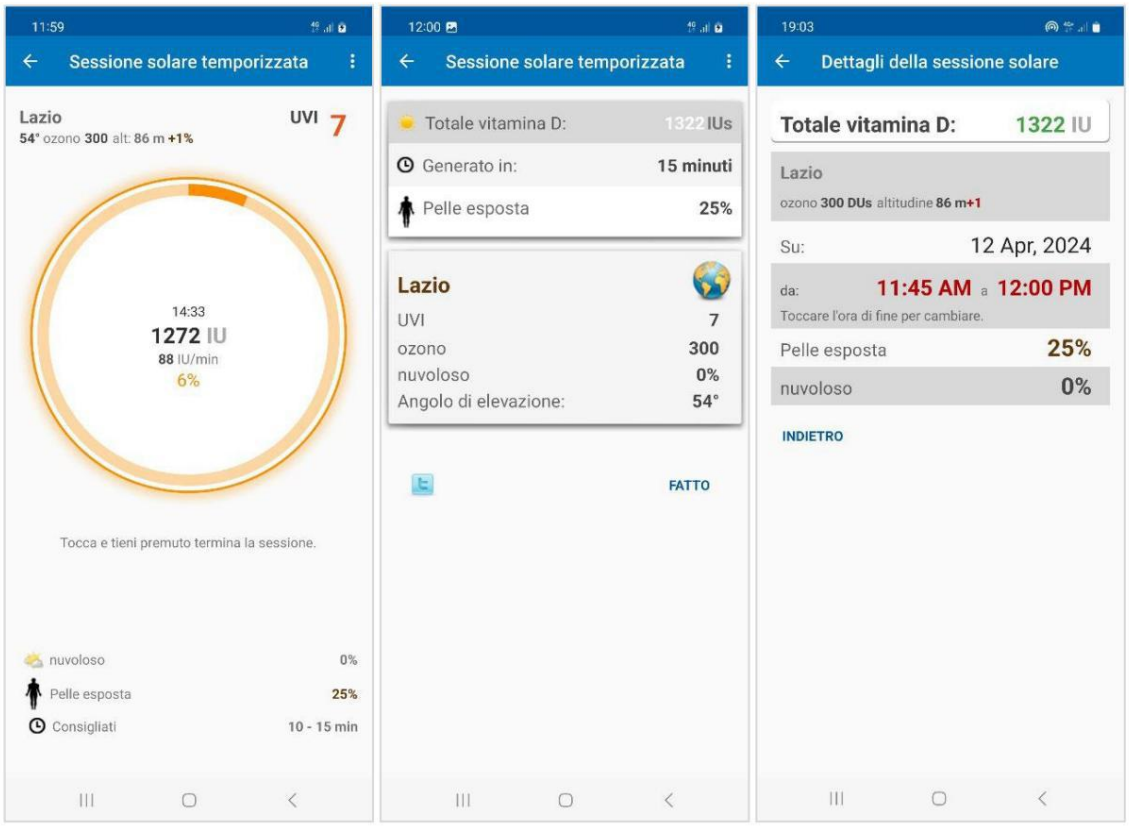


Figure 5. dminder app (Android): Runtime screenshots taken in Rome on March 6, 2024: on the left, the one at 8:27 (outside the recommended range for vitamin D synthesis); on the right, the one at 10:56 (within the recommended range for vitamin D synthesis).

The archives, present in the History command, accessible from the expandable menu in the top left, contain the stored sun exposure sessions, with the date and time of execution. Figure 6 shows three screens relating to a sun exposure session, carried out in Rome on April 12, 2024. The screen relating to the session currently in progress (Figure 6a) displays, in addition to some meteorological and atmospheric parameters, the UVI value and the percentage of exposed skin, the time point and the accumulated IU of vitamin D; the screen relating to the session at the end of execution before saving (Figure 6b) shows the IU accumulated in the elapsed time interval (in this case 15 minutes); the screen relating to the session stored in the archive (Figure 6c) shows the total amount of vitamin D synthesized.

Over time, some meteorological and atmospheric parameters and the percentage of exposed skin are taken into account. Unfortunately, the UVI value is not recorded in the archived session, which, in our opinion, is a significant shortcoming.



a b c

Figure 6. dminder app (Android): screenshots of a solar session carried out in Rome on April 12, 2024: (a) session in progress; (b) session at the end of execution, before saving; (c) session stored in archive

App Sun Index

As reported on the App's website, *Sun Index* (https://sunindex.co/) monitors UV radiation exposure, estimates vitamin D synthesis from the sun, intake from food and supplements, and provides personalized advice.

The App also comes with a wearable sensor device for more accurate real-time monitoring of sun exposure, but it is stated that the App also works without the sensor:

> "The Sun Index App works without the wearable device. However, you can enhance your sun safety experience with our Sun Index wearable device, which tracks your personal UV exposure in real time for more accurate recommendations." (https://sunindex.co/app/).

The app provides a page called *Track Sun Exposure* (Figure 7), where you can start tracking your exposure. This page displays your UVI value and sunscreen icons. For vitamin D, the app provides a page called *Vitamin D Intake.*

(right screen of Figure 7), which shows the set daily IU value and indicates how to achieve this goal through food, sun and supplements, by activating the relevant icons at the bottom *(Food; Sunlight; Supplement).*

Unfortunately, the free version of the app only provides a few basic information such as UVI and the time frame for vitamin D synthesis, and no measurements could be taken with this app.

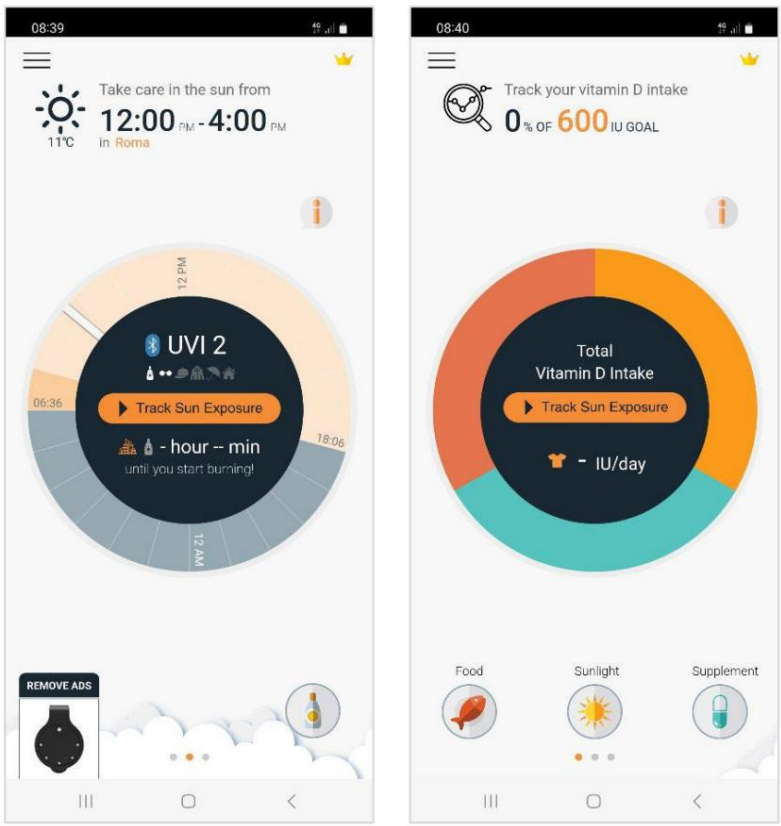


Figure 7. Sun Index app (Android): Runtime screenshots taken in Rome on March 6, 2024 around 8.40 am, with the "Track Sun Exposure" page displayed on the left and the "Vitamin D Intake" page displayed on the right

Conclusions

The research carried out revealed that there are many Apps that provide UVI values, but highlighted the lack of specific vitamin D Apps on the market. Furthermore, the Apps present on the market, especially those available free of charge, present major reliability problems and therefore it is desirable that studies are carried out to evaluate the validity of the measurements they provide. As an example, a validation work of some Apps is cited, carried out by comparing UVI measurements with dedicated devices (8). Moreover, the widespread diffusion of *smartphones* would allow a large-scale use of Apps which, only if adequately designed and evaluated (reliability, usability, etc.), could prove useful for the general population and, if specifically customized, for different groups of users.

Recently, there has been a growing need to provide a "quality label" for health and wellness apps, with the ultimate goal of providing quality products that meet the needs of healthcare professionals, patients, caregivers, and the general public. The applicable "quality criteria" are already defined in the ISO/TS 82304-2:2021 standard.

"Health software - Part 2: Health and wellness apps - Quality and reliability" (9) and concern the following aspects:

– health and safety;
– ease of use;
– data security;
– robustness.

User health and safety requirements address not only the benefits but also the risks that may arise from using apps, as well as ethical considerations.

With regards to ease of use, which is the most fundamental aspect for the diffusion and success of an App, Apps must have certain requirements

– *accessibility*

accessibility according to the *Web Content Accessibility Guidelines,* to ensure that users can use all relevant navigation and user interface components of the App, and related documents;

– *usability*

explicit understanding of users, tasks, and the user environment; instructions for use readily available to users.

The security of the data that Apps manage is certainly a fundamental aspect, especially regarding data confidentiality and protection *(privacy),* but also regarding data integrity and availability *(security).*

Last but not least, there is robustness, understood as both technical robustness (the APP must always be available and reliable) and interoperability (the APP must be compatible with different devices and must be able to interface with different systems).

It is hoped that the ISO technical specification will guide the development of health and wellness apps regardless of whether they are released for sale, including free ones.

What if an app in this sector aspired to be a medical device?

If the App were marketed in Europe it would have to meet the requirements of Regulation (EC) 2017/745 on medical devices (10). In fact, according to this regulation, the software, and
Therefore, the App is defined as a medical device. In the regulation, a medical device is defined as follows:

"Article 2 - Definitions
1) 'medical device' means any instrument, apparatus, equipment, software, implant, reagent, material or other article intended by the manufacturer to be used for human beings, alone or in combination, for one or more of the following specific medical purposes:

- diagnosis, prevention, *monitoring,* prediction, prognosis, treatment or alleviation of disease,

- diagnosis, monitoring, *treatment,* mitigation or compensation of an injury or of a disability,
- study, replacement or modification of the anatomy or of a physiological process or state or pathological,
- provide information through *in vitro* examination of samples from the human body, including donated blood and tissue,

and which does not exert its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but whose function may be assisted by such means."

Devices are divided into four risk classes (I, IIa, IIb, and III), depending on their intended use and the risks involved. Regarding the classification of software medical devices, Rule 11 of the regulation applies:

> *"6.3. Rule 11*
> Software intended to provide information used to make decisions for diagnostic or therapeutic purposes is in Class IIa, unless such decisions have such effects that they could cause:
> - the death or irreversible deterioration of the health condition of a person, in which case it falls into class III, or
> - a serious deterioration in a person's health conditions or an intervention surgical, in which case it falls into class IIb.
>
> Software intended to monitor physiological processes is classified as Class IIa, unless it is intended to monitor vital physiological parameters where the nature of the variations in those parameters is such that they could create immediate danger to the patient, in which case it is classified as Class IIb.
>
> All other software falls into class I."

In conclusion, our research has highlighted that there are many Apps on the market that provide information on UVI and vitamin D synthesized by the sun, but many of these Apps require validation studies.

For this reason, more in-depth research and validation of the Apps will be carried out in the future. considered more interesting also from the usability point of view, in order to provide a detailed overview of the market of these Apps and an appropriate analysis for the definition of the quality of to be.

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APP TO SUPPORT VITAMIN D SYNTHESIS FROM SOLAR RADIATION: THE EXPERIENCE OF THE BRITISH HEALTH CARE SYSTEM

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Impact of solar radiation on health

Solar radiation has both beneficial and harmful impacts on human health (Figure 1). In particular, exposure to solar radiation poses several risks, such as:

– possible development of erythematic reactions and skin burning;
– DNA damage that can cause premature skin aging (photoaging) and the development of skin cancers.

At the same time, solar radiation itself also has numerous beneficial effects and therapeutic, such as:

– synthesis of vitamin D, which is an essential component for health;
– prevention of cardiovascular risks;
– phototherapy with ultraviolet (UV) solar radiation to treat certain skin diseases like vitiligo;
– dynamic phototherapy based on natural solar radiation to treat cancerous or precancerous skin lesions, such as actinic keratosis, or other skin disorders such as acne.

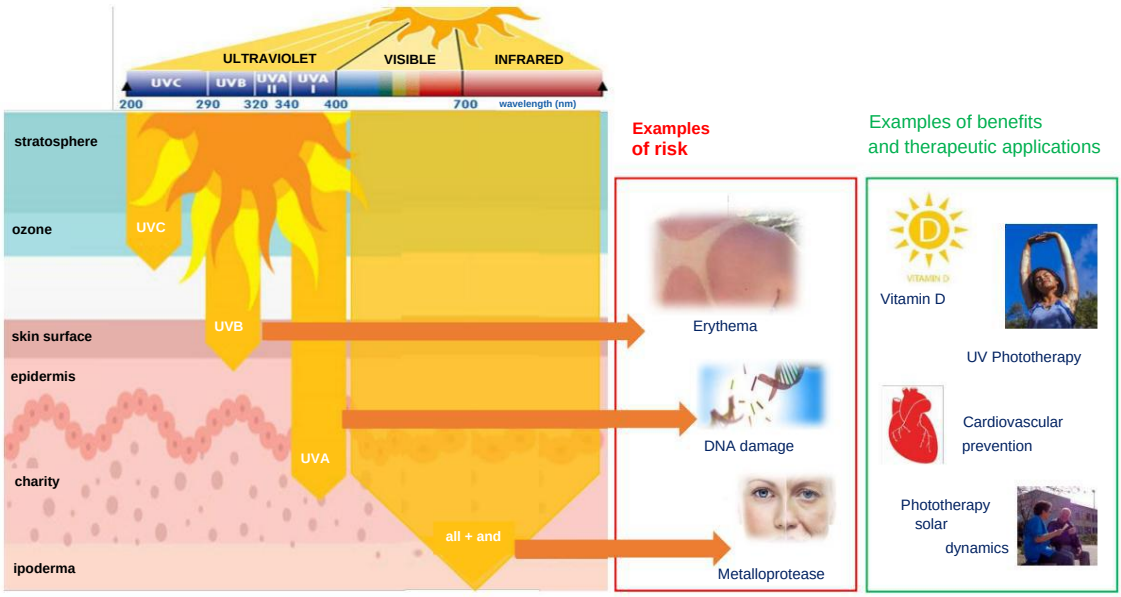

Figure 1. Beneficial and harmful effects of exposure to solar radiation

The beneficial or harmful effects of solar radiation depend on the body's response to the effective dose of solar radiation received. And the effective dose depends on the photobiological spectrum of each of these effects, which essentially defines how "relevant" it is.
the impact of solar radiation considered spectrally (i.e. for each wavelength) for the purposes of the effect considered.

In order to properly consider the impact of solar radiation on health, and ideally balance its beneficial and harmful effects, it is therefore necessary to consider the effective dose of solar radiation for each photobiologically relevant effect to which a person is exposed.
And this involves considering the received spectral solar radiation, integrating it spectrally with the action spectrum of the photobiological effect under consideration, obtaining the effective solar irradiance (usually expressed in units of Weff/m2) and then integrating it over the duration of the exposure to obtain the effective dose (usually expressed in units of Jeff/m2).

For example, if one wants to consider the impact of solar radiation on the development of reactions erythemal (skin redness), the process for calculating the effective erythemal dose is as follows:

– measurement of spectral solar radiation, particularly in the UV region (280-400 nm) which is the only one relevant for erythema;

– spectral integration (convolution) with the erythemal action spectrum (1) to obtain erythemal irradiation;

– temporal integration of erythemal irradiance over time, considering the entire period of sun exposure and that obviously solar irradiance varies over time.

The effective erythemal dose (or erythemal dose) is very important in dermatology, particularly in defining the minimum dose of solar radiation that can cause an erythemal reaction. This amount is different for each person and is usually referred to as the minimal erythemal dose *(MED).*

If we wanted to define an ideal health approach to sun exposure for each individual, it would be optimal to maximize all the beneficial effects (or at least the most important ones) without incurring any risks. And this can potentially be achieved only by considering the effective doses of each photobiological effect, balancing them appropriately to obtain maximum benefits and minimum risks.

It's important to emphasize that the key quantity for considering the health impact of solar radiation is the effective dose (i.e., integrated over time) and not the effective irradiance (instantaneous). Indeed, although the two quantities are related, the health benefits or risks are directly linked only to the dose of solar exposure. This implies that quantities commonly used to quantify the risk of sun exposure, such as the UV Index (UVI),

(which expresses the instantaneous erythemal irradiance) (1), although they are and remain of fundamental importance at the public communication level to provide “easy to understand” information to the population, are not in reality the optimal measures to quantify risks and benefits.

Just as an example, it is clear that:

– 1 minute of sun exposure with a very high UVI such as 10 (accumulated erythemal dose 15 Jeff/m2) does not pose any risk,

– 4 hours of exposure to a UVI as low as 2 (accumulated erythemal dose 720 Jeff/m2) poses certain health risks for most skin phototypes (i.e. phototypes I to IV which typically have MED between 100 Jeff/m2 and 600 Jeff/m2).

Therefore, the standard recommendation to apply sunscreen only when the UV index exceeds 2 may be completely ineffective if the exposure time, i.e. the actual accumulated erythemal dose, is not taken into account.

In conclusion, paraphrasing the famous phrase of Paracelsus (a 15th century Swiss physician) *sola dosis facit venenum,* the harm or benefit to health is due solely to the effective dose.

Satellite measurement of vitamin D synthesis due to sun exposure

Satellite monitoring could be an innovative solution for easily and accurately measuring the effective dose of solar radiation.

In particular, a patented satellite technology called *HappySun*® (developed and patented in Italy by siHealth Photonics srl and used under license by SiHealth Ltd, www.sihealth.co.uk) allows for near-real-time measurement of whole-body sun exposure for a user using a smartphone app *without* the need to expose the *smartphone* to the sun (e.g., by keeping it in a pocket or bag). This technology is based on the continuous processing of images captured by multiple Earth Observation satellites in different spectral bands, with an update frequency of every 5-15 minutes and a spatial resolution of approximately 3 km2 (at mid-latitudes, such as Italy). Essentially, satellite data is used to quantify the atmospheric components (e.g., clouds, ozone, water vapor) in the atmospheric column “above the user’s head” (who is geo-localized thanks to the *smartphone’s sensors)* and the spectral irradiance incident on the user’s skin on the ground is then calculated thanks to atmospheric radiative transfer models.

This "satellite dosimetry" is then made completely automatic thanks to a software component within the app that recognizes whether a user is indoors or outdoors. This component is based on the continuous analysis of signals sampled by the *smartphone,* updating every 1-2 minutes throughout the day and estimating with good accuracy (>85%) whether the user is indoors or outdoors.

HappySun® technology (www.happysun.co.uk) has been scientifically validated by comparison with ground-based spectroradiometric measurements in different spectral bands thanks to the collaboration of international research institutes (3-6). The results are excellent for any spectral band and in any weather conditions, with a correlation factor (R2) that is almost always higher than 90%.

As an application example, the *HappySun*® satellite technology allows to measure the effective dose for the synthesis of vitamin D accumulated during the day by applying the relevant action spectrum (7). This has allowed the development of a model to automatically estimate the level of vitamin D in the blood of a user who regularly uses a *smartphone App.*
In particular:

- the “baseline” level of vitamin D is estimated through a blood test or modeled based on personal and environmental parameters (e.g. minimum erythemal dose, age, body mass index, month of the year)
- the effective solar dose for the synthesis of vitamin D accumulated throughout the body is estimated thanks to *HappySun*® *satellite monitoring,* also taking into account any sunscreens applied (i.e. their spectral transmissivity) and the body surface exposed to the sun (i.e. taking into account the coverage due to clothing)
- Finally, the increase (or decrease) of vitamin D in the blood is calculated each day using a vitamin D synthesis model that takes into account personal characteristics (e.g., age, gender), the baseline vitamin D blood level, and the effective solar dose accumulated day by day by the user.

This model has been validated thanks to a first clinical study conducted by the British health system *(National Health Service,* NHS), where 70 volunteers used an App based on *HappySun*® technology (called *Sun4Health®,* www.sun4health.com) for 9 months and their vitamin D level in the blood was measured through a blood test every two weeks.

and then compared with the estimate from the App. The preliminary results in Figure 2 show good accuracy (R=81%), taking into account that the volunteers did not take vitamin D supplements during the study and that for now the model only considers vitamin D synthesis due to sun exposure (i.e. it does not take into account vitamin D obtained from food, which is less relevant but still not negligible).

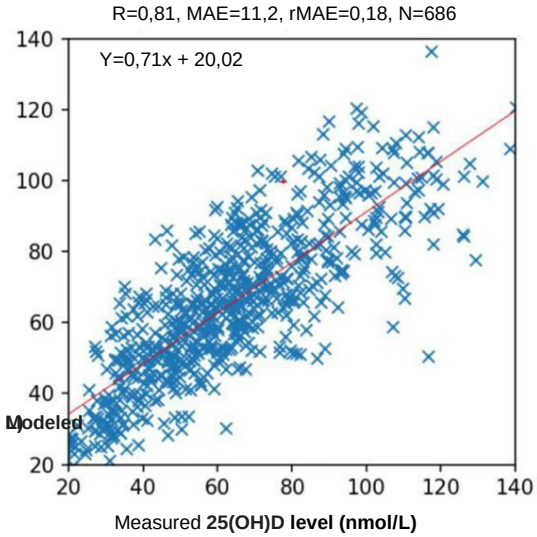

Figure 2. Preliminary results on the comparison between the measured blood vitamin D level and that obtained by the model implemented in the Sun4Health App during the clinical study of NHS Highland in the UK (ISRCTN 30217197)

Sun4Health® App and its clinical validation as a medical device

Sun4Health® is an app based on *HappySun*® satellite technology designed to provide real-time advice to maximize the benefits of sun exposure without risk. Specifically, the app constantly measures both the effective erythemal dose and the effective dose for vitamin D synthesis, taking into account the user's personal characteristics (e.g., minimum erythemal dose) and any sunscreen used.
This allows the App to provide personalized, real-time guidance for reaching the recommended daily dose of vitamin D from sun exposure without risking sunburn.

In addition to real-time monitoring, the app also includes a feature to help users optimally plan their sun exposure for the coming hours or days, even recommending the right sunscreen based on the time and location they plan to be outdoors. Furthermore, the app also allows users to view previous sun exposure and its impact on their health (sunburn risk, vitamin D synthesis), providing personalized advice on how to improve their sun-related *lifestyle .*

The *Sun4Health*® App was developed with the support of the European Space Agency *(European Space Agency,* ESA) and the collaboration of international research centres and experts in the fields of photobiology and photodermatology, such as Public Health England (Dr. Khazova), National Institute for Insurance against Accidents at Work (Dr. Borra), King's College London (Prof. Young), University of Brescia (Prof. Calzavara-Pinton),

National Health Service (Prof. Ibbotson), MedCin/University of São Paulo (Prof. Schalka), Israelite Hospital of Rome (Prof. Leone).

Furthermore, the App has been validated through a clinical study (6) which demonstrated its safety and efficacy, allowing it to be certified as a class I medical device with the CE mark.

This study was conducted in Brazil in December 2019, involving 59 healthy volunteers randomly divided into three groups. They were asked to use an app during two weekends at the beach in the same location and were provided with the same sunscreens (Figure 3). In particular:

– the first group received a "control" App, which measured the exposure sunny but without giving any personalized indication;

– the second group received the *Sun4Health® App,* which provided personalized advice but without showing the exposure over the whole body (i.e. in 3D);

– the third group received the *Sun4Health*® App in the "3D" version, which took into account sun exposure across the entire body, showing it with a digital "avatar".

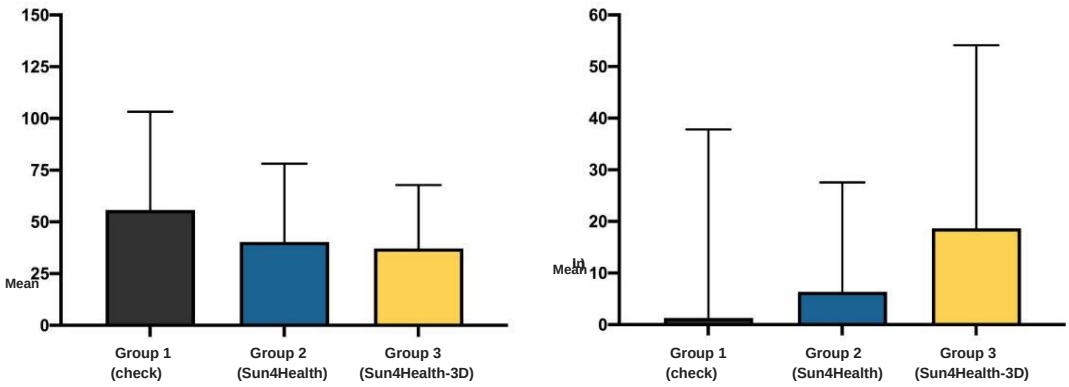

Figure 3. Results of the clinical study conducted to evaluate the safety and efficacy of Sun4Health® as a medical device

For each volunteer, skin erythema was assessed daily at six body sites, and vitamin D levels (serum vitamin D) were measured before and after the study. On average, the groups of volunteers who used the *Sun4Health*® App (groups 2 and 3) reported a lower increase in erythema index (therefore lower risk of sunburn) and a higher increase in vitamin D levels than the control group (group 1).

So, overall the results of the clinical study showed that the *Sun4Health*® App It is safe to use and can modify behavior to reduce skin erythema (sunburn) even in very high UV index conditions, without however depleting vitamin D. Prevention of erythema supported by the *Sun4Health*® App can reduce the risk of skin cancer and pre-cancer (e.g. melanoma, actinic keratosis) and reduce skin redness due to sun exposure.

Impact of Sun4Health® on sun-related lifestyle changes and vitamin D: A clinical study conducted by the UK NHS

The *National Health Service (NHS)* conducted a 9-month clinical study in the UK between April 2021 and March 2022 to evaluate the actual health benefits of using *Sun4Health*® in terms of maintaining a healthy level of

sufficient vitamin D in the blood (clinical study “Sun4Health-VitD”, reported in the international registry *International Standard Randomised Controlled Trial Number,* ISRCTN 30217197).

70 healthy volunteers, who were not taking any food supplements, were randomized into 2 groups:

– a first group (the “control” group) that was provided with an App that only monitored sun exposure (using *HappySun® technology)* but did not provide any personalized indications or recommendations to the user;

– a second group (the “intervention” group) which was instead provided with the App *Sun4Health®.*

Blood (serum) vitamin D levels were assessed for each volunteer on a monthly basis using a postal blood testing kit and analysed by an NHS laboratory, while skin erythema/sunburn was self-reported by volunteers.

The volunteers who had the opportunity to use *Sun4Health®* (intervention group) were subjected to a survey, and reported the following as the most important and innovative features of the App:

– automatic real-time warnings on the risk of sunburn (via *smartphone notification),* underlining the importance of automatic indoor/outdoor detection (so you're always safe and protected, even when you forget to check the app);

– personalized sun exposure time to reach your “daily goal” for vitamin D synthesis, so you can maintain healthy levels in your blood from sunlight (without the need for supplements, where possible).

Preliminary analysis of the collected vitamin D data shows excellent results (Figure 4).

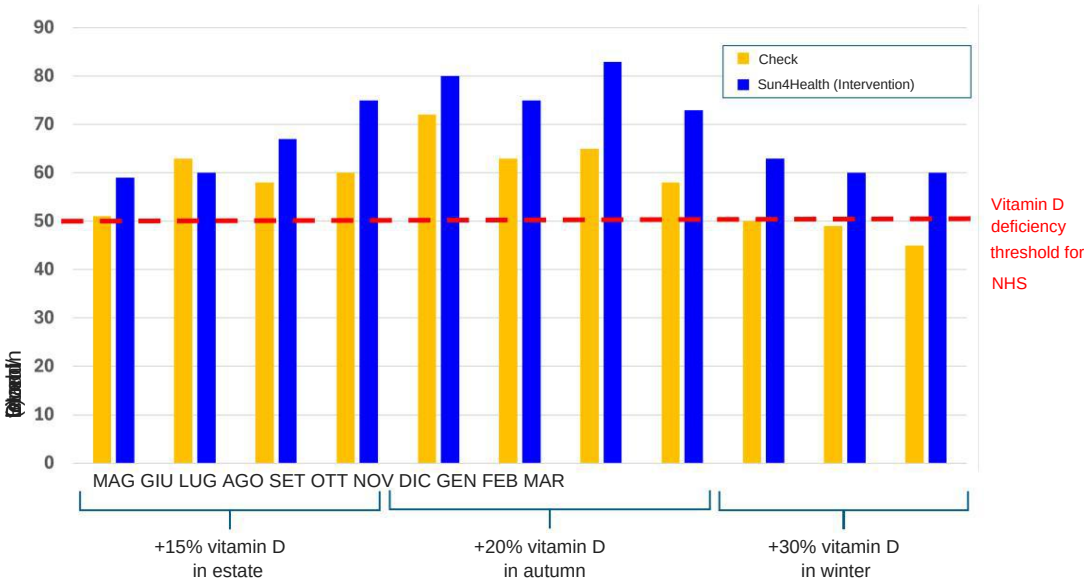

Figure 4. Preliminary results of the clinical study conducted by NHS Highland in the UK on the impact of the Sun4Health® App on vitamin D (ISRCTN 30217197): mean blood vitamin D level of volunteers (20-35 years) who actively used the Control App or Sun4Health®

Specifically, the results show that *Sun4Health*® can help users change their sun-related behavior and increase blood vitamin D levels by up to 30% (in winter, when it's most needed). This is completely risk-free, as *Sun4Health*® users have never experienced sunburn.

In summary, the clinical study demonstrates that the *Sun4Health*® App essentially guides users to protect themselves from the sun in spring/summer (when the risk of erythema/sunburn is higher) and instead during the autumn/winter period it “pushes” users to expose themselves more to sunlight, in a safe way, to avoid the risk of vitamin D deficiency.

Conclusions and perspectives

Solar radiation has both harmful (e.g. erythema) and beneficial/therapeutic (e.g. vitamin D, phototherapy) which can only be balanced by evaluating the effective solar doses.

Sun4Health® is a CE-marked (Class I) digital medical device app based on patented and scientifically validated technology *(HappySun®)* that uses real-time satellite data and AI-based algorithms to automatically and accurately monitor sun exposure. Specifically, the app simultaneously monitors the effective solar radiation dose accumulated across the entire body surface, taking into account both the skin's erythemal reaction and vitamin D synthesis. This allows the app to provide personalized recommendations to support users in achieving "healthily balanced" sun exposure in their everyday lives, maximizing vitamin D synthesis without ever risking erythema/sunburn, thanks also to the intelligent application of sunscreen when necessary.

A clinical study conducted by the National Health Service (NHS) in the UK has shown that *Sun4Health*® can make lifestyle changes to significantly increase vitamin D synthesis from sunlight without the risk of erythema/sunburn and without the need for sun supplements (in months when there is sufficient available solar radiation).

This automatic sun exposure monitor with personalized support allows:

– personalized “education” on a photoprotective lifestyle, reducing health risks in the population;

– have highly beneficial impacts on public health and the prevention of occupational diseases (e.g. for outdoor workers, who are particularly at risk);

– an unprecedented availability of an accurate history of sun exposure for epidemiological and clinical studies.

The *Sun4Health*® App is currently used in several pilot projects, including:

– a clinical study on sun protection in patients with Xeroderma Pigmentosum (XP) led by NHS Guy's and St Thomas';

– safe sun exposure clinical service provided by NHS Tayside for patients with hypersensitive skin;

– the “MySun” project for personalized sun protection for vitiligo patients conducted by Pierre Fabre Dermocosmetics in collaboration with the French Vitiligo Association (https://www.industries-cosmetiques.fr/les-jeunes-generations-face-au-defi-de-la-prevention-solaire);

– the project for solar safety for outdoor workers conducted by Sécurité Solaire (WHO collaborating centre in France).

A customized version of the *Sun4Health*® App that includes only the automatic collection of sun exposure data for photobiological studies and clinical trials, called ExpoDose®, is already available on the global market and currently used by numerous research centers in different countries (for more information visit www.expodose.com).

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