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Sunlight and health: shifting the focus from vitamin D3 to photobiomodulation by red and near-infrared light

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Highlights

- Sunlight exposure and vitamin D levels are associated with better health.
- It has been hypothesized that sunlight-derived vitamin D might improve health.
- Benefits of vitamin D have been undermined by evidence from clinical trials.
- Red and near-infrared light have shown health benefits in preliminary studies.
- Sunlight might improve health via multiple light-mediated mechanisms.

Abstract

Both sun exposure and serum vitamin D levels have been associated with lower risks of all-cause mortality and chronic age-related diseases, e.g., cancer, diabetes and cardiovascular disease, in epidemiological studies. These associations have mainly been ascribed to beneficial effects of vitamin D. However, a vast body of randomized controlled trials (RCTs) and Mendelian randomization studies have failed to confirm any major health benefits from vitamin D supplementation.

In this review, we present tentative evidence showing that red and near-infrared light, both being present in sunlight, could explain the associations between sunlight exposure and better health status. Body irradiation with red and near-infrared light, usually termed as photobiomodulation (PBM), has demonstrated beneficial effects in animal models of chronic diseases. Beyond this, preliminary evidence from RCTs suggest potential clinical benefit from PBM for chronic diseases. PBM is currently being investigated in many pre-registered clinical trials, results of which will eventually clarify the role of red and near-infrared light in the prevention and treatment of common age-related chronic diseases.

Keywords: sunlight, sun exposure, vitamin D, supplementation, photobiomodulation, disease

1. Introduction

Sunlight's effects on health have been a controversial topic in the medical research community. From the dermatological viewpoint, sunlight is a source of ultraviolet radiation, excessive exposures of which can contribute to harmful photoaging, immunosuppression and cancers of the skin. Sunlight has also been associated with the onset of episodes of bipolar disorder (Bauer et al., 2014), deaths from suicide (Vyssoki et al., 2014) as well as the increased risk of age-related macular degeneration (Sui et al., 2013). On the other hand, epidemiological data also has shown multiple inverse associations between sunlight exposure and a variety of chronic diseases (Table 1).

Table 1. Sunlight, season and latitude: associations with health status

Condition	Study type	Results	References
All-cause mortality	Prospective cohort; 20 years; 29 518 women	All-cause mortality was inversely associated with sun exposure habits. The mortality rate amongst subjects avoiding sun exposure was approximately twofold higher compared with the subjects with the highest sun exposure.	(Lindqvist et al., 2014)
Asthma	Asthma prevalence data of U.S. adult population	Asthma prevalence in United States adult population is related to the variation in winter insolation ($r=-0.46$).	(Krstic, 2011)
Cancer	Review	Sun exposure was inversely associated with incidence and mortality in colorectal, prostate and breast carcinoma and non-Hodgkin lymphoma in most of the ecological, case-control and prospective studies identified for this review.	(van der Rhee et al., 2009)
Cardiovascular disease	Prospective cohort; 20 years; 29 518 women	High sun exposure habits were associated with decreased risk of cardiovascular disease mortality, with subdistribution hazard ratio of 0.5 (95% CI 0.4−0.6) in a model adjusted for multiple confounders.	(Lindqvist et al., 2016)
	Data from Seven Countries Study	Latitude is associated with population mean cholesterol within Europe. Within 200 districts located in UK, annual hours of sunshine show an inverse association with death rate from coronary heart disease. Within UK, the mean blood cholesterol in population shows seasonal variation with lowest levels in summer and highest levels in winter.	(Grimes et al., 1996)
	Prospective 5-year study; 182 hypertensive patients	Systolic and diastolic mean blood pressures were higher in winter than summer (165 versus 134 mmHg for systolic; 90 versus 74 mmHg for diastolic).	(Charach et al., 2004)
	Ecological study; 180 countries	Age-standardized mean cholesterol in men and in women increased with the distance of their country from the equator.	(Liu et al., 2018)
Cognitive impairment	Cross-sectional study; 19 896 subjects	A trend for incident cognitive impairment with below the median solar radiation exposure was noted for all of the examined time periods and temperature tertiles.	(Kent et al., 2014)
Crohn's disease	Statistics of French insured population; 57 098 525 persons	The two quintiles with the lowest sun exposure were associated with an increased incidence rate ratios (IRR) of Crohn's disease with IRR of 1.12 (95% CI 1.00-1.26) and 1.42 (1.27-1.58). However, no such associations for ulcerative colitis was noted.	(Nerich et al., 2011)
Multiple sclerosis	Case-control data: 2251 cases and 4028 controls	Lowest reporter summer sun exposure during childhood and early adolescence were associated with 47% higher risk of multiple sclerosis compared to highest exposure.	(Magalhaes et al., 2019)
Parkinson's disease	Case-control data: 201 cases and 199 controls	Patients with newly-diagnosed Parkinson's disease had less weekly sunlight exposure than controls without neurodegenerative diseases (9.7 vs 12.1 hours).	(Wang et al., 2016a)

Stroke	Cohort of 16 606 subjects from USA	Previous year's monthly average insolation exposure below the median was associated with increased risk of stroke (HR = 1.61, 95% CI 1.15-2.26).	(Kent et al., 2013)
Type 1 diabetes	Age-standardised incidence rates of type 1 diabetes in 51 regions worldwide	Incidence of DM1 was generally higher at higher latitudes ($R2 = 0.25$, $p < 0.001$). In a multivariate regression model, UVB irradiance adjusted for cloud cover was inversely associated with DM1 incidence ($p < 0.05$)	(Mohr et al., 2008)
Type 2 diabetes	Cohort data: 29 518 women from Sweden	Women with active sun exposure habits were at a 30% lower risk of having diabetes mellitus, compared to those with non-active (sedentary) habits. Similar results were also seen among tanning bed users.	(Lindqvist et al., 2010)

Due to contradictory observational findings, with some associations suggesting possible benefits and others suggesting possible harm, an uncertainty exists about the overall effects of exposure to sunlight. The uncertainty is compounded by the fact that observational findings do not imply causation, since the correlations might be merely due to confounding factors and reverse causality.

However, based on the multitude of observations of inverse association between sunlight and disease, a hypothesis has been presented that sunlight might have beneficial effects on health status via yet unclear biological mechanisms. During recent years, the discussion has strongly revolved around the possible beneficial effects of vitamin D, which is synthesized within the skin during exposure to ultraviolet B light, an important part of sunlight's spectrum (Holick, 2008; Lindqvist, 2018; O'Sullivan et al., 2017).

While the vitamin D hypothesis has gathered a considerable amount of attention in the scientific literature due to inverse epidemiological associations with a number of chronic diseases (Pludowski et al., 2013), a growing number of randomized clinical trials and Mendelian randomization studies have reported no benefit from vitamin D. This might undermine the idea of improving general health status with vitamin D, possibly implying relevance of other sunlight-related factors that might have been overlooked (Weller, 2019).

During the 21st century, a rapidly growing body of literature suggests beneficial effects from exposure to red light and near-infrared radiation. Numerous scientific articles reporting improved tissue function, wound healing, anti-inflammatory effects and improved energy metabolism after irradiation with sources of red and near-infrared wavelengths as produced with lasers or light-emitting diodes have been published to this date (Chung et al., 2012).

In this review, our aim is to summarize the current evidence on the health-related effects of vitamin D supplementation and that of red-to-near-infrared light exposure. Our premise is that the positive associations between sunlight exposure and better health status could be driven at least partially by the red and near-infrared wavelengths within the spectrum of sunlight, while vitamin D might be predominantly a bystander, or a biomarker, without major health benefits (Caristia et al., 2019; Tunstall-Pedoe et al., 2015).

2. The vitamin D hypothesis

2.1. Introduction to vitamin D3

Vitamin D3 (cholecalciferol) is synthesized in the skin and converted to the prohormone calcidiol (25-hydroxycholecalciferol aka 25-hydroxyvitamin D) in the liver, which is turned into the active-form hormone calcitriol (1,25-dihydroxycholecalciferol) in the kidney. Most of the vitamin D-related functions are mediated by the vitamin D receptor (VDR) (Bikle, 2020).

Preclinical studies have reported beneficial effects from vitamin D supplementation in the animal models of a multitude of diseases, including asthma (Wang et al., 2016b), dementia (Mehri et al., 2020), metabolic syndrome (Mazzone et al., 2018), multiple sclerosis (Spanier et al., 2020), myocardial infarction (El Agaty, 2019), lung injury (Zheng et al., 2020), neuropathic pain (Banafshe et al., 2019), Parkinson's disease (Lima et al., 2018), retinal aging (Lee et al., 2012) and stroke (Evans et al., 2018). The wide distribution of VDR in animal tissues, accompanied with its broad ability to regulate gene expression related to cellular metabolism, cell morphology and inflammatory response, might account for these observations (Bikle, 2020; Koivisto et al., 2020). Then, a smaller proportion of preclinical studies has also reported lack of benefit (Niederstrasser et al., 2016; Peters et al., 2019), and even harmful effects, such as aggravation of breast cancer (Cao et al., 2018).

The interest in the possible health-promoting effects of vitamin D have increased substantially during the 21st century. Nowadays, approximately 4,000 vitamin D related articles are indexed to the PubMed database each year. The observational studies on vitamin D have received a considerable amount of attention due to a vast body of publications reporting inverse associations between vitamin D status and multiple diseases (Table 2).

Table 2. Vitamin D and chronic diseases: epidemiological evidence

Condition	Study type	Results	References
All-cause mortality	Meta-analysis of prospective studies: 26916 subjects for a median of 10.5 years	Compared to subjects with 25(OH)D serum concentrations of 75 to 99.99 nmol/L, the adjusted HRs for mortality in the 25(OH)D groups with 40 to 49.99, 30 to 39.99, and <30 nmol/L were 1.15 (95% CI 1.00-1.29), 1.33 (95% CI 1.16-1.51), and 1.67 (95% CI 1.44-1.89), respectively.	(Gaksch et al., 2017)
Autoimmune disease	Prospective population-based study: 12,555 individuals	The risk for a 10 nmol/l higher vitamin D was associated with significantly decreased incidence for any autoimmune disease (HR = 0.94) and thyrotoxicosis (HR = 0.83). The association was non-significant for type 1 diabetes (HR = 0.95), multiple sclerosis (HR = 0.89), iridocyclitis (HR = 1.00), Crohn's disease (HR = 0.95), ulcerative colitis (HR = 0.88), psoriasis vulgaris (HR = 0.99), seropositive rheumatoid arthritis (HR = 0.97) and polymyalgia rheumatica (HR = 0.94).	(Skaaby et al., 2015)
Cancer	Meta-analysis of longitudinal studies	An increase of 25(OH)D by 50 nmol/L was associated with summary risk ratios of 0.89 and 0.83 for total cancer incidence and mortality, respectively.	(Yin et al., 2013)
Cardiovascular disease	Meta-analysis of cross-sectional studies: 16434 subjects	Serum vitamin D level was negatively associated with carotid atherosclerosis (OR = 0.95; 95% CI 0.93-0.96), with substantial heterogeneity among the studies.	(Chen et al., 2018)
Inflammatory markers	Cross sectional cohort: 5870 subjects	The negative significant association between low 25(OH)D levels (<30 nmol/l) for CRP (OR = 1.23, 95% CI 1.00-1.51) and WBC (OR = 1.35, 95% CI 1.13-1.60) remained after adjustment for numerous	(de Oliveira et al.,

		covariates.	2017)
Type 2 diabetes	Meta-analysis of prospective studies: 76,220 participants	The relative risk for type 2 diabetes was 0.62 (95% CI 0.54-0.70) when comparing the highest to the lowest category of 25(OH)D levels. Every 10 nmol/L increment in 25(OH)D levels was associated with a 4% lower risk of type 2 diabetes.	(Lindqvist et al., 2010)

2.2. Epidemiological versus clinical evidence for vitamin D supplementation

Some authors suggest that observational evidence might be useful in demonstrating the effectiveness of vitamin D supplementation. This perspective is often associated with the optimistic view that vitamin D might be beneficial in a truly causal manner (Papadimitriou, 2017; Scragg, 2018b). On the other hand, other authors prioritize randomized controlled trials (RCTs) over observational evidence, often expressing more pessimistic views about the health effects of vitamin D (Allan et al., 2016; Jorde, 2018).

These two seemingly opposite perspectives appear to be mostly based on the different understandings on the strengths and limitations of the two different kinds of study methodologies (Table 3).

Table 3. Critical viewpoints on epidemiological and clinical studies of vitamin D.

Methodology	Quote	Reference
Cohort studies	"Despite thousands of vitamin D studies published, including hundreds of reviews and meta-analyses, it is still uncertain if supplementation with vitamin D will have positive health effects, except for the skeleton. This cannot be answered by doing more observational studies as it is impossible to control for confounding fators and reverse causality."	(Jorde, 2018)
	"[G]ood vitamin D status is generally a marker of good health, as high 25(OH)D concentration is associated with young age, normal body weight, and a healthy lifestyle, including healthy dietary and exercise habits (...) Similarly, low vitamin D levels may reflect chronic illness, which prevents outdoor activities and sun exposure."	(Muscogiuri, 2018)
	"It now seems safe to conclude that many prior epidemiological associations between vitamin D deficiency and adverse health outcomes were driven by unmeasured residual confounding or reverse causality."	(Lucas and Wolf, 2019)
Clinical studies	"RCTs also are prone to limitations that compromise their validity. These include low response rates that affect their external validity; and biases that affect their internal validity, such as recruitment of vitamin D sufficient people which decreases the power to detect beneficial effects, studies of long-term outcomes requiring participation for many years which decreases compliance and retention, and easy access for participants to vitamin D supplements and blood testing which increase contamination and unblinding. Because of these potential limitations, it is possible that RCTs of vitamin D supplementation may not to give a clear answer by themselves."	(Scragg, 2018b)
	"There are a number of reasons why all these [vitamin D] RCTs have not shown convincingly positive effects: the studies have been too small for sufficient statistical power; the intervention periods too short at least for hard endpoints like cancer, heart disease, fractures and mortality where positive effects of vitamin D may need to accumulate over many years before detectable; the supplements in some studies have been given once a week or month when daily doses probably are preferable, and most of all, the subjects included may not have been vitamin D deficient and/or not at risk of developing the disease(s) in question, and therefore no effect of additional vitamin D were	(Jorde, 2018)

	to be expected.	

The most common arguments against observational cohort studies are mainly related to the fact that the association between vitamin D and health might be explained by confounding factors and reverse causation(Jorde, 2018). According to the GRADE guidelines, body of evidence based on observational research is considered “low quality” to begin with, although the quality rating can be upgraded on certain occasions (Balshem et al., 2011).

A common argument against the clinical trials, on the other hand, is that they can fail to show the causal associations in many situations, even if the effect was real. For example, the baseline vitamin D levels might be too high, the treatment dose might be too low, and the study duration may be too short for the beneficial effects of the supplementation to emerge (Grant, 2016).

According to some authors, there are certain thresholds for the circulating vitamin D concentration that need to be passed in order to see the beneficial effects from the vitamin D supplementation (Scragg, 2018a, b). However, some pieces of observational and clinical evidence associate high intakes and higher blood levels of vitamin D with undesirable outcomes, such as the increased risks of accidental falls and premature mortality (Allan et al., 2016; Burt et al., 2019).

Overall, the dispute on the interpretation of evidence concerning vitamin D is still going on. Despite the confusion it might arouse, it might also provoke clinical researchers to plan their study designs in a way that takes into account the multiple challenges of bringing forth reliable findings in vitamin D supplementation trials.

2.3. Vitamin D in chronic disease: clinical and genetic evidence

In 2014, an umbrella review focusing on vitamin D and multiple health-related outcomes concluded that *“[despite] a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome”*. The review was based on 107 systematic reviews and 74 meta-analyses of observational studies as well as 87 meta-analyses of RCTs of vitamin D supplementation, thus representing the state of the art for the vitamin D research of that time (Theodoratou et al., 2014).

Since 2014, a large body of additional evidence from RCTs have been published the majority of the findings lending no clear support for the effectiveness of vitamin D supplementation for many indications. However, some tentatively positive results have been reported (Table 4).

Table 4. Vitamin D and chronic disease: clinical evidence.

Condition	Study information	Results	References
Acute respiratory infections	Meta-analysis: 25 RCTs with 11321 participants	Vitamin D supplementation reduced acute respiratory infections (adjusted OR = 0.88, p < 0.001). The effect was more pronounced in the patients with low baseline 25(OH)D serum levels (< 25 nmol/l).	(Martineau et al., 2019)
Alzheimer’s disease	RCT: 210 participants, 12 months, 800 IU/d	Improved information, arithmetic, digit span, vocabulary, block design and picture arrange scores (p<0.05) and improved full scale IQ (p<0.001).	(Jia et al., 2019)
Cancer	Meta-analysis: 10 RCTs with 6537 cases	Vitamin D supplementation significantly reduced total cancer mortality with RR = 0.87 (95% CI, 0.79-0.96), but it	(Keum et al., 2019)

		did not reduce total cancer incidence.	
Cardiovascular disease	Meta-analysis: 21 RCTs with 83291 participants	Vitamin D supplementation was not associated with major adverse cardiovascular events or all-cause mortality.	(Barbarawi et al., 2019)
	RCT: 422 participants, 4 months, 20,000 IU/wk	No effects on blood pressure, cholesterol levels or markers of insulin resistance.	(Kubiak et al., 2018)
Depressive symptoms	RCT; 155 elderly participants with low vitamin D levels; 1 year; 1200 IU/d	No beneficial effects on depressive symptoms or secondary outcomes were noted.	(de Koning et al., 2019)
Heart failure	RCT; 400 participants; 3 years; 4000 IU/d	No beneficial effects on mortality or secondary clinical endpoints were noted.	(Zittermann et al., 2017)
Inflammatory markers	Meta-analysis: 24 RCTs with 2302 participants	No beneficial effects on circulating CRP, TNF-a, IL-10 or IL-6 cytokine levels were noted.	(Mazidi et al., 2018)
Mortality	Meta-analysis: 52 trials with 75,454 participants	Vitamin D supplementation did not decrease all-cause mortality.	(Zhang et al., 2019)
Osteoporosis	Meta-analysis: 81 RCTs with 53,537 participants	No beneficial effects on fracture risk or bone mineral density.	(Bolland et al., 2018)
Type 2 diabetes	Meta-analysis: 28 RCTs with 3848 participants	The results suggested modest beneficial effects on glycemic control and insulin resistance	(Mirhosseini et al., 2018)

Despite several large trials having already been published lately, the results of several major clinical trials, including D2d (USA), D-Health (Australia), DO-HEALTH (Europe), FIND (Finland) and TIPS-3 (international), are yet to be published. These studies will provide additional useful information regarding the potential clinical effects of vitamin D (Giustina et al., 2020).

In addition to clinical studies, studies utilizing Mendelian randomization are able to provide causal evidence by utilizing genetic data. The methodology is based on the basis of random allocation of genetic material between individuals at conception (Lawlor et al., 2019; Welsh and Sattar, 2014). By 2019, there are 62 articles which have applied Mendelian randomization for analysis and have their focus on vitamin D, and a conclusion given from these studies is that small beneficial effects of vitamin D supplementation for certain diseases cannot be ruled out, but that large effects of vitamin D on the majority of studied outcomes can be excluded, and that "*most of its attributed causal associations are likely driven by confounding*" (Manousaki and Richards, 2019).

Large-scale Mendelian randomization studies have focused on a range of diseases, including atopic dermatitis and asthma (Manousaki et al., 2017), cancer (Ong et al., 2018), cardiovascular disease (Huang et al., 2019), inflammatory markers (Liefaard et al., 2015), mortality (Afzal et al., 2014), Parkinson's disease (Larsson et al., 2017) and multiple health-related outcomes (Meng et al., 2019). They mostly demonstrate a lack of association between the genetically determined vitamin D levels and disease outcome. This suggests that there is no significant benefit from higher vitamin D levels.

The aforementioned negative results have also prompted fierce criticism against the vitamin D hypothesis (Gatti et al., 2020; Lucas and Wolf, 2019). For example, some of the recent articles have phrased that the claimed benefits of vitamin D "*have been greatly oversold*" (Morley, 2019), and that stimulation of vitamin D supplement use "*should be reconsidered*" (Reijven and Soeters, 2020).

3. The therapeutic effects of red light and near-infrared radiation

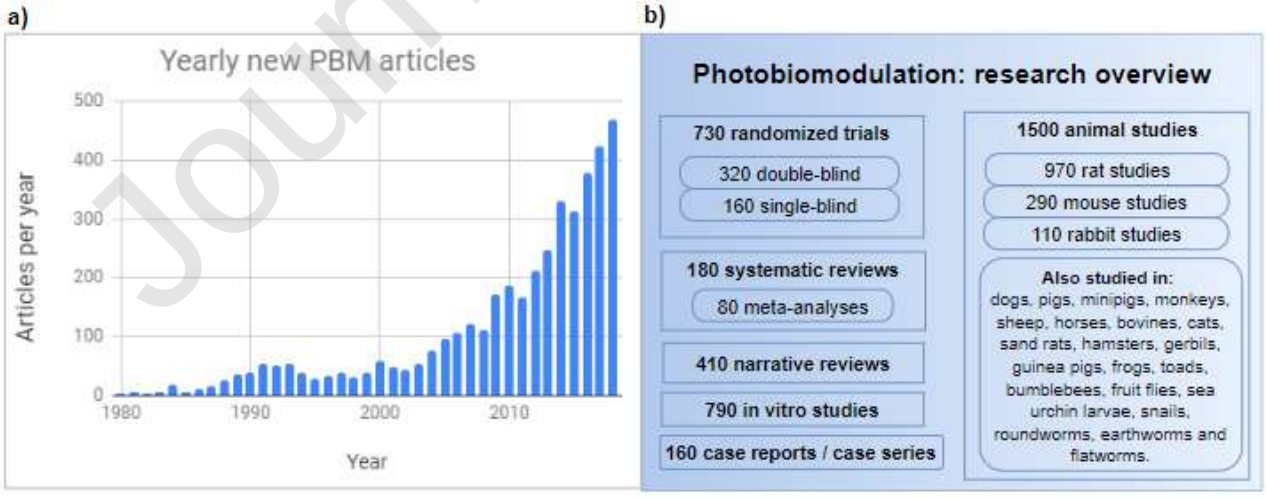
3.1. Introduction to photobiomodulation

To this date, a large body of evidence has been published concerning the physiological effects from irradiation by red or near-infrared wavelengths. These effects are usually termed as *photobiomodulation* (PBM), yet many authors also prefer the earlier popular term *low-level (laser) light therapy* (LLLT) (Chung et al., 2012).

Red and near-infrared wavelengths are able to penetrate inside biological tissue due to so-called optical near-infrared window. A large body of preclinical research has shown that irradiation of cells or animals by red and near-infrared wavelengths has resulted in favourable metabolic and anti-inflammatory effects in preclinical disease models (Hamblin, 2017, 2018; Zhang et al., 2020). As an example, irradiation of aged fruit flies with red light completely reversed the age-related decline in memory and retinal function as well as increased their mobility, while increasing the whole body ATP levels and decreasing the reactive oxygen species (Weinrich et al., 2017).

The exact mechanisms for these effects are not well known, though preliminary evidence suggests possible roles for mitochondrial cytochrome c oxidase and photolabile sources of nitric oxide (Serrage et al., 2019). The existence of mitochondria-related mechanism is supported by studies reporting photobiomodulation-induced changes in ATP levels, mitochondrial membrane potential ($\Delta\Psi m$), cytochrome c oxidase activity, oxygen consumption and activity of SIRT1/PGC1α pathway, as well as protection of mitochondria against toxins such as potassium cyanide and tetrodotoxin (Hamblin, 2018; Wong-Riley et al., 2005; Zhang et al., 2020).
Currently, the scientific literature concerning PBM encompasses more than 4,500 scientific articles, including more than 1500 animal trials and 700 randomized clinical trials. The publication rate of PBM research has increased rapidly during the 21st century, and the current publication rate is approximately 500 new articles annually (Figure 1).

Figure 1. a) The number of articles on photobiomodulation per year as being published and indexed in the PubMed database, and b) their categorization by contents. The overview is based on a personal database of approximately 4700 scientific articles related to PBM, compiled by manual literature search (http://www.bitly.com/PBM-database; Accessed on 3 March 2020).



3.2. Exposure to red and near-infrared wavelengths might improve health

In animal models of disease, PBM appears to alleviate many kinds of disorders, including allergy, brain diseases, cancer, cardiovascular diseases, diabetes, eye diseases, and pain (Table 5). It is of note that there is promising evidence from randomized controlled trials in humans as well, but for most of the indications, the level of evidence is not adequately high to include PBM therapy into clinical practice guidelines.

Table 5. Examples of photobiomodulation-related findings.

Category	Findings
Allergy	**Preclinical research:** PBM has been shown to improve allergic asthma (Ryu et al., 2020), allergic rhinitis (Bae et al., 2019) and allergic contact dermatitis (Sakihama, 1995) in mice. **Clinical research:** PBM improved subjective and objective symptoms of allergic rhinitis and nasal polyposis in a randomized study (Neuman and Finkelstein, 1997).
Autoimmune disease	**Preclinical research:** PBM has been shown to improve symptoms and biochemical markers in experimental autoimmune encephalitis, the animal model of multiple sclerosis (Goncalves et al., 2016; Muili et al., 2013; Muili et al., 2012). **Clinical research:** PBM improved chronic autoimmune hypothyroidism by decreasing thyroid peroxidase antibodies and lowering the levothyroxine requirements by over 60 percent compared to the placebo group in a RCT (Hofling et al., 2013).
Brain disease	**Preclinical research:** PBM has been shown to ameliorate a variety of animal models of Alzheimer's disease, depression, Parkinson's disease, stroke and traumatic brain injury (Salehpour et al., 2018). **Clinical research:** PBM improved symptoms of depression in a randomized pilot study (Cassano et al., 2018). Whole-body hyperthermia by near-infrared light also led to improvements in depressive symptoms (Janssen et al., 2016). PBM was associated with improved cognitive function in dementia in a small pilot trial (Chao, 2019). PBM failed to show any positive effects in acute stroke, which could be related to insufficient dosing (Lapchak and Boitano, 2016).
Cancer	**Preclinical research:** PBM has shown conflicting results in animal models of tumor growth. Some studies have observed increases in tumor volume while other studies report no effect or even a beneficial effect (Frigo et al., 2018; Hamblin et al., 2018). **Clinical research:** In head and neck cancer patients with PBM-treated oral mucositis, the progression-free survival was significantly higher compared to subjects in the placebo group, while overall survival was increased non-significantly (Antunes et al., 2017). Another study found no such benefit (Genot-Klastersky et al., 2019).
Cardiovascular disease	**Preclinical research:** PBM has been shown to ameliorate animal models of arterial restenosis (Kipshidze et al., 2001), atherosclerosis (Park et al., 2012), hypertension (Oishi et al., 2017), myocardial infarction (Carlos et al., 2016) and ventricular arrhythmia (Wang et al., 2019). **Clinical research:** PBM has shown promising results in the treatment of arterial restenosis (Derkacz et al., 2010) and acute myocardial infarction (Elbaz-Greener et al., 2018) in preliminary trials.
Diabetes	**Preclinical research:** PBM has been shown to ameliorate insulin resistance in high-fat diet (HFD)-fed mice (Gong et al., 2020). PBM has shown protective effects in diabetes-related pancreatic duct injury (Tatmatsu-Rocha et al., 2017), hyposalivation (Biswas et al., 2018), kidney injury (Lim et al., 2010), retinopathy (Saliba et al., 2015) and wound healing (Asghari et al., 2017). **Clinical research:** PBM has been shown to reduce ulcer area and improve healing rate in diabetic foot ulcer, evaluated by a meta-analysis (Li et al., 2018). A case series found that PBM was associated with amelioration of diabetic macular edema (Tang et al., 2014).
Exercise	**Preclinical research:** PBM has been shown to improve exercise performance and to improve

	skeletal muscle repair (Alves et al., 2014; Ferraresi et al., 2015). **Clinical research:** PBM has been shown to improve exercise performance and muscle recovery in athletes (resistance training, exercise biking, running) in a systematic review including 39 trials (Vanin et al., 2018).
Eyes	**Preclinical research:** PBM has been shown to ameliorate disease severity in animal models of age-related macular degeneration, bright light-induced damage, diabetic retinopathy, methanol toxicity, optic nerve injury and oxygen induced retinopathy (Geneva, 2016). **Clinical research:** PBM has been shown to improve visual acuity and contrast sensitivity in age-related macular degeneration in preliminary clinical trials (Ivandic and Ivandic, 2008; Markowitz et al., 2019; Merry et al., 2017).
Pain	**Preclinical research:** PBM has been shown to alleviate acute and neuropathic pain (Masoumipoor et al., 2014; Pigatto et al., 2017). **Clinical research:** PBM has shown amelioration of pain in knee osteoarthritis, low back pain, neck pain, shoulder tendinopathies and tennis elbow, according to meta-analyses of randomized controlled trials (Bjordal et al., 2008; Chow et al., 2009; Haslerud et al., 2015; Huang et al., 2015; Stausholm et al., 2019).

Currently, more than a hundred clinical trials are being carried out according to the ClinicalTrials.gov database. Here, a relevant selection of the pre-registered trials is described in Table 6.

Table 6. Examples of pre-registered photobiomodulation trials

Indication	Country	Light source	Methods	Estimated completion	NCT number
Alzheimer's disease	USA & Canada	LED	RCT, quadruple-blind 228 participants	5/2021	NCT03484143
Chronic low back pain	Brazil	LED	RCT, single-blind 76 participants	12/2020	NCT04003545
Cognitive impairment in aging	USA	LED	RCT, triple-blind 168 participants	1/2025	NCT04018092
Diabetic foot ulcer	Thailand	Laser	RCT, single-blind 100 participants	12/2020	NCT03788642
Diabetic macular edema	USA	LED	RCT, double-blind 134 participants	8/2020	NCT03866473
Distal radius fractures	Norway	Laser	RCT, single-blind 70 participants	2/2020	NCT03014024
Dry age-related macular degeneration	USA	LED	RCT, double-blind 96 participants	12/2021	NCT04065490
Major depressive disorder	USA	Laser	RCT, single-blind 200 participants	2/2020	NCT02898233
Radiation dermatitis	Belgium	Laser	RCT, single-blind 100 participants	6/2021	NCT03924011

3.3. Sunlight as an important source of therapeutic red and near-infrared wavelengths

We suggest that direct and indirect exposure to sunlight could act via photobiomodulation mechanisms to elicit beneficial physiological effects in humans, possibly explaining the positive associations between sunlight exposure and better health status. This possibility has already been

briefly mentioned in previous articles (Gonzalez Maglio et al., 2016; Karu, 2010; Mathewson, 2015; Veto, 2019).

Other authors in the field of photobiomodulation research have suggested that specific properties, e.g. coherence or monochromaticity of light, might be required for photobiomodulation effects to occur (Moskvin, 2017). The previously common term for photobiomodulation, low-level laser therapy (LLLT), also implied that the light-induced effects are specific for laser light. However, these assumptions have been strongly undermined by a vast body of experimental research showing PBM effects with light-emitting diodes (LEDs) and broadband light sources, accompanied by numerous head-to-head comparisons of lasers and LEDs reporting almost identical effects in both of the treatment arms (Heiskanen and Hamblin, 2018).

It's important to examine whether the amount of red light and near-infrared radiation delivered via sunlight is comparable to the amount delivered by devices used in PBM research. This is challenging for a variety of reasons. For one, solar irradiance of infrared light is influenced by a variety of factors, including (but not limited to) time of day, time of year, latitude, and cloud cover (Barolet et al., 2016). Nonetheless, some rough estimates of infrared light irradiance from sunlight have been attempted. According to calculations by Barolet and colleagues, the amount of infrared-A (760 to 1400 nm) from sunlight during mostly unobscured conditions may be around 20 mW/cm^2 (Barolet et al., 2016). The proportions of visible light (400-695 nm) and near-infrared radiation (695 - 2800 nm) in global solar radiation are approximately 49% and 47%, respectively, while the ultraviolet component is approximately 4% of global solar radiation (Escobedo et al., 2011; Muneer, 2007).

The characteristics of light used in PBM studies, meanwhile, are relatively variable. According to one review, an energy density range of 5 to 50 mW/cm^2 has commonly been utilized in preclinical research (Huang et al., 2011). A number of clinical studies on humans have also reported beneficial effects in this range, although in some cases, far higher intensities are employed than would be feasibly obtained from sunlight exposure (Cassano et al., 2018; Chung et al., 2012; Gautam et al., 2013; Paolillo et al., 2011).
In PBM research, a common convention has been to target only specific body parts. For example, when knee osteoarthritis pain is being treated, the light beam is directed to the knee. Daylight exposure would expose larger body surface areas to light, possibly yielding a biological response which is different from the targeted irradiation. In particular, the extensive skin exposure could potentially have systemic physiological effects, since irradiating a single body part has been observed to have effects other body parts (Kim et al., 2017). For example, irradiating the body of a mouse has been shown to protect the brain against a neurotoxin (Johnstone et al., 2014). In a human study, the irradiation of lower back decreased the pro-inflammatory cytokines circulating in the blood of human subjects (Zhevago and Samoilova, 2006). The remote and protective effect of light could be partially related to the modulation of the immune system via the circulatory system (Kim et al., 2017).

When considering sunlight as a source of red and near-infrared wavelengths, it is important to notice that a significant proportion of near-infrared wavelengths does penetrate through thin garments such as t-shirts. Thus, large skin areas can be exposed to near-infrared radiation during common outdoor activities, and photobiomodulation effects would not be limited to intentional tanning.

4. Other sunlight-derived wavelengths (ultraviolet, blue light and infrared)

4.1. Ultraviolet radiation

Ultraviolet radiation (UVR) elicits a complex physiological response in humans, thus possibly explaining some of the associations between sunlight and general health status (Queiros and Freitas, 2019). The preclinical evidence from animal trials has demonstrated beneficial effects of UVR in the prevention of obesity, metabolic syndrome, and atherosclerosis, as well as in the animal model of multiple sclerosis (Ferguson et al., 2019; Geldenhuys et al., 2014; Irving et al., 2019). These diverse physiological effects of UVR might be related to a range of mechanisms of action, including the increase in vitamin D production, photodecomposition of the cutaneous nitric oxide stores (Feelisch et al., 2010), regulation of the circadian rhythms (Nikkola et al., 2019) and immunomodulation (Hart et al., 2019).

However, the clinical evidence base is limited, and the RCTs investigating the effects of ultraviolet B (UV-B) phototherapy have not succeeded in achieving clinically meaningful metabolic outcomes (Gorman et al., 2019). The most well-known role of UV-B radiation in clinical medicine is its use in the treatment of skin diseases such as psoriasis, vitiligo, and atopic dermatitis (Juzeniene and Moan, 2012). Furthermore, preliminary evidence suggests that, on the one hand, UV-B radiation might increase β-endorphin in the epidermal keratinocytes of the human skin (Jussila et al., 2016) as well as improve mood in the evening type person (Toledo et al., 2019), and on the other hand, ultraviolet A (UV-A) radiation might lower systemic blood pressure by releasing nitric oxide from the intracutaneous photolabile nitric oxide derivatives (Liu et al., 2014; Oplander et al., 2009).

4.2. Blue light

Within sunlight's spectrum, the wavelengths corresponding to blue light at 460 nm, if being exposed to the eyes, produce the strongest effect on the suppression of melatonin secretion from the pineal gland in humans (Vartanian et al., 2015) via a subset of the intrinsically photosensitive retinal ganglion cells (Lazzerini Ospri et al., 2017). These eyes pass the effects of light exposure downstream on the timing of melatonin secretion as well as on the circadian rhythms through the actions within the circadian clock located in the suprachiasmatic nucleus of the anterior hypothalamus (Khalsa et al., 2003; Thapan et al., 2001). However, the pathways along which the acute effects of light exposure on body temperature are transmitted (Rupp et al., 2019) appear to differ from those which mediate the acute effects of light exposure on mood (Fernandez et al., 2018). Here, intriguingly, recent data show that exposure to visible bright light could protect mice against myocardial infarction via the mechanisms of action which are related to circadian rhythm regulation (Oyama et al., 2019).

Bright light therapy, which utilizes light exposure to wavelengths covering about the full spectrum visible to the human eye, has been the subject of extensive clinical research as a possible treatment for a variety of mood disorders. A growing body of evidence suggests light therapy can improve mood in seasonal affective disorder, albeit with moderate heterogeneity and moderate-to-high risk of bias in study results (Pjrek et al., 2020). Additionally, bright light therapy may reduce symptoms of non-seasonal depression, as the meta-analysis of 2016 reported improvements in depressive episodes accompanying mood disorders such as major depressive disorder and bipolar disorder, although it included studies being moderately heterogeneous by design and bearing a high risk of bias (Perera et al., 2016).

In addition, especially blue light wavelengths seem to increase the circulating β-endorphin concentration and decrease the systolic blood pressure in humans via nitric oxide related mechanisms in the skin (Albers et al., 2019; Stern et al., 2018). A body of preclinical evidence also suggests that low doses of blue light might have photobiomodulation-like effects in cells as well as in animals, though higher doses might lead to unfavourable outcomes (Serrage et al., 2019). As a downside, both UVR and blue light appear to contribute to the sunlight-related retinal degeneration (Sui et al., 2013).

4.3. Far-infrared radiation

Far-infrared radiation (FIR) may be another mechanism contributing the impact of sunlight on health (Shui et al., 2015). In particular, some evidence suggests FIR exposure can positively impact several indices of cardiovascular health. Animal models have reported beneficial effects of FIR exposure on blood pressure (Lin et al., 2016), depressive symptoms (Tsai et al., 2007), endothelial function (Chen et al., 2017), microcirculation (Yu et al., 2006), new blood vessel formation (Huang et al., 2012), restraint stress-related changes (Tran et al., 2016) and wound healing (Toyokawa et al., 2003). A few preliminary human studies on FIR have reported increased flow mediated dilation, thereby improving impaired vascular endothelial function in patients with at least one risk factor of coronary atherosclerosis (Imamura et al., 2001).

The biological mechanism underlying these apparent effects is unclear but has been proposed to be linked to an increase in nitric oxide synthesis (Huang et al., 2012) and/or the enzyme heme oxygenase-1 (Lin et al., 2008). However, it is worth noting that the effect of FIR in a number of studies may be explained via thermal effects. For example, a 2018 systematic review of human experimental and observational studies on sauna use (Hussain and Cohen, 2018) reported beneficial effects in the prevention and management of cardiovascular disease, regardless of whether the sauna emitted significant amounts of FIR light.

5. Conclusions

While the early observational research on vitamin D and health showed a myriad of promising associations, more recent clinical studies have shown that apart from the established role in calcium metabolism and osteomalacia, the effects of vitamin D on health status are far from clear.

Given the body of evidence regarding the health-promoting effects of red and near-infrared wavelengths, it is tempting to hypothesize that natural sources of these wavelengths, including sunlight and daylight, could have a wide variety of potential health-related effects that could be investigated further in detail using RCTs.

The total effects of environmental light on health status appear to be complex, as different wavelengths yield a variety of physiological responses (Shen and Tower, 2019). The level of certainty concerning the evidence for PBM in most of the evaluated indications has thus far been relatively low. Therefore, it is still not possible to estimate the magnitude of the possible effects of sunlight-induced PBM on diseases and general health status. However, the acknowledgement of this kind of phenomenon can be a valuable step forward in research on sunlight.

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