Photobiology and Photochemical Sciences - Perspective

Special edition: The health benefits of UV radiation exposure through vitamin D production or non-vitamin D pathways.

Title: Ultraviolet radiation, vitamin D and the development of obesity, metabolic syndrome and type-2 diabetes

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Abbreviations

1,25-dihydroxyvitamin D $(1,25(OH)_2D)$

25-hydroxyvitamin D (25(OH)D)

 α -melanocyte-stimulating hormone (α -MSH)

choline-deficient and iron-supplemented L-amino acid-defined (CDAA)

endothelial nitric oxide synthase (eNOS)

high-density lipoprotein-cholesterol (HDL-cholesterol)

low-density lipoprotein-cholesterol (LDL-cholesterol)

melanocortin-4 receptor (MC4R)

non-alcoholic fatty liver disease (NAFLD)

pro-opiomelanocortin (POMC)

ultraviolet radiation (UVR)

vitamin D-binding protein (VDBP)

vitamin D receptor (VDR)

Abstract. Obesity is increasing in prevalence in many countries around the world. Its causes have been traditionally ascribed to a model where energy intake exceeds energy consumption. Reduced energy output in the form of exercise is associated with less sun exposure as many of these activities occur outdoors. This review explores the potential for ultraviolet radiation (UVR), derived from sun exposure, to affect the development of obesity and two of its metabolic co-morbidities, type-2 diabetes and metabolic syndrome. We here discuss the potential benefits (or otherwise) of exposure to UVR based on evidence from pre-clinical, human epidemiological and clinical studies and explore and compare the potential role of UVR-induced mediators, including vitamin D and nitric oxide. Overall, emerging findings suggest a protective role for UVR and sun exposure in reducing the development of obesity and cardiometabolic dysfunction, but more epidemiological and clinical research is required that focuses on measuring the direct associations and effects of exposure to UVR in humans.

Introduction. The prevalence of obesity in adults and children is increasing in both developed and developing countries.^{1,2} It is a debilitating condition, associated with a range of metabolic disorders, two of which are type-2 diabetes and metabolic syndrome (see Table 1). In its simplest conception, obesity is caused by greater energy intake (in the form of increased dietary consumption of fats and sugars) than energy output (typically through physical activity). An inactive lifestyle is often associated with increased time indoors engaged in sedentary pursuits (e.g. screentime). This, in turn, reduces opportunity for sun exposure. While inactivity is a well-known contributor towards obesity, the consequences of reduced sun exposure are yet to be fully explored. With our increasingly indoor lifestyles, it is likely that more exercise is occurring at gyms (and other venues), further limiting opportunities for sun exposure.

Table 1: Commonly used obesity-related disease and physiological definitions

,	Definition 1	Definition 2	Definition 3					
Obesity	Body mass index:	Waist circumference:	Waist to hip ratio:					
,	>30 kg/m ²	>102 cm for men	>0.55 ⁴					
	G.	>88 cm for women ³						
	Description							
Obesity	A medical condition in which excessive fat accumulates in the body, we have detrimental effects on health							
Type-2 diabetes	'A progressive condition, in which the body becomes resistant to the norma							
		r gradually loses the capacity	to produce enough insulin					
	in the pancreas.'5							
Metabolic syndrome A cluster of metabolic dysfunctions including dyslipidemia, hyp								
	hyperglycemia, abdominal/central obesity, and/or insulin resistance. A number							
	of differing definitions exist as determined by the World Health Organisation							
	and other organisations. 6, 7							
Dyslipidemia	An abnormal quantity of lipids (including triglycerides and cholesterols) in							
	blood							
Glucose intolerance	_	els reported during a gluco	·					
	determines the capacity of an individual to maintain glucose hom							
	Blood glucose levels are measured in fasted individuals before and following							
	challenge with glucose.							
Hyperglycemia	Excessive glucose in blood							
Hypertension	Elevated blood pressure (can be diastolic (pressure in arteries when the heart							
		tions) and/or systolic (pressui	re in arteries during heart					
	contraction))							
Insulin resistance	A state in which cells fail to respond to the normal actions of insulin							
Liver steatosis	A reversible condition in which large vacuoles of lipids (e.g. triglyceride) accumulate in liver cells							
	S							

Solar radiation is composed of a spectrum of light spanning from infrared (>800 nm) over visible (400-800 nm) to ultraviolet (UV); the latter is divided into UVA (315-400 nm), UVB (290-315 nm) and UVC (100-290 nm) wavelengths. UVC is blocked by

gases in the stratosphere, such that only UVA and UVB radiation reach Earth's surface. UV radiation (UVR) has a range of biological effects, some harmful and others beneficial.⁸ Many of the reported benefits of UVR are assumed to be due to the synthesis and activity of vitamin D (Figure 1).

UVR triggers the release or formation of a variety of biological mediators, including nitric oxide (Figure 2) and α -melanocyte-stimulating hormone (Figure 3), which may also have effects on health. Below we review the experimental pre-clinical findings, observational studies in humans and the results of clinical trials that relate to the links between UVR and the development of obesity and the potential of UVR exposure as a means to treat signs of obesity, type-2 diabetes and the metabolic syndrome.

1 Experimental studies on the effects of exposure to UVR in rodents. Only a few preclinical studies have tested the potential of UVR to affect the development of obesity and metabolic dysfunction. We reported a protective effect of ongoing exposure (twice a week) to sub-erythemal UVR in controlling weight gain and type-2 diabetes in C57Bl/6 mice fed a high fat diet. UV-irradiated mice had reduced weight gain, and diminished signs of metabolic dysfunction including lower fasting glucose and insulin levels, improved glucose tolerance, reduced insulin resistance and less liver steatosis compared to sham-irradiated (control, see below) mice. 9 A higher erythemal dose administered once a fortnight had a more potent effect on these outcomes, and also suppressed elevated levels of fasting leptin levels (indicative of suppression of leptin resistance) as well as reducing circulating levels of LDL- and total cholesterol.9 These results suggest that there may be dose-dependent effects of exposure to UVR. To control for any stress effects of ongoing treatments, control mice were 'sham-irradiated' by housing them in same fashion (in Perspex boxes) under normal fluorescent lights, for the same time as mice treated with UVR. In other similar studies, Nakano et al (2011) administered a choline-deficient and iron-supplemented L-amino acid-defined (CDAA) diet to Lewis rats and examined the effects of phototherapy on the development of non-alcoholic steatohepatitis. 10 The phototherapy reduced both circulating and liver triglyceride levels as well as fasting insulin and leptin levels, but did not reduce weight gain. 10 Artificial lamps containing UVR were used to administer this phototherapy daily for 12 h a day for up to 12 weeks; the spectrum of light emitted by the lamps and the dose, were not defined. We exposed mice to suberythemal UVR twice a week from an artificial light source (FS40 sunlamps) that mainly emitted UVB radiation (~65%) for up to 12 weeks. UVR was administered from when mice started eating the high fat diet. Taken together, these studies support a beneficial effect for UVR in reducing signs of obesity and metabolic dysfunction; however, further pre-clinical investigations are required, using a range of rodent strains to better define these effects, and examining whether exposure to UVR modifies behaviours that contribute towards the development of obesity (such as food intake or physical activity) to better understand the mechanism(s) involved.

1.1 Vitamin D-dependent effects. Nakano et al suggested that their UVR-emitting light therapy acted through a vitamin D-dependent pathway to suppress signs of metabolic disturbance. The phototherapy not only increased circulating 25(OH)D and 1,25(OH)₂D levels in Lewis rats fed a CDAA diet, but also reduced signs of insulin and leptin resistance. The CDAA diet alone reduced the concentrations of these vitamin D metabolites to 20-30% of their original levels. Thus while the effects of UVR observed by Nakano et al may have been mediated by vitamin D, a direct causal link was not demonstrated.

When considered together, studies using animal models present a confusing picture as to whether dietary vitamin D modulates signs of obesity, metabolic syndrome and type-2 diabetes and – if so – in which direction (Table 2). High dose dietary vitamin D₃ (15,000 IU/kg) reduced weight gain and improved glucose homeostasis in C57Bl/6 mice fed a high fat diet for 10 weeks, compared to those fed a diet containing low dose vitamin D₃ (1,500 IU/kg).¹¹ Dietary vitamin D₃ was also protective in a similar model, with reduced circulating glucose levels (fasting), glucose intolerance and insulin resistance when compared to results obtained from mice fed a vitamin D₃-deficient diet.¹² However, C57Bl/6 or PTEN^{+/-} (female) mice fed a standard (normal) fat diet with a very high vitamin D₃ content (25,000 IU/kg) had increased weight gain compared to mice fed a diet containing standard quantities of vitamin D₃ (1,800 IU/kg).¹³ This contrary result could be explained by a differing capacity of female mice¹³ to respond to dietary vitamin D (as compared to the results obtained using male mice described above^{11, 12}). Other studies suggest that there are multiple sex differences in the way that male and female mice respond to dietary vitamin D. Our

own work suggests that serum levels of 25(OH)D are reduced in BALB/c male mice (as compared to female mice) fed a vitamin D-supplemented diet. Increased *Acinetobacter* operational taxonomic units were observed in the lungs of female mice fed a vitamin D-supplemented diet, compared to male mice, while dietary vitamin D reduced the bacterial load and lung inflammation observed in male (but not female) mice with allergic airway disease (asthma). A discussion of the potential for vitamin D supplementation to induce weight loss in a sex-specific fashion in humans is below (Section 3.3).

In other studies, we observed no significant effect of lower doses of dietary vitamin D₃ (2,280 IU/kg) on weight gain, white adipose tissue accumulation, circulating triglyceride and cholesterol levels and the degree of glucose intolerance or insulin resistance measured in C57Bl/6 (male) mice fed a high (or low) fat diet compared to mice fed a diet not supplemented with vitamin D₃. Similarly, feeding 10,000 IU vitamin D₃/kg to LDL-receptor^{-/-} mice for 8 weeks had no effect on weight loss or plasma triglyceride and cholesterol levels²⁰ and lower doses of dietary vitamin D₃ (≤1,000 IU/kg) had limited effects on these measures compared to diets containing very low or no dietary vitamin D₃. ^{21, 22} In one study, a vitamin D₃-low diet (25 IU/kg) had a protective effect, reducing weight gain, food intake, and signs of glucose intolerance, insulin resistance and hepatic steatosis in comparison to Institute for Cancer Research (ICR) mice fed a diet with higher vitamin D₃ content (1,000 IU/kg). 23 Other studies have found that the effects of vitamin D₃ on glucose tolerance are dependent on the age of the mice tested, where vitamin D₃ (10 ng/kg), administered with glucose orally as part of a glucose tolerance test, significantly suppressed signs of glucose intolerance and increased blood insulin in 30-34 week-old but not 12-14 week-old BALB/c mice.²⁴ Differences in the genetic background (mouse strain), sex, age and other experimental inconsistencies may explain these discrepant findings.

Table 2. Pre-clinical rodent studies examining the effects of dietary vitamin D on excessive weight gain and signs of type-2 diabetes or metabolic syndrome.

Rodent strain	Sex	Fat content (% energy as fat)	Time fed diet	Dietary vitamin D ₃ (IU/kg)	Observations	Ref
C57Bl/6J mice	male	High fat (45%)	10 weeks	15,000 1,500	• 15,000 IU/kg diet increased circulating 25(OH)D, reduced weight gain, fasting glucose and insulin	11
C57Bl/6 mice	male	Normal fat (23%)	8 weeks	Vitamin D-containing 0	Vitamin D-containing diet increased circulating 25(OH)D, reduced fasting glucose and insulin levels, insulin resistance and glucose intolerance	12
C57Bl/6 or PTEN ^{+/-} mice	female	Normal fat (18%) High fat (58%)	24 weeks	25,000 1,500	 25,000 IU/kg diet increased weight gain in both strains when fed normal fat diet Equivalent weight gain in both strains when fed high fat diet 	13
C57Bl/6J mice	male	Low fat (12%) High fat (53%)	12 weeks	2,280	 2,280 IU/kg diet increased circulating 25(OH)D but no effect on weight gain, white adipose tissue weight, lipids, glucose intolerance or insulin resistance High fat diet increased circulating 25(OH)D compared to low fat diet 	9
LDLR -/- mice	male	Western (20% sucrose, 20% lard per kg diet)	16 weeks	10,000 1,000 50	• 10,000 IU/kg diet had greatest circulating 25(OH)D but had no effect on weight loss or plasma triglyceride and cholesterol levels	20
LDLR -/- or ApoE-/- mice	both	High fat (42%)	8-10 weeks	1,000	• 1,000 IU/kg had no effect on body weight or body fat, glucose or serum lipids	21

Sprague- Dawley rats	male	Low fat (10%) High fat (45%) with fructose in water	10 weeks	1,000 25	• 1,000 IU/kg had no effect on body weight or white adipose tissue levels but reduced serum triglyceride and leptin levels and insulin resistance	22
ICR mice	male	Low fat (10%) High fat (45%)	14 weeks	1,000 25	• 25 IU/kg reduced weight gain, food intake, glucose intolerance, insulin resistance and hepatic steatosis	23

ApoE = Apolipoprotein E; LDLR = Low density lipoprotein cholesterol receptor; ICR = Institute of Cancer Research

Far more consistent have been the effects of feeding or treating rodents with the active vitamin D metabolite, 1,25(OH)₂D, where reduced body weight gain, hepatic steatosis, visceral adipose tissue accumulation and triglyceride levels were observed in Sprague-Dawley rats²⁵ and BALB/c mice.²⁶ It is likely that 1,25(OH)₂D has more potent effects than other vitamin D metabolites because it is the most bioactive metabolite. Potential mechanisms through which 1,25(OH)₂D may modulate weight, include through pathways that prevent adipose tissue differentiation, and the impairment of the expression of enzymes involved in lipogenesis.²⁷ However, one caveat of the studies reported above^{25, 26} is that systemic calcium levels were not reported, and so the effects of 1,25(OH)₂D may have been due to hypercalcemia. Even so, subcutaneous 1,25(OH)₂D reduced markers of lipolysis and insulin sensitivity in Wistar rats, without affecting serum calcium.²⁸ Other vitamin D metabolites were also effective at improving signs of obesity and metabolic dysfunction without inducing hypercalcemia in rodents, ^{29, 30} but had inconsistent effects on serum lipids and cholesterol levels. 25, 29, 31, 32 Interestingly, the VDR and the 1α-hydroxylase enzyme (encoded by the CYP27B1 gene) are important for lipogenesis and glucose metabolism as mice with a global knockout in either gene $(VDR^{-/-} \text{ or } CYP27B1^{-/-})$ had a lean phenotype³³⁻³⁵ with the $VDR^{-/-}$ mice also exhibiting reduced fasting glucose and insulin levels.³³ The VDR may also be important for mediating the progression of non-alcoholic fatty liver disease (NAFLD) and insulin resistance as reduced hepatic steatosis and triglyceride levels were observed in apoE^{-/-} VDR^{-/-} mice fed a high fat diet.³⁶ However, macrophage-specific deletion of VDR expression in mice induced insulin resistance and increased fasting glucose levels.³⁷ These observations suggest that the VDR and CYP27B1 have additional metabolic functions (along with their well-accepted roles in vitamin D biology).

1.2 Vitamin D-independent effects. Our studies show that ongoing or regular exposure to sub-erythemal UVR controlled the development of obesity and signs of type-2 diabetes in C57Bl/6 mice fed a high fat diet. Our observations were independent of a change in vitamin D status and, importantly, could not be reproduced by dietary vitamin D₃ supplementation. Instead, some of the beneficial effects of UVR, particularly in reducing fasting glucose levels and liver steatosis were dependent on skin release of

nitric oxide (Figure 2), as these protective effects of UVR were blocked by topical application of a nitric oxide scavenger (cPTIO).⁹ Nitric oxide is involved in the immunosuppression caused by skin exposure to UVR; inhibitors of nitric oxide prevented inflammation, DNA damage and migration of Langerhans cells usually induced by UVR exposure (reviewed in ³⁸). Below we discuss some of the evidence for the capacity of nitric oxide to prevent the development of obesity and signs of metabolic dysfunction from pre-clinical studies.

1.2.1 Nitric oxide-dependent effects. In addition to the protective effects of UVRinduced release of nitric oxide from storage forms in the skin (described above), repeated topical treatment of mice with a nitric oxide donor (S-nitrosopenicillamine; SNAP) reduced their body weights, visceral white adipose levels, and the degree of insulin resistance and hepatic steatosis when compared to control mice (treatment and control mice on identical high fat diets). A multitude of other animal experimentation studies have examined the effects of increasing or reducing nitric oxide, through various biological or chemical means, on the development of obesity and signs of metabolic dysfunction. Dietary supplementation with L-arginine, the natural substrate of nitric oxide synthase (NOS) and precursor of endogenous nitric oxide formation, increased circulating levels of nitric oxide metabolites such as nitrite and nitrate, 40 and improved insulin sensitivity and metabolic profiles, 40-44 reduced adiposity (reviewed by 42, 45, 46), increased energy expenditure 42 and improved liver function. 44 NOS inhibitors such as L-NAME (N^o nitro-L-arginine methyl ester), lowered endogenous nitric oxide production and reduced circulating levels of nitric oxide metabolites, 47, 48 but had inconsistent effects on the development of obesity and metabolic dysfunction. 47-51 eNOS-/- mice lack endothelial nitric oxide synthase (eNOS) activity, and have an impaired capacity to produce nitric oxide and its metabolites in the cardiovascular system.⁵² Besides being hypertensive, these mice have defective energy expenditure, increased white fat accumulation, exhibit insulin resistance and increased hepatic triglyceride levels.^{53, 54} Conversely, transgenic mice overexpressing **eNOS** (eNOS-TG mice) were resistant diet-induced obesity hyperinsulinemia.⁵⁵ A number of other studies suggest that treatment with nitric oxide, either administered as NO gas by inhalation or orally in the form of nitrate or nitrite (believed to be reduced, in part, to nitric oxide in vivo), prevented signs of cardiovascular disease, ischemia and arterial disease in animal models of chronic

tissue ischemia and ischemia-reperfusion cardiac injury (reviewed by ^{56, 57}). Mechanistic results obtained with nitrate suggested that the reversal of features of metabolic syndrome in eNOS^{-/-} mice might have been mediated by a modulation of mitochondrial function and energetics.^{58, 59} However, more recent data in rodent models demonstrated that nitrate administration, in doses that can be achieved through dietary supplementation, promotes the browning of white adipose tissue 60 and stimulates fatty acid oxidation in skeletal muscle via a mechanism involving the nitrate-nitrite-soluble guanylate cyclase-peroxisome proliferator activated receptor.⁶¹ Since nitrate has also been shown to increase the availability of L-arginine secondary to inhibition of arginase expression⁶² it remains unclear whether these metabolic effects are achieved via a reduction of nitrate to nitric oxide or by a nitrate-mediated enhancement of endogenous nitric oxide production. Further work is needed to investigate the effects of nitric oxide, nitrate and nitrite in pre-clinical models of obesity and metabolic dysfunction. Understanding the role of nitrate would seem to be important in this context as a short exposure of human healthy volunteers to UVA appears to be associated not only with the release of nitric oxide from storage forms in the skin⁶³ but also with a progressive lowering of circulating nitrate concentrations; the mechanistic basis for the latter has not been established but might be a consequence of a UVR-induced stimulated uptake of endogenous nitrate from blood into, for example, skeletal muscle and/or adipose tissue.

1.2.2 Other UVR-induced mediators. While UVR-induced nitric oxide was important for limiting fasting glucose and liver steatosis in our studies⁹, the mediator(s) responsible for other effects of low dose UVR on the development of obesity and signs of metabolic dysfunction are yet to be identified. Indeed, while we observed that the nitric oxide donor SNAP suppressed weight gain, white adipose tissue levels and insulin resistance, the nitric oxide scavenger cPTIO did not prevent the capacity of UVR to suppress these measures, suggesting that there are other UVR-mediators which exert similar effects to UVR-induced nitric oxide. Indeed, exposure to UVR results in the production and release of a multitude of biological mediators, many of which could have anti-obesogenic effects. One possible alternate mediator is α -melanocyte-stimulating hormone (α -MSH). Pro-opiomelanocortin (POMC)-expressing neurons release α -MSH upon activation with UVR (Figure 3).

Circulating levels of α -MSH increase in mice following skin or eye exposure to UVR. 65 A similar increase in plasma α-MSH levels between winter and summer has been reported in adult humans. ⁶⁶ Pre-clinical studies suggest that α-MSH may prevent obesity by inhibiting feeding and enhancing catabolic signals to promote energy consumption through melanocortin-3 and -4 receptors (reviewed by ⁶⁷). Suberythemal UVB irradiation also increases the expression of α-MSH and melanocortin-4 receptor (MC4R) in the arcuate nucleus of the hypothalamus of C57Bl/6 mice.⁶⁸ Skin but not eye exposure to UVR induced these effects. Further studies are needed to determine if there is a causal role for UVR-induced α-MSH and other mediators in preventing signs of obesity and metabolic dysfunction. An α-MSH homologue and MC4R agonist, RM-493, was recently awarded 'orphan drug status' by the US Food and Drug Administration, for the treatment of the rare condition, Prader-Willi syndrome, which causes obsessive eating and obesity. Short-term (72 h) subcutaneous infusion with RM-493 (1 mg/day) also increased energy expenditure in obese adults.⁶⁹ However, sub-cutaneous treatment of overweight-to-obese men with another MC4R agonist, MC4-NN2-0453, had no effect on weight loss and induced a significant number of adverse events including skin problems (benign melanocytic nevus and pigmentation), headache and sexual dysfunction, which resulted in termination of the trial.70

- **Evidence from observational studies in humans.** Below we summarise the results of a limited number of observational studies in humans, some of which examined the associations of proxies of sun exposure, including latitude, altitude and season on obesity and signs of type-2 diabetes and/or metabolic syndrome. It is important to note that studies of latitude, altitude and season may be confounded by genetic, cultural and other environmental factors that could explain the associations (or lack thereof) discussed below.
- **2.1** Latitude gradients. Positive latitude (distance from the equator) gradients are commonly used as a surrogate for reduced exposure to terrestrial UVR. Reduced serum triglyceride levels were observed in those living closer to the equator (Spain) compared to more northerly populations in Iceland and Ireland who participated in a weight loss dietary intervention study. The incidence of diabetes (mainly type-2) was affected by latitude in Canadian Inuit indigenous people, with the incidence decreasing with

increasing latitude north of the equator⁷² in a direction opposite to that observed by a previous study⁷¹. Further studies are required to examine the nature of the relationships between latitude and obesity, type-2 diabetes and metabolic syndrome.

- Altitude effects. Terrestrial UVB radiation increases in a linear fashion with 2.2 altitude. 73 A reduced risk of diabetes was observed in Americans (n>250,000) living at higher latitudes.⁷⁴ This study also reported reduced odds of obesity in men living at altitudes \geq 1500 m compared to \leq 500 m above sea level. ⁷⁴ Military personnel (n>98,000, >90% male) assigned to duty in higher altitude locations (>1.96 m above sea level) had reduced odds of being obese compared to those living at locations <0.98 m altitude, although this was not adjusted for physical activity. 75 Similar findings are reported in a number of other studies (reviewed in ⁷⁶). Increased altitude may also reduce fasting glucose levels and improve glucose tolerance (reviewed by ^{74, 76}). The most likely explanation of these observations is thought to be increased hypoxia (reduced atmospheric oxygen levels) 76,77, with less recognition for other environmental effects of increased altitude, such as greater UVR. Conversely, there are reports of dyslipidemia and increased cardiovascular disease risk at higher altitudes. ⁷⁶ It is difficult to tease out the specific effects of UVR by examining altitude, with a number of environmental changes (hypoxia, increased UVR, cold) as well as genetic and cultural differences between populations living at low and high altitudes.
- 2.3 Seasonal effects. A number of studies have reported seasonal changes in obesity and signs of type-2 diabetes. An increased odds for obesity (as determined through skin-fold measurement) was observed for winter data collection for 7119 children from the National Health Examination Survey (Cycle II, 1964-65; USA), compared to summer. Increased BMI, and abdominal obesity were also observed in Danish adults (n=17,824) in winter compared to summer (1993-1997). Total energy expenditure was greater in spring than autumn for Caucasian children from the USA. Winter increases in body fat, plasma HbA1c (glycated haemoglobin, a marker of average blood glucose levels) and insulin resistance were observed in Japanese patients with insulin-treated type-2 diabetes. Most studies have found that the incidence of type-2 diabetes is lowest in summer, with a concurrent nadir in fasting glucose; however, evidence around the seasonal effects on insulin secretion and sensitivity is inconclusive (reviewed by 83).

- 2.4 Populations with intentional or excessive sun exposure. Other observational studies in humans mainly suggest a protective effect of higher sun or UVR exposure in reducing the risk of obesity and metabolic disease. Swedish women (n=24,098, MISS Study), who had active sunbathing habits, or who used sun beds had a reduced risk of type-2 diabetes, 84 thromboembolic events (which usually peak in winter 85) and allcause mortality⁸⁶ after adjusting for exercise and other confounders. Other studies have assessed the nature of the associations between obesity and outcomes of excessive sun exposure like skin cancer. Obesity was associated with a reduced risk of squamous cell carcinoma (women only) and basal cell carcinoma (either sex) when adjusted for physical activity in >170,000 adult Americans. 87 Similar observations were made in post-menopausal women of the Women's Health Initiative study (n=93,676).⁸⁸ However, in a cross-sectional study of Korean adults (n=17,476; KNHANES) increased systolic blood pressure and risk of diabetes was observed in those obtaining >5 h/day of sun exposure. 89 In the same study, men who received >5 h/day of sun exposure (compared to <2h/day) had reduced body fat percentages, but increased waist circumference and reduced beta cell function, while women exposed to >5 h/day (compared to <2h/day) of sunlight had increased waist circumference and risk of type-2 diabetes. 89 A caveat of these observations was that those with >5 h/day sun exposure were older, more likely to be smokers and drink alcohol, and less likely to have a college education, ⁸⁹ perhaps indicating that unhealthy behaviours and eating habits were associated with high levels of sun exposure in this population. Additionally, in a small cross-sectional study (n=307) of Indian men (aged 40-60 years, mainly type V skin), there was no significant relationship between increasing daily sun exposure and BMI, body fat proportions, circulating triglyceride levels, and fasting blood sugar levels. 90 Clearly, more studies examining the associations between sun exposure and adiposity are necessary, particularly those that focus on longitudinal relationships, controlling for potential confounding factors, and considering differences in skin type, which may modify the capacity of sun exposure to modulate metabolic dysfunction.
- 2.5 Social stigma effects of obesity and sun exposure. The social stigma surrounding obesity is a barrier that may prevent the effective treatment of many overweight and obese people with cardiometabolic dysfunction. Indeed, stigma may alter sun exposure behaviours in obese people. In a cross-sectional study of Estonian adults, those who avoided the sun and exposed less of their skin to sunlight had

increased body fat and BMI compared to those who exposed their whole body to sunlight.⁹¹ There may be deeper cultural issues (perhaps relating to stigma) that reduce sun exposure in obese people. Other studies report unaltered sun exposure habits in terms of time spent in sun or amount of skin exposed to sunlight with increasing body fat,⁹² or unchanged sun protection practises in those with obesity.⁹³ These populations were from Universities located in USA⁹² and Turkey;⁹³ countries with greater rates of obesity than Estonia,¹ and possibly different social norms around the acceptable behaviours of people with obesity.

- 2.6 Obesity, UVR and circulating 25(OH)D. Many studies have detailed an inverse correlation between BMI and circulating 25(OH)D.^{27, 94} However, the nature of this association is unclear. Results from a bi-directional Mendelian randomisation analysis suggested that obesity caused vitamin D deficiency. 95 There may be increased capacity for vitamin D to be stored in fat deposits during obesity.²⁷ Reduced bioavailability of circulating 25(OH)D has been observed post-dietary supplementation of obese individuals with vitamin D₂.96 Others suggest a dilution effect of increased body volume for reduced circulating 25(OH)D.⁹⁷ There is also the possibility that reduced circulating 25(OH)D levels could be caused by sun aversion or impaired capacity to increase serum 25(OH)D following sun exposure in obese people. Indeed, increases in serum vitamin D₃ or 25(OH)D following skin exposure to UVB radiation were inversely related to BMI. 96, 98 However, other studies report a positive relationship between weight or BMI and the change in 25(OH)D induced by UVR. 99 Prodam et al found that 25(OH)D levels were associated with season, and UVR exposure (or UV index) 1 or 3 months before serum sampling, with the strongest association at 3 months. 100 Higher circulating lipid levels were associated with lower 25(OH)D in obese children and adolescents, and the strength of this association was dependent on the estimated extent of UVR exposure (or UV index) 3 months before measurement of 25(OH)D levels. 100 Clearly, disentangling the effects of UVR from the effects of UVR-induced vitamin D can be very difficult in observational studies.
- 3 Clinical trials. While there are many ongoing and complete clinical trials that have assessed the efficacy of vitamin D supplementation to induce weight loss or

reduce signs of type-2 diabetes and metabolic syndrome, there have been far fewer examining the efficacy of UVR or sun exposure.

Controlled UVR exposure. Most studies reported to-date have examined the effects of exposure to UVR on blood pressure, with some protective effects observed. Indeed, whole body exposure to UVB radiation lowered blood pressure in hypertensive subjects by ~5 mmHg, ^{101, 102} but had no effect in normotensive adults. ^{102, 103} Acute exposure to sub-erythemal UVA radiation lowered blood pressure in healthy (normotensive) young adults. ^{63, 104} However, a lasting effect was not observed beyond the window of treatment. ^{63, 101, 103} These anti-hypertensive effects of UVA radiation were independent of a change in vitamin D status, and instead may have been dependent on the release of nitric oxide from preformed skin stores. ⁶³

Some protective effects of UVB on signs of type-2 diabetes have been reported. Two weeks of whole body treatments with erythemal UVB radiation (4 times) increased insulin secretion in healthy adults challenged with glucagon. However, narrow-band UVB therapy administered to patients with psoriasis did not affect body fat levels nor measures of insulin resistance. Other studies show that exposure to either solar-simulated or narrowband UVR reduced high-sensitivity C-reactive protein levels in healthy humans and patients with psoriasis. C-reactive protein is a pro-inflammatory mediator and acute-phase protein, and its expression is increased as part of the low-level inflammatory response observed during obesity. Cumulatively, these studies suggest a beneficial role for UVR exposure, although there may be differences in the capacity of certain individuals to respond that could be dependent on age, genetic background and/or UV irradiation exposure protocol. The possible suppressive effects of therapeutically delivered UVR on obesity and signs of type-2 diabetes are worthy of more in-depth investigation.

3.2 Sun exposure trials. In a 12-month intervention, the incidence of metabolic syndrome was tracked in 69 non-diabetic overweight adults from Saudi Arabia, who were advised to regularly expose themselves to sunlight and to eat more vitamin Drich foods. Serum HDL-cholesterol levels increased after 6 months of the intervention, with reduced incidence of metabolic syndrome in the intervention arm at the study end. The effects of the sun exposure and dietary intervention on outdoor

activity levels were not reported. Further studies examining the effects of sun exposure, with an increased number of participants are necessary to better understand the impact of sun exposure per se on modulating signs of metabolic syndrome and its incidence.

- 3.3 Vitamin D supplementation. Recent meta-analyses report no consistent effects of vitamin D supplementation on adiposity measures, 94, 110 abnormal insulin and glucose metabolism, 94, 111-113 and signs or prevalence of type-2 diabetes. 94 Subgroup analyses of those who were initially-vitamin D deficient (25(OH)D <50 nM) suggest that there may be small benefits for these participants, with vitamin D supplementation reducing signs of insulin resistance and glucose intolerance. 112 Issues around the lack of efficacy of vitamin D supplementation could include a genuine lack of biological effect, small sample sizes, non-deficient baseline vitamin D status, accurate measurement of adiposity, the dose and scheduling of supplementation, and whether supplementation may be beneficial for some sub-groups only (based on genotype, age or other factors). It is possible that circulating concentrations of 25(OH)D are a biomarker of exposure to sunlight, and do not actively contribute to (cardio)metabolic regulation ¹¹⁴. As discussed above, animal studies suggest that there may be sex differences in the capacity of vitamin D supplementation to modulate weight gain 11, 1213. Many of the trials examining the effects of vitamin D on weight loss, were mainly or entirely composed of women, and so the potential for vitamin D to induce weight loss in men is unclear.¹⁹
- *Increasing nitric oxide bioactivity.* There are very few clinical trials that have directly examined the capacity of nitric oxide to modulate obesity and metabolic dysfunction. This may be due to concerns around the potential oncogenic effects of excessive dietary intake of nitrite and nitrate through the production and activities of *N*-nitroso compounds. However, the evidence available suggests that increasing the bioavailability of nitric oxide may be beneficial. Dietary supplementation of adult participants with cardiovascular risk factors (including obesity, hyperlipidemia and diabetes, n=30) with a nitrate-rich supplement (Neo40) twice a day for 30 days reduced circulating triglyceride levels. In premenopausal women with central obesity (n=84), six weeks of treatment with L-arginine (5 g/day) reduced waist circumferences. Finally, in a 21-day dietary and exercise intervention with type-2

diabetics (n=32), L-arginine supplementation (8.3 g/day) had positive effects in addition to the lifestyle intervention, further reducing fat mass and waist circumference, blood pressure (diastolic and systolic), fasting insulin and fructosamine levels. 118

4 **Conclusion.** Here we have discussed the evidence around the potential of regular exposure to sunlight or UVR to affect the development of obesity and signs of metabolic dysfunction. Rodent studies suggest that ongoing exposure may be suppressive through vitamin D- and nitric oxide-dependent pathways. Although not addressed here, other radiation emitted as part of the solar light spectrum may also be important. There are known links between blue light and melatonin for reducing signs of obesity, type-2 diabetes and cardiometabolic dysfunction, 119 but information about specific signalling pathways involved in UVR-associated metabolic effects are scarce. Whether or not the effects of UVR on metabolic health are additionally influenced by the composition of the gut microbiome is similarly unclear. More evidence on the suppressive capacity of UVR exposure for curbing obesity and metabolic dysfunction from human studies is needed. In future studies a greater emphasis should be placed on measuring sun exposure directly (by using dosimeters and questionnaires) rather than relying on proxies such as season, altitude and latitude. Finally, there is a need for (larger) clinical trials assessing whether therapeutically administered UVR (e.g. narrowband UVB or UVA) or safe sun exposure are effective for weight loss or reducing signs of adiposity and metabolic dysfunction in different populations of overweight or obese people.

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Figure legends

Figure 1. The vitamin D synthesis pathway. Vitamin D is synthesised following conversion of 7-dehydrocholesterol (7-DHC) into pre-vitamin D following exposure of 7-DHC-containing keratinocytes to UVB radiation. With heat, pre-vitamin D is further isomerised into vitamin D. Vitamin D is transported in the blood (or in chylomicrons for ingested vitamin D, e.g. from oily fish) to the liver where it undergoes hydroxylation, to form 25-hydroxyvitamin D (25(OH)D). A further hydroxylation step is required to convert it into the bioactive form, 1,25-dihydroxyvitamin (1,25(OH)₂D). This occurs through 1α -hydroxylases expressed by proximal tubule cells of the kidneys, or other cells throughout the body, such as disease-activated macrophages. Circulating vitamin D metabolites are largely bound to vitamin D binding protein (VDBP), with a smaller fraction bound to albumin or 'free' in the blood plasma. $1,25(OH)_2D$ exerts many of its biological effects by interacting with the nuclear vitamin D receptor (VDR), regulating gene transcription. Alternatively, $1,25(OH)_2D$ rapidly acts through membrane-bound (non-genomic) receptors (R) which activate signalling cascades that also regulate gene transcription and have other effects.

Figure 2. Skin release of nitric oxide activity by ultraviolet radiation. Both skin and dermal vasculature contain significant stores of nitric oxide that can be mobilised by exposure to ultraviolet (UV) radiation, increasing systemic nitric oxide availability and plasma/serum levels of nitric oxide metabolites such as nitrite.³⁹

Figure 3. Skin and eye exposure to ultraviolet radiation induces α -melanocyte-stimulating hormone (α -MSH). Exposure of either skin or eyes to ultraviolet (UV) radiation increases circulating levels of α -MSH levels. Skin exposure also increases α -MSH levels in the arcuate nucleus of the hypothalamus. α -MSH is a polypeptide product of pro-opiomelanocortin (POMC), which is produced by nerves. Increased levels of the melanocortin receptor-4 (MC4R) have also been reported in the hypothalamus of irradiated mice.

Fig. 1

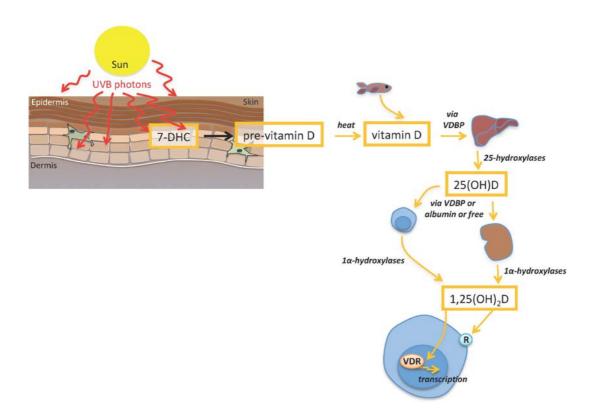


Fig. 2

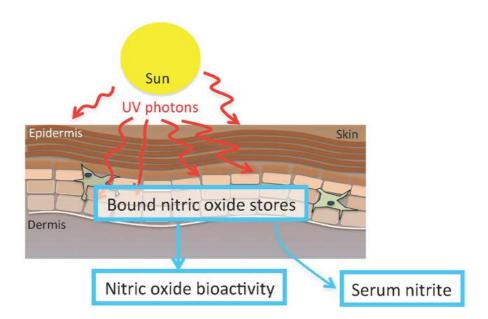


Fig. 3

