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Sunlight Has Cardiovascular Benefits Independently of Vitamin D

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Key Words
Ultraviolet · Skin · Nitric oxide · Blood pressure · Nitrate · Vitamin D · Sunlight · Cardiovascular

Abstract
Background: High blood pressure (BP) is the leading risk factor for disability adjusted life years lost globally. Epidemiological data show a correlation between increased sun exposure and reduced population BP and cardiovascular mortality. Individuals with high serum vitamin D levels are at reduced risk of hypertension, cardiovascular disease and metabolic syndrome, yet multiple trial data show that oral vitamin D supplementation has no effect on these endpoints. Sunlight is a risk factor for skin cancers, but no link has been shown with increased all-cause mortality. Cohort studies from Scandinavia show a dose-dependent fall in mortality with increased sun-seeking behaviour. Skin contains significant stores of nitrogen oxides, which can be converted to NO by UV radiation and exported to the systemic circulation. Human studies show that this pathway can cause arterial vasodilatation and reduced BP. Murine studies suggest the same mechanism may reduce metabolic syndrome. ***Summary:*** Sunlight has beneficial effects on cardiovascular risk factors independently of vitamin D. ***Key Messages:*** All-cause mortality should be the primary determinant of public health messages. Sunlight is a risk factor for skin cancer, but sun avoidance may carry more of a cost than benefit for overall good health.

The most recent data from the World Health Organisation's survey of the global burden of disease show that high blood pressure (BP) is the leading cause of premature death and disease worldwide [1]. This risk factor underlies stroke and coronary heart disease, which in combination have an age-standardised mortality of 237 per 100,000 in the United States [2]. Measures to control hypertension are thus of the greatest importance.

Epidemiology

Active management of hypertension with effective modern drugs has led to a fall in population BP within western economies. Plotting population BP in 1980 – before the availability and widespread use of effective pharmacological agents – against latitude, a clear correlation exists with around a quarter of variation in BP accountable for by latitude (fig. 1). This relationship persists when the data are stratified by country income level. Seasonal changes in BP are also well described, with individual BP being lower in summer than winter in temperate latitudes [3]. Around a quarter of cardiovascular mortality within Europe can be accounted for by latitude [4], and in a multicentre observational study of risk factors correlating with atherosclerosis, latitude was found to be the strongest predictor of carotid artery atheroma [5].

Biologically active vitamin D (1,25 di-hydroxy cholecalciferol) in man can be derived from the diet or syn-

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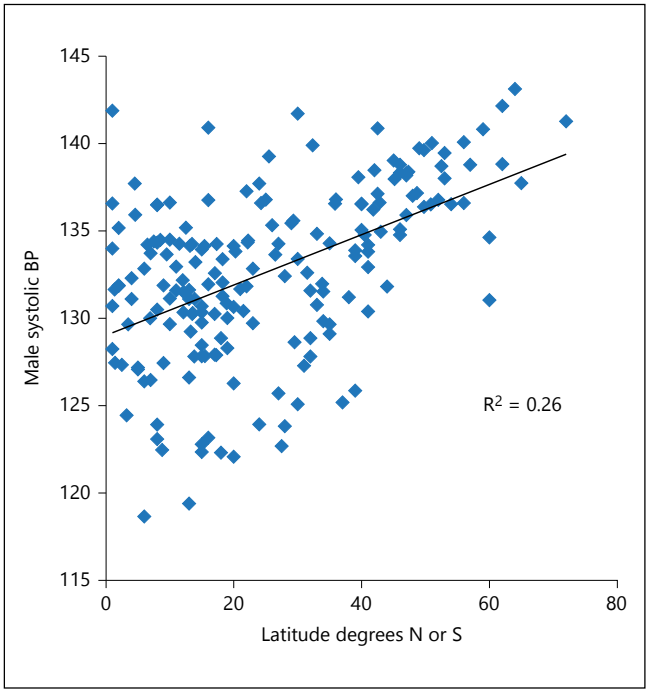

Fig. 1. Population BP correlates with latitude. Each point represents a country. Male systolic population BP is plotted against the latitude of the geographical mid-point of each country. BP values are from the MRC-HPA data in 1980.

thesised endogenously in a pathway dependent on UVB irradiation of the skin. Inadequate sun exposure with insufficient dietary intake can thus lead to deficiency (25(OH)D <20 ng/ml) and insufficiency (25(OH)D 20–29 ng/ml). Vitamin D receptors are expressed on most cell types, and they play a well-established role in skeletal metabolism. Additionally, in vitro mechanistic studies show vitamin D to have effects on cell differentiation and immune function [6]. Observational data from numerous large cohort studies, now summarised in several meta-analyses show that individuals with measured vitamin D levels in the lowest quartile have around twice the all-cause mortality of those in the upper quartile, and are more likely to have hypertension, cardiovascular disease, metabolic syndrome, and solid organ cancers [7–9]. Clinical trials of vitamin D supplementation have however shown that vitamin D is of no benefit in the prevention or treatment of hypertension, cardiovascular disease, cerebrovascular disease or metabolic syndrome, although it is important for bone health [8]. This is further supported by a recent Mendelian randomisation study, which showed that patients with genetic polymorphisms leading to lifelong reduced vitamin D levels have a higher standardised mortality and risk of solid organ cancer, but no difference in cardiovascular health [10].

These apparently conflicting observations may be explained by confounding; fit individuals, spending more time outside in the sun will synthesise more vitamin D, which is thus a marker for health. An alternative and non-exclusive explanation, consistent with the epidemiological data on latitude and season, is that sunlight, independently of vitamin D synthesis, has cardiovascular, cerebrovascular and metabolic benefits.

For almost a century, it has been known that the ultraviolet component of sunlight is a risk factor for skin cancer, and public health measures governing sun exposure have been largely determined by this. Skin cancer can be divided into 2 main types. Melanoma is due to malignant transformation of melanocytes. In all, 76,690 new cases occurred in 2013 in the United States with 9,480 deaths [11]. Non-melanoma skin cancer is much commoner and probably under-reported. Cases of NMSC outnumber all other cancer put together in the white-skinned populations, yet the mortality is exceedingly low [12]. Of the 2 main types of NMSC, basal cell cancers are the commonest and although they can be locally destructive if untreated, deaths are almost unknown. Squamous cell skin cancers are less common than BCC, but potentially more serious with a measurable mortality.

For the general white-skinned population, sunlight is the major preventable risk factor for skin cancers, but the pattern of sun exposure varies with cancer type. Intermittent sun exposure and sunburn, particularly in childhood, increase the risk of melanoma, whereas chronic occupational exposure may be protective [13]. Squamous cell skin cancer by contrast is predisposed in a dose-dependent fashion by chronic sun exposure. Immunosuppression particularly increases the risk of developing SCC, a link first made in patients who had undergone renal transplantation, with subsequent immunosuppression. SCCs in the immunosuppressed are clinically harder to diagnose than in the immunocompetent and are more likely to metastasise. Advice on sun avoidance is thus particularly important to renal allograft recipients, and these patients require regular screening, and a high index of suspicion from their dermatologist [14].

Skin cancers can be used as a proxy measure for lifetime sun exposure. A case–control study of 4.4 million Danish patients over the age of 40, showed that NMSC patients had a multi-factorially corrected OR of 0.97 (0.96–0.99) for all-cause mortality compared to age- and sex-matched 'healthy' controls. The reduction in cardio-

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vascular disease was greater, with an OR of 0.90 (0.88–0.92) for incident myocardial infarction [15, 16].

Prospective cohort studies are less prone to confounding and bias than case–control studies. Two Scandinavian studies, initiated in the early 1990s, have provided valuable information on sun exposure and all-cause mortality. In the Swedish Women's Lifestyle and Health cohort study, increased sun exposure, as recorded by the number of weeks spent on sun-bathing holidays, predicted reduced all-cause mortality 25 years later [17] even at the expense of increased melanoma [18]. Subjects in the Melanoma in Southern Sweden study were asked about sunbathing, sun-seeking holidays in summer, sun-seeking holidays in winter, and use of sunbeds to give a sun-exposure score of 0–4. Extensive adjustment for possible confounders was made, and subjects were re-polled 25 years after enrolment. Dose dependently, the higher the sun-seeking behaviour, the lower the all-cause mortality, with those scoring 4 having half the mortality of sun-avoiders. Extrapolating from these data, the authors calculate that 3% of deaths in Sweden can be accounted for by inadequate sun.

Scandinavian data on sunlight and all-cause mortality may not be generally applicable. A similar prospective design of study in the United States, the NIH-AARP Diet and Health Study, showed a small increase in mortality in those who had lived in the most insolated areas [19], although it showed no increase in the number of skin cancer deaths. The study did not measure individual sun exposure, but instead calculated environmental sun exposure based on the residence of the individual at the time of enrolment. It may be that higher levels of sun exposure than those experienced by north Europeans are unhealthy, or alternatively that individuals living in the sunniest areas adopt lifestyles that avoid the sun [20].

The balance of epidemiological and observational data thus suggests that sunlight exposure can reduce all-cause mortality, and has particular benefits on hypertension and cardiovascular disease. These benefits are at the cost of increasing the risk of skin cancer incidence, although the overall benefits outweigh the risks as demonstrated by dose-dependent reductions in all-cause mortality with increased sun exposure. Importantly, vitamin D is not solely responsible for these proposed health benefits of sunshine. Supplementation with oral vitamin D is not adequate to reduce cardiovascular disease. Alternative mechanisms must exist to account for these benefits of sunlight.

Nitric oxide has a wide range of roles, but the first described was as a vasodilator, synthesised by the actions of one of the family of 3 nitric oxide synthase (NOS) enzymes on L-arginine. NO has a half-life of a few seconds before being oxidised to nitrite (NO_2^-), which itself has biological actions, particularly in conditions of hypoxia and low pH, where it can be reduced to NO. Nitrite is further oxidised to nitrate (NO_3) and this was considered the inert end product of NO until recently. The dermis and epidermis contain significant stores of nitrogen oxides particularly nitrate, the quantity of which is about 10 times as much as in the total vascular space [21].

Although nitrate has been considered to be biologically inactive, it is now apparent that an alternative mechanism of NO synthesis involves sequential reduction of nitrate to nitrite and then NO [22]. This occurs on the skin surface, where nitrate-reducing bacteria generate nitrite from sweat nitrite. The nitrite in turn is reduced to NO in the slightly acidic conditions of the skin surface [23]. Bacterial nitrate reductases allow the use of nitrate as an electron acceptor in respiration in the absence of oxygen. Nitrate reductase enzymes have also been described in mammalian tissues [24]. Photochemical reduction of nitrate also occurs with ultraviolet wavelengths, and is enhanced in the presence of thiols [25]. Thiol-rich cysteine is a major component of keratins, the key structural components of skin.

Human skin brings together nitrate, thiols, environmental ultraviolet radiation, and a rich dermal vascular plexus giving access to the systemic circulation. Irradiation of healthy human volunteers with physiologically relevant doses of ultraviolet A radiation (which does not synthesise vitamin D) produces a fall in systemic BP and rise in heart rate, independently of temperature change, and concurrent with a rise in circulating nitrite (a marker for NO levels) and fall in nitrate [26, 27]. Forearm plethysmography studies in which UVA irradiation of the arm occurs simultaneously with intra-brachial artery infusion of a NOS antagonist, show arterial vasodilatation, confirming that this effect is independent of NOS [26].

While these human in vivo studies are recent, the observation that sunlight and ultraviolet could directly dilate the arterial vasculature was made by Robert Furchgott almost 40 years before his Nobel prize for the discovery that 'endothelium derived relaxant factor' was NO. Following a chance observation in the laboratory where organ baths were intermittently exposed to daylight on a cloudy day, he showed that isolated arterial smooth muscle from which the endothelium had been removed dilated in response to ultraviolet radiation [28]. The absence of endothelium in these experiments differentiated these results from his later classic Nobel Prize–winning work, where he demonstrated an acetyl choline–driven

release of a diffusible vasodilator from endothelial cells. The mechanism of NO synthesis differs in these 2 experimental set ups, but NO is the active mediator in both [29].

UV-induced release of NO from the skin may have more widespread cardiovascular actions than BP reduction. Oral nitrate reduces oxygen cost during exercise [30] due to an improvement in mitochondrial efficiency [31]. We have shown that the combination of UVA irradiation and oral nitrate supplementation produces an additive improvement in exercise performance with reduced oxygen demand in elite cyclists [32].

Metabolic syndrome and type 2 diabetes have a lower prevalence in summer than in winter. In a mouse model of diabetes, mice fed with a high-fat diet developed weight gain, impaired glucose and insulin tolerance, fatty livers, and gonadal fat deposition [33]. Irradiation of the mouse with a sub-erythemal dose of UV twice weekly reduced weight gain and development of markers of metabolic syndrome, but addition of oral vitamin D supplementation had no effect. Applying a topical NO donor to the dorsal skin of the mice reproduced the effects of UV, and treating the mice with an NO scavenger on the back blocked the beneficial effects of the UV [33].

Ultraviolet therapy might well have a therapeutic role beyond the treatment of skin disease. It should be avoided in those with particular risk factors, such as the immunosuppressed transplant patient, but as a non-pharmacological intervention it has several potential benefits. Hypertension, metabolic syndrome and diabetes are three of the major morbidities of our age. The mechanistic and early trial data I have outlined suggest that these may be amenable to a form of phototherapy. Hypertension is clearly a risk factor that must be treated. In patients with impaired renal function, pharmacological choices are reduced and phototherapy offers potential as an adjunctive therapy. The reduced oxygen demand demonstrated in athletes treated with UVA and nitrate supplementation suggests benefit in patients with heart failure and other conditions where oxygen delivery is compromised.

Public health advice on sunlight exposure is at the crossroads. Almost a century of data has confirmed the carcinogenic effects of UV radiation on the skin, and delineated the mechanisms by which this occurs. There is however a remarkable absence of any evidence that UV reduces lifespan, in sharp contrast to other risk factors (e.g. hypertension, smoking, alcohol) on which we advise. A substantial body of evidence shows that sunlight has health benefits and that these are independent of vitamin D and thus cannot be reproduced by oral supplementation. The UV-induced reduction of cutaneous nitrate and its export to the systemic vasculature, which I have helped delineate, is an additional mechanism by which sunlight may exert beneficial effects on health, but other mechanisms surely exist. All-cause mortality and its reduction should be the primary aim of physicians, not the narrow avoidance of skin cancer.

Disclosure Statement

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References

1 Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, Naghavi M, Salomon JA, Shibuya K, Vos T, Wikler D, Lopez AD: GBD 2010: design, definitions, and metrics. Lancet 2012;380:2063–2066.
2 Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB: Heart disease and stroke statistics – 2013 update: a report from the American heart association. Circulation 2013;127:e6–e245.
3 Brennan PJ, Greenberg G, Miall WE, Thompson SG: Seasonal variation in arterial blood pressure. Br Med J (Clin Res Ed) 1982;285:919–923.
4 Zittermann A: Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol 2006;92:39–48.
5 Baldassarre D, Nyyssönen K, Rauramaa R, de Faire U, Hamsten A, Smit AJ, Mannarino E, Humphries SE, Giral P, Grossi E, Veglia F, Paoletti R, Tremoli E: Cross-sectional analysis of baseline data to identify the major determinants of carotid intima-media thickness in a European population: the IMPROVE study. Eur Heart J 2010;31:614–622.
6 Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, Murad MH, Kovacs CS: The nonskeletal effects of vitamin D: an endocrine society scientific statement. Endocr Rev 2012;33:456–492.
7 Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP: Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014;348:g2035.
8 Bolland MJ, Grey A, Gamble GD, Reid IR: The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol 2014;2:307–320.
9 Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM: Systematic review: vitamin D and cardiometabolic outcomes. Ann Intern Med 2010;152:307–314.

10 Afzal S, Brøndum-Jacobsen P, Bojesen SE, Nordestgaard BG: Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. BMJ 2014;349:g6330.
11 Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
12 Lomas A, Leonardi-Bee J, Bath-Hextall F: A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069–1080.
13 Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, Melchi CF: Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41:45–60.
14 Tessari G, Girolomoni G: Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors, and management. Dermatol Surg 2012;38:1622–1630.
15 Brøndum-Jacobsen P, Nordestgaard BG, Nielsen SF, Benn M: Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. Int J Epidemiol 2013;42:1486–1496.
16 Weller RB: Skin cancer as a marker of sun exposure. Int J Epidemiol 2014;43:1991.
17 Yang L, Lof M, Veierød MB, Sandin S, Adami HO, Weiderpass E: Ultraviolet exposure and mortality among women in Sweden. Cancer Epidemiol Biomarkers Prev 2011;20:683–690.
18 Veierød MB, Adami HO, Lund E, Armstrong BK, Weiderpass E: Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. Cancer Epidemiol Biomarkers Prev 2010;19:111–120.
19 Lin SW, Wheeler DC, Park Y, Spriggs M, Hollenbeck AR, Freedman DM, Abnet CC: Prospective study of ultraviolet radiation exposure and mortality risk in the United States. Am J Epidemiol 2013;178:521–533.
20 van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, Eyles DW, Blizzard L, Dwyer T, Lucas R, Jones G: The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. Environ Health Perspect 2007;115:1132–1139.
21 Mowbray M, McLintock S, Weerakoon R, Lomatschinsky N, Jones S, Rossi AG, Weller RB: Enzyme-independent NO stores in human skin: quantification and influence of UV radiation. J Invest Dermatol 2009;129:834–842.
22 Lundberg JO, Gladwin MT, Ahluwalia A, Benjamin N, Bryan NS, Butler A, Cabrales P, Fago A, Feelisch M, Ford PC, Freeman BA, Frenneaux M, Friedman J, Kelm M, Kevil CG, Kim-Shapiro DB, Kozlov AV, Lancaster JR Jr, Lefer DJ, McColl K, McCurry K, Patel RP, Petersson J, Rassaf T, Reutov VP, Richter-Addo GB, Schechter A, Shiva S, Tsuchiya K, van Faassen EE, Webb AJ, Zuckerbraun BS, Zweier JL, Weitzberg E: Nitrate and nitrite in biology, nutrition and therapeutics. Nat Chem Biol 2009;5:865–869.
23 Weller R, Pattullo S, Smith L, Golden M, Ormerod A, Benjamin N: Nitric oxide is generated on the skin surface by reduction of sweat nitrate. J Invest Dermatol 1996;107:327–331.
24 Jansson EA, Huang L, Malkey R, Govoni M, Nihlén C, Olsson A, Stensdotter M, Petersson J, Holm L, Weitzberg E, Lundberg JO: A mammalian functional nitrate reductase that regulates nitrite and nitric oxide homeostasis. Nat Chem Biol 2008;4:411–417.
25 Dejam A, Kleinbongard P, Rassaf T, Hamada S, Gharini P, Rodriguez J, Feelisch M, Kelm M: Thiols enhance NO formation from nitrate photolysis. Free Radic Biol Med 2003;35:1551–1559.
26 Liu D, Fernandez BO, Hamilton A, Lang NN, Gallagher JM, Newby DE, Feelisch M, Weller RB: UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol 2014;134:1839–1846.
27 Opländer C, Volkmar CM, Paunel-Görgülü A, van Faassen EE, Heiss C, Kelm M, Halmer D, Mürtz M, Pallua N, Suschek CV: Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. Circ Res 2009;105:1031–1040.
28 Furchgott RF, Ehrreich SJ, Greenblatt E: The photoactivated relaxation of smooth muscle of rabbit aorta. J Gen Physiol 1961;44:499–519.
29 Rodriguez J, Maloney RE, Rassaf T, Bryan NS, Feelisch M: Chemical nature of nitric oxide storage forms in rat vascular tissue. Proc Natl Acad Sci U S A 2003;100:336–341.
30 Larsen FJ, Weitzberg E, Lundberg JO, Ekblom B: Effects of dietary nitrate on oxygen cost during exercise. Acta Physiol (Oxf) 2007;191:59–66.
31 Larsen FJ, Schiffer TA, Borniquel S, Sahlin K, Ekblom B, Lundberg JO, Weitzberg E: Dietary inorganic nitrate improves mitochondrial efficiency in humans. Cell Metab 2011;13:149–159.
32 Muggeridge DJ, Sculthorpe N, Grace FM, Willis G, Thornhill L, Weller RB, James PE, Easton C: Acute whole body UVA irradiation combined with nitrate ingestion enhances time trial performance in trained cyclists. Nitric Oxide 2015;48:3–9.
33 Geldenhuys S, Hart PH, Endersby R, Jacoby P, Feelisch M, Weller RB, Matthews V, Gorman S: Ultraviolet radiation suppresses obesity and symptoms of metabolic syndrome independently of vitamin D in mice fed a high-fat diet. Diabetes 2014;63:3759–3769.