Exposure to solar ultraviolet radiation limits diet-induced weight gain, increases liver triglycerides and prevents the early signs of cardiovascular disease in mice

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Abstract *Background and aims:* Sunlight exposure is associated with a number of health benefits including protecting us from autoimmunity, cardiovascular disease, obesity and diabetes. Animal studies have confirmed that ultraviolet (UV)-B radiation, independently of vitamin D, can limit diet-induced obesity, metabolic syndrome and atherosclerosis. The aim of this study is to investigate whether exposure to the UV radiation contained in sunlight impacts on these disease parameters.
Methods and results: We have trialled an intervention with solar UV in obese and atherosclerosis-prone mice. We have discovered that solar-simulated UV can significantly limit diet-induced obesity and reduce atheroma development in mice fed a diet high in sugar and fat. The optimal regime for this benefit was exposure once a week to solar UV equivalent to approximately 30 min of summer sun. Exposure to this optimal dose of solar UV also led to a significant increase in liver triglycerides which may protect the liver from damage.
Conclusion: Our results show that the UV contained in sunlight has the potential to prevent and treat chronic disease at sites distant from irradiated skin. A major health challenge going forward will be to harness the power of the sun safely, without risking an increase in skin cancers.
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Introduction

The relentless increase in the prevalence of obesity across the globe is paralleled by increases in related chronic diseases such as type 2 diabetes, cardiovascular disease and some cancers. Effective solutions to aid weight loss and prevent further weight gain need to be developed because even a 5% reduction in body weight confers significant health benefit and reduces the risk of chronic disease [1].

Solar ultraviolet (UV) radiation that reaches the skin is made up of ~5% UVB (290—320 nm) and ~95% UVA (320—400 nm). Although solar UV is best known for its

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role in causing skin cancer and producing vitamin D, epidemiological studies show that there is an association between a lack of UV and the likelihood of being obese, having type 2 diabetes, or living with an autoimmune disease [2]. Insufficient sunlight exposure also puts us at higher risk of developing heart disease [3] and dying from any cause [4]. A large number of people at risk of cardiometabolic disease have low levels of circulating vitamin D, which has led to numerous vitamin D-supplementation trials in the obese and people with diabetes [5]. However, the majority of these trials have had minimal or no impact on disease risk factors [6] leading to the conclusion that low vitamin D levels may be a marker of ill health rather than a causative factor [7]. This means that there is something else about exposure to UV that explains the health benefits gained from sunlight [2], and has led to suggestions that sunlight exposure should be taken into account in the clinic [8].

Animal studies have confirmed that UVB can limit diet-induced obesity and associated disorders like metabolic syndrome [9,10] and atherosclerosis [11] independently of vitamin D. Whether solar UV impacts on diet-induced obesity and related disorders has not been studied. This will go some way to explaining the latitude gradient effect observed for these diseases. In addition, the optimal dose (high or low) and frequency (intermittent or chronic) of UV that can limit weight gain is not known. This is important if the findings from animal studies are to be successfully translated into a phototherapy trial in humans or a revision of guidelines on safe sun-exposure habits. Here we report that exposure to intermittent, relatively "high" doses of solar simulated UV (ssUV) significantly reduced diet-induced weight gain in mice. Importantly, this protection was mainly attributed to a limit in fat mass accumulation and was observed when ssUV was given either before or after the start of a high fat, high sugar diet (HFHSD). Finally, although ssUV-exposed mice fed a HFHSD still developed an intolerance to glucose, they had higher triglyceride levels in their liver and were protected from atherosclerosis. Thus, exposure to the UV in sunlight limits diet-induced weight gain and protects from the signs of cardiovascular disease.

Methods

Housing, treatment and monitoring of mice

Male C57BL/6 (Australian BioResources Ltd, Moss Vale, Australia) and ApoE$^{-/-}$ mice (Australian Resource Centre, Perth, Australia) aged 7 weeks at the start of experiments were housed at 22 °C on a 12 h light-dark cycle with free access to water, and chow (23:12:65 (Protein:Fat:Carbohydrate), 14 kJ/g Specialty Feeds, WA) or a high saturated fat and high sugar diet (HFHSD; 20:45:35 (P:F:C), 21.8 kJ/g) made in house and provided ad libitum. The fluorescent lights used in the animal house did not emit any UV radiation. Fresh food was supplied regularly to avoid it becoming unpalatable. ssUV-exposed and control unirradiated mice were

shaved and housed together and provided with sufficient nesting material (~10 g) for them to self-regulate their body temperature. Total body fat mass was measured by Magnetic Resonance Imaging (MRI; EchoMRI, Houston, USA), while total body weight was measured weekly using digital scales, always in the morning and 72 h post-ssUV. Mean dorsal and abdominal surface body temperatures were measured before and 15 min after ssUV/sham irradiation using a handheld infrared camera (FLIR, Wilsonville, Oregon) directed at the mouse from a standardized distance of 25 cm.

UV exposure

Mice were irradiated with either "low" (6–32 kJ/m^2) or "high" (80 kJ/m^2) doses of ssUV generated with a 1000 W xenon arc solar simulator (Oriel, Stratford, CT) with an output of 8% UVB and 92% UVA. Controls were shaved and sham-irradiated but not exposed to ssUV. Full details on the UV spectra and exposure regimen has been published by us previously [12].

Metabolic phenotyping

Metabolic parameters including food and water intake, body mass, energy expenditure and total distance travelled, were recorded using multiplexed indirect calorimetry of individual metabolic monitoring cages (Promethion Metabolic Measurement System, Sable Systems, USA). Data were acquired 22 h pre-ssUV treatment (to establish the baseline) and 24 h post-ssUV treatment. To test glucose tolerance, mice were fasted for 5 h before 2 g glucose per kg lean body weight was injected intraperitoneally. Tail blood glucose levels were analysed at 0, 15, 30, 60, and 90 min post injection using the Accu-Check Performa II glucometer (Roche Diagnostics, Castle Hill, Australia). At the end of experiments involving ApoE$^{-/-}$ mice, the aorta and branching arteries were assessed macroscopically by a blinded pathologist for atheromata. To assess triglyceride levels, lipids extracted from 30 mg of snap-frozen liver were assayed using a commercially available triglyceride kit (OSR60118, Beckman Coulter Diagnostics; Brea, CA). All experiments were conducted with the approval of the University of Sydney animal ethics committee (Protocol numbers 2015/851 and 2013/5494).

Uncoupling Protein 1 gene expression in brown adipose tissue

The interscapular brown adipose tissue (BAT) was removed, weighed and processed for mRNA extraction as described [13]. cDNA was generated and Uncoupling Protein 1 (UCP-1) levels (Fwd: GGCCTCTACGACTCAGTCCA Rev: TAAGCCGGCTGAGATCTTGT) were assessed by qRT-PCR in comparison to the housekeeping gene (β-actin Fwd: AGATCAAGATCATTGCTCCTCCT Rev: ACGCAGCTCAGTAACAGTCC).

Statistical analysis

Data was analysed by one or two-way ANOVA with a Holm-Sidak multiple comparison test, a paired or un-paired two-tailed Student's t-test or Mann−Whitney as indicated (Prism v7.0b).

Results

During the conduct of an unrelated UV-carcinogenesis study, we noticed that female mice fed a chow diet and exposed to chronic low doses of cancer-causing solar simulated UV (ssUV) radiation gained weight more slowly than control, unirradiated mice (Supplementary Fig. 1). To determine whether ssUV could protect from diet-induced obesity, C57BL/6 mice were shaved and exposed weekly to 80 kJ/m^2 of ssUV. This dose of ssUV is double the minimum amount of ssUV that induces a significant increase in skin thickness (edema) in this mouse strain [12]. 80 kJ/m^2 induces a very mild sunburn reaction in most individuals, but is not considered a "high" dose by the general population, and is equivalent to ∼20−30 min of exposure to midday summer sunlight in Sydney, Australia. Controls were shaved, restrained and co-housed with ssUV-exposed mice but not exposed to ssUV. All mice were fed a regular chow diet during this initial 6 week prophylactic ssUV period, at which point half of the ssUV mice and half of the unirradiated controls were randomised to a HFHS diet. Weekly ssUV exposures were continued until the end of the experiment (12 more weeks). Exposure to ssUV led to a significant reduction in diet-induced weight gain (Fig. 1A). By the end of the experiment, HFHS-fed mice receiving ssUV (37.2 ± 1.6 g)

were 10% lighter than unirradiated controls (41.3 ± 0.8 g). More impressively, whole body magnetic resonance imaging revealed that ssUV reduced total fat mass by 23% (14.3 ± 1.0 g v 11.0 ± 1.3 g; Fig. 1B) in mice fed a HFHSD. There was no change in lean mass. These results suggested that a ssUV-induced reduction in body fat was primarily responsible for the overall limit placed on weight gain.

Next we asked whether altering the frequency and amount of ssUV would improve efficacy. In this experiment, groups of male C57BL/6 mice were fed a HFHSD, shaved and exposed to one of two ssUV regimens. The first, an "intermittent high" protocol was used which was similar to that described in Fig. 1A except that ssUV irradiation and diet were commenced simultaneously. This group received four doses of ssUV over four weeks for a cumulative total of 320 kJ/m^2 at which point their mass of total body fat was measured by MRI. For the second group, we used a "chronic low" protocol. Here mice received suberythemal doses of ssUV four times a week, with the starting dose of 6 kJ/m^2 increasing each week to a maximum of 32 kJ/m^2 per exposure as described in Supplementary Fig. 1. Six weeks after phototherapy, this group had received 24 doses for a total of 423 kJ/m^2 ssUV, at which point their total body fat mass was also measured by MRI. Mice receiving "intermittent high", but not "chronic low" doses of ssUV were protected from HFHSD-induced fat accumulation (Fig. 1C). Indeed, despite only receiving four doses and 75% of the cumulative amount of ssUV that chronic low mice received, HFHS-fed mice exposed to intermittent high doses of ssUV had 33% less body fat than no ssUV controls (2.7 ± 0.3 g v 1.8 ± 0.2 g). These fat masses are lower than those in Fig. 1B because the mice were on their diets for one third of the time (4−6 weeks vs 18 weeks).
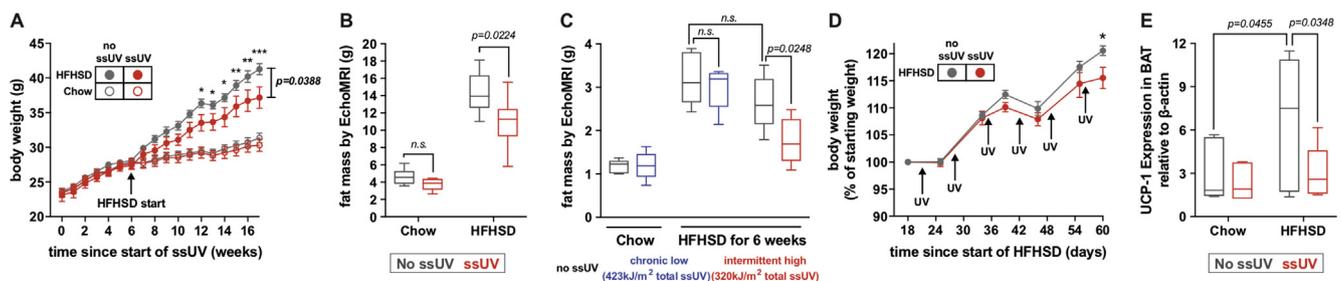

Figure 1 UV prevents diet-induced weight gain and UCP-1 upregulation in BAT. (A) Groups of male C57BL/6 mice were shaved and their backs exposed once a week to 80 kJ/m^2 solar simulated UV (red). Controls (grey) were shaved and restrained but not exposed to ssUV. 6 weeks after the start of ssUV, 2 groups (no ssUV and ssUV) commenced eating a high fat, high sugar diet (closed circles). The remaining mice continued being fed normal chow (open circles). The weekly ssUV exposures continued for another 12 weeks. n = 6 mice per group. Mean ± S.E.M. shown. 2-way RM-ANOVA with a Sidak's multiple comparisons test. (B) At the end of the experiment described in (A), all mice had their total body fat measured by EchoMRI. Bars represent min and max values. 2-way ANOVA with a Sidak's multiple comparisons test. (C) Male C57BL/6 mice were exposed to one of two ssUV regimens; "**intermittent high**" (red) or "**chronic low**" (blue). **Controls** (grey) were shaved, restrained and fed the same diet but not exposed to ssUV. The data shows the mass of total body fat as measured by MRI. n = 6 mice per group. Bars represent min and max values. 2-way ANOVA with a Sidak's multiple comparisons test. (D) Male C57BL/6 mice were fed a HFHSD for 20 days at which point they were exposed (red) once a week to 80 kJ/m^2 solar simulated UV (indicated by the arrows). Controls (grey) were shaved and restrained but not exposed to ssUV. n = 5 mice per group. Mean ± SEM shown. 2-way RM-ANOVA with a Sidak's multiple comparisons test. (E) At the end of the experiment described in (A), the interscapular brown adipose tissue (BAT) was removed and processed for mRNA extraction. qRT-PCR analysis of Uncoupling Protein 1 (UCP-1) levels compared to the housekeeping gene β-actin are shown. n = 5−6 mice per group. Bars represent min and max values. Statistics were by one-way ANOVA with a Holm-Sidak multiple comparison test. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

To investigate whether exposure to ssUV *after* the commencement of diet is efficacious, male C57BL/6 mice were started on a HFHS diet 20 days prior to the commencement of intermittent high ssUV-therapy. As shown in Fig. 1D, this therapeutic approach successfully limited the weight-gaining effects of a HFHS diet. MRI analysis at day 36 revealed that even though body weight wasn't significantly different after just 3 doses of ssUV, accumulated body fat was significantly reduced by ∼30% (3.0 ± 0.1 g v 2.1 ± 0.3 g; $p = 0.0338$, unpaired Student's t-test).

Since our MRI results showed that exposing the skin to ssUV led to significant systemic effects on overall fat mass, we tested whether ssUV-exposed mice were gaining less fat mass and weight because they were eating less food, expending more energy (e.g. by moving more), or preferentially metabolising fat. To investigate this possibility, we made use of the Promethion metabolic monitoring system which continuously measures food and water intake, movement and respiration (vCO_2 and vO_2). Here the ratio of CO_2 eliminated to O_2 consumed (the respiratory quotient) can provide an index of preference for carbohydrate or fat energy expenditure. We could not detect any overt ssUV-induced differences in water or food intake (Supplementary Fig. 2), nor in the distance travelled, energy expended or in the respiratory quotient.

Activation of brown adipose tissue (BAT) and induction of thermogenesis has been reported to limit weight gain in mice on obesogenic diets [14]. Although we detected no change in energy expenditure (Supplementary Fig. 2), we next tested for evidence of BAT activation in our model. First, we measured the surface body temperature of 10 mice using an infrared camera directed 25 cm from their shaved backs. Mice were then restrained and UV-irradiated. 15 min post-ssUV the IR measurement was repeated. Our solar simulator does not contain any infrared radiation, so mice are not exposed to heat. ssUV did not significantly affect surface body temperature (Supplementary Fig. 3A). To determine if exposure to four weekly high doses of fat-limiting ssUV (Supplementary Fig. 3B) affected surface temperatures over longer time periods, the mean back and abdominal skin temperatures of groups of 5 mice were measured. No differences in surface body temperatures were detected (Supplementary Fig. 3C). Thus, the ssUV regime we are using does not significantly impact food consumption, energy expenditure, respiratory quotient or body temperature.

We also investigated whether ssUV was affecting the expression of Uncoupling Protein 1 (UCP-1) in BAT. During times of excess energy intake, UCP-1 in BAT uncouples oxygen consumption from ATP synthesis thus allowing for the influx of protons to waste energy as heat (thermogenesis). As expected, and consistent with what others have shown [15], mice fed a HFHS diet upregulated UCP-1 in BAT (Fig. 1E). Intriguingly, UCP-1 upregulation in the BAT of HFHS-fed mice was prevented by ssUV exposure. This result suggests that UCP-1 induction is likely to be downstream of increased adiposity. Furthermore, limits on weight gain despite no change in body temperature or

upregulation of UCP-1 implies that ssUV is exerting its metabolic effects via other mechanisms.

Lastly we investigated whether the reduction in weight gain in ssUV-exposed mice would manifest in changes to other symptoms of metabolic syndrome; tolerance to glucose, atherosclerosis and changes to liver lipids. As expected, mice fed a HFHSD, but not those on chow, became glucose intolerant (Fig. 2A). However, mice receiving ssUV were also intolerant to glucose (GTT AUC = 1710 ± 45). We also tested whether ssUV-exposed HFHS-fed mice might be protected from signs of cardiovascular disease by exposing groups of wild type (WT) or ApoE$^{-/-}$ mice to the ssUV regime used in Fig. 1A. Twelve weeks after the start of the diet, the aorta and branching arteries were assessed macroscopically by a blinded pathologist for atheromata. As shown in Fig. 2B, all of the ApoE$^{-/-}$ mice had atheromata, and the size of the affected area was increased by a HFHS-diet. Importantly, exposure to a regimen of ssUV that reduces obesity led to a significant reduction in atheroma-affected arteries. A survival analysis (Supplementary Fig. 4) revealed that 11 out 15 (73%) unirradiated mice developed atheromata at 12 weeks. In contrast, only 6 out of 14 (43%) ssUV-exposed mice developed atheromata ($p = 0.1018$; Log-rank (Mantel−Cox) test). Of those mice that developed atheromata, almost half of the unirradiated mice (5 of the 11) had more than 15% coverage, whereas only 1 ssUV-irradiated mouse reached this threshold. Finally, in light of the UCP-1 results in BAT (Fig. 1E), we investigated whether exposure to ssUV would affect other internal organs and systemic metabolic pathways. We again observed a significant reduction in fat mass and although there was no significant ssUV-effect on muscle or liver weight, total liver triglycerides were significantly elevated in HFHSD-fed, ssUV-exposed mice (Fig. 2C).

Discussion

Our study shows that weekly exposure to a physiologically relevant dose of solar UV, one that is easily received by humans during recreational activities, can significantly limit diet-induced weight gain. Reduced total body fat largely explained this ssUV-effect. Indeed, significant limits on total body fat accumulation, as measured by MRI, could be detected well before changes in overall body weight were identified. The 20−30% reduction in total body fat accumulation we observed is a significant achievement, especially considering that the FDA regards an obesity drug to be efficacious if the difference in weight loss between placebo and treated is ≥5% [16]. Combatting the obesity epidemic by motivating people to move more and eat healthier food is proving extremely difficult, leading some to propose that halting weight gain may be a more feasible and achievable goal [17]. Our results show that exposure to solar UV halts weight gain in mice by at least 10%. If translated into humans, a sustained 10% reduction in weight gain could cut the number of years a patient has to live with hypertension and type 2 diabetes by more than 50% [18].
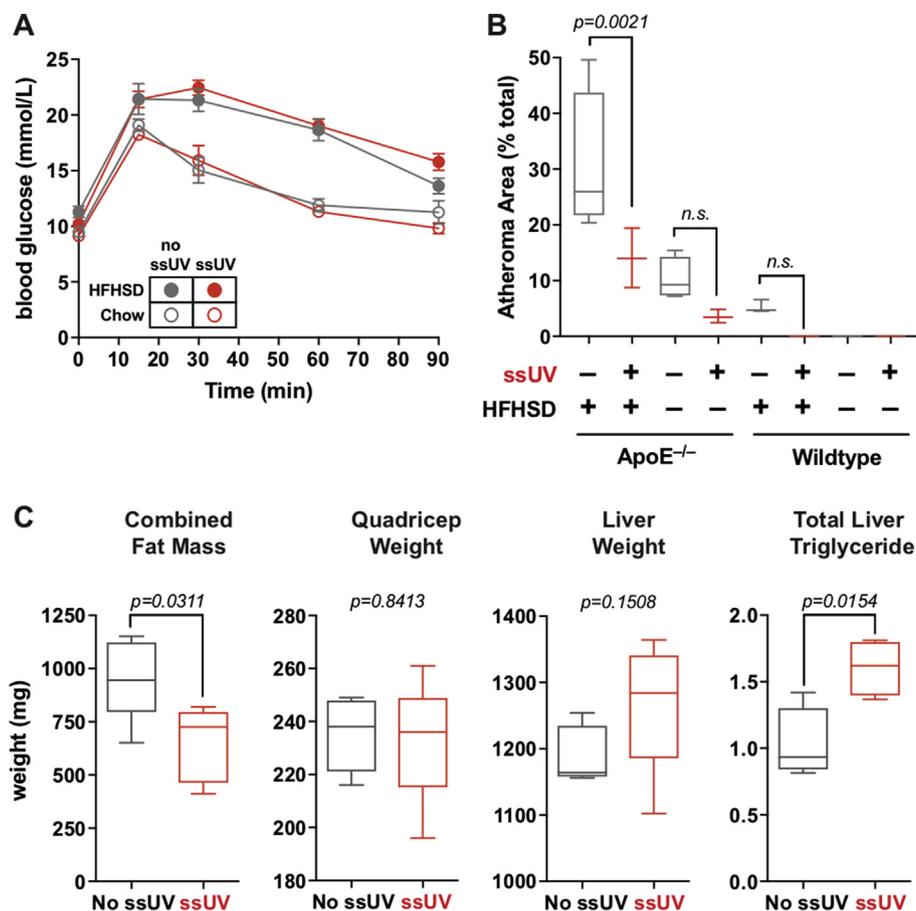
Figure 2   UV-exposed, HFHS-fed mice are protected from signs of atherosclerosis. (A) 12 weeks after the start of a HFHSD (closed circles), which was 18 weeks after the start of ssUV (red), C57BL/6 mice were subjected to a glucose tolerance test. n = 4–6 mice per group, mean ± SEM shown. (B) ApoE$^{-/-}$ and wild type C57BL/6 mice were fed a HFHSD, or regular chow (as indicated). Half the mice were exposed to 80 kJ/m^2 solar simulated UV each week for 12 weeks (red). Controls were treated in the same way but not exposed to ssUV (grey). At the end of this time, mice were euthanased, dissected and the aortic arch and associated arteries were macroscopically assessed for the presence of atheromas. n = 3–4 mice per group. Bars represent min and max values. Statistics were by one-way ANOVA with a Holm-Sidak multiple comparison test. (C) Wild type C57BL/6 mice were fed a HFHSD. Half the mice were exposed to 80 kJ/m^2 solar simulated UV each week for 6 weeks (red). Controls were treated in the same way but not exposed to ssUV (grey) as per Fig. 1C. Epididymal, inguinal and interscapular brown adipose tissue were collected, pooled and weighed (combined fat mass). Quadriceps and livers were also isolated and weighed. Lipids were extracted from 30 mg of frozen liver from each mouse and the levels of triglycerides measured. n = 4–5 mice per group. Bars represent min and max values. Statistics were by a Mann–Whitney test. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

In contrast to what has been shown for broad band UVB by others [9], solar UV was unable to rescue HFHS-fed mice from becoming glucose intolerant. Glucose tolerance is only one way to measure the impact of a reduction in weight gain on metabolic health. We predicted that an ssUV-mediated reduction in weight gain, especially one as high as 33%, might result in improvements in other diseases. Indeed, losses of this magnitude in overweight and obese subjects significantly lower the risk for type 2 diabetes and cardiovascular disease; the primary life-limiting diseases associated with obesity. To that end, we confirmed that solar UV can reduce the number of atheromata in atherosclerosis-prone mice. The mechanisms by which ssUV limits weight gain and protects from cardiovascular disease are not entirely clear. Nitric oxide release [9] and activation of regulatory T cells [11] are both likely to be involved. Other possibilities include UV-induced IL-33 [19], which has been shown to protect mice from

atherosclerosis [20]. Our results also show that exposure to ssUV significantly elevates liver trigylceride levels. Increased triglyceride synthesis ameliorates hepatocellular lipotoxicity by preventing free fatty acids from accumulating in the liver [21] and may explain how UV protects from liver damage [9].

The amount of time people spend in the sun is decreasing [22], which may be good news for lowering skin cancer incidence. But what if our successes in lowering sun exposure to combat cancer have longer term detrimental effects on other, equally serious, health outcomes? Obese patients struggle to sustain significant changes to their diet and exercise regimes. This often means that additional interventions are required to tackle obesity. It is important to remember that all irradiation conditions used in our study are potentially oncogenic. Balancing the human need for sunlight against the recognised harmful effects is a major health challenge. Our

results show that together with small changes to diet and exercise, exposure to solar UV, or phototherapy in a clinic, could lead to additional limits being placed on excessive weight gain. Importantly, solar UV had an impact on weight gain in mice even though they had already commenced eating a diet high in fat and sugar. Future studies in humans should investigate whether ssUV can play a role not only in limiting further weight gain, but possibly inducing weight loss in the already obese.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.02.006.

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