Skin photosensitivity is associated with 25-hydroxyvitamin D and BMD but not fractures independent of melanin density in older Caucasian adults

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Abstract

Introduction

Whether skin photosensitivity modulates sun exposure behaviours, consequent vitamin D status and skeletal health outcomes independently of constitutive pigmentation has not been systematically investigated.

Methods

1072 community-dwelling adults aged 50-80 years had skin photosensitivity quantified by questionnaire and melanin density by spectrophotometry. Bone mineral density (BMD), falls risk and 25-hydroxyvitamin D (25OHD) were measured using DXA, short form Physiological Profile Assessment and radioimmunoassay, respectively. Sun exposure and symptomatic fractures were assessed by questionnaire. Participants were followed up at 2.5 (n=879), 5 (n=767) and 10 (n=571) years.

Results

Higher resistance to sunburn and greater ability to tan were associated with reduced sun protection behaviours (RR 0.87, $p<0.001$ & RR 0.88, $p<0.001$), higher lifetime discretionary sun exposure in summer (RR 1.05, $p=0.001$ & RR 1.07, $p=0.001$) and winter (RR 1.07, $p=0.001$ & RR 1.08, $p=0.02$) and fewer lifetime sunburns (RR 0.86, $p<0.001$ & RR 0.91, $p=0.001$). Higher resistance to sunburn was associated with lower total body ($\beta=-0.006$, $p=0.047$) and femoral neck ($\beta=-0.006$, $p=0.038$) BMD, but paradoxically, fewer prevalent fractures (RR 0.94, $p=0.042$). Greater ability to tan was associated with higher 25OHD ($\beta=1.43$, $p=0.04$), lumbar spine ($\beta=0.014$, $p=0.046$) and total body ($\beta=0.013$, $p=0.006$) BMD, but not fracture or falls risk. These associations were independent of constitutive melanin density.

Conclusion

Cutaneous photosensitivity was associated with sun exposure behaviours, cutaneous sequelae and, consequently, 25OHD and BMD in older Caucasian adults independent of constitutive melanin density. There was no consistent association with fracture outcomes, suggesting environmental factors are at least as important.

Introduction

Vitamin D is a modifiable determinant of osteoporotic fracture risk. Vitamin D supplementation in deficient elderly individuals can reduce falls risk [1,2], increase muscle strength [2] and, with calcium supplementation, increase bone mineral density (BMD) [3] and reduce incident fractures [4]. While low 25-hydroxyvitamin D (25OHD) has been associated with reduced BMD and reduced muscle strength at several separate time points across the lifespan [5-14], this reflects only recent sun exposure [15]. We have shown that a diagnosis of non-melanoma skin cancer (NMSC) is associated with lower risk of osteoporotic fracture, particularly hip fracture [16], and that greater skin photoaging is associated with reduced osteoporotic fracture risk in older women independent of 25OHD concentration [17]. This suggests that cumulative lifetime ultraviolet radiation (UVR) exposure, even to levels that are harmful to skin, may protect against fracture.

Skin phenotype may impact sun exposure behaviours and, consequently, lifetime vitamin D status and skeletal health later in life. Classical studies have compared individuals from extreme ethnic and geographic backgrounds, producing complex and sometimes paradoxical findings [18,19]. Differentiating the impact of genetic, environmental and cultural influences from cutaneous vitamin D synthesis using this paradigm has proved challenging. More recently, we [20,21] and others [22] have shown that higher constitutive cutaneous melanin density is associated with higher 25OHD, higher BMD and more fractures in older Caucasian populations. Available literature describes the relationship between skin pigmentation and skeletal health. However, skin photosensitivity is determined by factors beyond constitutive skin pigmentation [23,24]. Skin photosensitivity may also impact sun exposure behaviours, consequent vitamin D status [25,26] and, potentially, skeletal health. Whether constitutive cutaneous melanin density fully predicts the skin phenotypic contribution to sun exposure behaviours and consequent skeletal health outcomes has not been systematically investigated. Therefore, the aim of this study was to determine if skin photosensitivity is associated with short- and long-term measures of sun exposure, osteoporotic fracture risk factors and fracture outcomes independent of constitutive melanin density in a cohort of older Caucasian adults.

Methods

This study was conducted as part of the Tasmanian Older Adult Cohort (TASOAC) study. The TASOAC study is a prospective, population-based study that was initiated in 2002 and is aimed at identifying the environmental, genetic, and biochemical factors associated with the development and progression of osteoporosis and osteoarthritis. Participants between the ages of 50 and 80 years were selected from the electoral roll in Southern Tasmania (population 229,000) using sex-stratified, simple random sampling without replacement. A total of 1099 adults (response rate = 57%) consented to participate in the study. Participants attended a baseline clinic assessment at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September 2004. They were invited for follow–up clinic assessments at 2.5, 5, and 10 years after the baseline assessment. All data included in the present analysis were collected at baseline unless otherwise stated (Supplemental Figure 1). All research was conducted in compliance with the Helsinki Declaration and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All participants provided written informed consent.

Skin phenotype and sun sensitivity

Skin phenotype was assessed by participant-administered questionnaire of skin reactivity to sun exposure and spectrophotometer (Minolta 580i Spectrophotometer) as previously described [27,28]. Skin phenotype measures included self-reported resistance to sunburn, ability to tan and natural hair colour. See Supplemental Table 1 for further information.

Sun exposure, sun exposure behaviours

Sun exposure and sun exposure behaviours were assessed by participant-administered questionnaire that included questions about the amount of 'leisure time' sun exposure during summer and winter as previously described [28]. At baseline self-reported leisure time sun exposure was assessed for the most recent year. At the 2.5 year follow-up, self-reported leisure time sun exposure and outdoor physical activity were assessed across the lifespan by asking participants to select the most appropriate exposure category for every 5 year period from 11-20 years of age and every decade of life thereafter (time periods included 11-15 years, 16-20 years, 21-30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years and last decade). Average lifetime leisure time sun exposure in winter and summer was calculated by taking the average sun exposure for each decade of life up to 70 years of age as previously described [28]. See Supplemental Table 1 for further information.

<u>Assessment of photodamage and non-melanoma skin cancer (NMSC) prevalence</u>

Greater cumulative UVR exposure is a key aetiological factor in the pathogenesis of NMSC [29]. Prevalent NMSC may therefore be seen as a biomarker for higher cumulative sun exposure across the lifespan. Prevalent NMSC and photodamage quantified by the Beagley-Gibson (BG) method were included as objective biomarkers to assess cutaneous toxicity of chronic ultraviolet radiation exposure.

With increasing cumulative ultraviolet radiation exposure skin undergoes progressive, stereotyped deterioration in surface microtopography [30]. The BG method utilises silicone skin cast impressions from a sun exposed area of the body, such as the dorsum of the hand, to quantify the degree of microtopographical deterioration according to a standard scoring system [30]. Higher BG grades represent greater cutaneous photodamage [30-34] with scores ranging between 1 (minimal photodamage) to 6 (extensive photodamage). Cutaneous photodamage was therefore assessed by grading silicone casts taken from the dorsum of both hands at the 2.5 year follow up according to the BG method, as previously described [28]. In brief, silicone casts were made of the dorsum of each hand, then visualised using a low-power dissecting microscope (Leica EZ4 D Stereomicroscope) at X10 magnification and graded according to the BG method [34,30] (Supplemental Figure 2 contains images of representative silicone casts from two study participants) . Cast quality was sufficient to allow the BG grade to be established for 96% of participants. The remaining 4% of participants were excluded from the photodamage analysis (*n* for this analysis = 812).

Prevalent NMSC were quantified by questionnaire. At the baseline clinic visit participants completed a questionnaire that included a question asking "*Has a doctor ever told you that you have non-melanoma skin cancer eg BCC, SCC*," with response categories of 0: No, 1: Yes and 2: Don't know. Participants (*n*=85, 7.7% of participants) who responded 'don't know' or did not answer the question (*n*=5, 0.4% of participants) were excluded from the NMSC analysis (*n*=1015 for NMSC analysis).

Anthropometric measures and smoking

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) with weight and height were measured after shoes, socks and bulky clothing had been removed. Weight was measured to the nearest 0.1kg using a single pair of calibrated electronic scales (Seca Delta Model 707) and height to the nearest 0.1cm using a stadiometer. Smoking status was recorded by questionnaire.

Osteoporotic fracture risk factors

Osteoporotic fracture risk factors were quantified as previously described [20]. In summary, 25OHD was quantified using the Immunodiagnostics Systems liquid-phase radioimmunoassay (Immunodiagnostics Systems Ltd, Boldon, Tyne & Wear, UK) at the Royal Hobart Hospital laboratory. The intra- and inter-assay coefficients of variation based on an average of 50 runs in our hands were 1.8% and 3.3%, respectively. The Royal Hobart Hospital laboratory participates in a national externally audited quality assurance program run by the Royal College of Pathologists of Australasia. Bone mineral density was measured using dual-energy x-ray absorptiometry (DXA) at the lumbar spine (L1-L4), femoral neck, total hip and total body sites. Participants were excluded from the DXA scans if their weight exceeded 130 kg (n=3). Precision estimates *in vivo* are 2–3% in our hands. Falls risk was objectively assessed using the short form of the Physiological Profile Assessment (Prince of Wales Medical Research Institute, Sydney, Australia) [35]. Physical activity was quantified using the average steps per day during a 7-day pedometer assessment [36].

Symptomatic fracture assessment

The prevalence and number of symptomatic fractures were assessed by questionnaire asking *"List any fractures you have had by the location of the fracture,"* with writing space and prompts for first, second, third etc fractures. A major fracture was defined as a fracture involving the femur, radius, ulnar, vertebrae, rib or humerus. Prevalent fractures were defined as any self-reported fracture in the lifetime at baseline. Incident fractures were identified by asking participants at each follow up visit to list by location any fractures they had since their previous visit.

Data analysis

Individual skin phenotypic traits were recoded from most photosensitive to least photosensitive (most photoresistant, Supplemental Table 2), so that those most able to tolerate high UVR doses had the highest score. Self-report of hair colour was consolidated to a four-category variable (Supplemental Table 2).

The exposure for all regression analyses was skin phenotype (resistance to sunburn, ability to tan or hair colour). Linear regression analyses were used to examine associations between skin photosensitivity, 25OHD, BMD, falls risk (Z score) and steps per day. Log-binomial regression analyses were used to investigate the association between skin photosensitivity, NMSC and fracture prevalence and incidence. Log-Poisson regression analyses with robust standard errors were used to examine the relationship between skin photosensitivity, self-reported sun exposure, BG grade and where log-binomial models failed to converge. Inverse probability weighted analysis was used to account for patients lost to follow up.

Standard diagnostic checks of model fit were made. Given the potential for skin phenotypic traits to be highly correlated, we assessed for multicollinearity using the variance inflation factor and accepted values <10 as having tolerable levels of collinearity. Statistical significance was defined as a two tailed p value ≤ 0.05. All statistical analyses were performed on Stata V.15.0 for Windows (StataCorp LP).

Results

Of the 1099 participants enrolled at baseline, seven had no spectrophotometric melanin density measurement available and were excluded from further analysis. Participants were invited for follow–up clinic assessments at 2.5 (n=879 attended), 5 (n=767 attended), and 10 (n=571 attended) years after the baseline clinic assessment (Supplemental Figure 1). Ethnicity was assessed at the 2.5 year follow up only. Ethnicity was therefore definitively determined for 878 participants with one participant not reporting their ethnicity and unavailable for 220 participants. Of the 878 participants for whom data on ethnicity was reported, twenty (2.3%) reported their ethnicity to be non-Caucasian. Given low frequency of study participants reporting non-Caucasian ethnicity at the 2.5 year follow up, the remaining 220 participants who attended the initial clinic visit were included in baseline cross-sectional analysis. Excluding these 220 participants and commencing analysis at the 2.5 year follow up resulted in minor changes that did not impact the overall conclusions derived (data not shown). The present study therefore consists of 1072 participants (baseline participant characteristics are summarised in Table 1). Compared to those excluded, participants included in the present study were similar with regard to age, sex, BMI, smoking status, current 25OHD, BMD at all sites, falls risk, steps per day, summer and winter leisure time sun exposure and fracture at every site, spectrophotometric melanin density and resistance to sunburn score. Participants excluded had higher hair colour (2.45±0.60 *vs* 1.84±0.66, $p<0.001$) and higher ability to tan (2.35±0.75 *vs* 1.52±0.90, $p<0.001$) scores.

Table 2 summarises the relationship between skin photosensitivity, short- and long-term measures of sun exposure. Higher resistance to sunburn was associated with less sun protection behaviours, higher self-reported outdoor activity in summer and leisure time sun exposure in summer and winter in the most recent year and across the lifespan, higher 25OHD, less skin photodamage and fewer NMSC diagnoses, but not outdoor physical activity in winter. These associations, with the exception of self-reported outdoor activity in summer, NMSC and current 25OHD concentration, were independent of spectrophotometric melanin density. Greater ability to tan was associated with less sun protection behaviours, higher self-reported outdoor physical activity and leisure time sun exposure in summer and winter in the most recent year and across the lifespan, higher 25OHD, less skin photodamage and fewer NMSC diagnoses. With the exception of NMSC, these relationships remained significant following adjustment for spectrophotometric melanin density. Higher resistance to sunburn (RR 0.86, $p<0.001$) and greater ability to tan (RR 0.91, $p=0.001$) were also associated with fewer lifetime sunburns independent of melanin density. Hair colour was not associated with any sun exposure measure independent of spectrophotometric melanin density except lower NMSC prevalence and less sun protection behaviours. As hair colour was not strongly associated with multiple sun exposure outcomes, it was not considered as an exposure variable in further analyses. Higher resistance to sunburn was correlated with greater ability to tan (Spearman's rho = 0.34, $p<0.001$).

Table 3 summarises the relationship between skin photosensitivity and fracture risk factors. Higher resistance to sunburn was associated with lower total body and femoral neck BMD in fully adjusted analyses, but not BMD elsewhere, 25OHD, falls risk or steps per day. The associations between higher resistance to sunburn and lower total body (β=-0.007, $p=0.041$) and femoral neck (β=-0.007, $p=0.024$) BMD remained significant after further adjustment for current 25OHD concentration.

Greater ability to tan was associated with higher 25OHD and higher lumbar spine and total body BMD independent of other skin phenotypic measures. The association between greater ability to tan, higher lumbar spine and total body BMD remained significant following further adjustment for pedometer-assessed ambulatory activity (β=0.014, p=0.048 & β=0.014, p=0.005, respectively), but not current 25OHD concentration (β=0.013, p=0.07 & β=0.009, p=0.09, respectively). Neither greater ability to tan (β=0.95, p=0.17) or higher resistance to sunburn (β=0.10, p=0.98) were significantly associated with 25OHD after inclusion of recent sun exposure in fully adjusted models.

Higher resistance to sunburn was associated with fewer prevalent fractures in fully adjusted analysis (Table 4) and more incident nonvertebral and major fractures at 2.5 years, but not 5 or 10 years (Table 5). The associations between resistance to sunburn and incident fracture outcomes were not significant after adjustment for melanin density. Greater ability to tan was not associated with any fracture outcome. Further adjustment for skin photosensitivity, BMD, falls risk and 25OHD did not materially change any association with incident fracture outcomes. Accounting for loss to follow up using inverse probability weighted analysis resulted in a non-significant Model 1 association between higher resistance to sunburn and incident nonvertebral fracture at 2.5 years, but no other meaningful change. There was no significant interaction between ability to tan and resistance to sunburn on sun exposure measures, fracture risk factors or outcomes with the exception of major prevalent fracture ($p_{interaction}$=0.03). The variance inflation factor index was <10 for all analyses.

Discussion

To the best of our knowledge this is the first study to systematically investigate the relationship between cutaneous photosensitivity, sun exposure, fracture risk factors and outcomes. Our data demonstrate that, even after adjustment for constitutive melanin density, self-report of a less photosensitive skin phenotype was associated with more short- and long-term sun exposure with fewer cutaneous sequelae despite less sun protection behaviours. Greater ability to tan and higher resistance to sunburn were further associated with fracture risk factors, specifically 25OHD and BMD, and fractures independent of constitutive melanin density. These data suggest that cutaneous response to sun exposure, not just basal pigmentation, impacts sun exposure behaviours and skeletal health.

Self-report of a less photosensitive skin phenotype was associated with greater sun exposure with fewer cutaneous sequelae despite less sun protection behaviours independent of constitutive melanin density. Constitutive cutaneous melanin is an important determinant of cutaneous response to UVR but does not perfectly predict it [37]. The degree of UVR-induced inflammatory response and subsequent increases in pigmentation and epidermis thickness as well as DNA repair capacity also contribute to photoadaptation [23,38]. Self-report of natural hair colour poorly predicted sun exposure behaviours or cutaneous sequelae of UVR exposure. In contrast, greater ability to tan and higher resistance to sunburn were associated with higher levels of short- and long-term leisure time sun exposure and fewer cutaneous sequelae including sunburn, chronic photodamage and NMSC diagnoses despite reduced sun protection behaviours. This is consistent with previous work [25,39,40] and supports the concept that cutaneous photosensitivity is determined by factors in addition to constitutive melanin density. This may impact skeletal health.

Serum 25OHD is a key intermediary linking sun exposure to skeletal health outcomes. Greater ability to tan was associated with higher 25OHD, higher total body and lumbar spine BMD independent of constitutive melanin density. This is consistent with data demonstrating that both constitutive and facultative melanin density were independently associated with higher 25OHD in cross-sectional analysis [41]. The association between greater ability to tan and higher 25OHD was not significant after inclusion of recent leisure time sun exposure, suggesting the association is mediated by behavioural modification with higher discretionary sun exposure. Thus, greater ability to tan, or facultative melanin response, may assist in creating a permissive skin phenotype facilitating greater sun exposure and consequently higher 25OHD concentration. The facultative melanin response was not quantified by basal melanin density alone. The associations between greater ability to tan and higher BMD remained significant following adjustment for current physical activity, but not 25OHD, consistent with the hypothesis that 25OHD mediates the relationship between ability to tan, sun exposure and BMD.

Despite the protective association with fracture risk factors, ability to tan was not associated with prevalent or incident fractures. Possible explanations include (1) insufficient variation in fracture risk factors to result in a change in the clinical outcome of fracture, or (2) behavioural modification and alteration in composition of activity which offsets a reduced fracture risk. The difference in spine and total body

BMD between least versus greatest ability to tan was 3.9% and 5.7%, respectively. Calcium and cholecalciferol randomised controlled trials have demonstrated a similar magnitude of difference in BMD and fewer incident fractures [3,42]. Therefore, the lack of association between ability to tan and fracture outcomes does not seem to be explained by insufficient variation in BMD. Alteration in composition of physical activity may contribute to the lack of association between ability to tan and fracture outcomes. Individuals with greater ability to tan reported engaging in more outdoor physical activity despite no difference in pedometer-assessed ambulatory activity or falls risk. The outdoor environment may predispose to falls and potentially be associated with higher fall events that offset the fracture risk reduction expected from higher BMD. Overall these data reinforce the importance of assessing fracture outcomes rather than surrogate markers of fracture risk alone.

Higher resistance to sunburn was associated with reduced BMD at the femoral neck and total body despite an association with more self-reported lifetime sun exposure and higher 25OHD. The association between greater resistance to sunburn and higher 25OHD was not significant after adjustment for recent discretionary sun exposure, consistent with mediation by behavioural modification, as previously suggested [25]. The association between higher resistance to sunburn and lower BMD was 25OHD-independent and contrary to the hypothesis that greater lifetime sun exposure contributes to higher BMD later in life. It may reflect a shared genetic basis. The melanocortin-1 receptor is a key genetic determinant of photosensitivity [38] and expressed [43] and functionally significant [44] in osteoblasts. As higher resistance to sunburn and greater ability to tan are correlated physiologically [45] and epidemiologically (herein) the disparate associations with BMD suggest that overall impact of skin photosensitivity on BMD is likely close to neutral.

Higher resistance to sunburn was associated with fewer prevalent fractures despite the detrimental associations with BMD. The paradoxical nature of this association may reflect multiple comparisons, rather than a true association. The association between higher resistance to sunburn and higher number of incident fractures was not significant following adjustment for melanin density. Higher constitutive melanin density is associated with higher resistance to sunburn [20] and more short-term incident fractures [21]. The association of higher resistance to sunburn with more short-term incident fractures therefore likely reflects the association of both with melanin density.

This study has potential limitations. Given the small number of TASOAC participants reporting non-Caucasian ethnicity and challenges in differentiating the impact of cutaneous vitamin D synthesis from genetic, environmental and cultural influences, we limited our analysis to Caucasian individuals. Our results therefore may not apply to other ethnicities, however, represent the most comprehensive analysis of Caucasian skin photosensitivity, sun exposure and skeletal health outcomes to date. Participants excluded from the present study had significantly different skin phenotypic traits. This likely reflects ethnicity and should not impact generalisability to the Caucasian population. Participants were otherwise well matched. We included 220 participants for who ethnicity data were unavailable in baseline cross-sectional analysis. However, the low frequency of participants reporting non-Caucasian ethnicity and minor differences in analyses when commenced at the 2.5 year follow up, suggest the overall impact of this was modest. Skin phototype is classically categorised according to the Fitzpatrick system [40], which combines ability to tan and resistance to sunburn into six phototypes. We chose to analyse individual skin phenotypic traits after considering (1) the inability to assign up to 40% of individuals a Fitzpatrick phototype in epidemiological research [39], (2) that the original TASOAC questionnaire did not precisely replicate the Fitzpatrick scale questions and (3) the lack of multiple interactions between ability to tan and resistance to sunburn for sun exposure, fracture risk factors and fracture outcomes (herein), suggesting these traits do not differentially modify each other's relationship with skeletal health outcomes.

In conclusion, cutaneous photosensitivity was associated with sun exposure behaviours, cutaneous sequelae and, consequently, 25OHD and BMD in older Caucasian adults independent of constitutive melanin density. Despite this, there was no consistent association between cutaneous photosensitivity and fracture outcomes, suggesting that environmental factors are at least as important in determining fracture events.

Table 1. Baseline characteristics of participants (*n*=1072)

Variable	Mean	Standard deviation
Age (years)	63.1	7.5
Female, *n (%)*	549	51.0%
Body mass index (kg/m^2)	27.9	4.7
Current smoking, *n (%)*	129	12.1%
Serum 25-hydroxyvitamin D (nmol/L)	52.5	18.6
Bone mineral density (g/cm^2)		
Total hip	0.97	0.13
Femoral neck	0.77	0.13
Lumbar spine	1.01	0.17
Total body	1.09	0.13
Fall risk (Z score)	0.18	0.84
Ambulatory activity (steps per day)	8632	3357
Fracture prevalence, *n (%)*		
Any fracture	475	44.3%
Vertebral fracture	32	3.0%
Nonvertebral fracture	465	43.4%
Major fracture	253	23.6%
Skin phenotype		
Melanin density (%)	2.05	1.03
Ability to tan (category, range 0-3)	1.5	0.9
Resistance to sunburn (category, range 0-4)	2.0	1.2
Hair colour (category, range 0-3)	1.8	0.7
Sun protection behaviour (category, range 0-3)	1.6	1.0
Discretionary sun exposure (category, range 0-4)		
Summer (lifetime)	2.1	1.4
Winter (lifetime)	1.6	1.4
Summer (last season)	1.9	1.4
Winter (last season)	1.6	1.3
Outdoor physical activity (category, range 0-3)		
Summer (lifetime)	1.7	0.7

Winter (lifetime)	1.5	0.8
Prevalent non-melanoma skin cancer*, n (%)*	249	24.5%
Beagley-Gibson grade (cutaneous photodamage, range 3-6)	4.57	0.80

Data reported as mean and standard deviation except for percentages.

Categories for ability to tan were 0: no tan, 1:light tan, 2: medium tan, 3: dark tan (4 categories); for resistance to sunburn were 0: burn within 30 minutes, 1: burn within 30-60 minutes, 2: burn within 1-2 hours, 3: burn over 2 hours and 4: never burn (5 categories); for hair colour were 0: red, 1: blond, 2: brown, 3: black (4 categories). ; for sun protection behaviours were 0:never/rarely, 1:occasionally, 2:most of the time, 3:always (4 categories); for leisure time sun exposure were 0:<1 hour, 1:1-2 hours, 2: 2-3 hours, 3: 3-4 hours and 4: >4 hours per day (5 categories); for outdoor physical activity 0: not that often, 1: a moderate amount, 2: quite a lot, 3: virtually all the time (4 categories).

Table 2. Association between skin photosensitivity, sun exposure and 25-hydroxyvitamin D

	Resistance to sunburn		Ability to tan		Hair colour	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Discretionary sun exposure (range 0-4)						
Lifetime (*n*=848)						
Summer	**1.06 (1.03 – 1.09)**	**1.05 (1.02 – 1.08)**	**1.09 (1.05 – 1.13)**	**1.07 (1.03 – 1.11)**	0.99 (0.95 – 1.04)	0.98 (0.94 – 1.02)
Winter	**1.09 (1.05 – 1.14)**	**1.07 (1.03 – 1.13)**	**1.11 (1.05 – 1.17)**	**1.08 (1.02 – 1.15)**	0.97 (0.91 – 1.03)	0.95 (0.89 – 1.01)
Most recent season						
Summer	**1.12 (1.08 – 1.17)**	**1.11 (1.06 – 1.15)**	**1.18 (1.12 – 1.24)**	**1.15 (1.09 – 1.22)**	1.05 (0.99 – 1.13)	1.03 (0.96 – 1.11)
Winter	**1.10 (1.06 – 1.14)**	**1.09 (1.05 – 1.13)**	**1.11 (1.05 – 1.18)**	**1.10 (1.04 – 1.17)**	1.06 (0.99 – 1.14)	1.05 (0.98 – 1.13)
Sun protection behaviours (range 0-3)	**0.85 (0.83 – 0.88)**	**0.87 (0.84 - 0.90)**	**0.85 (0.82 – 0.89)**	**0.88 (0.84 – 0.93)**	**0.87 (0.83 – 0.92)**	**0.90 (0.85 – 0.95)**
Biological surrogate markers of sun exposure						

Previous NMSC (no *v* yes, *n*=1015)*	**0.90 (0.82 – 0.98)**	0.93 (0.84 – 1.02)	**0.83 (0.74 – 0.94)**	0.89 (0.77 – 1.02)	**0.83 (0.72 – 0.96)**	**0.84 (0.72 – 0.98)**
BG grade *(n*=812)*	**0.98 (0.97 – 0.99)**	**0.99 (0.98 – 0.99)**	**0.97 (0.96 – 0.98)**	**0.98 (0.97 – 0.99)**	**0.98 (0.97 – 0.99)**	0.98 (0.97 – 1.00)
25-hydroxyvitamin D**	**1.20 (0.34 – 2.07)**	0.52 (-0.38 – 1.42)	**2.82 (1.68 – 3.96)**	**1.66 (0.35 – 2.98)**	0.43 (-1.12 – 1.99)	-0.22 (-1.78 – 1.33)
Lifetime outdoor physical activity (*n*=848, range 0-3)						
Summer	**1.03 (1.01 – 1.06)**	1.02 (1.00 – 1.05)	**1.08 (1.04 – 1.11)**	**1.06 (1.02 – 1.10)**	0.99 (0.95 – 1.03)	0.98 (0.93 – 1.02)
Winter	1.03 (1.00 – 1.07)	1.01 (0.98 – 1.05)	**1.08 (1.04 – 1.13)**	**1.06 (1.00 – 1.11)**	0.99 (0.94 – 1.05)	0.97 (0.92 – 1.03)

RR, relative risk per 1 category increase in exposure variable. **Expressed as β coefficient per 1 category increase in exposure variable.

Exposure variables were skin phenotypic traits (resistance to sunburn, ability to tan or hair colour).

Boldface denotes statistically significant result.

NMSC, non-melanoma skin cancer. BG grade, Beagley-Gibson grade (cutaneous photodamage). *Also adjusted for smoking.

Model 1: adjusted for age, sex and season of interview. Model 2: further adjusted for melanin density. Categories for ability to tan were 0: no tan, 1:light tan, 2: medium tan, 3: dark tan (4 categories); for resistance to sunburn were 0: burn within 30 minutes, 1: burn within 30-60 minutes, 2: burn within 1-2 hours, 3: burn over 2 hours and 4: never burn (5 categories); for hair colour were 0: red, 1: blond, 2: brown, 3: black (4 categories).

Analysis included entire cohort (*n*=1072) unless otherwise stated. Lifetime sun exposure in summer (*n*=848) and winter (*n*=846), physical activity in summer (*n*=848) and winter (*n*=846) and photodamage (BG grade, *n*=812) were quantified at the 2.5 year TASOAC follow up and consequently assessed in a fewer study participants. Participants who responded 'don't know' or did not answer the questions related to non-melanoma skin cancer at baseline were excluded from the non-melanoma skin cancer analysis (*n*=1015). Categories for sun exposure and outdoor physical activity variables are summarised in Supplemental Table 1.

Table 3. The association between skin photosensitivity and fracture risk factors

Fracture risk factors	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
Resistance to sunburn			
BMD (g/cm^2)			
Total hip	-0.002 (-0.009 – 0.004)	-0.003 (-0.010 – 0.003)	-0.005 (-0.012 – 0.002)
Femoral neck	-0.005 (-0.011 – 0.000)	**-0.006 (-0.012 – -0.004)**	**-0.006 (-0.012 – -0.000)**
Lumbar spine	-0.003 (-0.012 – 0.005)	-0.006 (-0.014 – 0.003)	-0.006 (-0.014 – 0.003)
Total body	-0.002 (-0.008 – 0.003)	-0.005 (-0.011 - 0.002)	**-0.006 (-0.013 - -0.000)**
25-hydroxyvitamin D (nmol/L)	**1.25 (0.40 – 2.10)**	0.60 (-0.28 – 1.49)	0.42 (-0.50 – 1.33)
Falls risk	0.03 (-0.01 – 0.07)	0.04 (-0.01 – 0.08)	0.04 (-0.00 – 0.08)
Ambulatory activity (steps per day)	99 (-60 – 259)	127 (-40 – 296)	105 (-68 – 279)
Ability to tan			
BMD (g/cm^2)			
Total hip	0.007 (-0.002 – 0.015)	0.007 (-0.002 – 0.018)	0.010 (-0.000 – 0.021)
Femoral neck	0.004 (-0.003 – 0.012)	0.005 (-0.004 – 0.013)	0.007 (-0.002 – 0.017)
Lumbar spine	**0.012 (0.001 – 0.023)**	**0.010 (-0.002 – 0.023)**	**0.014 (0.000 – 0.027)**
Total body	**0.011 (0.004 – 0.019)**	**0.010 (0.001 – 0.019)**	**0.013 (0.004 – 0.022)**
25-hydroxyvitamin D (nmol/L)	**2.55 (1.42 – 3.68)**	**1.40 (0.10 – 2.69)**	**1.43 (0.07 – 2.80)**

Falls risk	-0.02 (-0.07 – 0.04)	-0.00 (-0.07 – 0.06)	-0.01 (-0.08 – 0.05)
Ambulatory activity (steps per day)	59 (-153 – 272)	122 (-124 – 368)	40 (-219 – 299)

β coefficients represent per 1 category increase in exposure variable. Exposure variables were resistance to sunburn and ability to tan.

Boldface denotes statistically significant result.

BMD, bone mineral density. Model 1, adjusted for age, sex, body mass index and season of interview. BMD outcomes additionally adjusted for smoking status.

Model 2, further adjusted for constitutive melanin density.

Model 3, further adjusted hair colour and ability to tan (resistance to sunburn) or resistance to sunburn (ability to tan) as appropriate.

Categories for ability to tan were 0: no tan, 1:light tan, 2: medium tan, 3: dark tan (4 categories) and for resistance to sunburn were 0: burn within 30 minutes, 1: burn within 30-60 minutes, 2: burn within 1-2 hours, 3: burn over 2 hours and 4: never burn (5 categories).

Table 4. Multivariate associations between skin photosensitivity and prevalent fractures

Prevalent fracture outcomes	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)	Model 4 RR (95% CI)
Resistance to sunburn				
Any fracture	0.97 (0.92 – 1.03)	0.96 (0.91 – 1.02)	**0.94 (0.89 – 1.00)**	**0.94 (0.88 – 1.00)**
Vertebral fracture	1.06 (0.79 – 1.41)	1.07 (0.81 – 1.43)	0.97 (0.72 – 1.30)	0.93 (0.68 – 1.27)
Nonvertebral fracture	0.97 (0.92 – 1.03)	0.96 (0.91 – 1.02)	0.94 (0.89 – 1.00)	0.94 (0.89 – 1.00)
Major fracture	0.99 (0.91 – 1.09)	0.98 (0.90 – 1.07)	0.97 (0.86 – 1.08)	0.94 (0.86 – 1.04)
Ability to tan				
Any fracture	1.03 (0.95 – 1.11)	1.02 (0.95 – 1.10)	0.98 (0.90 – 1.07)	1.01 (0.92 – 1.10)
Vertebral fracture	1.34 (0.92 – 1.96)	1.37 (0.94 – 1.99)	1.15 (0.74 – 1.77)	1.08 (0.69 – 1.68)
Nonvertebral fracture	1.02 (0.95 – 1.10)	1.02 (0.94 – 1.10)	0.99 (0.90 – 1.07)	1.02 (0.93 – 1.11)
Major fracture	1.06 (0.94 – 1.20)	1.06 (0.93 – 1.20)	1.00 (0.87 – 1.14)	1.01 (0.87 – 1.16)

RR, relative risk per 1 category increase in exposure variable. Exposure variables were resistance to sunburn and ability to tan.

Boldface denotes statistically significant result.

Model 1: adjusted for age, sex, body mass index, smoking status and season of interview.

Model 2: further adjusted for fracture risk factors (25-hydroxyvitamin D, bone mineral density, falls risk).

Model 3: further adjusted for constitutive melanin density.

Model 4: further adjusted for hair colour and ability to tan (resistance to sunburn) or resistance to sunburn (ability to tan) as appropriate.

Categories for ability to tan were 0: no tan, 1:light tan, 2: medium tan, 3: dark tan (4 categories) and for resistance to sunburn were 0: burn within 30 minutes, 1: burn within 30-60 minutes, 2: burn within 1-2 hours, 3: burn over 2 hours and 4: never burn (5 categories).

Table 5. Association between skin photosensitivity and incident fracture over 2.5, 5 and 10 years

Incident fracture outcomes	2.5 year follow up (*n*=856) Model 1† RR (95% CI)	2.5 year follow up (*n*=856) Model 2‡ RR (95% CI)	5 year follow up (*n*=750) Model 1† RR (95% CI)	5 year follow up (*n*=750) Model 2‡ RR (95% CI)	10 year follow up (*n*=554) Model 1† RR (95% CI)	10 year follow up (*n*=554) Model 2‡ RR (95% CI)
Resistance to sunburn						
Any fracture	1.25 (0.958 – 1.58)	1.14 (0.88 – 1.47)	1.17 (0.98 – 1.38)	1.13 (0.94 – 1.35)	1.04 (0.91 – 1.19)	1.04 (0.90 – 1.19)
Nonvertebral fracture	**1.32 (1.02 – 1.71)**	1.25 (0.96 – 1.64)	1.18 (0.99 – 1.42)	1.15 (0.95 – 1.40)	1.05 (0.91 – 1.21)	1.05 (0.90 – 1.21)
Major fracture	**1.56 (1.06 – 2.28)**	1.37 (0.91 – 2.05)	1.22 (0.96 – 1.56)	1.24 (0.96 – 1.61)	1.07 (0.88 – 1.30)	1.11 (0.92 – 1.38)
Ability to tan						
Any fracture	1.14 (0.83 – 1.56)	0.88 (0.61 – 1.28)	1.08 (0.85 – 1.35)	0.96 (0.74 – 1.26)	1.00 (0.85 – 1.19)	0.99 (0.81 – 1.21)
Nonvertebral fracture	1.15 (0.82 – 1.62)	0.97 (0.65 – 1.44)	1.09 (0.86 – 1.39)	1.00 (0.75 – 1.33)	1.00 (0.83 – 1.21)	0.97 (0.78 – 1.21)
Major fracture	1.37 (0.84 – 2.26)	0.90 (0.50 – 1.62)	0.99 (0.72 – 1.35)	0.97 (0.66 – 1.41)	0.90 (0.70 – 1.16)	0.97 (0.72 – 1.31)

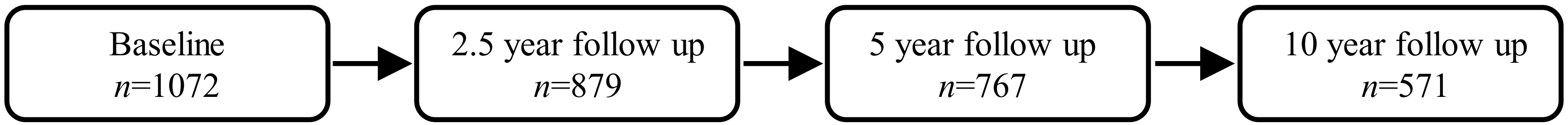
RR, relative risk per 1 category increase in exposure variable. Exposure variables were resistance to sunburn and ability to tan.

Boldface denotes statistically significant result.

Model 1: adjusted for age, sex, body mass index, current smoking and season of interview.

Model 2: further adjusted for constitutive melanin density. Categories for ability to tan were 0: no tan, 1:light tan, 2: medium tan, 3: dark tan (4 categories) and for resistance to sunburn were 0: burn within 30 minutes, 1: burn within 30-60 minutes, 2: burn within 1-2 hours, 3: burn over 2 hours and 4: never burn (5 categories).

Supplemental Figure 1. TASOAC follow up and data collection



Data analysed (Baseline):

- Age, sex, BMI
- Smoking status
- Skin photosensitivity
- Melanin density
- 25OHD, BMD, falls risk
- Steps per day
- Fracture
- NMSC
- Sun exposure (most recent season)
- Sun protection behaviours

Data analysed (2.5 year follow up):

- Fracture
- Ethnicity
- Photodamage (BG grade)
- Sun exposure (lifetime)
- Outdoor physical activity (lifetime)

Data analysed (5 year follow up):

- Fracture

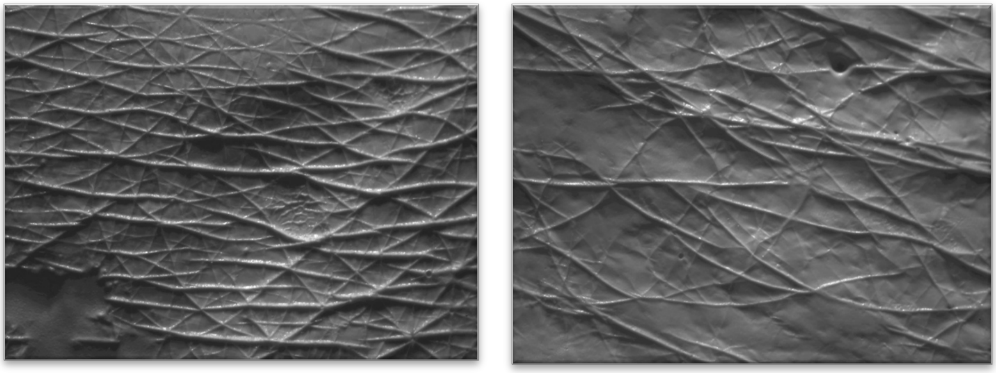
Data analysed (10 year follow up):

- Fracture

Timing of relevant data collection and number of participants at each TASOAC follow up.

BMI, body mass index; 25OHD, 25-hydroxyvitamin D; BMD, bone mineral density; NMSC, non-melanoma skin cancer; BG grade, Beagley-Gibson grade (cutaneous photodamage).

Supplemental Figure 2. Representative silicone skin casts



A B

Silicone skin casts were taken from a sun exposed area, such as the dorsum of the hand, and graded according to the Beagley-Gibson method. Pictured are representative skin casts demonstrating more (B) or less (A) microarchitectural deterioration.

Supplemental Table 1. Questions used to quantify skin phenotype and sun exposure variables

Variable	Assessment by participant-administered questionnaire	Categories
Ability of skin to tan	Question: *"At the end of summer or after a two week holiday in the sun, what kind of tan would you have?"*	0: Dark tan; 1: Medium tan; 2: Light tan; 3: Practically no tan
Resistance of skin to sunburn	Question: *"How does your skin react when you go out in the sun, in the middle of the day, for the first time in summer, without sunscreen?"*	0: Never burn; 1: Burn after more than 2 hours sun exposure; 2: Burn after 1 - 2 hours; 3: Burn after 1/2 - 1 hour; 4: Burn within half an hour
Lifetime number of sunburns where the pain lasted more than two days	Question: *"In your lifetime how many times have you been sunburnt, where the pain has lasted two or more days?"*	0: Never, 1: Once; 2: 2-5 times; 3: 6-10 times; 4: more than 10 times
Natural hair colour	Question: *"What was your natural hair colour as a young adult (20 - 30)?"*	0: Black; 1: Dark Brown; 2: Brown; 3: Light Brown; 4: Mousy Blond; 5: Light Blond; 6: Red
Leisure time sun exposure	Question: "*During* weekends and holidays, *how much time would you normally have spent in the sun?*" (Separately assessed for winter and summer).	Hours per day 0: <1; 1: 1-2; 2: 2-3; 3: 3-4; 5: >4
Sun protection behaviours	Question: *"When outside in the last summer, how often did you use a sunscreen or make sure you were covered up?"*	0: Never/rarely; 1: Occasionally; 2: Most of the time; 4: Always
Outdoor physical activity	Question: "*How much did your activities (day sports, spectator sports, gardening, walking, work activities, etc) take you outside*." (Separately assessed for winter and summer).	0: Not that often; 1: A moderate amount; 2: Quite a lot; 3: Virtually all the time

Participant-administered questionnaire questions and response categories used to quantify skin phenotype, sun exposure, outdoor physical activity, sun protection behaviours and non-melanoma skin cancer prevalence.

Supplemental Table 2. Coding of skin phenotypic traits

Coding	Skin phenotypic trait: Resistance to sunburn	Ability to tan	Hair colour
0	Burn within 30 minutes	No tan	Red
1	Burn within 30-60 minutes	Light tan	Blond
2	Burn within 1-2 hours	Medium tan	Brown
3	Burn after >2 hours	Dark tan	Black
4	Never burn		

Individual skin phenotypic traits were recoded from most photosensitive to least photosensitive (most photoresistant), so that those most able to tolerate high ultraviolet radiation doses had the highest score. Self-report of hair colour was consolidated to a four-category variable.

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