Looking for Sunshine: Genetic Predisposition to Sun Seeking in 265,000 Individuals of European Ancestry

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Despite growing public awareness of the adverse consequences of excessive sun exposure, modifying sun-seeking behavior is challenging because it appears to be driven by addictive mechanisms. This can have effects on health because sun exposure, although beneficial, when prolonged and repeated shows a causal relationship with skin cancer risk. Using data from 2,500 United Kingdom twins, we observed sun seeking to be significantly heritable (h2 $\geq$ 58%). In a GWAS meta-analysis of sun-seeking behavior in 261,915 subjects of European ancestry, we identified five GWAS-significant loci previously associated with addiction, behavioral and personality traits, cognitive function, and educational attainment and enriched for CNS gene expression: *MIR2113* ($P = 2.08 \times 10^{-11}$), *FAM76B/MTMR2/CEP57* ($P = 3.70 \times 10^{-9}$), *CADM2* ($P = 9.36 \times 10^{-9}$), *TMEM182* ($P = 1.64 \times 10^{-8}$), and *PLCL1/LINC01923/SATB2* ($P = 3.93 \times 10^{-8}$).
These findings imply that the behavior concerning UV exposure is complicated by a genetic predisposition shared with neuropsychological traits. This should be taken into consideration when designing awareness campaigns and may help improve people's attitudes toward sun exposure.

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INTRODUCTION

Sun-seeking behavior has considerably changed in the past hundred years. Before the 20th century, a tanned skin was considered inappropriate because it was linked to outdoor labor. Starting from the 1920s, this trend changed, and tanned skin became increasingly popular, with fashion magazines switching adverts about skin bleaching to tips about how to obtain a tan (Martin et al., 2009). In many contemporary Western societies, tanned skin is considered attractive and a sign of good health and wealth, and this can explain, in part, the rise in tanning habits and UV exposure (Holman and Watson, 2013). However, many factors are likely to play a role in sun-seeking behavior.

UV exposure is important for health because it is necessary for vitamin D synthesis. Vitamin D deficiency has been linked to rickets, higher cancer incidence, autoimmune diseases, psychiatric disorders, and increased all-cause mortality (Holick, 2004; Lindqvist et al., 2014). However, excessive levels of radiation and intentional tanning behavior are critical risk factors for skin cancers (Holick, 2004).

Individuals with fair skin are more likely to be sun seekers for cosmetic reasons than their counterparts with darker skin (Suppa et al., 2013), even though they are more susceptible to UV-related sunburns (Falk and Anderson, 2013). Moreover, subjects with fair complexion or with personal or family history of skin cancers, who should be aware of the risk of excessive sun exposure, have been reported to be as likely to seek the sun as individuals without these risk factors (Cartmel et al., 2013; Mayer et al., 2012).

It has been suggested that tanning behavior has an addictive component, with many sunbed users meeting addiction diagnostic criteria and reporting higher use of alcohol and marijuana than nonusers, together with symptoms of anxiety (Mosher and Danoff-Burg, 2010). The younger they start using sunbeds, the more they show addiction features similar to those for alcohol and drug abuse (Robinson and Fisher, 2014).

Experiments in humans and murine models seem to support the hypothesis that exposure to UV radiation might be addictive, acting through the increased blood release of beta endorphins lasting the entire duration of exposure (Fell et al., 2014; Jussila et al., 2016). Moreover, it has been shown that UV exposure is a reinforcing stimulus (Feldman et al., 2004).

Given that UV exposure can have both positive and negative effects on health, depending on the length and frequency of exposure as well as UV dosage, it is important to

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Abbreviations: DSUK, days spent sunbathing in the UK; DZ, dizygotic; LD, linkage disequilibrium; lncRNA, long noncoding RNA; MZ, monozygotic; UK, United Kingdom; WHC, weeks spent in hot climates

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understand what proportion of the observed variability in sun-seeking behavior is influenced by environmental factors and personal choices and whether heritable genetic factors are involved.

Using 2,500 participants from the TwinsUK cohort (Abbasian et al., 2019), for which detailed sun-seeking behavioral traits, skin phenotypes, and extensive health-related and demographic information have been collected, we first investigated whether sun-seeking behavior was under genetic control. Then, we looked for the underlying genetic factors through a GWAS of 260,000 participants in two large population-based cohorts (UK Biobank [Bycroft et al., 2018] and Harvard, which includes Nurses' Health Study, Nurses' Health Study 2 [Bao et al., 2016], and Health Professionals Follow-up Study [Lee et al., 2019]).

RESULTS

Tanning ability and socioeconomic status in TwinsUK

We firstly assessed the influence of tanning ability, evaluated through the Fitzpatrick classification (Fitzpatrick, 1988), on sun-seeking behavior in a sample of middle-aged female twins from the TwinsUK cohort (Abbasian et al., 2019). We used our largest sample of more than 2,700 individuals on whom we had sun-seeking and tanning ability information, which was reduced for further analyses owing to incomplete overlap with covariates (see Materials and Methods and Supplementary Table S2). Sun-seeking behavior was measured as the number of weeks spent abroad in hot climates (WHC) and the number of days spent sunbathing in the United Kingdom (UK) (DSUK). Both traits were significantly associated with tanning ability ($\beta = 0.19$, standard error = 0.04, P-value = 7.61×10^{-8} and $\beta = 0.30$, standard error = 0.03, P-value = 2.25×10^{-17} for WHC and DSUK, respectively), thus suggesting that subjects with higher ability to tan were more likely to seek sun exposure.

Then, considering that the possibility of enjoying sun exposure is influenced by socioeconomic status and more significantly so for holidays abroad in hot climates, we tested our traits for association with deprivation index, a well-accepted measure of social status (Blane et al., 1989), available for a subset of circa 2,500 individuals (see Materials and Methods). As expected, deprivation index was significantly associated with WHC and with people of higher socioeconomic status spending more time on holidays in hot countries ($\beta = -1.04$, standard error = 0.04, P-value = 7.28×10^{-6}) but not with DSUK (Supplementary Table S2).

Hence, further analyses were carried out using adjusted sun-seeking behavioral traits, controlling for both tanning ability and socioeconomic status.

Sun-seeking behavior is heritable

To assess the differences in concordance for sun-seeking behavior between monozygotic (MZ) and dizygotic (DZ) twins (that is, whether they seek sun exposure or do not seek sun exposure in the same way), we looked at differences in correlations within MZ pairs compared with those within DZ pairs, for both WHC and DSUK (see Materials and Methods). The intraclass correlations were significantly and consistently higher in MZ than in DZ twins (WHC empirical P-value = 3.71×10^{-3}, DSUK empirical P-value = 3.24×10^{-4}; see Materials and Methods). Significant differences were observed only after the age of 14 years for WHC—because WHC were also recalled for multiple age ranges (Supplementary Table S3 and Supplementary Figure S1). Heritability analyses supported an important genetic contribution to both traits, with WHC and DSUK showing a heritability of 58% (95% confidence interval = 54–63%) and 67% (95% confidence interval = 62–70%), respectively (Table 1).

Heritability estimates for WHC at different age ranges showed much lower genetic influence and a predominant role of common environmental effects before the age of 15 years (see Materials and Methods), highlighting an important influence of the family environment (and parental choice) on holidays habits in childhood. Common environmental effects were negligible after childhood, whereas the average heritability increased with age, reaching a plateau of 53% (minimum–maximum = 51–55%; Table 1 and Supplementary Figure S1) in adulthood.

Five genetic loci are associated with sun-seeking behavior

With the aim of identifying the genetic regions involved in sun-seeking behavior, we investigated two large samples of European origin from the UK (UK Biobank) and the US (Harvard), including 236,362 and 25,553 individuals, respectively, for whom genome-wide genetic data and information on hours of sun exposure were available. An adjustment for socioeconomic status was done for the UK Biobank analyses, whereas we deemed it not necessary for the Harvard sample sets because the participants in each cohort come from a homogeneous socioeconomic background (see Materials and Methods and Supplementary Tables S5–S7). The sample set was divided into two geographical subcohorts: North (n = 153,704) and South (n = 82,658) (Supplementary Table S6). The division was carried on considering the different sunshine hours in the two areas of the UK. Indeed, the number of sunshine hours in the Northern part of the country is significantly lower than that in the South. Interestingly, this also gives rise to different rates of melanoma in the two regions (Wallingford et al., 2013).

We then meta-analyzed the results from the UK Biobank and Harvard cohorts. The meta-analysis genomic inflation

Table 1. Heritability in the TwinsUK Cohort

Trait	n	A (95% CI)	C (95% CI)	E (95% CI)
WHC	2,500	0.58 (0.53–0.63)	—	0.42 (0.37–0.47)
WHC (age range, y)				
0–14	2,466	0.05 (0.04–0.06)	0.93 (0.92–0.94)	0.02 (0.01–0.02)
15–24	2,486	0.71 (0.68–0.75)	—	0.29 (0.25–0.32)
25–34	2,352	0.55 (0.50–0.61)	—	0.45 (0.39–0.50)
35–44	2,004	0.53 (0.46–0.59)	—	0.47 (0.41–0.54)
>44	1,548	0.51 (0.44–0.58)	—	0.49 (0.42–0.56)
DSUK	2,406	0.67 (0.62–0.71)	—	0.33 (0.29–0.38)

Abbreviations: A, genetic additive effect; C, common environmental effect; CI, confidence interval; DSUK, days spent sunbathing in the UK; E, unique environmental effect; UK, United Kingdom; WHC, weeks spent in hot climate.
ACE effects for WHC (both total and at different age ranges) and DSUK.

factor was 1.09, with linkage disequilibrium (LD) score regression analysis excluding the presence of confounding biases and highlighting an underlying polygenic architecture (intercept = 0.90 ± 0.01).

The meta-analysis identified 370 genome-wide significantly associated (*P*-value < 5×10^{-8}) SNPs and insertions and deletions, located in five distinct loci (Table 2 and Figure 1 and Supplementary Tables S9 and S10 and Supplementary Figures S9–S13).

Among the most significant associations, there were two insertions and deletions: rs5793745, whose closest genome-wide–significant SNP was rs1944080, 12 kilobases apart, with an association *P*-value = 8.09×10^{-9} and rs201815280, whose closest genome-wide–significant SNP, 315 base pairs apart, was rs10433525 (*P*-value = 1.21×10^{-8}).

Functional characterization

All associated loci pinpointed genes (*TMEM182, CADM2, MIR2113, MTMR2/CEP57/FAM76B,* and *PLCL1/LINC01923/SATB2*) that have previously been linked by GWASs to behavioral traits including addiction (Clifton et al., 2018; Erzurumluoglu et al., 2019; Hill et al., 2019; Karlsson Linnér et al., 2019; Lee et al., 2018; Liu et al., 2019; Nagel et al., 2018a; Pasman et al., 2018; Savage et al., 2018; Strawbridge et al., 2018), personality traits (Nagel et al., 2018a), cognitive function (Davies et al., 2015; Lam et al., 2017; Lee et al., 2018; Nagel et al., 2018a), or educational attainment (Lee et al., 2018; Okbay et al., 2016). Moreover, they are in LD with variants also associated with those traits (Supplementary Table S9).

Besides, a gene-based analysis showed that *CADM2* is associated with alcohol consumption (Sanchez-Roige et al., 2019b).

Interrogation of the miRTarBase database (Huang et al., 2020) identified 132 *MIR2113* target genes (Supplementary Table S15). A look up on the GWAS catalog (2020-06-10) (Buniello et al., 2019) revealed that some of these genes have been previously associated with alcohol consumption (*IGF2BP1*, *RPP25*) (Feitosa et al., 2018; Kranzler et al., 2019), smoking (*CHEK2*, *CNNM2*, *ERBB3*) (Erzurumluoglu et al., 2019; Karlsson Linnér et al., 2019; Liu et al., 2019; Sung et al., 2018; Wootton et al., 2019), or both (*ADRB1*) (Feitosa et al., 2018; Sung et al., 2018). Moreover, interestingly, *MIR2113* targets included *MDM2*, *NRAS,* and *MITF*, melanoma-related genes (Levy et al., 2006; Muthusamy et al., 2006; Riverso et al., 2017).

A total of 228 target genes for the long noncoding RNA were identified (Supplementary Table S16). A look up on the GWAS catalog (2020-06-10) (Buniello et al., 2019) revealed that among these, 13 were associated by the previous GWAS with addiction traits such as smoking (*KCNJ6*, *HYKK*, *MIR100HG*, *NFAT5*, and *ZNF207*) (Liu et al., 2019), alcohol use (*POU2F2*, *RPS6KA5*, *OTX2*) (Brazel et al., 2019; Evangelou et al., 2019; Karlsson Linnér et al., 2019; Liu et al., 2019), and both smoking and alcohol or drug dependence (*AGBL4*, *SDK1*, *SPATS2L*, *MDM4*, *ESRRG*) (Brazel et al., 2019; Cai et al., 2020; Erzurumluoglu et al., 2019; Feitosa et al., 2018; Kapoor et al., 2013; Karlsson Linnér et al., 2019; Kichaev et al., 2019; Liu et al., 2019; Sun et al., 2019; Sung et al., 2018; Treutlein et al., 2017). Moreover, one of *LINC01923*'s targets was *MDM2* (Muthusamy et al., 2006). SNPs functional characterization confirmed the meta-analysis results to be clustered at five independent genomic loci (see Material and Methods and Supplementary Table S10).

We further performed gene-based analysis (see Materials and Methods) using GWAS summary statistics to investigate the relationship between genes and sun-seeking behavior variables. This analysis highlighted 12 genes significantly associated with sun-seeking behavior (*P*-values < 0.05/18,798 = 2.66×10^{-6}; Supplementary Table S11). Four of these genes are located in two genome-wide–significant regions identified in our GWAS meta-analysis (*CADM2*, *MTMR2/CEP57/FAM76B*). The additional genes are also related to neuropsychological traits, such as cognitive function (*CAMKV*, *ARHGAP15*, *SPATA*, and *SNX29*), intelligence (*CAMKV*, *ARGHAP15*, and *SNX29*), educational attainment (*SNX29* and *CAMKV*), general risk tolerance (*BLK*), being a morning person (*CAMKV*, *ARGHAP15*, and *RNF123*), feeling fed up (*RNF123*), worry (*MCHR1*), and schizophrenia (*PTPN21*) (Chen et al., 2011; Davies et al., 2018, 2016, 2015; Jones et al., 2019; Karlsson Linnér et al., 2019; Lee et al., 2018; Luciano et al., 2018; Nagel et al., 2018a; 2018b; Okbay et al., 2016; Savage et al., 2018). Building on the gene-based analyses, we performed gene-set enrichment analyses, with no statistically significant result. However, significant tissue enrichment was identified for the brain

Table 2. Genome-Wide Meta-Analysis of Sun-Seeking Behavior

Genomic Variant	CHR	BP	A1	A2	N	*P*-value	Direction	Het I^2	Gene
rs76112426	6	98,532,427	T	G	261,915	2.08×10^{-11}	−−−	0	*MIR2113*
rs5793745	11	95,491,692	G	GT	259,010	3.70×10^{-9}	−−−	0	*FAM76B/MTMR2/CEP57*
rs201815280	3	85,546,181	A	ACACC	261,915	9.36×10^{-9}	+++	0	*CADM2*
rs2570497	2	104,441,546	T	C	261,915	1.65×10^{-8}	−−+	83.3	*TMEM182*
rs13393754	2	199,518,159	T	C	261,915	3.93×10^{-8}	−−−	43.5	*PLCL1/LINC01923/SATB2*

Abbreviations: BP, base pair; CHR, chromosome.

The top-associated variants are reported at each locus, along with their genomic coordinates (CHR and BP; GRCh37.p13), effect (A1) and alternative allele (A2), number of subjects for whom the variant was available (N), meta-analysis *P*-value, the direction of effects in the three cohorts (UK Biobank North, UK Biobank South, and Harvard), heterogeneity between studies (Het I^2), and encompassing gene(s).+ indicates that allele A1 is positively associated with sun seeking and – indicates that allele A1 is negatively associated with sun seeking.

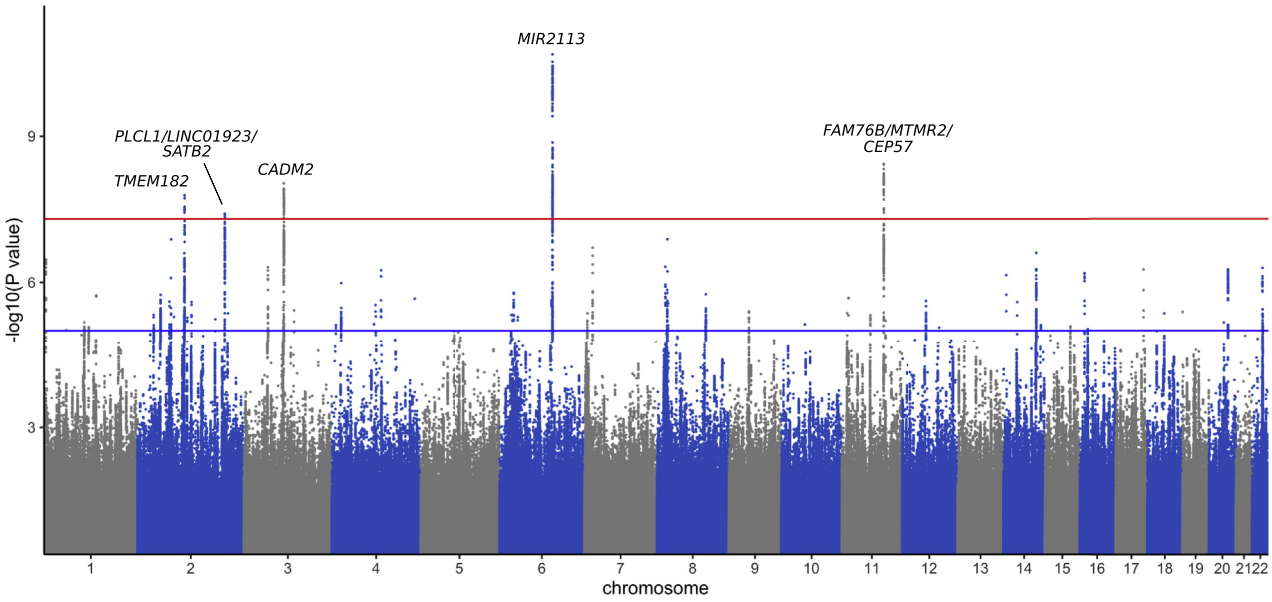

Figure 1. Manhattan plot of sun-seeking behavior for the meta-analysis of UK Biobank and Harvard GWASs results (N = 261,915). The x-axis shows the genomic coordinates (GRCh37.p13) of the tested genomic variants (N = 8,385,325), and the y-axis reports the $-\log_{10}$ (*P*-value). The horizontal red line indicates the threshold for genome-wide significance at *P*-value = 5.0×10^{-8}. The horizontal blue line indicates the suggestive threshold of *P*-value = 1.0×10^{-5}. UK, United Kingdom.

(*P*-value = 2.38×10^{-7}) and more specifically for CNS tissues except for the spinal cord (lowest *P*-value = 7.33×10^{-7}, Supplementary Tables S13–S14 and Supplementary Figure S14).

Heritability, evaluated with LD score regression (Bulik-Sullivan et al., 2015), equals 4.7%.

DISCUSSION

The deleterious effects of excessive sun exposure on the skin are well-known. Nonetheless, public health campaigns aiming at reducing sun exposure and skin cancer incidence have not been successful (Gordon and Rowell, 2015). Rewarding mechanisms after a tanning session have been observed (Feldman et al., 2004), and addiction to tanning has been suggested (Mosher and Danoff-Burg, 2010). Addictive behavior can be heritable (Kendler et al., 2000; Vink et al., 2005), and addiction to tanning may explain the high percentage of individuals who practice unsafe UV exposure, especially for those who are aware of their risk because of fair skin and personal or familial history of skin cancer (Mayer et al., 2012; Robinson and Fisher, 2014).

In this study, we analyzed sun-seeking behavioral data in circa 2,500 middle-aged women from the TwinsUK cohort, and more than 260,000 British and American men and women of European ancestry from the UK Biobank and Harvard cohorts.

Sun seeking in the TwinsUK cohort was positively associated with socioeconomic status and tanning ability, in line with previous literature (Falk and Anderson, 2013; Holman and Watson, 2013). Even after adjusting for these covariates, we still showed a higher intraclass correlation in MZ twins than in DZ twins for both WHC and DSUK. This suggests that sun-seeking behavior is more influenced by genetic than nongenetic factors. The heritability estimates confirmed a significant genetic component, with 58% and 67% heritability for WHC and DSUK, respectively. Negligible heritability and nonsignificant differences in intraclass correlation between MZ and DZ twins were observed before the age of 15 years, likely owing to parental choices. Thereafter, heritability increased. Overall, these results show that sun-seeking behavior is largely influenced by genetic factors independently of the individual tanning ability and socioeconomic status.

GWAS meta-analysis of sun-seeking data in 261,915 subjects from the UK Biobank and the Harvard cohorts identified five genetic loci involved in sun-seeking behavior: *TMEM182, CADM2, MIR2113, MTMR2/CEP57/FAM76B,* and *PLCL1/LINC01923/SATB2*. All the five genetic loci have previously been identified in GWAS for behavioral traits and addiction (Clifton et al., 2018; Erzurumluoglu et al., 2019; Hill et al., 2019; Karlsson Linnér et al., 2019; Lee et al., 2018; Nagel et al., 2018a; Pasman et al., 2018; Savage et al., 2018; Strawbridge et al., 2018), educational attainment (Lee et al., 2018; Okbay et al., 2016), personality traits (Nagel et al., 2018a), or cognitive function (Davies et al., 2015; Lam et al., 2017; Lee et al., 2018; Nagel et al., 2018a). Moreover, both the microRNA *MIR2113* and the long noncoding RNA (lncRNA) *LINC01923* identified in the study are likely involved in the wider regulation of addiction traits such as smoking and alcohol and drug use. Interestingly, they both seem to influence melanoma-related genes, thus suggesting a shared genetic background between the propensity to sun exposure and melanoma.

CADM2 plays a role in the regulation of behavioral traits and addiction, for example, anxiety levels and cannabis use (Pasman et al., 2018) and other risky behaviors, such as the number of sexual partners and automobile speeding propensity (Karlsson Linnér et al., 2019), alcohol consumption, Alcohol Use Disorders Identification Test score (which is in turn used to measure alcohol consumption) (Liu et al., 2019;

Sanchez-Roige et al., 2019b), as well as general risk tolerance (Karlsson Linnér et al., 2019). *CADM2* expression in the brain was also positively correlated with sensation seeking (Sanchez-Roige et al., 2019a). Both studies of Liu et al. (2019) and Pasman (2018) were carried on using subjects from the UK Biobank, and research of Liu et al. (2019) also included subjects from Harvard's cohorts. SNPs significantly associated with cannabis and alcohol use in these studies at the *CADM2* locus are in LD with our top hit ($r^2 = 1$).

Sun-seeking behavior can be rightly framed in the context of risky types of behavior. *CADM2*, taking account of what we know from the literature, in particular the association with addiction traits such as cannabis and alcohol use and the high LD between our variant and those discovered for cannabis use and other at-risk behaviors, is a sensible candidate for the modulation of sun-seeking behavior. Interestingly, *CADM2* is also associated with vitamin D metabolism, as reported in a recent study on the UK Biobank (Manousaki et al., 2020). The associated SNP rs1972994 reported in this study was in high LD with our top SNP at the same locus ($r^2 > 0.9$), with the same allele associated with increased blood vitamin D levels and increased sun exposure.

MIR2113 has been associated with a decline in episodic memory in a candidate SNP study with few thousand older adults from Australia (Andrews et al., 2017) as well as with cognitive function (Davies et al., 2015) and bipolar disorder (Mühleisen et al., 2014). Within the *MTMR2/CEP57/FAM76B* locus, *MTMR2* has been linked to worry (Nagel et al., 2018b) and educational attainment (Lee et al., 2018), whereas *CEP57* has been linked to intelligence (Savage et al., 2018), cognitive function (Davies et al., 2018; Lee et al., 2018), and educational attainment (Lee et al., 2018). *TMEM182* has been previously associated with smoking behavior by a GWAS meta-analysis of European (including UK Biobank) and South Asian individuals (Erzurumluoglu et al., 2019), with their genome-wide significant-top hit at SNP rs6738833 in LD ($r^2 = 0.75$) with our SNP rs264977 (P-value $= 3.2 \times 10^{-7}$). The same locus has also been associated with education years (Lee et al., 2018). GWASs have identified *PLCL1* gene as having a role in chronotype (being a morning person [Jones et al., 2019]) and cognitive function (Lee et al., 2018). Finally, *SATB2* is associated with intelligence (Savage et al., 2018), mathematics ability (Lee et al., 2018), educational attainment (Lee et al., 2018), worry (Nagel et al., 2018a), and schizophrenia (Lee et al., 2018). The gene-based analysis supported these findings, confirming some of the meta-analysis loci and identifying other genes involved in similar phenotypes. Moreover, the tissue-specificity analysis indicates the enrichment of our GWAS results for genes expressed in the CNS.

The discovery that addiction-related loci are also associated with sun-seeking behavior is intriguing and adds up to the body of literature describing the addictive pattern that characterizes the use of indoor tanning devices. Moreover, it has recently been shown that many sunbathers and beachgoers can be classified as tanning dependent or tanning abusers (Toledo et al., 2019). Therefore, it is likely that people who spend a long time at the beach do so mostly for tanning purposes rather than for socializing or to practice sports.

Considering that these loci are associated with several traits related to substance abuse or at-risk behavior, it is possible that a common genetic architecture regulates different types of addiction to different behaviors and/or substances. Therefore, subjects who are sunseekers might also be at risk for other types of dependence. It would be interesting to investigate the connections between sun-seeking and other addiction phenotypes and the genetic regulation and biology behind them.

The main limitation of the study is that it is based on self-reported data and that the questions answered by the participants were not standardized for all the groups analyzed. However, concordance in results between the analyzed cohorts suggests that the different sun-seeking questions were not likely to have affected the results to a great extent.

In summary, we unveiled a genetic basis for sun-seeking behavior, showing that seeking UV exposure is not exclusively influenced by environmental or social factors, and importantly, we identified shared genetic determinants with addiction, other behavioral traits, and cognitive functions. The findings of the addictive nature of sun-seeking behavior are strengthened by the association of the loci at *CADM2* and *TMEM182* with addiction traits such as cannabis use (Pasman et al., 2018), alcohol abuse (Liu et al., 2019; Sanchez-Roige et al., 2019b), and smoking (Erzurumluoglu et al., 2019; Liu et al., 2019).

Therefore, tackling excessive sun exposure might be more challenging because it depends on intrinsic genetic characteristics, which lead to this behavior becoming addictive. It would be helpful for the public to be aware that they can have a predisposition for unsafe practices in the sun because it could make people more conscious of their risky behavior. This could be used to implement new strategies to control excessive sun exposure.

MATERIALS AND METHODS

Intraclass correlation in the TwinsUK cohort

We compared the intraclass correlation of the sun-seeking behavioral traits (corrected for tanning ability and deprivation index) between MZ and DZ twins. Pearson's method was used to calculate intraclass correlations. Then, Fisher's Z transformation was used to evaluate the statistical significance of the observed differential correlation between the two classes for each trait, validating it through a permutation test. For each trait, we simulated 1,000,000 datasets by the permutation of the zygosity label among pairs. The empirical P-values were calculated as the probability of observing a difference in intraclass correlation between random groups of twin pairs equal to or larger than what was observed between the original MZ and DZ assortments. The analyses were carried on with the R statistical environment (version 3.3.3).

Heritability in the TwinsUK cohort

We further assessed the relative contribution of genetic and environmental factors on the WHC and DSUK sun-seeking behavioral variables, using the function twinlm implemented in the R package mets (Holst et al., 2016) (version 1.2.2), which fits a classical twin model for quantitative data. The model included tanning ability, deprivation index, and age (only for total life sun exposure), as covariates. We tested the contribution of both the ACE (A: additive genetic effects, C: common environmental effects, E: unique or

random environmental effects) and the AE (A: additive genetic effects, E: unique or random environmental effects) models, which allow us to identify the proportion of heritable trait variance and the proportion due to shared and nonshared environmental effects. We chose the appropriate model minimizing the Bayesian information criterion (Supplementary Table S4).

Meta-analysis of the GWAS results

A meta-analysis of the results obtained with UK Biobank North, UK Biobank South, and Harvard cohorts was carried on with the METAL software (http://csg.sph.umich.edu/abecasis/metal/; Willer et al., 2010), using a weighted Z-score method on the basis of sample size, *P*-value, and direction of effects. Associations were considered significant and taken forward for functional characterization if the meta-analysis *P*-value was lower than 5×10^{-8}. Genomic control was applied to each input file as implemented by the METAL's parameter GENOMICCONTROL. Manhattan and Q–Q plots were generated with the R package qqman (version 0.1.4) (SD Turner, unpublished data, 2014). Regional association plots were generated with LocusZoom (version 0.4.8; http://locuszoom.org/) (Pruim et al., 2010). The genomic inflation factors (λ) of the meta-analysis and each GWAS were evaluated by the LD Hub web portal (Zheng et al., 2017).

LD score regression analysis

LD score regression (Bulik-Sullivan et al., 2015), as implemented in LD Hub (Zheng et al., 2017), was used to evaluate the proportion of inflation that is due to the presence of polygenic inheritance and to other confounding biases, such as population stratification as well as the SNP heritability.

Functional characterization

To identify behavioral or cognitive traits, which have been previously associated with the significant variants in our study, we queried the GWAS catalog (January 11, 2019) exploring all variants reaching a meta-analysis *P*-value lower than 5×10^{-8} and those in high LD with them, as identified by the online tool LDlink (https://ldlink.nci.nih.gov/?tab=home; Machiela and Chanock, 2015) (version 3.6; maximum distance: 500 kilobases, minimum LD threshold $r^2 = 0.7$, population: Great Britain).

We also looked for potential target genes of the microRNA and lncRNA identified in the meta-analysis. For the microRNA targets, we used miRTarBase (http://mirtarbase.cuhk.edu.cn/php/search.php) (Huang et al., 2020), which contains information on more than 13,404 experimentally validated interactions between microRNA and their targets. For the lncRNA targets, we interrogated LncRRIsearch (http://rtools.cbrc.jp/LncRRIsearch/) (Fukunaga et al., 2019), a web server for predictions of lncRNA–lncRNA and lncRNA–mRNA interactions, including 27,674 lncRNAs and 20,360 mRNAs.

We used Functional Mapping and Annotation of GWAS (Watanabe et al., 2017) to functionally characterize our variants. Functional Mapping and Annotation of GWAS is a web-based tool that processes GWAS summary statistics and provides annotations from 18 biological data sources. For the functional annotation, we did not use any SNP filter and retained all the SNPs in the five independent loci, with a minimum LD threshold of $r^2 = 0.6$ and minor allele frequency ≥ 0.01. Variants were mapped to genes on the basis of their physical position using the default 10 kilobases maximum distance between variant and gene.

Gene-based and gene-set analyses

Gene-based and gene-set analyses were performed using MAGMA (https://ctg.cncr.nl/software/magma; de Leeuw et al., 2015) as implemented in Functional Mapping and Annotation of GWAS on the basis of the summary statistics from our meta-analysis using the mean SNPs *P*-value to represent genes.

We applied a Bonferroni correction for the total number of genes ($0.05/18{,}798 = 2.66\times10^{-6}$) to identify those statistically significant.

In addition, MAGMA performs gene-set analysis using the gene *P*-values produced in the previous step. A linear model is used to test the association of a gene-set with the phenotype, and this can accommodate covariates, such as gene expression levels, and test the relationship between trait–gene associations and tissue-specific expression profiles in a gene-property analysis (de Leeuw et al., 2015; Watanabe et al., 2017).

The tissue-specificity test was performed using data from Genotype-Tissue Expression (https://gtexportal.org/home/; GTEx Consortium et al., 2013); both the 30 general tissue types and the 53 (more specific) tissue types were queried, producing *P*-value thresholds of 1.6×10^{-3} and 9.4×10^{-4}, respectively.

Data availability statement

Data generated during the study are available as Supplementary Files. Data on TwinsUK twin participants are available to bona fide researchers under managed access owing to governance and ethical constraints. Raw data should be requested through the TwinsUK website (http://twinsuk.ac.uk/resources-for-researchers/access-our-data/), and requests are reviewed by the TwinsUK Resource Executive Committee regularly. Data on UK Biobank participants are available to all bona fide researchers for all types of health-related research, which is in the public interest, upon request on the UK Biobank website (http://www.ukbiobank.ac.uk/). Further information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-up Study is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: MS, VB, MF, PH; Data Curation: MS, AV, XL, SR, VB; Formal Analysis: MS, AV, XL, MBF; Funding Acquisition: MF, JH; Investigation: MS, AV, XL; Methodology: MS, AV, XL; Project Administration: MF, JH; Resources: MF, JH; Software: MS, AV, XL; CS; Supervision: MF, VB; JH; Validation: MS, PH, MF, AV; Visualization: MS; Writing - Original Draft Preparation: MS, MF; Writing - Review and Editing: VB, MBF, AV, XL, SR, JH, PH, CS

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.08.014.

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