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A genetically informed study reveals modifiable pathways in skin cancer

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Abstract

Background Identifying modifiable risk factors is essential for the prevention of skin cancer; however, establishing causality can be challenging in conventional epidemiological studies. This study aimed to determine the causal associations of potentially modifiable risk factors with skin cancer using Mendelian randomization (MR).

Methods Genetic instruments for 53 risk factors, including socioeconomic status, dietary and lifestyle factors, anthropometric measures, medication use, and comorbidities, were identified from previous genome-wide association studies. Two-sample MR analyses were performed using summary statistics for three major types of skin cancer: melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Findings were verified using multiple MR methods under different assumptions and replication datasets.

Results Genetic liability to sunburn occasions, actinic keratosis, and prior skin cancers was associated with a higher risk of all three types of skin cancer, whereas genetic liability to vitiligo was associated with a lower risk. For specific skin cancer types, genetically predicted higher nevus counts and occupational class were associated with an increased risk of melanoma. Genetic liability to rheumatoid arthritis, type 2 diabetes, and increased physical activity were associated with a lower risk of BCC. Genetically predicated body mass index showed a negative association with BCC, and a positive association with SCC.

Conclusions Our study reaffirmed several previously established risk factors and identified novel potential risk factors for skin cancer. Further work is needed to unravel the biological pathways in different skin cancer types and translate our findings to inform public health policies.

Keywords Basal cell carcinoma, Melanoma, Mendelian randomization, Modifiable factor, Squamous cell carcinoma

Background

Skin cancer is the most frequently diagnosed cancer globally, and its incidence continues to rise [1]. Among the different types of skin cancer, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), collectively known as non-melanoma skin cancer or keratinocyte cancer, are the most prevalent. Melanoma, despite representing only 2% of all skin cancer cases, accounts for the majority of skin cancer-related fatalities.

One of the key strategies in reducing the burden of skin cancer is primary prevention, focusing on mitigating the influence of modifiable risk factors [2]. Exposure

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to ultraviolet (UV) radiation from the sun is unequivocally recognized as the most important risk factor in the development of skin cancer. However, for other potentially modifiable risk factors, such as smoking [3], alcohol consumption [4], dietary factors [5], physical activity [6], obesity [7], circadian disruption [8], and socioeconomic status [9], associations with skin cancer are far from conclusive. This uncertainty arises primarily because much of the existing evidence derives from conventional observational studies, which are susceptible to residual confounding and reverse causation bias, while data from randomized trials are notably scarce.

Mendelian randomization (MR) is a genetic epidemiological approach for evaluating the causal impact of risk factors on diseases, utilizing alleles as proxies or genetic instruments for these putative risk factors [10]. Because genetic alleles are randomly assorted at conception and are unaffected by the onset of the disease, this method minimizes the potential for confounding bias and reverse causation that could distort observational findings. MR analyses are increasingly popular in shedding light on the etiology of diseases, especially when investigating exposures that are impractical to test through randomized trials. Previous MR studies have examined the causal roles of several nutritional, lifestyle, and anthropometric factors in melanoma [11–14], with relatively limited attention paid to keratinocyte cancer. In this study, we implemented an MR framework to systematically examine the causal relationships between a broad spectrum of potentially modifiable risk factors and the risks of different skin cancer types.

Methods

This is a two-sample MR study that relied on publicly available summary statistics from genome-wide association studies (GWASs), and no individual-level data were included. As such, ethical approval and informed consent were not required. The reporting of this study adhered to the STROBE-MR (Strengthening the reporting of observational studies in epidemiology using mendelian randomization) guidelines [15].

Selection of and data sources for risk factors

Our study focused on potentially modifiable risk factors organized into the following categories: socioeconomic status, dietary and lifestyle factors, anthropometric measures, medication use, and diseases. We did not consider risk factors specific to women, such as hormonal and reproductive factors, because sex-specific data for skin cancer are not yet available. Within these categories, we examined specific risk factors that had been discussed in relation to any of the three types of skin cancer (melanoma, BCC, and SCC) in reviews and/or meta-analyses of population-based epidemiological studies. The specific search terms and strategies used in PubMed are listed in Supplementary Table 1. Subsequently, we conducted searches in the GWAS catalog [16] and the OpenGWAS project [17] to retrieve GWASs of these modifiable risk factors in participants of European ancestry and identify relevant genetic variants. A total of 53 potentially modifiable risk factors were included in the MR analysis. An overview of the data sources and the characteristics of the risk factors under investigation is provided in Table 1.

Data sources for skin cancer

Summary statistics for melanoma (30,134 cases and 81,415 controls) were obtained from the largest GWAS meta-analysis in individuals of European ancestry to date, combining data from 21 studies (including the UK Biobank) [18]. For BCC (20,791 cases and 286,893 controls) and SCC (7,402 cases and 286,892 controls), we obtained summary statistics from a GWAS conducted using the UK Biobank [19]. To address the concern regarding sample overlap, specifically for risk factors partly or entirely derived from the UK Biobank samples, we utilized GWAS summary statistics for melanoma (3,960 cases and 286,874 controls), BCC (18,982 cases and 287,137 controls), and SCC (3,251 cases and 287,137 controls) from the FinnGen for replication [20]. All skin cancer cases were clinically confirmed, primarily through nationwide cancer registries. Across most GWASs, genetic associations were adjusted for age, sex, and principal components of genetic ancestry to control for population stratification.

Selection of instruments

To implement polygenic MR, we constructed genetic instruments using single-nucleotide polymorphisms (SNPs) associated with the respective risk factor at conventional genome-wide significance ($P<5\times10^{-8}$), with minor allele frequencies > 0.01, and clumped them based on linkage disequilibrium (LD) ($r^2<0.001$ within a 10,000 kb window) utilizing the 1000 Genomes Project European reference panel [17]. We further excluded SNPs located within the major histocompatibility complex (MHC) region (chr6:27,477,797 – 34,448,354, GRCh37) because of their high polymorphisms and complex LD structure. For the medications of interest, genetic instruments were extracted from a prior drug-target MR study [21]. Briefly, *cis*-acting SNPs within the drug-target genes (±100 kb of gene boundaries) associated with their corresponding downstream biomarkers (i.e., systolic blood pressure for antihypertensive drugs, low-density lipoprotein cholesterol for statins, and glycated hemoglobin for metformin) at the genome-wide significance threshold ($P<5\times10^{-8}$) served as proxies for pharmacological modulation. A relaxed LD clumping parameter ($r^2<0.2$ within a 250 kb window) was applied to boost the statistical

Table 1 Characteristics of the GWASs of potentially modifiable factors considered in the MR analysis

Potentially modifiable factor	Year of publication	PMID	Data source	Sample size	Unit	No. of SNPs
Socioeconomic status						
Deprivation (Townsend deprivation index)	2018	29,846,171	UK Biobank	462,464	One SD, 3 points	18
Education (years of schooling)	2022	35,361,970	SSGAC	3,037,499	One SD, 3.4 years of schooling	603
Income	2019	31,844,048	UK Biobank	286,301	One unit in category	28
Occupational class	2022	34,613,391	UK Biobank	248,847	One unit in category	29
Diet and lifestyle						
Alcohol consumption	2019	30,643,251	GSCAN	941,280	One SD, 9 additional alcoholic drinks/week	72
Beta-carotene	2012	23,134,893	Nurses' Health Study	2,344	One SD	1
Chronotype[a]	2019	30,696,823	Meta-analysis	372,765/278,530	One unit in log odds	216
Coffee consumption	2019	31,046,077	UK Biobank	375,833	One SD, 0.5 cup of coffee/day	29
Copper	2013	23,720,494	Meta-analysis	2,603	One SD	2
Iron	2014	25,352,340	Meta-analysis	48,972	One SD	2
Lycopene	2016	26,861,389	HAPI Heart Study	441	One SD	1
Monounsaturated fatty acids	2022	35,213,538	UK Biobank	115,006	One SD	70
Omega-3 polyunsaturated fatty acids	2022	35,213,538	UK Biobank	115,006	One SD	55
Omega-6 polyunsaturated fatty acids	2022	35,213,538	UK Biobank	115,006	One SD	64
Physical activity (accelerometer-based measurement)	2018	29,899,525	UK Biobank	91,084	One SD, 8 milli-gravities	8
Saturated fatty acids	2022	35,213,538	UK Biobank	115,006	One SD	53
Selenium	2015	25,343,990	Meta-analysis	4,162	One SD	1
Smoking (lifetime smoking index)	2020	31,689,377	UK Biobank	462,690	One SD, 0.7 point	126
Sunburns	2018	29,892,013	UK Biobank	350,232	One unit in log odds	81
Total fat consumption	2021	32,393,786	SSGAC	268,922	One SD	5
Vitamin A (retinol)	2011	21,878,437	Meta-analysis	5,006	One SD	2
Vitamin B12	2013	23,754,956	Meta-analysis	45,576	One SD	7
Vitamin B9 (folate)	2013	23,754,956	Meta-analysis	37,341	One SD	2
Vitamin C	2021	33,203,707	Meta-analysis	52,018	One SD, 20 mmol/L	10
Vitamin D (25-hydroxyvitamin D)	2018	29,343,764	SUNLIGHT consortium	79,366	One SD	6
Vitamin E (alpha-tocopherol)	2011	21,729,881	Meta-analysis	7,781	One SD	3
Zinc	2013	23,720,494	Meta-analysis	2,603	One SD	2
Anthropometric measure						
Birthweight	2019	31,043,758	EGG consortium	297,356	One SD	25
Body mass index	2018	30,124,842	GIANT consortium	681,275	One SD, 5 kg/m2	507
Body surface area	2022	36,502,284	UK Biobank	337,198	One SD, 0.21 point	249
Childhood body mass index	2020	33,045,005	EGG consortium	39,620	One SD	17
Height	2018	29,892,013	GIANT consortium	673,878	One SD, 0.07 m	874
Nevus count	2018	30,429,480	Meta-analysis	52,506	One SD	6
Medication use						
Angiotensin receptor blockers	2017	29,846,171	UK Biobank	436,419	One SD, 19 mmHg	2
Angiotensin-converting enzyme inhibitors	2017	29,846,171	UK Biobank	436,419	One SD, 19 mmHg	1
Beta-blockers	2017	29,846,171	UK Biobank	436,419	One SD, 19 mmHg	6
Calcium channel blockers	2017	29,846,171	UK Biobank	436,419	One SD, 19 mmHg	24
Metformin	2017	29,846,171	UK Biobank	344,182	One SD, 6.75 mmol/mol	59
Statins	2017	29,846,171	UK Biobank	440,546	One SD, 39 mg/dL	14
Disease						
Actinic keratosis	2022	35,449,187	GERA cohort	16,352/46,758	One unit in log odds	9
Atopic dermatitis	2023	37,794,016	Meta-analysis	60,653/804,329	One unit in log odds	62

Table 1 (continued)

Potentially modifiable factor	Year of publication	PMID	Data source	Sample size	Unit	No. of SNPs
Cutaneous melanoma	2020	32,341,527	Meta-analysis	36,760/375,188	One unit in log odds	68
Inflammatory bowel disease	2015	26,192,919	IIBDGC	31,665/33,977	One unit in log odds	134
Keratinocyte cancer	2019	31,174,203	Meta-analysis	47,742/634,413	One unit in log odds	59
Multiple sclerosis	2013	24,076,602	IMSGC	14,498/24,091	One unit in log odds	47
Obstructive sleep apnea	2021	33,243,845	FinnGen study	16,761/201,194	One unit in log odds	5
Parkinson's disease	2019	31,701,892	IPDGC	33,674/449,056	One unit in log odds	23
Periodontitis	2019	31,235,808	GLIDE consortium	17,353/28,210	One unit in log odds	1
Hidradenitis suppurativa	2023	37,494,057	Meta-analysis	1,963/832,732	One unit in log odds	2
Psoriasis	2022	34,927,100	Meta-analysis	15,967/28,194	One unit in log odds	59
Rheumatoid arthritis	2022	36,333,501	Meta-analysis	22,350/74,823	One unit in log odds	47
Systemic lupus erythematosus	2015	26,502,338	Meta-analysis	5,201/9,066	One unit in log odds	45
Type 2 diabetes	2022	35,551,307	DIAGRAM Consortium	80,154/853,816	One unit in log odds	182
Vitiligo	2016	27,723,757	Meta-analysis	4,680/39,586	One unit in log odds	48

Abbreviations DIAGRAM, Diabetes Genetics Replication and Meta-analysis; EGG, Early Growth Genetics; GERA, Genetic Epidemiology Research on Adult Health and Aging; GIANT, Genetic Investigation of Anthropometric Traits; GLIDE, gene-lifestyle interactions in dental endpoints; GWAS, genome-wide association study; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine Use; HAPI, Heredity and Phenotype Intervention; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium; IMSGC, International Multiple Sclerosis Genetics Consortium; IPDGC, international Parkinson's Disease Genomics Consortium; MR, Mendelian randomization; SD, standard deviation; SNP, single-nucleotide polymorphism; SSGAC, Social Science Genetic Association Consortium.

[a]Chronotype (morningness versus eveningness) was used as a proxied phenotype for disrupted circadian rhythms

power of the drug-target analysis. When instrumental SNPs were unavailable in the skin cancer datasets, we replaced them with SNPs in high LD ($r^2>0.8$). After harmonizing the datasets of the exposure and the outcome, ambiguous SNPs with intermediate effect allele frequencies (>0.42) were removed. The summarized data for SNPs used as genetic instruments are presented in Supplementary Table 2.

Statistical analysis

For the primary analysis, we calculated the Wald ratio to estimate the causal effects of each SNP. When risk factors had more than one SNP available as instruments, we applied the multiplicative random-effect inverse-variance weighted (IVW) method to combine the effects of multiple SNPs [22]. The IVW method can provide the most precise and robust estimates under the assumption that all genetic instruments are valid or have balanced horizontal pleiotropy, with the random-effects model accounting for the heterogeneity of instruments. To address the issue of multiple testing, we considered associations significant if they exceeded the Bonferroni-corrected threshold ($P<9.4\times10^{-4}$, accounting for 53 putative risk factors) in at least one skin cancer dataset, while also achieving nominal significance ($P<0.05$) with a consistent direction of effect in another skin cancer dataset. Associations with $P<0.05$ but above the Bonferroni-corrected significance threshold, while directionally consistent in both skin cancer datasets, were regarded as suggestive evidence. The IVW estimates from the two skin cancer datasets were combined using a random-effects meta-analysis.

The validity of MR analysis is based on three key assumptions regarding the genetic variants used as instruments: (1) the variants must be associated with the exposure (relevance); (2) they must not be related to the outcome through a confounding pathway (independence); and (3) they should influence the outcome only through the exposure (exclusion restriction) (Fig. 1). While the relevance assumption can be directly tested, the other two assumptions cannot be formally verified and must instead be justified either by scientific understanding or supported empirically through statistical methods [23].

To assess the relevance assumption, we calculated the F-statistic, with a value>10 indicating a sufficiently strong instrument [24]. For the independence and exclusion restriction assumptions, we conducted several sensitivity analyses. Complementary MR methods, including weighted median [25], weighted mode estimator [26], and MR-Egger regression [27], were employed, each providing valid estimates under varying assumptions. We also used the MR-PRESSO (Pleiotropy RESidual Sum and Outlier) test [28] and leave-one-out analysis to identify outlier or pleiotropic SNPs. Cochran's Q statistic was used to detect heterogeneity, and horizontal pleiotropy was assessed via the MR-Egger intercept. Additionally, for certain risk factors, we examined whether instrumental SNPs or their proxies ($r^2 > 0.8$) were associated ($P<1\times10^{-5}$) with potential confounders, such as UV exposure and pigmentation, through a phenome-wide

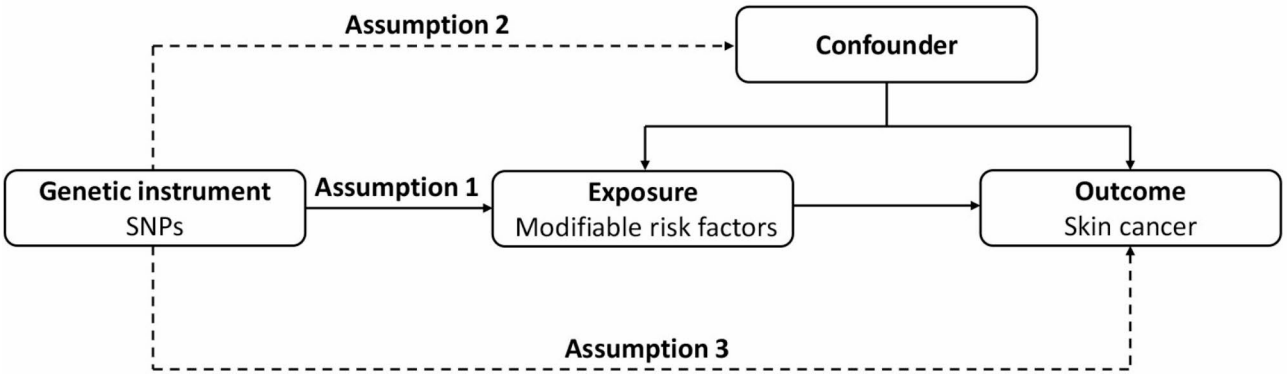

Fig. 1 Schematic overview of the MR design and the assumptions required to be satisfied. Assumption 1 (relevance): genetic variants used as instruments are robustly associated with modifiable risk factors; Assumption 2 (independence): genetic variants are not associated with any confounders; and Assumption 3 (exclusion restriction, also known as the 'no pleiotropy'): genetic variants influence skin cancer only through modifiable risk factors examined and not through any alternative pathways. Dashed lines represent direct causal or potential pleiotropic effects that could violate MR assumptions. MR, Mendelian randomization; SNP, single-nucleotide polymorphism

association search in PhenoScanner, a curated database of human variant-phenotype associations [29]. The Steiger test was also applied to ensure the correct direction of causal inference [30].

The results are reported as odds ratios (OR) along with their corresponding 95% confidence intervals (CI) of skin cancer per standard deviation increase in continuous risk factors, per 1 unit increase in categorical ordered risk factors, or per 1 unit increase in the log odds of binary risk factors. The general statistical power for the MR analysis was estimated using the mRnd web tool [31]. All analyses were conducted in the R environment (version 4.1.1) using the "TwoSampleMR" [17] and "MendelianRandomization" [32] packages.

Results

Instrument statistics

For the 53 putative risk factors included in this MR analysis, the number of SNPs used as genetic instruments ranged from one to 874 (Table 1). The mean *F*-statistic was 102 (range: 10 to 6,663), indicating adequate strength of all genetic instruments (Supplementary Table 2). Assuming that SNPs used as instruments explained > 1% of the phenotypic variance in the respective risk factor, our analysis would have >70% power to detect an OR of 0.82 or 1.20 for melanoma and BCC (Supplementary Table 3). However, the power was relatively limited in the analysis of SCC.

Primary analysis

Across the two skin cancer datasets, genetic liability to sunburn occasions (combined OR: 6.26; 95% CI: 4.85 to 8.08), a greater nevus count (combined OR: 3.81; 95% CI: 1.57 to 9.24), actinic keratosis (combined OR: 1.96; 95% CI: 1.45 to 2.66), and keratinocyte cancer (combined OR: 1.57; 95% CI: 1.36 to 1.80) were significantly associated with a higher risk of melanoma (Fig. 2). Conversely, genetic liability to vitiligo was significantly associated with a reduced melanoma risk (combined OR: 0.82; 95% CI: 0.77 to 0.87). We also noted a suggestive association between genetically predicted higher occupational class and an increased risk of melanoma (combined OR: 1.20; 95% CI: 1.05 to 1.38), although this association did not withstand correction for multiple testing.

For the risk of BCC, genetic liability to sunburn occasions (combined OR: 4.80; 95% CI: 3.82 to 6.03), actinic keratosis (combined OR: 2.54; 95% CI: 2.14 to 3.02), and melanoma (combined OR: 1.43; 95% CI: 1.26 to 1.61) showed significant positive associations, whereas genetic liability to vitiligo (combined OR: 0.83; 95% CI: 0.80 to 0.87), rheumatoid arthritis (combined OR: 0.89; 95% CI: 0.85 to 0.94), type 2 diabetes (combined OR: 0.93; 95% CI: 0.90 to 0.96), and higher levels of physical activity (combined OR: 0.94; 95% CI: 0.92 to 0.97) displayed inverse associations (Fig. 3). There was a suggestive association of genetically predicted higher body mass index (BMI) with a lower risk of BCC (combined OR: 0.90; 95% CI: 0.85 to 0.96).

Similar to the patterns observed for BCC, genetic liability to sunburn occasions (combined OR: 4.68; 95% CI: 1.37 to 16.03), actinic keratosis (combined OR: 2.13; 95% CI: 1.03 to 4.37), and melanoma (combined OR: 1.36; 95% CI: 1.01 to 1.83) were significantly associated with a higher SCC risk, while genetic liability to vitiligo exhibited a robust negative association (combined OR: 0.90; 95% CI: 0.78 to 1.03) (Fig. 4). In contrast to the direction of effect on BCC, genetically predicted BMI showed a significant positive association with SCC risk (combined OR: 1.37; 95% CI: 1.12 to 1.68).

In our analysis of dietary factors (vitamins, antioxidants, fatty acids, minerals, as well as alcohol and coffee consumption) and medications (antihypertensive drugs,

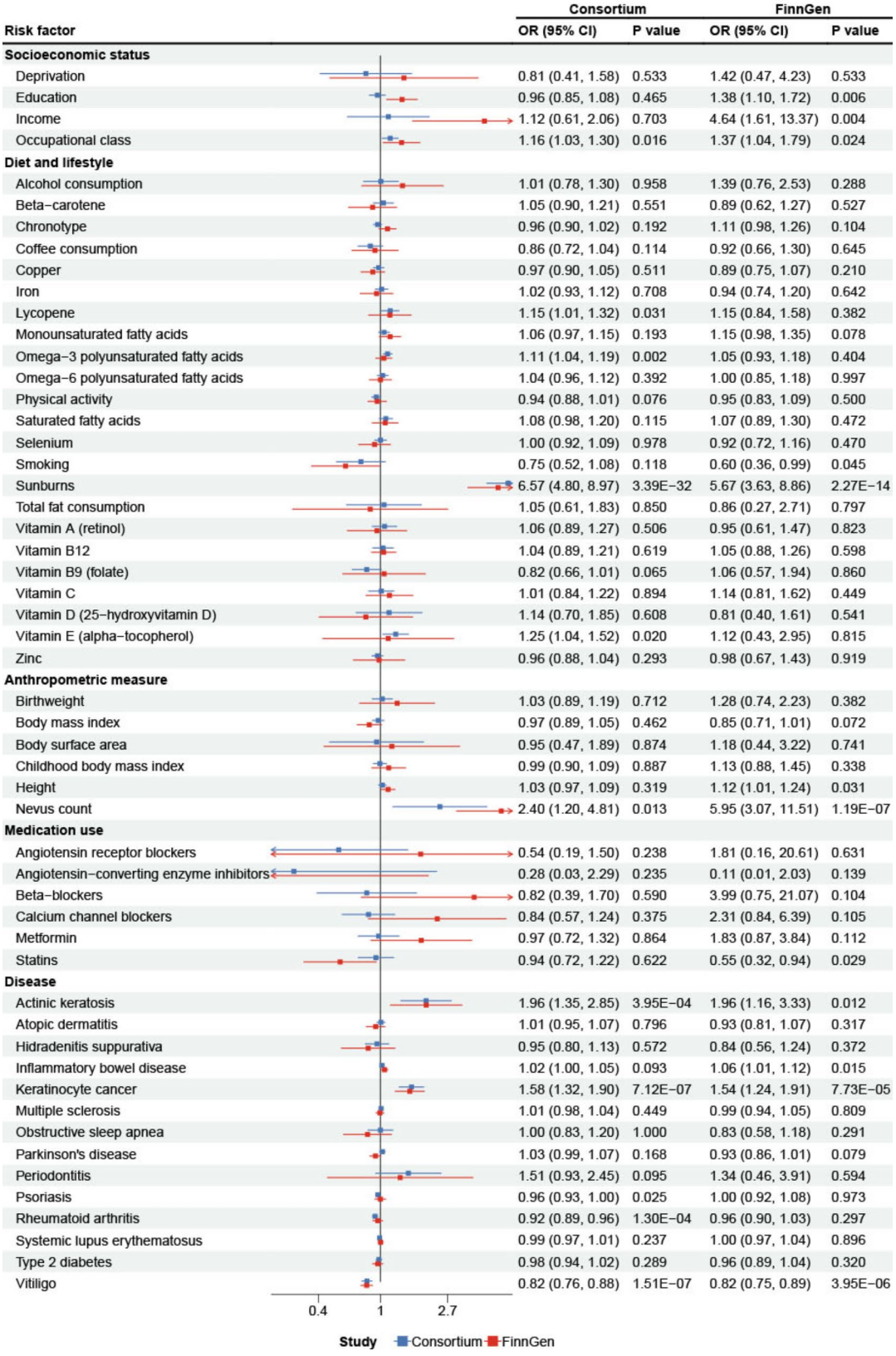

Fig. 2 Associations between genetically predicted modifiable risk factors and the risk of melanoma. Results were obtained from the multiplicative random-effect inverse-variance weighted method. CI, confidence interval; OR, odds ratio

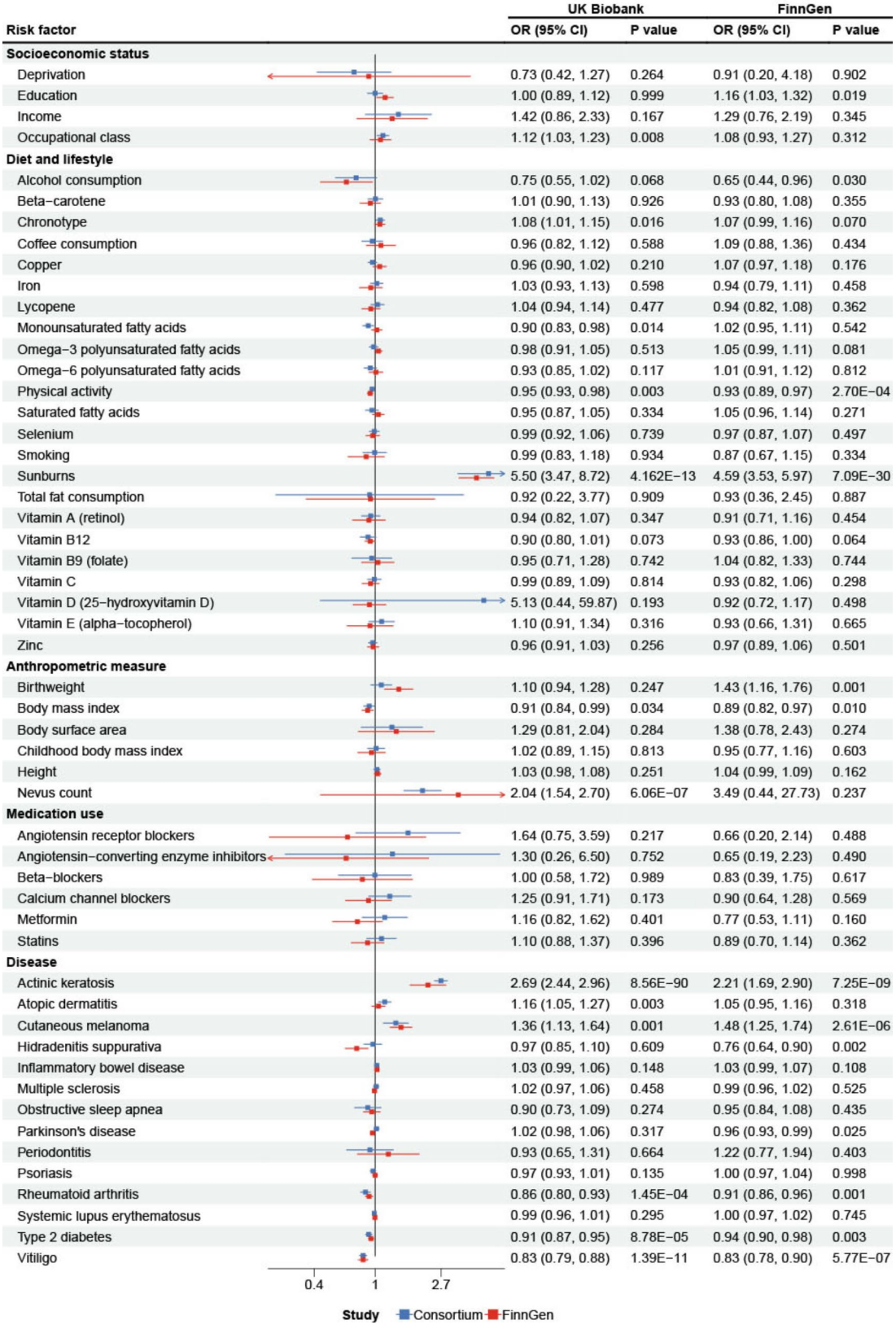

Fig. 3 Associations between genetically predicted modifiable risk factors and the risk of basal cell carcinoma. Results were obtained from the multiplicative random-effect inverse-variance weighted method. CI, confidence interval; OR, odds ratio

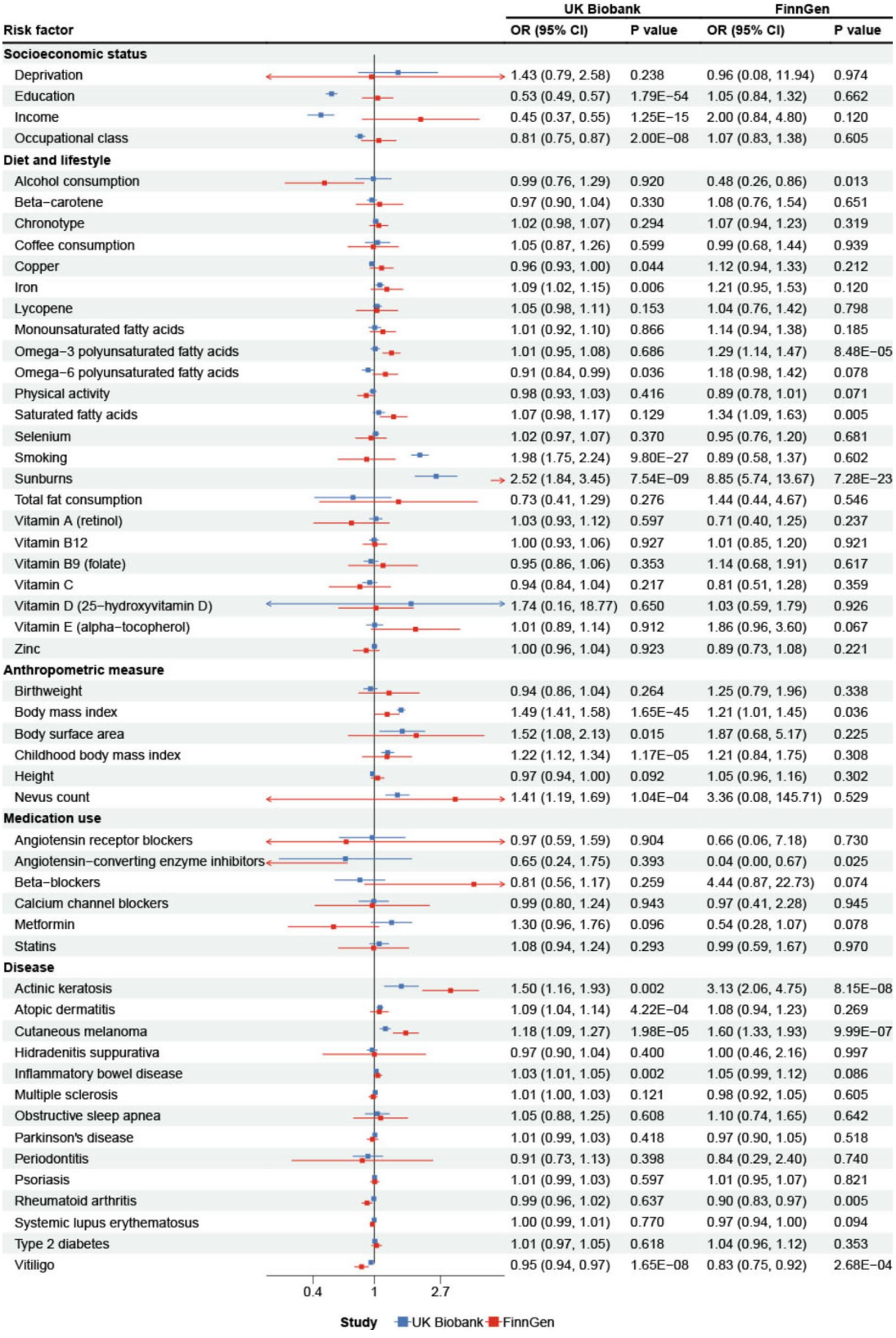

Fig. 4 Associations between genetically predicted modifiable risk factors and the risk of squamous cell carcinoma. Results were obtained from the multiplicative random-effect inverse-variance weighted method. CI, confidence interval; OR, odds ratio

statins, and metformin), no reliable associations were detected for any of the three types of skin cancer.

Sensitivity analysis

The results from alternative pleiotropy-robust methods were generally consistent in direction with the primary IVW results, albeit these methods exhibited lower precision (with wider 95% CIs) (Supplementary Table 4). There was moderate to high heterogeneity in most analyses, as suggested by Cochran's Q statistic (Supplementary Table 5). The MR-Egger intercept test indicated the presence of pleiotropy in the genetic instruments for sunburn occasions and vitiligo (*P* for MR-Egger intercept < 0.05). MR-PRESSO identified between zero and 22 outliers, and after the correction for these outliers, the associations remained largely unchanged (Supplementary Table 4). Leave-one-out analysis found no specific SNP that exerted a substantial influence on the IVW results across the two skin cancer datasets (data not shown). The Steiger test confirmed the validity of the inferred causal direction. Among the genetic instruments used for BMI, physical activity, occupational class, type 2 diabetes, and rheumatoid arthritis, only two SNPs exhibited associations with potential confounding factors in the PhenoScanner. Specifically, rs1007090 at *RALY*, included in the genetic instruments for type 2 diabetes, was associated with skin freckles ($P=6.03\times10^{-10}$) and other malignant neoplasms of the skin ($P=1.16\times10^{-7}$). Rs72928038 at *BACH2*, included in the genetic instruments for rheumatoid arthritis, was associated with other malignant neoplasms of skin ($P=3.85\times10^{-7}$) and vitiligo ($P=1\times10^{-14}$). The exclusion of these SNPs made essentially no difference to our principal results.

Discussion

By leveraging genetic variants as instruments, this MR study provided compelling evidence that sunburn occasions, actinic keratosis, and prior skin cancers were causally associated with a higher risk of all skin cancer types, whereas vitiligo was causally associated with a lower risk of skin cancer. There was also evidence for causal associations of nevus counts, occupational class, rheumatoid arthritis, type 2 diabetes, physical activity, and BMI with specific types of skin cancer. A summary of the principal findings is presented in Fig. 5.

Concordant with the well-established role of UV radiation in carcinogenesis, our study provided robust evidence supporting UV radiation-related skin disorders

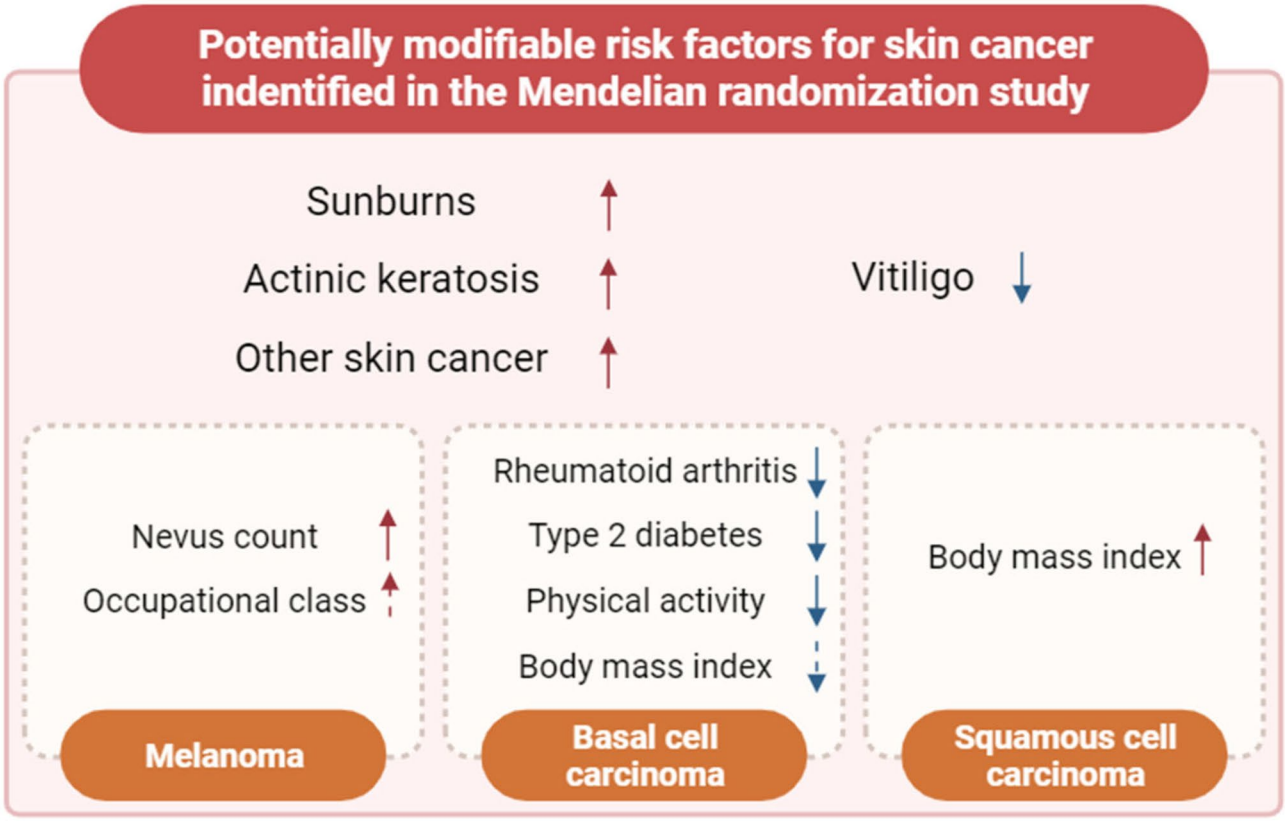

Fig. 5 Causal atlas of potentially modifiable risk factors for skin cancer using MR. Red arrows indicate positive associations; and blue arrows negative associations. Solid arrows denote significant associations that passed the Bonferroni-corrected threshold ($P<9.4\times10^{-4}$); and dash arrows suggestive associations

(i.e., sunburns, actinic keratosis, and other forms of skin cancer) as risk factors for skin cancer. Prolonged or intermittent UV exposure leads to chronic inflammation, unrepaired DNA mutations, and immunosuppression, all of which contribute to uncontrolled skin cell replication and eventual cancer formation [33]. Interestingly, despite the presumed higher susceptibility of vitiliginous skin to UV-induced damage due to a lack of melanin, which serves as protection against UV radiation, both a recent meta-analysis [34] and MR study [35] have demonstrated a reduced risk of melanoma and keratinocyte cancer in individuals with vitiligo. Our results align with these studies. Several mechanisms may explain this inverse association, including different or opposing biological pathways underlie vitiligo and skin cancer development, or heightened immune surveillance in individuals with vitiligo offers protection against cancer [36].

Nevus counts are considered an intermediate phenotype in the causal pathway leading to melanoma, via pigmentation-related mechanisms [37, 38]. However, the relationship between nevus counts and keratinocyte cancer is less well-defined. Wei et al. [39], using data from the Nurses' Health Study, found that nevus counts on the extremities strongly predicted melanoma and BCC, but not SCC. Similarly, Dusingize et al. [40], using polygenic risk scores, observed consistent associations between genetically determined nevus counts and melanoma, BCC, and SCC in two independent cohorts. In our MR study, we found positive associations between genetically predicted nevus counts and all three skin cancer types in one dataset. However, the associations with BCC and SCC did not replicate in another dataset, potentially due to limited statistical power. These findings suggest that while nevi may be linked to keratinocyte cancers, the association might be weaker or of lesser clinical significance compared to melanoma.

The relationship between obesity and skin cancer has been a topic of extensive research, yet the results are conflicting among studies and across different types of skin cancer [7]. Our results indicate an inverse association between BMI and BCC, as well as no significant association with melanoma, which aligns with several cohort studies [41, 42] and MR studies [13, 43]. In contrast, we observed a positive association between higher BMI and an increased risk of SCC, diverging from previous studies that reported either an inverse relationship [41, 42] or no association [44]. Biologically, a positive association between BMI and skin cancer appears more plausible, given the substantial evidence that adipose tissue secretes various cytokines promoting inflammation, cell proliferation, and angiogenesis, all of which can contribute to tumor growth [7]. The underlying mechanisms explaining the lower risk of BCC associated with obesity remain unclear; however, one hypothesis suggests that elevated estrogen levels due to obesity may provide a specific protection against BCC [45].

We additionally noted certain risk factors that appear to be specific to BCC. Data on the direct association between diabetes and BCC are very sparse. Our findings are concordant with those of a case-control study, in which individuals with diabetes had a markedly lower risk of trunk BCC, potentially due to the protective effect of a higher BMI [46]. Evidence from large-scale observational studies has indicated a higher risk of BCC in patients with rheumatoid arthritis, irrespective of the use of biologic drugs, when compared with the general population [47]. However, our MR study suggested that rheumatoid arthritis may actually confer protection against BCC, with a similar trend seen for SCC and melanoma. We speculated that enhanced immune activity in rheumatoid arthritis may play a role in protecting against BCC, paralleling the pathogenesis of another autoimmune disease, vitiligo. As for leisure time physical activity, observational studies generally do not provide clear support for its association with BCC [48, 49]. Although there are several biological mechanisms that may explain the observed preventive effect of physical activity on BCC, including inflammation, immune function, and oxidative stress [50], our results require further confirmation in studies of a causal nature.

Strengths of this study include the application of the MR technology to improve causal inferences, the evaluation of multiple risk factors (many of which have not been previously studied within the MR framework), and the use of large-scale GWAS data for skin cancer from two independent sources for replication. By combining summary statistics from all publicly available GWAS on skin cancer, our study also helped identify previously reported MR findings that may have been false positives. For instance, a prior two-sample MR study using data from the UK Biobank (4,869 melanoma cases) suggested that genetic liability to type 2 diabetes was associated with a reduced melanoma risk [51]. However, our updated analysis, which incorporated data from the UK Biobank alongside 21 additional studies (34,094 melanoma cases), found little evidence to support a causal link between type 2 diabetes and melanoma.

This study also has some limitations. First, as with any MR analysis, a notable challenge is the exclusion of pleiotropy, particularly for risk factors determined by multiple genetic variants. Although multiple sensitivity methods controlling for pleiotropy yielded similar results, potential bias from pleiotropy cannot be entirely ruled out, given that the biological basis of most instrumental SNPs remains largely unknown. Second, standard two-sample MR analyses using summary statistics assume a linear relationship between the exposure and outcome, which limits the ability to detect potential non-linear

associations. Third, although our study attempted to cover common modifiable risk factors for skin cancer, some risk factors may have been omitted due to a scoped review design or could not be assessed due to the lack of genetic instruments (e.g., citrus consumption, immunosuppressants, and chronic infections). Fourth, because of the limited power for some analyses, especially for SCC, we cannot exclude the possibility that some of the risk factors may have small-to-moderate effects on skin cancer. Fifth, despite the known sex dimorphism in skin cancer, we were unable to conduct a sex-stratified analysis, since sex-specific GWASs are not yet available. Lastly, our study was based on datasets in European populations with fair skin. Therefore, our findings should not be extrapolated to other ethnic groups.

Conclusions

This MR study reaffirmed several previously established risk factors and identified novel potential risk factors for skin cancers. Our findings emphasize the importance of reducing exposure to UV radiation as the most effective means of preventing all types of skin cancer. Further work is necessary to determine the potential role of obesity, physical activity, occupation, nevi, type 2 diabetes, vitiligo, and rheumatoid arthritis in different skin cancer types and to decipher the underlying biological pathways.

Abbreviations

BCC	Basal cell carcinoma
BMI	Body mass index
CI	Confidence intervals
GWAS	Genome-wide association study
IVW	Inverse-variance weighted
LD	Linkage disequilibrium
MR	Mendelian randomization
OR	Odds ratio
PRESSO	Pleiotropy RESidual Sum and Outlier
SCC	Squamous cell carcinoma
SNP	Single-nucleotide polymorphism
UV	Ultraviolet

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Material preparation, data collection and analysis were performed by HQ and JZ. The first draft of the manuscript was written by HQ and JZ. All authors commented on previous versions of the manuscript, read and approved the final manuscript.

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Data availability

Summary statistics for melanoma from the Melanoma Meta-analysis Consortium are publicly available in the dbGaP (accession code: phs001868.v1.p1). Summary statistics for keratinocyte cancer from the UK Biobank are publicly available in the GWAS catalog (accession code: GCST90137411 for basal cell carcinoma and GCST90137412 for squamous cell carcinoma). Summary statistics for skin cancer from the FinnGen are publicly available at https://finngen.gitbook.io/documentation/data-download.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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