Supplementary Information for manuscript

Uncovering the complex relationship between balding and skin cancers in men

Table of Contents

Supplementary Notes

Supplementary Notes 1. Study descriptions

GenoMEL

The Melanoma Genetics Consortium (GenoMEL) is the world's leading consortium for familial melanoma research. Participating studies from the GenoMEL were predominantly from populations of European ancestry, with the largest contributing study from Australia (by the Melanoma Institute of Australia). We used the GenoMEL GWAS summary data on melanoma susceptibility performed only on male participants for the present study. Details of the curation of phenotype and sample size contribution from participating studies involved in the Landi et al. GWAS analysis [1] had been previously provided. For study specific acknowledgement and funding information, please also see the supplementary information section in Landi et al. [1].

QSKIN cohort

The QSkin Sun and Health study is a prospective cohort study, with the first wave of recruitment collecting extensive health questionnaires (including self-report pigmentation and sun-protective behaviours), and medical record data linkage, for 43,794 participants between 2011 and 2016. All participants were recruited with informed consent, and ethical approval was managed by the Human Research Ethics committee of QIMR Berghofer Medical Research Institute. Melanoma and KC status was confirmed through a combination of linkage to cancer registry, pathology databases, and Australian Medicare records; this has been previously described [2,3].

Genome-wide genotyping was collected for a subset of 17,965 individuals, among which, 4049 men reported having been diagnosed with KC, with 1064 and 502 cases identified to have BCC and SCC based on pathological records, respectively. Healthy controls were selected from participants screened/self-reported to have no history of KC or actinic keratoses. Data on histology and location of the tumour were available for a subset of QSKIN participants (those identified to have BCC/SCC), which will be used in our MR analysis stratifying by body site of the cancer.

Melanoma Institute of Australia

The Melanoma Institute of Australia is a non-profit organisation based in Poche Centre in North Sydney, Australia and affiliated with The University of Sydney. The MIA primarily conducts research and education programs on the preventive strategies and potential treatment for melanoma. The MIA melanoma study is one of the contributors to the GenoMEL Phase 2 melanoma GWAS meta-analysis. The MIA datasets were used for conducting body site-specific melanoma GWAS analyses to enable the stratified MR analysis by body site and by Breslow

thickness (see main text). We used these data conduct stratified GWAS analyses for male participants on **cutaneous** melanoma; all-body sites (2238 cases), head and neck (537 cases), trunk (1060 cases), arm (280 cases) and leg (361 cases); matching them against 979 healthy men as controls from the Australian Genetics of Depression Study (AGDS)[4]. We obtained male controls (979) from the Australian Genetics of Depression Study (AGDS), an Australian cohort of over 20,000 participants aged 43 years on average (SD=15 years) at the time of recruitment. Cohort details have been published elsewhere [4]. For the stratified analysis on Breslow thickness, we adopted the following criteria based on the AJCC 8th Edition T1 guidelines[5]. In brief, the MIA set was split into those whose first primary melanomas was thin (<=1 mm cut off used as is the max thickness) (n=765) and thick (>1 mm) (n=1,440).

In the present study, both MIA and AGDS samples were genotyped using the Illumina Global Screening Array V.2.0 (GSA) at the National Cancer Institute, USA. The MIA and AGDS studies were approved by the Human Research Ethics committee at QIMR Medical Research Institute in Brisbane and the Sydney Local Health District Ethics Review Committee at the Royal Prince Alfred Hospital in Sydney, Australia, respectively. All participants provided informed consent.

Supplementary Notes 2. Definition of MPB in the UK Biobank

Data for male-pattern baldness is available for 227,354 men from the UK Biobank (UKB data-field 2395). In the UKB, MPB was defined using a 4 point scale, with each subsequent category/pattern indicating higher degree of baldness (see UKB resource 100423). We coded the MPB phenotype in the UKB as an ordinary phenotype, with larger values indicating increasing degree of baldness. Individuals reporting "do not know" were excluded in the analysis. We standardized the phenotype through an inverse-gaussian transformation prior to the GWAS analysis.

Supplementary Notes 3. Derivation of free testosterone in the UK Biobank

Data on free/bioavailable testosterone is currently not available in the UK Biobank. However, we used the following second order equation proposed in Vermeulen et al.[6] to derive and estimate free testosterone through solving a mathematical equation involving total testosterone (field ID: 30850), SHBG (30830) and albumin concentration (30600).

$$S_{alb} = K_{alb} * C_{alb}/F_{alb}$$

$$SHBG_{bound} = SHBG_{total} - T_{total} + S_{alb} * T_{free}$$

yield $T_{free} = \frac{T_{total} - S_{alb} * T_{free}}{K_{SHBG} * SHBG_{bound}}$

Where K_{alb} and K_{SHBG} are defined at K_{alb} =3.6*10^4 and K_{SHBG} = 1*10^9. The factor F_{alb} is set at 69000. C_{alb} is the defined concentration of albumin (in g/L) while T_{total} and T_{free}refers to the serum total and free testosterone concentration.

GWAS analysis was then conducted on the inverse-gaussian transformed free testosterone phenotype in white British males only using BOLT-LMM, having excluded individuals involved in the UKB KC GWAS.

Supplementary Notes 4. Estimation of genetic association with MPB and endogenous sex-hormones from non-overlapping UKB subsample for use in MR analyses

To maximise power for instrument detection, we obtained candidate SNP instruments for our MR analyses for totalT, freeT and SHBG based on the GWAS findings on endogenous sex-hormones from Ruth et al. [15]. We obtained 473, 274 and 101 genome-wide significant variants as SNP instruments for SHBG, totalT and freeT. However, SNP effect sizes can be driven by winner's curse bias when genetic associations for the exposure and the outcome is estimated from the same sample. To avoid bias driven by sample overlap, we re-estimated the SNP effect size for each sex-hormones instrument obtained from Ruth et al. [15] in our UKB testosterone and SHBG GWAS derived from participants not involved in the outcome GWAS (i.e. KC GWASs). For simplicity, we reported all our MR estimates based on a 1 SD change in endogenous totalT, freeT or SHBG levels. A scatter plot showing the SNP effect size correlation between the Ruth et al [15]. GWAS and our UKB GWAS is shown in Supplementary Figures 2-4. Similarly, SNP instruments for MPB were identified from independent genome-wide significant variants in the unstratified GWAS on all UKB male participants for MPB, but we adopt only effect size estimates for each MPB SNPs from the non-overlapping set to facilitate the MR analyses.

Supplementary Notes 5. Definition of site-specific skin cancers evaluated

To harness large sample sizes for our body-site specific skin cancer analysis, we collapsed . For ease of interpretation, we used the same category in both the melanoma and keratinocyte cancer analysis, where each of the body-site can be broadly classified as either [Head and neck], [Trunk], [Upper limb] or [Lower limb]. The number of cases in each category is shown in Supplementary Information - **Supplementary Table 2**.

Supplementary Notes 6. Power calculation for MR analysis

The calculation of statistical power for the MR analysis was conducted through the online web interface, mRnd (available here https://cnsgenomics.com/shiny/mRnd/). To assess whether adequate power can be achieved for MR to detect effect sizes at various OR thresholds, nominal sample size for KC (as a benchmark) was provided along with the proportion of variance on exposure traits explained by SNP instruments. The proportion of variance explained by *m* SNP instruments on the exposure of interest, R^2 can be derived through the formula below.

$$R^2 = \sum_{i=1}^{m} 2p_i(1-p_i)\beta_i^2$$

Where $p_i$and β_i refers to the effect allele frequency and the magnitude of association of the i-th SNP instrument with the exposure. Here we assume the exposure of interest (X) has been standardized prior to the analysis (i.e. var(X)~=1).

Supplementary Notes 7. Estimates derived from alternative MR models

Here we adopted a series of alternative MR estimators [11] to triangulate findings from the inverse-variance weighted (IVW) model in the presence of weak violation on key MR assumptions, potential heterogeneity among SNP estimates and unmeasured pleiotropy. These estimators include: The MR-Egger, MR-Weighted Median, MR-PRESSO and the Weighted-mode model. Technical details behind the methodology of each model have been previously described [11]. Below is a short summary highlighting the key strength for each model to circumvent weaknesses of the IVW estimate:

MR-Egger regression: Provide estimates that are unbiased in the presence of directional pleiotropy, assuming the InSIDE (Instrument strength independent of direct effect) assumption is valid. The intercept for the MR-Egger regression provides indication for potential directional pleiotropy biasing IVW findings, when the intercept term is different from zero.
MR-Mode based estimators: Provide consistent estimates of MR effect sizes based on the plurality assumption.
MR-Median based estimators: Provide consistent estimates of MR effect sizes even when up to 50% of the SNP instruments are invalid.
MR-PRESSO: Identifies potential SNP outliers contributing to genetic heterogeneity, and provides adjusted estimates robust against horizontal pleiotropy and heterogeneity among SNP effect sizes. The MR-PRESSO outlier test was also used to detect potential SNP-outliers, of which putative candidate traits associated with the SNP-outlier can be incorporated in a multivariable MR framework.

Supplementary Notes 8. Selection of pleiotropic variants for PheWAS analyses and validation via univariate MR analysis on MPB

The presence of horizontal pleiotropy between the SNP and outcome of interest can potentially invalidate the key MR assumptions. One way to identify SNP-confounder associations is to review the overall funnel plot/scatter plot for the MR association and evaluate potential outliers, or apply statistical models to test for outliers such as the outlier-test implemented in MR-PRESSO. However, these approaches very often remove potential causal effects implicated through a true vertical pleiotropic pathway (i.e. consistent with causality). To investigate whether the effect of identified pleiotropic variants are potentially linked with other putative skin-related risk factors in the same causal pathway on MPB, we performed the following. We applied MR-PRESSO [7] on the data (MPB against KC) to first obtain SNP-outliers driving genetic heterogeneity among the SNP-derived estimates. We used a total of 10,000 iterations to obtain stable distribution under the null in MR-PRESSO given that our SNP set is large (n~500 for MPB), and used a conservative SNP-outlier p-value cut-off of $p<0.05$. From there, we performed a PheWAS analysis on each outlier variant against a collection of pigmentation, and sun exposure phenotypes; as curated from the GeneATLAS[8] (see http://geneatlas.roslin.ed.ac.uk/) and OpenTarget[9] database (see https://genetics.opentargets.org/). Our inclusion criteria for candidate traits include any phenotype with the word "skin tones", "pigmentation", "sunburn", "skin colour", "hair colour", "tanning", "sunburn" and "skin related diseases". For traits with multiple GWAS available, the association statistics with the strongest association P-value and largest sample size was preferentially reported.

For each meaningful SNP-trait pair association, we then performed a univariate MR analysis regressing MPB on the trait of interest (to check for directionality of the MR association). Trait-pairs with strong evidence ($p<1e-5$) for a MR association were then incorporated in a MVMR framework alongside testosterone and MPB against skin cancer outcomes. Description of the instrument selection criteria and data curation for the MVMR analysis is provided below (MVMR section). Our approach is essentially a modification and application of the concepts introduced by Cho et al. [10] in the MR-TRYX (Treasure your exceptions) framework to derive an adjusted marginal effect from the trait of interest (in our case, MPB) after accounting for alternative biological pathways driving the association between the SNP-outlier and the outcome (i.e. skin cancers).

Estimates derived from the IVW estimator will be preferentially reported in the main text. However, results derived using these sensitivity MR models can be found in Supplementary Tables (see Results section in main text).

Supplementary Notes 9. Curation of instrument and assessment of instrument strength for MVMR analysis

MVMR analyses were performed to assess potential mediation effects to aid interpretation of our univariable MR analyses. Our SNP-outlier tests above revealed that both skin and hair colour are potentially associated with genetic MPB, and hence we incorporated both of these traits into our MVMR model. Note that we omitted the trait "ease of tanning" due to insufficient genetic predictors for MR. The GWASs for skin colour and hair colour conducted in the UK Biobank have been previously reported in another study (see Ong et al. [12]). We first combined all our SNP instruments (i.e. variants with genome-wide significant associations with the trait of interests) for each exposure of interest [hair colour, skin colour, totalT, freeT, SHBG and MPB] into one combined instrument set. We then removed duplicated signals by performing LD-clumping (kb=10000, r2=0.001) to ensure independence between SNP instruments, resulting in 1201 variants. Based on the newly curated set of 1201 SNPs, we then re-extract the effect size estimate for these SNPs on each exposure trait. SNPs with missing entries on at least one exposure trait or cannot be found in the outcome GWAS datasets were omitted from the analysis, resulting in 1132 variants. We assessed instrument strength for MVMR through the strength_mvmr() function implemented via the *MendelianRandomization* R package [13]. The MVMR analyses were performed using the mv_multiple() function in the *TwoSampleMR* R package. In our main analysis we provided estimates for two selected models **(**Supplementary Information - **Supplementary Table 5)**.

Original MVMR model (without modeling heterogeneous outlier). Initially, the conditional F-statistics based on our curated instrument set for the original 4 trait model [MPB, totalT, freeT, SHBG] is 28.87, 0.21 0.21 and 0.22 (See **Supplementary Table 5**). We then repeated the instrument curation process by excluding SHBG from our analyses due to the SHBG phenotype having the lowest correlation with both MPB and testosterone phenotypes and calculated the conditional F-statistics again. The conditional F-statistics in the reduced set (n=262 SNPs) is 10.5, 55.6 and 16.1 for freeT, MPB and totalT respectively, indicating that our curated instrument set satisfies the strong instrument criteria (cond.F>10) for MVMR [14]. We hence omitted the SHBG from the MVMR analyses for the original model. MVMR estimates derived from this model were also provided in Supplementary Information - **Supplementary Table 10**.

MVMR model with proxy traits tagging heterogenous SNP outliers. For the MVMR model involving the two other proxy traits (obtained via modeling PheWAS associations on genetic outliers; see Supplementary Notes section *Selection of pleiotropic variants for PheWAS analyses and validation via univariate MR analysis on MPB*) namely hair colour and skin colour, we selected model D1 on the basis of instrument strength for MVMR by excluding SHBG and freeT from the analysis (4 trait model yield better instrumentstrength than 6 trait model; See Supplementary Information - **Supplementary Table 5**).

Supplementary Tables

Supplementary Table 1. Description of cases and controls for individual studies involved in the GenoMEL Phase 2 GWAS meta-analysis.

Population	Study	Cases	Controls	Cases (males only)	Controls (males only)	Effective cases	Effective controls
European	GenoMEL Phase 1	1,075	2,163	449	893	1,436	1,436
European	GenoMEL Phase 2	925	1,128	356	520	1,016	1,016
US	MDACC	1,924	1,018	1,129	608	1,331	1,331
Australian	AMFS	535	427	176	177	475	475
Australian	Q-MEGA_610k	912	3,777	421	760	1,469	1,469
Australian	Q-MEGA_omni	656	538	316	422	591	591
UK	GSEdinCIDRulcer	4,328	5,780	1,879	2,435	4,950	4,950
Australian	WAMHS	1,237	1,977	720	932	1,523	1,523
German	Essen-Heidelberg	1,189	1,215	664	607	1,201	1,201
French	MELARISK	511	815			628	628
US	Harvard	410	2,920			719	719
US	NCI_CPSII+PLCO+Rose	171	2,684			322	322
UK	UK Biobank confirmed	3,499	13,996	1,438	6,344	5,598	5,598
European-derived	MIA_PAH	1,933	2,841			2,301	2,301
Australian	EPIGENE	773	910	510	392	835	835
Australian	QSKIN	1,285	2,493			1696	1696
Greek	Greek	1,194	1,279	605	578	1235	1235
Italian	Italy	1,726	3,142	786	2169	2228	2228
Spanish	Spain	3,523	3,400	1604	2105	3460	3460
US	Michigan	1,198	26,211			2,291	2,291
European-derived	BNMS	1,130	2,701			1593	1593
	Total confirmed	**30,134**	**81,415**	11,053	18,943	**36,898**	**36,898**
UK	UK Biobank SR	1,802	7,208	843	3,319	2,888	2,888
International	23andMe SR	4,824	286,565			9,488	9,488
	Total all Samples	**36,760**	**375,188**	11,896	22,262	**49,274**	**49,274**

Cf=confirmed. SR=self-reported

Supplementary Table 2. Distribution of cases and controls for analyses on major body-site categories

Trait	Site	Cohort	Cases	Controls
Distribution across all sites				
KC	all	UKB	13,463	96,620
	all	QSkin	4,049	1,957
BCC	all	UKB	10,718	96,620
	all	QSkin	992	1,957
SCC	all	UKB	3,483	96,620
	all	QSkin	462	1,957
Distribution across individual body-site categories				
BCC	Head and Neck	QSkin	439	1,957
	Trunk	QSkin	209	1,957
	Upper limb	QSkin	248	1,957
	Lower limb	QSkin	93	1,957
SCC	Head and Neck	QSkin	184	1,957
	Trunk	QSkin	23	1,957
	Upper limb	QSkin	149	1,957
	Lower limb	QSkin	102	1,957
CM	all	MIA	2,236	3,176
	all (thin: <= 1mm Breslow thickness)	MIA	765	3,176
	all (thick: > 1mm Breslow thickness)	MIA	1,440	3,176
	Head and Neck*	MIA	537	3,176
	Head and Neck (no scalp)	MIA	364	3,176
	Trunk	MIA	883	3,176
	Upper limb	MIA	448	3,176
	Lower limb	MIA	368	3,176
	Scalp	MIA	173	3,176
KC	Head and Neck**	UKB	6,114	96,620
	Trunk	UKB	1,709	96,620
	Upper limb	UKB	922	96,620
	Lower limb	UKB	449	96,620
	Scalp and neck	UKB	996	96,620
BCC	Head and Neck**	UKB	4,768	96,620
	Trunk	UKB	1,442	96,620
	Upper limb	UKB	636	96,620
	Lower limb	UKB	301	96,620

	Scalp and neck	UKB	650	96,620
SCC	Head and Neck**	UKB	1,427	96,620
	Trunk	UKB	298	96,620
	Upper limb	UKB	284	96,620
	Lower limb	UKB	143	96,620
	Scalp and neck	UKB	325	96,620
CM	Head and Neck**	UKB	390	96,620
	Trunk	UKB	925	96,620
	Upper limb	UKB	446	96,620
	Lower limb	UKB	290	96,620
	Scalp and neck	UKB	137	96,620

*includes scalp

**includes scalp and neck

Supplementary Table 3. Body-site specific sample size distribution for melanoma and keratinocyte cancer cases in the UK Biobank

Body region	Specific site definition	CM codes (ICD10/9)	KC codes (ICD10/9)	CM	KC - BCC	KC - SCC
Head and Neck	Lip	C43.0/1720	C44.0/1730	1	80	48
	Eyelid, including canthus	C43.1/1721	C44.1/1731	9	409	66
	Ear and external auricular canal	C43.2/1722	C44.2/1732	71	504	257
	Other and unspecified parts of face	C43.3/1723	C44.3/1733	172	3125	731
	Scalp and neck	C43.4/1724	C44.4/1734	137	650	325
Trunk	Trunk	C43.5/1725	C44.5/1735	925	1442	298
Upper limb	Upper limb, including shoulder	C43.6/1726	C44.6/1736	446	636	284
Lower limb	Lower limb, including hip	C43.7/1727	C44.7/1737	290	301	143

ICD10=International Classification of Diseases version 10. ICD9=International Classification of Diseases version 9. Body region are defined as anatomical categories covering specific body sites, for our analysis.

Supplementary Table 4. Body-site specific sample size distribution for melanoma and keratinocyte cancer cases in the Australian (QSKIN and MIA) datasets

Body region	Specific site	Diagnosis		
		CM (MIA)	BCC (QSKIN)	SCC (QSKIN)
Head and neck	Central forehead	1	-	-
	Ear	59	57	28
	Cheek	91	-	-
	Chin	4	-	-
	Face	16	299	112
	Scalp	173	24	21
	Nose	19	-	-
	Neck	100	59	23
	Jaw	1	-	-
	Eyelid	3	-	-
	Lip	5	-	-
	Forehead & temple	64	-	-
	Conjuctiva	1	-	-
Trunk	Lower abdomen	6	-	-
	Abdomen (NOS)	28	8	2
	Upper abdomen\upper chest	18	54	10
	Anus	1	-	-
	Back	3	34	2
	Caudal back	1	-	-
	Central back	1	-	-
	Interscapular back	1	-	-
	Left back	1	-	-
	Lower back	40	22	2
	Mid back	3	-	-
	Mid right back	5	-	-
	Central sternum	1	-	-
	Anterior thorax	118	17	3
	Posterior thorax (upper back)	594	74	4
	Thorax (NOS)	18	-	-

	Left chest wall	1	-	-
	Right Paravertebral (upper back)	1	-	-
	Flank	38	-	-
	Left flank	1	-	-
	Groin	1	-	-
	Left loin	1	-	-
	Penis	1	-	-
Upper Limb	Shoulder	164	103	13
	Arm	134	55	19
	Forearm	121	80	63
	Tricep	1	-	-
	Elbow	23	-	-
	Back of hand	-	9	48
	Wrist	1	-	-
	Clavicular region	1	-	-
	Scapula	2	-	-
	Palmer skin	-	1	6
	Suprascapular region	1	-	-
Lower Limb	Thigh	98	9	8
	Knee	30	-	-
	Calf	132	-	-
	Lower leg	2	-	-
	Shin	80	-	-
	Leg (NOS)	3	79	86
	Ankle	16	-	-
	Buttock	7	-	-
	Top of foot	-	4	7
	Hip	-	1	1

Note that all reported diagnosis are clinically confirmed diagnosis (not self-reports). We excluded specific sites that have no diagnosis instances across the 3 disease (CM, BCC, SCC) evaluated.

Supplementary Table 5. Conditional F-statistics to measure instrument strength for multivariable MR in various combination of traits

Traits	Model O (359 SNPs)		**Model A (262 SNPs)**		Model B (538 SNPs)		Model C (578 SNPs)		Model D (556 SNPs)		**Model D1 (560 SNPs)**		Model E (1132 SNPs)	
	Inc.	F	Inc.	F	Inc.	F	Inc.	F	Inc.	F	Inc.	F	Inc.	F
MPB	T	28.87	T	55.6	T	25.01	T	22.97	T	23.7	T	23.54	T	12.1
totalT	T	0.21	T	16.1	T	8.49	T	7.98	T	15.66	T	15.72	T	0.19
freeT	T	0.21	T	10.5	T	5.37	T	5.04	F	-	F	-	T	0.19
SHBG	T	0.22	F	-	F		F	-	F	-	F	-	T	0.2
skin colour	-		-	-	F		T	31.01	T	31.85	T	8.6	T	16.85
hair colour	-		-	-	T	130.85	T	75.38	T	77.44	T	14.04	T	33.04

Inc.=Include trait. T=True; F=False.

for MVMR: to obtain these subsets, we reclump the instruments, by retaining only genome-wide variants (p<5e-8) with the trait of interest as genetic instruments. for this reason, the MVMR SNP instrument for each individual trait might be more robust than its univariable counterpart (as we re-define instrument as SNPs that have association p<5e-8 in the UK Biobank non-overlapping subset itself).

Supplementary Table 6. Estimated univariate MR derived ORs for per 1 SD change increase in genetically predicted MPB score on skin cancer risk

outcome	exposure	method	All variants			Variants with p<1e-5 in subset		
			nsnp	pval	OR	nsnp	pval	OR
BCC QSKIN	MPB	MR Egger	471	0.06	1.6 (0.98 to 2.61)	287	0.1	1.70 (0.91 to 3.15)
BCC QSKIN	MPB	Weighted median	471	0.86	0.97 (0.66 to 1.41)	287	0.97	0.99 (0.67 to 1.46)
BCC QSKIN	MPB	IVW (fixed effect)	471	0.49	1.1 (0.84 to 1.43)	287	0.31	1.17 (0.87 to 1.58)
BCC QSKIN	MPB	Simple mode	471	0.09	0.45 (0.18 to 1.12)	287	0.32	0.61 (0.23 to 1.61)
BCC QSKIN	MPB	Weighted mode	471	0.37	0.79 (0.48 to 1.32)	287	0.43	0.80 (0.45 to 1.41)
BCC UKB	MPB	MR Egger	472	7.76E-03	1.26 (1.06 to 1.49)	287	0.01	1.37 (1.09 to 1.72)
BCC UKB	MPB	Weighted median	472	0.36	1.05 (0.95 to 1.16)	287	0.38	1.05 (0.94 to 1.16)
BCC UKB	MPB	IVW (fixed effect)	472	1.84E-03	1.15 (1.05 to 1.26)	287	0.02	1.14 (1.02 to 1.28)
BCC UKB	MPB	Simple mode	472	0.46	1.1 (0.86 to 1.41)	287	0.72	1.05 (0.81 to 1.37)
BCC UKB	MPB	Weighted mode	472	0.99	1 (0.87 to 1.15)	287	0.85	0.99 (0.85 to 1.14)
KC QSKIN	MPB	MR Egger	470	0.03	1.49 (1.05 to 2.11)	286	0.14	1.41 (0.90 to 2.20)
KC QSKIN	MPB	Weighted median	470	0.66	0.94 (0.73 to 1.23)	286	0.72	0.95 (0.72 to 1.25)
KC QSKIN	MPB	IVW (fixed effect)	470	0.78	1.03 (0.85 to 1.24)	286	0.35	1.11 (0.89 to 1.37)
KC QSKIN	MPB	Simple mode	470	0.46	0.79 (0.42 to 1.48)	286	0.76	0.90 (0.46 to 1.77)
KC QSKIN	MPB	Weighted mode	470	0.98	1.01 (0.69 to 1.47)	286	0.97	1.01 (0.67 to 1.51)
KC UKB	MPB	MR Egger	472	7.99E-03	1.23 (1.06 to 1.43)	287	0.01	1.32 (1.07 to 1.63)
KC UKB	MPB	Weighted median	472	0.28	1.05 (0.96 to 1.15)	287	0.31	1.05 (0.96 to 1.16)
KC UKB	MPB	IVW (fixed effect)	472	1.45E-04	1.17 (1.08 to 1.27)	287	3.86E-03	1.16 (1.05 to 1.28)
KC UKB	MPB	Simple mode	472	0.72	1.04 (0.83 to 1.3)	287	0.9	1.02 (0.80 to 1.29)
KC UKB	MPB	Weighted mode	472	0.83	0.99 (0.87 to 1.11)	287	0.86	0.99 (0.87 to 1.12)
Melanoma (phase2)	MPB	MR Egger	469	0.9	0.99 (0.85 to 1.15)	286	0.97	1.00 (0.83 to 1.19)
Melanoma (phase2)	MPB	Weighted median	469	0.64	0.97 (0.87 to 1.09)	286	0.6	0.97 (0.86 to 1.09)
Melanoma (phase2)	MPB	IVW (fixed effect)	469	0.76	0.99 (0.91 to 1.07)	286	0.38	0.96 (0.88 to 1.05)
Melanoma (phase2)	MPB	Simple mode	469	0.06	1.32 (0.99 to 1.76)	286	0.28	1.19 (0.87 to 1.62)
Melanoma (phase2)	MPB	Weighted mode	469	0.3	1.09 (0.93 to 1.27)	286	0.29	1.10 (0.92 to 1.31)
SCC QSKIN	MPB	MR Egger	471	0.05	1.93 (1.01 to 3.71)	287	0.04	2.41 (1.06 to 5.50)

SCC QSKIN	MPB	Weighted median	471	0.78	1.07 (0.65 to 1.76)	287	0.7	1.10 (0.66 to 1.84)
SCC QSKIN	MPB	IVW (fixed effect)	471	0.65	1.08 (0.77 to 1.53)	287	0.48	1.15 (0.77 to 1.72)
SCC QSKIN	MPB	Simple mode	471	0.66	0.76 (0.22 to 2.61)	287	0.52	0.63 (0.15 to 2.57)
SCC QSKIN	MPB	Weighted mode	471	0.73	1.14 (0.55 to 2.37)	287	0.68	1.19 (0.52 to 2.77)
SCC UKB	MPB	MR Egger	472	0.05	1.24 (1 to 1.53)	287	0.09	1.27 (0.97 to 1.67)
SCC UKB	MPB	Weighted median	472	7.45E-03	1.24 (1.06 to 1.46)	287	0.01	1.24 (1.06 to 1.46)
SCC UKB	MPB	IVW (fixed effect)	472	2.35E-06	1.31 (1.17 to 1.46)	287	1.33E-04	1.29 (1.13 to 1.48)
SCC UKB	MPB	Simple mode	472	0.16	1.31 (0.9 to 1.89)	287	0.11	1.37 (0.93 to 2.01)
SCC UKB	MPB	Weighted mode	472	0.04	1.23 (1.01 to 1.49)	287	0.12	1.21 (0.95 to 1.54)

Note: The fixed-effect meta-analysed *ORs combining QSKIN and UKB estimates can be found in the main text.*
Estimates for melanoma (phase 2) was derived from the GenoMEL Phase 2 melanoma GWAS meta-analysis which includes the cases from the MIA datasets.

Supplementary Table 7. Estimated univariate MR derived ORs for per 1 SD change increase in genetically predicted free testosterone on skin cancer risk

outcome	exposure	method	All variants			Variants with p<1e-5 in subset		
			nsnp	**pval**	OR	**nsnp**	**pval**	**OR**
BCC QSKIN	freeT	MR Egger	74	0.73	0.86 (0.36 to 2.07)	56	0.87	0.93 (0.39 to 2.21)
BCC QSKIN	freeT	Weighted median	74	0.73	0.89 (0.44 to 1.78)	56	0.75	0.89 (0.43 to 1.84)
BCC QSKIN	freeT	IVW (fixed effect)	74	0.75	0.93 (0.57 to 1.5)	56	0.54	0.87 (0.55 to 1.37)
BCC QSKIN	freeT	Simple mode	74	0.67	0.76 (0.21 to 2.73)	56	0.91	0.93 (0.27 to 3.16)
BCC QSKIN	freeT	Weighted mode	74	0.49	0.76 (0.35 to 1.65)	56	0.39	0.73 (0.35 to 1.50)
BCC UKB	freeT	MR Egger	86	0.56	0.91 (0.68 to 1.24)	66	0.67	0.93 (0.66 to 1.31)
BCC UKB	freeT	Weighted median	86	0.66	0.95 (0.78 to 1.17)	66	0.6	0.95 (0.77 to 1.16)
BCC UKB	freeT	IVW (fixed effect)	86	0.85	0.98 (0.83 to 1.16)	66	0.77	0.97 (0.81 to 1.17)
BCC UKB	freeT	Simple mode	86	0.06	1.52 (1 to 2.32)	66	0.21	1.32 (0.86 to 2.03)
BCC UKB	freeT	Weighted mode	86	0.42	0.91 (0.72 to 1.15)	66	0.42	0.91 (0.72 to 1.15)
KC QSKIN	freeT	MR Egger	74	0.66	1.18 (0.58 to 2.39)	56	0.56	1.25 (0.60 to 2.60)
KC QSKIN	freeT	Weighted median	74	0.72	0.91 (0.55 to 1.51)	56	0.74	0.91 (0.53 to 1.57)
KC QSKIN	freeT	IVW (fixed effect)	74	0.89	0.97 (0.66 to 1.44)	56	0.74	0.94 (0.63 to 1.39)
KC QSKIN	freeT	Simple mode	74	0.76	1.15 (0.47 to 2.79)	56	0.79	1.13 (0.47 to 2.68)
KC QSKIN	freeT	Weighted mode	74	0.92	0.97 (0.55 to 1.72)	56	0.75	0.91 (0.51 to 1.62)
KC UKB	freeT	MR Egger	86	0.47	0.9 (0.69 to 1.19)	66	0.58	0.92 (0.67 to 1.25)
KC UKB	freeT	Weighted median	86	0.27	0.91 (0.77 to 1.08)	66	0.29	0.91 (0.76 to 1.08)
KC UKB	freeT	IVW (fixed effect)	86	0.61	0.96 (0.83 to 1.12)	66	0.61	0.96 (0.81 to 1.13)
KC UKB	freeT	Simple mode	86	0.45	1.17 (0.78 to 1.73)	66	0.51	1.14 (0.78 to 1.66)
KC UKB	freeT	Weighted mode	86	0.25	0.9 (0.75 to 1.08)	66	0.27	0.89 (0.73 to 1.09)
melanoma	freeT	MR Egger	74	0.24	0.8 (0.55 to 1.16)	56	0.27	0.78 (0.51 to 1.21)
melanoma	freeT	Weighted median	74	0.31	0.89 (0.7 to 1.12)	56	0.28	0.88 (0.70 to 1.11)
melanoma	freeT	IVW (fixed effect)	74	0.91	0.99 (0.81 to 1.2)	56	0.84	0.98 (0.78 to 1.22)

melanoma	freeT	Simple mode	74	0.93	1.02 (0.66 to 1.57)	56	0.88	1.03 (0.67 to 1.61)
melanoma	freeT	Weighted mode	74	0.3	0.88 (0.7 to 1.11)	56	0.33	0.88 (0.68 to 1.14)
SCC QSKIN	freeT	MR Egger	74	0.31	1.78 (0.58 to 5.39)	56	0.34	1.80 (0.54 to 5.94)
SCC QSKIN	freeT	Weighted median	74	0.63	1.26 (0.49 to 3.24)	56	0.65	1.26 (0.46 to 3.44)
SCC QSKIN	freeT	IVW (fixed effect)	74	0.82	1.07 (0.58 to 1.99)	56	0.79	1.09 (0.57 to 2.09)
SCC QSKIN	freeT	Simple mode	74	0.82	1.22 (0.21 to 7)	56	0.78	1.28 (0.23 to 7.13)
SCC QSKIN	freeT	Weighted mode	74	0.9	1.08 (0.34 to 3.41)	56	0.94	1.04 (0.35 to 3.13)
SCC UKB	freeT	MR Egger	86	0.77	0.94 (0.64 to 1.39)	66	0.8	0.95 (0.64 to 1.41)
SCC UKB	freeT	Weighted median	86	0.36	0.88 (0.66 to 1.16)	66	0.37	0.88 (0.67 to 1.16)
SCC UKB	freeT	IVW (fixed effect)	86	0.46	0.92 (0.75 to 1.14)	66	0.59	0.94 (0.77 to 1.16)

Supplementary Table 8. Estimated univariate MR derived ORs for per 1 SD change increase in genetically predicted total testosterone on skin cancer risk

outcome	exposure	method	All variants			Variants with p<1e-5 in subset		
			nsnp	pval	OR	nsnp	pval	OR
BCC QSKIN	totalT	MR Egger	152	0.66	0.9 (0.54 to 1.47)	99	0.35	0.78 (0.46 to 1.32)
BCC QSKIN	totalT	Weighted median	15	0.3	0.76 (0.44 to 1.28)	99	0.28	0.75 (0.45 to 1.26)
BCC QSKIN	totalT	IVW (fixed effect)	152	0.29	1.18 (0.86 to 1.62)	99	0.5	1.12 (0.81 to 1.55)
BCC QSKIN	totalT	Simple mode	152	0.82	1.15 (0.35 to 3.81)	99	0.66	1.33 (0.37 to 4.84)
BCC QSKIN	totalT	Weighted mode	152	0.39	0.79 (0.47 to 1.34)	99	0.38	0.77 (0.42 to 1.38)
BCC UKB	totalT	MR Egger	168	0.6	0.96 (0.83 to 1.12)	111	0.58	0.95 (0.81 to 1.13)
BCC UKB	totalT	Weighted median	168	0.57	1.05 (0.9 to 1.22)	111	0.6	1.04 (0.90 to 1.21)
BCC UKB	totalT	IVW (fixed effect)	168	0.37	1.04 (0.95 to 1.15)	111	0.45	1.04 (0.94 to 1.15)
BCC UKB	totalT	Simple mode	168	0.84	0.97 (0.71 to 1.32)	111	0.85	0.97 (0.71 to 1.33)
BCC UKB	totalT	Weighted mode	168	0.97	1 (0.88 to 1.15)	111	0.81	1.02 (0.88 to 1.17)
KC QSKIN	totalT	MR Egger	152	0.95	1.01 (0.67 to 1.54)	99	0.52	0.86 (0.55 to 1.35)
KC QSKIN	totalT	Weighted median	152	0.22	0.79 (0.54 to 1.15)	99	0.23	0.79 (0.53 to 1.17)
KC QSKIN	totalT	IVW (fixed effect)	152	0.3	1.15 (0.88 to 1.5)	99	0.32	1.15 (0.87 to 1.52)
KC QSKIN	totalT	Simple mode	152	0.7	1.21 (0.46 to 3.13)	99	0.82	1.11 (0.45 to 2.78)
KC QSKIN	totalT	Weighted mode	152	0.41	0.86 (0.6 to 1.23)	99	0.37	0.84 (0.58 to 1.23)
KC UKB	totalT	MR Egger	168	0.63	0.97 (0.85 to 1.1)	111	0.58	0.96 (0.83 to 1.11)
KC UKB	totalT	Weighted median	168	0.54	1.04 (0.91 to 1.19)	111	0.55	1.04 (0.91 to 1.20)
KC UKB	totalT	IVW (fixed effect)	168	0.83	1.01 (0.93 to 1.1)	111	0.81	1.01 (0.93 to 1.10)
KC UKB	totalT	Simple mode	168	0.8	1.04 (0.78 to 1.39)	111	1	1.00 (0.76 to 1.32)
KC UKB	totalT	Weighted mode	168	0.98	1 (0.88 to 1.13)	111	0.99	1.00 (0.87 to 1.15)
melanoma	totalT	MR Egger	151	0.28	0.91 (0.76 to 1.08)	99	0.23	0.89 (0.73 to 1.08)

melanoma	totalT	Weighted median	151	0.65	0.96 (0.8 to 1.15)	99	0.66	0.96 (0.80 to 1.16)
melanoma	totalT	IVW (fixed effect)	151	0.29	0.94 (0.84 to 1.05)	99	0.34	0.94 (0.84 to 1.06)
melanoma	totalT	Simple mode	151	0.69	1.07 (0.76 to 1.5)	99	0.56	1.11 (0.79 to 1.56)
melanoma	totalT	Weighted mode	151	0.54	0.95 (0.81 to 1.12)	99	0.57	0.95 (0.81 to 1.12)
SCC QSKIN	totalT	MR Egger	152	0.86	1.06 (0.55 to 2.05)	99	0.65	0.85 (0.42 to 1.72)
SCC QSKIN	totalT	Weighted median	15	0.21	0.66 (0.35 to 1.26)	99	0.2	0.64 (0.33 to 1.27)
SCC QSKIN	totalT	IVW (fixed effect)	152	0.31	1.24 (0.82 to 1.87)	99	0.42	1.19 (0.77 to 1.84)
SCC QSKIN	totalT	Simple mode	152	0.57	1.5 (0.36 to 6.17)	99	0.79	1.21 (0.30 to 4.99)
SCC QSKIN	totalT	Weighted mode	152	0.61	0.85 (0.45 to 1.59)	99	0.46	0.77 (0.39 to 1.52)
SCC UKB	totalT	MR Egger	168	0.93	0.99 (0.8 to 1.23)	111	0.75	0.96 (0.77 to 1.21)
SCC UKB	totalT	Weighted median	168	0.73	0.96 (0.76 to 1.22)	111	0.74	0.96 (0.75 to 1.23)
SCC UKB	totalT	IVW (fixed effect)	168	0.24	0.92 (0.81 to 1.05)	111	0.49	0.95 (0.83 to 1.09)
SCC UKB	totalT	Simple mode	168	0.85	1.05 (0.65 to 1.69)	111	0.71	1.09 (0.68 to 1.76)
SCC UKB	totalT	Weighted mode	168	0.79	0.97 (0.79 to 1.19)	111	0.73	0.96 (0.76 to 1.21)

Supplementary Table 9. Estimated univariate MR derived ORs for per 1 SD change increase in genetically predicted SHBG on skin cancer risk

outcome	exposure	method	All variants			Variants with p<1e-5 in subset		
			nsnp	pval	OR	nsnp	pval	OR
BCC QSKIN	SHBG	MR Egger	234	0.42	1.15 (0.82 to 1.61)	226	0.47	1.13 (0.81 to 1.59)
BCC QSKIN	SHBG	Weighted median	234	0.62	0.91 (0.63 to 1.32)	226	0.63	0.92 (0.64 to 1.31)
BCC QSKIN	SHBG	IVW (fixed effect)	234	0.39	1.11 (0.88 to 1.39)	226	0.35	1.11 (0.89 to 1.40)
BCC QSKIN	SHBG	Simple mode	234	0.48	1.37 (0.58 to 3.24)	226	0.46	1.36 (0.60 to 3.11)
BCC QSKIN	SHBG	Weighted mode	234	0.52	1.12 (0.8 to 1.55)	226	0.54	1.11 (0.79 to 1.56)
BCC UKB	SHBG	MR Egger	262	0.79	0.98 (0.87 to 1.11)	254	0.74	0.98 (0.87 to 1.11)
BCC UKB	SHBG	Weighted median	262	0.54	1.03 (0.93 to 1.15)	254	0.54	1.03 (0.93 to 1.15)
BCC UKB	SHBG	IVW (fixed effect)	262	0.13	1.07 (0.98 to 1.16)	254	0.12	1.07 (0.98 to 1.16)
BCC UKB	SHBG	Simple mode	262	0.81	1.03 (0.83 to 1.27)	254	0.82	1.03 (0.82 to 1.29)
BCC UKB	SHBG	Weighted mode	262	0.53	1.03 (0.95 to 1.11)	254	0.53	1.03 (0.95 to 1.11)
KC QSKIN	SHBG	MR Egger	233	0.86	0.98 (0.76 to 1.26)	225	0.85	0.97 (0.76 to 1.26)
KC QSKIN	SHBG	Weighted median	233	0.27	0.86 (0.65 to 1.13)	225	0.26	0.86 (0.65 to 1.12)
KC QSKIN	SHBG	IVW (fixed effect)	233	0.59	1.05 (0.88 to 1.24)	225	0.59	1.05 (0.88 to 1.25)
KC QSKIN	SHBG	Simple mode	233	0.01	0.38 (0.18 to 0.81)	225	0.01	0.39 (0.18 to 0.83)
KC QSKIN	SHBG	Weighted mode	233	0.44	0.9 (0.7 to 1.17)	225	0.41	0.90 (0.71 to 1.15)
KC UKB	SHBG	MR Egger	262	0.77	0.98 (0.89 to 1.09)	254	0.74	0.98 (0.88 to 1.09)
KC UKB	SHBG	Weighted median	262	0.54	1.03 (0.94 to 1.13)	254	0.55	1.03 (0.93 to 1.14)
KC UKB	SHBG	IVW (fixed effect)	262	0.22	1.05 (0.97 to 1.12)	254	0.22	1.05 (0.97 to 1.12)
KC UKB	SHBG	Simple mode	262	0.31	1.11 (0.91 to 1.37)	254	0.29	1.12 (0.91 to 1.39)
KC UKB	SHBG	Weighted mode	262	0.47	1.03 (0.95 to 1.11)	254	0.63	1.02 (0.94 to 1.10)
melanoma	SHBG	MR Egger	235	0.33	0.94 (0.84 to 1.06)	227	0.26	0.93 (0.83 to 1.05)

melanoma	SHBG	Weighted median	235	0.68	0.97 (0.86 to 1.11)	227	0.67	0.97 (0.86 to 1.10)
melanoma	SHBG	IVW (fixed effect)	23	0.22	0.95 (0.88 to 1.03)	227	0.25	0.95 (0.88 to 1.03)
melanoma	SHBG	Simple mode	235	0.72	0.95 (0.72 to 1.25)	227	0.75	0.96 (0.72 to 1.26)
melanoma	SHBG	Weighted mode	235	0.61	0.97 (0.88 to 1.08)	227	0.42	0.96 (0.86 to 1.07)
SCC QSKIN	SHBG	MR Egger	234	0.69	1.1 (0.7 to 1.72)	226	0.73	1.08 (0.69 to 1.70)
SCC QSKIN	SHBG	Weighted median	234	0.24	0.75 (0.46 to 1.21)	226	0.3	0.77 (0.47 to 1.26)
SCC QSKIN	SHBG	IVW (fixed effect)	234	1	1 (0.74 to 1.36)	226	0.96	1.01 (0.74 to 1.37)
SCC QSKIN	SHBG	Simple mode	234	0.46	1.53 (0.49 to 4.72)	226	0.36	1.72 (0.54 to 5.42)
SCC QSKIN	SHBG	Weighted mode	234	0.7	0.92 (0.6 to 1.41)	226	0.68	0.91 (0.60 to 1.39)
SCC UKB	SHBG	MR Egger	262	0.63	0.96 (0.83 to 1.12)	254	0.7	0.97 (0.83 to 1.13)
SCC UKB	SHBG	Weighted median	262	0.73	0.97 (0.82 to 1.15)	254	0.72	0.97 (0.82 to 1.14)
SCC UKB	SHBG	IVW (fixed effect)	262	0.92	0.99 (0.9 to 1.1)	254	0.86	0.99 (0.90 to 1.10)
SCC UKB	SHBG	Simple mode	262	0.85	1.03 (0.73 to 1.47)	254	0.82	1.05 (0.72 to 1.51)
SCC UKB	SHBG	Weighted mode	262	0.56	0.96 (0.83 to 1.11)	254	0.4	0.94 (0.82 to 1.08)

Supplementary Table 10. Estimated Multivariable MR derived marginal OR on skin cancer risk from MVMR model including totalT, freeT and MPB

Outcome	Exposure	UKB		QSKIN		Meta-analysis combining UKB and QSKIN		
		Pval	Marginal OR (95% CI)	Pval	Marginal OR (95% CI)	Pval	Marginal OR (95% CI)	P-het
KC	freeT	0.71	0.96 (0.79 to 1.17)	0.90	1.03 (0.65 to 1.63)	0.77	0.97 (0.81 to 1.17)	0.79
KC	MPB	3.85E-03	1.16 (1.05 to 1.29)	0.20	1.16 (0.92 to 1.47)	1.55E-03	1.16 (1.06 to 1.28)	0.99
KC	totalT	0.65	1.03 (0.90 to 1.19)	0.44	1.13 (0.82 to 1.56)	0.47	1.05 (0.92 to 1.19)	0.60
SCC	freeT	0.93	1.01 (0.77 to 1.33)	0.70	1.18 (0.51 to 2.72)	0.84	1.03 (0.79 to 1.33)	0.73
SCC	MPB	3.49E-04	1.29 (1.12 to 1.49)	0.19	1.32 (0.87 to 2.00)	1.39E-04	1.30 (1.13 to 1.48)	0.92
SCC	totalT	0.63	0.95 (0.79 to 1.16)	0.57	1.18 (0.66 to 2.11)	0.78	0.97 (0.81 to 1.17)	0.49
BCC	freeT	0.75	0.97 (0.78 to 1.19)	0.82	0.93 (0.50 to 1.73)	0.71	0.96 (0.79 to 1.18)	0.91
BCC	MPB	0.02	1.15 (1.03 to 1.28)	0.13	1.27 (0.93 to 1.73)	5.22E-03	1.16 (1.04 to 1.29)	0.54
BCC	totalT	0.46	1.06 (0.91 to 1.23)	0.27	1.27 (0.83 to 1.96)	0.29	1.08 (0.94 to 1.24)	0.42
Melanoma	freeT	-	-	-	-	0.91	1.01 (0.83 to 1.23)	-
Melanoma	MPB	-	-	-	-	0.27	0.95 (0.86 to 1.04)	-
Melanoma	totalT	-	-	-	-	0.33	0.94 (0.82 to 1.07)	-

P-het=Pvalue of the heterogeneity test.

Supplementary Table 11. PheWAS summary on detected MR-PRESSO SNP outliers on a range of skin-related risk factors and disease traits

SNP	CHR	ID (OpenGWAS)	Trait description	IA	P	SE	N	Beta	EAF
rs3847069 (EA:T; NEA:C)	7	ukb-d-C_OTHER_SKIN	**Other malignant neoplasms of skin**		9.64E-15	0.0005	361194	-0.004	0.25
	7	ukb-d-C3_SKIN	**Malignant neoplasm of skin**		8.54E-13	0.0006	361194	-0.004	0.25
	7	ukb-d-C_SKIN	**Cancer of skin**		8.54E-13	0.0006	361194	-0.004	0.25
	7	ukb-a-518	Diagnoses - main ICD10: C44 Other malignant neoplasms of skin		2.93E-10	0.0003	337199	-0.002	0.25
	7	ukb-b-10248	Type of cancer: ICD10: C44.3 Skin of other and unspecified parts of face		6.50E-10	0.0003	463010	-0.002	0.25
	7	ukb-a-303	**Hair/balding pattern: Pattern 4**	YES	1.16E-08	0.0016	154988	0.009	0.25
	7	ukb-d-2395_1	Hair/balding pattern: Pattern 1		1.10E-06	0.0019	165649	-0.009	0.25
rs2669871 (EA:T; NEA:C)	12	ukb-d-C_OTHER_SKIN	**Other malignant neoplasms of skin**		2.37E-11	0.0005	361194	-0.003	0.49
	12	ukb-d-C_SKIN	**Cancer of skin**		8.35E-10	0.0005	361194	-0.003	0.49
	12	ukb-d-C3_SKIN	**Malignant neoplasm of skin**		8.35E-10	0.0005	361194	-0.003	0.49
	12	ukb-a-518	Diagnoses - main ICD10: C44 Other malignant neoplasms of skin		3.60E-07	0.0003	337199	-0.001	0.49
rs1805007 (EA:T; NEA:C)	16	ukb-b-19560	**Skin colour**	YES	0	0.0019	456692	-0.225	0.1
	16	ukb-b-13246	**Childhood sunburn occasions**		0	0.0035	346955	0.196	0.1
	16	ukb-b-533	**Ease of skin tanning**	YES	0	0.0032	453065	0.428	0.1
	16	ukb-d-1747_2	**Hair colour (natural, before greying): Red**	YES	0	0.0008	360270	0.162	0.1
	16	ukb-d-1747_4	**Hair colour (natural, before greying): Dark brown**	YES	0	0.0018	360270	-0.143	0.1
	16	ukb-b-7422	**Use of sun/uv protection**		1.50E-272	0.003	459416	0.104	0.1
	16	ukb-d-1747_5	**Hair colour (natural, before greying): Black**	YES	8.18E-258	0.0008	360270	-0.027	0.1
	16	ukb-d-1747_1	**Hair colour (natural, before greying): Blonde**	YES	7.03E-130	0.0012	360270	0.03	0.1
	16	ukb-d-C3_SKIN	**Malignant neoplasm of skin**		2.85E-80	0.0008	361194	0.015	0.1
	16	ukb-d-C_SKIN	**Cancer of skin**		2.85E-80	0.0008	361194	0.015	0.1
	16	ukb-d-C_OTHER_SKIN	Other malignant neoplasms of skin		3.88E-59	0.0007	361194	0.012	0.1
	16	ukb-d-1747_6	**Hair colour (natural, before greying): Other**	YES	9.98E-56	0.0004	360270	0.007	0.1
	16	ukb-d-1747_3	**Hair colour (natural, before greying): Light brown**	YES	5.40E-50	0.0019	360270	-0.028	0.1
	16	ukb-b-12915	Cancer code, self-reported: malignant melanoma		4.40E-38	0.0003	462933	0.004	0.1
	16	ukb-d-C3_MELANOMA_SKIN	**Malignant melanoma of skin**		5.24E-36	0.0003	361194	0.004	0.1
	16	ukb-a-58	Cancer code self-reported: malignant melanoma		1.68E-30	0.0004	337159	0.004	0.1
	16	ukb-b-10787	Standing height		3.30E-28	0.0022	461950	-0.024	0.1

	16	ukb-d-C43	Diagnoses - main ICD10: C43 Malignant melanoma of skin		3.35E-25	0.0003	361194	0.003	0.1
	16	ukb-a-518	Diagnoses - main ICD10: C44 Other malignant neoplasms of skin		1.30E-23	0.0005	337199	0.005	0.1
	16	ukb-b-8837	Cancer code, self-reported: basal cell carcinoma		3.50E-22	0.0003	462933	0.003	0.1
	16	ukb-b-5945	Relative age of first facial hair		1.90E-20	0.0022	204568	0.021	0.1
	16	ukb-a-389	Standing height		3.92E-19	0.0028	336474	-0.025	0.1
	16	ukb-b-2148	**Facial ageing**		8.10E-19	0.0017	423999	0.015	0.1
	16	ukb-b-660	Number of self-reported cancers		7.70E-18	0.0011	462925	0.009	0.1
	16	ukb-b-6772	Operation code: removal of mole/skin lesion		1.60E-17	0.0004	462933	0.003	0.1
	16	ukb-a-59	Cancer code self-reported: basal cell carcinoma		6.67E-17	0.0004	337159	0.003	0.1
	16	ukb-a-21	Number of self-reported cancers		4.19E-15	0.0012	337154	0.01	0.1
	16	ukb-a-299	Relative age of first facial hair		2.04E-14	0.0026	151113	0.02	0.1
	16	ukb-b-15918	Treatment speciality of consultant (recoded): Dermatology		2.70E-14	0.0005	444587	0.004	0.1
	16	ukb-b-4141	Diagnoses - main ICD10: C44.3 Skin of other and unspecified parts of face		6.70E-14	0.0003	463010	0.002	0.1
	16	ukb-b-10248	Type of cancer: ICD10: C44.3 Skin of other and unspecified parts of face		2.10E-13	0.0004	463010	0.003	0.1
	16	ukb-b-9537	Operative procedures - main OPCS: S06.9 Unspecified other excision of lesion of skin		3.30E-13	0.0006	463010	0.004	0.1
	16	ukb-b-1852	Main speciality of consultant (recoded): Dermatology		9.90E-13	0.0005	461170	0.003	0.1
	16	finn-a-L12_ACTINKERA	Actinic keratosis		1.52E-12	0.0789		0.558	0.07
	16	ukb-b-16855	Cancer diagnosed by doctor		4.60E-12	0.0009	461311	0.006	0.1
	16	finn-a-L12_NONIONRADISKIN	Skin changes due to chronic exposure to nonionizing radiation		8.02E-12	0.0762		0.521	0.07
	16	finn-a-L12_RADIATIONRELATEDSKIN	Radiation-related disorders of the skin and subcutaneous tissue		3.33E-11	0.0712		0.472	0.07
	16	ukb-b-2951	Operative procedures - secondary OPCS: Z50.1 Skin of arm		3.40E-11	0.0003	463010	0.002	0.1
	16	ukb-d-L12_NONIONRADISKIN	Skin changes due to chronic exposure to nonionizing radiation		4.27E-11	0.0002	361194	0.002	0.1
	16	ukb-a-307	Cancer diagnosed by doctor		6.44E-11	0.0011	336272	0.007	0.1
	16	prot-a-2310	Melanocyte protein PMEL		7.59E-11	0.0415	3301	-0.27	0.1
	16	ukb-d-L12_ACTINKERA	Actinic keratosis		1.07E-10	0.0002	361194	0.002	0.1
	16	ukb-b-6591	Age first had sexual intercourse		1.50E-10	0.0035	406457	0.023	0.1
	16	ukb-b-5394	Reported occurrences of cancer		2.10E-10	0.0054	73231	0.034	0.11
	16	ukb-d-30260_irnt	Mean reticulocyte volume		3.30E-10	0.0039	344728	-0.024	0.1
	16	ukb-d-2395_1	Hair/balding pattern: Pattern 1		3.97E-10	0.0026	165649	-0.016	0.1

	16	ukb-b-1431	Place of birth in UK - north co-ordinate		1.10E-09	0.0027	434576	0.016	0.1
	16	ukb-b-8938	Main speciality of consultant (recoded): Plastic surgery		1.10E-09	0.0007	461218	0.004	0.1
	16	ukb-b-13285	Treatment speciality of consultant (recoded): Plastic surgery		4.40E-09	0.0007	445128	0.004	0.1
	16	ukb-b-13653	Worry too long after embarrassment		6.90E-09	0.0017	443918	0.01	0.1
	16	finn-a-C3_OTHER_SKIN	**Other malignant neoplasms of skin**		8.97E-09	0.1004		0.577	0.07
	16	finn-a-C3_SKIN	**Malignant neoplasm of skin**		8.97E-09	0.1004		0.577	0.07
	16	finn-a-C3_SKIN_EXALLC	**Malignant neoplasm of skin (ICD C excluded)**		1.44E-08	0.0999		0.567	0.07
	16	finn-a-C3_OTHER_SKIN_EXALLC	**Other malignant neoplasms of skin (ICD C excluded)**		1.44E-08	0.0999		0.567	0.07
rs12203592 (EA:T; NEA:C)	6	ukb-b-533	**Ease of skin tanning**	YES	0	0.0024	453065	0.261	0.22
	6	ukb-b-13246	**Childhood sunburn occasions**		0	0.0025	346955	0.153	0.22
	6	ukb-b-19560	**Skin colour**	YES	0	0.0014	456692	-0.088	0.22
	6	ukb-b-2148	**Facial ageing**	YES	0.00E+00	0.0013	423999	0.049	0.22
	6	ukb-b-7422	**Use of sun/uv protection**		1.40E-258	0.0021	459416	0.073	0.22
	6	ukb-b-10248	Type of cancer: ICD10: C44.3 Skin of other and unspecified parts of face		1.10E-61	0.0003	463010	0.005	0.22
	6	ukb-b-5945	**Relative age of first facial hair**	YES	2.00E-37	0.0016	204568	-0.021	0.22
	6	ukb-b-4141	Diagnoses - main ICD10: C44.3 Skin of other and unspecified parts of face		2.20E-34	0.0002	463010	0.003	0.22
	6	ieu-b-32	lymphocyte cell count		1.37E-30	0.0024	520692	0.027	0.21
	6	ukb-b-8837	Cancer code, self-reported: basal cell carcinoma		2.70E-26	0.0002	462933	0.003	0.22
	6	ukb-b-15685	Type of cancer: ICD10: C44.5 Skin of trunk		4.70E-24	0.0002	463010	0.002	0.22
	6	ieu-b-33	eosinophil cell count		1.35E-23	0.0025	470024	0.025	0.22
	6	ieu-b-30	white blood cell count		1.61E-21	0.0023	544160	0.022	0.21
	6	ukb-b-10817	Particulate matter air pollution (pm2.5); 2010		6.20E-17	0.0026	423796	0.022	0.21
	6	ukb-b-9942	Nitrogen dioxide air pollution; 2010		7.00E-16	0.0024	456380	0.02	0.22
	6	ukb-b-3169	Number of vehicles in household		1.90E-15	0.0021	459696	-0.017	0.22
	6	ukb-b-12417	Nitrogen oxides air pollution; 2010		3.20E-15	0.0025	456380	0.019	0.22
	6	ukb-b-8416	Type of cancer: ICD10: C44.9 Malignant neoplasm of skin, unspecified		6.60E-15	0.0002	463010	0.002	0.22
	6	ukb-b-5620	Nitrogen dioxide air pollution; 2006		9.90E-15	0.0024	456380	0.019	0.22
	6	ukb-b-660	Number of self-reported cancers		1.80E-13	0.0008	462925	0.006	0.22
	6	ukb-b-13184	Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging)		6.50E-13	0.0012	460376	-0.009	0.22
	6	ukb-b-10011	Townsend deprivation index at recruitment		1.70E-12	0.0024	462464	0.017	0.22

	6	ebi-a-GCST004606	Eosinophil counts		2.16E-12	0.0043	172275	0.03	0.22
	6	ukb-b-1260	Spells in hospital		3.50E-12	0.0024	303963	0.017	0.22
	6	ebi-a-GCST004624	Sum eosinophil basophil counts		3.76E-12	0.0043	171771	0.03	0.22
	6	ukb-b-11231	Diagnoses - secondary ICD10: Z85.8 Personal history of malignant neoplasms of other organs and systems		1.20E-11	0.0002	463010	0.001	0.22
	6	ukb-b-2618	Nitrogen dioxide air pollution; 2005		3.60E-11	0.0024	456380	0.016	0.22
	6	ukb-b-11312	Particulate matter air pollution (pm2.5) absorbance; 2010		1.20E-10	0.0026	423796	0.017	0.21
	6	ukb-b-16878	Alcohol usually taken with meals		1.30E-10	0.0016	235645	-0.01	0.22
	6	ukb-b-15918	Treatment speciality of consultant (recoded): Dermatology		1.40E-10	0.0004	444587	0.002	0.22
	6	prot-a-1255	Transmembrane glycoprotein NMB		1.45E-10	0.0317	3301	-0.203	0.2
	6	ukb-b-20544	Nervous feelings		1.50E-10	0.0011	450700	0.007	0.22
	6	ebi-a-GCST004627	Lymphocyte counts		4.56E-10	0.0044	171643	0.027	0.22
	6	ukb-b-969	Time spend outdoors in summer		4.80E-10	0.0023	419314	-0.014	0.22
	6	ukb-b-1996	Salad / raw vegetable intake		1.30E-09	0.0017	435435	-0.01	0.22
	6	prot-a-1256	Transmembrane glycoprotein NMB		1.78E-09	0.0317	3301	-0.191	0.2
	6	ukb-b-4630	Neuroticism score		1.90E-09	0.0088	374323	0.053	0.22
	6	ukb-b-1285	Nitrogen dioxide air pollution; 2007		1.90E-09	0.0024	456380	0.014	0.22
	6	finn-a-L12_ACTINKERA	Actinic keratosis		3.74E-09	0.1204		0.71	0.03
	6	ieu-b-69	sepsis		3.90E-09	0.0169	462918	0.047	0.22
	6	finn-a-L12_NONIONRADISKIN	Skin changes due to chronic exposure to nonionizing radiation		4.30E-09	0.1165		0.684	0.03
	6	ukb-b-698	How are people in household related to participant: Husband, wife or partner		5.90E-09	0.0011	459600	-0.006	0.22
	6	ukb-b-4263	Number of full brothers		1.60E-08	0.0019	455347	0.011	0.22
	6	ieu-b-34	neutrophil cell count		1.66E-08	0.0024	515057	0.014	0.21
	6	ukb-b-6306	Overall health rating		1.80E-08	0.0018	460844	0.01	0.22
	6	finn-a-L12_RADIATIONRELATEDSKIN	Radiation-related disorders of the skin and subcutaneous tissue		2.08E-08	0.1091		0.612	0.03
	6	ebi-a-GCST006948	Feeling nervous		2.46E-08	0.0028	373121	0.016	0.21
	6	ukb-b-11582	Diagnoses - main ICD10: K62.5 Haemorrhage of anus and rectum		2.90E-08	0.0004	463010	0.002	0.22
	6	ukb-b-16751	Diagnoses - secondary ICD10: J44.9 Chronic obstructive pulmonary disease, unspecified		3.10E-08	0.0002	463010	0.001	0.22
	6	ukb-b-3460	Alcohol intake versus 10 years previously		3.30E-08	0.0019	428117	0.01	0.22

IA=SNP Instruments available (obtainable from GWAS data on exposure risk factors).

Supplementary Table 12. Univariate MR association between skin/hair colour and MPB score (incl alt models)

Outcome	Exposure	MR method	*Original estimates*				*Removing the IRF4 variant*		
			SNPs	**beta**	**se**	**Pvalue**	**beta**	**se**	**Pvalue**
MPB	Hair colour	MR Egger	139	0.177	0.028	3.35E-09	0.025	0.041	0.55
		Weighted median	139	0.252	0.016	1.97E-57	0.011	0.022	0.62
		Inverse variance weighted	139	0.128	0.025	1.90E-07	-0.001	0.031	0.98
		Simple mode	139	0.007	0.059	0.90	0.007	0.059	0.91
		Weighted mode	139	0.250	0.021	1.49E-22	0.007	0.018	0.71
MPB	Skin colour	MR Egger	39	-0.501	0.091	2.80E-06	-0.025	0.088	0.78
		Weighted median	39	-0.143	0.064	0.03	0.006	0.049	0.90
		Inverse variance weighted	39	-0.284	0.072	8.31E-05	0.033	0.055	0.54
		Simple mode	39	-0.014	0.079	0.86	-0.012	0.076	0.87
		Weighted mode	39	-0.708	0.044	1.05E-18	-0.019	0.048	0.69

Instruments defined at SNP association p-value < 1e-10 with exposure.
MR beta reflect the change in MPB SD units (positive indicate increased rates of balding) per 1 SD unit change in the underlying pigmentation variable (skin:increased degrees of tanning; hair: increased brightness (black - red) of hair).

Supplementary Table 13. Estimated Multivariable MR derived marginal OR on skin cancer risk from MVMR model including totalT, freeT, hair colour and MPB

Outcome	Exposure	UKB		QSKIN		Meta-analysis combining UKB and QSKIN		
		Pval	Marginal OR (95% CI)	Pval	Marginal OR (95% CI)	Pval	Marginal OR (95% CI)	P-het
KC	freeT	0.53	0.95 (0.8 to 1.13)	0.59	0.89 (0.58 to 1.37)	0.43	0.94 (0.80 to 1.10)	0.79
KC	hair colour	7.49E-04	1.18 (1.07 to 1.3)	0.01	1.34 (1.07 to 1.7)	4.79E-05	1.20 (1.10 to 1.31)	0.31
KC	MPB	8.06E-04	1.18 (1.07 to 1.3)	0.11	1.21 (0.96 to 1.52)	2.11E-04	1.18 (1.08 to 1.29)	0.85
KC	totalT	0.53	1.04 (0.92 to 1.17)	0.47	1.12 (0.83 to 1.5)	0.39	1.05 (0.94 to 1.17)	0.67
SCC	freeT	0.91	1.01 (0.8 to 1.29)	0.83	0.92 (0.43 to 1.98)	0.97	1.00 (0.80 to 1.26)	0.82
SCC	hair colour	6.72E-04	1.26 (1.1 to 1.44)	0.01	1.71 (1.12 to 2.61)	6.67E-05	1.30 (1.14 to 1.47)	0.18
SCC	MPB	2.21E-04	1.29 (1.13 to 1.47)	0.06	1.49 (0.98 to 2.25)	4.23E-05	1.30 (1.15 to 1.48)	0.51
SCC	totalT	0.59	0.96 (0.81 to 1.13)	0.63	1.14 (0.67 to 1.92)	0.72	0.97 (0.83 to 1.14)	0.54
BCC	freeT	0.52	0.94 (0.78 to 1.13)	0.23	0.71 (0.4 to 1.25)	0.32	0.91 (0.76 to 1.09)	0.35
BCC	hair colour	2.91E-03	1.17 (1.06 to 1.3)	0.02	1.46 (1.07 to 1.99)	3.26E-04	1.20 (1.09 to 1.32)	0.18
BCC	MPB	3.83E-03	1.17 (1.05 to 1.3)	0.03	1.39 (1.03 to 1.89)	6.02E-04	1.19 (1.08 to 1.31)	0.28
BCC	totalT	0.30	1.07 (0.94 to 1.22)	0.36	1.2 (0.81 to 1.76)	0.21	1.08 (0.96 to 1.23)	0.60
						GenoMEL Phase 2 meta-analysis		
Melanoma	freeT	-	-	-	-	0.73	0.97 (0.79 to 1.18)	-
Melanoma	hair colour	-	-	-	-	0.98	1 (0.96 to 1.04)	-
Melanoma	MPB	-	-	-	-	0.34	0.95 (0.86 to 1.05)	-
Melanoma	totalT	-	-	-	-	0.99	1 (0.88 to 1.14)	-

P-het=Pvalue of the Heterogeneity test.

Supplementary Table 14. Estimated Multivariable MR derived marginal OR on skin cancer risk from MVMR model including totalT, freeT, hair colour, skin colour and MPB

Outcome	Exposure	UKB		QSKIN		Meta-analysis combining UKB and QSKIN		
		Pval	Marginal OR (95% CI)	Pval	Marginal OR (95% CI)	Pval	Marginal OR (95% CI)	P-het
KC	freeT	0.53	0.96 (0.85 to 1.09)	0.67	0.92 (0.65 to 1.32)	0.46	0.96 (0.85 to 1.08)	0.85
KC	hair colour	3.72E-33	1.59 (1.47 to 1.72)	1.31E-16	2.4 (1.95 to 2.95)	<1E-100	1.67 (1.56 to 1.79)	2.70E-04
KC	*MPB*	*0.10*	*1.06 (0.99 to 1.14)*	*0.85*	*0.98 (0.81 to 1.19)*	*0.14*	*1.05 (0.98 to 1.13)*	*0.45*
KC	skin colour	5.40E-106	0.24 (0.21 to 0.27)	1.11E-55	0.06 (0.04 to 0.09)	<1E-100	0.20 (0.18 to 0.23)	2.90E-13
KC	totalT	0.50	1.03 (0.94 to 1.13)	0.52	1.08 (0.85 to 1.39)	0.40	1.04 (0.95 to 1.13)	0.71
SCC	freeT	0.90	1.01 (0.82 to 1.25)	0.99	1.01 (0.52 to 1.96)	0.90	1.01 (0.83 to 1.24)	0.98
SCC	hair colour	4.57E-17	1.71 (1.51 to 1.94)	2.92E-14	4.78 (3.19 to 7.15)	<1E-100	1.87 (1.66 to 2.11)	1.86E-06
SCC	*MPB*	*0.01*	*1.17 (1.04 to 1.31)*	*0.61*	*1.1 (0.76 to 1.58)*	*0.01*	*1.16 (1.04 to 1.30)*	*0.77*
SCC	skin colour	3.53E-39	0.24 (0.2 to 0.3)	5.07E-40	0.01 (0 to 0.02)	<1E-100	0.18 (0.15 to 0.23)	0.00E+00
SCC	totalT	0.50	0.95 (0.82 to 1.1)	0.72	1.09 (0.69 to 1.72)	0.59	0.96 (0.84 to 1.11)	0.59
BCC	freeT	0.57	0.96 (0.83 to 1.1)	0.24	0.75 (0.47 to 1.21)	0.38	0.94 (0.82 to 1.08)	0.33
BCC	hair colour	7.20E-30	1.63 (1.49 to 1.77)	5.66E-16	3.18 (2.4 to 4.2)	<1E-50	1.72 (1.58 to 1.86)	6.85E-06
BCC	*MPB*	*0.29*	*1.04 (0.96 to 1.13)*	*0.55*	*1.08 (0.84 to 1.4)*	*0.24*	*1.05 (0.97 to 1.13)*	*0.80*
BCC	skin colour	4.56E-102	0.21 (0.19 to 0.25)	9.41E-51	0.03 (0.02 to 0.04)	<1E-100	0.18 (0.16 to 0.21)	2.22E-16
BCC	totalT	0.24	1.06 (0.96 to 1.17)	0.39	1.15 (0.83 to 1.6)	0.17	1.07 (0.97 to 1.17)	0.63
Melanoma	freeT	-	-	-	-	0.98	1 (0.82 to 1.21)	-
Melanoma	hair colour	-	-	-	-	1.29E-06	1.19 (1.11 to 1.28)	-
Melanoma	*MPB*	-	-	-	-	*0.08*	*0.91 (0.82 to 1.01)*	-
Melanoma	skin colour	-	-	-	-	5.82E-09	0.5 (0.4 to 0.64)	-
Melanoma	totalT	-	-	-	-	0.69	1.03 (0.9 to 1.16)	-

Estimates for MPB are shown in italic font. KC = any BCC or SCC.

Supplementary Table 15. Sensitivity analyses assessing the influence of the 4 detected MR-PRESSO SNP outliers on MVMR marginal OR estimates

Outcome	Trait	Before removing SNP-outlier		After removing SNP-outlier	
		Pvalue	marginal OR (95% CI)	Pvalue	marginal OR (95% CI)
KC	hair colour	3.35E-45	1.67 (1.56 to 1.80)	1.36E-10	1.56 (1.36 to 1.79)
KC	*MPB*	*0.16*	*1.05 (0.98 to 1.12)*	*0.13*	*1.05 (0.98 to 1.13)*
KC	skin colour	8.25E-149	0.20 (0.18 to 0.23)	1.09E-31	0.22 (0.17 to 0.28)
KC	totalT	0.70	1.01 (0.94 to 1.09)	0.66	1.02 (0.94 to 1.10)
SCC	hair colour	8.15E-25	1.87 (1.66 to 2.11)	1.47E-03	1.45 (1.15 to 1.81)
SCC	*MPB*	*0.01*	*1.16 (1.04 to 1.29)*	*0.02*	*1.15 (1.02 to 1.28)*
SCC	skin colour	3.86E-61	0.18 (0.15 to 0.22)	2.06E-08	0.29 (0.19 to 0.45)
SCC	totalT	0.61	0.97 (0.85 to 1.10)	0.61	0.97 (0.86 to 1.10)
BCC	hair colour	1.14E-39	1.72 (1.59 to 1.86)	5.59E-10	1.62 (1.39 to 1.88)
BCC	*MPB*	*0.27*	*1.04 (0.97 to 1.13)*	*0.21*	*1.05 (0.97 to 1.13)*
BCC	skin colour	5.96E-136	0.18 (0.16 to 0.21)	4.65E-31	0.18 (0.14 to 0.24)
BCC	totalT	0.39	1.04 (0.95 to 1.13)	0.35	1.04 (0.96 to 1.13)
Melanoma	hair colour	9.41E-07	1.19 (1.11 to 1.28)	1.17E-15	1.57 (1.41 to 1.76)
Melanoma	*MPB*	*0.08*	*0.91 (0.82 to 1.01)*	*0.30*	*0.95 (0.86 to 1.05)*
Melanoma	skin colour	6.71E-09	0.51 (0.4 to 0.64)	1.07E-17	0.2 (0.14 to 0.29)
Melanoma	totalT	0.81	1.01 (0.91 to 1.14)	0.34	0.95 (0.85 to 1.06)

Estimates for MPB are shown in italic font. KC = any BCC or SCC.

Supplementary Table 16. Estimated heterogeneity among SNP estimates on MPB and skin cancer

Outcome	Exposure	Model	Original estimate			After removing SNP-outliers identified in MR-PRESSO		
			Cochran Q	Q_df	Q_pval	Cochran Q	Q_df	Q_pval
KC UKB*	MPB	MR Egger	1154.7	470	2.05E-59	561.2	466	1.58E-03
		IVW	1156.1	471	2.09E-59	563.6	467	1.41E-03
KC QSKIN	MPB	MR Egger	650.6	468	4.35E-08	457.1	464	5.82E-01
		IVW	658.9	469	1.52E-08	459.0	465	5.70E-01
SCC UKB	MPB	MR Egger	680.1	470	6.92E-10	476.0	466	3.65E-01
		IVW	680.6	471	7.71E-10	480.8	467	3.20E-01
SCC QSKIN	MPB	MR Egger	662.0	469	9.46E-09	503.9	465	1.03E-01
		IVW	668.0	470	4.62E-09	505.1	466	1.02E-01
BCC UKB*	MPB	MR Egger	1149.3	470	1.02E-58	591.9	466	6.56E-05
		IVW	1152.8	471	5.54E-59	592.5	467	6.97E-05
BCC QSKIN	MPB	MR Egger	677.2	469	9.11E-10	504.2	465	1.02E-01
		IVW	681.7	470	5.41E-10	504.7	466	1.05E-01
Melanoma	MPB	MR Egger	626.6	469	1.41E-06	616.5	466	3.36E-06
		IVW	626.6	470	1.64E-06	616.5	467	3.89E-06

Cochran Q=The Cochran Q test statistics. Q_df =degree of freedom for the Cochran Q test statistics. Q_pval=Pvalue of the Cochran Q test statistics.

Supplementary Table 17. Estimated heterogeneity among SNP estimates on MPB and skin cancer using MPB variants with p<1e-5 in the independent UKB subset.

Outcome	Exposure	Model	Original estimate			After removing SNP-outliers identified in MR-PRESSO		
			Cochran Q	Q_df	Q_pval	Cochran Q	Q_df	Q_pval
KC UKB	MPB (P<1e-5 only)	MR Egger	958.8	285	8.19E-74	370.3	281	2.75E-04
		IVW	965.6	286	1.39E-74	370.4	282	3.13E-04
KC QSKIN	MPB (P<1e-5 only)	MR Egger	468.6	284	3.12E-11	274.1	280	0.59
		IVW	471.0	285	2.51E-11	274.1	281	0.60
SCC UKB	MPB (P<1e-5 only)	MR Egger	519.8	285	6.41E-16	315.9	281	0.07
		IVW	519.8	286	8.62E-16	318.8	282	0.06
SCC QSKIN	MPB (P<1e-5 only)	MR Egger	469.8	285	3.22E-11	313.0	281	0.09
		IVW	476.4	286	1.09E-11	314.5	282	0.09
BCC UKB	MPB (P<1e-5 only)	MR Egger	938.5	285	1.04E-70	386.4	281	2.96E-05
		IVW	949.0	286	4.72E-72	386.5	282	3.46E-05
BCC QSKIN	MPB (P<1e-5 only)	MR Egger	477.0	285	7.31E-12	304.4	281	0.16
		IVW	480.1	286	5.08E-12	304.5	282	0.17
Melanoma	MPB (P<1e-5 only)	MR Egger	391.7	284	2.29E-05	381.9	281	5.68E-05
		IVW	392.0	285	2.62E-05	381.9	282	6.68E-05

Cochran Q=The Cochran Q test statistics. Q_df =degree of freedom for the Cochran Q test statistics. Q_pval=Pvalue of the Cochran Q test statistics. MPB (P<1e-5 only)=The analysis using MPB variants (SNP instruments) with association p-value<1e-5 in the MPB GWAS conducted on the independent UKB subset (see methods).

Supplementary Table 18. Estimated MR ORs for per 1 SD change increase in genetically predicted MPB score on skin cancer risk after removal of (n=4) pleiotropic SNP outliers

outcome	exposure	method	All variants			Variants with p<1e-5 in subset		
			nsnp	pval	OR	nsnp	pval	OR
KC UKB	MPB (outliers removed)	MR Egger	468	0.72	1.02 (0.92 to 1.14)	283	0.49	1.05 (0.92 to 1.20)
KC UKB	MPB (outliers removed)	Weighted median	468	0.29	1.05 (0.96 to 1.15)	283	0.3	1.05 (0.96 to 1.15)
KC UKB	MPB (outliers removed)	IVW (fixed effect)	468	3.43E-03	1.09 (1.03 to 1.15)	283	0.04	1.07 (1.00 to 1.14)
KC UKB	MPB (outliers removed)	Simple mode	468	0.65	1.05 (0.84 to 1.31)	283	0.88	1.02 (0.80 to 1.29)
KC UKB	MPB (outliers removed)	Weighted mode	468	0.91	0.99 (0.89 to 1.11)	283	0.95	1.00 (0.87 to 1.13)
SCC UKB	MPB (outliers removed)	MR Egger	468	0.88	1.01 (0.85 to 1.21)	283	0.98	1.00 (0.81 to 1.25)
SCC UKB	MPB (outliers removed)	Weighted median	468	0.01	1.24 (1.06 to 1.45)	283	0.01	1.24 (1.05 to 1.47)
SCC UKB	MPB (outliers removed)	IVW (fixed effect)	468	1.66E-04	1.20 (1.09 to 1.32)	283	2.85E-03	1.17 (1.06 to 1.31)
SCC UKB	MPB (outliers removed)	Simple mode	468	0.1	1.35 (0.94 to 1.93)	283	0.1	1.38 (0.94 to 2.04)
SCC UKB	MPB (outliers removed)	Weighted mode	468	0.1	1.20 (0.97 to 1.48)	283	0.1	1.22 (0.96 to 1.55)
BCC QSKIN	MPB (outliers removed)	MR Egger	467	0.85	1.04 (0.68 to 1.61)	283	0.96	1.01 (0.61 to 1.68)
BCC QSKIN	MPB (outliers removed)	Weighted median	467	0.65	0.92 (0.63 to 1.34)	283	0.77	0.94 (0.64 to 1.40)
BCC QSKIN	MPB (outliers removed)	IVW (fixed effect)	467	0.46	0.92 (0.73 to 1.15)	283	0.7	0.95 (0.75 to 1.22)
BCC QSKIN	MPB (outliers removed)	Simple mode	467	0.06	0.41 (0.16 to 1.05)	283	0.21	0.56 (0.23 to 1.37)
BCC QSKIN	MPB (outliers removed)	Weighted mode	467	0.39	0.81 (0.51 to 1.30)	283	0.43	0.80 (0.46 to 1.39)
BCC UKB	MPB (outliers removed)	MR Egger	468	0.59	1.03 (0.91 to 1.17)	283	0.37	1.07 (0.92 to 1.25)
BCC UKB	MPB (outliers removed)	Weighted median	468	0.34	1.05 (0.95 to 1.15)	283	0.4	1.05 (0.94 to 1.16)
BCC UKB	MPB (outliers removed)	IVW (fixed effect)	468	0.03	1.07 (1.00 to 1.14)	283	0.16	1.05 (0.98 to 1.13)
BCC UKB	MPB (outliers removed)	Simple mode	468	0.52	1.09 (0.84 to 1.40)	283	0.66	1.06 (0.82 to 1.37)
BCC UKB	MPB (outliers removed)	Weighted mode	468	0.84	0.99 (0.86 to 1.13)	283	0.82	0.98 (0.85 to 1.14)
KC QSKIN	MPB (outliers removed)	MR Egger	466	0.67	1.07 (0.79 to 1.44)	282	0.73	0.94 (0.66 to 1.34)
KC QSKIN	MPB (outliers removed)	Weighted median	466	0.61	0.93 (0.70 to 1.23)	282	0.68	0.94 (0.71 to 1.25)
KC QSKIN	MPB (outliers removed)	IVW (fixed effect)	466	0.14	0.89 (0.76 to 1.04)	282	0.48	0.94 (0.79 to 1.11)
KC QSKIN	MPB (outliers removed)	Simple mode	466	0.42	0.77 (0.41 to 1.45)	282	0.79	0.91 (0.46 to 1.79)
KC QSKIN	MPB (outliers removed)	Weighted mode	466	0.91	0.98 (0.67 to 1.42)	282	0.99	1.00 (0.65 to 1.55)

SCC QSKIN	MPB (outliers removed)	MR Egger	467	0.67	1.13 (0.63 to 2.02)	283	0.5	1.27 (0.64 to 2.53)
SCC QSKIN	MPB (outliers removed)	Weighted median	467	0.83	1.06 (0.64 to 1.74)	283	0.75	1.09 (0.65 to 1.83)
SCC QSKIN	MPB (outliers removed)	IVW (fixed effect)	467	0.35	0.87 (0.64 to 1.18)	283	0.51	0.89 (0.64 to 1.24)
SCC QSKIN	MPB (outliers removed)	Simple mode	467	0.74	0.79 (0.19 to 3.20)	283	0.45	0.60 (0.16 to 2.26)
SCC QSKIN	MPB (outliers removed)	Weighted mode	467	0.76	1.13 (0.51 to 2.51)	283	0.63	1.23 (0.54 to 2.78)
melanoma	MPB (outliers removed)	MR Egger	466	0.74	0.97 (0.84 to 1.14)	283	0.73	0.97 (0.81 to 1.16)
melanoma	MPB (outliers removed)	Weighted median	466	0.59	0.97 (0.86 to 1.09)	283	0.61	0.97 (0.85 to 1.10)
melanoma	MPB (outliers removed)	IVW (fixed effect)	466	0.39	0.96 (0.88 to 1.05)	283	0.39	0.96 (0.88 to 1.05)
melanoma	MPB (outliers removed)	Simple mode	466	0.05	1.32 (1.00 to 1.76)	283	0.31	1.16 (0.87 to 1.57)
melanoma	MPB (outliers removed)	Weighted mode	466	0.3	1.09 (0.93 to 1.27)	283	0.43	1.08 (0.89 to 1.30)

Variants with P<1e-5 in subset=The analysis using MPB variants (SNP instruments) with association p-value<1e-5 in the MPB GWAS conducted on the independent UKB subset (see methods).

Supplementary Table 19. Estimated (meta-analysed) MR ORs for per 1 SD change increase in genetically predicted MPB score on skin cancer risk stratified by major body site categories.

Cancer	Category	MR Method	Original estimate			After removal of SNP-outliers	
			SNPs	Pvalue	OR	Pvalue	OR
BCC	Head and Neck	MR Egger	442	0.06	1.16 (0.99 to 1.35)	0.10	1.14 (0.97 to 1.33)
		Weighted median	442	0.26	1.08 (0.94 to 1.23)	0.28	1.08 (0.94 to 1.23)
		Inverse variance weighted	442	0.05	1.08 (1.00 to 1.17)	0.08	1.08 (0.99 to 1.17)
		Simple mode	442	0.76	1.05 (0.77 to 1.43)	0.83	1.04 (0.74 to 1.44)
		Weighted mode	442	0.39	1.08 (0.91 to 1.28)	0.40	1.08 (0.90 to 1.29)
	Upper limb	MR Egger	441	0.46	1.14 (0.81 to 1.61)	0.80	1.05 (0.74 to 1.48)
		Weighted median	441	0.80	1.04 (0.76 to 1.42)	0.93	0.99 (0.73 to 1.33)
		Inverse variance weighted	441	0.77	0.97 (0.81 to 1.17)	0.43	0.93 (0.77 to 1.12)
		Simple mode	441	0.79	1.11 (0.51 to 2.42)	0.90	1.05 (0.50 to 2.22)
		Weighted mode	441	0.34	1.23 (0.80 to 1.89)	0.60	1.13 (0.71 to 1.79)
	Trunk	MR Egger	441	0.10	1.23 (0.96 to 1.58)	0.23	1.17 (0.91 to 1.50)
		Weighted median	441	0.06	1.24 (0.99 to 1.56)	0.10	1.22 (0.96 to 1.54)
		Inverse variance weighted	441	0.18	1.10 (0.96 to 1.25)	0.28	1.08 (0.94 to 1.23)
		Simple mode	441	0.88	1.04 (0.61 to 1.79)	0.97	1.01 (0.59 to 1.72)
		Weighted mode	441	0.21	1.22 (0.89 to 1.66)	0.28	1.17 (0.88 to 1.56)
	Lower limb	MR Egger	441	0.40	1.24 (0.75 to 2.06)	0.77	1.08 (0.65 to 1.81)
		Weighted median	441	0.73	0.92 (0.59 to 1.45)	0.60	0.89 (0.57 to 1.39)
		Inverse variance weighted	441	0.95	0.99 (0.76 to 1.30)	0.69	0.95 (0.72 to 1.24)
		Simple mode	441	0.61	0.75 (0.24 to 2.28)	0.60	0.75 (0.26 to 2.21)
		Weighted mode	441	0.83	0.94 (0.51 to 1.71)	0.70	0.89 (0.49 to 1.62)
SCC	Head and Neck	MR Egger	441	0.99	1.00 (0.77 to 1.29)	0.74	0.96 (0.74 to 1.24)
		Weighted median	441	0.30	0.89 (0.71 to 1.11)	0.26	0.87 (0.69 to 1.10)
		Inverse variance weighted	441	0.29	0.93 (0.81 to 1.06)	0.22	0.92 (0.80 to 1.05)
		Simple mode	441	0.79	0.93 (0.52 to 1.65)	0.76	0.92 (0.54 to 1.57)
		Weighted mode	441	0.69	0.94 (0.69 to 1.28)	0.68	0.94 (0.68 to 1.29)
	Upper limb	MR Egger	441	0.16	1.41 (0.87 to 2.31)	0.39	1.24 (0.76 to 2.04)
		Weighted median	441	0.16	1.37 (0.88 to 2.13)	0.23	1.31 (0.84 to 2.03)
		Inverse variance weighted	441	0.54	1.08 (0.84 to 1.41)	0.88	1.02 (0.78 to 1.32)
		Simple mode	441	0.98	0.98 (0.34 to 2.86)	0.90	0.93 (0.30 to 2.86)
		Weighted mode	441	0.07	1.82 (0.96 to 3.46)	0.11	1.70 (0.89 to 3.24)
	Trunk	MR Egger	441	0.36	0.77 (0.44 to 1.34)	0.16	0.67 (0.38 to 1.17)

		Weighted median	441	0.91	1.03 (0.64 to 1.66)	0.91	0.97 (0.59 to 1.59)
		Inverse variance weighted	441	0.76	1.05 (0.78 to 1.41)	1.00	1.00 (0.74 to 1.35)
		Simple mode	441	0.50	1.53 (0.44 to 5.29)	0.51	1.53 (0.43 to 5.47)
		Weighted mode	441	0.79	0.91 (0.47 to 1.79)	0.63	0.84 (0.42 to 1.70)
	Lower limb	MR Egger	441	0.20	1.56 (0.79 to 3.07)	0.38	1.35 (0.69 to 2.66)
		Weighted median	441	0.96	1.01 (0.56 to 1.84)	0.88	1.05 (0.58 to 1.90)
		Inverse variance weighted	441	1.00	1.00 (0.70 to 1.43)	0.69	0.93 (0.65 to 1.33)
		Simple mode	441	0.53	0.65 (0.16 to 2.54)	0.47	0.60 (0.15 to 2.40)
		Weighted mode	441	0.98	0.99 (0.45 to 2.19)	0.91	1.05 (0.46 to 2.37)
CM	Head and Neck	MR Egger	443	0.07	1.43 (0.97 to 2.11)	0.24	1.26 (0.86 to 1.85)
		Weighted median	443	1.18E-02	1.52 (1.10 to 2.11)	0.02	1.50 (1.07 to 2.10)
		Inverse variance weighted	443	**9.67E-03**	**1.31 (1.07 to 1.61)**	**0.05**	**1.23 (1.00 to 1.50)**
		Simple mode	443	0.11	1.91 (0.87 to 4.17)	0.11	1.95 (0.87 to 4.39)
		Weighted mode	443	0.25	1.33 (0.81 to 2.18)	0.36	1.25 (0.78 to 2.00)
	Head and Neck (excl. Scalp)	MR Egger	443	0.35	1.37 (0.71 to 2.63)	0.66	1.15 (0.61 to 2.19)
		Weighted median	443	0.20	1.43 (0.83 to 2.45)	0.39	1.29 (0.73 to 2.28)
		Inverse variance weighted	443	**0.11**	**1.32 (0.94 to 1.87)**	**0.28**	**1.21 (0.86 to 1.69)**
		Simple mode	443	0.52	1.58 (0.40 to 6.30)	0.54	1.55 (0.38 to 6.36)
		Weighted mode	443	0.35	1.43 (0.68 to 3.00)	0.27	1.55 (0.71 to 3.38)
	Head and Neck (Scalp only)	MR Egger	443	0.13	1.98 (0.81 to 4.83)	0.52	1.34 (0.54 to 3.30)
		Weighted median	443	0.54	1.28 (0.57 to 2.87)	0.69	1.18 (0.53 to 2.64)
		Inverse variance weighted	443	**0.01**	**1.89 (1.18 to 3.03)**	**0.06**	**1.57 (0.98 to 2.54)**
		Simple mode	443	0.64	1.58 (0.23 to >10)	0.64	1.58 (0.23 to 10.78)
		Weighted mode	443	0.86	1.11 (0.36 to 3.42)	0.86	1.10 (0.38 to 3.22)
	Upper limb	MR Egger	443	0.99	1.00 (0.68 to 1.46)	0.50	0.88 (0.60 to 1.28)
		Weighted median	443	0.85	0.97 (0.70 to 1.35)	0.46	0.88 (0.63 to 1.23)
		Inverse variance weighted	443	0.08	0.84 (0.68 to 1.02)	0.02	0.79 (0.65 to 0.97)
		Simple mode	443	0.35	0.68 (0.31 to 1.51)	0.14	0.55 (0.24 to 1.22)
		Weighted mode	443	0.91	0.98 (0.63 to 1.51)	0.78	0.94 (0.60 to 1.46)
	Trunk	MR Egger	443	0.92	0.99 (0.75 to 1.29)	0.67	0.94 (0.72 to 1.24)
		Weighted median	443	0.93	0.99 (0.78 to 1.25)	0.65	0.95 (0.75 to 1.20)
		Inverse variance weighted	443	0.30	0.93 (0.80 to 1.07)	0.19	0.91 (0.79 to 1.05)
		Simple mode	443	0.61	0.85 (0.46 to 1.57)	0.53	0.82 (0.44 to 1.54)
		Weighted mode	443	0.78	1.05 (0.73 to 1.53)	0.97	0.99 (0.66 to 1.48)
	Lower limb	MR Egger	443	0.57	1.13 (0.74 to 1.74)	0.68	1.10 (0.71 to 1.69)
		Weighted median	443	0.27	0.81 (0.55 to 1.18)	0.29	0.81 (0.56 to 1.19)

		Inverse variance weighted	443	0.22	0.87 (0.69 to 1.09)	0.17	0.85 (0.68 to 1.07)
		Simple mode	443	0.43	0.69 (0.28 to 1.73)	0.44	0.71 (0.29 to 1.72)
		Weighted mode	443	0.22	0.74 (0.46 to 1.20)	0.26	0.76 (0.48 to 1.22)

SNP-outliers here refer to the 4 detected MR-PRESSO SNP outliers (shown in Supplementary Table 11)

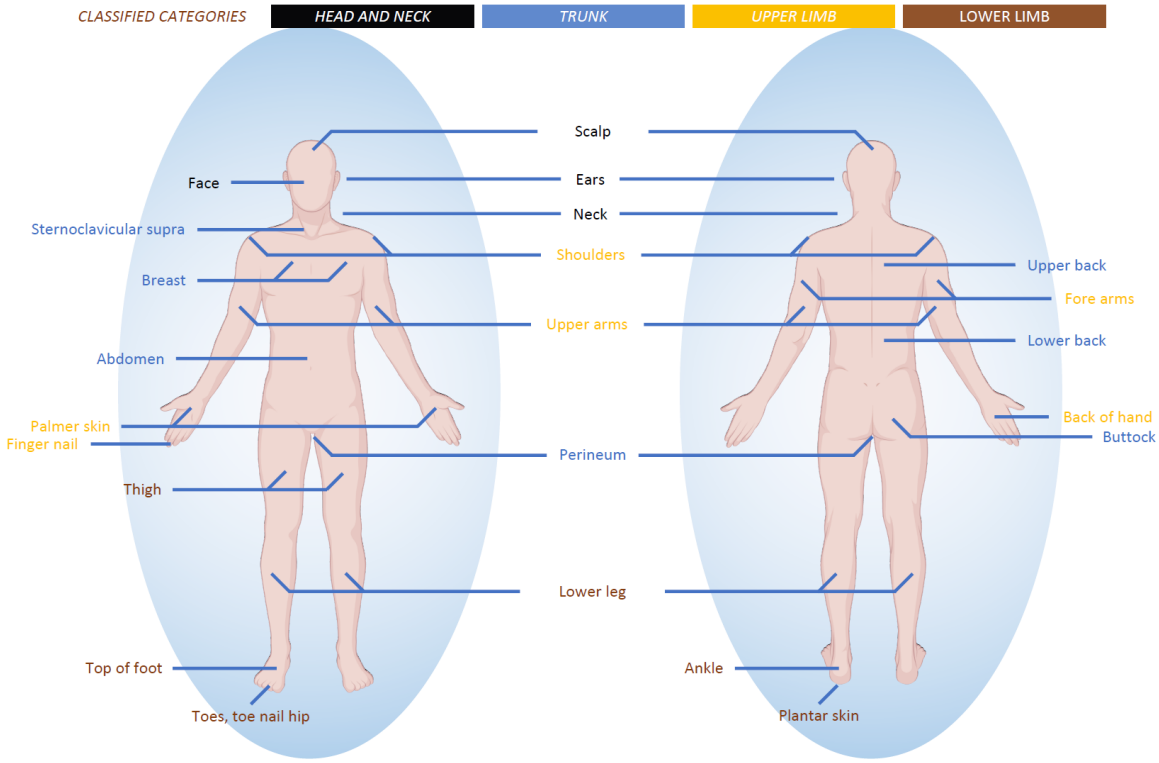
Supplementary Table 20. Estimated MR ORs for per 1 SD change increase in genetically predicted MPB score on cutaneous melanoma risk stratified by (thick vs thin) Breslow thickness in the MIA dataset.

Cancer	MR Method	Original estimate		After removal of SNP-outliers	
		Pvalue	OR	Pvalue	OR
Cutaneous melanoma (all thickness)	MR Egger	0.90	1.02 (0.71 to 1.47)	0.49	0.89 (0.63 to 1.25)
	Weighted median	1.00	1.00 (0.75 to 1.34)	0.92	0.98 (0.74 to 1.32)
	Inverse variance weighted	**0.52**	**1.07 (0.88 to 1.29)**	**0.88**	**0.99 (0.82 to 1.18)**
	Simple mode	0.76	1.11 (0.56 to 2.19)	0.65	1.17 (0.59 to 2.30)
	Weighted mode	0.92	0.98 (0.64 to 1.49)	0.93	0.98 (0.64 to 1.51)
Cutaneous melanoma (thick)	MR Egger	0.85	1.04 (0.69 to 1.58)	0.46	0.86 (0.58 to 1.27)
	Weighted median	0.99	1.00 (0.71 to 1.41)	0.73	0.94 (0.66 to 1.33)
	Inverse variance weighted	**0.33**	**1.12 (0.89 to 1.39)**	**0.90**	**1.01 (0.82 to 1.25)**
	Simple mode	0.67	1.19 (0.54 to 2.59)	0.65	1.21 (0.53 to 2.79)
	Weighted mode	0.88	0.96 (0.59 to 1.58)	0.94	0.98 (0.62 to 1.55)
Cutaneous melanoma (thin)	MR Egger	0.82	1.05 (0.66 to 1.67)	0.90	0.97 (0.62 to 1.53)
	Weighted median	0.58	1.12 (0.76 to 1.65)	0.93	1.02 (0.68 to 1.52)
	Inverse variance weighted	**0.73**	**1.04 (0.82 to 1.33)**	**0.96**	**0.99 (0.78 to 1.26)**
	Simple mode	0.77	0.86 (0.32 to 2.36)	0.81	0.88 (0.31 to 2.49)
	Weighted mode	0.98	1.01 (0.57 to 1.76)	0.83	0.94 (0.53 to 1.66)

Definition of thick (Breslow thickness) melanoma=melanoma with >1mm Breslow thickness, thin (Breslow thickness) ≤1mm.

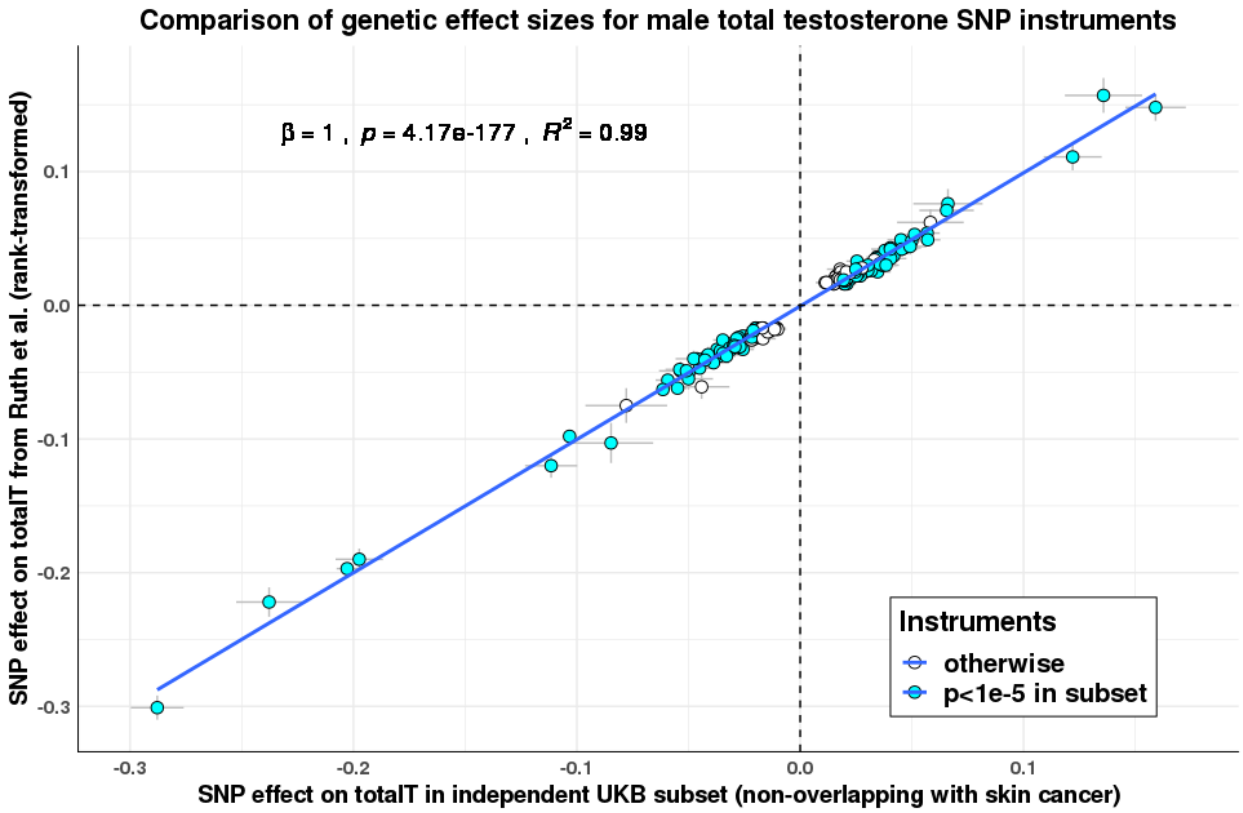
Supplementary Figures

Supplementary Figure 1. The anatomical definition for body site categories used in the present analyses



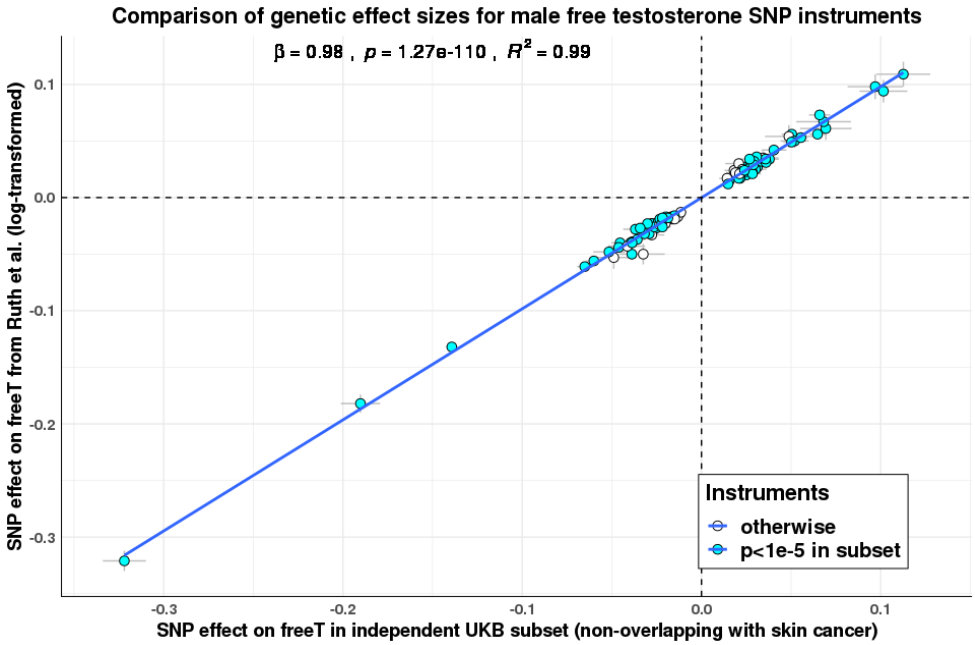
Note that the labeled body site regions are approximated.

Supplementary Figure 2. Comparison of SNP effect sizes between the Ruth et al total testosterone GWAS and those derived from the UK Biobank (non-overlapping) subset.



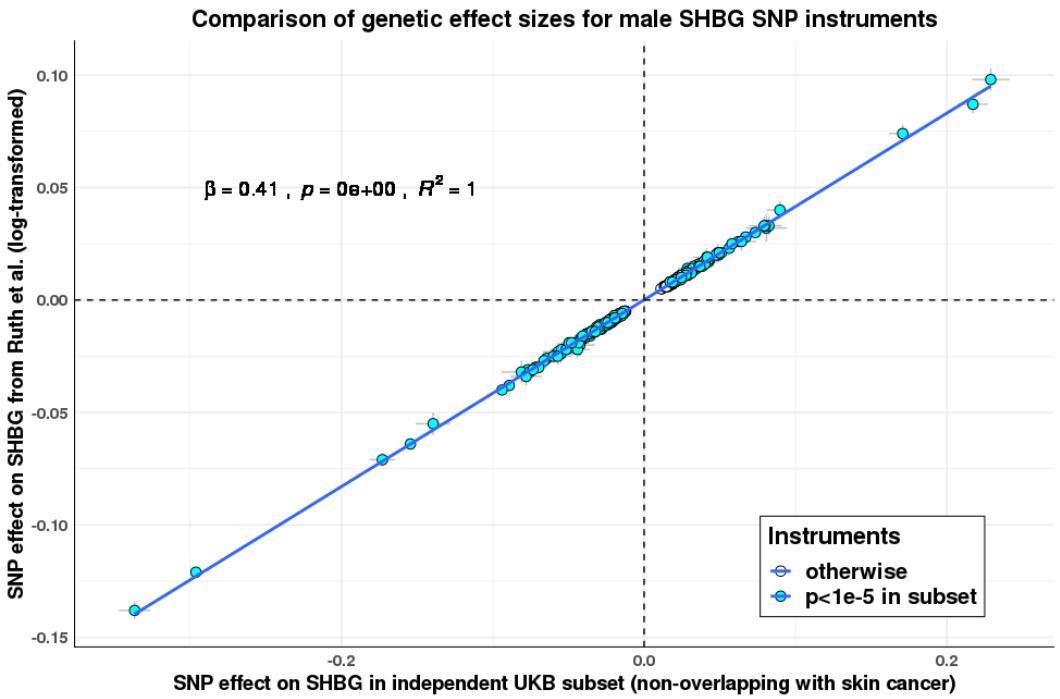
The number of independent SNPs associated with total testosterone evaluated in the regression above is 274. Error bars represent the standard error of the magnitude of association estimated in the respective GWASs. P-values are calculated from a two-tailed Z-test (on the regression estimate).

Supplementary Figure 3. Comparison of SNP effect sizes between the Ruth et al free testosterone GWAS and those derived from the UK Biobank (non-overlapping) subset.



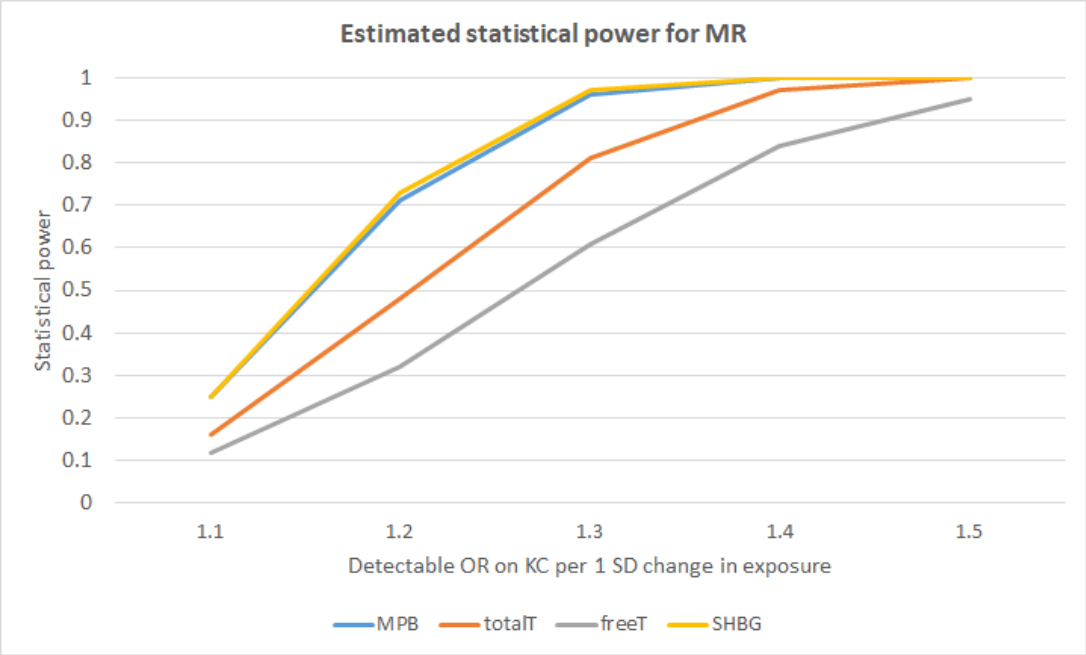
The number of independent SNPs associated with derived free testosterone evaluated in the regression above is 101. Error bars represent the standard errors of the magnitude of association estimated in the respective GWASs. P-values are calculated from a two-tailed Z-test (on the regression estimate).

Supplementary Figure 4. Comparison of SNP effect sizes between the Ruth et al SHBG GWAS and those derived from the UK Biobank (non-overlapping) subset.



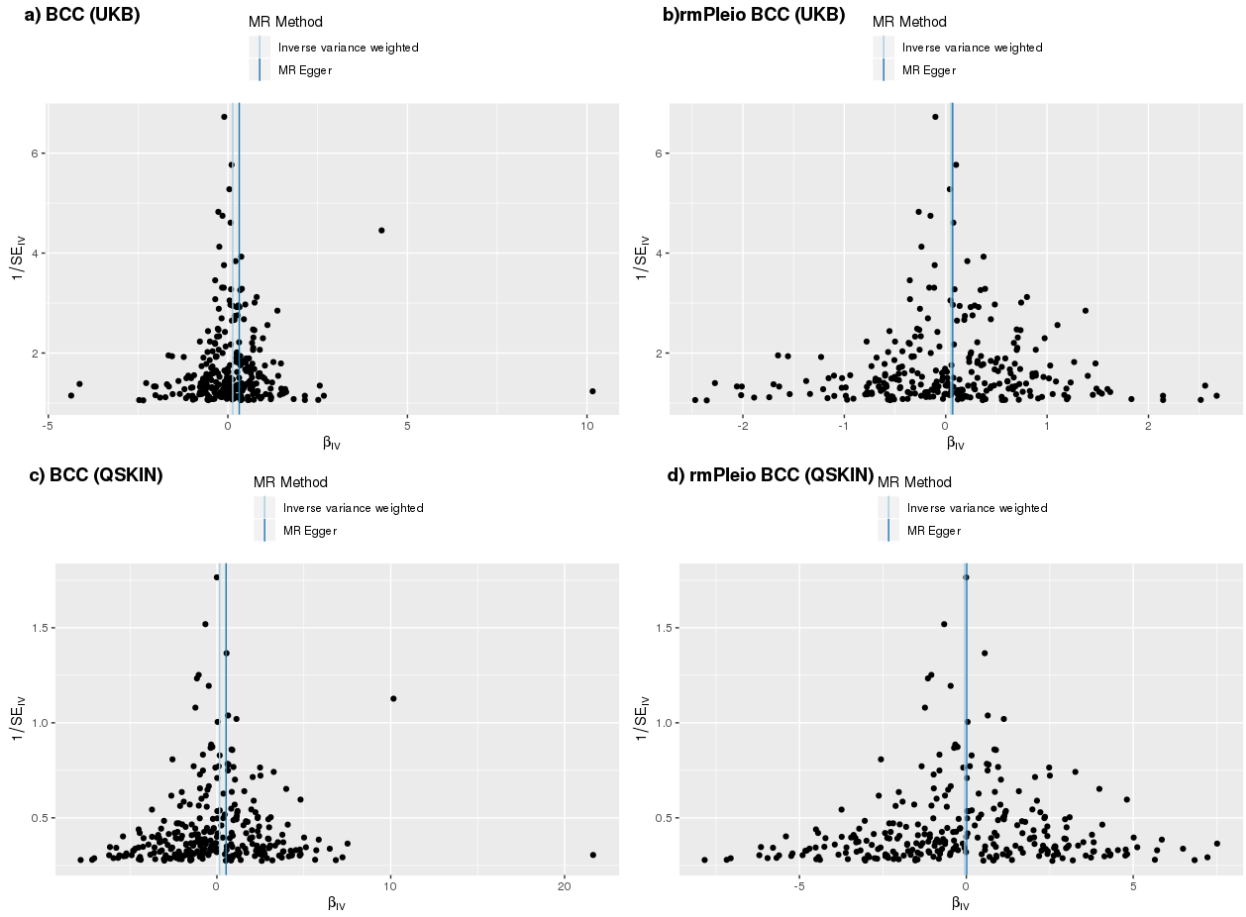
The number of independent SNPs associated with SHBG evaluated in the regression above is 473. Error bars represent the standard errors of the magnitude of association estimated in the respective GWASs. P-values are calculated from a two-tailed Z-test (on the regression estimate).

Supplementary Figure 5. Estimated statistical power for MR analysis to detect plausible OR effect sizes in our present analysis.



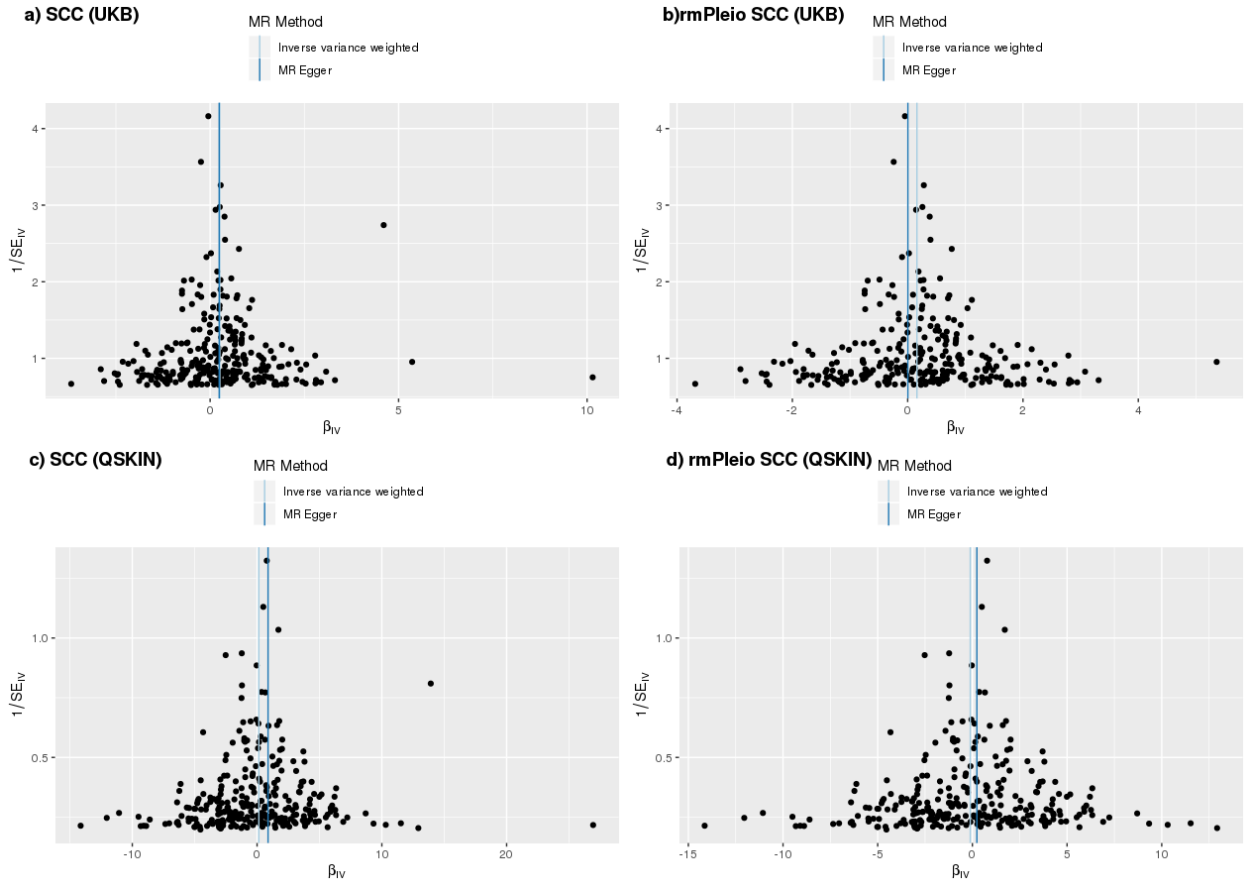
Power estimates were derived using the mRnd online MR power calculator based on estimated phenotypic variance explained by SNPs for each trait and sample size from the skin cancer GWASs.

Supplementary Figure 6. MR funnel plots for the univariable MR association between MPB and BCC in the UK Biobank and QSKIN datasets



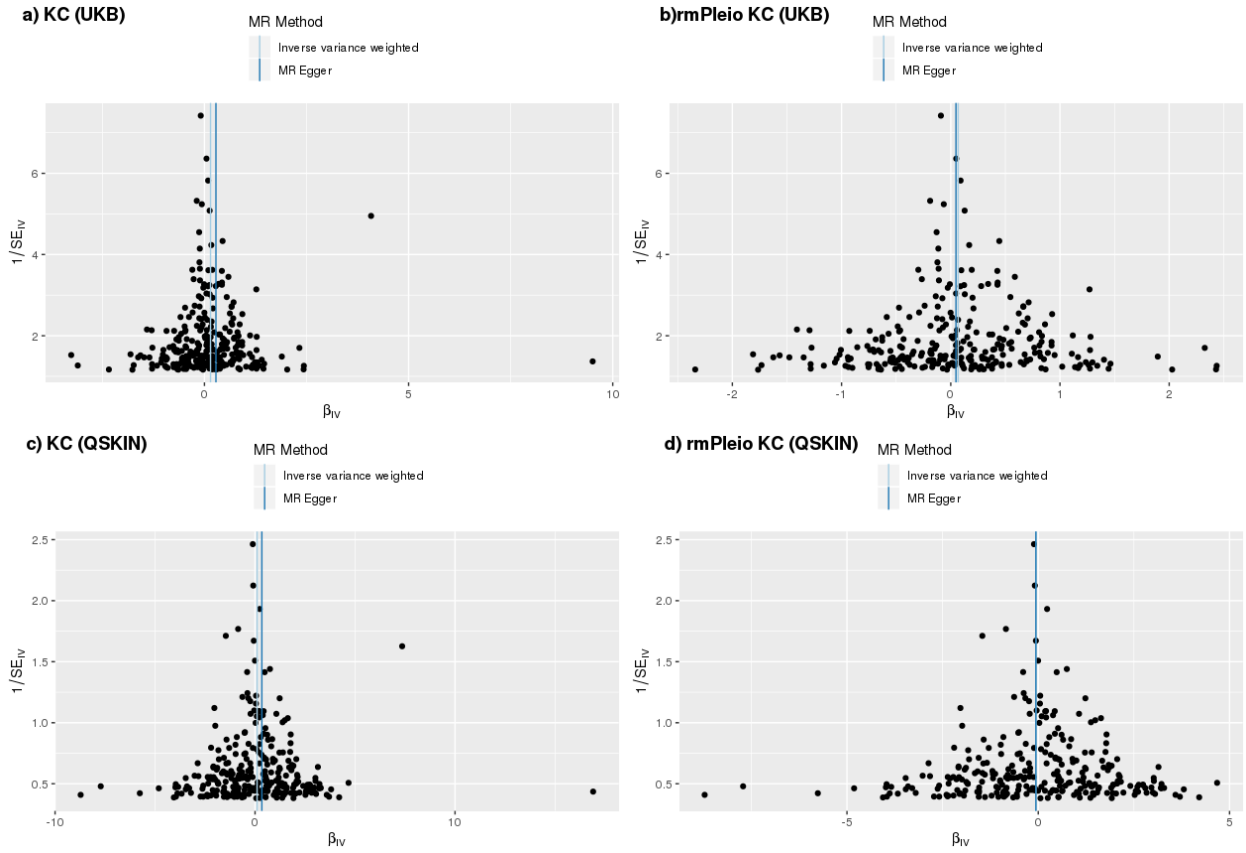
The label **rmPleio** refers to the trait-outcome MR association between MPB and the relevant skin cancer outcome after removing the pleiotropic SNP outliers from the analysis.

Supplementary Figure 7. MR funnel plots for the univariable MR association between MPB and SCC in the UK Biobank and QSKIN datasets



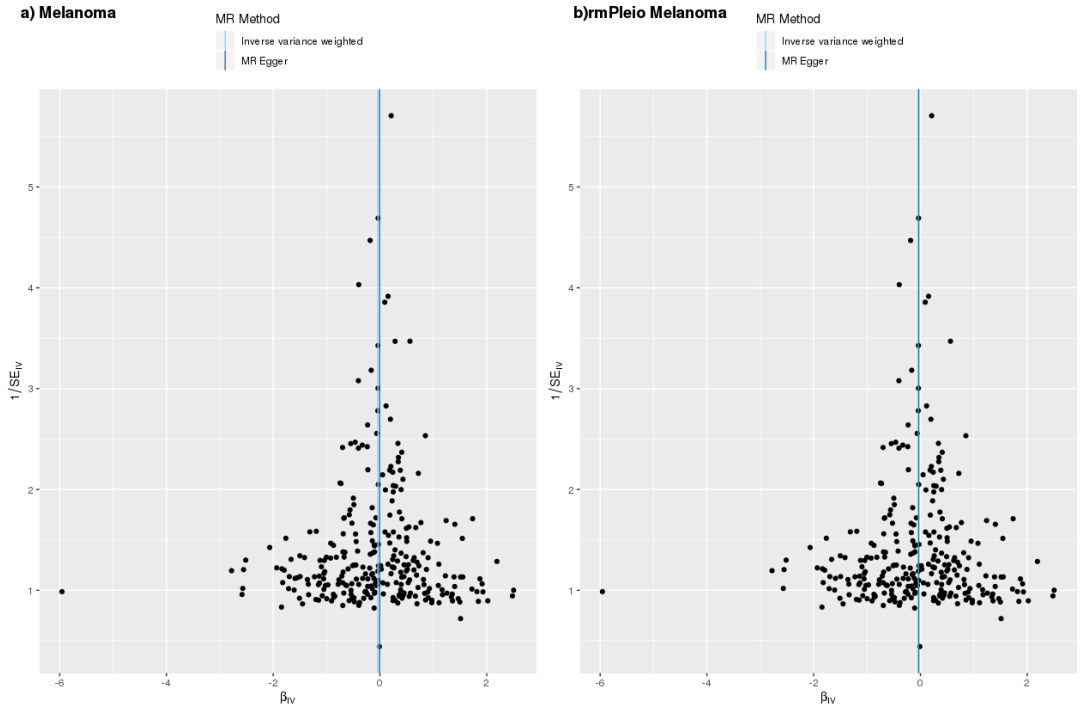
The label **rmPleio** refers to the trait-outcome MR association between MPB and the relevant skin cancer outcome after removing the pleiotropic SNP outliers from the analysis.

Supplementary Figure 8. MR funnel plots for the univariable MR association between MPB and all KC in the UK Biobank and QSKIN datasets



The label **rmPleio** refers to the trait-outcome MR association between MPB and the relevant skin cancer outcome after removing the pleiotropic SNP outliers from the analysis.

Supplementary Figure 9. MR funnel plots for the univariable MR association between MPB and melanoma

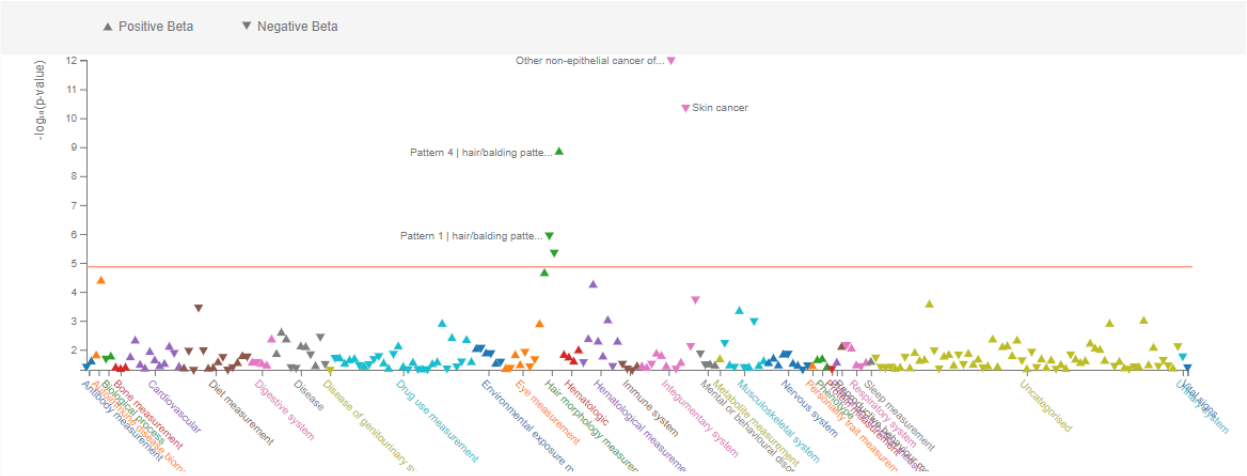


The label **rmPleio** refers to the trait-outcome MR association between MPB and the relevant skin cancer outcome after removing the pleiotropic SNP outliers from the analysis.

Supplementary Figure 10. PheWAS plot for rs2669871

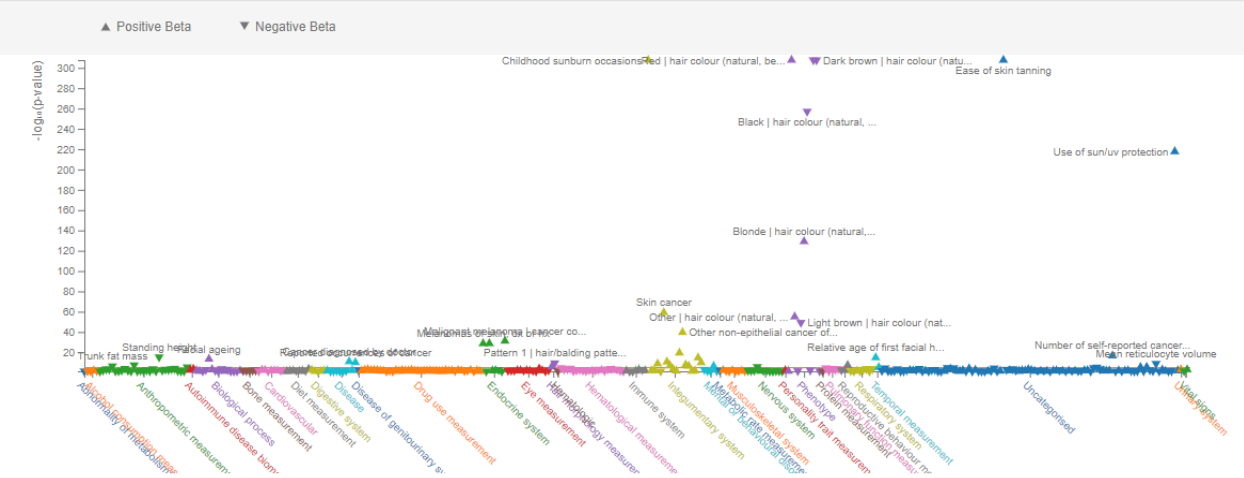
The y-axis of the plot represents the -log10 p-value of the association between the SNP and the relevant trait (in the x-axis) derived from GWAS data. The red bar refer to the (nominal) strength of association approximately at p-value=5x10e-5. The PheWAS lookup was performed by manually querying the SNP against the Open-target online platform (https://genetics.opentargets.org/). P-values are derived from a two-tailed Z-test on the association between the SNP and the relevant trait, unadjusted for multiple comparison.

Supplementary Figure 11. PheWAS plot for rs3847069



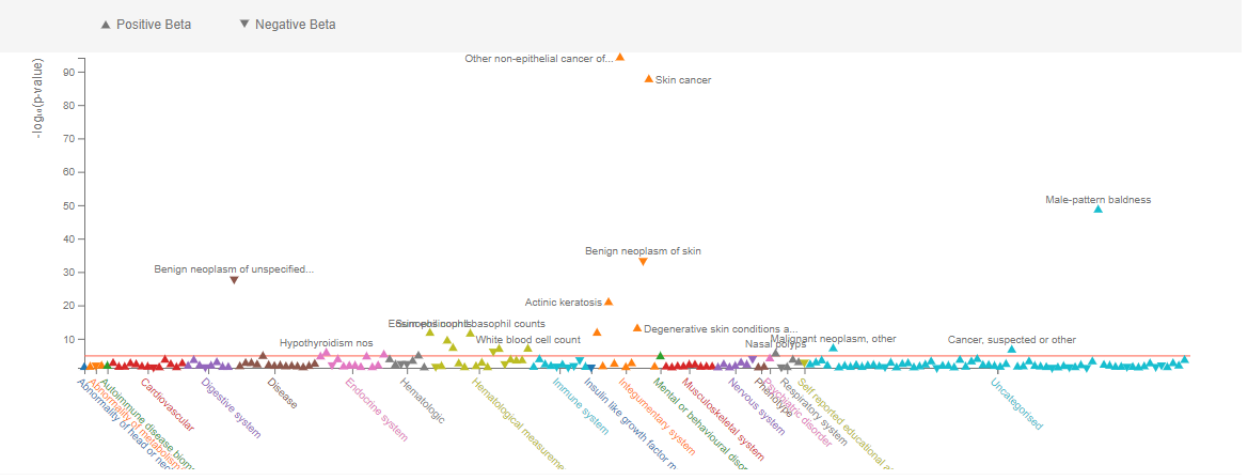
The y-axis of the plot represents the -log10 p-value of the association between the SNP and the relevant trait (in the x-axis) derived from GWAS data. The red bar refer to the (nominal) strength of association approximately at p-value=5x10e-5. The PheWAS lookup was performed by manually querying the SNP against the Open-target online platform (https://genetics.opentargets.org/). P-values are derived from a two-tailed Z-test on the association between the SNP and the relevant trait, unadjusted for multiple comparison.

Supplementary Figure 12. PheWAS plot for rs1805007



The y-axis of the plot represents the -log10 p-value of the association between the SNP and the relevant trait (in the x-axis) derived from GWAS data. The red bar refer to the (nominal) strength of association approximately at p-value=5x10e-5. The PheWAS lookup was performed by manually querying the SNP against the Open-target online platform (https://genetics.opentargets.org/).P-values are derived from a two-tailed Z-test on the association between the SNP and the relevant trait, unadjusted for multiple comparison.

Supplementary Figure 13. PheWAS plot for rs12203592



The y-axis of the plot represents the -log10 p-value of the association between the SNP and the relevant trait (in the x-axis) derived from GWAS data. The red bar refer to the (nominal) strength of association approximately at p-value=5x10e-5. The PheWAS lookup was performed by manually querying the SNP against the Open-target online platform (https://genetics.opentargets.org/). P-values are derived from a two-tailed Z-test on the association between the SNP and the relevant trait, unadjusted for multiple comparison.

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