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SUPPLEMENTARY ONLINE-ONLY FILE

SUPPLEMENTARY METHODS

Data collection

Data for pigimentary variables and naevus counts were collected from participants through self-administered questionnaires including skin colour, eye colour, hair colour, freckling, usual tanning and sunburn response to prolonged or repeated exposure of skin to sunlight in summer, and number of naevi (naevus density) covering their body (described pictorially as none, few, some, many).¹ A phenotypic pigmentation score, created using factor analysis and described previously,¹ summarised the contribution of five correlated, well-established phenotypic variables: skin colour, eye colour, hair colour, childhood freckling, and skin phototype (tanning and burning skin reaction to the sun) and was categorised as tertiles.

Detailed past UV exposure information was collected by telephone interview using a structured questionnaire and a pre-completed lifetime residence calendar. It included frequency of sunburn and sunbed use, and hours per day outdoors between 9am and 5pm separately for weekdays, weekends, and holidays in warmer months and in cooler months.^{2,3} The raw data from the two studies were combined into one dataset and harmonised data variables were created for analysis. Estimates of lifetime sun-related exposure were derived as a weighted sum of hours assessed at ages 10, 15, 20, 30, 40, 50, 60 and 70 years. Total outdoor hours at each age was calculated by summing weekday, weekend and holiday hours, with warmer and cooler months each contributing 6 months, and annual weeks of holidays (across warmer and cooler months) assumed to be 12 if at school or university, four if working and none if not working. A separate summary variable was created for summer holidays, based on separate questions on the number of weeks and hours per day at different summer holiday destinations. If a sun exposure value for a particular year was missing, it was imputed from an adjacent year using the mean ratio of the values between adjacent years calculated from non-missing values. Blood samples were collected for DNA extraction.⁴

Polygenic risk scores

Polygenic risk scores (PRS) represent a weighted estimate of the combined effects of multiple common genomic variants. The PRS was created using previously published methods⁵ and summarised the combined effects of 21 genes/loci (including 45 independent single nucleotide polymorphisms, SNPs) that had a confirmed association with melanoma risk by genome-wide association studies⁶ or whole-genome sequencing.⁷ We also created pathway-specific PRS based on associations of each SNP with naevi, pigmentation, or telomere/other pathways, as previously described.⁴ The genotyping, imputation and quality control methods were performed concurrently for both studies and have been described elsewhere.⁴

SUPPLEMENTARY REFERENCES

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Supplementary Table 1: Characteristics of melanoma cases and controls in the Australian Melanoma Family Study

	Control N (%)	Case N (%)				Total
		Head and Neck	Trunk	Upper-Limb	Lower-Limb	
Total	470 (100.0)	82 (100.0)	211 (100.0)	128 (100.0)	183 (100.0)	1074 (100.0)
Sex						
Male	199 (42.3)	40 (48.8)	97 (46.0)	37 (28.9)	59 (32.2)	432 (40.2)
Female	271 (57.7)	42 (51.2)	114 (54.0)	91 (72.1)	124 (67.8)	642 (59.8)
Age at diagnosis/interview (years)						
18-29	94 (20.0)	35 (42.7)	72 (34.1)	33 (25.8)	52 (28.4)	286 (26.6)
30-39	297 (63.2)	47 (57.3)	139 (65.9)	95 (74.2)	131 (71.6)	709 (66.0)
40-49	79 (16.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	79 (7.4)
Ethnic background						
English	269 (57.2)	59 (72.0)	132 (62.6)	86 (67.2)	124 (67.8)	670 (62.4)
Scottish, Irish, Welsh	18 (3.8)	5 (6.1)	12 (5.7)	6 (4.7)	11 (6.0)	52 (4.8)
Other Northern European	27 (5.7)	2 (2.4)	10 (4.7)	3(2.3)	6 (3.3)	48 (4.5)
Southern European	7 (1.5)	0 (0.0)	5 (2.4)	0 (0.0)	0 (0.0)	12 (1.1)
Eastern European	132 (28.1)	9 (13.4)	47 (22.3)	28 (21.9)	36 (19.7)	254 (23.7)
Mixed/Other European	17 (3.6)	5 (6.1)	5 (2.4)	5 (3.9)	6 (3.3)	38 (3.5)
Family history of melanoma in a first degree relative						
No	424 (90.2)	74 (90.2)	171 (81.0)	102 (79.7)	150 (82.0)	921 (85.8)
Yes	46 (9.8)	8 (9.8)	40 (19.0)	26 (20.3)	33 (18.03)	153 (14.3)

Supplementary Table 2: Characteristics of melanoma cases and controls in the Leeds Melanoma Case-Control Study

	Control	Case N (%)				Total
	N (%)	Head and Neck	Trunk	Upper-Limb	Lower-Limb	
Total	505 (100.0)	207 (100.0)	699 (100.0)	397 (100.0)	710 (100.0)	2518 (100.0)
Sex						
Male	207 (41.0)	118 (57.0)	444 (63.5)	150 (37.8)	149 (21.0)	1068 (42.4)
Female	298 (59.0)	89 (43.0)	255 (36.5)	247 (62.2)	561 (79.0)	1450 (57.6)
Age at diagnosis/interview (years)						
18-29	7 (1.4)	12 (5.8)	32 (4.6)	13(3.2)	37 (5.2)	101 (4.0)
30-39	53 (10.5)	16 (7.7)	78 (11.2)	42 (10.6)	89 (12.5)	278 (11.0)
40-49	84 (16.6)	19 (9.2)	124 (17.7)	88 (22.2)	139 (19.6)	454 (18.0)
50-59	131 (25.9)	42 (20.3)	184 (26.3)	87 (21.9)	172 (24.2)	616 (24.5)
>60	230 (45.6)	118 (57.0)	281 (40.2)	167 (42.1)	273 (38.5)	1069 (42.5)
Ethnic background						
English	471 (93.3)	200 (96.6)	643 (92.3)	372 (94.2)	660 (93.0)	2346 (93.3)
Scottish, Irish, Welsh	21 (4.2)	7 (3.4)	38 (5.5)	13 (3.3)	40 (5.6)	119 (4.7)
Other Northern European	2 (0.4)	0 (0.0)	5 (0.7)	3 (0.8)	3 (0.4)	13 (0.5)
Southern European	3 (0.6)	0 (0.0)	1 (0.1)	1 (0.3)	1 (0.1)	6 (0.2)
Eastern European	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.3)	3 (0.1)
Mixed/Other European	8 (1.6)	0 (0.0)	9 (1.3)	6 (1.5)	4 (0.6)	27 (1.1)
Family history of melanoma in a first degree relative						
No	495 (98.0)	200 (96.6)	644 (92.3)	370 (93.2)	671 (94.5)	2380 (94. 6)
Yes	10 (2.0)	7 (3.4)	54 (7.7)	27 (6.8)	39 (5.5)	137 (5.4)

Supplementary Table 3. Associations between melanoma and naevus and pigmentation phenotypes, stratified by anatomical site, in the Australian Melanoma Family Study

Phenotype variables	Controls		Head and Neck		Trunk			Upper Limb			Lower Limb			P-het
	N (%)	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	
Naevi														0.2
none	33 (7.13)	6 (7.4)	1.0		6 (2.9)	1.0		4 (3.2)	1.0		5 (2.8)	1.00		
few	228 (49.2)	28 (34.6)	0.6 (0.2-1.7)	0.04	50 (23.9)	1.2 (0.5-3.0)	<0.001	36 (28.6)	1.2 (0.4-3.6)	<0.001	52 (29.4)	1.4 (0.5-3.9)	<0.001	
some	153 (33.1)	34 (42.0)	1.3 (0.5-3.3)		89 (42.6)	3.2 (1.2-8.1)		56 (44.4)	2.3 (0.9-8.3)		79 (44.6)	3.3 (1.2-9.0)		
many	49 (10.6)	13 (16.1)	1.4 (0.5-4.1)		64 (30.6)	7.5 (2.8-20.0)		30 (23.8)	4.6 (1.5-14.5)		41 (23.2)	5.4 (1.9-15.3)		
Hair colour														0.1
dark brown/black	176 (37.8)	29 (35.8)	1.0		48 (22.9)	1.00		32 (25.4)	1.0		41 (22.9)	1.0		
light brown	203 (43.6)	29 (35.8)	0.8 (0.5-1.5)	0.1	93 (44.3)	1.7 (1.1-2.5)	<0.001	51 (40.5)	1.2 (0.74-2)	0.001	66 (36.9)	1.3 (0.8-2.1)	<0.001	
fair or blonde	64 (13.7)	14 (17.3)	1.4 (0.7-3.0)		52 (24.8)	3.0 (1.8-5.0)		30 (23.8)	2.4 (1.3-4.3)		41 (22.9)	2.7 (1.6-4.7)		
red	23 (4.9)	9 (11.1)	2.3 (0.9-5.8)		17 (8.1)	2.5 (1.2-5.2)		13 (10.3)	2.7 (1.2-6.0)		31 (17.3)	5.6 (2.9-10.9)		
Eye colour														1.0
brown or black	94 (20.3)	14 (17.3)	1.0		39 (18.7)	1.00		22 (17.5)	1.0		29 (16.5)	1.0		
green or hazel	162 (35.1)	34 (42.0)	1.5 (0.8-3.1)	0.7	73 (34.9)	1.2 (0.7-1.9)	0.3	46 (36.5)	1.2 (0.7-2.1)	0.5	65 (36.9)	1.4 (0.8-2.3)	0.2	
blue or grey	206 (44.6)	33 (40.7)	1.2 (0.6-2.5)		97 (46.4)	1.3 (0.8-2.0)		58 (46.0)	1.3 (0.7-2.2)		82 (46.6)	1.4 (0.9-2.4)		
Skin colour														0.4
olive or brown	77 (16.6)	9 (11.1)	1.0		22 (10.6)	1.0		14 (11.2)	1.0		10 (5.7)	1.00		
fair	323 (69.5)	58 (71.6)	1.6 (0.8-3.5)	0.3	151 (72.6)	1.6 (1.0-2.8)	0.2	86 (68.8)	1.4 (0.8-2.6)	0.1	123 (69.9)	3.0 (1.5-6.0)	<0.001	
very fair	65 (12.0)	14 (17.3)	1.7 (0.7-4.2)		35 (16.8)	1.6 (0.9-3.1)		25 (20.0)	1.8 (0.8-3.7)		43 (24.43)	4.4 (2.04-9.6)		
Freckles in childhood														0.6
none	107 (23.1)	16 (19.8)	1.0		43 (20.5)	1.0		20 (15.9)	1.0		32 (18.3)	1.0		
very few	158 (34.1)	25 (30.9)	1.0 (0.5-2.0)	0.5	73 (34.8)	1.1 (0.7-1.7)	0.7	39 (31.0)	1.2 (0.7-2.2)	0.3	44 (25.1)	0.9 (0.5-1.6)	0.03	
few/some	151 (32.5)	32 (39.5)	1.4 (0.7-2.7)		71 (33.8)	1.1 (0.7-1.7)		56 (44.4)	1.7 (0.9-3.0)		73 (41.7)	1.5 (0.9-2.4)		
many	48 (10.3)	8 (9.9)	1.1 (0.4-2.8)		23 (11.0)	1.1 (0.6-2.1)		11 (8.7)	1.0 (0.4-2.2)		26 (14.9)	1.6 (1.0-3.1)		
General skin reaction to sun (skin phototype)														0.9
sometimes/never burns	269 (58.2)	41 (50.6)	1.0		95 (45.7)	1.00		55 (44.4)	1.0		85 (47.8)	1.0		
usually/always burns	193 (41.8)	40 (49.4)	1.4 (0.8-2.2)	0.2	113 (54.3)	1.7 (1.2-2.3)	0.004	69 (55.7)	1.6 (1.1-2.4)	0.02	93 (52.3)	1.5 (1.0-2.1)	0.04	
Pigmentation score														0.02
Tertile 1	190 (37.9)	45 (22.6)	1.0		196 (29.8)	1.0		79 (21.2)	1.0		144 (21.4)	1.0		
Tertile 2	170 (33.9)	54 (27.1)	1.8 (1.0-3.1)	<0.001	214 (32.6)	1.5 (1.0-2.1)	<0.001	117 (31.4)	1.2 (0.8-1.9)	<0.001	233 (34.7)	1.5 (1.1-2.0)	<0.001	
Tertile 3	141 (28.1)	100 (50.3)	4.3 (2.6-7.2)		247 (37.6)	2.0 (1.4-2.9)		176 (47.3)	2.6 (1.7-4.0)		295 (43.9)	2.6 (1.8-3.7)		

Models were adjusted for age (continuous), sex, city of recruitment in Australia. The denominator may differ slightly due to missing values for some variables.

Supplementary Table 4. Associations between melanoma and naevus and pigmentation phenotypes, stratified by anatomical site, in the Leeds Melanoma Case-Control Study

Phenotype variables	Controls		Head and Neck		Trunk			Upper Limb			Lower Limb			P-het
	N (%)	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	
Naevi														0.03
none	99 (19.6)	32 (15.8)	1.0		54 (8.0)	1.0		27 (7.1)	1.0		62 (9.1)	1.0		
few	254 (50.3)	90 (44.3)	1.2 (0.7-1.9)	0.01	241 (35.9)	1.8 (1.2-2.6)	<0.001	164 (42.8)	2.4 (1.5-3.8)	<0.001	267 (39.0)	1.7 (1.2-2.4)	<0.001	
some	118 (23.4)	60 (29.6)	1.8 (1.1-3.0)		252 (37.5)	3.7 (2.4-5.6)		137 (35.8)	4.2 (2.6-7.0)		261 (38.1)	3.4 (2.3-5.1)		
many	34 (6.7)	21 (10.3)	2.1 (1.0-4.1)		125 (18.6)	6.0 (3.5-10.1)		55 (14.4)	6.0 (3.2-11.0)		95 (13.9)	4.6 (2.3-7.7)		
Hair colour														0.7
dark brown/black	288 (57.1)	85 (41.1)	1.0		294 (42.1)	1.0		151 (38.1)	1.0		302 (42.6)	1.0		
light brown	119 (23.6)	51 (24.6)	1.5 (1.0-2.3)	<0.001	189 (27.1)	1.7 (1.3-2.3)	<0.001	113 (28.5)	1.8 (1.3-2.5)	<0.001	180 (25.4)	1.4 (1.0-1.9)	<0.001	
fair or blonde	68 (13.5)	43 (20.8)	2.2 (1.4-3.5)		142 (20.3)	2.3 (1.6-3.2)		83 (21.0)	2.4 (1.6-3.4)		131 (18.5)	1.8 (1.3-2.5)		
red	29 (5.8)	28 (13.5)	3.5 (2.0-6.3)		73 (10.5)	2.7 (1.7-4.4)		49 (12.4)	3.4 (2.0-5.6)		96 (13.5)	2.8 (1.8-4.5)		
Eye colour														0.3
brown or black	94 (18.7)	37 (17.2)	1.0		108 (15.5)	1.0		53 (13.5)	1.0		117 (16.6)	1.00		
green or hazel	182 (36.1)	48 (23.2)	0.7 (0.4-1.2)	0.03	215 (30.9)	1.1 (0.8-1.6)	0.004	125 (31.7)	1.2 (0.8-1.8)	0.002	221 (31.3)	0.9 (0.7-1.3)	0.02	
blue or grey	228 (45.2)	122 (58.9)	1.4 (0.8-2.1)		372 (53.5)	1.6 (1.11-2.2)		216 (54.8)	1.7 (1.2-2.5)		369 (52.2)	1.3 (1.0-1.8)		
Skin colour														0.01
olive or brown	60 (11.9)	14 (6.8)	1.0		56 (8.0)	1.0		26 (6.6)	1.0		50 (7.0)	1.00		
fair	365 (72.4)	126 (60.9)	1.5 (0.8-2.8)	<0.001	494 (70.8)	1.5 (1.0-2.3)	0.01	260 (65.8)	1.7 (1.0-2.7)	<0.001	471 (66.3)	1.6 (1.0-2.3)	<0.001	
very fair	79 (15.7)	67 (32.4)	3.6 (1.8-7.0)		148 (21.2)	1.9 (1.2-3.0)		109 (27.6)	3.1 (1.8-5.4)		189 (26.6)	2.8 (1.7-4.5)		
Freckles in childhood														0.3
none	187 (37.1)	55 (27.4)	1.0		224 (33.8)	1.0		94 (24.9)	1.0		152 (22.4)	1.0		
very few	131 (26.0)	64 (31.8)	1.8 (1.1-2.7)	0.01	181 (27.3)	1.2 (0.9-1.6)	0.1	108 (28.6)	1.6 (1.1-2.2)	<0.001	206 (30.3)	1.7 (1.3-2.4)	<0.001	
few/some	160 (31.8)	66 (32.8)	1.6 (1.1-2.5)		212 (32.0)	1.2 (0.9-1.6)		143 (37.8)	1.7 (1.2-2.4)		265 (39.0)	1.7 (1.3-2.3)		
many	26 (5.2)	16 (8.0)	2.4 (1.2-4.8)		46 (6.9)	1.6 (0.9-2.8)		33 (8.7)	2.5 (1.4-4.3)		57 (8.4)	2.1 (1.3-3.6)		
General skin reaction to sun (skin phototype)														0.02
sometimes/never burns	375 (74.7)	127 (62.0)	1.0		474 (67.9)	1.0		228 (57.7)	1.00		446 (63.3)	1.0		
usually/always burns	127 (25.3)	78 (38.1)	2.0 (1.4-2.8)	<0.001	224 (32.1)	1.4 (1.1-1.9)	0.01	167 (42.3)	2.1 (1.61-2.84)	<0.001	259 (36.7)	1.6 (1.3-2.1)	<0.001	
Pigmentation score														0.9
Tertile 1	133 (29.2)	17 (21.0)	1.0		40 (19.5)	1.0		27 (21.8)	1.0		29 (16.9)	1.0		
Tertile 2	140 (30.7)	27 (33.3)	1.4 (0.7-2.8)	0.2	65 (31.7)	1.5 (0.9-2.4)	0.02	33 (26.6)	1.1 (0.6-1.9)	0.1	55 (32.0)	1.7 (1.0-2.8)	0.004	
Tertile 3	183 (40.1)	37 (45.7)	1.5 (0.8-2.9)		100 (48.8)	1.8 (1.1-2.8)		64 (51.6)	1.5 (0.9-2.5)		88 (51.2)	2.0 (1.3-3.3)		

Models were adjusted for age (continuous) and sex. The denominator may differ slightly due to missing values for some variables, or due to a shorter questionnaire being used in the later years of the Leeds study.

Supplementary Table 5: Multivariable-adjusted associations between melanoma and naevus and pigmentation phenotypes, stratified by anatomical site, in the pooled Australian Melanoma Family Study and Leeds Melanoma Case-Control study.

Phenotype variables	Controls		Head and Neck		Trunk			Upper Limb			Lower Limb			P-het
	N (%)	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	N (%)	OR (95% CI)	P-trend	
Naevi														0.003
none	132 (13.6)	38 (3.9)	1	0.08	60 (6.2)	1	<0.001	31 (3.2)	1	<0.001	67 (6.9)		<0.001	
few	482 (49.8)	118 (12.2)	1.0 (0.6-1.6)		291 (30.1)	1.7 (1-2.7)		200 (20.7)	1.8 (1-3.3)		319 (33)	1.6 (1-2.5)		
some	271 (28)	94 (9.7)	1.4 (0.8-2.4)		341 (35.2)	3.7 (2.2-6.2)		193 (19.9)	3.9 (2.1-7.2)		340 (35.1)	3.1 (2-4.9)		
many	83 (8.6)	34 (3.5)	1.4 (0.7-2.7)		189 (19.5)	7.1 (4.1-12.4)		85 (8.8)	5.8 (3-11.5)		136 (14)	4.4 (2.6-7.5)		
Hair colour														0.5
dark brown/black	464 (47.8)	114 (39.6)	1	<0.001	342 (37.7)	1	<0.001	183 (35.1)	1	<0.001	343 (38.6)	1	<0.001	
light brown	322 (33.2)	80 (27.8)	1.2 (0.8-1.8)		282 (31.1)	1.5 (1.1-2)		164 (31.4)	1.5 (1.1-2)		246 (27.7)	1.2 (0.9-1.5)		
fair or blonde	132 (13.6)	57 (19.8)	2.4 (1.5-3.8)		194 (21.4)	2.8 (2-4)		113 (21.6)	2.6 (1.8-3.9)		172 (19.4)	2.3 (1.7-3.2)		
red	52 (5.4)	37 (12.8)	3.1 (1.8-5.4)		90 (9.9)	2.3 (1.5-3.7)		62 (11.9)	2.8 (1.7-4.6)		127 (14.3)	3.7 (2.4-5.6)		
Eye colour														0.9
brown or black	188 (19.5)	51 (17.7)	1	0.06	147 (16.3)	1	0.02	75 (14.4)	1	0.009	146 (16.5)	1	0.01	
green or hazel	344 (35.6)	82 (28.5)	1.0 (0.6-1.5)		288 (31.9)	1.1 (0.8-1.5)		171 (32.9)	1.3 (0.9-1.9)		286 (32.4)	1.1 (0.8-1.5)		
blue or grey	434 (44.9)	155 (53.8)	1.4 (0.9-2.2)		469 (51.9)	1.4 (1-1.9)		274 (52.7)	1.6 (1.1-2.4)		451 (51.1)	1.4 (1.1-2)		
Skin colour														0.4
olive or brown	137 (14.1)	23 (8)		<0.001	78 (8.6)	1	<0.001	40 (7.7)	1	<0.001	60 (6.8)	1	<0.001	
fair	688 (71)	184 (63.9)	1.5 (0.9-2.6)		645 (71.2)	1.5 (1-2.2)		346 (66.5)	1.3 (0.8-2.1)		594 (67)	1.5 (1.0-2.2)		
very fair	144 (14.9)	81 (28.1)	3.2 (1.8-5.9)		183 (20.2)	2.1 (1.3-3.2)		134 (25.8)	2.6 (1.6-4.3)		232 (26.2)	3.0 (1.9-4.6)		
Freckles in childhood														0.4
none	294 (30.4)	71 (25.2)	1	0.03	267 (30.6)	1	0.3	114 (22.6)	1	0.2	184 (21.5)	1	<0.001	
very few	289 (29.9)	89 (31.6)	1.4 (0.9-2.2)		254 (29.1)	1.1 (0.8-1.5)		147 (29.2)	1.1 (0.8-1.6)		250 (29.2)	1.2 (0.9-1.7)		
few/some	311 (32.1)	98 (34.8)	1.5 (1-2.3)		283 (32.4)	1.1 (0.8-1.5)		199 (39.5)	1.3 (0.9-1.8)		338 (39.5)	1.6 (1.2-2.2)		
many	74 (7.6)	24 (8.5)	1.9 (1-3.6)		69 (7.9)	1.3 (0.8-2.1)		44 (8.7)	1.3 (0.8-2.2)		83 (9.7)	2.1 (1.3-3.2)		
Skin phototype														0.3
sometimes/never burns	644 (66.8)	168 (58.7)	1	<0.001	569 (62.8)	1	<0.001	283 (54.5)	1	<0.001	531 (60.1)	1	0.004	
usually/always burns	320 (33.2)	118 (41.3)	1.9 (1.4-2.7)		337 (37.2)	1.5 (1.2-1.9)		236 (45.5)	1.6 (1.2-2.2)		352 (39.9)	1.4 (1.1-1.8)		
Pigmentation score														0.3
Tertile 1	323 (33.8)	62 (22.1)	1	<0.001	236 (27.4)	1	<0.001	106 (21.4)	1	<0.001	173 (20.5)	1	<0.001	
Tertile 2	310 (32.4)	81 (28.9)	1.6 (1.0-2.5)		279 (32.4)	1.3 (1-1.8)		150 (30.2)	1.1 (0.7-1.6)		288 (34.1)	1.4 (1.1-2)		
Tertile 3	324 (33.9)	137 (48.9)	2.9 (1.9-4.5)		347 (40.3)	1.8 (1.4-2.5)		240 (48.4)	2.1 (1.5-2.9)		383 (45.4)	2.1 (1.6-2.9)		

Odds ratios (OR) were calculated using logistic regression models that compared melanoma cases at each anatomical site to all controls. Models were adjusted for age (continuous), sex, city of recruitment, sunbed use, sunburn and total sun exposure.

Supplementary Table 6: Interactions between phenotypic characteristics and sex in associations with melanoma risk, stratified by anatomical site

Phenotype variables	Head and Neck		Trunk		Upper Limb		Lower Limb	
	ORR (95% CI)	P-interaction	ORR (95% CI)	P-interaction	ORR (95% CI)	P-interaction	ORR (95% CI)	P-interaction
Naevi*female								
none	1.0		1.0		1.0		1.0	
few	1.2 (0.5-2.8)	0.7	1.1 (0.5-2.3)	0.8	0.6 (0.2-1.5)	0.3	0.4 (0.2-0.9)	0.02
some	1.0 (0.4-2.4)	1.0	1.3 (0.6-2.6)	0.5	0.6 (0.2-1.5)	0.3	0.4 (0.2-1.0)	0.04
many	1.8 (0.6-5.4)	0.3	2.1 (0.9-4.9)	0.1	0.8 (0.3-2.3)	0.6	0.5 (0.2-1.5)	0.2
Hair colour*female								
dark brown/black	1.0		1.0		1.0		1.0	
light brown	1.0 (0.5-2.0)	1.0	1.3 (0.9-2.1)	0.2	0.8 (0.5-1.4)	0.5	0.9 (0.6-1.6)	0.8
fair or blonde	1.1 (0.5-2.4)	0.8	1.3 (0.8-2.4)	0.3	0.9 (0.5-1.8)	0.8	0.7 (0.4-1.4)	0.3
red	2.9 (1.1-7.8)	0.04	1.2 (0.6-2.7)	0.6	1.4 (0.6-3.3)	0.5	1.0 (0.5-2.3)	1.0
Eye colour*female								
brown or black	1.0		1.0		1.0		1.0	
green or hazel	1.9 (0.8-4.4)	0.1	1.4 (0.8-2.4)	0.3	1.5 (0.7-2.9)	0.3	0.8 (0.4-1.5)	0.6
blue or grey	1.2 (0.6-2.5)	0.6	1.3 (0.7-2.2)	0.4	1.1 (0.6-2.1)	0.8	1.0 (0.5-1.8)	1.0
Skin colour*female								
olive or brown	1.0		1.0		1.0		1.0	
fair	0.8 (0.3-2.0)	0.6	1.3 (0.7-2.5)	0.4	0.9 (0.4-1.9)	0.7	1.0 (0.5-2)	1.0
very fair	1.0 (0.3-2.8)	1.0	1.5 (0.7-3.1)	0.3	1.2 (0.5-2.9)	0.7	1.2 (0.5-2.6)	0.7
Freckles in childhood*female								
none	1.0		1.0		1.0		1.0	
very few	1.2 (0.6-2.6)	0.6	2.5 (1.5-4.3)	<0.001	1.3 (0.7-2.4)	0.4	1.2 (0.7-2.1)	0.6
few/some	1.4 (0.7-3.0)	0.3	2.4 (1.4-4)	<0.001	1.3 (0.7-2.3)	0.4	0.9 (0.5-1.5)	0.6
many	3.4 (1.1-10.8)	0.04	2.8 (1.3-6.3)	0.01	1.3 (0.5-3.2)	0.6	2.2 (0.8-5.9)	0.1
Skin phototype*female								
sometimes/never burns	1.0		1.0		1.0		1.0	
usually/always burns	1.6 (0.9-2.9)	0.1	1.3 (0.9-2)	0.2	1.2 (0.7-1.9)	0.6	0.8 (0.5-1.3)	0.4

ORR, ratio of odds ratios. In each ORR, the numerator is the odds ratio for the risk factor among females, and the denominator is the odds ratio for the risk factor among males. For example, the odds ratio for the effect of red hair (vs. dark brown/black) on head and neck melanomas is 2.9-fold higher in females compared with males (95%CI 1.1-7.8). Models were adjusted for age (continuous), sex and city of recruitment.

Supplementary Table 7: Associations between melanoma and UV exposure, stratified by anatomical site, in the Australian Melanoma Family Study

Sun exposure (Australia)	Controls		Head and Neck		Trunk		Upper-Limb		Lower-Limb		P-het ²			
	N	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	
Daily exposure (h/d)¹														
minimally-adjusted	469	82	1.1 (0.8-1.3)	0.7	210	1.0 (0.9-1.2)	0.7	128	1.2 (0.9-1.4)	0.2	182	1.0 (0.9-1.3)	0.6	1.0
multivariable-adjusted	469	82	1.1 (0.8-1.4)	0.5	210	1.0 (0.9-1.2)	0.7	128	1.1 (0.9-1.4)	0.3	182	1.0 (0.8-1.2)	0.9	0.9
Weekday exposure (h/d)¹														
minimally-adjusted	469	82	1.1 (0.9-1.4)	0.4	293	1.0 (0.9-1.3)	0.9	128	1.1 (0.9-1.4)	0.3	182	1.0 (0.8-1.2)	0.9	0.5
multivariable-adjusted	469	82	1.1 (0.9-1.4)	0.3	293	1.0 (0.9-1.3)	0.6	128	1.1 (0.9-1.4)	0.5	182	0.9 (0.8-1.2)	0.5	0.6
Weekend exposure (h/d)¹														
minimally-adjusted	469	82	0.9 (0.8-1.1)	0.4	210	1.0 (0.9-1.2)	0.6	128	1.1 (0.9-1.3)	0.2	182	1.0 (0.9-1.2)	0.8	0.1
multivariable-adjusted	469	82	0.9 (0.8-1.1)	0.5	210	1.0 (0.9-1.2)	0.9	128	1.1 (0.9-1.3)	0.5	182	1.0 (0.9-1.2)	0.9	0.2
Summer holiday exposure (h/d)¹														
minimally-adjusted	470	82	1.0 (0.9-1.1)	0.8	211	0.9 (0.9-1.0)	0.1	128	1.0 (0.9-1.1)	0.9	183	0.9 (0.9-1.0)	0.2	0.3
multivariable-adjusted	470	82	1.0 (0.9-1.1)	0.9	211	0.9 (0.9-1.0)	0.1	128	1.0 (0.9-1.1)	0.8	183	1.0 (0.9-1.1)	0.4	0.7
Sunbed use														
minimally-adjusted														
Never	385	68	1.0		158	1.0		101	1.0		138	1.0		
Ever	83	13	1.1 (0.6-2.2)	0.8	51	1.8 (1.2-2.8)	0.008	27	1.1 (0.7-1.9)	0.7	83	1.4 (0.9-2.2)	0.1	0.2
multivariable-adjusted														
Never	385	68	1.0		158	1.0		101	1.0		138	1.0		
Ever	83	13	1.1 (0.5-2.2)	0.9	51	1.8 (1.1-2.9)	0.01	27	1.1 (0.6-1.9)	0.7	83	1.1 (0.7-1.8)	0.6	0.3
Painful sunburns														
minimally-adjusted														
Never	95	26	1.0		43	1.0		36	1.0		50	1.0		
Ever	375	56	0.6 (0.3-1.0)	0.3	148	1.1 (0.7-1.7)	0.6	92	0.7 (0.4-1.1)	0.2	133	0.7 (0.5-1.1)	0.5	0.1
multivariable-adjusted														
Never	95	26	1.0		43	1.0		36	1		50	1.0		
Ever	375	56	0.5 (0.3-0.8)	0.008	148	0.8 (0.5-1.3)	0.4	92	0.5 (0.3-0.8)	0.004	133	0.5 (0.3-0.8)	0.005	0.2
Sunburn causing blisters														
minimally-adjusted														
Never	293	51	1.0		117	1.0		75	1.0		116	1.0		
Ever	177	31	1.1 (0.7-1.9)	0.6	94	1.6 (1.1-2.3)	0.01	53	1.2 (0.8-1.8)	0.4	67	1.1 (0.7-1.4)	1.0	0.2
multivariable-adjusted														
Never	293	51	1.0		117	1.0		75	1.0		116	1.0		
Ever	177	31	1.0 (0.6-1.7)	0.9	94	1.2 (0.8-1.7)	0.5	53	0.9 (0.6-1.5)	0.8	67	0.7 (0.4-1.0)	0.07	0.1

UV, ultraviolet radiation.

Minimally-adjusted models were adjusted for age (continuous), sex and city of recruitment in Australia.

Multivariable-adjusted models were adjusted for age (continuous), sex and city of recruitment in Australia, and phenotypic characteristics: naevi, hair colour, eye colour, skin colour, freckles in childhood, skin phototype.

¹ OR per 1-hour/day increase in sun exposure.

² Heterogeneity p-values were computed using variables categorised in tertiles.

Supplementary Table 8: Associations between melanoma and UV exposure, stratified by anatomical site, in the Leeds Melanoma Case-Control Study

Sun exposure (Leeds)	Controls N	N	Head and Neck OR (95% CI)	P-value	N	Trunk OR (95% CI)	P-value	N	Upper-Limb OR (95% CI)	P-value	N	Lower-Limb OR (95% CI)	P-value	P-het ²
Daily exposure (h/d)¹														
minimally-adjusted	438	117	1.2 (0.9-1.4)	0.2	303	1.0 (0.9-1.2)	0.6	181	0.8 (0.7-1)	0.1	366	0.9 (0.8-1.1)	0.2	0.9
multivariable-adjusted	438	117	1.2 (0.9-1.4)	0.1	303	1.0 (0.9-1.2)	0.6	181	0.9 (0.7-1)	0.3	366	0.9 (0.8-1.1)	0.2	0.7
Weekday exposure (h/d)¹														
minimally-adjusted	478	118	1.2 (1.1-1.5)	0.01	308	1.1 (1.0-1.2)	0.1	181	0.9 (0.8-1.1)	0.4	378	1.0 (0.9-1.2)	0.8	0.1
multivariable-adjusted	478	118	1.3 (1.1-1.6)	0.002	308	1.1 (1.0-1.2)	0.1	181	1.0 (0.8-1.2)	0.8	378	1.1 (0.9-1.2)	0.4	0.2
Weekend exposure (h/d)¹														
minimally-adjusted	476	117	0.9 (0.8-1.0)	0.1	308	0.9 (0.8-1.0)	0.1	181	0.9 (0.8-1.0)	0.2	376	0.9 (0.8-1.0)	0.02	0.9
multivariable-adjusted	476	117	0.9 (0.8-1.1)	0.2	308	0.9 (0.8-1.0)	0.1	181	0.9 (0.8-1.1)	0.3	376	0.8 (0.7-0.9)	0.001	0.9
Summer holiday exposure (h/d)¹														
minimally-adjusted	505	207	0.8 (0.7-0.8)	<0.001	699	0.8 (0.8-0.9)	<0.001	397	0.8 (0.7-0.9)	<0.001	710	0.8 (0.7-0.9)	<0.001	0.2
multivariable-adjusted	505	207	0.9 (0.8-1.0)	0.1	699	0.9 (0.8-1.0)	0.1	397	0.9 (0.8-1.1)	0.3	710	0.9 (0.8-1.0)	0.01	1.0
Sunbed use														
minimally-adjusted														
Never	271	76	1.0		158	1.0		91	1.0		193	1.0		
Ever	234	47	0.8 (0.5-1.2)	0.2	158	1.1 (0.8-1.5)	0.5	97	1.0 (0.7-1.4)	0.9	204	0.9 (0.7-1.2)	0.5	0.5
multivariable-adjusted														
Never	271	76	1.0		158	1.0		91	1.0		193	1.0		
Ever	234	47	0.8 (0.5-1.3)	0.5	158	1.1 (0.8-1.6)	0.5	97	0.9 (0.6-1.3)	0.6	204	0.9 (0.7-1.3)	0.6	0.5
Painful sunburns														
minimally-adjusted														
Never	288	112	1.0		57	1.0		212	1.0		394	1.0		
Ever	217	94	1.2 (0.8-1.6)	0.4	43	1.1 (0.9-1.4)	0.4	184	1.1 (0.8-1.4)	0.5	314	1.0 (0.8-1.3)	1.0	0.9
multivariable-adjusted														
Never	288	112	1.0		57	1.0		212	1.0		394	1.0		
Ever	217	94	1.1 (0.7-1.7)	0.6	43	1.4 (1.0-1.9)	0.05	184	1.2 (0.8-1.7)	0.4	314	1.2 (0.9-1.6)	0.3	0.7
Sunburn causing blisters														
minimally-adjusted														
Never	432	173	1.0		606	1.0		348	1.0		615	1.0		
Ever	73	34	1.2 (0.8-1.9)	0.4	92	0.8 (0.6-1.2)	0.3	49	0.8 (0.5-1.2)	0.3	93	0.9 (0.6-1.2)	0.5	0.4
multivariable-adjusted														
Never	432	173	1.0		606	1.0		348	1.0		615	1.0		
Ever	73	34	1.3 (0.8-2.2)	0.3	92	0.8 (0.5-1.3)	0.4	49	0.9 (0.5-1.5)	0.6	93	1.0 (0.7-1.5)	0.9	0.5

UV, ultraviolet radiation.

Minimally-adjusted models were adjusted for age (continuous), sex and city of recruitment in Australia.

Multivariable-adjusted models were adjusted for age (continuous), sex and city of recruitment in Australia, and phenotypic characteristics: naevi, hair colour, eye colour, skin colour, freckles in childhood, skin phototype.

¹ OR per 1-hour/day increase in sun exposure.

² Heterogeneity p-values were computed using variables categorised in tertiles.

Supplementary Table 9: Associations between melanoma and genetic pathway scores, stratified by anatomical site, in the Australian Melanoma Family Study

Genetic pathways	Controls	Head and Neck			Trunk			Upper-Limb			Lower-Limb			P-het
	N	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	
Pigmentation pathway	470	82	3.3 (1.9-5.6)	<0.001	211	2.7 (1.9-3.9)	<0.001	128	2.9 (1.9-4.4)	<0.001	183	4.1 (2.8-5.8)	<0.001	0.1
Naevus pathway	470	82	0.6 (0.3-1.6)	0.3	211	1.6 (0.8-2.9)	0.2	128	2.3 (1.1-4.8)	0.03	183	1.2 (0.7-2.4)	0.5	0.1
Telomere/Other pathway	470	82	2.6 (0.7-10.4)	0.2	211	3.1 (1.2-7.9)	0.02	128	1.5 (0.5-4.7)	0.5	183	2.8 (1.1-7.6)	0.04	0.8
All variants	470	82	2.8 (1.7-4.5)	<0.001	211	2.7 (2.0-3.8)	<0.001	128	2.8 (1.9-4.1)	<0.001	183	3.6 (2.6-5.0)	<0.001	0.4

Models were adjusted for age (continuous), sex, city of recruitment in Australia. Odds ratios (OR) were calculated using logistic regression models that compared melanoma cases at each anatomical site to all controls. ORs were calculated per 1-standard deviation increase and heterogeneity p-values were computed using variables categorised into tertiles.

Supplementary Table 10: Associations between melanoma and genetic pathway scores, stratified by anatomical site, in the Leeds Melanoma Case-Control Study

Genetic pathways	Controls	Head and Neck			Trunk			Upper-Limb			Lower-Limb			P-het
	N	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value	
Pigmentation pathway	505	207	4.0 (2.6-6.1)	<0.001	699	3.5 (2.5-5.0)	<0.001	397	3.3 (2.3-4.7)	<0.001	710	3.0 (2.2-4.0)	<0.001	0.2
Naevus pathway	505	207	2.0 (1.1-3.8)	0.03	699	1.4 (0.9-2.3)	0.2	397	1.7 (1.0-3.0)	0.1	710	1.3 (0.8-2.0)	0.3	0.3
Telomere/Other pathway	505	207	3.1 (1.1-8.6)	0.03	699	2.2 (1.0-4.8)	0.05	397	2.0 (0.8-4.8)	0.1	710	2.7 (1.3-5.6)	0.007	0.1
All variants	505	207	3.2 (2.2-4.7)	<0.001	699	2.8 (2.1-3.8)	<0.001	397	2.8 (2.1-3.9)	<0.001	710	2.5 (1.9-3.2)	<0.001	0.2

Models were adjusted for age (continuous) and sex. Odds ratios (OR) were calculated using logistic regression models that compared melanoma cases at each anatomical site to all controls. ORs were calculated per 1-standard deviation increase and heterogeneity p-values were computed using variables categorised into tertiles.

Supplementary Table 11: Multivariable-adjusted associations between melanoma and genetic pathway scores, stratified by anatomical site, in the pooled Australian Melanoma Family Study and Leeds Melanoma Case-Control Study

Genetic pathways			Head and Neck		Trunk		Upper-Limb		Lower-Limb		P-het							
			OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI		P-value						
Pigmentation pathway	975	289	3.8	(2.7-5.4)	<0.001	910	3.1	(2.4-4.0)	<0.001	525	2.9	(2.2-3.8)	<0.001	893	3.3	(2.6-4.2)	<0.001	0.67
Nevus pathway	975	289	1.2	(0.7-2.1)	0.5	910	1.4	(0.9-2.1)	0.1	525	1.9	(1.2-3)	0.01	893	1.3	(0.9-2)	0.14	0.90
Telomere pathway	975	289	3.0	(1.3-7.2)	0.01	910	2.7	(1.5-5.1)	0.002	525	1.8	(0.9-3.7)	0.1	893	2.8	(1.5-5.2)	<0.001	0.70
All variants	975	289	3.1	(2.3-4.3)	<0.001	910	2.8	(2.2-3.4)	<0.001	525	2.7	(2.1-3.5)	<0.001	893	2.9	(2.3-3.5)	<0.001	0.36

Odds ratios (OR) were calculated using logistic regression models that compared melanoma cases at each anatomical site to all controls. Models were adjusted for age (continuous), sex, city of recruitment, sunbed use, sunburn and total sun exposure. ORs were calculated per 1-standard deviation increase and heterogeneity p-values were computed using variables categorised into tertiles.