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Risk factors for melanoma by anatomical site: an evaluation of aetiological heterogeneity*

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Summary

Background Melanoma aetiology has been proposed to have two pathways, which are determined by naevi and type of sun exposure and related to the anatomical site where melanoma develops.

Objectives We examined associations with melanoma by anatomical site for a comprehensive set of risk factors including pigmentary and naevus phenotypes, ultraviolet radiation exposure and polygenic risk.

Methods We analysed harmonized data from 2617 people with incident first invasive melanoma and 975 healthy controls recruited through two population-based case–control studies in Australia and the UK. Questionnaire data were collected by interview using a single protocol, and pathway-specific polygenic risk scores were derived from DNA samples. We estimated adjusted odds ratios using unconditional logistic regression that compared melanoma cases at each anatomical site with all controls.

Results When cases were compared with control participants, there were stronger associations for many naevi vs. no naevi for melanomas on the trunk, and upper and lower limbs than on the head and neck (P-heterogeneity < 0·001). Very fair skin (vs. olive/brown skin) was more weakly related to melanoma on the trunk than to melanomas at other sites (P-heterogeneity = 0·04). There was no significant difference by anatomical site for polygenic risk. Increased weekday sun exposure was positively associated with melanoma on the head and neck but not on other sites.

Conclusions We found evidence of aetiological heterogeneity for melanoma, supporting the dual pathway hypothesis. These findings enhance understanding of risk factors for melanoma and can guide prevention and skin examination education and practices.

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Conflicts of interest
The authors declare they have no conflicts of interest.

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The full list of Australian Melanoma Family Study investigators and Leeds Case–Control Study investigators is provided in Appendix 1.

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What is already known about this topic?

- Two main biological pathways have been proposed for the aetiology of melanoma – determined by naevi and type of sun exposure and related to the anatomical site at which melanoma develops.
- Risk factors for melanoma may differ by anatomical site, but analyses are often limited by study sample size and most have focused on sun exposure.

What does this study add?

- This study provides an examination of a comprehensive set of risk factors for melanoma by anatomical site, using a harmonized dataset from two population-based studies with 3592 participants.
- The presence of increased numbers of naevi was more strongly associated with melanomas on the trunk and limbs than on the head and neck.
- Very fair skin was more weakly related to melanoma on the trunk than on other sites.
- The association of pathway-specific polygenic risk scores with melanoma did not differ by anatomical site.

Cutaneous melanoma incidence is increasing in many countries with populations of predominantly European origin, despite improvements in prevention.[1,2] Most of the risk for melanoma is driven by intensity and pattern of sun exposure, host factors such as pigmentary phenotypes, propensity to develop naevi, genetic susceptibility and the complex association among these factors.[3–6] The aetiology of melanoma is also indicated by the anatomical site on which it develops,[7,8] with two main biological pathways proposed.[9–12] The first of these is a naevus pathway that is initiated by early-life sun exposure to epidermal melanocytes, promoted by intermittent sun exposure or host factors, and is predominant on areas less exposed to sun (e.g. trunk) and in younger individuals. The second is a chronic (more continuous) sun-exposure pathway, predominant in sun-sensitive and older people, in which sun damage progressively accumulates on areas of skin that are habitually exposed (e.g. head and neck).[12–14] A third pathway involving increased germline telomere length has been implicated through genetic studies,[15] but its association with pigmentation and naevus count is thus far largely undescribed.

Most epidemiological studies that have examined this hypothesis have focused on the association of sun exposure (or a proxy such as solar elastosis) with melanoma risk stratified by anatomical site.[14,16,17] Few studies have examined associations of other risk factors by anatomical site, such as pigmentary and naevus characteristics, despite their strong associations with melanoma risk and the importance of host characteristics in the dual pathway hypothesis.[3,6,12,18–22] Most of these studies have been case-only designs with small sample sizes and limited statistical power, have captured data for only a few risk factors or have been limited to one sex.[3,14,23] Therefore, we aimed to examine associations with melanoma by anatomical site for a comprehensive set of risk factors including pigmentary and naevus characteristics [measured both phenotypically and genetically using a polygenic risk score (PRS)] and ultraviolet (UV) radiation exposure using two population-based studies from Australia and the UK.

Materials and methods

We analysed data from 3592 participants, including 2617 people with newly diagnosed melanoma (cases) and 975 people without melanoma (controls). Participants were recruited through the Australian Melanoma Family Study, which is a multicentre population-based case–control study, and through the Leeds (UK) population-based case–control study (Leeds Melanoma Case–Control Study). A detailed description of the study designs and data collections for these two studies has been given previously.[6] Identical questionnaires and assessment measures were applied across the study sites. Approval to conduct this study was obtained from the ethics committees of the coordinating centres and cancer registries in Australia, and from the UK Multicentre Research Ethics Committee and the Patient Information Advisory Group. All participants provided written informed consent.

Study participants

For the Australian Melanoma Family Study, 629 individuals residing within Queensland, New South Wales and Victoria who had histopathologically confirmed first primary invasive cutaneous melanoma diagnosed between 1 July 2000 and 31 December 2002 at ages 18–39 years were included.[24] They were recruited through population-based cancer registries and participation was 54%. Frequency matched population

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controls for age, sex and city (n = 240) were recruited through electoral rolls (registration to vote is compulsory for adult Australian citizens) and were frequency matched to cases by age (within 5 years) and sex using proportional random sampling; participation was 23% of those eligible. Eligible spouse/partner or friend controls (n = 295) were nominated by case participants as a potential control; 80% of those nominated consented to participate. They were ineligible if they had a previous invasive or *in situ* melanoma.

For the Leeds case–control study, cases were aged 18–82 years with histopathologically confirmed first primary invasive melanoma, living in a geographically defined area of Yorkshire and the northern region of the UK (67% participation). Between September 2000 and June 2003, all people with invasive melanoma were included, and from July 2003 to September 2011, only cases with Breslow thickness ≥ 0·75mm were included. Age and sex frequency matched population-based controls identified as not having cancer were recruited from general practices (55% participation).

Data collection

Details of the data collection are described in File S1 (see Supporting Information).

Statistical analysis

All pigmentary and naevus phenotype variables were analysed as categorical variables. Sun exposure and PRS were analysed as continuous variables. Missing exposure values were excluded from the relevant analysis.

Adjusted odds ratios (ORs), approximating the relative risk,[25] and 95% confidence intervals (CIs) for melanoma were calculated using unconditional logistic regression models fitted separately for each anatomical site (head and neck, trunk, lower limbs, upper limbs) and compared with all controls. Thus, unlike case-only analyses where one anatomical site is used as a reference group for the other sites, in this analysis the cases from each site were compared with the single control group, and the reference category for each exposure corresponded to the lowest exposure level or darkest phenotype. For continuous measures of sun exposure, the ORs were calculated per 1-h increase in sun exposure per day. For continuous measures of PRS, the ORs were calculated per SD increase in PRS. We adjusted regression models for age (continuous), sex and city of recruitment, and for the PRS we additionally adjusted for self-reported ethnicity. We also further adjusted UV-exposure associations for pigmentary and naevus phenotype characteristics, and vice versa. Population controls and spouse/partner/friend controls were combined into one control group for this analysis, as we have previously shown that associations for standard risk factors were similar when either control group or both groups were used.[24]

To examine potential interaction between pigmentary phenotypes and sex, we fitted additional site-specific models including main effects and interaction terms. To test whether the associations for risk factors differed by anatomical subtype, we calculated *P*-values for aetiological heterogeneity as described by Zabor and Begg[26] using the R package 'riskclustr'.[27,28] Data were analysed using R version 3·5. Statistical significance was assessed using a two-sided threshold $P < 0·05$. *P*-values were not adjusted for multiple testing as we had clearly defined hypotheses informed by prior research.[29,30] We reported the study according to STROBE guidelines for observational studies.

Results

Analysis dataset

Of the 629 Australian cases and 535 controls, 25 cases and 65 controls were excluded from this analysis because of missing anatomical site (cases), presence of *CDKN2A* mutation (as genetic factors in this analysis focus on polygenic risk), non-European ancestry or age over 45 years (partner/friend controls). This resulted in 604 Australian cases and 470 controls for analysis. In the Leeds study, 2184 cases and 513 controls were recruited, from which 171 cases and eight controls were excluded owing to either missing or rare anatomical site, presence of *CDKN2A* mutation, or missing data for some exposures (a shorter questionnaire was used after 2007 when only cases were being recruited), resulting in 2013 cases and 505 controls for analysis. Combined, a total of 2617 cases and 975 controls were included in the analysis.

Participant characteristics

The characteristics of the pooled study sample are presented in Table 1 and stratified by study in Table S1 (Australia) and Table S2 (Leeds) (see Supporting Information). Melanoma most commonly occurred on the trunk (35%) and lower limbs (34%), followed by the upper limbs (20%) and the head and neck (11%). Compared with male participants, female participants had a higher frequency of melanomas on the upper and lower limbs (male to female ratio 1 : 1·8 and 1 : 3·3, respectively), while the opposite was true for trunk and head and neck melanomas (male to female ratio 1 : 0·68 and 1 : 0·83, respectively). The proportion of melanomas occurring in those aged 70 and older was higher for head and neck (21%) than for any other site (9–10%; χ^2-test, $P < 0·001$). Family history of melanoma in a first-degree relative was more common for cases with melanoma on the upper limb or trunk (10%) compared with other anatomical sites (5–8%; χ^2-test, $P < 0·001$).

Pigmentary and naevus phenotypic characteristics

The associations between key pigmentary phenotypic characteristics and melanoma by anatomical site are presented in Figure 1 for the pooled analysis, and separately for Australia and Leeds in Table S3 and Table S4. In the pooled analysis,

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Table 1 Characteristics of melanoma cases and controls in the pooled Australian Melanoma Family Study and Leeds Melanoma Case–Control Study

		Cases (N = 2617)			
	Controls, n = 975	Head and neck, n = 289	Trunk, n = 910	Upper limb, n = 525	Lower limb, n = 893
Study					
Leeds	505 (51·8)	207 (71·6)	699 (76·8)	397 (75·6)	710 (79·5)
Australia	470 (48·2)	82 (28·4)	211 (23·2)	128 (28·4)	183 (20·5)
Sex					
Male	406 (41·6)	158 (54·7)	541 (59·5)	187 (35·6)	208 (23·3)
Female	569 (58·4)	131 (45·3)	369 (40·6)	338 (64·4)	685 (76·7)
Age at diagnosis/interview (years)					
18–29	101 (10·4)	47 (16·3)	104 (11·4)	46 (8·8)	89 (10·0)
30–39	350 (35·9)	63 (21·8)	217 (23·9)	137 (26·1)	220 (24·6)
40–49	163 (16·8)	19 (6·6)	124 (13·6)	88 (16·8)	139 (15·6)
50–59	131 (13·4)	42 (14·5)	184 (20·2)	87 (16·6)	172 (19·3)
60–69	133 (13·6)	58 (20·1)	197 (21·7)	117 (22·3)	186 (20·8)
≥ 70	97 (9·9)	60 (20·8)	84 (9·2)	50 (9·5)	87 (9·7)
Ethnic background					
English	740 (75·9)	259 (89·6)	775 (85·4)	458 (87·6)	784 (87·8)
Scottish, Irish, Welsh	39 (4·0)	12 (4·2)	50 (5·5)	19 (3·6)	51 (5·7)
Other Northern European	29 (3·0)	2 (0·7)	15 (1·7)	6 (1·2)	9 (1·0)
Southern European	10 (1·0)	0 (0·0)	6 (0·7)	1 (0·2)	1 (0·1)
Eastern European	132 (13·5)	11 (3·8)	48 (5·3)	28 (5·4)	38 (4·3)
Mixed/other European	25 (2·6)	5 (1·7)	14 (1·5)	11 (2·1)	10 (1·1)
Family history of melanoma (in a first-degree relative)					
No	919 (94·3)	274 (94·8)	815 (89·7)	472 (89·9)	821 (91·9)
Yes	56 (5·7)	15 (5·2)	94 (10·3)	53 (10·1)	72 (8·1)

Data are presented as n (%).

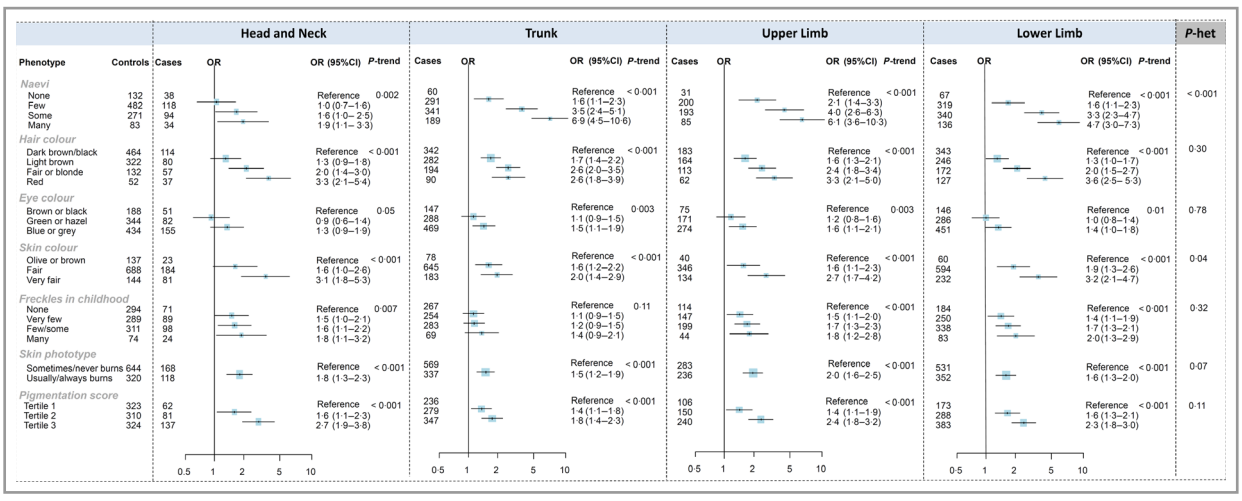

Figure 1 Associations between melanoma and naevus and pigmentation phenotypes, stratified by anatomical site, in the pooled Australian Melanoma Family Study and Leeds Melanoma Case–Control Study. P-het, P-heterogeneity; CI, confidence interval. Odds ratios (ORs) were calculated using logistic regression models that compared melanoma cases at each anatomical site with all controls. Models were adjusted for age (continuous), sex and city of recruitment.

increased naevus density was associated with higher odds of melanoma for all sites, but the strength of the association differed by anatomical site (P-heterogeneity < 0·001). The association of naevi was stronger for melanoma on the trunk and upper limbs (OR for many naevi compared with no naevi 6·9, 95% CI 4·5–10·6 and 6·1, 95% CI 3·6–10·3,

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respectively) and lower limbs (OR 4·7, 95% CI 3·0–7·3) than head and neck melanoma (OR 1·9, 95% CI 1·1–3·3).

The association of skin colour also differed by site (P-heterogeneity = 0·04), with very fair skin being more weakly related to melanoma on the trunk (OR 2·0, 95% CI 1·4–2·9 compared with olive or brown skin) than on other sites (ORs 2·7–3·2). When examined separately by study, the association with skin colour appeared stronger for melanoma on the head and neck in the Leeds study (OR 3·6 for very fair skin), and for melanoma on the lower limbs in the Australian study (OR 4·4).

Red or blonde hair, blue or grey eye colour, increasing number of freckles in childhood, propensity to sunburn, skin phototype and pigmentation score were associated with increased odds of melanoma for all sites, with no significant heterogeneity among the different sites in the pooled analysis (P-heterogeneity > 0·05). When examined separately by study, sun-sensitive skin (skin phototype) was more weakly related to melanoma on the trunk in the Leeds study, and in the Australian study pigmentation score was more strongly related to head and neck melanoma (both P-heterogeneity = 0·02).

The associations did not materially change when the pooled results were adjusted by UV exposures (Table S5).

Given the sex differences in the development of melanoma at different anatomical sites, we examined whether the association of phenotypic characteristics with melanoma risk was modified by sex, separately for each anatomical site (Table S6). The OR for freckles in childhood, comparing many with none, was higher for female participants compared with male participants for melanomas on the head and neck (ratio of ORs 3·4, 95% CI 1·1–10·8) and for melanomas on the trunk (ratio of ORs 2·8, 95% CI 1·3–6·3). Potential interactions with sex were also present for the association of red hair with melanomas on the head and neck (stronger association in female participants), and the association of naevi with melanomas on the lower limb (weaker association in female participants).

Ultraviolet radiation exposure

The associations between UV exposures and melanoma by anatomical site are presented in Figure 3for the pooled multivariable analysis, and separately for Australia and Leeds in Table S7 and Table S8. In the pooled analysis, increased weekday sun exposure was associated with head and neck melanoma (for 1 h per day increase in exposure, OR 1·2, 95% CI 1·1–1·4) but there was no significant heterogeneity by site (P-heterogeneity = 0·43). Summer holiday sun exposure was associated with reduced risk of melanoma on the lower limbs and trunk, and weekend sun exposure was associated with reduced risk of melanoma on the lower limbs, but there was no significant heterogeneity by site.

There was borderline-significant heterogeneity by site (P = 0·07) for sunbed use, which had a stronger association with melanoma on the trunk (Figure 3); this association with the trunk was more apparent in the Australian study (OR 1·8, 95% CI 1·1–2·9; Table S7). There was no association with sunburns at any site in the pooled analysis (Figure 3). Increased risk of melanoma on the trunk was associated with painful sunburns in the Leeds study and blistering sunburns in the Australian study, although there was no significant heterogeneity by site (Tables S7, S8). Painful sunburns were associated with reduced risk of melanoma for all sites except the trunk in the Australian study.

Some risk estimates changed after adjustment for pigmentation and naevus phenotypic characteristics (Tables S7, S8); the inverse associations between sun exposure during weekends and summer holidays and melanoma risk were partly attenuated, associations with sunburns were mostly strengthened, and associations with sunbed use were mostly unchanged.

Genetic risk factors

The PRS was used to examine the risk of melanoma across different anatomical sites conferred by common genomic variants in several biological pathways that are important for melanoma development (pigmentation, naevus and telomere/other pathways) (Figure 2 for the pooled analysis and separately for Australia and Leeds in Table S9 and Table S10). Associations with melanoma were strongest for the pigmentation pathway PRS, with more than threefold higher odds per SD increase of melanoma across all anatomical sites without evidence of heterogeneity (P-heterogeneity = 0·14). Similarly, the telomere/other pathway PRS was consistently associated

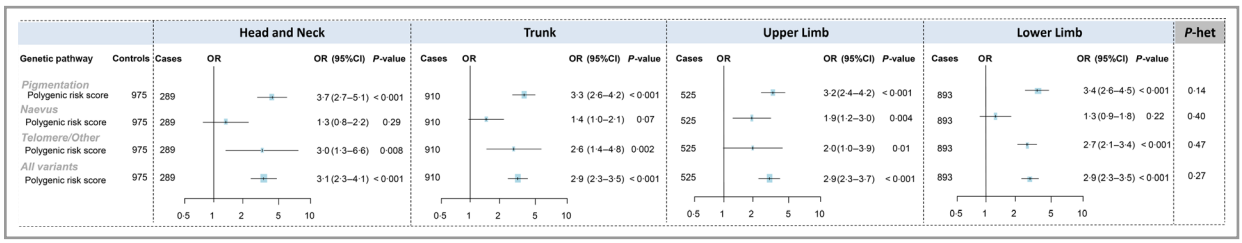

Figure 2 Associations between melanoma and genetic pathway scores, stratified by anatomical site, in the pooled Australian Melanoma Family Study and Leeds Melanoma Case–Control Study. P-*het*, P-heterogeneity; CI, confidence interval. Odds ratios (ORs) were calculated using logistic regression models that compared melanoma cases at each anatomical site with all controls. Models were adjusted for age (continuous), sex and city of recruitment. ORs were calculated per SD increase in polygenic risk score and heterogeneity P-values were computed using variables categorized into tertiles.

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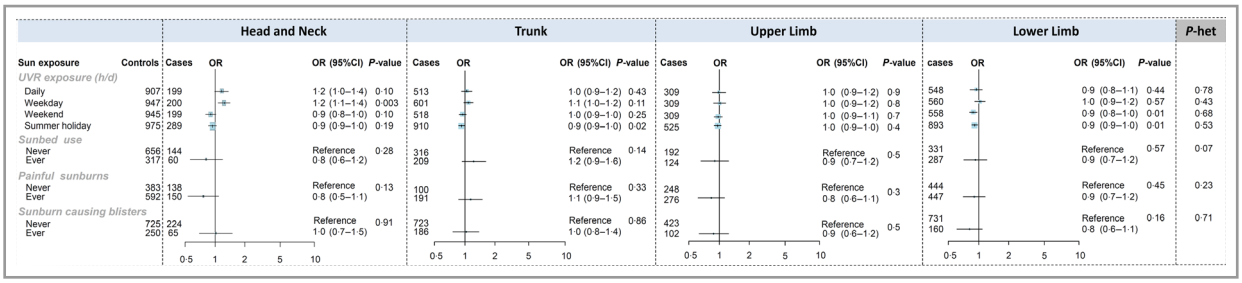

Figure 3 Associations between melanoma and ultraviolet radiation (UVR) exposures, stratified by anatomical site, in the pooled Australian Melanoma Family Study and Leeds Melanoma Case–Control study. P-het, P-heterogeneity; CI, confidence interval. Odds ratios (ORs) were calculated using logistic regression models that compared melanoma cases at each anatomical site with all controls. Models were adjusted for age (continuous), sex, city of recruitment and the following phenotypic characteristics: naevi, hair colour, eye colour, skin colour, freckles in childhood and skin phototype. For continuous measures of sun exposure, the ORs were calculated per 1-h increase in sun exposure per day and heterogeneity P-values were computed using variables categorized into tertiles.

with melanoma at all anatomical sites. The naevus pathway PRS had a statistically significant association only with upper-limb melanoma (OR per SD 1·9, 95% CI 1·2–3·0) and a borderline association with trunk melanoma (OR 1·4, 95% CI 0·97–2·1) but there was no evidence of heterogeneity. For head and neck melanoma, the pooled OR associated with the naevus pathway PRS was 1·3, but it appeared to differ between Australia (OR 0·6) and Leeds (OR 2·0) (Cochran's Q, P = 0·046). A PRS combining all genetic variants indicated an approximate threefold increased odds of melanoma, with no evidence of heterogeneity by anatomical site. The associations did not materially change when the pooled results were adjusted by UV exposures (Table S11).

Discussion

To shed light on the aetiological heterogeneity of melanoma, we analysed a harmonized dataset of two population-based case–control studies in Australia and the UK to characterize risk factors for cutaneous melanoma according to anatomical site. Several of our findings are consistent with the dual pathway hypothesis, which proposes that there is heterogeneity in the aetiological pathways to melanoma such that risk of melanomas on the trunk is determined by propensity to form naevi (which are both genetically determined and caused by early-life sun exposure)[6,31–33] and intermittent sun exposure, whereas melanoma on the head and neck is more likely to be caused by chronic (more continuous) sun exposure.[11,12,14,16,34] Consistent with this, we found that the number of naevi was more strongly associated with trunk melanoma than head and neck melanoma. Increased weekday sun exposure (a proxy for occupational sun exposure) was associated with head and neck melanoma, which has been reported by other studies,[7,16,17] although not consistently.[35] This positive association with head and neck melanoma was more apparent for the Leeds study than the Australian study, which may be due to the older age distribution of the Leeds study than that of the Australian study, as melanomas associated with chronic UV exposure are more common among older ages.[36] Sunbed use and sunburns, considered intermittent exposures, appeared more strongly associated with trunk melanoma, which is also consistent with the dual pathway hypothesis and other studies,[37,38] although there was no statistical evidence for heterogeneity and the risk estimates differed between studies.

Evidence for melanoma on the limbs is less clear, but one recent study suggested that lower-limb melanoma, similar to trunk melanoma, may tend to arise via a naevus-related pathway whereas upper-limb melanoma, similar to head and neck melanomas, may tend to arise via the sun-damage pathway.[23] In contrast with this suggestion, we found the strongest associations with naevi for upper-limb melanoma and trunk melanoma, although the association of naevi with melanomas on the lower limb was weaker for female participants than male participants.

In addition to number of naevi, the other risk factor with heterogeneity by anatomical site in our study was skin colour. In particular, the increased risk associated with very fair skin was weaker for melanoma on the trunk than for other sites, although this difference was smaller than for the number of naevi. A similar difference by site was also observed in a previous meta-analysis.[7] Taken together, our results do not support a clear classification of upper- and lower-limb melanoma into the two pathways indicated by melanoma on the trunk and head or neck. Rather, they suggest that both pathways may be important for development of melanoma on the limbs.

While certain findings based on phenotypic risk factors showed clear support for aetiological heterogeneity by anatomical site, we did not find clear evidence of heterogeneity in associations with PRS quantifying genetic pathways for pigmentation, naevi and telomere/other biological processes. Unlike the phenotypic naevus and skin colour variables, the naevus and pigmentation pathway PRS ORs were similar between melanoma on the head/neck and on the trunk. Despite naevi being one of the strongest risk factors for melanoma,[39] a naevus-pathway PRS has a relatively weak overall association with melanoma risk.[20] This discrepancy may be

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because our current naevus PRS captures only a small proportion of the total variation in naevus phenotypes.[40]

Contrary to previous studies,[4,7,17,41] we did not observe positive associations between melanoma risk and sunburn at all anatomical sites, nor with measures of recreational sun exposure. The inverse association with weekend and summer holidays and melanoma risk has been previously reported for the Leeds study and was hypothesized to be mediated by photoadaptation or higher vitamin D levels.[22] This study also observed a stronger association with melanoma for sunburns after the age of 20 years.[22] Interestingly, painful sunburns (but not sunburns causing blisters) were inversely associated with melanoma risk on all sites except the trunk in the Australian study, and this was stronger after adjustment for phenotypic characteristics. Sun sensitivity may modify or confound this association,[42] and we previously showed that the association with sunburn was modified by host factors because a positive association was observed only in people who tended to tan rather than burn and in people who had few naevi.[43] We observed null associations with total sun exposure at all sites. A meta-analysis by Chang *et al.* also found mostly null associations at different body sites except for an increased risk of melanoma on the limbs at low latitudes.[17]

The key strengths of our study are its size and comprehensive genetic and phenotypic risk factor measures, which allowed detailed analysis by anatomical sites of melanoma, and which was achieved by pooling two population-based case–control studies that used the same measures for data collection. The approach of pooling these data sources was supported by our previous finding that the associations between melanoma and self-reported pigmentary and naevus phenotypes were similar across countries.[6] We also examined the associations by site in each study separately, although these subgroup analyses had limited statistical power.

The younger age of participants in the Australian study (< 40 years at diagnosis) is a limitation for the study of divergent pathways of melanoma, particularly for the UV-related exposures. However, as ambient sun exposure varies greatly between Australia and Leeds, at any given age the cumulative dose of UV exposure is expected to be higher for Australia than the UK. The main focus of our analysis was on pigmentary and naevus characteristics, as fewer studies have examined associations of these risk factors by anatomical site. Other limitations of our study include the lack of detailed pathological information, as some studies have suggested that the presence of solar elastosis and naeval remnants influence aetiologically distinct subtypes.[8,44] When using self-reported risk factors people tend to underestimate their naevus counts and pigmentation;[45] although associations with melanoma have been shown to be very similar for most self-reported and clinically-assessed risk factors.[6] Measurement error, recall bias and selection bias may have also influenced the observed sun-exposure associations. Participation was higher for cases than controls. Sun exposure is a widely known risk factor for melanoma, and controls with high sun exposure may have been more interested in participating in the study, which would lead to inverse associations. Personal lifetime sun exposure is also a complex behaviour to measure,[46] and non-differential measurement error usually biases the result towards the null.[47] We previously showed stronger associations of childhood total sun exposure and sunburn with melanoma risk when exposure level was recalled concordantly by participants and their parents.[43] We had lower numbers of controls than cases in our analysis. Most previous studies have conducted a case-only analysis; however, including controls produces risk estimates that are more easily communicated to the public and comparable with other risk factor studies. The Leeds study recruited people with thicker melanomas (≥ 0·75 mm) in the later years of the study, but stratification of our results by this factor did not materially alter the results.

In conclusion, in our analysis by anatomical site we found evidence of aetiological heterogeneity for melanoma, supporting the dual pathway hypothesis. The evidence was strongest for naevus phenotype measures, but weaker for pigmentary phenotype, sun exposure and genetically measured risk factors. These findings promote a better understanding of melanoma development. They may also be helpful for guiding skin examination education and practices, for example by highlighting to patients and clinicians which areas of the body may require closer or more regular examination, according to their risk factor profile.

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Appendix

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

File S1 Supplementary methods.

Table S1 Characteristics of melanoma cases and controls in the Australian Melanoma Family Study.

Table S2 Characteristics of melanoma cases and controls in the Leeds Melanoma Case–Control Study.

Table S3 Associations between melanoma and naevus and pigmentation phenotypes, stratified by anatomical site, in the Australian Melanoma Family Study.

Table S4 Associations between melanoma and naevus and pigmentation phenotypes, stratified by anatomical site, in the Leeds Melanoma Case–Control Study.

Table S5 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.

Table S6 Interactions between phenotypic characteristics and sex in associations with melanoma risk, stratified by anatomical site.

Table S7 Associations between melanoma and ultraviolet exposure, stratified by anatomical site, in the Australian Melanoma Family Study.

Table S8 Associations between melanoma and ultraviolet exposure, stratified by anatomical site, in the Leeds Melanoma Case–Control Study.

Table S9 Associations between melanoma and genetic pathway scores, stratified by anatomical site, in the Australian Melanoma Family Study.

Table S10 Associations between melanoma and genetic pathway scores, stratified by anatomical site, in the Leeds Melanoma Case–Control Study.

Table S11 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.

Powerpoint S1 Journal Club Slide Set.

Video S1 Author video.

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