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Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls

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Background Melanoma risk is related to sun exposure; we have investigated risk variation by tumour site and latitude.

Methods We performed a pooled analysis of 15 case–control studies (5700 melanoma cases and 7216 controls), correlating patterns of sun exposure, sunburn and solar keratoses (three studies) with melanoma risk. Pooled odds ratios (pORs) and 95% Bayesian confidence intervals (CIs) were estimated using Bayesian unconditional polytomous logistic random-coefficients models.

Results Recreational sun exposure was a risk factor for melanoma on the trunk (pOR = 1.7; 95% CI: 1.4–2.2) and limbs (pOR = 1.4; 95% CI: 1.1–1.7), but not head and neck (pOR = 1.1; 95% CI: 0.8–1.4), across latitudes. Occupational sun exposure was associated with risk of melanoma on the head and neck at low latitudes (pOR = 1.7; 95% CI: 1.0–3.0). Total sun exposure was

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associated with increased risk of melanoma on the limbs at low latitudes (pOR = 1.5; 95% CI: 1.0–2.2), but not at other body sites or other latitudes. The pORs for sunburn in childhood were 1.5 (95% CI: 1.3–1.7), 1.5 (95% CI: 1.3–1.7) and 1.4 (95% CI: 1.1–1.7) for melanoma on the trunk, limbs, and head and neck, respectively, showing little variation across latitudes. The presence of head and neck solar keratoses was associated with increased risk of melanoma on the head and neck (pOR = 4.0; 95% CI: 1.7–9.1) and limbs (pOR = 4.0; 95% CI: 1.9–8.4).

Conclusion Melanoma risk at different body sites is associated with different amounts and patterns of sun exposure. Recreational sun exposure and sunburn are strong predictors of melanoma at all latitudes, whereas measures of occupational and total sun exposure appear to predict melanoma predominately at low latitudes.

Keywords Melanoma, recreational sun exposure, occupational sun exposure, total sun exposure, sunburn, solar keratoses

Introduction

Sun exposure has been identified in epidemiological studies as the leading environmental cause of melanoma, but the lack of a simple dose–response relationship between total sun exposure and risk of melanoma has been perplexing. In general, studies have reported a positive association for recreational (intermittent) sun exposure and an inverse association with occupational (more continuous) exposure.[1–4] It has been noted that differing odds ratios (ORs) for melanoma resulting from the use of differing statistical methods and adjustment for different confounding factors have made the pooling of studies problematic in meta-analysis.[2,3] Moreover, studies have been carried out at a range of different latitudes where people are exposed to very different levels of solar ultraviolet radiation. Detailed comparisons between studies carried out at different latitudes have the potential to shed light on these complicated issues. The primary aim of this pooled analysis was to investigate the complex relationship between sun exposure and melanoma risk at different latitudes. An understanding of this relationship will be very important for developing health promotion messages for different countries.

Recent studies have suggested that there are multiple pathways to melanoma[5–8] involving different body sites, different pathology (naevus remnants, solar damage and genetic mutations) and different sun exposure patterns (intermittent or more continuous). An analysis based on a large number of study participants may help to further clarify this complex relationship, and this was a secondary aim of these analyses. Elwood *et al*.[9] suggested that the relationship between occupational sun exposure and melanoma might be non-linear with some beneficial effect related to long continued exposure. A further aim of this pooled analysis was to consider melanoma risk by tumour site and by latitude to investigate this hypothesis.

Methods

Summary of studies included in the pooled analyses

Information regarding study location, time period, number of participating cases and controls, and detailed definitions of collected sun-exposure risk factors were tabulated for each of the 15 studies included in these analyses[9–23] (Table 1). Wide inclusion criteria were adopted to allow more data in the pooled analyses. Selection procedures were described in a previous pooled analysis paper on naevus phenotype.[24] The pooled data set consisted of seven studies from Europe, five studies from North America, one study from Hawaii and two studies from Australia. There were a total of 5700 melanoma cases and 7216 controls.

Categorization of sun-exposure data across studies

Information collected on recreational sun exposure varied greatly between studies. Several studies had collected detailed information on all leisure-related sun-exposure activities during vacations and weekends, whereas others recorded average non-working hours spent outdoors during the summer or at weekends. Many European studies had only asked specific questions on sunbathing and/or activities wearing swimsuits during vacations (abroad and/or in the country of residence). We derived two measures: first, total hours (or weeks or years) of recreational sun exposure were calculated as the sum of all reported outdoor recreational activities weighted

Table 1 Description of sun exposure information collected in the 15 case–control studies included in the pooled analysis (ordered from highest to lowest latitude)

Study	Geographic location	Average latitude[a]	Diagnosis years	Cases/ controls	Type of melanoma[e]	Recreational exposure/sun bathing and water activities	Ever sunburn	Occupational exposure
Westerdahl *et al.*[10]	South Sweden	56N	1988–90	400/641	IMM in 130 reviewed cases	Frequency of holidays abroad for sunbathing or swimming: four categories	Child/ adult	Outdoor work hours from April to September
Westerdahl *et al.*[11]	South Sweden	56N	1995–97	571/913	SSM, NM, LMM, AM	Frequency of holidays abroad for sunbathing or swimming: four categories	Child/ adult	Outdoor work hours from April to September
Osterlind *et al.*[12 b]	East Denmark	55N	1982–85	293/536	SSM, NM, LMM, AM	Total hours of outdoor recreational activities except sunbathing/total hours of sun-bathing vacation in the Mediterranean, North Africa or equivalent vacation places	Child	Total outdoor work hours throughout lifetime
Swerdlow *et al.*[13]	Scotland, UK	55N	1979–84	180/197	SSM, NM, LMM, AM	Total outdoor sunbathing hours during short trips abroad in past 5 years	Adult	Total outdoor work hours throughout lifetime
Elwood *et al.*[14]	East Midlands, UK	53N	1984–86	195/195	SSM, NM	Total hours of outdoor recreational activities/total hours of outdoor activities wearing swimsuits during holidays abroad (four time periods: 5 years prior to diagnosis, 18–22 years prior to diagnosis, age 18–22, age 8–12)	Child/ adult	Total outdoor work hours throughout lifetime
Bataille *et al.*[15]	North East Thames, UK	52N	1989–93	434/421	SSM, NM, LMM, AM	Holidays abroad in hot countries; sunbathing in UK	Child/ adult	Total summer outdoor work hours since age of 16
Kennedy *et al.*[16c]	Leiden, The Netherlands	52N	1998–99	123/385	SSM, NM, LMM	Life-long sun exposure limited to recreation, vacations and weekends	Child/ adult	Life-long sun exposure limited to working hours
Elwood *et al.*[9]	Western Canada	49N	1979–81	595/595	SSM, NM	Total hours of outdoor recreational activities/total hours of activities wearing swimsuits during weekend and vacation time	Child	Total outdoor work hours throughout lifetime
Titus-Ernstoff *et al.*[17]	New Hampshire, USA	43N	1995–98	423/678	SSM, NM, LMM	Total hours of outdoor recreational activities/total hours of sunbathing activities after age of 10	Child/ adult	Total outdoor work hours after age of 20 (plus out-door work hours as a child or teenager)
Berwick *et al.*[18]	Connecticut, USA	41N	1987–89	650/549	SSM, NM, LMM, AM	Number of vacations to places sunnier than residence; time spent in outdoor recreational activities wearing swimsuits or light clothes in past 10 years and before age 15: recreational index	Child/ adult	Total years of outdoor jobs as lifeguard, construction worker, farmer

(continued)

Table 1 Continued

Study	Geographic location	Average latitude[a]	Diagnosis years	Cases/controls	Type of melanoma[b]	Recreational exposure/sun bathing and water activities	Ever sunburn	Occupational exposure
Kanetsky *et al.*[19d]	Pennsylvania, USA	39N	1997–99	363/150	SSM, NM, LMM, AM	Self-reported recreational sun exposure throughout lifetime: three categories (a lot, average, little or none)	Child/adult	Self-reported occupational sun exposure throughout lifetime: three categories (a lot, average, little or none)
Holly *et al.*[20b]	San Francisco, CA, USA	37N	1981–86	452/935	SSM, NM, LMM, AM	Frequency of lying out in the sun during summer with arms and legs exposed in past 10 years: five categories (never, less than once a month, once a month, two to three times a month, once a week or more)	Child/adult	Arms and legs exposed in the sun during week-days in past 10 years: five categories (none, less than 1/4 of time, 1/4–1/2 of time, 1/2–3/4 of time, more than 3/4 of time)
Holman *et al.*[23]	Western Australia	31S	1980–81	511/511	SSM, NM, LMM	Total hours of outdoor recreational activities, excluding sunbathing since leaving school/sun-bathing; frequency and hours of listed activities wearing swimsuits in last 10 years	Child/adult	Total outdoor work hours since leaving school
Green *et al.*[22]	Queensland, Australia	27S	1979–80	232/232	SSM, NM, LMM	Total hours of outdoor recreational activities since leaving school/beach visit frequency (five categories) and hours spent during each visit	Child/adult	Total outdoor jobs hours since leaving school
Le Marchand *et al.*[21]	Hawaii, USA	21N	1986–92	278/278	SSM, NM, LMM	Total hours of outdoor recreational activities during vacation/total hours of activities wearing swimsuits during vacation	Child/Adult	Total outdoor work hours since leaving school

[a]Three geographic regions were defined as high latitudes (average latitude above 45N), middle latitudes (average latitude between 45N and 35N) and low latitudes (average latitude between 34 and 20 N/S).
[b]Women only.
[c]Included unpublished data in the pooled analysis.
[d]Cases coming to the Pigmented Lesion Clinic for presence of pigmented lesions but without diagnoses of melanoma in the original study were excluded from pooled analysis.
[e]IMM: invasive malignant melanoma; SSM: superficial spreading melanoma; NM: nodular melanoma; LMM: lentigo maligna melanoma; AM: acral lentiginous melanoma.

by frequency and duration; secondly, total hours (or weeks or years) of all reported sunbathing activities and/or activities wearing swimsuits were calculated, weighted by their frequency and duration. A recreational exposure index was used for the Connecticut study as described in the original article.[18]

Many studies have collected comprehensive calendar data on type of job, duration and clothing worn for all outdoor employment. Some studies have recorded only average hours spent outdoors on weekdays. For occupational sun exposure analyses, outdoor weekday hours (weeks or years) were summed across all jobs and weighted by duration. Information collected on recreational and occupational sun exposure was in the same age periods and measured in the same time-units in seven studies, so for these studies total sun exposure was estimated by summing across all recreational and occupational exposures.

Recreational, occupational and total sun-exposure data each were classified into sex- and study-specific quarters based on the distribution in the control population. If >25% of the controls had not engaged in the relevant sun-exposure activities (occupational, recreational or total), then controls in this 'non-exposed' group formed the lowest exposure level, and the remaining controls were equally divided into three groups representing thirds of controls with non-zero exposure of that type. The quantile cut-off points obtained from the controls were then applied to melanoma cases of the same sex in the same study. The resulting four study-specific sun exposure groups represent low, intermediate–low, intermediate–high and high sun-exposure categories. For studies using pre-defined categories, controls were classified into four groups distributed as evenly as possible, and these groupings were also applied to the corresponding cases.

Many studies had collected sunburn information in several age periods, and pooled analyses on sunburns in childhood and in adulthood were conducted. Childhood was defined as younger than 15 years of age, and adulthood was defined as aged 20 years and older. Evaluation of the risk of sunburn was based on presence or absence of any reported painful sunburn experience within the considered age intervals.

Solar keratoses (SK) are believed to be caused by excessive long-term exposure to sunlight in fair-skinned people. They are therefore markers of high epidermal sun exposure given a certain level of susceptibility to sun-induced skin damage. Three studies[15,16,22] had recorded the presence of SK on the face and neck by examination, which was coded as presence or absence in the pooled analysis.

The amount of ultraviolet (UV) in ambient sunlight varies greatly by latitude. Individual-level latitude data were not available and some studies covered regions with a large latitude range. Average latitude was thus used as an approximate index of the latitude range of a study, and studies were classified into three categories. Those carried out at average latitudes above 45° north were classed as 'high latitude', between 45° and 35° north as 'middle latitude' and between 34° north/south and 20° north/south as the 'low latitude'.

Melanoma tumour-site information was available for all except the New Hampshire study.[17] Most studies included cases of superficial spreading melanoma (SSM), nodular melanoma (NM) and lentigo maligna melanoma (LMM). Seven studies also included acral lentiginous melanoma (AM, with a total of 61 cases) (see Table 1). LMM and AM were excluded in the East Midlands, UK, and the Western Canada studies.[9,14]

Statistical methods

Bayesian unconditional polytomous logistic random coefficient regression models were employed to study the overall effects of sun exposure on the risk of developing melanoma. Analyses were conducted to evaluate the risk of melanoma anywhere on the body and melanoma occurring specifically on the trunk, limbs, and head and neck. Heterogeneity was accounted for by allowing the effects to vary between studies in a structured manner, and the variance of each effect was estimated using random coefficients models. The estimated variances of the study-specific log ORs quantified the degree of heterogeneity in relative risk estimates among studies. For each risk factor its 'relative heterogeneity' was measured by the ratio of the estimated among-study standard deviation to the range of log OR estimates.[25] This measure allows comparisons between the degrees of heterogeneity associated with different risk factors.

Three dummy variables were created for all participants to define the sun-exposure groups (intermediate–low, intermediate–high, high vs low category) in the analysis. If only three originally pre-defined categories (low, middle, high) were available in a study, then the middle class was treated as the average of the intermediate–low and intermediate–high categories. Pooled ORs (pORs) adjusted only for age and sex (referred to as pOR1 in the tables/figures) were reported, as well as pORs adjusted for age, sex, hair colour, ability to tan (or propensity to burn if ability to tan was not recorded) and freckling (if available) (referred to as pOR2 in the tables/figures).

To examine the potential influence of latitude on the effects of sun exposure [without assuming a linear relationship between log(OR) and latitude], we allowed the pORs to vary among the three pre-defined geographical regions. However, the among-study variance was assumed to be the same across all regions.

The Markov chain Monte Carlo (MCMC) method was used to estimate the risk of melanoma in relation to sun exposure using WinBUGS software.[26] Flat priors with low precisions were assigned for all parameters. Detailed specifications of the models and prior distributions were described in the supplementary data of our previous report.[24]

Results

Age distribution, histological subtype and site of melanoma

The age distribution of cases corresponded reasonably well with that of controls except for cases with head and neck melanoma who were much older than other cases and controls ($P < 0.0001$ for both comparisons).

Of the 3035 confirmed SSM cases with tumour site information, 1180 (38.9%), 1599 (52.7%) and 256 (8.4%) had melanoma on the trunk, limbs and head and neck, respectively. Within the 662 NM cases, the proportions were 222 (33.5%), 343 (51.8%) and 97 (14.7%), and within the 445 LMM cases, the proportions were 64 (14.4%), 107 (24.0%) and 274 (61.6%). The site distribution of LMM cases was significantly different from those of SSM and NM ($P < 0.0001$ for both comparisons).

Recreational sun exposure

Thirteen studies recorded sunbathing and activities wearing a swimsuit, and nine studies recorded all outdoor recreational activities. In the recreational sun-exposure analyses, 5567 melanoma cases and 7033 controls were included (Table 2). Sunbathing data were aggregated across latitude regions, since many studies recorded information on sunbathing during holiday abroad. The among-study variance for the effects of sunbathing activities was 0.032, and the relative heterogeneity was 0.07. Compared with the relative heterogeneity of other measures (see below), the slightly higher relative heterogeneity for sunbathing could be due to the different periods of life for which sunbathing data were collected in different studies and to combining sunbathing with other activities requiring a swimsuit. Forest plots of study- and tumour-site-specific fully adjusted ORs and pORs for the highest category of sunbathing exposure compared with the lowest group are shown in Figure 1. The pORs for melanoma on the trunk and limbs were significantly >1 for the three highest categories of sunbathing exposure compared with lowest exposure and were little changed by adjustment for measures of susceptibility such as ability to tan and freckling (Table 2).

The among-study variance for effects of outdoor recreational sun exposure was 0.007, and the relative heterogeneity was 0.03. Similar to the finding for sunbathing activities, the fully adjusted pORs for the highest category of all recreational sun exposure compared with low exposure were significantly >1 for both trunk and limb melanoma (Table 2). The pOR2s for the highest recreational sun exposure category compared with the lowest group were 1.7 (95% CI: 1.4–2.2), 1.4 (95% CI: 1.1–1.7) and 1.1 (95% CI: 0.8–1.4) for trunk, limb and head and neck melanoma, respectively, across all latitude regions. There was no evidence of a systematic relationship of risk to latitude (Figure 1). In addition, total recreational sun exposure correlated reasonably well with sunbathing frequency. Spearman correlations coefficients were 0.34 and 0.81 in the high–middle and low latitudes, respectively. Omission of the two high-latitude studies that excluded LMM had little impact on the high latitude pOR2s (data not shown).

Occupational sun exposure

In the occupational sun-exposure analyses, 5578 melanoma cases and 7024 healthy controls from 15 studies were included (Table 3). The majority of the participants living in the high latitudes did not report any outdoor work exposure (58%). Similarly, >50% of the participants from the middle latitudes were in the low and intermediate–low categories. The distribution of occupational sun exposure among those living at low latitudes was more evenly distributed between categories (Table 3).

The among-study variation for effects of occupational sun exposure was 0.023, and the relative heterogeneity was 0.05. Forest plots of study-specific occupational sun-exposure risks for the highest versus lowest category are shown in Figure 2. The fully adjusted pORs for the highest category of occupational sun exposure compared with the lowest group across all latitude regions were 1.0 (95% CI: 0.8–1.2), 0.9 (95% CI: 0.8–1.1) and 1.2 (95% CI: 0.9–1.6) for melanoma on the trunk, limbs and head and neck, respectively. Increased occupational sun exposure was not associated with melanoma risk on the trunk and limbs regardless of latitude (Table 3). There was evidence of increased risk for occupational sun exposure for melanoma on the head and neck at low latitudes, with a pOR2 of 1.7 (95% CI: 1.0–2.0) for the highest occupational sun exposure category compared with the lowest. Omission of the two high-latitude studies that excluded LMM had little impact on the adjusted pOR2s (data not shown). Similar pORs were observed when the models for occupational sun exposure were adjusted for recreational sun exposure, and vice versa (results not shown).

Fair-skinned people were less likely to work outdoors, especially at low latitudes ($P < 0.0001$ compared with darker skinned people). For control participants at low latitudes who worked at least 4 h per day outdoors during any period of their life, 17% had skin type I/II compared with 29% of indoor workers. In the two studies that recorded detailed outdoor occupation in the middle latitudes, 13% of controls who pursued outdoor work had skin type I/II compared with 20% who mainly worked indoors ($P = 0.015$). There was little difference in distribution of skin types between control participants who worked outdoors and indoors at high latitudes.

Table 2 pORs and 95% confidence internals (CIs) for sunbathing across latitudes and all outdoor recreational activities within latitude regions

Recreational sun exposure	Controls	Cases by melanoma site[a]											
		Trunk			Limbs			Head and neck			All		
	No	No	pOR1[b]	pOR2[c]	No	pOR1[b]	pOR2[c]	No	pOR1[b]	pOR2[c]	No	pOR1[b]	pOR2[c]
Sunbathing activities[d]													
Low[e]	2179	424	1	1	720	1	1	287	1	1	1575	1	1
Intermediate–low	1658	395	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	581	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	151	0.9 (0.7, 1.2)	1.0 (0.7, 1.2)	1240	1.1 (1.0, 1.3)	1.2 (1.0, 1.4)
Intermediate–high	1427	402	1.5 (1.2, 1.8)	1.5 (1.2, 1.9)	475	1.2 (1.0, 1.4)	1.3 (1.0, 1.5)	130	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	1145	1.2 (1.0, 1.4)	1.3 (1.1, 1.5)
High	1382	381	1.5 (1.2, 1.9)	1.5 (1.2, 1.9)	475	1.2 (1.0, 1.5)	1.4 (1.1, 1.7)	118	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	1121	1.3 (1.1, 1.5)	1.3 (1.1, 1.6)
All outdoor recreational activities[f]													
High/middle latitudes[g]													
Low[e]	696	147	1	1	259	1	1	66	1	1	568	1	1
Intermediate–low	545	75	1.2 (0.8, 1.7)	1.2 (0.8, 1.7)	142	1.1 (0.8, 1.4)	1.0 (0.8, 1.4)	28	1.0 (0.6, 1.8)	1.0 (0.6, 1.6)	357	1.1 (0.9, 1.4)	1.2 (0.9, 1.4)
Intermediate–high	546	69	1.3 (0.9, 1.8)	1.4 (1.0, 2.0)	162	1.2 (0.9, 1.6)	1.3 (1.0, 1.8)	30	1.1 (0.9, 1.7)	1.2 (0.7, 2.1)	386	1.3 (1.0, 1.6)	1.4 (1.1, 1.7)
High	594	169	1.9 (1.4, 2.6)	2.0 (1.4, 2.7)	211	1.2 (0.9, 1.6)	1.3 (1.0, 1.7)	50	1.2 (0.7, 1.8)	1.3 (0.9, 1.9)	560	1.4 (1.2, 1.7)	1.5 (1.2, 1.8)
Low latitudes													
Low[e]	322	107	1	1	120	1	1	75	1	1	310	1	1
Intermediate–low	233	72	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	101	1.1 (0.8, 1.6)	1.1 (0.8, 1.5)	36	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	214	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)
Intermediate–high	240	76	1.1 (0.8, 1.6)	1.2 (0.8, 1.7)	104	1.2 (0.9, 1.7)	1.3 (0.9, 1.7)	45	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)	232	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)
High	226	85	1.5 (1.1, 2.3)	1.6 (1.0, 2.2)	115	1.4 (1.0, 2.0)	1.5 (1.0, 2.1)	59	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)	265	1.3 (1.0, 1.6)	1.3 (1.0, 1.7)

[a]Melanoma site data were not available for one study.[17]
[b]Adjusted for age and sex only.
[c]Adjusted for age, sex, hair colour, ability to tan and freckling.
[d]Sunbathing data were available for 13 studies (Table 1).
[e]Low sun exposure was set as reference group.
[f]Summed outdoor recreational activities data were available for nine studies (Table 1).
[g]Only two studies[17,19] in the middle latitudes collected outdoor recreational activities data, and they were combined with studies in the high latitudes in the pooled analysis.

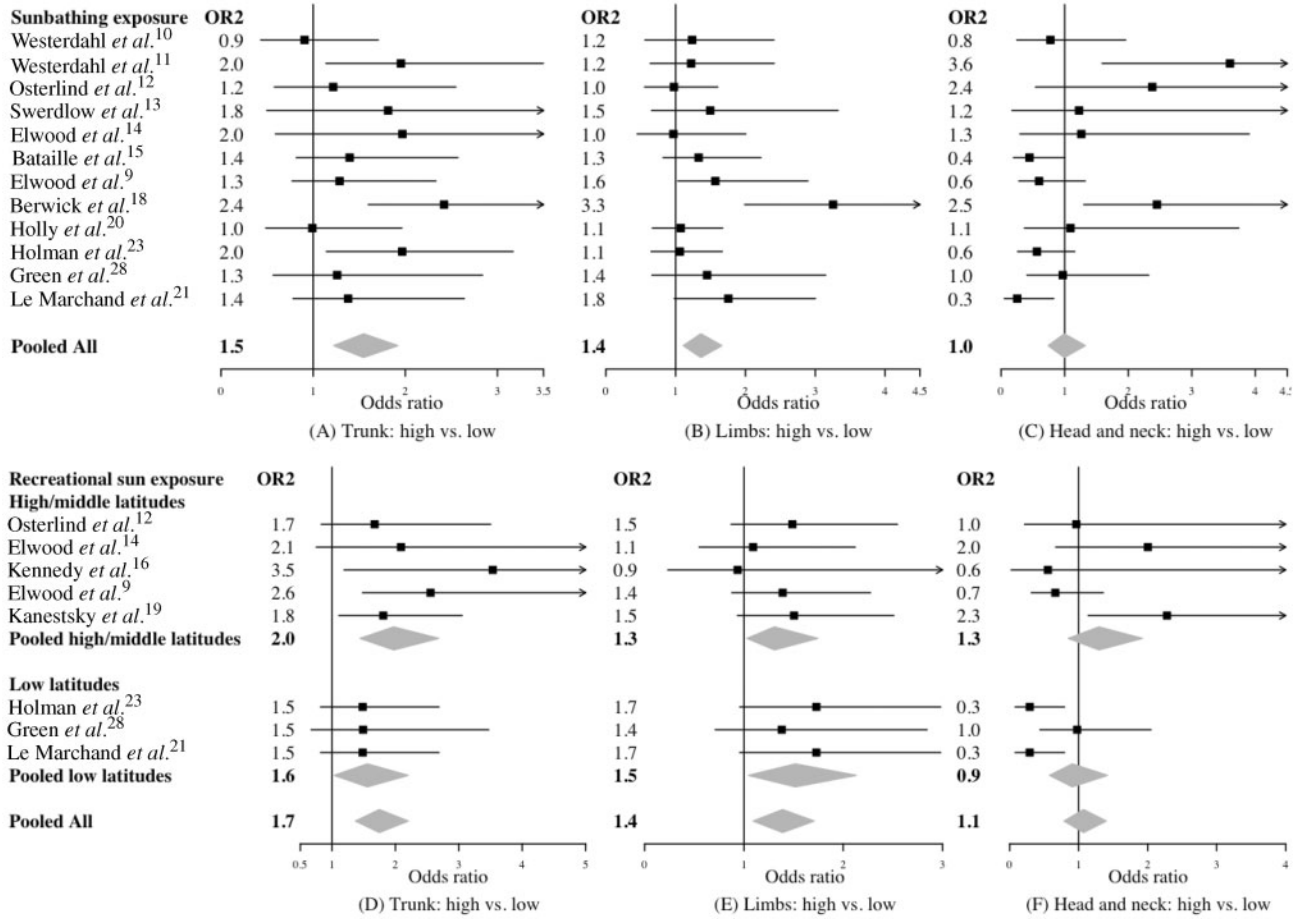

Figure 1 Forest plots of the association between (A–C) the highest sun-bathing exposure and (D–F) the highest total recreational sun exposure and melanoma risk. Each line represents results from an individual study, with the length of the horizontal line indicating the 95% CIs, and the square box indicating the study-specific adjusted OR (OR2) for the 'High vs Low' recreational sun-exposure category. Adjusted pOR2s and 95% CIs are represented by grey diamonds

Total sun exposure

Seven studies recorded total outdoor sun exposure (sum of occupational and recreational sun exposure) (Table 4). The among-study variation for effects of total sun exposure was 0.012, and the relative heterogeneity was 0.05. Overall, increased total sun exposure was not associated with melanoma risk at any site in the high latitudes or with melanoma on the trunk and head and neck at any latitudes (Table 4). It was, however, associated with melanoma on the limbs and, more weakly, the head and neck, at low latitudes: the fully adjusted pORs were 1.5 (95% CI: 1.0–2.2) and 1.3 (95% CI: 0.8–2.2). The lack of LMM in two of the three studies[9,14] in the high latitudes could affect the estimated association between total sun exposure and head and neck melanoma. The forest plots of study-specific adjusted ORs for total sun exposure are shown in Figure 3.

Solar keratoses

Of the 1035 controls from three studies[15,16,22] that recorded SK on the face and neck, 159 (15.4%) participants had at least one SK present; the corresponding percentages for cases with melanoma on the trunk, limbs and head and neck were 14.8, 23.2 and 39.0%, respectively (Table 4). Within those 159 controls who had at least one SK, only 15 of them were <50 years old. The among-study variance was 0.12 with a relative heterogeneity of 0.20, which was much larger than for other measures of sun exposure, probably because of the smaller number of studies that were included and possibly because of differences in phenotyping between studies. The pORs for melanoma with at least one SK adjusted for age and sex only were 1.9 (95% CI: 0.9–4.1), 4.0 (95% CI: 1.9–8.4) and 4.0 (95% CI: 1.7–9.1), respectively, for melanoma on the trunk, limbs and head and neck. For all sites together, the pOR was 3.2 (95% CI: 1.0–8.2). The pORs were slightly attenuated after additional adjustment for hair colour, ability to tan and freckling.

Cases with SK had similar recreational sun exposure compared with other cases ($P = 0.16$), but controls with SK had higher recreational sun exposure than

Table 3 pORs and 95% CI by occupational sun-exposure category within latitude regions

Occupational sun exposure[a]	Controls	Cases by melanoma site[b]											
		Trunk			Limbs			Head and neck			All		
	No	No	pOR1[c]	pOR2[d]	No	pOR1[c]	pOR2[d]	No	pOR1[c]	pOR2[d]	No	pOR1[c]	pOR2[d]
High latitudes													
Low[e]	2229	542	1	1	855	1	1	185	1	1	1634	1	1
Intermediate–low	515	127	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	199	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	59	1.3 (0.9, 1.8)	1.2 (0.8, 1.8)	393	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)
Intermediate–high	483	123	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	162	0.8 (0.6, 1.1)	0.9 (0.6, 1.1)	52	1.1 (0.7, 1.6)	1.1 (0.7, 1.7)	350	0.9 (0.7, 1.1)	0.9 (0.8, 1.2)
High	576	133	0.9 (0.7, 1.2)	1.0(0.7, 1.3)	168	0.8 (0.6, 1.0)	0.8 (0.7, 1.1)	67	1.1 (0.8, 1.6)	1.2 (0.8, 1.7)	384	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)
Middle latitudes													
Low[e]	815	298	1	1	300	1	1	107	1	1	913	1	1
Intermediate–low	816	104	0.7 (0.4, 1.0)	0.7 (0.5, 1.1)	201	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	37	0.7 (0.4, 1.3)	0.8 (0.4, 1.4)	430	0.8 (0.6, 1.1)	0.9 (0.7, 1.1)
Intermediate–high	327	59	0.8 (0.5, 1.3)	0.9 (0.6, 1.5)	62	0.7 (0.4, 1.1)	0.8 (0.5, 1.3)	15	0.5 (0.2, 1.0)	0.7 (0.3, 1.3)	219	0.8 (0.6, 1.1)	0.9 (0.7, 1.3)
High	243	65	1.0 (0.7, 1.5)	1.1 (0.7, 1.7)	69	1.0 (0.6, 1.4)	1.1 (0.7, 1.7)	18	0.7 (0.4, 1.3)	0.9 (0.5, 1.7)	230	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)
Low latitudes													
Low[e]	296	129	1	1	136	1	1	35	1	1	304	1	1
Intermediate–low	241	78	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	97	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	51	1.5 (0.9, 2.5)	1.5 (0.9, 2.6)	232	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)
Intermediate–high	243	67	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	96	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	53	1.3 (0.8, 2.1)	1.3 (0.8, 2.3)	225	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)
High	240	66	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)	109	1.0 (0.7, 1.5)	1.1 (0.7, 1.6)	76	1.6 (0.9, 2.7)	1.7 (1.0, 3.0)	258	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)

[a]Occupational sun-exposure data were available for all 15 studies.
[b]Melanoma site data were not available for one study.[17]
[c]Adjusted for age and sex only.
[d]Adjusted for age, sex, hair colour, ability to tan and freckling.
[e]Low sun exposure was set as reference group.

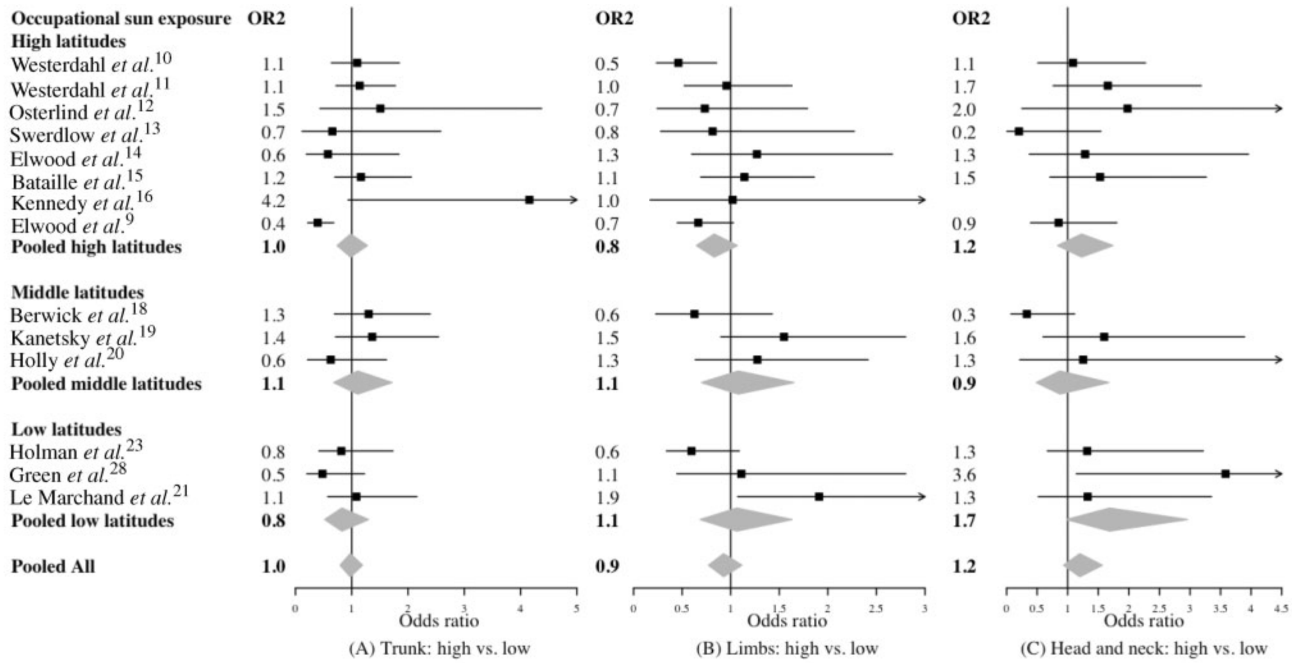

Figure 2 Forest plots of the association between the highest occupational sun exposure and melanoma risk. Each line represents results from an individual study, with the length of the horizontal line indicating the 95% CIs, and the square box indicating the study-specific adjusted OR (OR2) for the 'High vs Low' occupational sun-exposure category. Adjusted pOR2s and 95% CIs are represented by grey diamonds

other controls ($P = 0.04$). Participants with SK had higher occupational sun exposure in both cases and controls ($P < 0.0001$ in both groups).

Sunburn

Fourteen studies had collected data on sunburn in childhood (<15 years of age), and 13 studies had information on sunburn in adulthood (>20 years of age) (Table 5). The among-study variances were 0.003 and 0.005 (relative heterogeneities were 0.03 and 0.04) for effects of childhood and adult sunburn, respectively, suggesting negligible heterogeneity. Forest plots of study-specific ORs adjusted for age and sex only for childhood and adult sunburn are shown in Figure 4.

Sunburn before the age of 15 was a consistently significant risk factor for all three latitude regions. There was no evidence of a systematic relationship of risk to latitude. The pORs for melanoma in relation to any sunburn before the age of 15 across three latitude regions, adjusted for age and sex only (pOR1s) were 1.5 (95% CI: 1.3–1.7), 1.5 (95% CI: 1.3–1.7) and 1.4 (95% CI: 1.1–1.7) for melanoma on the trunk, limbs, and head and neck, respectively. Excluding the two high latitude studies that left out LMM had little effect on the pORs for childhood sunburn (data not shown).

Sunburn after the age of 20 years was significantly associated with melanoma on the trunk and limbs, but less strongly than was childhood sunburn (Table 5 and Figure 4); the pOR1s across latitude regions were 1.4 (95% CI: 1.2–1.6), 1.2 (95% CI: 1.1–1.4) and 1.1 (95% CI: 0.9–1.3) for melanoma on the trunk, limbs and head and neck, respectively. Sunburn after the age of 20 was also less strongly associated with melanoma in the middle and low latitudes than in the high latitudes. The pOR1 for sunburn after the age of 20 in the high latitudes changed little when the two studies that did not include LMM were left out (data not shown).

There was a strong correlation between sunburn before age 15 and sunburn after age 20 ($P < 0.0001$), and the association of sunburn after age 20 with melanoma diminished if sunburn before age 15 was included in the models. However, sunburn after age 20 remained significantly associated with melanoma on the trunk in the high and middle latitudes after adjusting for childhood sunburn: the adjusted pORs were both 1.3 (95% CI: 1.0–1.7). Furthermore, sunburn as an adult remained significantly associated with melanoma on the limbs in the high latitudes after adjusting for childhood sunburn with a pOR of 1.3 (95% CI: 1.0–1.6).

The pORs for sunburn before age 15 and sunburn after age 20 adjusted for age, sex, hair colour, ability to tan and freckling were slightly lower than their corresponding pORs adjusted for age and sex only.

There were strong correlations between sunburn at any age and more frequent sunbathing for both cases and controls ($P < 0.0001$ in both groups).

Table 4 pORs and 95% CI by recalled total sun-exposure category within latitude regions and by presence of SK across latitudes

Total sun exposure	Controls	Cases by melanoma site[a]											
		Trunk			Limbs			Head and neck			All		
	No	No	pOR1[b]	pOR2[c]	No	pOR1[b]	pOR2[c]	No	pOR1[b]	pOR2[c]	No	pOR1[b]	pOR2[c]
Recalled total sun exposure[d]													
High/middle latitudes[e]													
Low[f]	427	81	1	1	122	1	1	25	1	1	320	1	1
Intermediate–low	425	59	0.9 (0.6, 1.5)	1.0 (0.6, 1.4)	115	1.1 (0.7, 1.6)	1.1 (0.8, 1.7)	35	1.5 (0.9, 2.8)	1.5 (0.8, 2.6)	319	1.1 (0.9, 1.5)	1.2 (0.9, 1.5)
Intermediate–high	427	56	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)	115	1.1 (0.8, 1.7)	1.2 (0.8, 2.0)	21	1.0 (0.5, 2.1)	0.9 (0.4, 2.0)	306	1.1 (0.9, 1.5)	1.2 (0.9, 1.6)
High	422	40	0.9 (0.5, 1.4)	0.9 (0.5, 1.4)	86	0.9 (0.6, 1.4)	1.0 (0.7, 1.6)	20	1.0 (0.5, 2.2)	1.0 (0.5, 2.1)	279	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)
Low latitudes													
Low[f]	258	118	1	1	95	1	1	35	1	1	251	1	1
Intermediate–low	253	75	0.7 (0.5, 1.1)	0.7 (0.5, 1.0)	110	1.2 (0.8, 1.7)	1.2 (0.8, 1.7)	53	1.3 (0.8, 2.3)	1.3 (0.7, 2.2)	246	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
Intermediate–high	257	67	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	112	1.2 (0.8, 1.8)	1.3 (0.9, 2.0)	52	1.1 (0.6, 1.9)	1.0 (0.6, 1.7)	240	1.0 (0.7, 1.4)	1.0 (0.7, 1.3)
High	252	80	1.0 (0.7, 1.5)	1.0 (0.6, 1.5)	121	1.4 (0.9, 2.1)	1.5 (1.0, 2.2)	75	1.3 (0.8, 2.2)	1.3 (0.8, 2.2)	282	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)
Presence of SK on face[g]													
None[h]	876	218	1	1	265	1	1	72	1	1	599	1	1
At least one	159	38	1.9 (0.9, 4.1)	1.6 (0.8, 3.4)	80	4.0 (1.9, 8.4)	3.2 (1.6, 6.6)	46	4.0 (1.7, 9.1)	3.1 (1.4, 6.7)	186	3.2 (1.0, 8.2)	2.7 (1.1. 6.0)

[a]Melanoma site data were not available for one study.[17]
[b]Adjusted for age and sex only.
[c]Adjusted for age, sex, hair colour, ability to tan and freckling.
[d]Recalled total sun-exposure data were available for seven studies (Table 1).
[e]Only one study[17] in the middle latitudes collected total sun-exposure data, and it was combined with studies in the high latitudes in the pooled analysis.
[f]Low sun exposure was set as reference group.
[g]Three studies recorded SK data.[15,16,22]
[h]Zero SK was set as reference group.

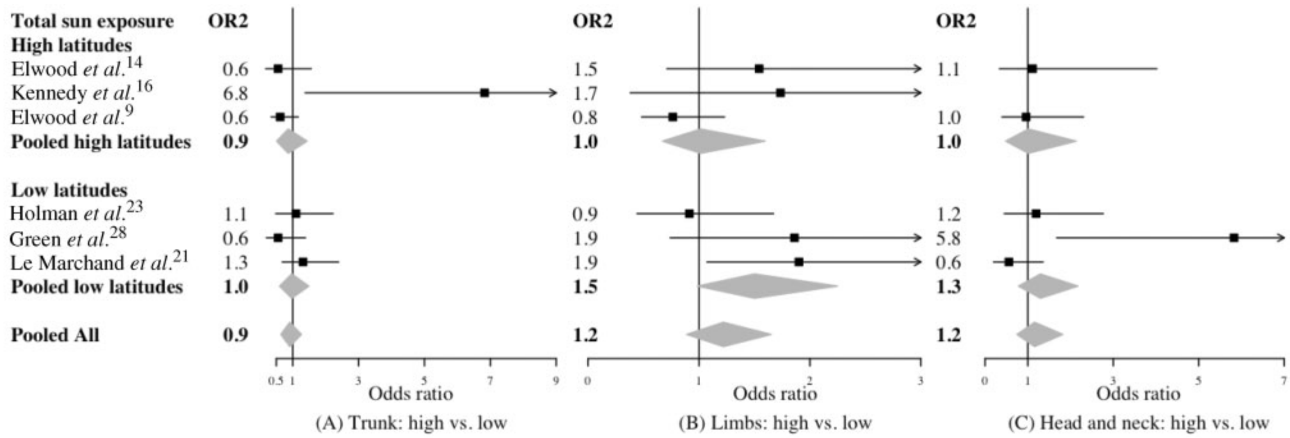

Figure 3 Forest plots of the association between total sun exposure and melanoma risk by tumour sites. Each line represents results from an individual study, with the length of the horizontal line indicating the 95% CIs, and the square box indicating the study-specific adjusted OR (OR2). Adjusted pOR2 and 95% CIs are represented by grey diamonds

However, there was no association between sunburn and total recreational sun exposure. There was also a significant inverse association between sunburn after age 20 and occupational sun exposure in the control participants ($P < 0.0001$), which echoed the association of skin type and outdoor occupation.

Discussion

We used original data from 15 case–control studies across a range of latitudes to examine the relationship of risk of melanoma to recreational (9 studies), occupational sun exposure, total sun exposure (7 studies), reported sunburn and the presence of SK on the face (3 studies). Our analysis has the limitations inherent in all pooled analyses of studies done by different investigators according to different protocols. The accurate quantification of sun exposure is a difficult task at any time and is made more difficult in this analysis by the use of different questionnaires and by probable differences in the sun-exposure habits in the populations studied. The analysis also carried with it the inevitable weakness of retrospective studies, recall error. If differential between cases and controls, which would be plausible for reported sun-exposure if melanoma diagnosis affects recall, recall error, would have a largely unpredictable effect on estimates of association. If non-differential, it would lead to weakening of associations and thus was probably an important contributor to the weakness in the associations observed. In addition, our use of the quantile method to categorize exposure for each study could reduce our ability to detect an association if melanoma risks were higher only above some threshold sun-exposure level and only a few studies had a substantial number of participants exposed above this threshold. That a relatively objective measure of high total sun exposure of usually exposed skin, the presence of SK on the face, was the factor most strongly associated with melanoma, even after adjustment for measured phenotypic factors, may give some indication of the impact of measurement error on our other risk estimates: phenotype-adjusted pOR of melanoma in the presence of SK was more than double that for the highest vs lowest level of recalled total sun exposure.

In spite of the probable bias towards the null induced by non-differential measurement error, the statistical power of this pooled analysis is sufficient to suggest some important patterns. First, high sunbathing and total recreational sun exposure increase risk of melanoma of the trunk and limbs but not melanoma of the head and neck (Figure 1 and Table 2). The relative risk associated with these intermittent pattern sun exposures appears largely uninfluenced by latitude of residence and, by inference, ambient UVB radiation. Secondly, occupational sun exposure appeared neither to increase nor decrease risk of melanoma on the trunk and limbs, but may increase risk of melanoma on the head and neck especially at low latitudes (Figure 2 and Table 3). Thirdly, high total sun exposure, as inferred from SK on the face, increases risk of melanomas on the limbs and head and neck but increases risk of melanoma of the trunk less, if at all (Figure 3 and Table 4). The results from recalled total sun exposure suggest that its effect may be more evident in low than in high latitudes. Fourthly, reasonably consistent with the pattern for sunbathing and recreational sun exposure, sunburn in childhood increases the risk of melanoma at all body sites but increases risk on the trunk and limbs more than it does on the head and neck, and these patterns are largely consistent across latitudes (Figure 4 and Table 5).

Table 5 pORs and 95% CI for ever having sunburnt as a child and as an adult within latitude regions

Sunburn history[a]	Controls	Cases by melanoma site[b]											
	Controls	Trunk			Limbs			Head and neck			All		
	No	No	pOR1[c]	pOR2[d]	No	pOR1[c]	pOR2[d]	No	pOR1[c]	pOR2[d]	No	pOR1[c]	pOR2[d]
Before age of 15													
High latitudes													
Never[e]	2012	397	1	1	673	1	1	188	1	1	1305	1	1
At least once	1248	391	1.4 (1.2, 1.7)	1.2 (1.0, 1.5)	473	1.5 (1.2, 1.8)	1.2 (1.0, 1.4)	129	1.3 (1.0, 1.7)	1.1 (0.8, 1.4)	1025	1.4 (1.3, 1.7)	1.2 (1.0, 1.4)
Middle latitudes													
Never[e]	991	208	1	1	228	1	1	78	1	1	676	1	1
At least once	1262	361	1.5 (1.2, 2.0)	1.4 (1.0, 1.8)	435	1.5 (1.2, 1.9)	1.2 (1.0, 1.6)	111	1.4 1.0, 2.1)	1.2 (0.8, 1.8)	1169	1.5 (1.3, 1.8)	1.3 (1.1, 1.5)
Low latitudes													
Never[e]	557	145	1	1	208	1	1	123	1	1	486	1	1
At least once	439	187	1.6 (1.2, 2.2)	1.5 (1.1, 2.1)	226	1.6 (1.2, 2.2)	1.4 (1.1, 2.0)	89	1.4 (1.0, 2.2)	1.2 (0.8, 1.8)	518	1.6 (1.2, 2.0)	1.4 (1.1, 1.8)
After age of 20													
High latitudes													
Never[e]	1357	268	1	1	448	1	1	140	1	1	901	1	1
At least once	1260	369	1.5 (1.2, 1.9)	1.4 (1.1, 1.7)	413	1.3 (1.1, 1.7)	1.2 (1.0, 1.5)	117	1.1 (0.8, 1.6)	1.0 (0.8, 1.4)	939	1.3 (1.1, 1.6)	1.2 (1.0, 1.5)
Middle latitudes													
Never[e]	727	223	1	1	246	1	1	84	1	1	627	1	1
At least once	1511	337	1.4 (1.1, 1.9)	1.4 (1.1, 1.8)	415	1.2 (0.9, 1.5)	1.1 (0.8, 1.4)	104	1.3 (0.9, 1.8)	1.2 (0.8, 1.7)	1218	1.2 (1.0, 1.5)	1.1 (0.9, 1.4)
Low latitudes													
Never[e]	722	217	1	1	297	1	1	167	1	1	693	1	1
At least once	299	123	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	143	1.1 (0.8, 1.5)	1.1 (0.8, 1.4)	48	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	328	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)

[a]Data for sunburn before age of 15 and after age of 20 were available for 14 and 13 studies, respectively (Table 1).
[b]Melanoma site data were not available for one study.[17]
[c]Adjusted for age and sex only.
[d]Adjusted for age, sex, hair colour, ability to tan and freckling.
[e]Never sunburnt was set as reference group.

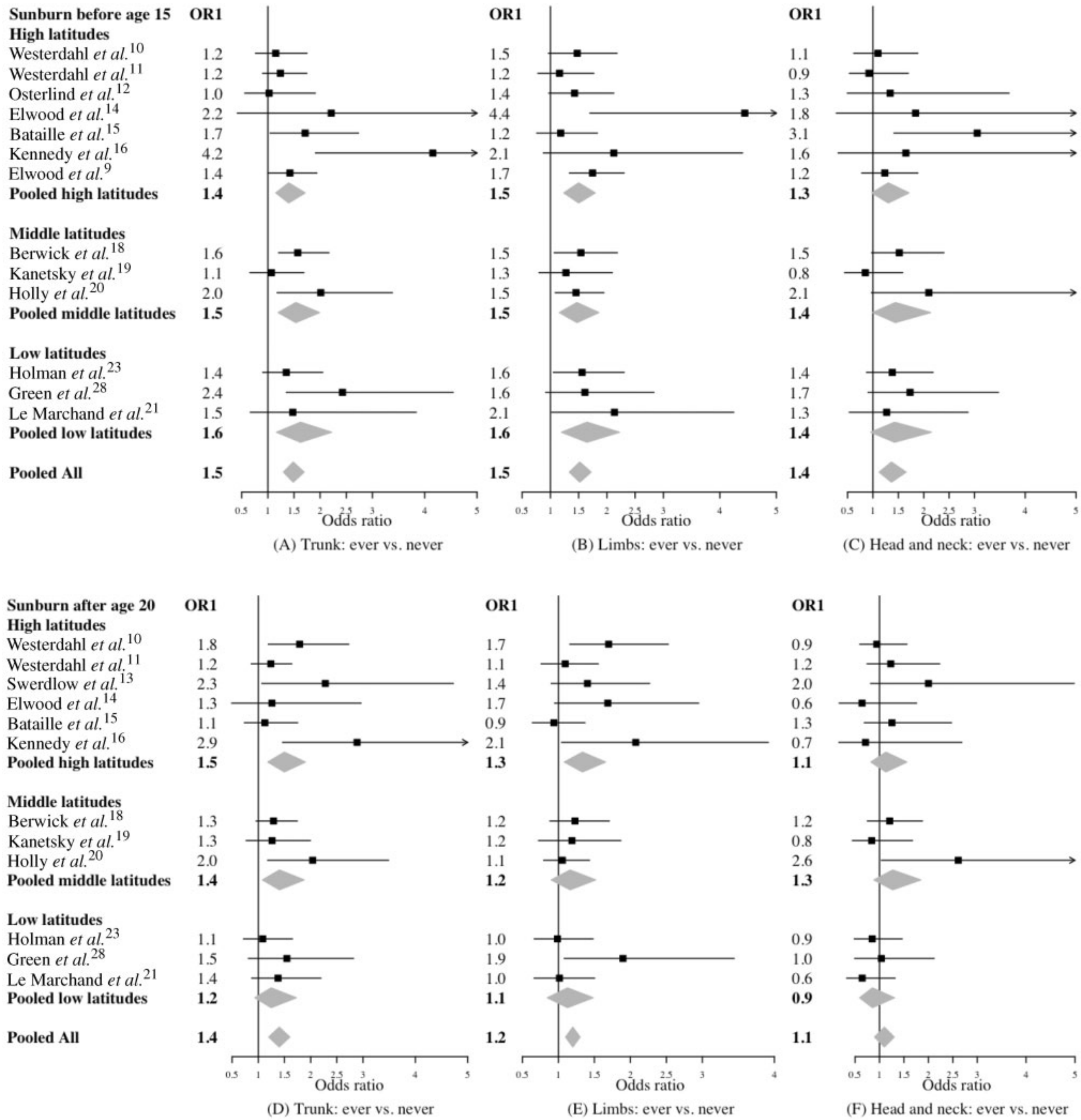

Figure 4 Forest plots of the association between (A–C) ever sunburn before age 15 and (D–F) ever sunburn after age 20 and melanoma risk by tumour sites. Each line represents results from an individual study, with the length of the horizontal line indicating the 95% CIs, and the square box indicating the study-specific OR (OR1). pOR1s and 95% CIs are represented by grey diamonds

Sunburn in adulthood shows a similar pattern but with little evidence of an increase in risk of melanoma of the head and neck.

The pooled analyses were consistent in identifying sunbathing, recreational sun exposure and reported sunburn as being important risk factors for melanoma on body sites that are not usually exposed to the sun. Although the relative risks for these exposures were similar across latitude bands, the baseline risk in the least-exposed categories, and hence the absolute risk, would be expected to increase with increasing ambient UV. Sunburn history has been considered as an important risk factor for melanoma, consistent with the view that host factors including sensitivity to excessive sun exposure are important in melanoma. Our pooled analysis confirmed this association for tumours on the trunk and limbs, and less conclusively, for the head and neck. Our pORs for ever having had sunburn as a child and as an adult were similar to results adjusted for publication bias reported in the meta-analysis by Gandini *et al*.[3] Whiteman and Green[27] reviewed 16 case–control studies regarding sunburn history and estimated a 2-fold increased risk of melanoma in those ever sunburned, with a 3.7-fold increase risk among those in the highest category of sunburn exposure, compared with those never sunburned.

Meta-analyses of published data have shown an inverse association between occupational sun exposure and risk of melanoma overall.[1–4] We did not find a significant inverse association in this pooled analysis. In addition, there was some evidence that occupational sun exposure increased risk, but only for melanoma of the head and neck at low latitudes (Figure 2). It is possible that participants living in the high- or middle-latitude regions were not exposed to sufficiently high ambient UV radiation to increase melanoma risk, even when they were in the highest occupational sun-exposure category. Self-selection against outdoor work by fair-skinned people living at low latitudes, which we have demonstrated, could also lower the estimates of melanoma risk in those who had high occupational exposure.

Whilst the 'two pathways to melanoma' hypothesis suggests that more continuous sun exposure is more relevant for melanoma on the head and neck and intermittent exposure to melanoma on the trunk and limbs, we found only a weak relationship between occupational sun exposure and risk of melanoma on the head and neck, particularly in temperate climates. However, increased total sun exposure was associated with melanoma on the limbs at low latitudes, which is probably due to the fact that distal parts of the limbs are usually exposed to the sun in many people, particularly in areas of high ambient UV.

The presence of SK has been reported as a risk factor for melanoma in a few studies.[28,29] Green and O'Rourke[28] reported an OR of 2.8 for SK on the face, and in a joint UK and Australia study, the presence of 10 or more SK compared with none on the left forearm was associated with an OR of 4.7.[29] In our pooled data analysis we found that SK are a risk factor for melanoma overall and particularly for primaries in usually sun-exposed sites, although the analysis is limited by the fact that only three studies included SK as a measure. Our estimated pORs for presence of any SK compared with none for melanoma on the head and neck or limbs are similar to those of other studies. We have found no indication of an association between presence of SK and melanoma on the trunk.

SK are postulated to be caused by damage to the skin by solar UV radiation over a long period of time. In addition, they probably reflect inherent susceptibility to sun-caused skin damage and individual DNA repair deficiency.[30,31] Our analyses suggested that their presence was associated both with recreational and occupational sun exposure, but more strongly and consistently with the latter.

In conclusion, these pooled data analyses suggest melanoma risk at different body sites is associated with different amounts and patterns of sun exposure. Recreational sun exposure and sunburns are strong predictors of melanoma on less frequently sun-exposed body sites, at all latitudes. It is known that intermittent sun exposure is associated with DNA damage and induced immunosuppression,[32–35] and it seems likely that this more acute sun-induced damage is relevant to melanoma at all latitudes. In addition, more continuous sun exposure is important when exposure level is high, as occupational and total sun exposure at low latitudes and SK across latitudes showed a relationship to melanoma on more frequently sun-exposed body sites. These observations are consistent with the 'two pathways to melanoma' hypothesis recently explored.[5–8,36,37]

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Conflict of interest: None declared.

KEY MESSAGES

- Melanoma risk at different body sites is associated with different patterns of sun exposure.
- Recreational sun exposure and sunburn are strong predictors of melanoma on less frequently sun-exposed body sites, at all latitudes.
- More continuous sun exposure is important when exposure level is high, as occupational and total sun exposure at low latitudes and SK across latitudes showed a relationship to melanoma on more frequently sun-exposed body sites.

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