IJC
International Journal of Cancer

Challenges in assessing the sunscreen-melanoma association

Corina S. Rueegg[1], Jo S. Stenehjem[2], Matthias Egger[3], Reza Ghiasvand[1], Eunyoung Cho[4,5,6], Eiliv Lund[7], Elisabete Weiderpass[2,7,8,9], Adele C. Green[10,11] and Marit B. Veierød[1]

[1]Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway
[2]Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
[3]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[4]Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, RI
[5]Department of Epidemiology, Brown School of Public Health at Brown University, Providence, RI
[6]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[7]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway
[8]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[9]Genetic Epidemiology Group, Folkhälsan Research Center, and Faculty of Medicine, Helsinki University, Helsinki, Finland
[10]QIMR Berghofer Medical Research Institute, Brisbane, Australia
[11]CRUK Manchester Institute, University of Manchester, Manchester, United Kingdom

Whether sunscreen use affects melanoma risk has been widely studied with contradictory results. To answer this question we performed a systematic review of all published studies, accounting for sources of heterogeneity and bias. We searched for original articles investigating the sunscreen-melanoma association in humans to February 28, 2018. We then used random-effects meta-analysis to combine estimates of the association, stratified by study design. Stratified meta-analysis and meta-regression were used to identify sources of heterogeneity. We included 21,069 melanoma cases from 28 studies published 1979–2018: 23 case–control (11 hospital-based, 12 population-based), 1 ecological, 3 cohort and 1 randomised controlled trial (RCT). There was marked heterogeneity across study designs and among case–control studies but adjustment for confounding by sun exposure, sunburns and phenotype systematically moved estimates toward decreased melanoma risk among sunscreen users. Ever- *vs.* never-use of sunscreen was inversely associated with melanoma in hospital-based case–control studies (adjusted odds ratio (OR) = 0.57, 95%confidence interval (CI) 0.37–0.87, $p_{heterogeneity} < 0.001$), the ecological

Key words: sunscreen, melanoma, skin cancer, meta-analysis, sun protection

Abbreviations: CI: confidence interval; GRADE: grading of recommendations assessment, development and evaluation; HR: hazard ratio; N: Nord; NOS: Newcastle-Ottawa scale; OR: odds ratio; p: *p* Value; RCT: randomised controlled trial; RR: rate ratio; SE: summary estimate; SPF: sun protection factor; USA: United States of America; UV: ultraviolet

Additional Supporting Information may be found in the online version of this article.

Conflict of interest: No conflict of interest for any of the authors.

CSR is the guarantor of the paper. CSR and MBV conceived and designed the study, CSR conducted the literature research, CSR and JSS conducted the study selection, CSR and MBV conducted the data extraction, CSR analysed the data, all authors interpreted the data, all authors wrote the paper, and all authors approved the final draft of the study. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The study's guarantor (CSR) affirms that the study is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as registered have been explained in the PROSPERO registry.

The funding sources had no role in the study conception, literature research, data extraction, data analysis and interpretation, writing of the study or the decision to submit it for publication.

Grant sponsor: FP7 People: Marie-Curie Actions (FP7-PEOPLE-2013-COFUND) to CSR; **Grant numbers:** 609020-Scientia Fellow, co-founded by the Institute of Basic Medical Sciences, University of Oslo; **Grant sponsor:** Kreftforeningen (Norwegian Cancer Society); **Grant numbers:** 6823329, 2197685, 5829980; **Grant sponsor:** National Institutes of Health to EC; **Grant numbers:** CA198216

DOI: 10.1002/ijc.31997

History: Received 13 Jun 2018; Accepted 2 Nov 2018; Online 16 Nov 2018

Correspondence to: Dr. Corina S. Rueegg, Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, P.O. Box 1122 Blindern, 0317 Oslo, Norway, Tel.: +47-228-40-231, Fax: +47-228-51-280, E-mail: c.s.rueegg@medisin.uio.no

study (rate ratio = 0.48, 95%CI 0.35–0.66), and the RCT (hazard ratio (HR) = 0.49, 95%CI 0.24–1.01). It was not associated in population-based case–control studies (OR = 1.17, 95%CI 0.90–1.51, $p_{heterogeneity} < 0.001$) and was positively associated in the cohort studies (HR = 1.27, 95%CI 1.07–1.51, $p_{heterogeneity} = 0.236$). The association differed by latitude ($p_{interaction} = 0.042$), region ($p_{interaction} = 0.008$), adjustment for naevi/freckling ($p_{interaction} = 0.035$), and proportion of never-sunscreen-users ($p_{interaction} = 0{\cdot}012$). Evidence from observational studies on sunscreen use and melanoma risk was weak and heterogeneous, consistent with the challenges of controlling for innate confounding by indication. The only RCT showed a protective effect of sunscreen.

What's new?

Effectiveness of sunscreen in reducing UV-induced skin damage has been proven in experimental studies, but effectiveness in reducing melanoma in humans remains inconclusive. This is the first meta-analysis to analyze data from four study designs, stratify hospital- and population-based case–control studies, and include as many as five prospective studies. Evidence from observational studies on the sunscreen-melanoma association was heterogeneous, consistent with the challenges of controlling for innate confounding by indication. The only randomized controlled trial showed a protective effect. Public health recommendations should place greater emphasis on the proper use of sunscreen in conjunction with other means of sun protection.

Introduction

Cutaneous melanoma is the leading cause of skin cancer death,[1] accounting for 1–2% of all cancer deaths.[2,3] In 2015, melanoma occurred in 351,880 people and resulted in 59,782 deaths worldwide.[4]

The aetiology of cutaneous melanoma (hereafter termed melanoma) is a complex interaction of genetic, epigenetic and environmental risk factors.[5,6] Melanoma is mainly caused by ultraviolet (UV) radiation exposure in sun-sensitive subjects and it is estimated that more than 85% of melanoma cases in Europe are attributed to sun exposure.[7–10] Genomic sequencing confirms that the majority of the mutations in melanomas are caused by UV radiation.[11,12] It follows that melanoma is preventable through reduction of UV exposure, making primary prevention highly cost-effective.[10,13] Use of sunscreen is generally regarded as a major primary prevention measure alongside seeking shade, wearing protective clothes, and avoiding sunbeds,[14–17] and is a popular method of sun protection.[18] However effectiveness of sunscreen to reduce UV-induced damage to the skin has been proven only in experimental studies,[19] and evidence of its effectiveness in preventing melanoma in humans is inconclusive. Only one randomised controlled trial (RCT) of daily sunscreen application to prevent skin cancer has been performed, showing a reduced risk of melanoma (hazard ratio = 0.50, p value = 0.051) in those randomly assigned to daily compared to discretionary sunscreen use.[20,21] The compliance to daily sunscreen application was approximately 75%; the majority of participants in the discretionary sunscreen group either did not apply sunscreen (38%) or applied at most once or twice a week (35%).[21] All other studies of sunscreen and melanoma risk have been observational, mainly case–control, yielding contradictory results.[22–40]

The main problem with investigating this question with observational studies is confounding by indication, i.e. sunscreen users tend to be more susceptible to melanoma and more exposed to the sun than non-users *a priori*.[41] The contradictory and heterogeneous results of previous systematic reviews reflect this problem.[42–48] In the current study we aimed to overcome these known limitations by performing in-depth statistical analyses, comparing different patterns of sunscreen use and identifying the major sources of heterogeneity. Furthermore we wanted to update the field with new evidence.

Specifically, we aimed to 1) systematically summarise the existing literature on sunscreen use and melanoma in humans; 2) investigate the effect of ever- *vs.* never-use on melanoma risk; 3) assess the effect of different levels and patterns of sunscreen use; 4) identify sources of bias and between-study heterogeneity; and 5) describe the relationship between site of sunscreen application and site of melanoma.

Methods

The study protocol of this systematic review (PROSPERO ID: CRD42017063980[49]) was written according to PRISMA-P[50,51] and the reporting in this article follows the PRISMA recommendations.[52]

Data sources and searches

We searched the electronic databases PubMed (including Medline), Embase and Cochrane Database of Systematic Reviews with search terms adapted for each of them (Supporting Information Appendix **I**). In addition, we searched the protocol database PROSPERO to identify relevant ongoing reviews and screen their reference lists. To

ensure literature saturation we also screened the reference lists of relevant published reviews.

Study selection

We included all original articles published by 28.02.2018 in peer-reviewed journals arising from case–control studies, ecological studies (population-level rather than individual-level observational studies), cohort studies, intervention studies and clinical trials performed in humans with melanoma as endpoint and sunscreen use as exposure. We only included studies where the exposure clearly preceded the outcome. We had no restrictions regarding length of follow-up or language.

Studies on childhood melanoma were included in the qualitative synthesis but excluded from the meta-analyses because UV exposure does not seem to be a risk factor in the aetiology of melanoma occurring before 15 years of age.[53]

All records from the literature research were imported into EndNote (Thomson Reuters, version X8), de-duplicated and then imported to Microsoft Excel (version 2010) to perform the selection process. Study selection was performed by two independent reviewers (CSR and JSS) by first screening titles and abstracts, then screening full texts. We calculated the proportion of agreement between the two reviewers for each of the two selection steps. Discrepancies were solved by discussion between the two reviewers. References were excluded based on the hierarchical exclusion criteria displayed in Figure 1.

Data extraction and quality assessment

Data were extracted using a data extraction form[54] (Supporting Information Appendix **II**) after piloting the process with three studies of different design and publication year. Data extraction was performed by CSR and the estimates of interest were double-checked by MBV. Discrepancies were discussed among a subgroup of the authors until consensus was reached. We contacted study authors and requested the estimate of interest if it was not reported but the respective analysis was described. If necessary, additional articles from the same study were used to complete data extraction.

For each study we extracted the following estimates on the association of sunscreen use and melanoma, if reported: a) ever- *vs.* never-use of sunscreen from minimally adjusted model; b) ever- *vs.* never-use of sunscreen from maximally adjusted model; c) three-level estimate of sunscreen use from maximally adjusted models for frequency of use, sun protection factor (SPF) used and duration of use (Supporting Information Table 1). The minimally and maximally adjusted model was the model with no or only basic adjustment and the model with most variables included, respectively, in the original study. We chose the ever- *vs.* never-use label because most underlying studies analysed ever- *vs.* never-use or use *vs.* no use of sunscreen based on their questionnaires. In addition, we extracted bibliographic and demographic information of the studies, assessment of sunscreen use, and study quality to identify sources of heterogeneity. Study quality was assessed based on the Cochrane Handbook's tool for assessing risk of bias[54] and the Newcastle-Ottawa Scale (NOS).[55] Level of bias (high, medium, low) was rated by the data extractor (CSR) after reading the methods part of the study and blinded toward the study results.

Data synthesis and analysis

All analyses were performed in STATA (StataCorp LP, Release 14.1). In the analysis of ever- *vs.* never-use of sunscreen we used the method of Hamling and colleagues to aggregate estimates if more than two categories of sunscreen use were reported.[56] For example, if a study reported an estimate with three categories of sunscreen use: never, sometimes, and often, we aggregated 'sometimes' and 'often' into ever-use. This was done to make the estimates across studies more comparable. Without this aggregation we would end up pooling estimates across studies where some estimates reflected the effect of the highest sunscreen category *vs.* no sunscreen use, while others reflected ever- *vs.* never use. The same method was used to change the reference category, if necessary. To investigate three-level, different patterns and high sunscreen use, we extracted all estimates with at least three categories on frequency of sunscreen use, SPF used, and duration of use. For each study, the lowest and highest categories were categorised as lowest and highest groups, respectively and all intermediate categories were aggregated.[57]

We performed random-effects meta-analysis[58] stratified by study design for the minimally and maximally adjusted estimates of ever- *vs.* never-use of sunscreen, and for each three-level variable on sunscreen use, comparing the intermediate to the lowest level and the highest to the lowest level. Heterogeneity between studies was tested with the Q-test.[59] The I^2-index was used to quantify the extent of heterogeneity, with I^2-values >50%, and > 75% being indicative of moderate and high heterogeneity, respectively.[54] We included one case-cohort study that was analysed together with the cohort studies because it was conducted prospectively.

To explore sources of heterogeneity we performed random-effects meta-analyses stratified by important variables predefined in the protocol, and univariable random-effects meta-regression analyses, on the maximally adjusted ever- *vs.* never-use estimate. We considered the following variables: study design; year of the end of the data collection (1975–1984, 1985–1999, 2000–2012); mean latitude (>42°N, ≤42°N); region; most frequent melanoma site in the study population (trunk, head/neck, lower limbs); duration of sunscreen use (not specified, specified period, lifetime); whether sunscreen use was assessed in detail or not; level of bias (high, medium, low); whether or not the estimate of interest was adjusted for nevi and/or freckles, history of sunburn, or sun exposure; and, the proportion of participants with blond/red hair (<30%, ≥30%), blue/green eyes (<50%, ≥50%), history of

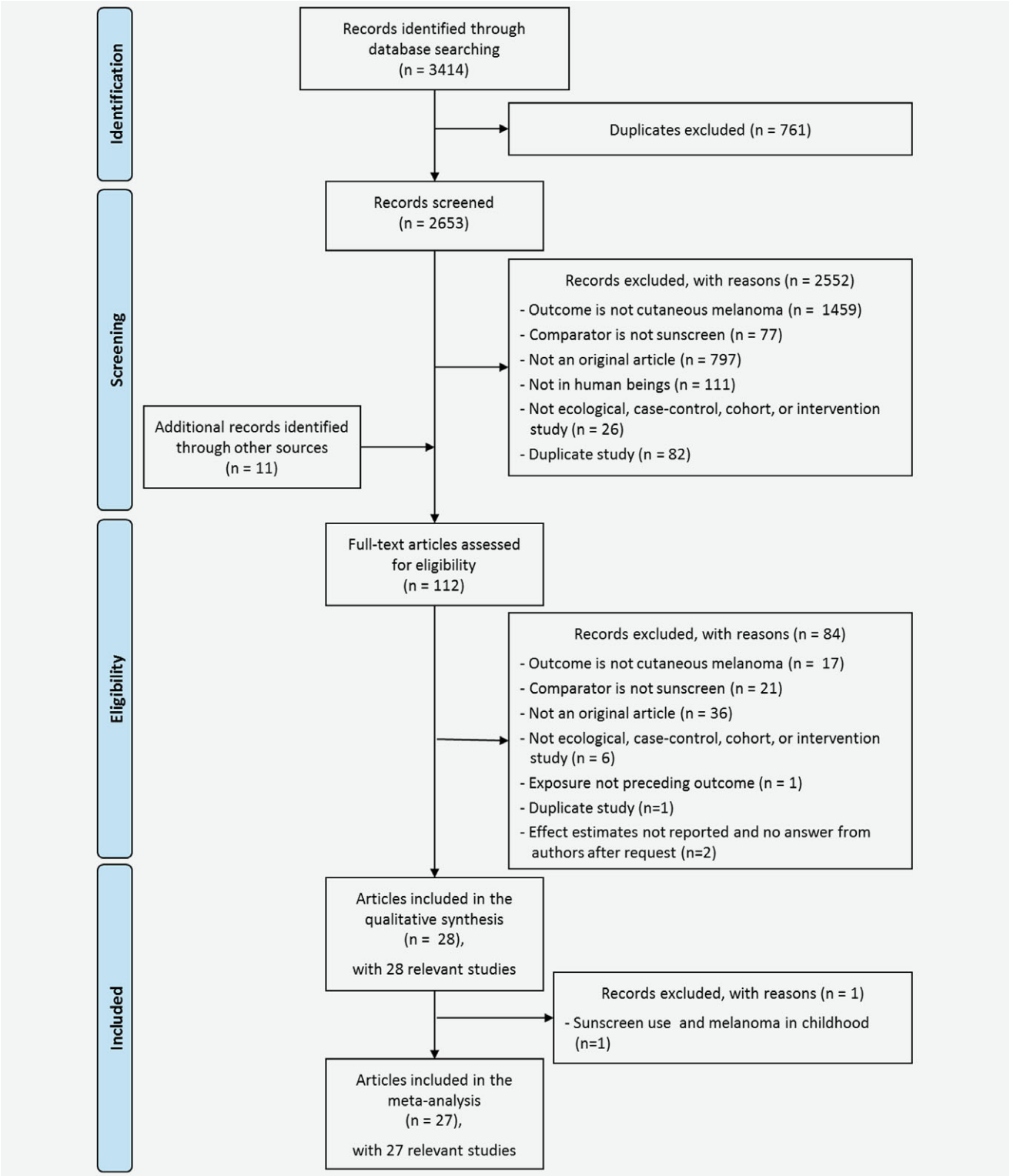

Figure 1. Flow diagram on inclusion of studies. The figure shows the process of selecting eligible studies for the current review and meta-analysis. [Color figure can be viewed at wileyonlinelibrary.com]

sunburn (<75%, ≥75%), and who never used sunscreen (<55%, ≥55%). The cut-offs in the proportions were chosen based on the distribution of the respective characteristic across the studies. We used tau-squared to estimate the remaining between-study variance in the meta-regression model by residual maximum likelihood.[58]

Publication bias was investigated by the funnel plot and Egger's regression test for the maximally-adjusted ever-never estimates.[60] We used contour-enhanced funnel plots to define regions of the plot in which a new study would have to be located to change the statistical significance of the meta-analysis and thereby assess the robustness of the current meta-analysis.[61]

Grading of the evidence

The confidence in the cumulative evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[62] GRADE rates the quality of evidence across the domains risk of bias, consistency, directness, precision, and publication bias and rates it into one of the four categories *high* (further research is very unlikely to change our confidence in our effect estimate), *moderate* (further research is likely to change our confidence in our effect estimate), *low* (further research is very likely to change our effect estimate), or *very low* (our effect estimate is very uncertain).

Results

Study selection

We identified 3,414 records in the three databases Pubmed (n = 1,054), Embase (n = 2,132), and Cochrane (n = 228), of which 761 were duplicates and 2,552 were rated as ineligible on first screening by two reviewers (agreement = 95%; Fig. 1). Eleven studies were identified through other sources resulting in the assessment of 112 full-texts, of which 84 (agreement = 89%) were excluded, leaving 28 studies included in the qualitative synthesis and 27 studies in the meta-analysis after exclusion of the childhood melanoma study.[32]

Characteristics of included studies

The 28 articles (11 hospital-based case–control studies,[22,23,31,33–35,37,39,63–65] 12 population-based case–control studies,[24–30,32,36,38,40,66] one ecological study,[67] three cohort studies (one of them a case-cohort study),[68–70] and one RCT[21]) were published between 1979 and 2018, included 208 to 178,155 participants and 33 to 11,535 melanoma cases: in total, 21,069 melanoma cases, who originated from Australia (n = 4), Europe (n = 16), Brazil (n = 2) and the USA (n = 6; Table 1). The median latitude of the study locations was 43°N (range − 30°S-65°N). On average, 21% of participants (range 9–61%) were blond or red-haired, 47% (range 19–86%) blue or green eyed, 48% (range 28–70%) had freckles, and 55% (range 24–85%) were fair-skinned (Supporting Information Table 2). Most studies only assessed sunscreen use or sunscreen use frequency (Table 1). Fourteen studies defined a timeframe for the sunscreen use,[21,24,25,29,32,35,36,38,40,63,65–68] eight studies assessed the SPF used,[21,35–37,39,40,66,69] three the reapplication,[40,65,66] three the body sites or body coverage,[21,36,40] two the product used,[35,69] two the thickness,[21,40] and one study the reasons for sunscreen use.[36]

Methodological quality of included studies

The methodological quality of the case–control studies was very heterogeneous with 11 hospital-based case–control studies based on non-representative cases and controls (Supporting Information Table 3). The ecological study, cohort studies and RCT fulfilled almost all of the methodological requirements.[54,55]

The method and detail of assessment of sunscreen use also varied greatly between the studies (Table 2); the same was true for the level of adjustment of the "maximally-adjusted" estimate, though most studies adjusted in some way for UV exposure and some host factors of participants.

Ever sunscreen use and melanoma risk

The forest plot of minimally-adjusted estimates showed substantial heterogeneity both within hospital-based (I^2 = 86%, $p < 0.001$) and population-based case–control studies (I^2 = 80%, $p < 0.001$), and between the different study designs (Fig. 2).

The forest plot of maximally-adjusted estimates showed that adjustment moved most estimates toward a more reduced risk of melanoma among sunscreen users (Figs. 2 and 3) though substantial heterogeneity remained (Fig. 3), especially within case–control studies (I^2 = 86%, $p < 0.001$ for hospital-based; 81%, $p < 0.001$ for population-based) but also between study designs. We found an inverse sunscreen-melanoma association in hospital-based case–control studies (summary odds ratio (OR) = 0.57, 95%CI 0.37–0.87), the ecological study (rate ratio (RR) = 0.48, 95%CI 0.35–0.66), and the RCT (hazard ratio (HR) = 0.49, 95%CI 0.24–1.01). No association was found on summarising results from population-based case–control studies (OR = 1.17, 95%CI 0.90–1.51) and a positive sunscreen-melanoma association was seen on summarising the three cohort studies (HR = 1.27, 95%CI 1.07–1.51).

Three-level estimates of sunscreen use and melanoma risk

Sixteen studies reported at least a three-level estimate on the frequency of sunscreen use (never, sometimes, often/always),[22,24–26,29–31,33,35,36,38,40,63,68–70] six studies distinguished low from high SPF sunscreen use (compared to no use),[35–37,40,66,69] and four studies distinguished short- from long-term use of sunscreen (compared to no use)[24,25,35,36] (Supporting Information Table 4). We did not observe a trend or U-shaped association comparing the intermediate- and high-users of sunscreen to the non-users for each of the three-level estimates (Supporting Information Fig. 1). The summary estimates comparing sometimes- to never-use were 1.07 (95% CI 0.80–1.42) in the hospital-based case–control studies, 1.13 (95%CI 0.98–1.30) in the population-based case–control studies, and 1.38 (95%CI 1.17–1·62) in the cohort studies. The summary estimates comparing often/always- to never-use were 1.01 (95%CI 0.38–2.67) in the hospital-based case–control studies, 1.01 (95%CI 0.67–1.52) in the population-based case–control studies, and 1.32 (95%CI 1.10–1.59) in the cohort studies (Supporting Information Fig. 1A).

Table 1. Overview of the studies included (n = 28)

First author (year)	Data collection	Country	Matching[1]	Total no. of participants	No. of cases	Proportion of males (%)	Age range at dx (mean)	Sunscreen information assessed[2]
Hospital-based case–control studies								
Klepp (1979)[22]	1974–1975	Norway	Unmatched	209	78	61	>20 (nr)	Questionnaire: sunscreen use frequency during solar irradiation
Graham (1985)[23]	1974–1980	USA	Unmatched	420	218	100	nr (nr)	Interview: sunscreen use
Ródenas (1996)[31]	1989–1993	Spain	Unmatched	243	105	35	20–79 (52)	Interview: sunscreen use frequency
Wolf (1998)[33]	1993–1994	Austria	Unmatched	512	193	42	18–89 (54)	Questionnaire: sunscreen use frequency before formation of melanoma
Espinosa A. (1999)[34]	1990–1994	Spain	Individual (age, sex)	351	116	47	21–87 (56)	Questionnaire: sunscreen use
Naldi (2000)[35]	1992–1995	Italy	Unmatched	1,080	542	42	nr (nr)	Interview: sunscreen use frequency and duration, product type used, SPF used
Bakos (2002)[37]	1995–1998	Brazil	Individual (age, sex, Ethnic group, region)	309	103	nr	20–84 (53)	Questionnaire: sunscreen use, SPF used
Nikolaou (2008)[64]	2000–2004	Greece	Individual (age, sex)	400	200	49	19–84 (53)	Interview: sunscreen use
Klug (2010)[39]	1991–1992	USA	Frequency (age, sex, Ethnic group, study site)	1,662	717	55	20–79 (nr)	Interview: sunscreen use, sunscreen use ≥8 SPF, regular use ≥8 SPF
Luiz (2012)[63]	2004–2008	Brazil	Frequency (age, sex)	424	202	50	15–79 (48)	Interview: sunscreen use frequency in childhood, lifetime sunscreen use frequency
Vranova (2012)[65]	2010–2011	Czech Republic	Frequency (age)	518	216	46	nr (54)	Questionnaire: sunscreen use frequency in childhood, sunscreen use frequency in adulthood, number of sunscreen applications when sunbathing
Population-based case–control studies								
Holman (1986)[24]	1980–1981	Australia	Individual (age, sex, electoral subdivision)	1,014	507	46	10–79 (nr)	Interview: sunscreen use frequency and duration
Østerlind (1988)[25]	1982–1985	Denmark	Frequency (age, sex)	1,400	474	41	20–79 (52)	Interview: sunscreen use frequency and duration
Beitner (1990)[26]	1978–1983	Sweden	Individual (age, sex)	1,028	523	45	nr (nr)	Questionnaire: sunscreen use frequency
Herzfeld (1993)[27]	1982–1983	USA	Unmatched	739	324	100	>18 (nr)	Interview: sunscreen use frequency
Autier (1995)[28]	<1990	France, Germany, Belgium	Individual (municipality)	856	418	nr	nr (nr)	Questionnaire: sunscreen use
Holly (1955)[29]	nr	USA	Frequency (age)	1,382	452	0	25–59 (42)	Questionnaire: sunscreen use frequency in 5 years previously
Westerdahl (1995)[30]	1988–1990	Sweden	Individual (age, sex, parish)	1,040	400	49	15–75 (nr)	Questionnaire: sunscreen use frequency when spending time in the sun
Whiteman[3] (1997)[32]	1994	Australia	Individual (sex, school, grade)	208	52	nr	3–14 (nr)	Questionnaire: sunscreen use frequency at school and on holidays in childhood

(Continues)

Table 1. Overview of the studies included (n = 28) (Continued)

First author (year)	Data collection	Country	Matching[1]	Total no. of participants	No. of cases	Proportion of males (%)	Age range at dx (mean)	Sunscreen information assessed[2]
Westerdahl (2000)[36]	1995–1997	Sweden	Individual (age, sex, parish)	1,449	558	50	16–80 (nr)	Questionnaire: sunscreen use frequency, regular use, age at first use, SPF used, body parts applied, reasons for sunscreen use
Youl[4] (2002)[38]	1987–1994	Australia	Individual (age, sex, region)	406	201	50	15–19 (17)	Interview: sunscreen use frequency at school, at home, on holidays for ages 5–10, 10–15, ≥15 years
Lazovich (2011)[40]	2004–2009	USA	Frequency (age, sex)	2,268	1,167	40	25–59 (nr)	Interview: lifetime sunscreen use frequency during outdoor activities, SPF used, thickness applied, amount of skin covered, reapplication, routine use
Savoye (2018)[66]	1989–2008	France	Individual (age, birth county, education)	1,219	366	0	nr (57)	Questionnaire: sunscreen use at ages ‹15, 15–25, ›25 years, SPF used, re-application
Prospective ecological study								
Kojo (2006)[67]	1920–1985	Finland	na	11,535	11,535	47	nr (nr)	Sales of sunscreen preparations 5 and 10 years before diagnosis
Prospective cohort studies								
Cho (2005)[68]	1976–2000	USA	na	178,155[5]	535[5]	32[5]	nr (53)	Questionnaire: sunscreen use frequency at the pool or beach as a teenager and in the past summer
Ghiasvand (2016)[69]	1991–2012	Norway	na	143,844	722	0	42–83 (60)	Questionnaire: sunscreen use in low and high latitudes, SPF used, brands of sunscreen used
Stenehjem[6] (2017)[70]	1999–2012	Norway	na	1,755	112	100	33–84 (58)	Questionnaire: present sunscreen use frequency
Randomised controlled trial								
Green (2011)[21]	1992–2006	Australia	na	1,621	33	44	nr (nr)	Intervention to daily apply sunscreen on head, neck, arms and hands, weight of returned sunscreen bottles, questionnaire on weekly sunscreen use frequency

Abbreviations: dx, diagnosis; na, not applicable; nr, not reported; no., number; SPF, sun protection factor.
[1]Only relevant for case–control studies; variables given as reported in the underlying article.
[2]This column gives an overview of the sunscreen information assessed in the study. The detailed descriptions of the sunscreen estimates used in the meta-analyses are given in Table 2 and Supporting Information Table 4.
[3]Sunscreen and melanoma in childhood.
[4]Sunscreen and melanoma in adolescence.
[5]Data received upon author request with some differences to the article cited.
[6]Case-cohort study design.

Table 2. Description of the two-level estimates extracted for each study (described exactly as reported in the articles)

First author (Publ. year)	Estimate reported in the publication	Aggregated[1] two-level estimate	Effect measure	Minimally adjusted estimate (95% CI)	Adjustment of minimally adjusted estimate[2]	Maximally adjusted estimate (95% CI)	Adjustment of maximally adjusted estimate[2]
Hospital-based case–control studies							
Klepp (1979)[22]	Use of any kind of sun lotion/oil during solar irradiation: almost never - very rarely - sometimes - quite often - always	Use of any kind of sun lotion/oil during solar irradiation: almost never - ever	OR	2.05 (1.06–4.03)	None	nr	
Graham (1985)[23]	Use of sun screening lotion: no - yes	Use of sun screening lotion: no - yes	OR	2.20 (1.20–4.10)	Age	nr	
Ródenas (1996)[31]	Sunscreen use: never - sometimes - always	Sunscreen use: never - ever	OR	0.38 (0.20–0.70)	None	0.43 (0.21–0.90)	Age, skin colour, skin type, recreational sun exposure, occupational sun exposure, nevi
Wolf (1998)[33]	Use of sunscreens: never - rarely - often	Use of sunscreens: never - ever	OR	1.74 (1.18–2.57)	Age, sex	2.15 (1.37–3.37)	Age, sex, skin colour, sunbaths, sunburns
Espinosa A. (1999)[34]	Use of sunscreens: no - yes	Use of sunscreens: no - yes	OR	0.38 (0.28–0.63)[3]	None	0.45 (0.33–0.67)[3]	Skin type, freckles, age
Naldi (2000)[35]	Sunscreen use: never - sometimes - often	Sunscreen use: never - ever	OR	1.14 (0.89–1.45)	None	0.90 (0.68–1.18)	Age, sex, demographic area, education, skin colour, eye colour, hair colour, freckles, nevi, sunburns, tanning pattern, sunny holiday weeks per year
Bakos (2002)[37]	Sunscreen use habit: never - SPF <8, SPF 8–15, SPF 15+	Sunscreen use habit: never - ever (all SPF)	OR	0.46 (0.29–0.74)[3]	None	0.34 (0.18–0.63)[3]	Eye colour, hair colour, phototype, freckles, nevi, dysplastic nevi, physical protection, sunburn
Nikolaou (2008)[64]	Sunscreen use: never/rarely - during summer/sunny months	Sunscreen use: never/rarely - during summer/sunny months	OR	0.56 (0.34–0.90)	Conditional regression	0.37 (0.14–0.98)	Age, gender, phototype, skin colour, outdoor leisure activities, weeks/year of sun exposure, sunburns <20 years of age, common nevi, atypical nevi, lentigenes
Klug (2010)[39]	Sunscreen use: no use - ever use	Sunscreen use: no use - ever use	OR	1.05 (0.82–1.35)	Matched logistic regression analysis	0.90 (0.70–1.19)	Gender, age, study site, Ethnic group, ambient resident UV, hours outdoors, tan type, sunburns, gender, age group, study site

(Continues)

Table 2. Description of the two-level estimates extracted for each study (described exactly as reported in the articles) (Continued)

First author (Publ. year)	Estimate reported in the publication	Aggregated[1] two-level estimate	Effect measure	Minimally adjusted estimate (95% CI)	Adjustment of minimally adjusted estimate[2]	Maximally adjusted estimate (95% CI)	Adjustment of maximally adjusted estimate[2]
Luiz (2012)[63]	Lifetime sunscreen use: never/almost never - occasionally - modified - often	Lifetime sunscreen use: never/almost never - ever	OR	0.53 (0.22–1.24)	Age, sex, education	0.34 (0.11–1.01)	Age, sex, education, ethnicity, eye colour, history of pigmented lesion removal, sunburns age 5–19, severe lifetime sunburns
Vranova (2012)[65]	Use of the sunscreen in the adulthood: never - occasionally - regularly	Use of the sunscreen in the adulthood: never - ever	OR	0.63 (0.36–1.12)[4]	None	0.19 (0.09–0.43)[4]	Freckles/nevi, sunburns in childhood, sunscreen in childhood, sunbathing in adulthood, sun exposure, time of day of sun exposure, holidays at seaside, holidays in mountains, solarium use
Population-based case–control studies							
Holman (1986)[24]	Use of sunscreens: never - <10 years - ≥10 years	Use of sunscreens: never - ever	OR	nr		1.11 (0.82–1.49)	Age, sex, electoral subdivision, chronic and acute skin reaction to sunlight, hair colour, ethnic origin, age at arrival in Australia
Østerlind (1988)[25]	Use of sunscreens: never - <10 years - ≥10 years	Use of sunscreens: never - ever	OR	1.23 (0.98–1.55)[4]	None	nr	
Beitner (1990)[26]	Employment of sun protection agents: never - rarely - often/very often	Employment of sun protection agents: never - ever	OR	nr		1.59 (1.17–2.15)[3]	Age, sex, hair colour
Herzfeld (1993)[27]	Using sunscreens: no - yes	Using sunscreens: no - yes	OR	0.81 (0.58–1.12)	None	nr	
Autier (1995)[28]	Regular sunscreen use: never - ever	Regular sunscreen use: never - ever	OR	1.59 (1.18–2.14)	Conditional regression	1.50 (1.09–2.06)	Age, sex, hair colour, holiday weeks in sunny resorts, municipality
Holly (1995)[29]	Use of sunscreen 5 years before diagnosis: never - sometimes - almost always	Use of sunscreen 5 years before diagnosis: never - ever	OR	0.67 (0.51–0.87)[4]	None	0.52 (0.37–0.73)	Sunburns ≤12 years, skin reaction to sun, hair colour, nevi, complexion, maternal ethnicity, history of skin cancer, age
Westerdahl (1995)[30]	Use of sunscreens: never - sometimes - almost always	Use of sunscreens: never - ever	OR	1.65 (1.24–2.20)	Matched analysis	1.47 (1.08–2.01)	Sunburns, sunbathing in summer, outdoor employment in summer, nevi, hair colour, eye colour, freckling, age, gender, parish

(Continues)

Int. J. Cancer: 144, 2651–2668 (2019) © 2018 The Authors. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC

Table 2. Description of the two-level estimates extracted for each study (described exactly as reported in the articles) (Continued)

First author (Publ. year)	Estimate reported in the publication	Aggregated[1] two-level estimate	Effect measure	Minimally adjusted estimate (95% CI)	Adjustment of minimally adjusted estimate[2]	Maximally adjusted estimate (95% CI)	Adjustment of maximally adjusted estimate[2]
Whiteman[5] (1997)[32]	Sunscreen use at school: never/rarely - sometimes - often - always	Sunscreen use at school: never/rarely - ever	OR	1.73 (0.97–3.08)	Matched analysis	1.01 (0.50–2.05)	Tanning ability, freckling, nevi, sex, school, grade
Westerdahl (2000)[36]	Use of sunscreens: never - sometimes - always initially of the year then sometimes - always	Use of sunscreens: never - ever	OR	1.35 (1.08–1.69)	Conditional regression	1.30 (0.90–1.90)	Hair colour, sunburns, sunbathing in summer, duration of sunbathing, age, sex, parish
Youl[6] (2002)[38]	Average lifetime index of sunscreen use at home: never/rarely - sometimes - often/ always	Average lifetime index of sunscreen use at home: never/rarely – ever	OR	1.05 (0.63–1.74)	Conditional regression	nr	
Lazovich (2011)[40]	Routine sunscreen use: nonusers in both decades - middle - high in both decades	Routine sunscreen use: nonusers in both decades - users in both decades	OR	1.33 (0.91–1.95)	Age, gender	1.12 (0.78–1.62)	Age, gender, phenotype risk score, moles, income, education, family history, sunburns, sun exposure, solarium use
Savoye (2018)[66]	Sunscreen use since age 25: no protection - SPF ‹8 - SPF 8–15 - SPF ›15	Sunscreen use since age 25: no protection - SPF ‹8/SPF 8-15/ SPF ›15	OR	1.71 (1.29–2.27)	Conditional regression	1.50 (1.10–2.06)	Skin sensitivity, nevi, freckling, eye colour, skin colour, hair colour, hours of recreational sun exposure, recreational UV score, sunburns ›25 years, age, birth county, education
Prospective ecological study							
Kojo (2006)[67]	Rate ratio for CM per 1 euro increase *per capita* in sunscreen sales	Rate ratio per 1 euro increase *per capita* in sunscreen sales	RR	nr		0.48 (0.35–0.66)	Age, gender, 10 year lag time, sunny resort holidays, holiday duration
Prospective cohort studies							
Cho[7] (2005)[68]	Percent of time of sunscreen use when outside at the pool or beach in the past summer: 0–25 - 50 - 75 - 100	Percent of time sunscreen used outside at the pool or beach in past summer: 0 - ≥25	HR	1.66 (1.41–1.96)	Age	1.42 (1.21–1.68)	Age, alcohol consumption, sunburns, childhood reaction to sun, hair colour, smoking, BMI, exercise, UV flux, moles, caffeine, family history of CM
Ghiasvand (2016)[69]	Sunscreen use from time-dependent analysis: never - ever	Sunscreen use from time-dependent analysis: never - ever	HR	1.45 (1.11–1.90)	Age, calendar year	1.13 (0.85–1.50)	Age, calendar year, hair colour, freckles, ambient UV, weeks sunbathing, sunburns, solarium use

(Continues)

Table 2. Description of the two-level estimates extracted for each study (described exactly as reported in the articles) (Continued)

First author (Publ. year)	Estimate reported in the publication	Aggregated[1] two-level estimate	Effect measure	Minimally adjusted estimate (95% CI)	Adjustment of minimally adjusted estimate[2]	Maximally adjusted estimate (95% CI)	Adjustment of maximally adjusted estimate[2]
Stenehjem[8] (2017)[70]	Present sunscreen use: never/rarely - often - almost always	Present sunscreen use: never/rarely - often/ almost always	HR	1.11 (0.69–1.76)	Age	1.10 (0.77–1.57)	Age, benzene exposure, education
Randomised controlled trial							
Green (2011)[21]	Random assignment to daily or discretionary sunscreen application to head and arms	Sunscreen application to head and arms: daily - discretionary	HR	0.50 (0.24–1.02)		0.49 (0.24–1.02)	Sex, skin type, nevi, history of cancer, sun exposure

Abbreviations: BMI, body mass index; CI, confidence interval; CM, cutaneous melanoma; HR, hazard ratio; nr, not reported; OR, odds ratio; Publ., publication; SPF, sun protection factor; RR, rate ratio; RCT, randomised controlled trial; UV, ultraviolet.
[1]If sunscreen exposure was reported in more than two categories they were aggregated into two categories (ever- *vs.* never-use).
[2]As reported by the authors.
[3]Estimate from individual-matched case–control study that did not take the matching into account in the statistical analysis, or did not report it.
[4]Estimate from frequency-matched case–control study that did not adjust for the matching variables in the statistical analysis, or did not report it.
[5]Sunscreen and melanoma in childhood.
[6]Sunscreen and melanoma in adolescence.
[7]Estimates received upon author request because they were not reported in the cited article.
[8]Case-cohort study design.

Sources of heterogeneity

The association between sunscreen use and melanoma from stratified analyses is presented in Table 3 and Supporting Information Figure 2. Studies conducted in lower latitudes showed an inverse association between sunscreen use and melanoma (summary estimate = 0.64, 95%CI 0.47–0.89 for studies ≤42°N) but there was no association in studies from higher latitudes (summary estimate = 1.09, 95%CI 0.83–1.44, $p_{interaction}$ = 0·042). Further statistically significant interactions were observed between the association of sunscreen use and 1) the region of the study ($p_{interaction}$ = 0.008); 2) adjustment for nevi and/or freckles (with an inverse association only in studies adjusting; $p_{interaction}$ = 0.035); and, 3) the proportion of sunscreen users in the study (with an inverse association of sunscreen use and melanoma only in studies where ≥55% of participants never used sunscreen; $p_{interaction}$ = 0.012). Remaining between-study variance was generally high after all stratifications (0.131 ≤ tau-squared ≤ 0.492).

Site of sunscreen application and site of melanoma

Two studies[21,36] assessed the body site of sunscreen application but neither related this to the site of melanoma.

Meta bias and quality of the cumulative evidence

The funnel plot (Supporting Information Fig. 3) shows the effect estimates from the individual studies against the precision of the studies (standard error in reversed scale), placing the largest studies toward the top. In the absence of bias and between-study heterogeneity, the plot would have resembled a symmetric inverted funnel, while our plot showed evidence of asymmetry confirmed by an Egger's test for small-study effects (p = 0.010). The funnel plot with contours of statistical significance (Supporting Information Fig. 4) shows which combinations of effect size and standard error would be required in an additional study, to change or maintain the statistical significance of the current summary estimate. In our meta-analysis, the plot showed that all of the current studies were lying in the area where future studies (if lying in the same area) would change the current effect estimate toward a significantly positive association between sunscreen use and melanoma risk (significant effect estimate >1).

The GRADE assessment resulted in an overall very low quality of evidence from the case–control studies, ecological study and cohort studies, and in a moderate quality of evidence from the RCT (Supporting Information Table 5).

Discussion

We assessed the sunscreen-melanoma association in 21,068 melanoma patients based on 28 studies in this comprehensive systematic review. The main body of evidence came from observational studies with high between-study heterogeneity. We found an inverse association between sunscreen use and melanoma in hospital-based case–control studies, the ecological study and the RCT. There was no association in the population-based case–control studies and positive association between sunscreen use

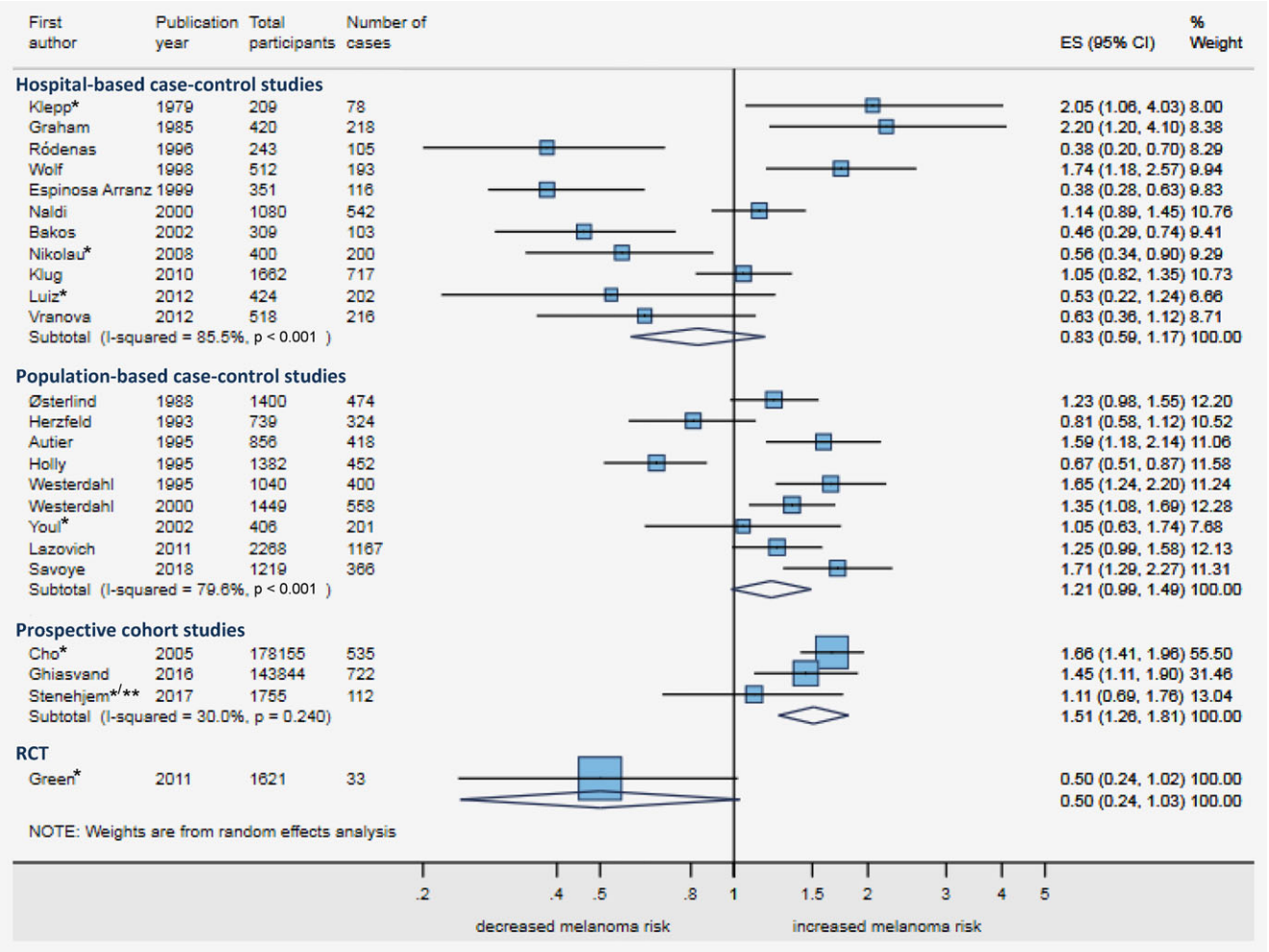

Figure 2. Forest plot for ever- *vs.* never-use of sunscreen and melanoma risk, minimally adjusted estimates stratified by study design. The figure shows the forest plot for melanoma risk comparing ever- *vs.* never-use of sunscreen for all studies that reported a minimally adjusted estimate, stratified by study design. The estimates of the case–control studies are reported in odds ratios with 95% confidence intervals (CIs); and, the estimates of the cohort studies and the RCT as hazard ratios with 95% CIs. Minimal adjustment of some estimates (e.g. age and sex) and exact definition of the estimates is described in Table 2. Abbreviations: CI, confidence interval; ES, effect size; RCT, randomised controlled trial. * Not ever- *vs.* never-use of sunscreen; see Table 2 for the exact definition of the estimate. **Case-cohort study. [Color figure can be viewed at wileyonlinelibrary.com]

and melanoma in the cohort studies. No clear pattern resulted when comparing the few studies that reported three-level estimates of sunscreen use regarding frequency of use, SPF of sunscreen used or duration of use. The association between sunscreen use and melanoma differed by latitude, region, adjustment for nevi/freckling, and proportion of never sunscreen users.

Comparison with previous meta-analyses

Our study is the first systematic review and meta-analysis to present results from four different study designs, the first to include five prospective studies, and the first to stratify the case–control studies into hospital-based and population-based studies. Five meta-analyses of the association of sunscreen use and melanoma have been published (in 2002[43], 2003[44], 2007[45], 2015[46], and 2018[48]). Only Dennis and colleagues (2003)[44] aggregated three-level estimates of sunscreen use into ever- *vs.* never-use, as we did, but the final estimate (pooled OR = 1.0, 95%CI 0.8–1.2, from 18 case–control studies) was unadjusted for confounding factors. Consistent with our findings, they showed that adjustment moved estimates toward a reduced risk of melanoma in sunscreen users, by pooling only the nine studies that adjusted for sun sensitivity (OR = 0.8, 95%CI 0.6–1.0).[44] Similar to our approach, Dennis and colleagues tried to go beyond "ever-use" of sunscreen and pooled 12 case–control studies that reported at least a three-level estimate on the frequency of sunscreen use (aggregated by ordered regression models) but found no association.[44]

Despite high heterogeneity, the other four meta-analyses pooled results using quite different definitions of sunscreen use into one estimate (for example always- *vs.* never-use and ever- *vs.* never-use), across very different study designs or different types of skin cancer, and across estimates from adjusted and unadjusted models. The earliest meta-analysis (2002)[43] included

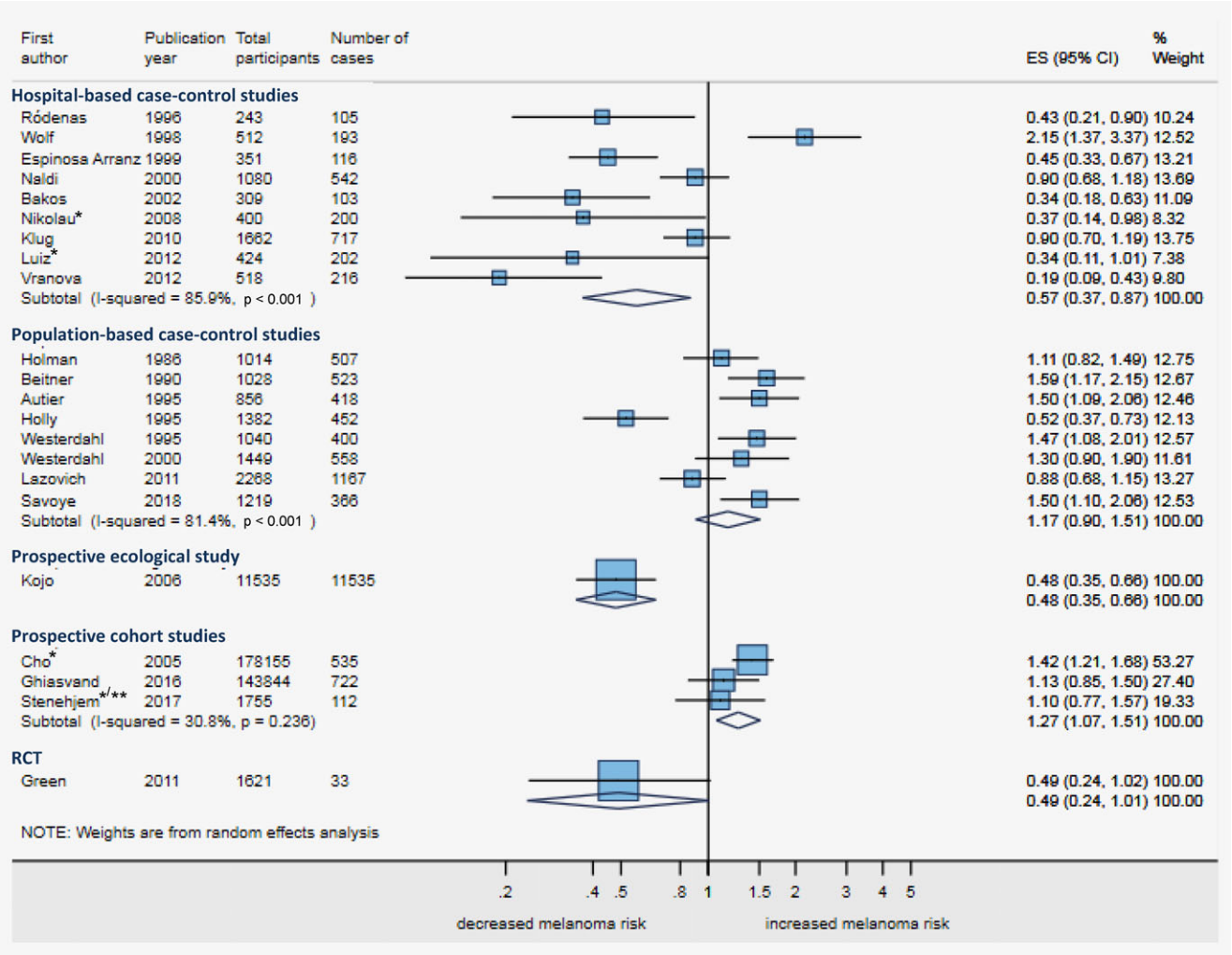

Figure 3. Forest plot for ever- *vs.* never-use of sunscreen and melanoma risk, maximally adjusted estimates stratified by study design. The figure shows the forest plot for melanoma risk comparing ever- *vs.* never-use of sunscreen for all studies that reported a maximally adjusted estimate, stratified by study design. The estimates of the case–control studies are reported as odds ratios with 95% confidence intervals (CIs); the estimates of the cohort studies and the RCT as hazard ratios with 95% CIs; and, the estimate of the ecological study as rate ratio with 95% CI. Adjustment and exact definition of the estimates is described in Table 2. Abbreviations: CI, confidence interval; ES, effect size; RCT, randomised controlled trial. *Not ever- *vs.* never-use of sunscreen; see Table 2 for the exact definition of the estimate. **Case-cohort study. [Color figure can be viewed at wileyonlinelibrary.com]

11 case–control studies but pooled only the four registry-based, resulting in no association (OR = 1.01). Gorham and colleagues (2007)[45] included 17 case–control studies with a pooled OR = 1.2 (95%CI 0.9–1.6). Similar to our review, they found statistically significant interaction with study latitude. Xie and colleagues (2015)[46] included 21 studies and calculated a summary estimate of 1.15 (95%CI 0.91–1.44; I^2 = 84%, $p_{heterogeneity}$ < 0.001). This review[46] also tried to identify sources of heterogeneity by meta-regression but found no significant interactions. The most recent meta-analysis (2018)[48] included 30 studies but only 25 were related to melanoma. They included only two prospective studies compared to five in our review, included cross-sectional study designs and calculated a summary estimate despite high heterogeneity (summary estimate = 1.08, 95%CI 0.91–1.29, including melanoma and other skin cancers). It is not possible to directly compare the aggregated estimates of association from these previous meta-analyses with our sorted and stratified estimates.

Interpretation of results

When interpreting our results, we needed to account for the different levels of evidence of the study designs included in our meta-analyses. In the hierarchy of strength of evidence, ecological studies are the weakest, and cohort studies and RCTs are the strongest.[71] Our funnel plot showed small-study effects, meaning that the results in small studies differed from the results in large studies. We suspect that this funnel plot asymmetry is due to poor methodological quality in small studies rather than publication bias.[60] This supports the fact that our results need to be interpreted taking the methodological quality and level of evidence into account as was done in the GRADE assessment.

Table 3. Association between sunscreen use and melanoma from stratified analyses

	No[1]	Estimate	95% CI	p^2	Tau[2 3]
Study design				0.069	0.221
Hospital-based case–control studies	9	0.57	0.37–0.87		
Population-based case–control studies	8	1.17	0.91–1.51		
Ecological study	1	0.48	0.35–0.66		
Cohort studies	3	1.27	1.07–1.51		
Randomised controlled trial	1	0.49	0.24–1.01		
Year of the end of data collection				0.319[4]	0.320
1975–1984	2	1.33	0.93–1.89		
1985–1999	10	0.86	0.61–1.21		
2000–2012	9	0.82	0.60–1.13		
Mean latitude of the study				0.042	0.248
› 42° N	11	1.09	0.83–1.44		
≤ 42° N	11	0.64	0.47–0.89		
Region of the study				0.008	0.131
Northern Europe	6	1.10	0.78–1.57		
Northern America	4	0.89	0.59–1.34		
Eastern Europe	1	0.19	0.09–0.42		
Western Europe	3	1.61	1.32–1.97		
Southern Europe	4	0.55	0.33–0.89		
Southern America	2	0.34	0.20–0.59		
Australia	2	0.79	0.36–1.74		
Most frequent melanoma site				0.825	0.256
Trunk	8	0.72	0.49–1.05		
Head/neck	3	0.93	0.57–1.54		
Lower limbs	2	0.74	0.29–1.90		
Duration of sunscreen use				0.482	0.313
Not specified (general habit)	11	0.94	0.69–1.28		
Specified period	10	0.81	0.60–1.10		
Lifetime	1	0.34	0.11–1.03		
More detailed assessment than “sunscreen yes-no”				0.493	0.319
No (only sunscreen yes-no)	10	0.93	0.66–1.32		
Yes (more than sunscreen yes-no)	12	0.80	0.60–1.05		
Level of bias				0.884	0.345
High	6	0.76	0.42–1.40		
Medium	12	0.84	0.64–1.12		
Low	4	1.02	0.73–1.41		
Adjusted for nevi/freckling				0.035	0.238
No	8	1.25	0.99–1.56		
Yes	14	0.69	0.51–0.92		
Adjusted for history of sunburn				0.587	0.323
No	6	0.95	0.63–1.44		
Yes	16	0.82	0.64–1.05		
Adjusted for sun exposure				0.253	0.295
No	6	0.64	0.38–1.09		
Yes	16	0.95	0.77–1.18		
Proportion with blond/red hair				0.150	0.411
‹ 30%	10	0.65	0.44–0.97		
≥ 30%	3	1.24	0.80–1.93		

(Continues)

Table 3. Association between sunscreen use and melanoma from stratified analyses (Continued)

	No[1]	Estimate	95% CI	p^2	Tau$^{2\ 3}$
Proportion with blue/green eyes				0.326	0.492
< 50%	7	0.57	0.35–0.93		
≥ 50%	4	0.93	0.48–1.79		
Proportion with history of sunburn				0.406	0.429
< 75%	6	0.62	0.33–1.15		
≥ 75%	7	0.98	0.72–1.31		
Proportion of never[5] sunscreen user				0.012	0.164
< 55%	13	1.03	0.83–1.28		
≥ 55%	4	0.42	0.32–0.55		

Abbreviations: CI, confidence interval; No, number; *p*, *p* value.
[1]Number of studies in each group.
[2]*p* Value for interaction from univariable meta-regression model.
[3]Remaining between-study variance estimated by residual maximum likelihood.
[4]*p* Value for trend.
[5]A few studies included rare sunscreen users in the "never user" category. See Table 2 for the exact definition of the sunscreen variable.

Careful interpretation of the results of the observational studies is essential because of their multiple methodological limitations when assessing the sunscreen-melanoma association: recall bias (in the case–control studies); ecological fallacy (in the ecological study, where we do not know whether the specific individuals who used sunscreen were those with lower incidence of melanoma because the association was measured at the population level); difficulty in meaningfully assessing sunscreen use by *ad hoc* questionnaires; and, by far the most concerning, residual confounding since the determinants of sunscreen use and melanoma (susceptibility to sunburn and high sun exposure) are almost inseparable in observational studies.[41] Furthermore, in their large population-based cohort study,[69] Ghiasvand and colleagues found significant differences between sunscreen users and non-users in regard to phenotype and sun exposure. Our review highlights the profound influence of residual confounding by showing that increasing adjustment systematically moved effect estimates toward a more reduced risk of melanoma among sunscreen users. The problems incorporated in observational studies have also led to an overall very low quality of evidence in the GRADE rating.[72] To overcome this problem we suggest performing cohort studies that also explore reasons for sunscreen use and non-use, and how sunscreen users' behaviour differs from that of non-users,[73] or analysing cohort studies using newer statistical methods (for example inverse probability weighting of using sunscreen) that can adjust for confounding by indication and mimic an RCT design.[74] In observational studies, "treatment selection" (sunscreen use in our case) is often influenced by subject characteristics. As a result, baseline characteristics of subjects using sunscreen differ systematically from those not using sunscreen. A propensity score such as inverse probability weights is the probability of using sunscreen conditional on observed baseline characteristics. Applying such weights allows one to analyse an observational (nonrandomized) study so that it mimics an RCT by balancing the distribution of observed baseline covariates between sunscreen users and non-users.[75]

The strongest existing evidence comes from the one RCT, as suggested by the pyramid of evidence.[76] The RCT was performed in an Australian population with high year-round sun exposure and skin cancer awareness.[21,77] There is therefore a need for additional high-quality, large RCTs in countries of higher latitude, but these are highly unlikely to be conducted because of ethical constraints (vulnerable study participants cannot be denied regular use of sunscreen) and the need to enrol extremely large numbers of participants in order to prospectively assess the rare outcome of melanoma.[19] However, future RCTs could examine intermediate endpoints (biomarkers, genetic mutations) to improve the evidence-base for sunscreen use.[19]

Because of the imprecise definition of ever- *vs.* never-use of sunscreen and highly variable assessment of sunscreen use across studies, we compared the studies reporting at least three-levels and different patterns of sunscreen use. Unfortunately very few studies reported such estimates, and therefore we could not provide evidence about what pattern of use would be most effective and whether there is a discernible trend with increasing frequency of sunscreen use. We generally observed that very few studies assessed sunscreen use behaviour in depth such as exploring thickness of sunscreen applied, re-application or proportion of body covered with sunscreen. Such information would be crucial to assess in future research in relation to melanoma risk since we know that most people do not apply sunscreen properly.[78,79]

Of further concern is the high heterogeneity between studies that could not be fully explained by the variables we investigated in the meta-regression analysis (see also heterogeneity between study participants in Supporting Information Table 2). We found a more protective effect of sunscreens in lower latitudes and Southern countries. This might be due to sun exposure being more

homogeneous in these studies (everybody is exposed to some degree) and to sunscreen use being regarded as a routine preventive measure rather than being regarded as a means to prolong sun exposure by some at higher latitudes.[80,81] It would therefore be important to distinguish between studies where sunscreen was used for intentional sun exposure and tan acquisition *versus* for protection from sun damage. This was not possible with currently available evidence. Also, people from lower and higher latitude might differ in their interpretation of frequencies of sunscreen use. For example higher latitude participants might consider "often" using sunscreen means applying on sunny days, whereas lower latitude participants may think of "often" using sunscreen as daily application.

We further found an inverse association between sunscreen use and melanoma in studies where the estimate was adjusted for number of naevi and/or freckling, while no association was found in studies without such adjustment. This might be due to the fact that number of naevi/freckling are especially important predictors of melanoma,[82] and self-reported assessment of number of naevi/freckling as confounding factor might be more valid than other factors (e.g. sun exposure or sunburns long time ago).[83,84] We found an inverse association of sunscreen use and melanoma in studies with a high proportion of never sunscreen users. This makes sense because of a better contrast between sunscreen users and non-users, revealing the effect of sunscreen in populations where the majority is not using it.

Strengths and limitations

This systematic review has several strengths. Compared to previous reviews, it adds several new studies and study designs, including three large cohort studies, and performs in-depth statistical analyses. We have extracted a variety of descriptive variables to identify sources of heterogeneity. To make the sunscreen variable as comparable as possible between studies, we attempted to aggregate or transform the estimates into ever- *vs.* never-use of sunscreen in order to combine the studies, but this inherited the weakness that the sunscreen measure was very broad, further obscuring any true effect of sunscreen.

Other limitations include the relatively low number of eligible studies, especially intervention studies and studies reporting three-level estimates on sunscreen use, the difference in study designs, and the between-study heterogeneity. Because of the high heterogeneity we could not calculate an overall summary estimate. Due to the limited number of studies we could not perform multivariable meta-regression analysis, and were forced to collapse the meta-regression and stratified meta-analysis over the different study designs. Also, we could not identify enough studies to answer our last research question on a possible relationship between body sites of sunscreen application and of melanoma. Furthermore, we used the label ever- *vs.* never-use because never or no use were the terms mostly used in the original studies included in the meta-analysis. This might be somewhat misleading as the never-users probably include some who used sunscreen rarely.

Conclusion

We found overall weak and heterogeneous published evidence for an association between sunscreen use and melanoma. Observational studies showed an inverse association in hospital-based case–control studies and the ecological study, no association in population-based case–control studies and a positive association in the three cohort studies. A protective effect of sunscreen was found in the only RCT performed. We therefore advocate for studies examining intermediate (biological) endpoints to be used in high-quality RCTs. The effectiveness of sunscreen to reduce UV radiation to the skin has been proven after acute exposure in human studies and in experimental studies.[19] In our review, this translated into a reduced melanoma risk in the long-term for only some studies and we attribute this to residual confounding of observational studies and the misuse of sunscreen to increase rather than decrease sun exposure in some high latitude populations. Public health recommendations should place greater emphasis on the proper use of sunscreen (for sun protection *vs.* to prolong time in the sun) in conjunction with other means of sun protection.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. *Cancer incidence and mortality worldwide: IARC CancerBase no. 11 [internet]*. Lyon, France: International Agency for Research on Cancer, 2012.
2. American Cancer Society. *Cancer Facts & Figures 2012*. Atlanta, GA: American Cancer Society, 2012.
3. SEER - Surveillance. Epidemiology and end result program: turning cancer data into discovery: NCI - National Cancer Institute, 2014; Available from https://seer.cancer.gov.
4. Karimkhani C, Green AC, Nijsten T, et al. The global burden of melanoma: results from global burden of disease study 2015. *Br J Dermatol* 2017; 177:134–40.
5. Ossio R, Roldan-Marin R, Martinez-Said H, et al. Melanoma: a global perspective. *Nat Rev Cancer* 2017;17:393–4.
6. Berwick M, Buller DB, Cust A, et al. Melanoma Epidemiology and Prevention. *Cancer Treat Res* 2016;167:17–49.
7. IARC, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Radiation. Lyon, France: International Agency for Cancer Research, 2012.
8. Lucas RM, McMichael AJ, Armstrong BK, et al. Estimating the global disease burden due to ultraviolet radiation exposure. *Int J Epidemiol* 2008;37:654–67.
9. Parkin DM, Mesher D, Sasieni P. 13. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. *Br J Cancer* 2011;105-(Suppl 2):S66–9.
10. Whiteman DC, Wilson LF. The fractions of cancer attributable to modifiable factors: a global review. *Cancer Epidemiol* 2016;44: 203–21.
11. Sample A, He Y-Y. Mechanisms and prevention of UV-induced melanoma. *Photodermatol Photoimmunol Photomed* 2018;34:13–24.
12. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. *Cell* 2012; 150:251–63.
13. Gordon LG, Scuffham PA, van der Pols JC, et al. Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. *J Invest Dermatol* 2009;129:2766–71.
14. Langer T, Follmann M. Das Leitlinienprogramm Onkologie (OL): Nukleus einer evidenzbasierten, patientenorientieren, interdisziplinären Onkologie? *Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen* 2015;109: 437–44.
15. Sun Exp Dermatol - Recommendations, vol. 2016 USA: Centers for Disease Control and Prevention (CDC), Providing National and World Leadership

to Prevent Workplace Illnesses and Injuries (NIOSH), 2016.
16. Sun Safety, vol. 2017 USA: Centres for Disease Control and Prevention (CDC), 2014.
17. Sun protection, vol. 2017: World Health Organization (WHO) INTERSUN programme, 2016.
18. Berwick M. The good, the bad, and the ugly of sunscreens. *Clin Pharmacol Ther* 2011;89:31–3.
19. Olsen CM, Wilson LF, Green AC, et al. Prevention of DNA damage in human skin by topical sunscreens. *Photodermatol Photoimmunol Photomed* 2017;33:135–42.
20. Iannacone MR, Hughes MC, Green AC. Effects of sunscreen on skin cancer and photoaging. *Photodermatol Photoimmunol Photomed* 2014;30:55–61.
21. Green AC, Williams GM, Logan V, et al. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol* 2011;29:257–63.
22. Klepp O, Magnus K. Some environmental and bodily characteristics of melanoma patients. A case-control study. *Int J Cancer* 1979;23:482–6.
23. Graham S, Marshall J, Haughey B, et al. An inquiry into the epidemiology of melanoma. *Am J Epidemiol* 1985;122:606–19.
24. Holman CD, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J Natl Cancer Inst* 1986;76:403–14.
25. Osterlind A, Tucker MA, Stone BJ, et al. The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. *Int J Cancer* 1988;42:319–24.
26. Beitner H, Norell SE, Ringborg U, et al. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 1990;122:43–51.
27. Herzfeld PM, Fitzgerald EF, Hwang SA, et al. A case-control study of malignant melanoma of the trunk among white males in upstate New York. *Cancer Detect Prev* 1993;17:601–8.
28. Autier P, Dore JF, Schifflers E, et al. Melanoma and use of sunscreens: an Eortc case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. *Int J Cancer* 1995;61:749–55.
29. Holly EA, Aston DA, Cress RD, et al. Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. *Am J Epidemiol* 1995;141:923–33.
30. Westerdahl J, Olsson H, Masback A, et al. Is the use of sunscreens a risk factor for malignant melanoma? *Melanoma Res* 1995;5:59–65.
31. Rodenas JM, Delgado-Rodriguez M, Herranz MT, et al. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. *Cancer Causes Control* 1996;7:275–83.
32. Whiteman DC, Valery P, McWhirter W, et al. Risk factors for childhood melanoma in Queensland, Australia. *Int J Cancer* 1997;70:26–31.
33. Wolf P, Quehenberger F, Mullegger R, et al. Phenotypic markers, sunlight-related factors and sunscreen use in patients with cutaneous melanoma: an Austrian case-control study. *Melanoma Res* 1998;8:370–8.
34. Espinosa Arranz J, Sanchez Hernandez JJ, Bravo Fernandez P, et al. Cutaneous malignant melanoma and sun exposure in Spain. *Melanoma Res* 1999;9:199–205.
35. Naldi L, Gallus S, Imberti GL, et al. Sunscreens and cutaneous malignant melanoma: an Italian case-control study. *Int J Cancer* 2000;86:879–82.
36. Westerdahl J, Ingvar C, Masback A, et al. Sunscreen use and malignant melanoma. *Int J Cancer* 2000;87:145–50.
37. Bakos L, Wagner M, Bakos RM, et al. Sunburn, sunscreens, and phenotypes: some risk factors for cutaneous melanoma in southern Brazil. *Int J Dermatol* 2002;41:557–62.
38. Youl P, Aitken J, Hayward N, et al. Melanoma in adolescents: a case-control study of risk factors in Queensland, Australia. *Int J Cancer* 2002;98:92–8.
39. Klug HL, Tooze JA, Graff-Cherry C, et al. Sunscreen prevention of melanoma in man and mouse. *Pigment Cell Melanoma Res* 2010;23:835–7.
40. Lazovich D, Vogel RI, Berwick M, et al. Melanoma risk in relation to use of sunscreen or other sun protection methods. *Cancer Epidemiol Biomarkers Prev* 2011;20:2583–93.
41. Green AC, Williams GM. Point: sunscreen use is a safe and effective approach to skin cancer prevention. *Cancer Epidemiol Biomarkers Prev* 2007;16:1921–2.
42. Bastuji-Garin S, Diepgen TL. Cutaneous malignant melanoma, sun exposure, and sunscreen use: epidemiological evidence. *Br J Dermatol* 2002;146-(Suppl 61):24–30.
43. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. *Am J Public Health* 2002;92:1173–7.
44. Dennis LK, Beane Freeman LE, Vanbeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med* 2003;139:966–78.
45. Gorham ED, Mohr SB, Garland CF, et al. Do sunscreens increase risk of melanoma in populations residing at higher latitudes? *Ann Epidemiol* 2007;17:956–63.
46. Xie F, Xie T, Song Q, et al. Analysis of association between sunscreens use and risk of malignant melanoma. *Int J Clin Exp Med* 2015;8:2378–84.
47. IARC, IARC Handbook of Cancer Prevention. Sunscreens. International Agency for Research on Cancer. *World Health Organisation*, Lyon, France: International Agency for Research on Cancer, 2001.
48. Silva ESD, Tavares R, Paulitsch FDS, et al. Use of sunscreen and risk of melanoma and non-melanoma skin cancer: a systematic review and meta-analysis. *Eur J Dermatol* 2018;28:186-201.
49. Rueegg C, Stenehjem J, Egger M, et al. Melanoma and sunscreen use - systematic review and meta-analysis. *PROSPERO* 2017:CRD42017063980.
50. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1-9.
51. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;349:g7647.
52. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
53. Wallingford SC, Iannacone MR, Youlden DR, et al. Comparison of melanoma incidence and trends among youth under 25 years in Australia and England, 1990-2010. *Int J Cancer* 2015;137:2227–33.
54. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane collaboration, 2011; Available from http://handbook.cochrane.org.
55. Wells G, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*, vol. 2017. Ottawa: Ottawa Hospital Research Institute, 2014.
56. Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;27:954–70.
57. Pandey A, Garg S, Khunger M, et al. Dose response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation* 2015;132:1786–94.
58. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
59. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
60. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315:629–34.
61. Langan D, Higgins JPT, Gregory W, et al. Graphical augmentations to the funnel plot assess the impact of additional evidence on a meta-analysis. *J Clin Epidemiol* 2012;65:511–9.
62. Group GW. Grading quality of evidence and strength of recommendations. *Br Med J* 2004;328:1490.
63. Luiz OC, Gianini RJ, Goncalves FT, et al. Ethnicity and cutaneous melanoma in the city of Sao Paulo, Brazil: a case-control study. *PLoS One* 2012;7:e36348.
64. Nikolaou VA, Sypsa V, Stefanaki I, et al. Risk associations of melanoma in a southern European population: results of a case/control study. *Cancer Causes Control* 2008;19:671–9.
65. Vranova J, Arenbergerova M, Arenberger P, et al. Incidence of cutaneous malignant melanoma in the Czech Republic: the risks of sun exposure for adolescents. *Neoplasma* 2012;59:316–25.
66. Savoye I, Olsen CM, Whiteman DC, et al. Patterns of ultraviolet radiation exposure and skin cancer risk: the E3N-SunExp study. *J Epidemiol* 2018;28:27–33.
67. Kojo K, Jansen CT, Nybom P, et al. Population exposure to ultraviolet radiation in Finland 1920-1995: exposure trends and a time-series analysis of exposure and cutaneous melanoma incidence. *Environ Res* 2006;101:123–31.
68. Cho E, Rosner BA, Feskanich D, et al. Risk factors and individual probabilities of melanoma for whites. *J Clin Oncol* 2005;23:2669–75.
69. Ghiasvand R, Weiderpass E, Green AC, et al. Sunscreen use and subsequent melanoma risk: a population-based cohort study. *J Clin Oncol* 2017;185:147–56.

70. Stenehjem JS, Robsahm TE, Bratveit M, et al. Ultraviolet radiation and skin cancer risk in offshore workers. *Occup Med (Oxford, England)* 2017;67:569–73.
71. Ahrens W, Krickeberg K, Pigeot I. An Introduction to epidemiology. In: Ahrens W, Pigeot I, eds Handbook of Epidemiology*ed*. Berlin: Springer, 2006:1–42.
72. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.
73. Vainio H, Miller AB, Bianchini F. An international evaluation of the cancer-preventive potential of sunscreens. *Int J Cancer* 2000;88:838–42.
74. Hernan MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidimiology* 2008;19:766–79.
75. Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res* 2011; 46:399–424.
76. Murad MH, Asi N, Alsawas M, et al. New evidence pyramid. *Evidence Based Med* 2016;21:125–7.
77. Green A, Battistutta D, Hart V, et al. The Nambour skin cancer and actinic eye disease prevention trial: design and baseline characteristics of participants. *Control Clin Trials* 1994;15:512–22.
78. Vasicek BE, Szpunar SM, Manz-Dulac LA. Patient knowledge of sunscreen guidelines and frequency of physician counseling: a cross-sectional study. *J Clin Aesthet Dermatol* 2018;11:35–40.
79. Olsen CM, Wilson LF, Green AC, et al. How many melanomas might be prevented if more people applied sunscreen regularly? *Br J Dermatol* 2018;178:140–7.
80. Autier P, Boniol M, Dore JF. Sunscreen use and increased duration of intentional sun exposure: still a burning issue. *Int J Cancer* 2007;121:1–5.
81. Autier P, Boniol M, Dore JF. Is sunscreen use for melanoma prevention valid for all sun exposure circumstances? *J Clin Oncol* 2011;29: e425-6.
82. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. *Pigment Cell Melanoma Res* 2011; 24:879–97.
83. Veierod MB, Parr CL, Lund E, et al. Reproducibility of self-reported melanoma risk factors in a large cohort study of Norwegian women. *Melanoma Res* 2008;18:1–9.
84. English DR, Armstrong BK, Kricker A. Reproducibility of reported measurements of sun exposure in a case-control study. *Cancer Epidemiol Biomarkers Prev* 1998;7:857–63.