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## AN ADDITION TO THE CONTROVERSY ON SUNLIGHT EXPOSURE AND MELANOMA RISK: A META-ANALYTICAL APPROACH

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**Abstract**—Case control studies on the association between sunlight exposure and melanoma risk show considerable differences in design; this could be responsible for the variation in study results. In an attempt to resolve the controversy between study results, the results of 25 publications on case control studies were evaluated using meta-analytical techniques. Comparison of odds ratios between subgroups of studies revealed that the range of odds ratios was far greater for hospital-based studies than for population-based studies. For the latter type of studies, the odds ratios were homogeneous and the pooled odds ratios were 1.57 (95% confidence interval [CI], 1.29–1.91) for intermittent sunlight exposure and 0.73 (95% CI, 0.60–0.89) for chronic exposure. However, among other problems, the lack of standardized measures for sunlight exposure warrants cautious interpretation of these results. It is concluded that evidence to support the intermittent sunlight theory is still far from complete.

Melanoma      Sunlight      Review      Meta-analysis

### INTRODUCTION

The incidence of cutaneous melanoma has risen dramatically over the past decades. Sunlight exposure is now suspected to be an important risk factor. However, the results from epidemiological studies are inconsistent [1–25]. If there is a relationship between sunlight exposure and melanoma risk, it is not a straightforward one. Melanoma risk does not simply increase with an increasing amount of accumulated exposure to ultraviolet radiation. This is illustrated by the fact that the incidence of melanoma is higher among indoor than among outdoor workers and that melanoma does not predominantly occur on body sites that are most frequently exposed to the sun [26, 27]. To explain these paradoxical observations the “intermittent sunlight hypothesis” was put forward: especially short bursts of

intense exposure to sunlight increase the risk of melanoma, while more regular, chronic exposure has a neutral or even protective effect [28].

In the past decade, more than 20 case control studies have been published on the relation between cutaneous melanoma and sunlight exposure. Curiously, these studies showed striking differences with respect to the histological types of melanoma that were included in the study populations, the way in which sunlight exposure was measured, the classification of exposure levels, and other important methodological issues that may be responsible for producing biased results. Owing to these differences, it is difficult to gain an insight into the strength and exact nature of the relation between sunlight exposure and melanoma risk. Even the critical question concerning which pattern of sunlight exposure (intermittent or total accumulated exposure to

the sun [29]) is important remains difficult to answer.

Previous reviews on case control studies mostly had a narrative style [29–33]. In our opinion a more systematic way of assessing information from independent studies can be achieved with meta-analytical techniques. We did not apply meta-analysis merely as a statistical analysis, which combines or integrates the results of independent studies, because for this stringent conditions would have to be met [34]. Nonexperimental studies, such as case control studies, do not allow for the assumption that the variation in study results is solely attributable to statistical sampling error. It is unlikely that this so-called homogeneity assumption is fulfilled. Part of the variation in the odds ratios probably results from differences in the definitions and measurements of disease and exposure, differences in the study populations, and from other potential biases, such as selection, information, and confounding bias. Therefore, we prefer to regard a meta-analysis as any “structured and systematic *qualitative* and/or quantitative integration of results from independent studies” [35]. According to this definition, an important function of a meta-analysis can be the exploration of sources of variation in study results [36]; statistical sampling error is only one such source. A systematic evaluation of differences in odds ratios as a function of differences in design and study size can help to explain the controversy between study results.

#### METHODOLOGICAL PITFALLS

Several important implications of the intermittent sunlight hypothesis and the relevant methodological problems for studying this theory in case control studies are briefly discussed below.

The model underlying the intermittent sunlight exposure hypothesis implies that ultraviolet radiation leads to an increase in melanoma risk if the skin is not yet accustomed to the sun. It is assumed that regular exposure results in gradual tanning of the skin or in thickening of the stratum corneum (in patients who cannot tan) and thereby provides protection of the skin against sunlight. A higher frequency of exposure to the sun results in more protection. Therefore the dose–response relation between the frequency of sunlight exposure and melanoma risk is not a linear one. Beyond a certain peak, the risk may actually decline as the exposure to sunlight further increases [14]. The transition from an increasing dose–response relationship to a

decreasing one, depends on the individual pigmentary response. In persons with a fair skin complexion, a reduction in risk may not occur at all. This hypothetical dose–response curve implies that the relative risk associated with sunlight exposure is modified by background rates of exposure and individual pigmentation characteristics [14]. Several methodological problems may bias the association between sunlight exposure and melanoma risk.

*Histological types of melanoma.* Cutaneous melanoma has four subtypes: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acro-lentiginous melanoma [37]. Superficial spreading melanoma and nodular melanoma, together accounting for about 85% of all melanomas, are the only histological types relevant to the intermittent sunlight exposure hypothesis. Lentigo maligna melanoma (about 10% of all melanomas) and acro-lentiginous melanoma (about 5% of melanomas in whites) are considered to have a different etiology. As lentigo maligna melanoma is associated with the total accumulated sun exposure [38], including this melanoma type could result in an overestimation of the relative risk.

In studies on risk factors for melanoma, it is advisable to have an independent pathologist verify the histological type of the melanomas diagnosed in the participants.

*Measurement of sunlight exposure.* The intermittent sunlight hypothesis implies that different patterns of sunlight exposure involve different risks of melanoma. Therefore, it is important to classify studies according to the type of sunlight exposure that was measured. In general, recreational activities, such as sunbathing, water sports, and vacations in sunny resorts, are considered to be indicators of intermittent sunlight exposure, while occupational exposure to the sun is considered to be more regular (chronic). Total accumulation exposure is a sum of both types of exposure. Several case control studies also assessed the effect of biological responses to sunlight, such as sunburn, as a measure for intermittent exposure.

It is important to have adequate definitions of irregular and regular sunlight exposure. Inadequate definitions result in nondifferential misclassification, that is, errors in the exposure classification that are independent of the case control status. Nondifferential misclassification must be avoided as much as possible, because it biases the results toward no effect [39].

*Country where the study was performed.* Whether or not recreational exposure to the sun is intermittent will depend on the background level of exposure [14]. If the background level is high, then recreational exposure will simply add to an exposure that is already approaching a continuous pattern. One of the determinants of background exposure is latitude. It is reasonable to assume that the effect of intermittent sunlight exposure can best be studied in populations living at higher latitudes [14, 18].

*Induction period.* Adequate definitions of exposure must account for the right induction period. Conflicting results have been reported with respect to the induction period for cutaneous melanoma. Migrant studies and several case control studies have indicated that childhood exposure plays a crucial role [38, 40, 41], while other studies point to shorter induction periods [4, 42]. The risk estimates of studies are expected to vary according to the period in which sunlight exposure was measured. Studies with an inappropriate assumption about the timing of etiologically relevant sunlight exposure are expected to give too-low odds ratios owing to non-differential misclassification of exposure [39].

*Recall bias.* If patients with a melanoma, or the interviewers, are aware that sun exposure might be related to the disease, it is more likely that sun exposure will be reported. Therefore errors in the measurement of exposure will be systematically different across the study groups. Recall bias results in spurious positive associations [43]. It can be reduced by blinding procedures, such as not informing the subjects and the interviewers about the hypothesis under study, or concealing the case control status of the respondent from the interviewer [44].

*Skin complexion.* The presence of constitutional factors that increase the sensitivity of the skin to sunlight is an important risk indicator for cutaneous melanoma. A large proportion of patients with a melanoma have red or blond hair, blue eyes, and a light skin color; they burn more easily and tan more poorly than do control subjects [45]. If increased sensitivity of the skin to sunlight results in the tendency to avoid sunlight exposure, not controlling for this host factor leads to underestimation of the relative risk. If the light skin complexion of melanoma patients leads to sun-seeking behavior, then not controlling for this factor will result in overestimation of the effect of sunlight exposure.

*Number of nevi.* A high number of nevi is associated both with increased sensitivity of the

skin to sunlight [13, 46, 47] and with melanoma risk [48]. How this risk factor is managed in the study design depends heavily on which model about causal mechanisms the researcher has in mind. On the one hand, the number of nevi can be regarded as a potential confounder. On the other hand, if nevi are precursors of melanomas that are caused by sunlight, they lie in the cause-effect chain, and therefore controlling for the number of nevi will introduce bias toward no effect [29]. There is no consensus on this issue; some investigators treat the number of nevi as a confounder, while others consider nevi to be intermediates.

*Study population.* In so-called hospital-based studies, it is more difficult to ensure comparability of the patient and control groups. Selection bias as a result of unknown referral patterns cannot easily be overcome [49]. If the referral pattern is associated with sun exposure habits and the referral patterns are different for cases and controls, then the risk estimates will be affected by selection bias. The extent and direction of the resulting bias are unpredictable. Furthermore, to obtain an unbiased estimate of the relative risk, it is important that the conditions of the control patients not be related to past sunlight exposure. In population-based studies, selection of an appropriate control group is easier than in hospital-based studies.

These methodological issues were outlined before performing the meta-analysis, because theoretically these issues are potential sources for variation in study results.

## MATERIALS AND METHODS

A search was conducted for studies on risk factors for cutaneous melanoma. An online search using Medline for the years up to 1990 produced several original articles and reviews. Additional studies were traced through the references listed in the reviews.

Studies were included in the analysis if they assessed risk factors for cutaneous melanoma on an individual level; employed a case control design; were published in the period 1979–1990; and were written in the English language.

The following data were collected from each study:

- Inclusion or exclusion of specific melanoma types
- Type(s) of sunlight exposure studied

Measures of chronic and intermittent sun exposure used  
 Country where the study was performed  
 Period of sun exposure considered to be relevant  
 Blinding procedures  
 Control for other risk factors  
 Type of base population  
 Type of controls  
 Numbers of cases and controls  
 Analysis methods  
 Effect estimates (odds ratios) and corresponding measures of precision according to specific type(s) of sun exposure

If available, odds ratios adjusted for multiple risk factors (including pigmentary characteristics) were preferred for the meta-analysis. Some studies did not present odds ratios; if these studies reported proportions of exposed cases and controls, crude odds ratios were calculated on the basis of these data. The odds ratios selected for the meta-analysis compared the highest categories of sunlight exposure to the lowest categories.

In so-called funnel plots, logarithms of the odds ratios were plotted on the vertical axis against the corresponding standard errors on the horizontal axis [36]. Smaller standard errors corresponded with increasing precision. Funnel plots show the variation in study results according to the study size. If all studies were conducted on a single underlying population, then the graphs should look like a funnel, with the odds ratios homing in on the true underlying value as their precision increases. As the odds ratios become less precise (i.e., have larger standard errors) there is more scatter around the true value. Gaps in the funnel plot can also indicate potentially missing studies [36].

Graphic displays were also used to assess whether the odds ratios of studies whose methodology was susceptible to a specific bias differed systematically from the odds ratios of studies that were designed to prevent that specific pitfall.

In view of the hypothesized differences in the effect of intermittent and chronic sunlight exposure, analyses were performed separately for both types of exposure.

### *Statistical analysis*

For the calculation of pooled odds ratios, the odds ratios were transformed into their natural logarithms (log OR) and the standard errors (SE)

of these log odds ratios were used to weigh the studies according to the precision of the odds ratios. The weights were derived by  $w = 1/SE^2$ , where SE stands for the standard error of the log ratio [50]. The weighted average of the study results,  $B$ , was the weighted sum of the log odds ratios,  $\sum w(\log OR)$ , divided by the sum of the weights,  $\sum w$  [50].

An important prerequisite for the computation of a pooled odds ratio is that the odds ratios derived from the reviewed studies represent one underlying "true" value, that is, the variation in results is due only to statistical sampling error. This so-called homogeneity assumption must be tested using a homogeneity test, which is given by

$$\chi^2 = \sum w(\log OR - B)^2$$

The log OR for each study was the logarithm of the odds ratio reported in that study. Variable  $B$  was the weighted average of the log odds ratios from all the studies. If the studies estimated the same effect, this test statistic had a chi-square distribution with degrees of freedom (df) of one less than the number of studies [50]. If the homogeneity assumption is not fulfilled, then pooled odds ratios cannot be calculated.

## RESULTS

Table 1 shows a summary of the studies published between 1979 and 1990, the measures of intermittent and chronic sun exposure used in these studies, and the corresponding odds ratios [1–25]. Exposure to sunlight during leisure-time activities, vacations in sunny areas, and the use of sunbeds were regarded as indicators of intermittent sun exposure. Occupational or cumulative hours of exposure to sunlight were regarded as indicators of chronic exposure. The analyses with respect to intermittent sun exposure were based on 16 studies; analyses on the effect of chronic sun exposure were conducted on the risk estimates reported in 15 studies (Table 1).

In several studies, the history of sunburn was also used as a measure of intermittent exposure to sunlight. The associated odds ratios are presented separately in Table 2. Odds ratios with corresponding 95% confidence intervals could be derived from 12 studies.

Characteristics of the studies included in the meta-analysis are summarized in Table 3.

### *Results of graphic analysis methods*

In most of the studies, the log odds ratios for intermittent sun exposure were positive (Fig. 1).

Table 1. Odds ratios and 95% confidence intervals for measures of intermittent and chronic sunlight exposure in 25 publications on case control studies

Ref.	First author	Year of publication	Measure of intermittent sun exposure	Odds ratio (95% CI) <sup>a</sup>	Measure of chronic sun exposure	Odds ratio (95% CI) <sup>a</sup>
1	Klepp	1979	Holidays in Southern Europe: yes vs no	2.36 (1.04–5.38)	Outdoor occupation: 3+ hr daily vs less	1.45 (0.65–3.23)
2	Adam	1981	Deliberate tanning of trunk: yes vs no	1.58 (1.01–2.49)	Work time spent outdoors	No difference
3	Beral	1982	Various measures of recreational sun exposure	No consistent relation	Work outdoors: ever vs never	0.93 (0.55–1.61)
4	MacKie	1982	Recreational: ≥16 vs <16 hr/wk	0.44 (0.21–0.91)	Occupational: 16+ vs <16 hr/wk	0.52 (0.23–1.16)
5	Lew	1983	Vacations in sunny places: >0 days vs 0 days	1.79 (0.99–3.22)	Not given	Not given
6	Rigel	1983	Recreation: outdoor vs indoor	2.41 (0.82–5.28)	Occupation location: rest vs fully indoors	0.83 (?)
7, 10, 13	Green	1984–1986	Recreation on the beach: 5000+ vs 0 hr/lifetime	1.30 (0.39–4.29)	Cumulative hours of exposure: 50,000+ vs <2000/lifetime	1.70 (0.38–7.54)
8	Elwood	1985	Swimming + beach activities: 8+ vs 0 hr/wk	1.70 (1.08–2.67)	Occupational, summer: 16+ vs <16 hr/wk	0.90 (0.57–1.41)
9	Graham	1985	Vacations in southern regions: yes vs no	No relation	Average annual hours <sup>b</sup> : 3200+ vs ≤1600 hr/yr	0.38 (0.19–0.75)
11	Sorahan	1985	Holidays abroad in hot climate: yes vs no	Not significant	Occupation type: outdoor vs indoor	Not significant
12	Elwood	1986	Use of sunlamps: ever vs never	1.30 (0.56–3.01)	Occupational exposure: ever vs never outdoor	0.70 (0.27–1.82)
14	Holman	1986	ROEP <sup>c</sup> : >60% vs 0–29%	1.57 <sup>d</sup> (0.87–2.82)	Outdoor work in summer	0.41 (0.22–0.77)
15	Bell	1987	Frequent sunbathing: yes vs no	0.84 (0.64–1.11)	Occupation: outdoor vs indoor	1.31 (0.99–2.27)
16	Cristofolini	1987	Not given	Not given	Main occupation: outdoor vs indoor	1.65 (0.93–2.92)
17	Holly	1987	Sunbathing: number of times per year	No difference	Exposure to sunlight while at work	No difference
18	Østerlind	1988	Sunbathing: at some time vs never	1.60 (1.08–2.37)	Working outside in summer	0.70 (0.52–0.93)
19	Swerdlow	1988	Use of sunbeds: ever vs never	4.22 (0.81–21.9)	Not given	Not given
20	Dubin	1989	Recreation type: mostly outdoors vs mostly indoors	1.54 (1.00–2.37)	Occupation type: mostly out- vs mostly indoors	1.77 (0.83–3.78)
21	Garbe	1989	Free time sun exposure	No significant association	Occupational sun exposure	11.6 (2.10–64.1)
22	Weinstock	1989	Not given	Not given	Not given	Not given
23	Beitner	1990	No. of sunbaths April–Sept: >30 vs <20 per year	1.80 (1.22–2.67)	Outdoor workers	0.60 (0.38–0.94)
24	Grob	1990	Leisure sun exposure: >60 vs 0 SU <sup>e</sup>	8.41 (3.63–19.6)	Outdoor occupation: ever vs never	0.83 (0.55–1.25)
25	Walter	1990	Use of sunbeds: ever vs never	1.54 (0.96–2.46)	Not given	Not given

<sup>a</sup>CI, Confidence interval.<sup>b</sup>Average annual hours = total hours of sun exposure accumulated through life divided by age.<sup>c</sup>ROEP = recreational outdoor exposure proportion = recreational exposure as a proportion of total outdoor exposure.<sup>d</sup>Odds ratio for superficial spreading melanoma (SSM).<sup>e</sup>SU, sun exposure unit; = days with at least 2 hr of direct sun exposure.

Table 2. Odds ratios (adjusted for age) and 95% confidence intervals for sunburn history in 13 publications on case control studies

Ref.	First author	Year of publication	Odds ratio (95% CI) <sup>a</sup>	Adjusted for host factors	Adjusted for sun exposure
4	MacKie	1982	3.67 (1.99–6.75)	+	+
5	Lew	1983	2.05 (1.18–3.56) <sup>b</sup>	?	?
10	Green	1985	2.40 (1.00–6.10)	Adjusted for nevi	–
11	Sorahan	1985	4.0 (not given)	+ <sup>c</sup>	–
12	Elwood	1986	1.50 (0.70–3.50)	+ <sup>c</sup>	–
14	Holman	1986	0.98 (0.53–1.82) <sup>b</sup>	+ <sup>c</sup>	–
16	Cristofilini	1987	0.68 (0.28–1.47)	+	+
17	Holly	1987	3.80 (1.40–10.4)	+	–
18	Østerlind	1988	2.40 (1.60–3.60) <sup>b</sup>	–	–
			1.90 (1.20–3.10) <sup>b</sup>	+	–
20	Dubin	1989	1.61 (1.04–2.56)	–	–
			0.89 (not given)	+	–
22	Weinstock	1989	2.20 (1.20–3.80) <sup>b</sup>	–	–
24	Grob	1990	1.71 (0.63–4.63)	+	–
47	Elwood	1985	1.8 (1.11–2.86)	–	–
			1.4 (not given)	+ <sup>c</sup>	–

<sup>a</sup>CI, confidence interval.

<sup>b</sup>Sunburn during adolescence or early adulthood (between 15–24 years).

<sup>c</sup>Including tendency to burn.

The log odds ratios of the more precise studies varied around the value 0.5, which is equivalent to an odds ratio of 1.6. Figure 2 shows that for chronic exposure, both positive and negative odds ratios were reported. With respect to a positive sunburn history, most of the log odds ratios were positive with the exception of those reported by Holman *et al.* [14] and Cristofilini *et al.* [16] (Fig. 3).

The methodology and study populations varied between studies. Therefore an important function of the meta-analysis was to explore whether these differences were sources of the variation in study results. Figure 4 presents the results for design aspects, such as the exclusion of lentigo maligna melanoma (versus inclusion), blinding of subjects and/or interviewers (versus no blinding), control for nevi (versus no control),

Table 3. Characteristics of the studies included in the meta-analysis<sup>a</sup>

Ref.	First author	LMM <sup>b</sup> incl.	Induction period	Blinding	Control for host factors	Control for nevus number	Base population	Country (latitude, in degrees)
1	Klepp	+	Short	+	–	–	Hospital	Norway (65)
2	Adam	+	Short	–	–	–	Population	U.K. (50)
3	Beral	+	Short	–	–	–	Population	Australia (28)
4	MacKie	–	Short	+	+	–	Hospital	Scotland (55)
5	Lew	+	Childhood	–	–	–	Hospital	U.S.A. (43)
6	Rigel	+	Short	–	–	–	Hospital	U.S.A. (43)
7, 10, 13	Green	–	Short	–	–	+	Population	Australia (20)
8	Elwood	–	Short	+	+	–	Population	Canada (55)
9	Graham	+	Short	–	–	–	Hospital	U.S.A. (43)
12	Elwood	+	Short	+	–	–	Population	U.K. (52)
14	Holman	–	Ages 15–24 yr	–	+	–	Population	Australia (25)
15	Bell	–	Short	+	–	–	Hospital	U.K. (50)
16	Cristofilini	+	Short	–	+	+	Hospital	Italia (45)
18	Østerlind	–	Short	+	+	+	Population	Denmark (56)
19	Swerdlow	+	>5 yr bd <sup>c</sup>	–	+	+	Hospital	Scotland (56)
20	Dubin	+	Short	–	– <sup>d</sup>	– <sup>d</sup>	Hospital	U.S.A. (43)
21	Garbe	+	Short	–	+	+	Hospital	West Germany (53)
23	Beitner	+	Short	–	+	–	Hospital	Sweden (60)
24	Grob	–	Short	–	+	+	Hospital	France (45)
25	Walter	+	>5 yr bd <sup>c</sup>	+	–	–	Population	Canada (42)

<sup>a</sup>The studies by Sorahan and Grimley [11] and Holly *et al.* [17] could not be included, because odds ratios were not presented. Weinstock *et al.* [22] presented only odds ratios for sunburn.

<sup>b</sup>LMM, Lentigo maligna melanoma.

<sup>c</sup>>5 yr bd, More than 5 years before diagnosis.

<sup>d</sup>Results were presented separately for susceptibility subgroups indicated by tanning ability.

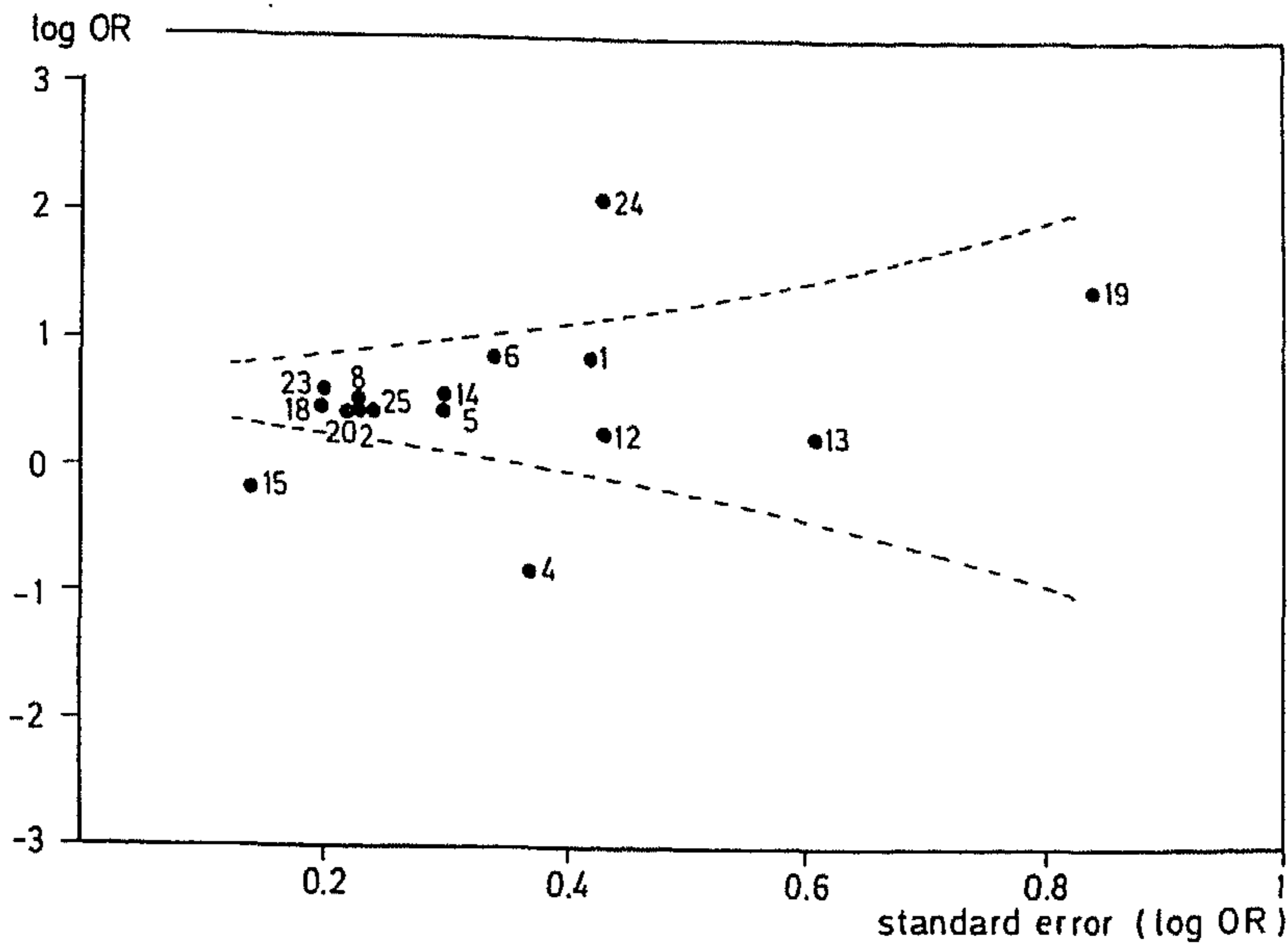


Fig. 1. The natural logarithms of the odds ratios (log OR) for intermittent sunlight exposure plotted against the corresponding standard errors of the log OR. Values are indicated with the reference number of the publication from which they were derived.

and population-based studies versus hospital-based studies. Figure 4 shows that irrespective of the design, most of the results clustered around the value of 0.5 (which is equivalent to an odds ratio of 1.6). The differences in design seemed to produce scatter rather than bias. This effect is most pronounced when the population-based studies were compared to the hospital-

based studies. The results of the population-based studies clustered around one value, while the hospital-based studies showed a greater diversity of results. Three of the studies without blinding reported fairly high odds ratios. The two studies that reported negative odds ratios for irregular sunlight exposure [4, 15] were studies that had excluded lentigo maligna melanoma and

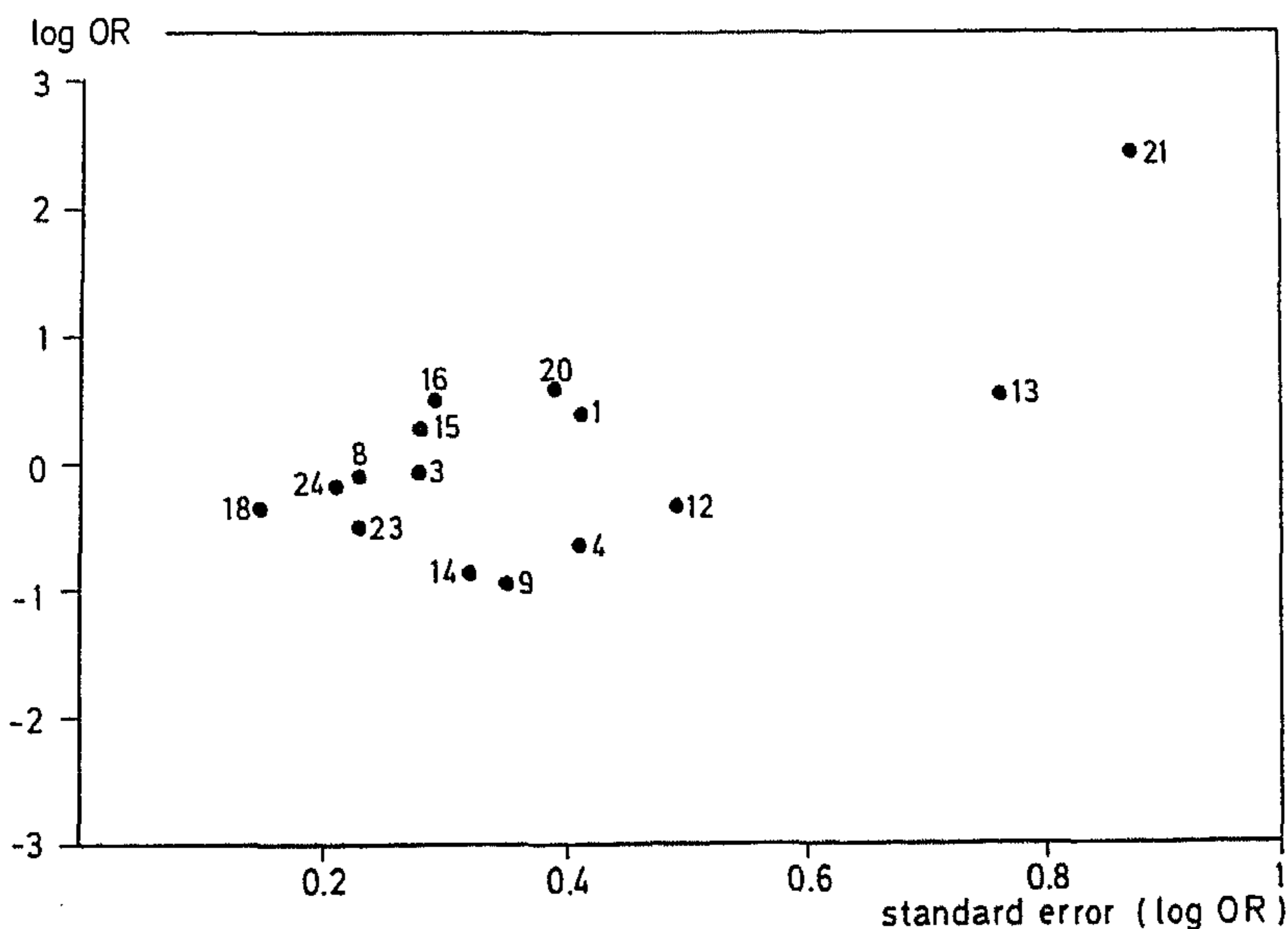


Fig. 2. The natural logarithms of the odds ratios (log OR) for chronic sunlight exposure plotted against the corresponding standard errors of the log OR. Values are indicated with the reference number of the publication from which they were derived. A funnel plot is not shown, because the odds ratios were not homogeneous.



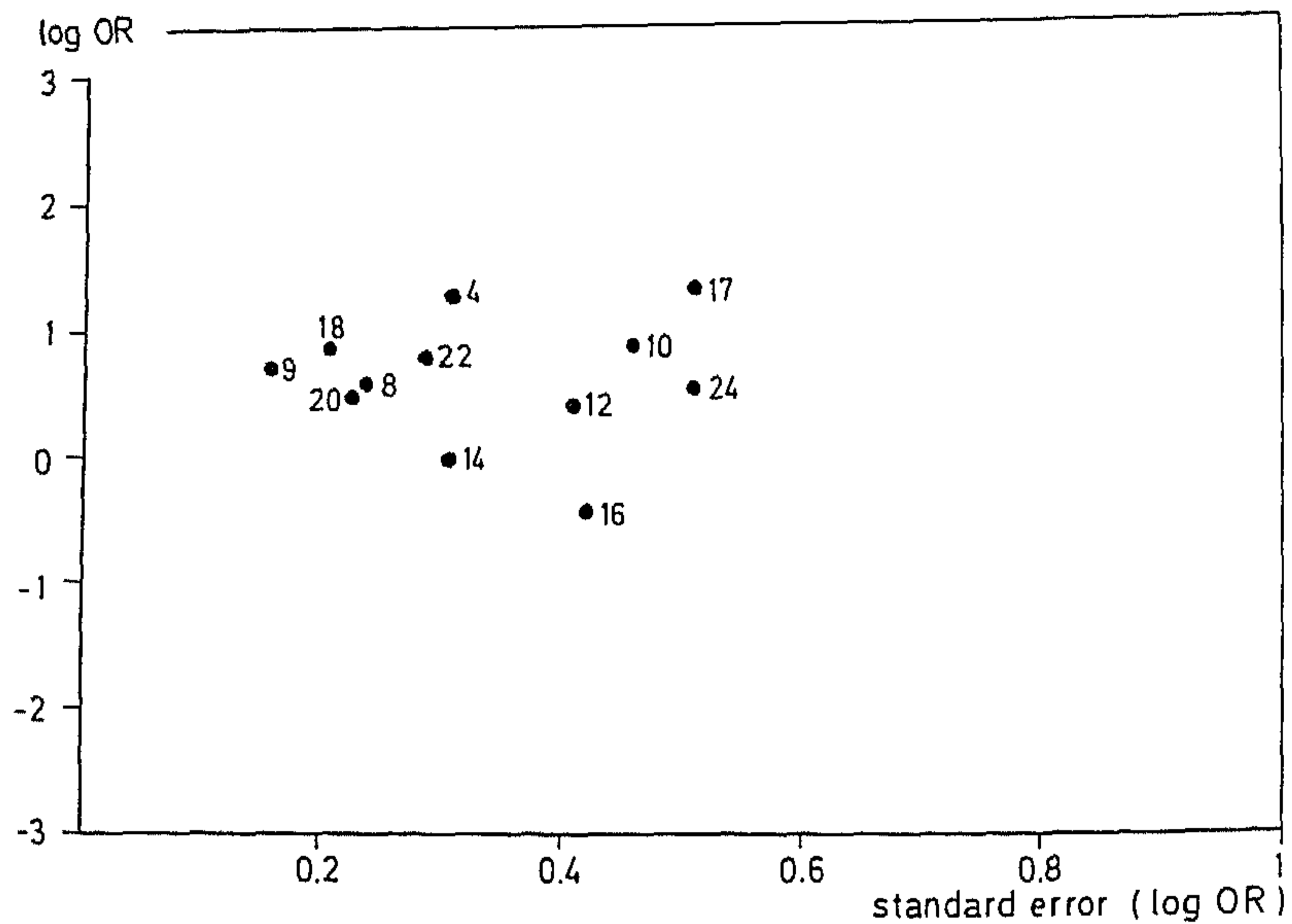


Fig. 3. The natural logarithms of the odds ratios (log OR) for sunburn history plotted against the corresponding standard errors of the log OR. Values are indicated with the reference number of the publication from which they were derived. A funnel plot is not shown, because the odds ratios were not homogeneous.

had used a blinding procedure. The other variations in study design, such as the length of the induction time and controlling for constitutional risk factors, did not appear to be associated with systematic increases or decreases in the relative risk. Odds ratios did not increase with increasing latitudes of the regions where the studies were performed.

*Subgroup analysis*

Within the group of population-based studies the results clustered around one value (Fig. 4). The homogeneity test on risk estimates for intermittent sun exposure derived from the population-based studies yielded  $\chi^2 = 0.4$ ; greater variation was observed in the rest

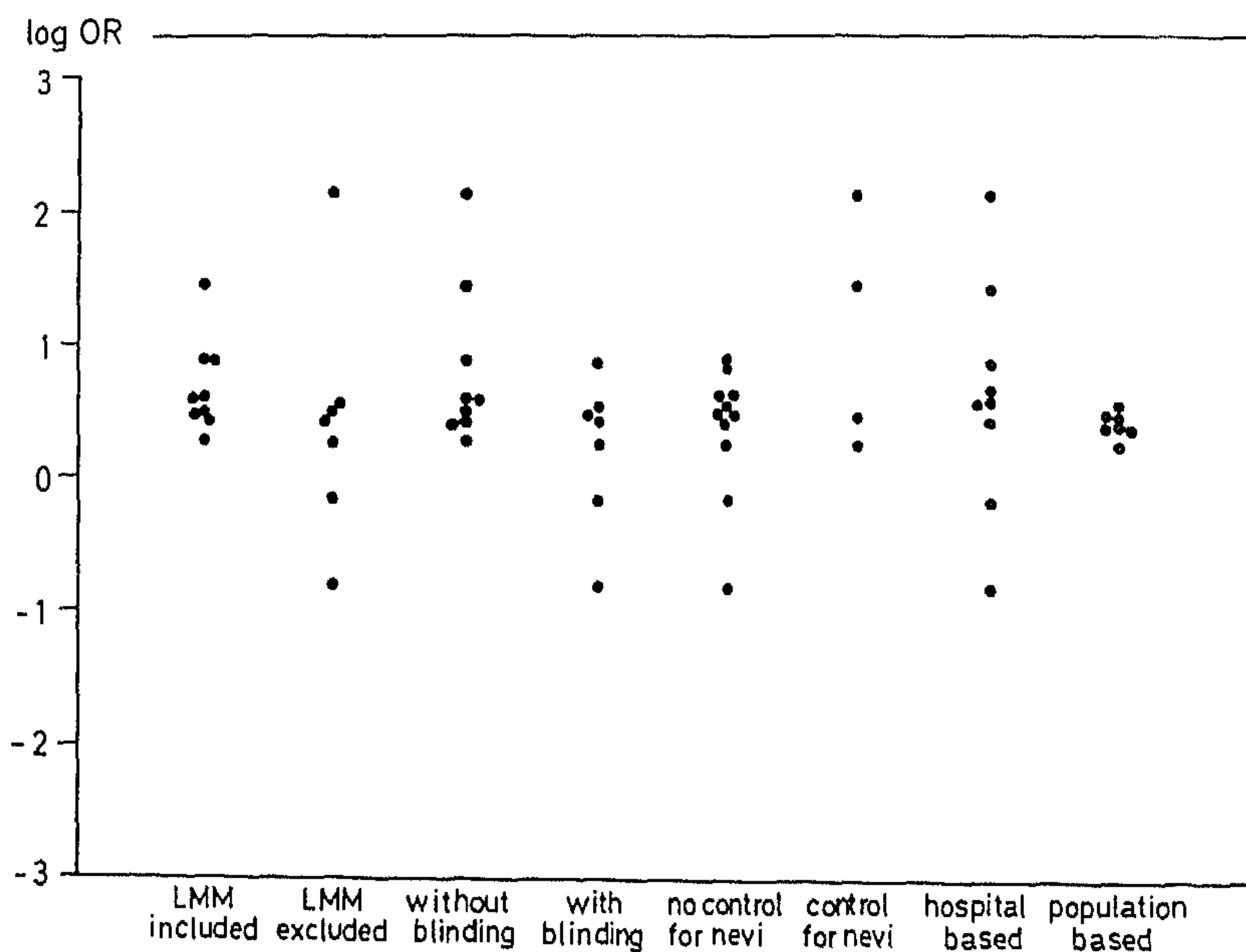


Fig. 4. The natural logarithms of the odds ratios (log OR) for intermittent sunlight exposure in relation to the methodology used in the studies from which the odds ratios were derived.

nine hospital-based studies ( $\chi^2 = 48.80$ ). For chronic sun exposure measures, the  $\chi^2$  values were 6.12 and 30.17 for the population-based and hospital-based studies, respectively. Using data from the population-based studies to calculate the pooled odds ratios resulted in a pooled odds ratio of 1.57 with a 95% confidence interval ranging from 1.29 to 1.91 for intermittent exposure, and in an odds ratio of 0.73 (0.60–0.89) for chronic sunlight exposure.

## DISCUSSION

Meta-analytical techniques were used to evaluate the results of 25 case control studies on the role of sunlight exposure in melanoma risk. Funnel plots were made to show the variation in results against the study size. Variation in the study results in relation to differences in the study designs was also assessed. The studies were classified according to methodological issues that may have been responsible for the differences in odds ratios outlined above. This qualitative analysis suggested that differences in design resulted in scatter rather than bias of the results. This effect was most pronounced for population-based studies versus hospital-based studies. We had expected in advance that specific methodological approaches, such as blinding or the exclusion of lentigo maligna melanomas, would be associated with a systematic decrease in the odds ratios. The most probable explanation for the lack of systematic bias was that the effects of specific study characteristics were confounded by the effects of other characteristics. A solution to this problem would be "meta-regression," that is, regressing the study results on several study characteristics simultaneously [50], but the number of studies used in this meta-analysis was too low to produce reliable results.

For the population-based studies, the odds ratios were homogeneous. The pooled odds ratio from the population based studies was 1.57 for intermittent sunlight exposure and 0.73 for chronic sunlight exposure. Although these results seem to support the intermittent sunlight hypothesis, they should be interpreted with caution.

Fleiss and Gross mentioned several questions that must be addressed in the application of meta-analysis to epidemiological studies [34].

1. Should all studies be included, or only the published ones?

2. Should all published studies be included, or only the "good" ones?
3. When the study results are heterogeneous, how should they be included, or should they be meta-analyzed at all?
4. Has proper control or adjustment been made for biases that frequently occur in epidemiological studies?

We decided to include only published studies. A problem with this approach is that because of publication bias and "the file drawer phenomenon," studies with negative results are less likely to be published or submitted [51] and will therefore be underrepresented in a meta-analysis on published studies. Funnel plots can help to identify publication bias [36]. Bias due to the omission of small-sample studies with nonsignificant, small effects would show up in Fig. 1 in the form of a bite out of the funnel where it approaches zero [36]. However, the funnel plot includes two studies with larger standard errors and nonsignificant results [12, 13], which suggests that with respect to the effect of intermittent sunlight exposure, publication bias may be limited. In Fig. 2, the middle of the funnel plot appears to be hollow. This indicates that studies in which no effect was reported for chronic sunlight exposure on melanoma risk may be underrepresented in the literature. Therefore the weighted average of 0.73 for chronic exposure in the population-based studies may be biased and in reality could be closer to 1.

In answer to the second question, concerning whether all studies or only the "good" ones should be included, we decided to include all the studies that presented one or more odds ratios with some corresponding measure of precision, irrespective of quality. At present there are no generally accepted methods for measuring the quality of nonexperimental studies. All the studies analyzed showed weaknesses with respect to one or more design aspects, but it was not clear how these weaknesses should be weighted or to what extent they resulted in invalid study results.

As we expected, when all the studies were considered, the results were not homogeneous. This means that we could not pool all the study results. Therefore studies were divided into subgroups according to design aspects that might have influenced the odds ratios. Within the group of population-based studies, graphically, the odds ratios clustered around one value and a homogeneity test indicated that the results

could be combined. For this reason, we calculated pooled odds ratios for intermittent and chronic sunlight exposure. Whether the results were valid can still be disputed because of the different ways in which sunlight exposure was measured. The lack of standardized measures for intermittent and chronic sunlight exposure, and the use of different baseline and exposure categories, form a serious problem in assessing the effect of ultraviolet (UV) exposure on melanoma risk. However, this argument also pertains to the more classical reviews that had to cope with this problem, too [29–33]. The fourth question, concerning whether proper adjustment had been made for biases, was extensively addressed in this meta-analysis. From Table 3 it can be concluded that only a minority of authors considered a few of the methodological problems that might be sources of bias. Only 7 of the 20 authors mentioned in Table 3 excluded lentigo maligna melanoma, only 7 authors used a blinding strategy to reduce recall bias, while both these methodological shortcomings can lead to overestimation of the relative risk. Only 11 authors adjusted for the number of nevi or other important constitutional risk factors.

Several important questions concerning the melanoma–sunlight association could not be answered by this meta-analysis. Owing to the diversity of measures of sunlight exposure, the study data did not allow any definite conclusions about dose–response relations. More consistent measures of intermittent sun exposure, and the use of similar exposure categories to compare findings for different doses of ultraviolet radiation, would help to integrate evidence about dose–response effects.

Whether the risk was underestimated as a result of inadequate techniques of measurement of intermittent sunlight exposure could not be evaluated either. The measurement of intermittency of sunlight exposure is a complicated issue and failing to find strong associations with melanoma risk could be due to the nondifferential misclassification of exposure [29]. Generally, the authors of the case control studies paid little attention to this problem. Some authors expressed the view that regions with low background levels of sun exposure provide a more ideal situation for distinguishing intermittent from chronic exposure and are thereby more suitable for observing stronger associations between melanoma risk and recreational exposure [14, 18]. This assumption could not be confirmed in this meta-analysis: odds ratios did not increase with in-

creasing latitudes of the regions where the studies were performed. The intriguing question concerning whether the association between sun exposure and melanoma risk is modified by pigmentation characteristics could not be answered. This issue was considered in only a few studies [8, 14, 20] and only one study presented separate odds ratios for sun exposure in persons with good and poor tanning abilities [20]. In this study, the odds ratio for recreational sun exposure in the subgroup of “no or light tanners” was higher (OR = 2.82) than that among “average or dark tanners” (OR = 1.13).

An argument that is often used to support the intermittent sunlight hypothesis is that sunburn history is consistently associated with melanoma risk. This observation, however, is interpreted in various ways in the literature. Several authors considered sunburn history to be an important indicator of intermittent sunlight exposure [5, 10, 17, 18, 22]. Others conclude that sunburn history indicates sensitivity of the skin to the sun and is not itself a causal factor for melanoma [14, 52]. In these latter studies, the odds ratios associated with sunburn decreased and became nonsignificant after controlling for the confounding effects of constitutional factors, including reactions of the skin to sunlight [8, 14, 52]. The tendency to burn easily was more strongly associated with melanoma risk than a history of sunburn [52]. In view of these differences in interpretation, it remains a matter of dispute whether the positive association of melanoma risk with past sunburn can be seen as definite evidence for the etiological importance of ultraviolet radiation.

We conclude that although the weighted averages of odds ratios from the population-based studies were 1.57 and 0.73 for intermittent and chronic sunlight exposure, respectively, there are many reasons why these results should be interpreted with caution. There is too little information about dose–response curves and about the modification of melanoma risk by individual pigmentation characteristics. It is concluded that the evidence for the intermittent sunlight theory is far from complete. There is a strong need for future studies to use standardized exposure measures and methodology techniques.

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