PROTOCOL: The effect of sunlight exposure on mortality: a systematic review

NIHR Bristol Evidence Synthesis Group

1 Document history

24 October 2023	Version 1
28 November 2023	Version 2 (funding statement and protocol registration details added; team updated; further exclusion criterion clarified: studies of phototherapy; formatting changes)

2 Authors

This protocol was prepared by members of the NIHR Bristol Evidence Synthesis Group:

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The full project team is listed in Section 9.

3 Protocol registration

This review was registered on PROSPERO (ID 474157) on 25 October 2023.

4 Funding statement

This review is funded by the NIHR Evidence Synthesis Programme.

5 Plain English summary

5.1 What is the problem?

Being outside in direct sunlight is known to cause damage to our skin. Being sunburnt can increase the chance of getting skin cancer. In fact, sunlight is one of the main causes of cancer. Because of this, sun safety advice in the UK is mainly focused on avoiding the harmful impacts of sunlight. Organizations that provide advice on keeping safe in the sun, such as the British Skin Foundation, say that you should aim to stay in the shade between 11am and 3pm and wear clothing that covers as much skin as possible.

There are also positive effects of sunlight exposure. Sunlight has been shown to increase the amount of vitamin D your body produces. Vitamin D is important for our health. It is not only good for our bones; it may also help our immune system and reduce our risk of developing cancer. Recently, researchers have suggested that sunlight might have other health benefits including reducing the risk of dying from cardiovascular disease.

We also know that different skin types react to sunlight in different ways. People with darker skin need more exposure to sunlight than people with lighter skin to produce the same amount of vitamin D. On

the other hand, people with darker skin might have less risk of developing sun-related skin cancer. However, sun safety advice in the UK doesn't tend to account for differences in skin type.

5.2 What are we trying to find out?

We aim to gather all the available studies that have measured both sunlight exposure and mortality (death) rates. We are interested in the overall number of deaths (by any cause), as well as deaths specifically caused by cardiovascular disease or cancer. By combining the findings of these studies, we hope to find out whether long-term sunlight exposure increases or decreases our risk of dying.

6 Scientific abstract

Current UK sun safety advice focuses on avoidance of exposure to sunlight, based on the long-established relationship between exposure to ultraviolet radiation and skin cancer. Sunlight also has beneficial effects, and there is a need to consider the extent of these effects alongside the harmful effects, particularly for people with skin types that are less susceptible to skin cancer. The aims of this systematic review are to determine the association between sunlight exposure and (i) all-cause mortality; (ii) cardiovascular-related mortality; and (iii) cancer-related mortality (including specific types of cancer) and to examine whether the associations vary according to skin type. We will search MEDLINE, Embase and other resources for epidemiological studies in the general population. These studies might have used either direct methods to measure sunlight exposure, such as self-reported cumulative sun exposure or frequency of sunbathing, or indirect methods to measure sunlight exposure, such as ultraviolet levels in participants' area of residence or occupational data. We will follow methods broadly as described in the Cochrane Handbook and assess risk of bias using the ROBINS-E tool. We will use the five GRADE domains (risk of bias, indirectness, inconsistency, imprecision and publication bias) to assess the certainty of the evidence.

7 Background and objectives

7.1 Sun safety advice

Current sun safety advice in the UK is primarily focused on the avoidance of exposure to sunlight. Cancer Research UK recommends keeping to the shade between 11am and 3pm, and to cover up with clothes[1]. This advice is echoed by the NHS[2] and the British Skin Foundation[3]. As part of the development of the NICE guidelines on sunlight exposure[4], an expert review of UK-based sun safety messaging showed that this advice was ubiquitous across organizations[5].

The advice to avoid strong sunlight is based on the long-established relationship between exposure to ultraviolet (UV) radiation and skin cancer[6]. It is estimated that 86% of melanoma skin cancer cases are attributable to UV radiation[7]. Furthermore, the risk of developing basal cell carcinoma, the most common form of non-melanoma skin cancer, has been shown to be 2.12 times greater with every five sunburns experienced as an adult[8].

7.2 Beneficial effects of sunlight

There is a need to consider the extent of any beneficial effects of sunlight exposure alongside the harmful effects. Advice regarding the benefits of sunlight tends to focus on its role in vitamin D production. Vitamin D has been shown to be important in various aspects of health, such as bone health, reducing cancer risk, and improving the immune system[9-11]. It is estimated that sunlight accounts for at least 80% of vitamin D that the body produces[12].

The large-scale Melanoma in Southern Sweden (MISS) cohort trial has produced several reports on the benefits of sunlight exposure. For example, in a review of the risks and benefits of UV, it was shown that, among their Swedish cohort, individuals with low sun exposure habits were at the highest risk of cardiovascular disease (CVD) mortality compared with those with moderate and high sun exposure[13].

Although vitamin D levels have been shown to be inversely associated with risk of CVD, other studies have shown that vitamin D supplements have no such effect[14]. As such, it may be that the link to vitamin D is indirect, with other mechanisms responsible. Liu et al[15] suggest that sunlight converts nitric oxide metabolites, stored in the skin, to nitric oxide. This in turn helps to reduce blood pressure, among other actions that may be beneficial to cardiovascular health.

7.3 Effect of skin type

Another issue with sun protection advice is that it often fails to consider different skin types, instead focusing on a consistent message to avoid strong sunlight exposure. However, different skin types absorb and react to UV radiation in different ways, resulting in different needs. For example, a UK-based study[16] demonstrated that people with brown skin (Fitzpatrick Type V[17]) need more UV radiation than people with white skin types in order to make the same amount of vitamin D. Moreover, people with darker skin have been shown to have higher levels of vitamin D deficiency than those with lighter skin[18]. In contrast, those with darker skin types might suffer less harm from exposure to the sun. For example, a recent review[19] found little evidence of an association between melanoma incidence and UV radiation in people with skin of colour, suggesting that sunlight exposure may not be a risk factor for skin cancer in those with darker skin types, as it is for those with lighter skin types[20].

7.4 Relevant health inequalities

Sun exposure affects all people. However, some groups may be at particular risk of either excessive or insufficient exposure. This includes those who work outdoors or spend more time outside[21], and those who live in geographical regions with higher UV radiation[22]. The risks of under-exposure to sunlight may be highest for those who are unable to access outdoor space (for example, those who are housebound, work indoors, or have certain disabilities) or people who regularly wear clothing that limits sun exposure (e.g. for cultural or religious reasons). Skin type and skin colour are also likely to affect the relative risks and benefits of sun-exposure; for example, it has been observed that people with darker skin may be more at risk of vitamin D deficiency[18].

7.5 Aims and objectives

Given the various risks and benefits associated with sunlight exposure, there is a need to examine the overall effect on population mortality to inform the current sun safety advice and to help people to find the right balance between gaining the benefits of sunlight exposure whilst avoiding the risks.

The aim of this review is to determine the association between sunlight exposure and mortality. The specific objectives are:

1. to estimate the effect of exposure to sunlight on:
    a. all-cause mortality;
    b. cardiovascular-related mortality; and
    c. cancer-related mortality (including specific types of cancer); and
2. to assess whether the effects of exposure to sunlight on mortality vary according to skin type.

7.6 Public involvement

We will involve members of the public, particularly people with skin types and skin colours associated with higher risk of excessive or insufficient exposure to sunlight, to contribute to the review and its dissemination.

8 Methods

The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[23] and the *Cochrane Handbook for Systematic Reviews of Interventions*[24].

8.1 Eligibility criteria

Participants	*Inclusion criteria:* • General population *Exclusions*: • Studies restricted to people with pre-existing disease
Exposure	*Inclusion criteria:* Any direct measure of long-term sunlight exposure. This includes, but is not limited to: • self-reported cumulative sun exposure; • frequency of sunbathing; • number of holidays to high UV exposure destinations; • outdoor recreational activities and/or sports; • episodes of sunburn; and • interventions altering sunlight exposure. We will also include non-direct or proxy measures of long-term sunlight exposure, where sunlight is the exposure of interest in the study. This includes, but is not limited to: • residential/geographical exposure, e.g. average UV levels in area of residence; • occupational exposure, e.g. indoor, mixed or outdoor work; • meteorological, e.g. the calculated average daily insolation exposure; and • vitamin D levels, e.g. levels of serum 25-hydroxyvitamin D, as a proxy for sunlight exposure. We will exclude studies in which the intended purpose is not to measure sunlight exposure. For example, studies investigating the effects of vitamin D levels where the intention is not to use vitamin D levels as a proxy for sunlight. Additionally, we will exclude studies that focus on artificial UV exposure, such as sunbed use and of also prescribed phototherapy (e.g. for treating psoriasis).
Outcomes	**Primary outcome:** • All-cause mortality (death from any cause) **Secondary outcomes:** • Cancer mortality (including all cancer-related deaths, and specific types of cancer) • Cardiovascular disease (CVD) mortality (any death involving the cardiovascular system, i.e., those found within Chapter 11 of the ICD-11: Diseases of the circulatory system[25]) *Exclusions*:

	We will exclude studies that report on mortality from specific, individual diseases (other than cancers and cardiovascular diseases, as specified above)
Study design	*Inclusion criteria:* Nested case-control studies Case-control studies Cohort studies Ecological studies Randomized controlled trials (e.g. of interventions to alter sunlight exposure) Quazi-experimental (e.g. Mendelian randomization (MR) studies)
Other considerations	No date limitation will be applied. *Exclusions*: • animal studies • studies reported only as registry entries for ongoing clinical trials • studies reported only in editorials, letters, news items and commentaries • studies reported only in conference abstracts and posters

8.2 Study identification

We will identify studies using bibliographic and non-bibliographic search methods.

8.2.1 Bibliographic searching

To identify potentially eligible studies, we will search the following databases using relevant subject headings (controlled vocabularies), text-words and search syntax, appropriate to each resource:

- MEDLINE (Ovid) 1946 onwards);
- Embase (Ovid) 1974 onwards;
- Web of Science Core Collection (Clarivate) (1900 onwards).

An example search strategy for MEDLINE (Ovid) is included in Appendix-1.

We will also search medRxiv for preprints. We will not apply any date restrictions to the search. We will exclude studies reported only in conference abstracts and ongoing trial protocols. We will check for any relevant retraction statements or errata of included studies.

8.2.2 Non-bibliographic search methods

To help identify further published or unpublished research, we will scan the reference lists of included studies and any relevant systematic reviews.

8.2.3 Managing the searches

Search results will be exported to EndNote for deduplication using the default deduplication settings and manual review of records. Search results will be exported to Rayyan or a similar system for screening.

8.3 Review strategy

Two reviewers will independently screen titles and abstracts identified by the searches. We will obtain full copies of all reports considered potentially relevant and two reviewers will independently assess these for inclusion. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Data will be extracted using standardized data extraction forms developed in Microsoft Excel, Microsoft Access or a similar system depending on the quantity of data available. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. Descriptive data will be extracted by one reviewer and checked by a second reviewer; results of the studies will be extracted by two reviewers independently. Any disagreements will be resolved by consensus or discussion with a third reviewer.

We will collect the following data: study design (nested case-control, case-control, cohort, ecological, trial, quasi-experimental), funding sources (public, industry, mixed), study location, sex, age, ethnicity/race, skin type/colour, occupation, inclusion criteria, method/definition of sunlight exposure, period of exposure (childhood, adolescence, adulthood), length of exposure (specific, lifetime), target condition (all-cause, cancer, CVD). We will extract summary data relating to the association between sun exposure and mortality overall and for all CVD and cancer-related causes. We anticipate that this may be reported differently across the studies included in this review, and may include odds ratios, risk ratios, hazard ratios or regression coefficients.

8.4 Risk-of-bias assessment

The risk of bias in results of will be assessed using the ROBINS-E tool for observational studies[26], the RoB 2 tool for randomized trials[27] or the tool developed by Mamluk et al for MR studies[28]. These assessments will be undertaken by two reviewers independently, with any disagreements resolved by consensus or discussion with a third reviewer. We will compile a list of important confounding factors (common causes of sunlight exposure and mortality) before undertaking the assessments, obtained through examination of literature and discussion with clinical experts. These will include age, sex/gender, ethnicity, smoking status, socio-economic status (with particular reference to occupation) and physical activity.

8.5 Synthesis methods

We will present a narrative summary of all the included studies. This will include a summary of the study characteristics (e.g. study designs, sample size, year, baseline population characteristics, exposure evaluated), their findings and the risks of bias in the findings. We will group the studies by whether measures of sunlight exposure were direct or indirect. Results assessed as at very high risk of bias will be excluded from syntheses.

We will consider whether it is appropriate to provide summary estimates of effect, depending on the similarities among included studies. If appropriate, where multiple studies are identified for the same outcome, fixed-effects and random-effects meta-analysis will be performed. Heterogeneity and inconsistency across studies will be quantified statistically using the tau and I^2 statistics, respectively[29]. If it is not appropriate or possible to conduct a meta-analysis then we will summarize the results using alternative methods, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*[24].

8.5.1 Subgroup analyses

Where disaggregation is possible, we will repeat analyses according to the following subgroups:

- People with different skin colour (dark skin, light skin)
- People with different skin phototypes (e.g. burning, non-burning)

8.5.2 Certainty of the evidence

The five GRADE domains[30] (risk of bias, indirectness, inconsistency, imprecision and publication bias) will be used to assess the certainty of the evidence for all outcomes. These assessments will be

completed by two authors independently, and any disagreements will be resolved by consensus, or through recourse to a third author.

9 Competing interests of authors

None of the authors have any competing interests.

10 Project team

Tom Parkhouse	Reviewer
Francesca Spiga	Reviewer
Katie Webster	Reviewer
Monika Halicka	Reviewer
Sarah Dawson	Information specialist
Joy, Sheetal, Sharon, Robin	Public involvement
Lesley Rhodes	Clinical advisor
Adam Bray	Clinical advisor
Christie Cabral	Health inequalities advisor
Deborah Caldwell	Deputy senior lead
Julian Higgins	Senior lead

11 Timetable/milestones

Milestone	**Date to be completed**
Draft protocol	26 September 2023
Final protocol	24 October 2023
Draft report	31 March 2024
Final report	TBC

12 References

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13 Appendix 1: search strategy for Ovid MEDLINE

Ovid MEDLINE(R) ALL <1946 onwards>	
1	((sun or sunbath* or sunlight or sunshine or solar) and (exposure or radiation)).ti,hw.
2	(exp *Sunlight/ or *Sunbathing/ or (sun or sunbath* or sunlight or sunshine or solar).ti.) and adverse effects.fs.
3	or/1-2
4	sunlight/ or sunbathing/ or *infrared rays/ or *ultraviolet rays/
5	(sun or sunbath* or sunlight or sunshine or solar).ti. or ((sun or sunbath* or sunlight or sunshine or solar) adj3 (expos* or overexpos* or radiation or rays)).ab,kf.
6	(sun or sunbath* or sunlight or sunshine or solar).mp. and ((infrared or ultraviolet).mp. or (UV or UVA or UVB or UVR or IR or IRA or IRB or IRC).tw,kf.)
7	Seasons/ and Vitamin D/
8	((sun or sunbath* or sunlight or sunshine or solar or ultraviolet or UV or UVA or UVB or UVR) and Vitamin D* and (environment* or outdoor? or out-door? or outside or out-side or (natur* adj1 expos*) or season* or spring or summer or autumn or winter)).mp.
9	Sunburn/
10	(sunburn* or sun burn* or sun damage).tw,kf.
11	Tanning/
12	(solarium? or sunbed? or sun bed? or sunlamp? or sun lamp?).tw,kf.
13	(tanning and (sun or sunbath* or sunlight or sunshine or solar or infrared or ultraviolet or UV or UVA or UVB or UVR or IR or IRA or IRB or IRC)).tw,kf.
14	or/4-13
15	Dose-Response Relationship, Radiation/
16	dose-response.tw,kf.
17	risk/ or risk factors/
18	risk?.ti,kf. or (risk adj3 (allerg* or benefi* or complication* or disease or factor? or harm or harms or harmful or hazard* or health or hypersensitiv* or hyper-sensitiv* or factor or photo* or potential or negative or reaction* or safety or side effect* or toler*)).ab.
19	(risk adj3 (cancer* or skin or carcinoma* or malignan* or lymphoma* or melanoma* or neoplas* or noncancer* or nonmelanoma* or NMSC or nonlymphoma* or tumour? or tumor?)).tw,kf.
20	((risk adj3 (CVD or nonCVD or cardio* or cardiac* or heart or hypertensi* or myocard* or thrombo* or VTE)) or ((antihypertens* or anti-hypertens*) adj3 (effect? or factor? or outcome?))).tw,kf.
21	((advers* or carcinogen* or damag* or danger* or detriment* or disadvantag* or exacerbat* or harm or harms or harmful or hazard* or injur* or negative or serious or undesirable or unsafe) adj3 (effect? or factor? or reaction? or event? or outcome?)).tw,kf.
22	exp Mortality/ or Morbidity/
23	(morbidit* or mortalit* or survival).tw,kf.

24	protective factors/
25	((advantag* or benefi* or favo#r* or mitigat* or positive or protecti* or safe or safety) adj3 (effect? or factor? or reaction? or event? or outcome?)).tw,kf.
26	or/15-25
27	14 and 26
28	3 or 27
29	case-control studies/ or cohort studies/ or follow-up studies/ or exp longitudinal studies/
30	(registry or registries or regist* based).tw,kf,hw.
31	((association or epidemiologic or cohort or longitudinal or observational or prospective or retrospective) adj3 study).tw,kf.
32	(case control* or case series or (cases and control?)).tw,kf.
33	((cases or patients) adj5 (data* or study)).tw,kf.
34	(population adj2 (based or data* or study or regist* or surveillance)).tw,kf.
35	((compar* adj3 (study or risk?)) and population).tw,kf.
36	(cohort? or follow-up or followup or longitudinal or observational or population).ti.
37	(cohort? adj3 (analys* or compar* or data or prospective or retrospective or study or trial)).tw,kf.
38	((disease or health* or lifestyle or longitudinal or national or MISS or melanoma or "Melanoma in Southern Sweden") adj cohort).tw,kf.
39	or/29-38
40	28 and 39
41	(exposure? adj5 (questionnaire? or survey?)).ab.
42	((cross-section* or questionnaire? or survey?) and (death* or mortalit* or survival or progression or prognosis or predict*)).ti,hw.
43	(41 or 42) and 14
44	40 or 43
45	exp animals/ not humans/
46	44 not 45
47	"Seguimiento Universidad de Navarra".af. or ((sun adj (cohort or project or study)).tw,kf. and spain*.af.)
48	46 not 47