INPLASY PROTOCOL

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None declared.

The effects of local and whole-body heating on pain, burns, cataract, and heat-related illness: A protocol for four systematic reviews with meta-analysis

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Review question / Objective: **To assess the effect of local and whole-body heating on pain (SR10A), burns (SR10B), cataract (SR10C), and heat-related illness (i.e., heat exhaustion and heat stroke; SR10D) in human and non-human mammal randomized controlled trials and observational studies. This protocol follows the PRISMA-P reporting guidelines.**
Eligibility criteria: **We will consider for inclusion studies reporting on the effects of local and whole-body heating from any source on pain (SR10A), cataract (SR10C), and heat-related illness (i.e., heat exhaustion and heat stroke; SR10D) in humans. In SR10B, we will consider for inclusion studies reporting on burns caused by local and whole-body heating (SR10B) in humans and non-human mammals.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 June 2023 and was last updated on 05 June 2023 (registration number INPLASY202360018).

INTRODUCTION

Review question / Objective: **To assess the effect of local and whole-body heating on pain (SR10A), burns (SR10B), cataract (SR10C), and heat-related illness (i.e., heat exhaustion and heat stroke; SR10D) in human and non-human mammal randomized controlled trials and observational studies. This protocol follows the PRISMA-P reporting guidelines.**

Condition being studied: **Local and whole-body heating on pain, burns, cataract, and heat-related illness (i.e., heat exhaustion and heat stroke) in human and non-human mammals.**

METHODS

Participant or population: SR10A: Any human: general population, adults, children, specific groups (e.g., patients, workers). SR10B: Any human: general population, adults, children, specific groups (e.g., patients, workers); Any non-human mammal. SR10C: Any human: general population, adults, children, specific groups (e.g., patients, workers). SR10D: Any human: general population, adults, children, specific groups (e.g., patients, workers, athletes).

Intervention: Not-applicable.

Comparator: To be eligible for inclusion, studies must compare the effects of local or whole-body heating by any source to the effects measured at: normal local tissue temperature or lower levels of local tissue temperature (in SR10A-B), normal local tissue temperature or lower levels of eye lens temperature (in SR10C), and normal body-core temperature or lower levels of body-core temperature (in SR10D).

Study designs to be included: SR10A: Experimental (randomized controlled trial, controlled trial) studies with human volunteers. SR10B: Observational study with human volunteers; Experimental (randomized controlled trial, controlled trial) or observational study with non-human mammals. SR10C: Observational study with human volunteers. SR10D: Experimental (randomized controlled trial, controlled trial) or observational study with human volunteers.

Eligibility criteria: We will consider for inclusion studies reporting on the effects of local and whole-body heating from any source on pain (SR10A), cataract (SR10C), and heat-related illness (i.e., heat exhaustion and heat stroke; SR10D) in humans. In SR10B, we will consider for inclusion studies reporting on burns caused by local and whole-body heating (SR10B) in humans and non-human mammals.

Information sources:
Pubmed (https://pubmed.ncbi.nlm.nih.gov)
Embase (https://www.embase.com)
EMF portal (https://www.emf-portal.org/en)

Main outcome(s): 3.1.4. Types of outcomes
We will assess the effect of exposure (i.e., local or whole-body heating from any source) with any measurement related to:
3.1.4.1. Pain (SR10A): A local increase in skin temperature beyond 41-43°C typically leads to painful sensations where the pain sensation and pain intensity are related to the increase and the rate of increase in temperature from a given initial temperature. This is because the heat-sensitive neurons that are spread across the human skin and internal organs such as the gastrointestinal tract and the spinal cord are the same cells that generate the sensation of pain. As such, pain is the initial adverse health effect of local skin temperature increase. For internal organs, temperature thresholds for pain may vary. The most commonly used self-reporting methods to assess pain intensity (categorical verbal rating scales, visual analogue scales, and numerical rating scales) will be the optimum outcome measurements of interest for this review. Yet, we will also consider other pain measurement tools such as multidimensional scales. To be considered for this review, studies should be based on self-reported pain data.
3.1.4.2. Burns (SR10B): This term is used to describe an injury to the skin or other organic tissue primarily caused by heat, friction or contact with chemicals and that destroys some or all of the cells in the skin or other tissues. For superficial dermal burns in adult human skin, potent thermal stimuli causing the basal layer of the epidermis to reach 44°C typically lead to pathological burn injury, characterized by irreversible damage to the uppermost dermis. Beyond this point, the rate of tissue damage increases logarithmically with every Celsius degree increase in local temperature, while the effects are difficult to estimate once local temperature surpasses 70°C. In total, the magnitude of burn injury is primarily dependent on the anatomical location, regional blood flow,

and the ability for post-burn cooling. The most commonly used measurement techniques for the assessment of burn wounds (classified as laser Doppler techniques, thermography or thermal imaging, other measurement techniques) will be the optimum outcome measurements of interest for this review. At a minimum, studies should include data for burns that have been diagnosed and assessed by an expert / physician to be considered for this review. Studies using self-reported burns will be excluded.

3.1.4.3. Thermal cataract (SR10C): The lens in the eye is prone to the damaging effect of heat. Increase in temperature with more than several degrees Celsius has been shown to coagulate protein in the lens leading to the lens becoming opaque. This condition, known as thermal cataract, has been effectively addressed in the vast majority of cases (e.g., in glass factories, furnace industry) in recent years due to improvements in occupational health and safety, yet it still remains relevant in lasers given the likelihood of injury. Thermal cataract occurs in the cortex of the lens leaving the other parts of the lens intact. The most commonly used measurement techniques for the assessment of cataract (slit lamp examination, visual acuity test, and fundus examination) will be the optimum outcome measurements of interest for this review, though other validated and objective measures will be also considered if present in the identified studies. At a minimum, to be considered for this review, studies should include data for thermal cataract that has been diagnosed and assessed by an expert / physician. Studies presenting biological/physiological data from self-reported thermal cataracts will be excluded. However, studies reporting on self-reported pain from thermal cataract that has been diagnosed and assessed by an expert / physician will be included in this review. Commonly used self-reporting methods for pain such as visual analog scales and Likert scales (e.g., from 1 to 10, where 1 is minimum pain and 10 is maximum pain) will be acceptable outcome measurements of interest for this review.

3.1.4.4. Heat-related illness (SR10D): In this review protocol, the two main adverse health outcomes of heat-related illness will be considered: heat exhaustion and heat stroke. Heat exhaustion, also known as "heat injury", is associated with physical effort and describes a spectrum of increasing severity from mild, moderate, to severe illness. It is characterized by cardiovascular dysfunction (i.e., inability to sustain cardiac output and blood pressure) caused by high skin blood flow requirements and/or dehydration that may or may not be combined with marked hyperthermia. In cases where severe hyperthermia (usually ≥39°C body core temperature) is present, there is an increased likelihood of organ (e.g., kidney, liver) and/or tissue (e.g., gut and skeletal muscle) damage. Heat exhaustion is typically assessed via measures of cardiovascular function, including cardiac output, heart rate, stroke volume, right ventricular preload and pulmonary afterload, left ventricular preload and afterload, as well as blood volume. These will be the optimum outcome measurements of interest for this review. Yet, we will also consider other cardiovascular, thermoregulatory, and clinical measurements that have been previously adopted. To be considered for this review, studies may include indicators for heat exhaustion that has been diagnosed and assessed by an expert / physician. Yet, studies based on self-reported heat exhaustion will be also considered.

Heat stroke is a life-threatening condition defined by profound central nervous system dysfunction (e.g., severe disorientation, aggressiveness, seizures, coma), severe hyperthermia (usually ≥40°C body core temperature), organ/tissue damage, and often coagulopathy and systemic inflammatory response syndrome. As no laboratory test can confirm the diagnosis of heat stroke, the presence of hyperthermia and neurologic abnormalities have been proposed as diagnostic indicators for the condition. Therefore, these will be the optimum outcome measurements of interest for this review. When available, we will also extract

information on coagulation, cell injury, cytotoxicity, organ dysfunction, inflammatory response, as well as heat-shock protein activation. At a minimum, to be considered for this review, studies should include indicators for heat stroke that has been diagnosed and assessed by an expert / physician. Studies using self-reported heat stroke will be excluded.

Quality assessment / Risk of bias analysis: The risk of bias of the eligible publications will be assessed using the Office of Health Assessment and Translation (OHAT) tool. Risk of bias will be examined independently by two investigators, with mediation from a third researcher in case of conflicts. In cases where eligible publications have been co-authored by any of these investigators, the assessment will be performed by the other researchers in the team. To address inconsistencies and questions, all assessors will be trained in the approach used to assess the risk of bias, during a pilot study performed after completion of the study selection.

Strategy of data synthesis: Strategy - We will perform a keyword algorithmic search in scientific databases that focus on research topics relevant to our research question, as follows:
Pubmed (https://pubmed.ncbi.nlm.nih.gov)
Embase (https://www.embase.com)
EMF portal (https://www.emf-portal.org/en)
The search algorithms will be built according to the PECO approach described in Section 1.5 and will be adjusted in the environment of each database. In the algorithmic searching we will use Booleans (i.e. OR, AND, NEXT etc.) and possibly truncations as well as wildcards (*, ?). The reference lists of included studies will be hand-searched for unidentified publications eligible to the present PECO criteria.
We will re-run all searches shortly before the final analyses to comply with WHO requirements regarding the updating of the searches within 6 months before publication of a systematic search. Any further relevant studies identified will be retrieved for inclusion. New records from this process will be screened and evaluated based on the inclusion and exclusion criteria set above.
Synthesis of results
We will perform a meta-analysis of the results of studies that are considered similar enough according to their PECOS elements to be combined. In case suitable data for a meta-analysis will be retrieved, we will perform a random effects meta-analysis of similar studies for each outcome:
If studies have measured the outcomes at more than two levels of exposure, we will conduct a dose-response meta-analysis, the generalised least squares for trend estimation of summarised dose-response (glst) method will be adopted, as implemented in the statistical programme R. Means (i.e., temperature, humidity, wind speed, radiation) will be used to express the level of heat exposure dose, to ensure that they are specific and reflect the physiological state and the body's heat balance, for instance by calculating thermal stress indicators such as the Wet-Bulb Globe Temperature. The process for developing thresholds for heat exposure will follow that used in existing international standards and guidelines. For studies reporting several effect sizes within the same outcome category from the same sample, we will take the median of these effect sizes. We will include each subgroup as a unique sample in meta-analyses for studies reporting effect sizes from independent subgroups.
Where possible, we will model the exposure in different ways to assess the effect of different models. In case a dose-response meta-analysis is not possible, we will compare exposures based on intensity as well as on duration (e.g., high- vs. low-exposure groups). Furthermore, we will contrast the incremental risk increases across different units of exposure (i.e., higher vs. lower unit of exposure).
All meta-analyses will be conducted using the 'metafor' and 'meta' packages for R language (Rstudio, Version 1.3.1093, PBC, Boston, Massachusetts, United States). Funnel plots will only be generated for those meta-analyses that include more than 10 studies.
For outcomes / studies where meta-

analysis is not possible, we will synthesize in a narrative way. To develop our narrative synthesis and approach transparently, we will follow the "Synthesis Without Meta-analysis" (SWiM) reporting guidelines.

Subgroup analysis: Based on well-established inter- and intra-individual differences on the impacts of local and/or whole-body heating on health outcomes, we will conduct subgroup analyses of the following study characteristics where relevant:
Age: children vs. young adults (≤30 years old) vs. middle-aged adults (31-55 years old) vs. older adults (>55 years old);
Aerobic fitness level: above vs. below a peak oxygen uptake of 48.3 (for men) 41.4 (for women) mlO2/kg fat free mass/min;
Acclimatization/acclimation status: acclimatized/acclimated vs. non-acclimatized/acclimated;
Body composition: above vs. below a body fat percentage of 28.8 (for men) 34.9 (for women);
Body morphology: above vs. below a body surface area of 2.0 (for men) 1.7 (for women) m2;
Sex: males vs. females;
Smoking status: smokers vs. non-smokers;
Health status: healthy individuals vs. people with diabetes mellitus vs. people with hypertension.

Sensitivity analysis: Sensitivity analysis will be performed to test the robustness of study findings.

Country(ies) involved: Greece; Japan; Sweden; China; Denmark.

Keywords: Heat; radiofrequency electromagnetic fields; exposure; non-ionizing radiation; thermal; heat exhaustion; heat stroke; systematic review protocol; meta-analysis protocol.

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