NextGEM

Next Generation Integrated Sensing and Analytical System for Monitoring and Assessing Radiofrequency Electromagnetic Field Exposure and Health

D5.2: Umbrella review of RF-EMF exposure from far-field sources and cancer in humans

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Table of Contents

List of Figures

List of Tables

Glossary of terms and abbreviations used

Abbreviation / Term	Description
ALL	Acute Lymphocytic Leukemia
AML	Acute Myeloid Leukemia
AM	amplitude modulated
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BS	Base station
CNS	Central Nervous System
EMF	Electromagnetic fields
ICES-IEEE	International Committee on Electromagnetic Safety of the Institution of Electrical and Electronic Engineers
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IoT	Internet of Things
FM	frequency modulated
GA	Grant Agreement
Mw	microwave
NextGEM	Next Generation Integrated Sensing and Analytical System for Monitoring and Assessing Radiofrequency Electromagnetic Field Exposure and Health
NIKH	NextGEM Innovation and Knowledge Hub
NOS	Newcastle-Ottawa Quality Assessment Scale
PECOS	Population Exposure, Comparator, Outcome, Study type
PRS	Primary Relevant Studies
RF	Radiofrequency
RF-EMF	Radiofrequency Electromagnetic Fields
RoB	Risk of Bias
SCCR	Swiss Childhood Cancer Registry
SMR	Standardized Mortality Rate
SR	systematic review

TV	television
UR	Umbrella Review
UR-A	Umbrella Review on RF-EMF exposure from near-field sources
UR-B	Umbrella Review on RF-EMF exposure from far-field sources
WHO	World Health Organization

Executive Summary

The deliverable D5.2 evaluates the association between far-field RF-EMF exposure and cancer risk through an umbrella review of published meta-analyses and systematic reviews of human observational studies. At exposure levels below International Commission on Non-Ionizing Radiation (ICNIRP) guidelines, no clear carcinogenic mechanisms have been established. The review systematically included studies focusing on both environmental and occupational RF-EMF exposure, using rigorous methodologies like the PECOS framework, AMSTAR-2 quality assessments, and a registered PROSPERO protocol. The findings revealed significant heterogeneity, methodological flaws, and inconsistent conclusions across the included reviews. Four systematic reviews addressed environmental exposures, particularly childhood cancer risks, with results ranging from suggested associations to no evidence of harm. Occupational exposure reviews, analyzing risks for tumors like leukemia, and brain cancers among specific workforces, also reported limited evidence of cancer risk, albeit with critically low-quality scores. Despite its rigorous approach, the review underscores the limitations of current systematic reviews on RF-EMF exposure and cancer risks, including methodological inconsistencies, selective reporting, and biases that undermine reliability. The evidence remains inconclusive, with findings contributing more to confusion than clarity. This highlights the critical need for improved review methodologies, standardized reporting protocols, and enhanced researcher training to strengthen evidence synthesis. By addressing these challenges, future systematic reviews can provide clearer and more actionable evidence to guide public health decisions, address ongoing concerns, and ensure transparency and reliability in evaluating RF-EMF-related cancer risks.

1 Introduction

While modern society heavily relies on emerging technologies utilizing radiofrequency electromagnetic fields (RF-EMF, 100 kHz-300 GHz), especially in telecommunication applications, there is concern about their potential negative impact on human health. This concern is amplified by the potential accumulation of various RF-EMF signal types. In particular, some citizen advocate groups have voiced concern that fifth-generation telecommunication systems (5G; 5G New Radio; 5G NR) may pose a more substantial risk to public health compared to earlier generation systems. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the International Committee on Electromagnetic Safety of the Institution of Electrical and Electronic Engineers (ICES-IEEE) have issued exposure guidelines and standards to mitigate scientifically proven adverse health effects. Cancer was identified as one of the most critical health outcomes requiring systematic evaluation of RF-EMF hazard at exposure levels below current international guidelines, according to 164 experts consulted by the World Health Organisation on priorities ranking [1]. Cancer is also the most extensively studied health outcome in research on prolonged exposure to EMF from mobile communication. These studies account for about 40% of all related epidemiological studies currently indexed in the specialized literature database EMF-Portal (https://www.EMF-portal.org/en). In order to establish a solid scientific foundation for evidence-based risk assessment regarding the potential carcinogenicity of RF-EMF exposure, NextGEM will conduct two umbrella reviews of systematic reviews and meta-analyses of human observational studies on cancer risk associated with exposure to RF-EMF. Umbrella reviews, if executed and interpreted accurately, have the potential to yield the highest level of evidence. The published systematic reviews and meta-analyses will be subjected to a comparative evaluation of their methodological quality, taking into account factors such as transparency, adherence to predefined protocols, effectiveness in addressing the relevant scientific inquiries, and the reliability of their conclusions. This assessment will be based on reference benchmarks and expert evaluation.

1.1 Mapping NextGEM Outputs

The purpose of this section is to map NextGEM's Grant Agreement (GA) commitments, both within the formal Task Description and Deliverable Description, against the project's respective outputs and work performed.

Table 1: Adherence to NextGEM's GA Tasks and Deliverables Descriptions

TASKS	
Task Number & Title	**Respective extract from formal Task Description**
Task 5.1 - Umbrella reviews of systematic reviews and meta-analyses of epidemiological studies on RF-EMF exposure and cancer risk	The goal is to systematically summarize the evidence regarding near- and far-field exposure to RF-EMF and cancer risk in the general and working population provided by human observational studies, using the novel approach of the umbrella review. Umbrella reviews systematically compile evidence from multiple systematic reviews and meta-analyses into one document that is accessible and usable deliverable for public health policymaking. However, it is common that systematic reviews and meta-analyses on the same topic, even published in the same year, come to different conclusions. By systematically summarizing and comparing results of all relevant systematic reviews and meta-analyses on exposure to RF-EMF and cancer risk, Task 5.1 can provide the highest quality of evidence and complete overview of the literature body. The level of evidence from human observational studies will be integrated with those relating to experimental studies of carcinogenic effects of EMF in animal and cells models.
DELIVERABLE	
Deliverable: D5.2: Umbrella review of RF-EMF exposure from far-field sources and cancer in humans (M30) This deliverable presents and discusses the results of the umbrella review of the evidence from the available epidemiological studies on EMF exposure from far-field sources and cancer risks.	

1.2 Deliverable overview and report structure

Based on the objectives and work carried out in Task 5.1, the document starts with the Executive Summary followed by the introduction of the document in Section 1.

Section 2 focuses on the general motivation and rationale for conducting umbrella reviews with the research question of exposure to RF-EMF and associated risk of cancer in humans (Section 2.1). The section finishes with the objectives of the far-field umbrella reviews (Section 2.2) in this document, based on the protocol previously developed within NextGEM (deliverable 5.1).

Section 3 of the deliverable document outlines the methods used in the conduct of the far-field RF-EMF exposure and cancer (UR-B).

Section 4 provides the results of the review. We describe the results of the search strategy, the study screening and the selection process (Section 4.1). Further described in detail are the results of the data extraction, and data synthesis (Section 4.2). We then describe the results of the critical appraisal of the identified studies, which includes the Risk of Bias (RoB) assessment of all included systematic reviews and meta-analyses (Section 4.3). Then, the relationship of the UR-B with the NIKH is addressed (Section 4.4).

Section 5 discusses the main findings and their implications and addresses the general strengths and weaknesses of the UR-B.

Finally, Section 6 concludes the deliverable.

2 Rationale

Exposure to radiofrequency electromagnetic fields (RF-EMF; frequencies 100 kHz to 300 GHz) is ubiquitous. The use of RF-EMF has grown steadily since the 1950s and includes various applications in medicine, industry, domestic appliances, security, military activity, navigation and especially telecommunications [2]. In telecommunications, RF-EMF is employed for radio and TV broadcasting, and for mobile telephony [3].

Since the late 1990s and early 2000s, when mobile telephony became widely adopted by the general public, concerns have been raised by citizens, governments, and experts about the potential health effects of this technology. With the introduction of new technological advancements, such as 5G mobile networks and the growing wireless connectivity of devices through the Internet of Things (IoT), these concerns remain pertinent. Therefore, an evidence-based health risk assessment of RF-EMF is essential to inform decision-makers and address concerns among the public.

In 2018, the World Health Organization (WHO) conducted a comprehensive global survey, targeting scientists in the field of RF-EMF health effect research to ascertain the most relevant health effects potentially associated with RF-EMF. Based on the survey findings, six key areas of concern were identified, and the WHO commissioned a series of systematic reviews of observational and experimental studies on the following topics: cancer [1], adverse reproductive outcomes, cognitive impairment, human self-reported symptoms, oxidative stress, heat-related effects, tinnitus, migraine, and non-specific symptoms. Based primarily on evidence from human studies and public concern, cancer was most frequently rated as critical [1].

2.1 Rationale for umbrella review on far-field RF-EMF and cancer in humans

At exposure levels below limits defined by the ICNIRP [2], no mechanism for carcinogenicity of RF-EMF has been unambiguously established by the hundreds of experimental studies carried out so far.

To inform the general public and support policymakers and healthcare professionals in making well-founded decisions, all relevant and available scientific evidence must be considered. In the presence of numerous, and sometimes conflicting, primary studies, systematic reviews offer a comprehensive overview by applying predefined criteria for the inclusion and exclusion of primary studies and assessing the overall quality of the evidence. As such, systematic reviews are an essential tool for synthesizing evidence and play a critical role in evidence-based decision-making [4]. A surge of systematic reviews published over the past two decades bears testament to the strong demand for this form of evidence synthesis [5]. However, concerns have been raised regarding the potential susceptibility to bias in systematic reviews and meta-analyses, and the massive production of conflicting, redundant, low-quality evidence synthesis articles that are potentially misleading [6]. These concerns also apply to the topic of the association between RF-EMF and cancer. Ioannidis [6] reported on 12 meta-analyses published between 2006 and 2014, with conclusions varying from some potentially increased risk for long-term mobile phone use (≥10 years) and ipsilateral gliomas, to the interpretation of the results as consistent with a null effect.

To synthesize and evaluate the entire body of evidence, it is essential to conduct overviews of systematic reviews and meta-analyses, often referred to as umbrella reviews [7, 8]. Umbrella reviews provide a comprehensive overview of the total evidence on a given topic. Since they are conducted with the same rigorous methodology as systematic reviews, their results are built on a more solid foundation compared to traditional overviews, which may rely on selective or ad-hoc approaches. Furthermore, quantitative tools, such as the AMSTAR (A MeaSurement Tool to Assess systematic Reviews), can be applied in umbrella reviews to assess the quality and reliability of the evidence on a specific subject [9].

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[1] Cancer is a group of diseases involving malignant neoplasms that result from uncontrolled cell division and the ability of these cells to invade surrounding tissues or spread to distant body parts (metastasis). It can affect virtually any tissue in the body.
Neoplastic diseases refer to conditions characterized by abnormal and uncontrolled cell growth, forming masses or tumors. These can be benign (non-cancerous), meaning they do not invade surrounding tissues or spread to other parts of the body, or malignant (cancerous), which can invade nearby tissues and metastasize to distant organs. Malignancies are cancerous tumors or neoplasms that grow uncontrollably, invade surrounding tissues, and can metastasize.

[2] International Commission on Non-Ionizing Radiation Protection (ICNIRP). (2020). Guidelines for limiting exposure to electromagnetic fields (100 kHz to 300 GHz). Health Physics, 118(5), 483–524. https://doi.org/10.1097/HP.0000000000001210

2.2 Objective of umbrella reviews on far-field RF-EMF and cancer in humans

The aim of this far-field umbrella review is to collect and assess all available evidence from published systematic reviews and meta-analyses of human observational studies on a possible association between exposure to far-field RF-EMF and the risk of neoplastic diseases. The following specific objectives were included in this umbrella review:

- Identify relevant systematic reviews and meta-analyses of subject-relevant epidemiological studies;
- Extract and synthesize the evidence;
- Assess heterogeneity across systematic reviews and meta-analyses on the same exposure-outcome association;
- Appraise critically the quality of the included studies.

In order to account for the variety of the literature and exposure conditions, two bodies of evidence have been reviewed separately to assess the neoplasia hazard in relation to RF-EMF:

- UR-A on RF-EMF exposure from near-field sources.
- UR-B on RF-EMF exposure from far-field sources, which is the topic of this Deliverable.

3 Methods

3.1 Eligibility criteria

Studies were included based on the following eligibility criteria as presented in a PECOS (Population Exposure, Comparator, Outcome, Study type) scheme.

Population: The umbrella review includes members of the general population and occupationally active individuals. No restrictions on sex, age, or other individual characteristics were applied.

Exposure: Far-field whole-body environmental or occupational RF-EMF exposure from radio-television transmitters, base stations or any other fixed-site transmitter occurring prior to the outcome event was investigated. The umbrella review depended on the exposure variables and metrics most commonly used in the published systematic reviews and meta-analyses, namely indirect measures, for example measurements or modelled levels of electric fields, magnetics fields or (incident) power density, e.g., at the subject's residence. Systematic reviews and meta-analyses that included epidemiological studies on occupational RF-EMF exposure assessed, e.g., via personal exposure measurements, Job Exposure Matrices, or job titles were also considered, provided that the assessment of the impact of RF-EMF exposure was a predefined research objective and that the exposure is well characterized in terms of source and type.

Comparator: The eligible systematic reviews or meta-analyses should include one or more studies appropriate to provide estimates of the relative risk of diseases based on exposure, i.e., comparing a group of unexposed or less exposed individuals with exposed or highly exposed individuals.

Outcomes: The umbrella review includes all types of neoplasms reported in published systematic reviews and meta-analyses on exposure to RF-EMF that are either histologically confirmed or based on unequivocal diagnostic imaging or ascertainment through cancer registries, hospitals, or any other source that has sufficient coverage of the study base during the time of the study. Self-reported outcomes were also included if they were included in a systematic review or meta-analysis identified in our umbrella review. Systematic reviews and meta-analyses eligible for inclusion in the umbrella review were based preferably on studies investigating incident tumour cases, but systematic reviews and meta-analyses based on studies analyzing cancer mortality were not excluded.

Study type: Systematic reviews and meta-analyses of epidemiological studies were eligible for inclusion if they were informative for hazard assessment purposes, i.e., they summarized the evidence provided by aetiological studies of cohort or case-control design (including variants thereof) published in peer-reviewed journals. Non-systematic reviews such as narrative reviews, scoping reviews or evidence maps were not included. Primary-level studies were not included, regardless of their design (such as ecological studies, cross-sectional studies, case-case analyses, case-control studies, cohort studies and nested case-control studies). Pooled studies of e.g. case-control or cohort studies were considered primary-level studies and, therefore, were not included.

3.2 Information sources and search strategy

The following electronic databases were searched from inception to 15 May 2024 for eligible studies: MEDLINE (PubMed) [3], Web of Science Core Collection (Clarivate) [4], EMF-Portal [5], and Epistemonikos [6]. The search strategy was structured to represent the PECOS schematic of this review. We imposed no restrictions on language or publication date on any of the searches. For our MEDLINE search we added a filter for identifying Systematic Reviews and Meta-analyses[7]. The approach to study identification from this umbrella review is transparently reported in Appendix A. Furthermore, a manual search of all reference lists of the included articles was performed to identify additional systematic reviews of relevance. Relevant articles found via a manual search of the author's personal libraries were also included. However, unpublished articles and grey literature were not sought. Searches were planned to be re-run prior to the final analysis and additional relevant systematic reviews or meta-analyses identified were planned to be included. A final search was planned to be performed in EMF-Portal shortly before

[3] Medline PubMed, https://pubmed.ncbi.nlm.nih.gov

[4] Web of Science, Clarivate, https://www.webofscience.com/

[5] EMF Portal, https://www.emf-portal.org/en

[6] Epistemonikos, https://www.epistemonikos.org

[7] Health Sciences Library System. PubMed Search Filters for Systematic Reviews and Meta-Analyses: University of Pittsburgh. https://hsls.libguides.com/PubMed-search-filters/systematic-reviews#SR-MA-combined. Accessed 29 June 2024.

the results would be published. Given the planned joint publication of the near-field and far-field umbrella reviews in the peer-reviewed literature, it was decided that the re-run of the searches would be conducted at the same time for both umbrella reviews, prior to the final analyses and publication.

3.3 Selection process/study screening

The EndNote 21 software[8] was used to gather the results of the literature search and to manage further data during the process. For duplicate removal, the Deduplicator tool of The Systematic Review Accelerator [10] was used in combination with a self-written R script (Appendix B). Two team members (DB, JZ) independently evaluated the eligibility of identified articles for inclusion using RAYYAN [11], first screening the title and abstract and later assessing the full text of those articles, which passed the first step of screening. If no consensus could be achieved, a third reviewer (ID) was involved in the process to resolve any conflicts.

3.4 Data extraction process

We conducted a pilot of the data extraction on five studies to test and improve the data extraction form. Data was extracted independently by two reviewers (RD, JZ) using pre-designed and pre-piloted forms (Appendix C), to ensure accuracy and consistency. These standardized abstraction forms were established in Microsoft Excel. The entire text (including title, abstract and main text) and tables of the paper, and when available and relevant, supplementary files were used. Ambiguities related to data extraction were resolved by discussion or by a third reviewer (ID) if the two primary reviewers were unable to achieve consensus. The extracted data was thoroughly checked during analysis of the results.

3.5 Risk of bias assessment

To assess the methodological quality and risk of bias of the included systematic reviews and meta-analyses in the umbrella review, AMSTAR 2 [12] and ROBIS [13] were used during the pilot (Appendix D and E). After the pilot, we retained the tool AMSTAR 2, and this deviation from the protocol is explained below. The critical appraisal was performed independently by three reviewers (RD, KR, JZ). One researcher (JZ) appraised all studies, while the other two researchers (RD, KR) split appraisal without overlap. Conflicts in the rating of the studies were resolved by consensus. If no consensus between the two reviewers was achieved, the conflict was resolved by arbitration by the third reviewer of the team. The initial individual ratings and the final modified rating after resolving potential conflicts were recorded. Review authors did not extract data or assess the risk of bias in any study on which they were authors.

3.6 Protocol registration

Following the Prisma guidelines for the conduct of a systematic review, the protocol of this review was registered in PROSPERO (reference number CRD42024529007). The IARC Ethics Committee was notified of the conduct of this study, reference number 24-36.

3.7 Deviation from published protocol

We removed three studies during the data extraction step, after they were deemed eligible. We evaluated that these publications belonged to the category of narrative reviews [14], or that they did not clearly follow a Population, Exposure, Comparator, Outcome, Study type scheme [15, 16]. Since our umbrella review is a review of systematic reviews, the primary studies might be included multiple times, up to once in each systematic review included in the umbrella review; this multiple inclusion of a primary study inflates the influence of said primary study. To keep track of this situation, we decided to examine to what extent systematic reviews included the same primary study and therefore presented a table of the overlap in primary studies in the included systematic reviews. Following the conduct of the pilot study, we performed several modifications to our protocol. We modified the data extraction tool after the pilot. During the pilot on the risk of bias assessment, we observed that the ROBIS tool was fairly subjective and difficult to use, adding heterogeneity rather than clarifying issues (Appendix E). We decided to only use the AMSTAR 2.

[8] https://endnote.com.

3.8 Deployment of the literature review tool in the NIKH

In parallel with the above-described procedure for conducting an umbrella review that involves multiple steps and tools, NextGEM developed the Literature Review tool as integrated into the NextGEM Innovation & Knowledge Hub (NIKH) platform to streamline and automate the entire process within a single platform. The Literature Review Tool simplifies the process of collecting and storing relevant publications from various sources, catering effectively to the needs of researchers. Fully integrated into the NIKH platform, this tool leverages and extends the platform's existing functionalities. Equipped with a user-friendly interface, it offers a centralized solution for evaluating and managing literature reviews, streamlining assessment activities through an intuitive and efficient interface. The NIKH platform allows registered users to initiate a new literature review, supporting tasks such as searching for publications, eliminating duplicates from multiple sources, and combining queries to expand search covers. A key objective of the Tool is to facilitate literature searches within existing scientific libraries and to orchestrate the steps involved in the literature review process, aligning with the umbrella review protocol outlined in Deliverable D5.1 and evaluated in this deliverable, as described below and depicted in Figure 1.

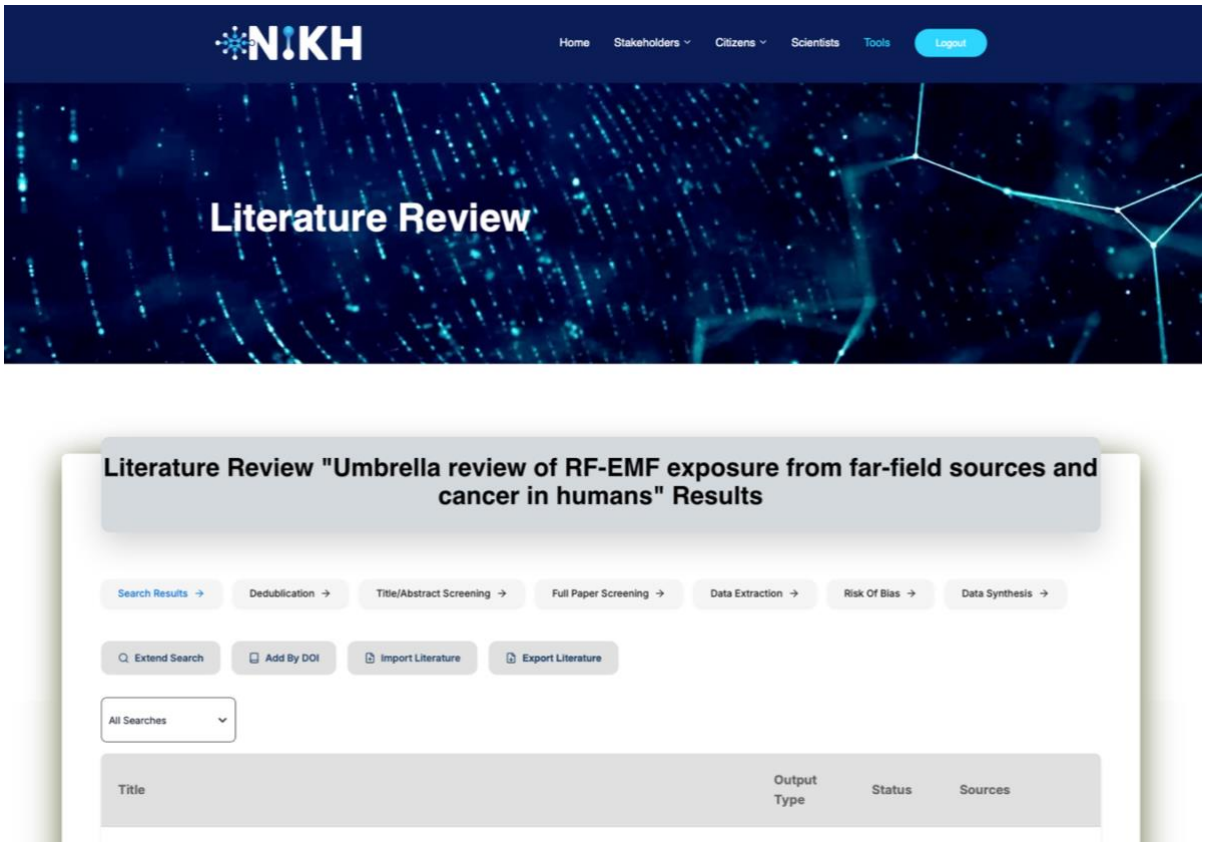

Figure 1: Literature review tool in the NIKH platform

Search Results: The Literature Review Tool facilitates searches across various sources, including Zenodo, EMF-Portal, PubMed, and Web of Science, with the potential to extend to additional sources. Users can customize their searches by specifying fields such as Title, Author, and Study Type, and can broaden their results by applying different criteria across multiple sources. Search results are displayed and stored, including key publication details such as title, authors, abstract, publication date, DOI, and other metadata, ensuring convenient access for analysis and review. All the results are visible in the first tab of the tool.

Deduplication: The tool enables the deduplication of papers based on selected parameters such as title and DOI. This allows users to merge duplicates retrieved from different sources efficiently. Additionally, the tool allows the collection of diverse data and metadata from multiple sources, such as identifying a paper available in Zenodo that may not be present in other repositories.

Title/Abstract Screening: At this stage, papers can be categorized in the NIKH as irrelevant, relevant, or unclear based on a review of their title and abstract. To streamline the process, users can either examine each paper's metadata individually by clicking the "More" button in the GUI or download all metadata in Excel format for bulk review. Users can assign a classification value (0, 1, or 9) from the corresponding dropdown menu.

Full Paper Screening: Papers marked as relevant (1) or unclear (9) during the Title/Abstract Screening phase are forwarded for Full Paper Screening. The tool allows users to download the complete list of papers, including all metadata and full-text documents, if available from the sources. Users can then classify each paper as irrelevant (1), relevant but ineligible (2), or relevant and eligible for inclusion (3). The Literature Review Tool saves the finalized list of relevant and eligible papers for further analysis.

Data Extraction: Once papers are classified as relevant and eligible for inclusion (3), the tool provides a form for each paper, allowing users to extract and record the necessary data for the paper review process.

Risk of Bias: The tool also includes a dedicated form for evaluating the risk of bias for each paper. Users can answer predefined questions based on the selected risk of bias assessment method (e.g., AMSTAR 2).

Data Synthesis: The final step in the protocol involves synthesizing the results, and incorporating insights gained through the risk of bias evaluation process.

4 Results

4.1 Study selection

From the searches conducted in MEDLINE (PubMed) (553 records), Web of Science Core Collection (Clarivate) (2034 records), EMF-Portal (529 records), and Epistemonikos (305 records) and team member's personal library (1 record), we identified a total of 3422 records eligible for both umbrella review B and A. After deduplication, 712 duplicates were removed, leaving 2710 records for the title and abstract screening, which resulted, after full-text screening, in 8 studies eligible for inclusion in UR-B. The full details of the study identification and screening process are provided in Figure 2, presented according to the Prisma 2020 flow diagram for systematic reviews, including searches of databases and registers only [17].

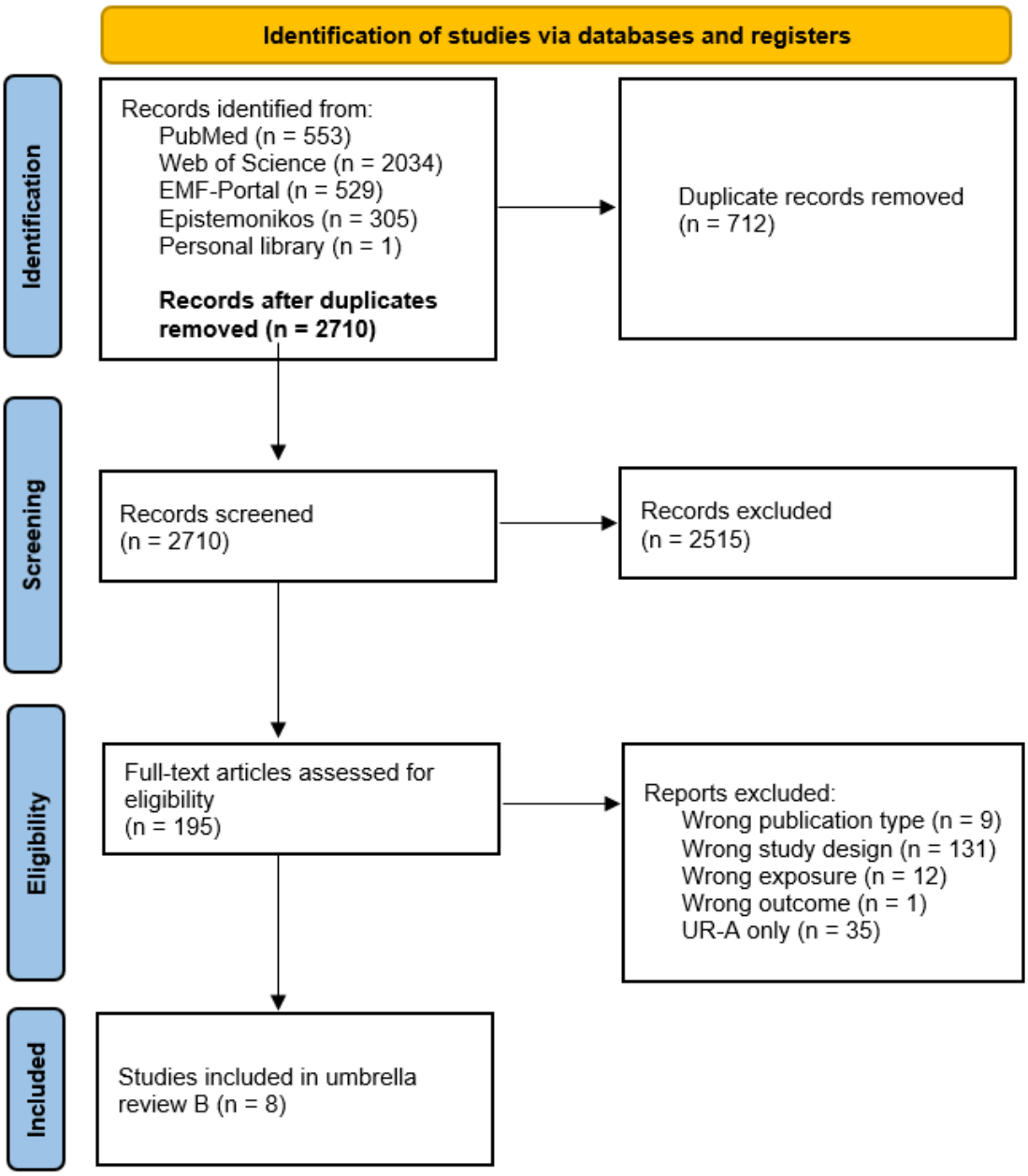

Figure 2: Flow diagram for study selection, presented according to the 2020 PRISMA updated guidelines.

4.2 Study characteristics

The study screening resulted in the inclusion of the following systematic reviews (SR) publications:

- **Balmori (2022) [18]**: Balmori, A., 2022. Evidence for a health risk by RF on humans living around mobile phone base stations: From radiofrequency sickness to cancer. *Environmental Research*, *214*, p.113851.
- **Beranger (2013) [19]:** Béranger, R., Le Cornet, C., Schüz, J. and Fervers, B., 2013. Occupational and environmental exposures associated with testicular germ cell tumours: systematic review of prenatal and life-long exposures. *PLoS One*, *8*(10), p.e77130.
- **Breckenkamp (2003) [20]:** Breckenkamp, J., Berg, G. and Blettner, M., 2003. Biological effects on human health due to radiofrequency/microwave exposure: a synopsis of cohort studies. Radiation and Environmental Biophysics, 42, pp.141-154.
- **Calvente (2010) [21]:** Calvente, I., Fernandez, M.F., Villalba, J., Olea, N. and Nuñez, M.I., 2010. Exposure to electromagnetic fields (non-ionizing radiation) and its relationship with childhood leukemia: a systematic review. *Science of the total environment*, *408*(16), pp.3062-3069.
- **Karipidis (2021) [22]:** Karipidis, K., Mate, R., Urban, D., Tinker, R. and Wood, A., 2021. 5G mobile networks and health—a state-of-the-science review of the research into low-level RF fields above 6 GHz. *Journal of Exposure Science & Environmental Epidemiology*, *31*(4), pp.585-605.
- **Kashani (2023) [23]:** Kashani, Z.A., Pakzad, R., Fakari, F.R., Haghparast, M.S., Abdi, F., Kiani, Z., Talebi, A. and Haghgoo, S.M., 2023. Electromagnetic fields exposure on fetal and childhood abnormalities: Systematic review and meta-analysis. *Open Medicine*, *18*(1), p.20230697.
- **Lim (2023) [24]:** Lim, H., Choi, J., Joo, H. and Ha, M., 2023. Exposures to radio-frequency electromagnetic fields and their impacts on children's health–What the science knows?. Current Opinion in Environmental Science & Health, 32, p.100456.
- **Safari Variani (2019) [25]:** Variani, A.S., Saboori, S., Shahsavari, S., Yari, S. and Zaroushani, V., 2019. Effect of occupational exposure to radar radiation on cancer risk: a systematic review and meta-analysis. Asian Pacific Journal of Cancer Prevention: APJCP, 20(11), p.3211.

This comprehensive umbrella review highlights the potential health risks of far-field RF-EMF exposure, emphasizing occupational and environmental sources.

- **Exposure Sources:** Mobile phone base stations, broadcast towers for amplitude modulated (AM) radio transmissions, frequency modulated (FM) radio transmissions, television (TV) transmission, occupational RF exposure, including from radar.
- **Outcomes:** Associations examined with various cancers, particularly leukemia, brain and testicular cancer.
- **Geographic scope:** Authors of the SR were from high-income countries (Spain (2), France, Germany, South-Korea, Australia), and middle-income countries (Iran (2)). Primary level studies spanned mainly high-income countries, including European countries (Germany, France, Norway, Italy), North-American countries (USA, Canada), Asian countries (Taiwan, South-Korea), and from other areas.

Characteristics of the included systematic reviews are presented in Table 2. The oldest systematic reviews included was from 2003, and 4 systematic reviews were published in the last 3 years (2021, 2022, and two systematic reviews in 2023). However, the range of publication dates of the primary relevant studies spans from 1980 to 2016, with most of the primary studies published in the 2000s and 2010s.

Systematic reviews had various objectives, more or less aligned with our umbrella review research question. For most systematic reviews, only a small fraction (less than 14%) of the primary studies they included met our inclusion criteria and were therefore classified as relevant to this umbrella review. The objectives of these reviews were either significantly broader in terms of outcomes (e.g. "effect on humans"[18], "biological and health effects"[22]) or in terms of exposures considered (e.g. "prenatal and life-long environmental and occupational exposures"[19] or the whole spectrum of "non-ionizing radiation"[21]) than the objectives of our review, explaining why the information relevant to us constituted only a small portion of these reviews. We also included a systematic review that focused on the effects of "EM waves on fetal and childhood abnormalities"[23], as it contained statements regarding the effects of ionizing and non-ionizing radiation on childhood cancer risk, albeit with a focus on prenatal exposures. One systematic review addressed a research question that was directly aligned with ours, specifically ("occupational exposure to radar and cancer risk"), and we determined that all the primary studies included in this systematic review were relevant to our umbrella review [25]. The earliest review [20], from 2003, focused on cohort studies. Despite its broad objective with respect to outcomes - namely, the "biological effects on human health" - all the primary studies it reviewed reported on cancer risk and were deemed relevant to our umbrella review.

The types of relevant studies across the systematic reviews include a mix of case-control and cohort studies. Case-control studies investigate individuals with specific health outcomes (i.e. cancers) compared to controls without those outcomes to explore exposure links. Cohort studies follow groups over time, examining outcomes based on varying levels of RF exposure. Of the two systematic reviews which produced meta-risks[23, 25]; one included only a single study relevant to the umbrella review [23]. Consequently, the meta-risk estimate, which was primarily based on studies not relevant to the umbrella review, was not informative for this work. Meta-risk estimation is discussed further later in this document.

The systematic reviews included in the umbrella review focused on either the general population (N=4) or occupationally exposed populations (N=4). Details on the overlap of primary relevant studies across the systematic reviews are provided in Appendix F. Overlap would typically be expected when systematic reviews share similar objectives, as older primary studies could be included multiple times, as long as systematic reviews authors considered them relevant for their review. However, there was no overlap in primary relevant studies between the systematic reviews that focused on the general population and those examining occupationally exposed populations.

For the systematic reviews addressing environmental exposures in the general population, including children, the umbrella review identified seven unique primary relevant studies (three cohort studies and four case-control studies) across the four systematic reviews. Among occupationally exposed populations, 24 unique primary studies were identified as relevant (13 cohort studies and 11 case-control or nested case-control studies). In total, the umbrella review included eight systematic reviews, within which a combined total of 31 unique primary studies were identified as relevant. These figures highlight the impact of accounting for overlap, as ignoring it would have resulted in an inflated count of 25 case-control studies and 22 cohort studies.

4.2.1 Environmental exposure to general adult and childhood populations

In systematic reviews focusing on the general population, the exposure considered varied by study. It included

- Mobile phone base stations (BS): Exposure assessed by distance from BS or estimates of RF exposure.
- Broadcast transmitters: RF fields from amplitude modulated (AM) radio, frequency modulated (FM) radio and television (TV) transmitters, categorized by distance or estimates of RF exposure.

One systematic review focused exclusively on the effects of mobile phone base stations, with a clear alignment between its stated objectives and the exposure data reported [18]. The other systematic reviews, with broader scopes, analyzed the effects of radiofrequency fields emitted by radio and television towers alone [21, 23], or together with those emitted by mobile phone base stations [24]. These broader reviews addressed topics such as "environmental exposure to non-ionizing radiation," effects of “electromagnetic fields," and "radiofrequency fields," reflecting the diversity of their objectives and the availability of primary relevant studies Details of the overlaps are presented in Appendix F. However, it is notable that the overlap between Kashani’s and Lim’s systematic reviews [23, 24], published in the same year, is limited to one single primary relevant study from South Korea. This limited overlap raises questions about whether it is attributable to a lack of focus in Kashani’s systematic review - whose aim was to address fetal and childhood abnormalities, nevertheless reporting on the association between radiofrequency fields and childhood cancer risks -, poor keyword selection - they did not include any cancer related keyword-, or other factors. A primary study conducted in Great Britain was presented differently depending on the systematic review [18, 24]. In the most complete systematic review, the study design of this primary study was described as “case-control, cases from the cancer registry, controls from national birth registration data” ([24], Supplementary material Table 1). However, another systematic review reported the design of this same original study as “data on all registered cases of cancer in Great Britain and data on mobile phone base stations”, without mentioning controls [18]. This primary study was confusingly presented as a descriptive registry-based study and therefore excluded at full-text screening from our umbrella review, as per umbrella review criterias, limited to case-control and cohort studies. Overlap was, therefore, missed from the umbrella review on that occasion. While inevitably some level of information gets lost in a systematic review compared to the original report of a study, the information on primary studies was provided with widely varying level of detail depending on the systematic review considered. In [18], it was difficult to abstract the type of design of the original epidemiological study from the information provided.

With respect to exposure metrics, the simplest measure (distance) was reported more frequently than more detailed estimates of radiofrequency exposure. The RF estimates were described in various ways: as “average annual power density” ([18] referring to the Taiwanese primary study), “classified according to the exposure received” ([21] regarding the South Korean primary study), “estimated RF power” ([24] also about the South Korean primary study) or “quantitatively estimated RF power” ([24] about the German primary study), “RF exposure density

(WYs/km²) average annual power density" ([24] referring to the Taiwanese primary study, understood as Watts*Years/km²) and "estimated RF fields (V/m)" ([24] related to the Swiss primary study). No further information was provided. This might partly result from the complexity of the estimation methods used in some primary studies, which made synthesis challenging in any systematic review. Moreover, these methods varied significantly across the four primary studies that attempted to quantify exposure, which makes it difficult to compare the relative merits of the exposure assessment. This might be part of the explanation why these important epidemiological issues for the interpretation of primary studies' findings are hardly addressed in some of the systematic review.

Systematic reviews considered mainly children populations (N=3), of these, two of them reported on childhood leukemia risks only – specifically "children with leukemia" or "leukemia" ([23] regarding the South Korean primary study, [21] about the South Korean and German primary studies). The leukemias subtypes were called by different names "Acute Lymphoid Leukemia" ([21], ALL abbreviation list), "Acute lymphoblastic leukemia" ([21]main text, abbreviation definition), "lymphotic leukemia" (sic) ([21], table reporting on South Korean study), "Acute Myeloid Leukemia" ([21], AML abbreviation list and main text abbreviation definition about the South Korean and German primary studies). One systematic review reported on all childhood cancer risks, including childhood leukemias, brain cancers, central nervous system (CNS) cancers and non-Hodgkin lymphomas, and this one reported the leukemia subtypes as "Leukemia (all, lymphocytic, myelocytic)" ([24] about the South Korean primary study), "all neoplasm, leukemia, brain neoplasm" ([24] about the Taiwanese primary study), and the classification and codes used to identify entities ([24] about the German, British, and Swiss study). The last systematic review considered both adult and childhood populations and all childhood and adult cancer outcomes.

Details of the systematic reviews on far-field environmental exposure to the general and childhood population are reported in Table 3. MEDLINE (Pubmed) database was searched by all systematic reviews, as well as a variety of other databases. From the data provided, it is not clear whether this makes a difference. The presentation of primary studies varied slightly across the systematic reviews. The reported population size differed depending on how the data had been extracted. For instance, the number of participants in the Taiwanese primary study was presented differently in [18] and in [24]: in [18], the reported number referred to the total cases before any exclusions ("N=3481 children"), whereas in [24], it reflected the number of cases included in the analyzed dataset (N=2606) and the number of controls was reported (N=78,178). Similarly, for the South Korean primary study, the number of leukemia cases was consistently reported as 1928 in [21] and [24], but differed in [23]. In [23], the study described "cases: children with leukemia (N=808); control group: N=676; study size: N=1928." Upon comparison with the primary study publication, the figure of 808 cases corresponded to the sum of cases in the reference category and the category associated with the reported risk estimate, and similarly for controls [26].

Details about the study participants and study settings were scattered in the text and in the tables, another challenge for data extraction. In general, information was less complete for the controls. Exposed categories were the same between systematic reviews, but the reporting of the reference group was sometimes missing [18, 23]. It is important to acknowledge that some primary studies publications, such as the Swiss primary study publication, involved multiple analyses on distinct datasets. For example, [24] described the Swiss primary study as comprising two different approaches: "1) Time-to-event analysis: 0 - 16 aged who lived in Switzerland from 2000 census (f/u to 2008) 2) Incidence density cohort analysis : using census of 1990 and 2000, and all the Swiss Childhood Cancer Registry (SCCR)-registered patients in 1985-2008". This complexity, with two separate study sizes, would have made the task of synthesis in any systematic review particularly challenging. Systematic reviews provided various levels of detail on primary studies, and the most complete systematic review on cancer risk of environmental exposures to general population was that of Lim (2023)[24]. While its supplementary material provided synthetic information on the original studies, the review text provided a synthesis. The South Korean primary study deserves particular attention, however. Indeed, in a letter to the editor, the primary study authors indicated that they identified "a technical error in the code" used for the analyses of quartiles of radio-frequency exposure in relation to the leukemia subtypes, and provided corrected results[27]. This correction appeared to have been unnoticed in subsequent systematic reviews, so [21] and [24] quoted the earlier incorrect results and not the later corrected results for unclear reasons.

Risk of bias was performed in two reviews [23, 24], one used the Newcastle-Ottawa quality assessment scale, and the other used the risk of bias tool of the Office of Health assessment and Translation. In Kashani's review[23], the only relevant primary study included, the South Korean study was graded as "good" corresponding to a case-control study with quality assessment score of 5. Lim's review [24], which included five studies considered as relevant to our umbrella review, graded all of them in the first tier of its ROB assessment.

Three systematic reviews narratively synthesized the evidence. Lim's systematic review, which was the most complete, concluded that all the studies graded as lowest risk of bias showed no association between environmental RF exposure and cancer in childhood, which suggested no evidence for carcinogenic effects on children.

Calvente's review, which evaluated the extremely low frequency and radiofrequency fields, albeit in separate sections of their review, did not specifically conclude on radiofrequencies [21]. The majority of the studies included pertained to the extremely low frequency fields range, which presumably influenced the conclusion that the studies had not convincingly confirmed or ruled out an association between non-ionizing radiation and childhood leukemia risk. Balmori's overall conclusion was that most studies found "effects" of base station antennas on cancer risk. This conclusion is based on "73.6% namely 10 out of 13 studies" reviewed by the authors[18], which is an inadequate way to characterize the evidence as it does not account for the quality and information content of each study. The three studies identified as relevant in this systematic review were reported as finding significantly increased risks of cancer; this review had numerous limitations. Kashani's review produced a meta-analysis of "fetal and childhood abnormalities" risk, creating an ad-hoc measure to combine risks for the various health effects and biological parameter changes and extremely low frequency, radiofrequency, and X-rays exposures considered[23]. The unique study included in Kashani's review that was evaluated as relevant to our umbrella review was reported as showing increased risks of childhood leukemia in relation to exposure to radio frequencies emitted by radio transmitters.

4.2.2 Occupationally exposed population

The occupationally exposed population were described in four SR. The original studies reviewed were primarily examining the association between various occupational exposures, including from the proximity to radars (military and police personnel), and cancer risks such as testicular germ cell tumors, leukemia, brain tumors, and other malignancies. Key cohorts involved military personnel from the US Navy and Air Force, Motorola employees, electrical and police workers, and female workers in specific sectors like plasticware and radio operators. Time periods for follow-up varied, spanning from the 1950s to the 2000s. Some studies used interview-based or questionnaire-based methods, while others relied on self-reported or expert assessments of exposure. Additionally, some studies involved the use of health surveillance and occupational data to estimate exposure levels and cancer risks.

Overlaps are presented in detail in Appendix F. Not unexpectedly, SR overlapped partly, and the largest, which included most primary studies relevant to our UR, was on the health effect of low level RF fields above 6 GHz [22]. It included 11 relevant case-control and 6 relevant cohort studies. It included all the 6 primary studies also considered in the SR focused on radar and cancer risk [25], owing to interest in the same frequency range, and 10 additional relevant primary studies reported as investigating radar risk and exposed person's cancer risk. It is not entirely clear why Safari-Variani's SR did not include these 10 primary studies, that we considered as relevant to our UR. A possibility is that they were deemed ineligible, because these were "studies with other occupational or non-occupational carcinogenic risk factors (such as solvents, workplace air pollution, environmental air pollution, smoking, etc)", which was an exclusion criterion in Safari-Variani's SR, or for other unexplained reasons; of note, these were all relatively old primary studies, as they had all been published in the 1980's to 2001 [25]. The earliest review [20] focused on only one type of epidemiological design, namely cohort studies, but considered the entire frequency range of radiofrequencies. It reported on ten primary studies, of which three were presented as analysing radar exposure and cancer risk. These original studies published in 1980, 1998 and 2002 were also included in Karipidis systematic review [22]. With respect to organ-specific risks, Karipidis et al. [22] chose to report on all cancer mortality or all cancer incidence when it was available, while Breckenkamp et al. [20] reported risk estimates for all malignant neoplasms and 26 organs- or system-specific cancer risks, reporting multiple risk estimates for the same primary study. Another review focused on testicular germ cell cancer risk [19]; it reported on seven original studies listed in other SRs [20, 22] as reporting on testicular cancer risk. It is unclear why one Swedish case-control study was not included in [19], whereas it was included in [22], possibly because it comprised few exposed cases("result based on only 2 radar workers and 3 controls", [22] about the Swedish study). However, the exposure of the primary studies were considered differently between SR: in [19], the exposure as an electrician was discussed among the group risk for "construction workers", while in [20], the same study was considered as investigating risk in relation to extremely low frequency fields and radio-frequency fields exposure. Similarly, another study was discussed in terms of exposure as "policemen"[19], while [20] considered the same study as analyzing risk in relation to "radar" exposures; in all these, exposure was based on job titles. In addition, one primary study was described as a retrospective cohort in one SR ([22] about the Canadian study) and as cluster study, thereby not relevant to our UR, in another ([19] about the Canadian study, not listed in the tables). This explains the overlaps or absence thereof. Three studies were specifically discussed in [19] with respect to radar exposure, and all these were in [22]. Additionally, while the primary studies that had considered the radar or other

exposures above 6 GHz were also included in several later SR, seven of the early occupational RF primary studies, with workers exposed to the lower part of the RF spectrum were not considered elsewhere.

In addition to overlaps between SR, it is important that authors are aware of multiple publications resulting from multiple, distinct analyses of the same study population. This can occur, for example, when a cohort study is analysed twice, the second publication has a longer follow-up, and, therefore, increased power. Since these two primary-level studies are not independent from each other, the risks reported by the publications are not statistically independent either, and this should be recognized by SR authors. Therefore, the information provided should be carefully examined, and transparently reported, or the reported risk estimates could be selected to avoid overlaps, if at all possible. As far as we could tell from the information provided, this was not the situation in reviews which considered two analyses of a cohort of US Navy personnel with follow up till 1974 and extended follow-up till 1997 [20, 22]; these 2 analyses of the same cohort were only a small fraction of their study base, however, and therefore exclusion of one of these might not have changed the overall conclusion.

With respect to exposures, Beranger and Breckenkamp's SRs considered the whole frequency range of radiofrequencies (from 30kHz-100kHz to 300 GHz), while Karipidis SR considered only the upper frequency range above 6 GHz, for which at that time, only epidemiological investigations considering occupational exposure to radars were relevant, and Safari-Variani SR was focused on occupational radar exposures.

Comparison groups varied and were often reported as low or background-exposed group versus high exposed group, based on job titles, duration in the job, or expert assessment, for internal comparisons, or comparison were carried out versus a reference external population. With respect to outcomes, SR on workers considered mortality from cancer and cancer disease risk, for a variety of cancer types, including all cancers, and up to 42 different organ-specific risks. One review focused on testicular germ cell tumours risk [19], the others were interested in all cancer types, as part of wider health risk assessments (effects on "human health" [20], on "health" [22], on "cancer risk" [25]).

Details of the SRs on populations occupationally exposed to far-radiofrequency fields and cancer risk are reported in Table 3. The PubMed (i.e. Medline) database was searched by all SR, and a variety of other databases. From the information provided, it cannot be evaluated if including more database searches impacted the results of the SR. The original study sizes and the original study types, when included in multiple studies, were fairly consistently reported between SR. While inevitably, some precisions are lost in an SR, and the information provided also depends on the information available in the original study, the details of the original relevant studies were generally consistent among all the SRs, with few exceptions. In Safari-Variani's study, the sample size for a study from USA was mentioned as a cohort of "sex: female and male, sample size: 40,890"([25] about USA primary study); however, referring to the original paper, the final analyzed dataset consisted of 40,581 men after excluding women; the analysis appears to be exclusively on men, and this number is not reported in any of the three SR which included this publication.

Three SRs synthesized the evidence narratively, and one study provided in addition, information about the statistical methods of synthesis and analysis used to summarize the evidence; it also produced a meta-risk estimate [25]. However, this calculation appears to have combined cancer mortality risks for different organ systems - 26 estimates from three relevant studies—such as lip, mouth, and pharynx cancer mortality risk with that of respiratory and intrathoracic organs. This practice should be discouraged, as the resulting estimate cannot be meaningfully attributed to any specific organ or group of organs, rendering it uninterpretable.

In two systematic reviews, the primary studies were appraised with the Newcastle-Ottawa Quality Assessment Scale (NOS) (N=2 [19, 25]), and one of these employed Cochrane's Q-test to assess the existence of heterogeneity among studies and to evaluate publication bias. One study [22] reported evaluating the primary studies' quality, without detailing the methods. The early review [20] did not report on quality appraisal.

All studies concluded in the same direction, i.e. there was limited evidence of cancer risks associated to occupational exposure to radiofrequency fields.

Table 2: Characteristics of included systematic reviews according to Population, Exposure, Comparator, Outcome, and Study type (PECOS) scheme.

Study	Review type and objectives	Total studies (N)	Relevant studies types (N)	Population: Country of origin of relevant studies	Exposure information of relevant studies	Comparator information	Outcomes of relevance
Balmori (2022)	SR; effects of base stations on humans living around the antennas.	38	Case-control (1), cohort (2)		For all, mobile phone BS antennas		
				Germany	Distance to two BS	Within 400m distance to two BS during 1994-2004 versus beyond 400 m	All cancers
				Israel	Area "A" exposed to one BS	Incidence rates of cases in area "A" compared to those of a nearby clinic out of area "A"	All cancers
				Taiwan	Estimated averaged annual power density from BS within 5 years prior to cases diagnosis (no information for controls)	Higher-than-median estimated exposure (no information on reference group)	Childhood neoplasms (including leukaemia and brain tumors).
Beranger (2013)	SR; prenatal and life-long environmental and occupational exposures associated with testicular germ cell tumors	72	Case-control (3)	**Germany** **USA** **France**	Occupational exposure to microwaves and other radiowaves Radar equipment use	NA	Testicular germ cell tumors
Brecken kamp (2003)	SR; biological effects of exposure to RF/mw on human health in cohorts	10	Cohort (10)	**Italy**	RF from occupational exposure as dielectric heat sealers: length of time in job as RF sealer operator or other laborers, exposure max. >10 W/m² in the mid-1980s (no metal-shielding, no earthing);	Two sub cohorts compared to internal and external population;	All cancer mortality;
				USA	License of amateur radio operator as indicator of possible RF exposure, exposed period from date of licence to end of study or death compared to external (USA) population;	Compared to USA death rates (standardised mortality rate SMR)	Mortality from all malignant neoplasms, and 16 organ specific cancer mortality including lymphatic /hematopoietic system
				Norway (2)	Exposure to light at night, RF and to some extent, ELF fields, defined by time in the job, 405 kH-25 MHz, below detection level at operators desk; 70–200 V/m and 0.1–0.5 A/m (0.5 m from the front of the tuner and 1.5–2 m above floor level); 1,400 V/m and 7.5 A/m (close to unshielded antenna); Extremely low frequencies and radio frequencies, defined by job description from census data;	Spot measurements RF fields and time in the job, compared to Norwegian female population. (standardised incidence rate SIR) and odds ratio OR Occupation classified into 5 categories of exposure, compared to internal and external population;	Incidence of all malignant neoplasms and 15 organ specific cancer incidence including breast cancer Cancer incidence (leukemia and brain tumors);

				Canada	Microwaves (traffic radar units), 10.525 GHz (early devices), 24.15 GHz (since 1975), 35.0 GHz (devices introduced in mid of the 1990s, but not widespread);	Exposure duration (years) from employment or department entry date compared to external population;	Cancer incidence: testis, leukemia, brain, eye, skin;
				USA (4)	Microwaves from radar equipment, defined by job title, mean exposure <1 mW/cm2, infrequently exposure >100 mW/cm2 (assumptions); Radio frequencies (wireless communication technologies) qualitative job exposure matrix, in 4 groups by job title; Nuclear-exposition-related electromagnetic pulses, 10 kHz-100 MHz; Radio frequencies, no other information. Microwaves (radar equipment), defined by job title, mean exposure <1 mW/cm2, infrequently exposure >100 mW/cm2 (assumptions).	high and low exposed group, compared to internal and external population; Background, low, moderate, high exposed group, compared to internal and external population; Potential exposure >= 30 days/6 months, compared to external population; High and low exposed group, compared to internal and external population.	Mortality by cause of death(including cancer) Mortality: all cancers (brain cancer, all lymphatic/ hematopoietic system cancers combined, leukemia); Cause of death(including cancer); Cause of death(including cancer); Cause of death (including cancer);
				Poland	Exposure to radio frequencies/microwaves (pulse-modulated high frequency electromagnetic fields) defined by professional activity, 150 MHz-3.5 GHz, <2W/m2, 2–6 W/m2, incidental exceeding 6 W/m2;	High and low exposed group, compared to internal population;	All cancer morbidity;
Calvente (2010)	SR; association between environmental exposure to non-ionizing radiation and childhood leukaemia risk	15	Case-control (2)	**South Korea**	Exposure to AM RF fields from 31 towers and 49 antennas, transmitting with a power ≥20 kW and operating 24 h/day, distance and classification according to quartile of estimated RF exposure	Children living within 2 km of source in comparison to those residing at distances >20 km; distance (continuous), risk reported in quartile 2 and 3 of RF exposure distribution	Childhood leukaemia (ALL and AML)
				Germany	Exposure from all high-power radio and television broadcast towers (1 AM and 8 FM and TV transmitters) in West Germany. Distance of residence of study subjects to tower and distribution of RF fields, a year before diagnosis	Compared individuals residing ≤2 km distant and at 30 km from a radio/TV station; Risks for 0-<2 km, 2-6 km, 6-10 km compared to reference group 10-15 km (in table)	Childhood Acute Lymphocytic Leukemia, Acute Myeloid Leukemia and ALL+AML
Karipidis (2021)	SR; biological and health effects of RF fields above 6 GHz at exposure levels below the ICNIRP	138	Case-control (11), cohort (6)	**Germany (2) USA (7) France (3) Canada Belgium Sweden Italy Brazil**	Occupational exposure to radar at frequencies above 6 GHz similar to 5G	For cohort studies the exposure assessment of most studies was based on job title, and comparisons were made between occupations with presumed high exposure to RF fields and other	Testicular cancer, all-cancer mortality, neuroblastoma in offspring, non-hodgkin's lymphoma, melanoma, brain cancer, uveal

	occupational limits					occupations with presumed lower exposure.	melanoma, bladder cancer
Kashani (2023)	SR+MA; effect of EM waves on fetal and childhood abnormalities	14	Case-control (1)	**South Korea**	Chronic exposure in children under 15 years old to RF from 31 AM radio transmitters with a power ≥20 kW. Distance of residence and estimates of RF exposure in quartiles	Residence address <2 km from nearest radio transmitter vs. >20 km	Childhood leukaemia (in text and tables) Childhood brain tumors (in text)
Lim (2023)	SR; RF EMF exposure effects on children's health	51	Case-control (4), cohort (1)	**South Korea**	Exposure assessed using residential address at time of diagnosis (for cases and controls). Distance to the nearest AM radio transmitter and estimated individual total RF exposure (power density) from all transmitters. All transmitters had a power (≥20 kW)	Comparison by distance (<=2km vs >20km, 2-4km vs >20km, 4-6km vs >20km, 6-8km vs >20km, 8-10km vs >20km, 10-20km vs >20km) and by quartile of exposure.	Childhood leukaemia and brain cancer;
				Germany	Exposure assessed using residence 1 year before diagnosis. Estimated RF-EMF exposure from radio and TV broadcast transmitters and distance to the transmitters.	Comparison for 90-95 %tile group vs 0-90 %tile group of estimated RF-EMF exposure and for 95-100 %tile group vs 0-90 %tile group and by distance (>=15km vs 10–15km, 6-10km vs 10–15km, 2-6km vs 10–15km, 0-2km vs 10–15km)	Childhood leukemia;
				UK	Exposure assessed using registered address at birth 1. Distance from nearest BS(m), 2. Total power output(kW) within 700m radius, and 3. Modelled power density (dBm) within 1,400m radius	Comparison for 85th%tile vs 15th%tile (for decrease distance of 1212m from nearest BS) 85th%tile vs 15th%tile (for increase of total power output of 6.75 kW) 85th%tile vs 15th%tile (for increase of power density of 57.2 dBm)	All childhood cancers (brain and CNS cancers and leukemia and non-Hodgkin's lymphoma;)
				Taiwan	Exposure assessed over period of 5 years prior to diagnosis. RF exposure density (WYs/km2; average annual power density) from mobile phone BS;	Comparison >=Median vs <Median (RF exposure density), and per 10 WYs/km² increase	All childhood neoplasms including leukemia and brain;
				Switzerland	Residential exposure. Estimated RF-EMF from broadcast transmitters (VHF, UHF) with an output power of more than 100 kW, as well as transmitters with an output power between 10 kW and 100 kW if more than 30,000 persons lived within a 5-km radius	Comparison: low (<0.05V/m), medium (0.05-0.2V/m), and high exposure (>0.2V/m), and Per 0.1 V/m	All childhood cancers including leukemia , CNS cancer, non-Hodgkin's lymphoma.
Safari-Variani (2019)	SR+MA; association between cancer risk and occupational exposure to radar radiation	6	Case-control (3), cohort (3)	**USA (2)** **Germany (2)** (one of these is reported as from Belgium in other SR) **France (2)**	Occupational exposure to radar radiation in military workers	Overall relative risk and mortality ratio of cancer among workers with occupational exposure to radar radiation in comparison to control group (matched for age, sex, region, cancer type, job title)	All cancers

Note: Abbreviations: %tile means percentile.

Table 3: Detailed assessment of systematic reviews on the general population, including children.

Study	Database names	Study size	Population: Details about participants	Setting and context of the original studies reviewed	Instrument(s) used to appraise the primary studies and rating of their quality	Conclusion	Funding of the study
Balmori (2022)	EMF-Portal Google Scholar PubMed	**Germany:** cohort N=1045 in exposed area	Residents of Naila (Saarland)	Study design compared number of newly developed cancer cases in inner area with expected number derived from Saarland cancer register, with an average population (check) and with "patients who had lived further away".	NA	76.9% (10/13) of studies showed an effect for cancer (this includes two reviews, one ecological study and one biological study and several surveys); the three studies included in this UR are reported as finding an increased risk for cancer in association with exposure to mobile phone base stations.	NA
		Israel: Cohort (N total = 622, N cases = NA) in exposed area "A"	Residents of Netanya town	Cohort with external comparison (cases of individuals from a nearby clinic outside the exposed area, to national incidence rates, and to rates of the entire town of Netanya.)			
		Taiwan: cases (N=NA) / controls (N=NA)	Incident cancer cases aged less than 15 years, admitted over period 2003-2007, controls randomly selected	Population based case-control study in Taiwan (N=3481 children); (This study is described as 2606 cases of neoplasms in other SR)			
Calvente (2010)	PubMed	**South Korea**: 1928 cases / 3082 controls	Cases (diagnostics 1993-99) and controls from the national medical insurance data system.	Case-control study leukemia and matched controls, cancer risk adjusted for socioeconomic status, area of residence and population density.	NA	No conclusion from SR authors on RF fields. General conclusion on non-ionising radiation: Studies to date have not convincingly confirmed or ruled out association between non ionising radiation and childhood leukemia risk.	Spanish Ministry of Health (FIS PI080728), and Spanish Ministry of Science and Innovation (Ramon y Cajal Program — for MFFC).
		Germany: 1959 cases / 5848 controls	Cases from the German childhood cancer registry (diagnostics 1984-2003) and matched controls	Case-control study in West-Germany on the risk for any type of leukemia (ALL, AML and ALL+AML examined), reported for distance from either AM or FM/TV transmitters.			
Kashani (2023)	PubMed Scopus Web of Science ProQuest Cochrane	Cases=808, Controls=676 (This study is described as 1928 leukemia cases / 3082 controls in other SR)	Children under age 15 years with leukemia	NA	Newcastle-Ottawa Quality Assessment Scale (NOS)	Regarding RF EMF, only one relevant study was found, which suggests an association with the risk of childhood leukemia.	Alborz University of Medical Sciences (IR.ABZUMS.REC.1400 .124)

Lim (2023)	PubMed Scopus	**South Korea**: 2,884 cases / 3,082 controls;	0 - 14 years old children study period 1993-99; 1,928 leukemia and 956 brain cancer cases and 3,082 controls (diagnosed with respiratory illnesses), selected on the same diagnosis date matching age and sex	The studies were conducted in various residential settings. Study subjects from National Health Insurance Dataset. Multivariate	RoB tool of Office of Health Assessment and Translation (OHAT). All studies at low risk of bias.	There was no association between environmental RF exposure and cancer in childhood, which suggests no evidence for carcinogenic effect on children.	Institute of Information & communications Technology Planning & Evaluation (IITP) grant funded by Korean government (MSIT) (2019-0-00102, A Study on Public Health and Safety in a Complex EMF Environment).
		Germany: 1,959 cases / 5,848 controls;	0 - 14 years old children study period 1984-2003; 1,959 cases and 5,848 controls matched by sex, birth date, region at diagnosis;	cases assessed from the virtually complete German Childhood Cancer Registry.			
		UK: 1,397 cases/ 5,588 controls;	0 – 4 years old children study period 1999-2001, 1,397 cases and 5,588 matching birth controls;(4 control per case)	Cases from cancer registry, controls from national birth registration data			
		Taiwan: 2,606 cases/78,180 controls;	0 - 15 years old children study period 2003-2007, 2,606 neoplastic disease cases, including 939 leukemias and 394 brain neoplasms and 78,180 randomly selected matched controls;	Cases from the from the National Health Insurance Research Database; 30 controls per index case randomly selected by matching the year of birth and year of index case's neoplasm diagnosis for each case.			
		Switzerland cohort (N=NA)	Time to event analysis: 0 - 16 years old children study period 2000-2008 Incidence density cohort analysis using census of 1990 and 2000, and all the Swiss Childhood Cancer Registry (SCCR)-registered patients in 1985-2008	Cancer diagnoses from the Swiss Childhood Cancer Registry and the Swiss National Cohort 2 analyses conducted: time to event and incidence density cohort.			

Table 4: Detailed assessment of systematic reviews on occupationally exposed populations.

Study	Database names	Study size	Population: Details about participants	Setting and context of the original studies reviewed	Instrument(s) used to appraise the primary studies and rating of their quality	Combined Estimate (MA only) and conclusion	Funding of the study
Beranger (2013)	PubMed	**Germany**: 269 cases / 797 controls	Individuals aged 15–69 years, diagnosed between 1995 and 1997	Interview-based case-control study	Newcastle-Ottawa Quality Assessment Scale (NOS)	No association was found between risk and radar equipment use, working near visual display units, or being in a "complex electronic environment."	Rhône-Alpes region (grant n°12 008645 01); French national cancer institute (grant n°2010-372); 'Cancéropole CLARA' (no grant number)
		USA: 266 cases / 271 controls	Individuals aged 18–42 years, diagnosed in Washington between 1976 and 1981	Interview-based case-control study conducted in Washington			
		France: 229 cases / 800 controls	Individuals aged 20–45 years, diagnosed between 2002 and 2005	Questionnaire-based case-control study, adjusted for or excluding cryptorchidism.			
Breckenkamp (2003)	Medline (Pubmed) CancerLit HealthStar EMF database of the WHO	**USA**: Cohort of 40,890 men (represented in two studies)	US Naval personnel (men), who served during Korean War period, 1950–1997 and US Naval personnel, who served during Korean War period, 1950–1974	Based on measurements which the Navy had performed on ships, two sub-cohorts were formed to determine the effects of an exposure to microwaves (radar).	NA	The results regarding malignant neoplasms were inconsistent: three studies reported statistically significant increases in SIR and SMR, three other studies found lower levels of disease or mortality in the exposed cohort, and the remaining three showed insignificant results with ratios close to 1.	NA
		USA: Cohort of 195,775 persons	Employees of Motorola in USA, 1976–1996	Using a qualitative job-exposure matrix, job titles were grouped into background exposure categories. Mortality rates were analysed for the cohort included all Motorola employees who worked for at least six months.			
		Canada: Cohort of 22,197 persons	Ontario police officers, 1970–1995	population-based data were used as a reference to determine SIR. The vocational activity was considered as exposure, a measurement or estimation of exposure was not available.			
		Italy: cohort of women (N=481, PY=10,609, N cases=14)	Plasticware female workers	Occupational cohort of women employed between 1962 and 1992 in 1 company, compared to regional cancer mortality (SMR for all malignant neoplasms).			
		Norway: cohort of women (N=2619, PY= 72105, N cases =140)	Female radio and telegraph operators working at sea 1961–1991	The study analyzed breast cancer incidence in women working at sea as radio or telegraph operators, exposed to light at night, organized into three cohorts.			

		Poland: Cohort of 128,000 persons a year (N=NA, PY=NA)	Polish military career personnel, 1971–1985	All cancers in military personnel were recorded. Analyses compared exposed and non-exposed groups within cohort.			
		USA: Cohort of electromagnetic pulse test workers, 304 men	Male workers in an electromagnetic pulse test program, 1970-1986	Mandatory health surveillance participation was used as an indirect marker of exposure for employees in the testing program.			
		Norway: Cohort of electrical workers, 37,945 men**,** 824,321 person-years	Male electrical workers, 1961–1985	Leukemia and brain tumor incidence was studied in an electrical industry cohort, with occupational data from the 1960 and 1970 censuses.			
		USA: Cohort of amateur radio operators (N=67,829 men, 232,499 PY, N deaths=2485).	Amateur radio operators, 1979–1984	A cohort in Washington State and California (USA) was studied for the SMR of all malignant neoplasms.			
Karipidis (2021)	Embase EMF-Portal Google Scholar PubMed, Web of Science	**Germany**: 269 cases/797 controls	General population of five German cities	Both self-reported and expert assessments were used.	Quality was appraised, methods not described.	The epidemiological studies provided limited evidence of health effects, including cancer at various sites. This review found no conclusive evidence that low-level RF fields above 6 GHz, such as those used by the 5G network, are harmful to human health.	Australian Government's Electromagnetic Energy Program (no grant number), National Health and Medical Research Council (grant no. 1042464)
		France: Cohort of 39,850 men	French male Navy personnel followed from 1975 to 2000	25-year follow-up of military personnel who served in the French Navy.			
		USA: Cohort of 340 men	Male officers from two police departments in Washington, US, followed from 1979 to 1991				
		USA/Canada: 538 cases/504 controls, children	General US and Canadian population	Multi-generational study: parent's professional exposure to radar on offspring cancer risk examined.			
		Belgium: Cohort of 7,349 men,	Belgian professional male military personnel followed from 1968 to 2004				
		France: 445 cases/ 1025 controls	General population of Languedoc Roussillon, France				
		Canada: Cohort of 22,197 men in Ontario	Male officers from police departments in Ontario, Canada, followed from 1964 to 1995	Ontario police officers exposed to traffic radar and followed for 31 years			
		USA (2): Cohort of 40,890 men (represented in two studies)	US Navy Korean war veterans male personnel -followed from 1950 to 1997 -followed from 1950 to 1974	All cancer mortality investigated in military personnel with potential exposure to millimeter waves from radar			

		USA: 230 cases/ 920 controls, men	US Air Force service male personnel	Occupational and environmental risk factors associated with non-Hodgkin lymphoma.			
		USA: 271 cases/ 259 controls, men	Subjects selected from military medical institutions in Washington	Hospital based case-control study, self-reported exposure			
		USA: 221 cases/ 447 controls, men	Male patients from the Ocular Oncology Unit at the University of California	Population based case-control study on association between self-reported exposure to radar or microwaves and uveal melanoma			
		Sweden: 148 cases/ 314 controls, men	General Swedish population (men)				
		Italy: 263 cases/ 287 controls	General population in Milan	Hospital-based case-control study, on occupational agents and risk of bladder cancer			
		Brazil: 40 cases/ 671 controls, men	Brazilian male Navy personnel, exposure based on job title				
		Germany: 118 cases/ 475 controls	General population of Essen, Germany;				
		France: 229 cases/ 800 controls, men	Male patients from 5 cities in France	Hospital based case-control study			
Safari-Variani (2019)	Cochrane PubMed Scopus Google Scholar Web of Science	**Germany**: Case-control study on 1066 men	Case-control study of male ships-airport-military airplane workers in 1995-1997	Case–control and cohort studies, carried out from 1993 to 2016 in various countries, with 53,008 sample size and range of ages 15–69 years that examined the relationship between occupational exposure to radar radiation and cancer strength among workers. All the studies focused on determining cancer rates and assessing risk estimates in military workers.	Newcastle-Ottawa Quality Assessment Scale (NOS)	No significant increase in overall cancer risk or mortality rate was found due to occupational exposure to radar in workers.	Qazvin University of Medical Sciences in Islamic Republic of Iran (project number 40426).
		Germany: Cohort of 7349 men;	Cohort study of male military personnel from 1963 to 1994				
		USA: Case-control study on 1150 men	Case-control study of US air force male personnel in 1970-1989				
		USA: 40890 men and women; (this cohort is described as men-only in the other SRs)	Cohort study of navy personnel from 1950 to 1997				
		France: Case-control study on 1029 men	Cohort study of male navy personnel from 1975 to 2000				
		France: Cohort of 1184 men.	Case-control study of male radar activity workers in 2002-2005				

Notes: Abbreviation PY means Person-Years.

4.3 Results of the assessment of risk of bias

During the feasibility phase, we worked with two different tools (AMSTAR2 and ROBIS) but ultimately decided that AMSTAR2 was more appropriate for this type of study. Whereas AMSTAR2 provides straightforward and relatively objective criteria for quality assessment, ROBIS is rather subjective and impractical in its rating process.

The AMSTAR2 consists of 16 items/questions (Q) with the options to respond with yes, partial yes and no as detailed below:

1) Did the research questions and inclusion criteria for the review include the components of PICO?
2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3) Did the review authors explain their selection of the study designs for inclusion in the review?
4) Did the review authors use a comprehensive literature search strategy?
5) Did the review authors perform study selection in duplicate?
6) Did the review authors perform data extraction in duplicate?
7) Did the review authors provide a list of excluded studies and justify the exclusions?
8) Did the review authors describe the included studies in adequate detail?
9) Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?
10) Did the review authors report on the sources of funding for the studies included in the review?
11) If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12) If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13) Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?
14) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15) If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16) Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Based on the assessment of risk of bias for the selected papers, the results can be found in the Table 5 below:

Table 5 shows the results of the risk of bias assessment using AMSTAR2. Overall, the systematic reviews performed poorly. Most systematic reviews did not include information on the comparator group (Q1), none of them explained why they chose to include both case-control studies and cohort studies (Q3) and none of them reported on the funding of the included studies (Q10). In addition, only two out of eight systematic reviews reported to have an (in some reviews incomplete) a priori written protocol (Q2). Data extraction was performed in duplicate in two systematic reviews (Q6) and selection of studies was performed in duplicate in three systematic reviews (Q5). Two systematic reviews provided a list of excluded studies and justified the exclusions (Q7).

Four systematic reviews, in part, had a comprehensive search strategy (i.e. at least two databases, provided keywords/search strategy, and justified publication restriction). The other four systematic reviews did not use a comprehensive search strategy (Q4). Most systematic reviews described the included studies in adequate detail (Q8). In four systematic reviews, the authors used a satisfactory technique for assessing the risk of bias of included studies, of which only one assessed all the relevant aspects of risk of bias according to AMSTAR2 (Q9). The risk of bias and heterogeneity were sufficiently discussed in four and five systematic reviews, respectively (Q13 and 14). In five systematic reviews, the potential sources of conflict of interest were identified, including any funding they received for conducting the review (Q16).

Questions 11, 12 and 15 apply only to systematic reviews that also performed a meta-analysis. Kashani et al. (2023) and Safari Variani et al. (2019) performed meta-analyses. Safari Variani et al. (2019) scored well on all three questions. Kashani et al. (2023) scored well on the question regarding publication bias (Q15). Because Kashani et al. (2023) only included one study relevant for our research question, we did not evaluate the meta-analysis performed by Kashani et al. (2023). One possible explanation might be that their systematic review was focused on maternal exposure.

Overall evaluation

Following Shea et al. (2017), we gave an overall rating of the quality of systematic reviews. The overall rating is based on the number of critical weaknesses. Shea et al. (2017) considered the following seven questions to critically affect the validity of a review and its conclusions:

- Protocol registered before commencement of the review (Q2);
- Adequacy of the literature search (Q4);
- Justification for excluding individual studies (Q7);
- Risk of bias from individual studies being included in the review (Q9);
- Appropriateness of meta-analytical methods (Q11);
- Consideration of risk of bias when interpreting the results of the review (Q13);
- Assessment of presence and likely impact of publication bias (Q15).

Out of the eight systematic reviews, seven publications received an overall quality score of 'Critically low', and one was given an overall quality score of 'Low' (Kashani et al., 2023).

Table 5: Risk of bias assessment of included systematic reviews: responses to each item/question of the AMSTAR 2 tool and overall rating.

	AMSTAR-2 items/questions															
	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Q 15	Q 16	Overall
Balmori (2022)																	CL
Beranger et al. (2013)																	CL
Breckenkamp et al. (2003)																	CL
Calvente et al. (2010)																	CL
Karipidis et al. (2021)																	CL
Kashani et al. (2023)																	L
Lim et al. (2023)																	CL
Safari-Variani et al. (2019)																	CL

Notes: Q means Item/question of Amstar 2 risk of bias evaluation

Yes	*H: High*
Partial Yes	*M: Moderate*
No	*L: Low*
No meta-analysis conducted	*CL: Critically low*

4.4 Evaluation of literature review tool for conducting an umbrella review

To evaluate the applicability of the Literature review tool for conducting an umbrella review, a new literature review was created on the NIKH platform. The review form was populated with details, including the name of the review, the institution involved, the study description, the editors, and the type of study, as shown in Figure 3

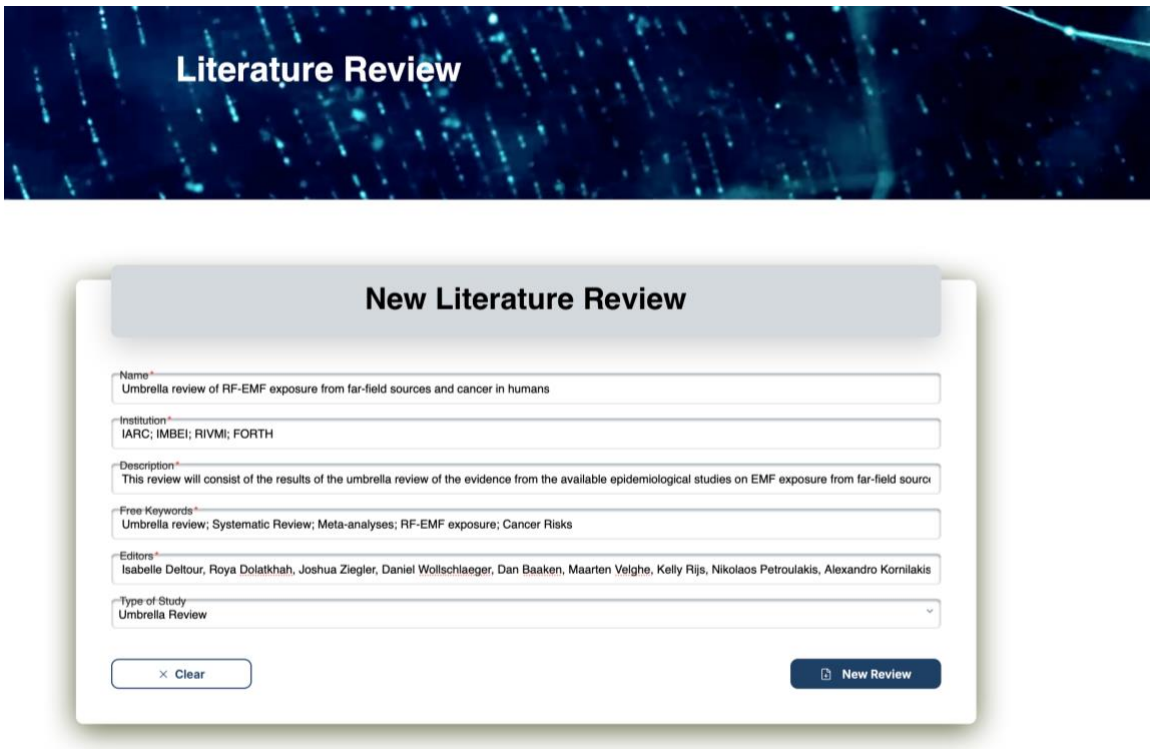

Figure 3: Creation of a new Umbrella Review

The next step of the review involved identifying relevant systematic reviews to conduct the umbrella review of RF-EMF exposure from far-field sources and cancer in humans. The review tool allows users to search existing databases (e.g., EMF-Portal, PubMed, Web of Science), import a list of papers, or add papers using their DOI. This functionality makes the tool highly versatile, enabling both automated and manual paper identification, in alignment with the procedures outlined in the previous subsections and the umbrella review protocol. Additionally, the tool can support the protocol steps, including managing search results, deduplication, Title/abstract screening, and full-paper screening. Figure 4, illustrates the final list of eight identified papers resulting from this process.

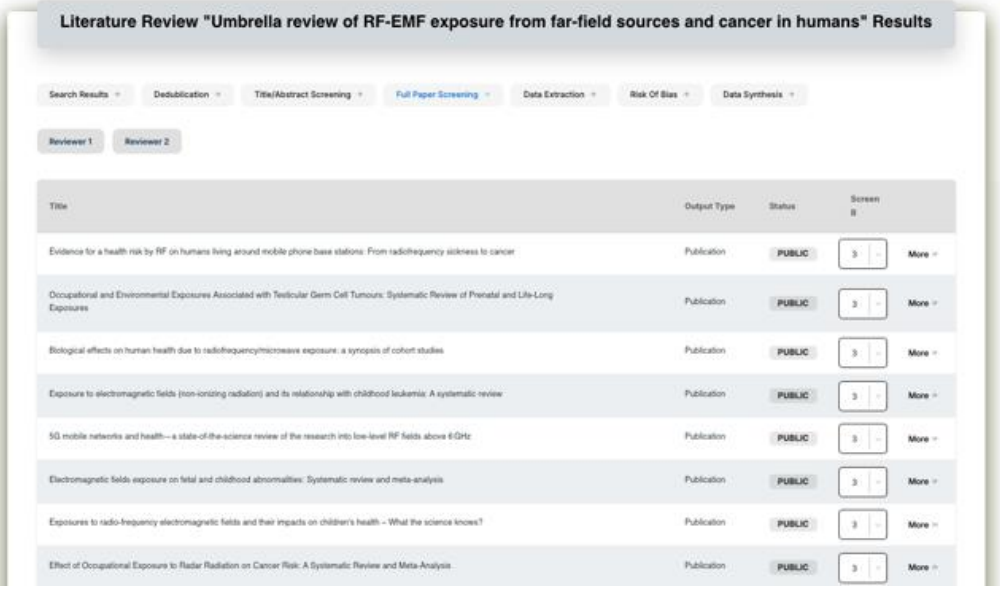

Figure 4: (a) Search results and (b) paper screening of the Umbrella Review related literature

The next step of the protocol involves data extraction from the eight identified papers and completing the relevant fields, as presented in Tables 2–4. For each selected paper, the two reviewers can input the corresponding details into the developed form, as shown in Figure 5.

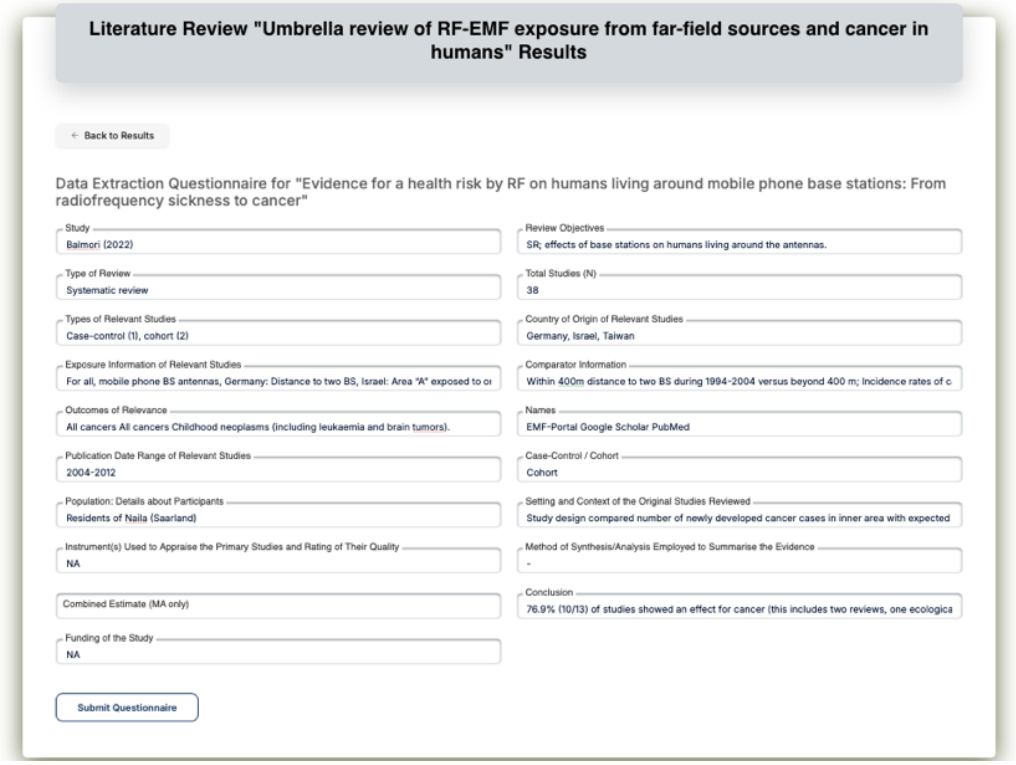

Figure 5: Data extraction from selected papers

After completing the data extraction form, the final step involves filling out the AMSTAR Checklist (Figure 6). The results are summarized in Figure 7, which follows a similar format and presents comparable results to those shown in Table 5.

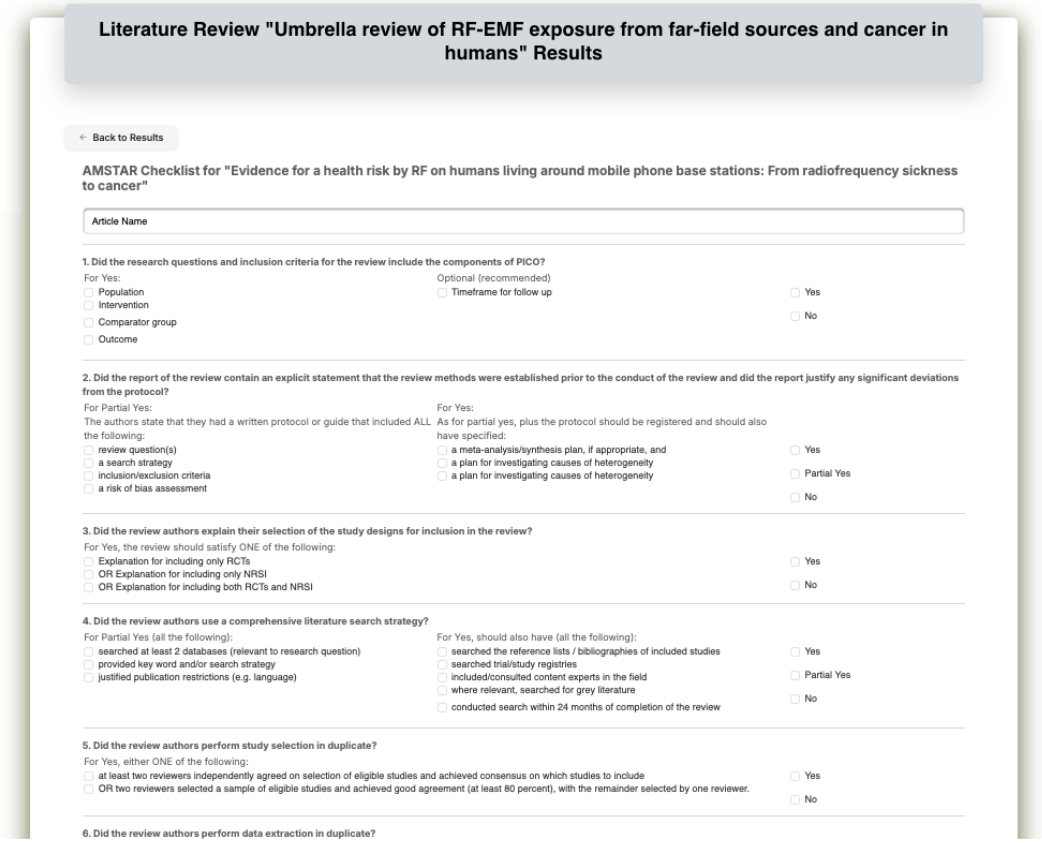

Figure 6: AMSTAR 2 Checklist

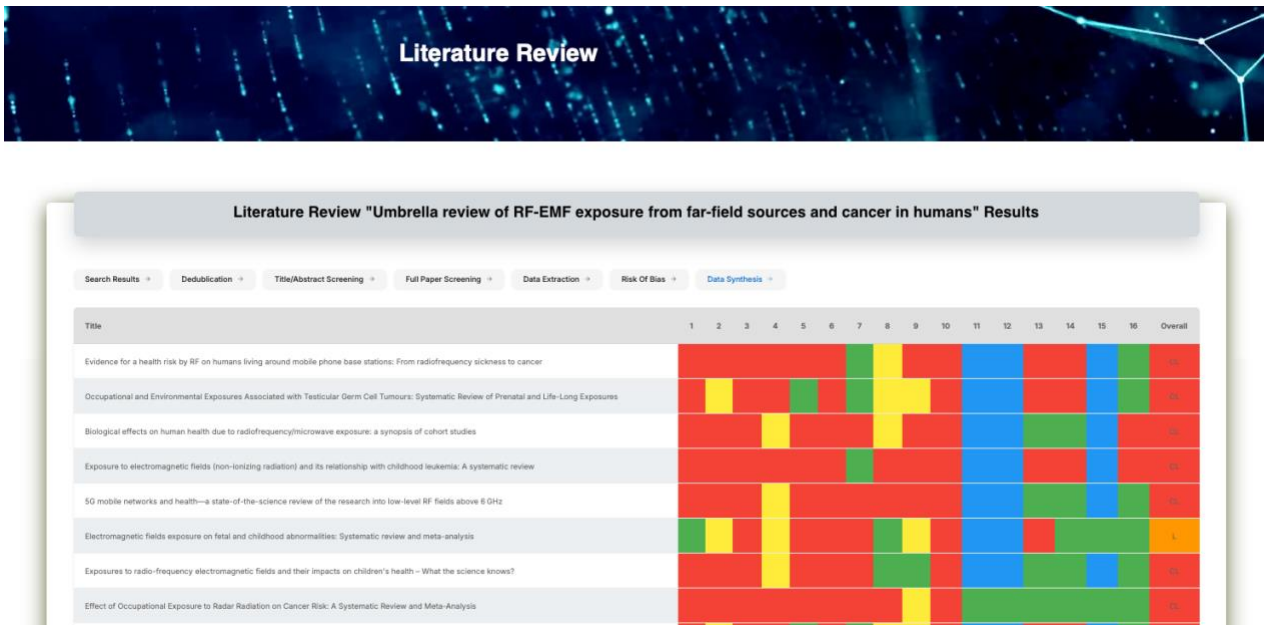

Figure 7: Risk of bias and data synthesis table

The final part of the review tool involves generating a report that compiles all selected papers, the data extraction details, and the Risk of Bias (AMSTAR2) checklist responses, along with the discussion of results and the conclusions.

5 Discussion

5.1 Summary of the evidence and interpretation of the results

The selected systematic reviews (SRs) all adhered to a PECOS framework, which was applied more rigorously in the most recently published reviews following updates to systematic review guidelines. However, the scope of some reviews was occasionally poorly focused [23]. Several reviews had very wide scopes, from the exposure or the outcomes perspective.

Inevitably, there is a loss of information as data moves from primary studies to systematic reviews, and even more so to umbrella reviews. Reporting was heterogeneous; we can only speculate that primary studies may not always have provided all the desired information, requiring SR authors to make decisions about how to present the data. While minor reporting differences might not significantly affect overall conclusions, reporting quality was sometimes very poor [18]. In human observational studies, especially in cancer epidemiology, the exposures encountered are typically multiple, and complex. Systematic reviews must carefully classify exposures and outcomes into coherent categories and groups. This is a challenging aspect of conducting an SR, as the strength of evidence provided by an epidemiological primary study heavily depends on the quality of exposure assessment. For complex exposures, such as radiofrequency fields, synthesizing this information into concise yet accurate terms is particularly difficult, and little information was provided on this aspect. This requires not only expertise in systematic review and meta-analysis methodology but also specialized knowledge of radiofrequency fields. When producing a meta-risk from several primary studies, it is crucial that the combined estimates are comparable in terms of both the exposure groups analyzed and the cancer outcomes assessed. This ensures a meaningful interpretation, such as estimating the cancer risk for a specific organ (or group of organs) at a well-defined exposure level compared to a similarly well-defined reference group. However, primary studies often do not provide data that fully supports such precise analyses. None of the meta-risks in the reviews we evaluated could be meaningfully interpreted [23, 25]. While some flexibility in achieving this ideal is acceptable, it is often unattainable due to limitations in the primary studies, leaving most SR authors to rely on narrative reporting of the evidence [19, 20, 22, 24].

A significant challenge was the limited number of studies, particularly for childhood populations, where only five relevant primary studies were identified. These same studies were reviewed across four systematic reviews. In contrast, the evidence base for occupationally exposed populations was broader but still faced challenges related to data quality and consistency.

Systematic reviews are inherently constrained by the availability of primary studies. Another critical issue in this field is the generally low quality of many reviews, which further complicates efforts to draw reliable and meaningful conclusions.

5.2 Practical implications of the gathered data

The gathered data underscores both the limitations and opportunities within the field of systematic reviews on far-field radiofrequency electromagnetic field exposure and cancer risk. While the low quality of many reviews presented challenges for synthesizing reliable evidence, this finding also highlights the urgent need for improvements in the review process. Specifically, it revealed gaps in methodological rigour, inconsistent reporting standards, and variable inclusion criteria across studies. Addressing these issues in future research could significantly enhance the reliability and utility of systematic reviews.

Although some reviews did not directly contribute to our specific objectives, they were valuable in revealing areas requiring refinement. For instance, heterogeneity in study selection, selective reporting and inappropriate application of meta-analysis methods were recurrent challenges. By identifying these issues, the data highlights a clear path for future research to develop and adhere to more robust methodologies and standardized reporting practices.

Improving systematic review quality will not only benefit researchers conducting evidence syntheses but will also support policymakers and public health practitioners. High-quality reviews can provide clearer guidance for all stakeholders. Moreover, greater methodological transparency can facilitate reproducibility and strengthen the evidence base for understanding the impacts or the absence of impacts of far-field radiofrequency exposure on cancer risk.

Future efforts should prioritize the development of rigorous protocols, training for researchers in systematic review methodologies, and clearer frameworks for quality appraisal. Investing in these improvements will be essential to produce reliable and actionable findings in this critical area of research.

5.3 Strengths and limitations

This study adhered to rigorous inclusion criteria, with studies included based on the eligibility criteria outlined in the PECOS framework, in adequate detail. At least four databases were searched by two independent reviewers, who evaluated the eligibility of the identified articles for inclusion. Data extraction was performed independently by two reviewers. The critical appraisal was conducted independently by three reviewers to ensure the quality of the studies included.

The use of RAYYAN software for screening and the registration of the protocol in PROSPERO also enhances the transparency and reproducibility of the review process.

A strength of the umbrella review is that the quality of the systematic reviews was evaluated using AMSTAR2. Seven out of eight systematic reviews were critically low. One systematic review had a low overall quality. However, they only included one study relevant to the current umbrella review, which was likely caused by their inclusion criteria.

The main limitation is in the methodological flaws of the majority of the systematic reviews included in the umbrella review, which made it difficult to draw meaningful conclusions on the research question at hand. In addition, any outcome that has yet to be included in a systematic review but has been studied in primary research could not be included in the umbrella review.

Therefore, high-quality reviews are lacking.

5.4 Role of literature review tool in an umbrella review

The role of the Literature Review Tool in the NIKH platform appears to be highly applicable for conducting umbrella reviews. Since the primary objective of the NIKH platform is to establish a comprehensive hub focused on EMF and Health, the tool enables registered users to initiate literature reviews and integrate various functionalities. These include conducting literature searches, identifying and eliminating duplicates across multiple sources, and combining multiple queries for a more comprehensive search. Additionally, integrating different tools required for an umbrella review into a single platform minimizes the time needed to transition between tools and platforms, thereby enhancing the quality and efficiency of the review process. The Literature Review Tool aims to provide a standardized framework that allows scientists to translate scientific requirements into technical specifications, supporting its overarching goal of facilitating high-quality umbrella reviews. In the umbrella review of RF-EMF exposure from far-field sources and cancer in humans, the first version of the Literature Review Tool was developed based on the steps required for conducting an umbrella review. For the next deliverable, focused on RF-EMF exposure from near-field sources and cancer in humans, the intention is to utilize the review tool from the outset as the primary tool for conducting the umbrella review.

6 Conclusion

Umbrella reviews rely on existing systematic reviews, which, in turn, are based on primary studies. Regardless of their quality, systematic reviews were inherently dependent on the available primary studies. For far-field and childhood cancer risks, only five primary studies were available, which limited the evidence base. For occupational exposures to radiofrequency fields, a greater number of primary studies existed; many were relatively old.

Systematic reviews examining the association between far-field radiofrequency fields and cancer risk were heterogeneous and varied in quality, with notable differences in methodology and reporting standards. Among studies on cancer risk in the general population, including childhood cancer, the most comprehensive and recent review concluded that there was no evidence of increased risks. In contrast, other reviews had unclear study selection criteria, and some selectively reported increased risks, potentially leading to biased conclusions.

For occupational exposures, the reviews were generally larger and less problematic, though none received high ratings in our risk-of-bias assessment. These reviews were more consistent in concluding that there is limited evidence of cancer risks associated with occupational exposure to radiofrequency fields.

The significant variability in quality and consistency among these reviews, combined with issues such as incomplete reporting and methodological flaws, made it difficult to draw definitive conclusions. Several reviews contributed more heterogeneity than clarity to the research area, potentially misleading readers and rendering them unreliable for addressing the research question. Therefore, high-quality systematic reviews are urgently needed to provide a more reliable understanding of these risks.

Finally, the deployment and development of relevant reviewing tools and protocols are necessary to support the different steps required for conducting high-quality systematic and umbrella reviews.

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Appendices

Appendix A: Search strategies

Search strategies from MEDLINE via PubMed, Web of Science, Epistemonikos and EMF-Portal, as performed on May 15th 2024

Table 1: Search strategies from MEDLINE via PubMed

#	Search Term	Results
1	"Electromagnetic Fields"[MeSH Terms] OR "RF-EMF"[Title/Abstract] OR "radiofrequency electromagnetic field*"[Title/Abstract] OR "radiofrequency field*"[Title/Abstract] OR "radio frequency field*"[Title/Abstract] OR "Far-field"[Title/Abstract] OR "near-field"[Title/Abstract] OR "Wireless Technology"[MeSH Terms] OR "Cell Phone"[MeSH Terms] OR "Cell Phone Use"[MeSH Terms] OR "Radio"[MeSH Terms] OR "mobile telephone*"[Title/Abstract] OR "smartphone*"[Title/Abstract] OR "smart phone*"[Title/Abstract] OR "cell phone*"[Title/Abstract] OR "mobile phone*"[Title/Abstract] OR "cellular phone*"[Title/Abstract] OR "cellular telephone*"[Title/Abstract] OR "Radio Waves"[MeSH Terms] OR "broadcasting"[Title/Abstract] OR "radiation, nonionizing"[MeSH Terms:noexp] OR "nonionizing radiation*"[Title/Abstract] OR "non ionizing radiation*"[Title/Abstract] OR "radio wave*"[Title/Abstract] OR "radiowave*"[Title/Abstract] OR "hertzian wave*"[Title/Abstract] OR "high frequency wave*"[Title/Abstract] OR "short wave*"[Title/Abstract] OR "microwave*"[Title/Abstract] OR "micro wave*"[Title/Abstract] OR "ultrahigh frequency wave*"[Title/Abstract] OR "ehf wave*"[Title/Abstract]	154,475
2	"neoplasms"[MeSH Terms] OR "adenosarcoma*"[Title/Abstract] OR "blastoma*"[Title/Abstract] OR "cancer*"[Title/Abstract] OR "carcinoma*"[Title/Abstract] OR "carcinosarcoma*"[Title/Abstract] OR "glioma*"[Title/Abstract] OR "leukemia*"[Title/Abstract] OR "leukaemia*"[Title/Abstract] OR "liposarcoma*"[Title/Abstract] OR "lymphangiom*"[Title/Abstract] OR "lymphoma*"[Title/Abstract] OR "melanoma*"[Title/Abstract] OR "metastatic"[Title/Abstract] OR "myeloma*"[Title/Abstract] OR "neoplasm*"[Title/Abstract] OR "osteosarcoma*"[Title/Abstract] OR "sarcoma*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "meningioma*"[Title/Abstract] OR "acoustic neuroma*"[Title/Abstract] OR "vestibular schwannoma"[Title/Abstract]	5,281,013
3	#1 and #2	14,189
4	("plants"[MeSH Terms] OR "animals"[MeSH Terms]) NOT "humans"[MeSH Terms]	5,408,761
5	#3 not #4	12,983
6	(("Systematic Review"[Publication Type:noexp] OR "Systematic Reviews as Topic"[MeSH Terms:noexp] OR "Cochrane Database Syst Rev"[Journal] OR "evid rep technol assess full rep"[Journal] OR "evid rep technol assess summ"[Journal] OR "scoping"[Title] OR "systematic"[Title] OR ((("comprehensive analysis"[Title/Abstract:~1] OR "comprehensive review"[Title/Abstract:~1] OR "comprehensively reviewed"[Title/Abstract:~1] OR "literature search"[Title/Abstract:~1] OR "literature searches"[Title/Abstract:~1] OR "scoping search"[Title/Abstract:~1] OR "scoping searches"[Title/Abstract:~1]) NOT "narrative review"[Title]) OR "pooled study"[Title/Abstract:~1] OR "systematic search"[Title/Abstract:~1] OR "systematic searches"[Title/Abstract:~1] OR "systematically searched"[Title/Abstract:~1])) AND ("databases"[Title/Abstract] OR "cinahl"[Title/Abstract] OR "cochrane"[Title/Abstract] OR "embase"[Title/Abstract] OR "psycinfo"[Title/Abstract] OR "pubmed"[Title/Abstract] OR	599,790

	"medline"[Title/Abstract] OR "scopus"[Title/Abstract] OR "web science"[Title/Abstract:~1] OR "bibliographic review"[Title/Abstract:~1] OR "bibliographic reviews"[Title/Abstract:~1] OR "literature review"[Title/Abstract:~1] OR "literature reviews"[Title/Abstract:~1])) OR (("electronic database"[Title/Abstract:~1] OR "electronic databases"[Title/Abstract:~1] OR "databases searched"[Title/Abstract:~3]) AND ("eligibility"[Title/Abstract] OR "excluded"[Title/Abstract] OR "exclusion"[Title/Abstract] OR "included"[Title/Abstract] OR "inclusion"[Title/Abstract])) OR ("comparative effectiveness"[Title/Abstract:~1] AND "effectiveness review"[Title/Abstract:~2]) OR ("critical interpretive"[Title/Abstract:~1] AND ("interpretive review"[Title/Abstract:~0] OR "interpretive synthesis"[Title/Abstract:~0])) OR ("diagnostic test"[Title/Abstract:~0] AND ("accuracy review"[Title/Abstract] OR "accuracy reviews"[Title/Abstract] OR "accuracy studies"[Title/Abstract] OR "accuracy study"[Title/Abstract]) AND ("meta analysis"[Title/Abstract] OR "scoping"[Title/Abstract] OR "systematic"[Title/Abstract])) OR ("evidence assessment"[Title/Abstract] AND "GRADE"[Title/Abstract]) OR ("evidence gap"[Title/Abstract:~2] AND "gap map"[Title/Abstract:~0]) OR "evidence mapping"[Title/Abstract] OR "evidence review"[Title/Abstract] OR "exploratory review"[Title/Abstract] OR "framework synthesis"[Title/Abstract] OR "mapping review"[Title/Abstract:~1] OR "meta epidemiological"[Title/Abstract] OR "meta ethnographic"[Title/Abstract:~0] OR "metaethnographic"[Title/Abstract] OR "meta ethnography"[Title/Abstract:~0] OR "metaethnography"[Title/Abstract] OR "meta interpretation"[Title/Abstract:~1] OR "meta narrative"[Title/Abstract:~1] OR "meta review"[Title/Abstract:~1] OR "meta study"[Title/Abstract:~1] OR "meta synthesis"[Title/Abstract:~0] OR "metasynthesis"[Title/Abstract] OR "meta summary"[Title/Abstract:~1] OR "meta theory"[Title/Abstract:~1] OR "methodological review"[Title/Abstract:~1] OR "methodology review"[Title/Abstract:~1] OR ("mixed methods"[Title/Abstract:~0] AND "methods review"[Title/Abstract:~1]) OR ("mixed methods"[Title/Abstract:~0] AND "methods synthesis"[Title/Abstract:~1]) OR "narrative synthesis"[Title/Abstract:~1] OR "overview reviews"[Title/Abstract:~4] OR ("PRISMA"[Title/Abstract] AND ("guideline"[Title/Abstract] OR "guidelines"[Title/Abstract] OR "preferred"[Title/Abstract] OR "reporting"[Title/Abstract] OR "requirements"[Title/Abstract])) OR "PRISMA-P"[Title/Abstract:~0] OR "prognostic review"[Title/Abstract:~1] OR "psychometric review"[Title/Abstract:~1] OR ("qualitative evidence"[Title/Abstract:~0] AND "evidence synthesis"[Title/Abstract:~0]) OR ("qualitative research"[Title/Abstract:~0] AND "research synthesis"[Title/Abstract:~0]) OR ("rapid evidence"[Title/Abstract:~0] AND "evidence assessment"[Title/Abstract:~0]) OR "rapid realist"[Title/Abstract:~0] OR "rapid review"[Title/Abstract:~1] OR "rapid reviews"[Title/Abstract:~1] OR "realist review"[Title/Abstract:~1] OR ("review economic"[Title/Abstract:~1] AND ("economic evaluation"[Title/Abstract:~1] OR "economic evaluations"[Title/Abstract:~1])) OR "review reviews"[Title/Abstract:~1] OR "realist syntheses"[Title/Abstract:~1] OR "realist synthesis"[Title/Abstract:~1] OR "scoping review"[Title/Abstract:~2] OR "scoping reviews"[Title/Abstract:~2] OR "scoping studies"[Title/Abstract:~2] OR "scoping study"[Title/Abstract:~2] OR "systematic evidence map"[Title/Abstract] OR "systematic mapping"[Title/Abstract:~2] OR "systematic literature"[Title/Abstract:~1] OR "systematic Medline"[Title/Abstract:~2] OR "systematic PubMed"[Title/Abstract:~2] OR "Systematic Review"[Title/Abstract:~2] OR "systematic reviews"[Title/Abstract:~2] OR "systematical review"[Title/Abstract:~1] OR "systematical reviews"[Title/Abstract:~2] OR "systematically identified"[Title/Abstract:~1] OR "systematically review"[Title/Abstract:~1] OR "systematically reviewed"[Title/Abstract:~1] OR "systematized review"[Title/Abstract:~1] OR "umbrella review"[Title/Abstract:~2] OR "umbrella reviews"[Title/Abstract:~2] OR "meta-analysis as topic"[MeSH Terms:noexp] OR "meta analysis"[Publication Type] OR "network meta-analysis"[MeSH Terms:noexp] OR "indirect comparison"[Title/Abstract:~1] OR "meta analyses"[Title/Abstract] OR	

	"meta analysis"[Title/Abstract] OR "meta analytic"[Title/Abstract] OR "meta analytical"[Title/Abstract] OR "meta analytics"[Title/Abstract] OR "meta analyze"[Title/Abstract] OR "meta analyzed"[Title/Abstract] OR "metaanalyses"[Title/Abstract] OR "metaanalysis"[Title/Abstract] OR "metaanalytic"[Title/Abstract] OR "metaanalyze"[Title/Abstract] OR "metaanalyzed"[Title/Abstract] OR "network comparison"[Title/Abstract:~1] OR "network meta analyses"[Title/Abstract] OR "network meta-analysis"[Title/Abstract] OR "network metaanalyses"[Title/Abstract] OR "network metaanalysis"[Title/Abstract] OR ("systematic"[Title/Abstract] AND ("meta regression"[Title/Abstract] OR "metaregression"[Title/Abstract]))	
7	#5 and #6	553

Table 2: Search strategies from the Web of Science Core Collection

#	**Search Term**	**Results**
1	TS=(RF-EMF)	647
2	TS=((radiofrequency OR radio-frequency) near/3 field*)	5,988
3	TS=(near-field)	50,965
4	TS=(Far-field)	40,297
5	TS=((mobile or cellular) NEAR/3 telephone*)	2,965
6	TS=(smartphone*)	72,629
7	TS=((smart OR cell OR mobile OR Cellular) NEAR/3 phone*)	61,629
8	TS=(broadcasting)	61,806
9	TS=((nonionizing OR ""non ionizing"") NEAR/3 radiation*)	2,032
10	TS=(radiowave*)	2,016
11	TS=((hertzian or radio or ""high frequency"" or ""short"" or micro or ehf or ""ultrahigh frequency"") near/3 wave*)	61,754
12	TS=(microwave*)	328,031
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	657,287
14	TS=(adenosarcoma* OR blastoma* OR cancer* OR carcinoma* OR carcinosarcoma* OR glioma* OR leukemia* OR leukaemia* OR liposarcoma* OR lymphangiom* OR lymphoma* OR melanoma* OR metastatic OR myeloma* OR neoplasm* OR osteosarcoma* OR sarcoma* OR tumor* OR tumour* OR meningioma* OR ""acoustic neuroma*"" OR ""vestibular schwannoma"")	5,468,746
15	#13 AND #14	17,543
16	#13 AND #14 and Review Article (Document Types)	2,034

Table 3: Search strategies from Epistemonikos

#	**Search Term**	**Results**
	(title:(adenosarcoma* OR blastoma* OR cancer* OR carcinoma* OR carcinosarcoma* OR glioma* OR leukemia* OR leukaemia* OR liposarcoma* OR lymphangiom* OR lymphoma* OR melanoma* OR metastatic OR myeloma* OR neoplasm* OR osteosarcoma* OR sarcoma* OR tumor* OR tumour* OR meningioma* OR "acoustic neuroma" OR "vestibular schwannoma") OR abstract:(adenosarcoma* OR	2,095

	blastoma* OR cancer* OR carcinoma* OR carcinosarcoma* OR glioma* OR leukemia* OR leukaemia* OR liposarcoma* OR lymphangiom* OR lymphoma* OR melanoma* OR metastatic OR myeloma* OR neoplasm* OR osteosarcoma* OR sarcoma* OR tumor* OR tumour* OR meningioma* OR "acoustic neuroma" OR "vestibular schwannoma")) AND (title:("RF-EMF" OR "radiofrequency electromagnetic field" OR "radiofrequency field" OR "radio frequency field" OR "Far-field" OR "near-field" OR "mobile telephone" OR smartphone* OR "smart phone" OR "cell phone" OR "mobile phone" OR "cellular phone" OR "cellular telephone" OR broadcasting OR "nonionizing radiation" OR "non ionizing radiation" OR "radio wave" OR "radiowave" OR "hertzian wave" OR "high frequency wave" OR "short wave" OR microwave* OR "micro wave" OR "ultrahigh frequency wave" OR "ehf wave" OR "radiofrequency electromagnetic fields" OR "radiofrequency fields" OR "radio frequency fields" OR "near-fields" OR "Far-fields" OR "mobile telephones" OR smartphone* OR "smart phones" OR "cell phones" OR "mobile phones" OR "cellular phones" OR "cellular telephones" OR broadcasting OR "nonionizing radiations" OR "non ionizing radiations" OR "radio waves" OR "radiowaves" OR "hertzian waves" OR "high frequency waves" OR "short waves" OR microwave* OR "micro waves" OR "ultrahigh frequency waves" OR "ehf waves") OR abstract:("RF-EMF" OR "radiofrequency electromagnetic field" OR "radiofrequency field" OR "radio frequency field" OR "Far-field" OR "near-field" OR "mobile telephone" OR smartphone* OR "smart phone" OR "cell phone" OR "mobile phone" OR "cellular phone" OR "cellular telephone" OR broadcasting OR "nonionizing radiation" OR "non ionizing radiation" OR "radio wave" OR "radiowave" OR "hertzian wave" OR "high frequency wave" OR "short wave" OR microwave* OR "micro wave" OR "ultrahigh frequency wave" OR "ehf wave" OR "radiofrequency electromagnetic fields" OR "radiofrequency fields" OR "radio frequency fields" OR "near-fields" OR "Far-fields" OR "mobile telephones" OR smartphone* OR "smart phones" OR "cell phones" OR "mobile phones" OR "cellular phones" OR "cellular telephones" OR broadcasting OR "nonionizing radiations" OR "non ionizing radiations" OR "radio waves" OR "radiowaves" OR "hertzian waves" OR "high frequency waves" OR "short waves" OR microwave* OR "micro waves" OR "ultrahigh frequency waves" OR "ehf waves"))	
	Filter: Publication type = Systematic Review	305

Table 4: Search strategies from EMF-Portal

#	**Search Term**	**Results**
	cancer OR tumour AND (topic=epidemiological OR topic=review_survey_summary) AND (frequencyRange=radio_frequency OR frequencyRange=mobile_communications)	529

Appendix B: Deduplication R script

```
##############################################################################

# REMOVE (FUZZY) DUPLICATES FROM BIBLIOGRAPHY
# Joshua Ziegler, IMBEI Mainz, 2024

##############################################################################

# These steps are necessary to double check
# SR-Accelerators De-duplicator.

##############################################################################

# Procedure:
# 0. Data Import
# 1. Create Comparator Variable
# 2. Duplicates
## 2.1. Flag Exact Duplicates
## 2.2. Scan for Fuzzy duplicates
## 2.3. Flag Fuzzy Duplicates
## 2.4. Remove Duplicates
# 3. Export to RIS
# 4. Export to csv for excel

##############################################################################

library(tidyverse)
library(tidystringdist)
library(revtools)
library(stringi)

##############################################################################

# 0. Data Import

# Filename (without ".txt"-suffix, usually "exportlist")
filename <- "exportlist_SR"

# For bibliography exported from SR-accelerator:
# remove "TY  - " + lower-case letter
# maybe: add line break before each TY
SR_dirty <- read_file(paste0(filename, ".txt"))
```

```
# "TY" + space + space + "-" + space + lowercase letter + any number of word characters + line break (\n)
SR_clean <- gsub("SN\\s\\s-", "SP\\s\\s-", SR_clean)
write_file(SR_clean, paste0(filename, ".txt"))

# Prevent unnecessary steps in case the data has already been reformatted to ascii
if (file.exists(paste0(filename, "_ascii.txt"))) {
  lit_raw <- read_bibliography(paste0(filename, "_ascii.txt"))
} else {
  lit_raw <- read_bibliography(paste0(filename, ".txt"))
}

# Check for special characters
if (any(grepl("<\\w\\w><\\w\\w>", lit_raw$author))) { # checks for pattern "<a1><b2>"

  # if TRUE -> recode to ascii (method by D. Wollschläger)

  con <- file(paste0(filename, ".txt"), encoding="UTF8")
  f_utf8 <- readLines(con)
  close(con)

  f_ascii0 <- stringi::stri_trans_general(f_utf8, id="Latin-ASCII")
  f_asciil <- iconv(as.character(f_ascii0), "", "ASCII", "byte")
  Encoding(f_asciil) <- "latin1"
  f_ascii <- stringr::str_remove_all(f_asciil, "<.+?>")

  writeLines(f_ascii, paste0(filename, "_ascii.txt"))

  rm(con, list=ls(pattern = "f_"))

  # import again
  lit_raw <- read_bibliography(paste0(filename, "_ascii.txt"))

  # recode indicator
  recode <- TRUE

}

################################################################################

# 1. Create Comparator Variable (year + lower-case title + initials of first author)
lit_raw <-
  lit_raw %>%
  replace_na(list(year = "", title = "", author = "")) %>% # replaces NAs with ""
  mutate(comparator = paste0(year,
                             tolower(title),
                             str_replace_na( # wraps around str_extract to avoid pasted "NA"s in case of non-match
                               str_extract(author, "^\\w"), ""), # initial last name
                             str_replace_na(
                               str_extract(author, "(?<=,\\s)\\w"), "") # initial first name
                             ),
         language = case_when(language == "en" ~ "eng", # clean up language codes
                              language == "de" ~ "ger", # still a bit clumsy, but might be necessary to check individually
                              TRUE ~ language),
         pages = gsub(" ", "", pages), # clean up pages variable
         pages = gsub("ss-", "", pages)
         )


################################################################################

# 2. Duplicates

######## next steps:
# duplicate comparator vairable but remove []
# use that to flag exact duplicates,
# same as with fuzzy duplicates, flag those that contain brackets
########
dup_exact <-
  lit_raw %>%
  mutate(
    comparator_clean = gsub("[][]", "", comparator)
  )

## 2.1. Flag Exact Duplicates
dup_exact <-
  dup_exact %>%
  mutate(exact_dup = duplicated(.$comparator_clean))
```

```
## 2.2. Check exact duplicates
dup_exact_check <-
  dup_exact %>%
  group_by(comparator_clean) %>%
  mutate(duplicate = case_when(n() > 1 ~ n(), # if number of occurrences is greater than 1
                               TRUE ~ NA
                               )
         ) %>%
  ungroup() %>%
  select(author, year, title, comparator, duplicate) %>%
  filter(!is.na(duplicate)) %>%
  arrange(comparator)

##############################################################################

## 2.2. Scan for Fuzzy duplicates
dup_fuzzy <-
  lit_raw %>%
  tidy_comb_all(comparator) %>%
  tidy_stringdist() %>%
  filter(qgram <= 3 & osa <= 2) %>% # threshold: qgram <= 3 & osa <= 2
  mutate(deletor = case_when(grepl("^\\d{4}\\[", V1) ~ V1, # check for titles translated from a foreign language (indicated by the use of "[]")
                             TRUE ~ V2))

# check manually!

##############################################################################

## 2.3. Flag Fuzzy Duplicates
# Mark all fuzzy duplicates that are to be deleted as fuzzy_dup == TRUE
final <-
  dup_exact %>%
  mutate(fuzzy_dup = case_when(comparator %in% dup_fuzzy$deletor ~ TRUE,
                               TRUE ~ FALSE)
         )
##############################################################################

## 2.4. Remove Duplicates
# Clean data by removing all exact_dup == TRUE & fuzzy_dup == TRUE
clean <-
  final %>%
  filter(exact_dup == F) %>%
  filter(fuzzy_dup == F)


##############################################################################

# 3. Export to RIS
write_bibliography(clean, "importlist.ris")

##############################################################################


# 4. Export to csv for excel
write_csv2(clean %>%
             select(label, author, title, year, journal, volume, issue, pages),
           "final_excel.csv")

# Weakness of this method: Special characters in names of authors are replaced
# by letters of the English alphabet to ensure precision, but as of yet are not
# restored later on.

##############################################################################
```

Appendix C: Data extraction form

Description	Type	Input
Paper details	Study_ID	
	Author	
	Title	
	Year	
	Journal	
	Volume	
	Issue	
	Pages	
	Objectives	
	Type of review	
Databases sourced and searched	Names	
	Number	
	Date range of database searching	
	Publication date range of studies included that inform each outcome of interest	
Number of studies	In total	
	Of relevance	
Details of Studies	Types of studies of relevance	
	Country of origin of studies of relevance	
Number of participants relevant to the research question	Case-Control	
	Cohort	
Additional details	Details about participants	
	Comparator information	
	Setting and context of the original studies reviewed	
	Exposure information	
	Instrument(s) used to appraise the primary studies and rating of their quality	
	Outcomes reported that are relevant to the umbrella review research question	
	Method of synthesis/analysis employed to summarise the evidence	
	Combined Estimate (MA only)	
	Conclusion	
	Funding of the study	
	Comments or notes	

Appendix D: AMSTAR 2

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☐ Yes
☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs
For Yes:
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI
For Yes:
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:
- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:
- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:
- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:
- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:
- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

AMSTAR 2 guidance document

Many of the items in AMSTAR 2 are written to be self-explanatory. However, the underlying issues are often complex, and subject to varying interpretation, particularly when judgments are made across a wide spectrum of interventions. Here we provide additional guidance on use of AMSTAR 2. Material in this document overlaps with that in the published paper. This is intentional, as this Appendix is intended to be a stand-alone document.

We emphasise this is guidance – it gives an indication of how we think the criteria should be applied in settings where reviews are conducted of well-defined (usually clinical) interventions. Individual users, of course, may find it necessary to deviate from the guidance both in addressing individual domains and in making an overall appraisal of a systematic review. We ask that in doing so they document these variations so that others can benefit from their experiences

AMSTAR 2 is not designed to generate an overall 'score'. A high score may disguise critical weaknesses in specific domains, such as an inadequate literature search or are a failure to assess risk of bias (ROB) with individual studies that were included in a systematic review. In making an overall rating of systematic review it is important to take account of flaws in critical domains, which may greatly weaken the confidence that can be placed in a systematic review.

Item 1: Did the research questions and inclusion criteria for the review include the components of PICO?

It is common practice to use PICO description (population, intervention, control group and outcome) as an organising framework for a study question. Sometimes timeframe should be added if this is critical in determining the likelihood of a study capturing relevant clinical outcomes (e.g. an effect of the intervention is only expected after several years). PICO identifies the elements that should be described in detail in the report of the systematic review and should enable the appraiser to judge selection of studies, and their combinability, and enable the user of the review to determine applicability of the results. Authors of systematic reviews do not always make the elements of PICO explicit but they should be discernable through a careful reading of the abstract, introduction and methods sections. To score 'Yes' appraisers should be confident that the 4 elements of PICO are described somewhere in the report.

Item 2: Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?

Systematic reviews are a form of observational research and the methods for the review should be agreed on before the review commences. Adherence to a well-developed protocol reduces the risk of bias in the review. Authors should demonstrate that they worked with a written protocol with independent verification. This can take the form of registration (e.g. at PROSPERO - https://www.crd.york.ac.uk/PROSPERO/), an open publication journal (e.g. BMJ Open) or a dated submission to a research office or research ethics board. The research questions and the review study methods should have been planned ahead of conducting the review. At a minimum this should be stated in the report (scores 'Partial Yes'). To score 'Yes' authors should demonstrate that they worked with a written protocol with independent verification (by a registry or another independent body, e.g. research ethics board or research office) before the review was undertaken. Appraisers should compare the published report of the review with the registered protocol, when the latter is available. If there are deviations from the protocol appraisers should determine whether these are reported and justified by review authors. Obvious unexplained discrepancies should result in downgrading of the rating.

Item 3: Did the review authors explain their selection of the study designs for inclusion in the review?

The selection of study types for inclusion in systematic reviews should not be arbitrary. The authors should indicate that they followed a strategy. The general rule (this may have to be inferred from what the authors actually wrote) is that they asked first whether a review restricted to RCTs would have given an incomplete summary of the effects of a treatment. This might be because there were no relevant RCTs or because of missing outcomes in available RCTs [usually harms], inadequate statistical power, restrictive populations, or unrepresentative control/intervention treatments. If the answer to this general question is yes the inclusion of non- randomized studies of the intervention(s) is justified. Conversely, to justify restriction of the review to RCTs the authors should argue that they can provide a complete picture of the effects they are interested in. Restriction of a review to only NRSI is justified when RCTs cannot provide the necessary outcome data, or in the case where reviews of RCTs have been completed and the review of NRSI will complement what is already known. Inclusion of both RCTs and NRSI may be justified to get a complete picture of the effectiveness and harms associated with an intervention. In this situation we recommend (see below) that these two types of studies are assessed and combined

independently (if meta-analysis is appropriate). This is a somewhat neglected area and even with guidance it can be difficult to judge the extent to which a review meets the rating criteria. The justification for selection of study designs may have to be inferred from a careful reading of the complete study report.

Item 4: Did the review authors use a comprehensive literature search strategy?

At least two bibliographic databases should be searched. The report should include years and databases examined (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms should be reported and the full search strategy available on request. Searches should be supplemented by checking published reviews, specialized registers, or experts in the particular field of study, and by reviewing the reference list from the studies found. Sometimes it is necessary to approach authors of original studies to clarify results or obtain updates or corrections. Publications in all relevant languages should be sought and a justification provided when there are language restrictions. We have highlighted the need for searching the grey literature in some cases. Grey literature is sometimes important with reports of policy and program evaluations that are only available from web sites (e.g. government, non-government or health technology agencies). These may or may not have been subject to peer review and such appraisals should be looked for. Where the grey literature is considered important, authors should have searched appropriate sources, such as trial registries, conference abstracts, dissertations, and unpublished reports on personal websites (e.g. universities, ResearchGate). In addition, trials of medical interventions may not have been published in peer-reviewed journals but can be obtained directly from company sponsors or directly from investigators. To score

'Yes' appraisers should be satisfied that all relevant aspects of the search have been addressed by review authors.

Item 5: Did the review authors perform study selection in duplicate?

Best practice requires two review authors to determine eligibility of studies for inclusion in systematic reviews. This involves checking the characteristics of a study (from title, abstract and full text) against the elements of the research question In the response options, we point to the desirability of review authors describing inter-rater agreement across a sample of studies being considered for inclusion in the review. A consensus process should have been used when disagreements arose in study selection. If one individual carried out selection of all studies, with a second reviewer checking agreement on a sample of studies, we recommend that a Kappa score indicating 'strong' agreement (0.80 or greater) should have been achieved. There should have been at least two independent assessors for study selection. A consensus process should have been used when disagreements arose in study selection. In the event that one individual carried out selection of studies a second reviewer should have checked agreement on a sample of representative studies and they should have achieved a kappa score of 0.80 or greater.

Item 6: Did the review authors perform data extraction in duplicate?

As in Item 5, there should have been at least two independent assessors performing data extraction. A consensus process should have been used when disagreements arose. In the event that one individual carried out data extraction a second reviewer should have checked agreement on a sample of studies and they should have achieved a kappa score of 0.80 or greater.

Item 7: Did the review authors provide a list of excluded studies and justify the exclusions?

This item requires review authors to provide a complete list of potentially relevant studies with justification for the exclusion of each. Non-inclusion of studies may be necessary for a range of reasons, based on inappropriate/ irrelevant populations, interventions and controls. Exclusion should not be based on risk of bias, which is dealt with separately and later in the review process. Unjustified exclusion may bias the review findings and we encourage an inclusive approach in the early stages of a review. This item requires review authors to provide a complete list of potentially relevant studies with justification for the exclusion of each one.

Item 8: Did the review authors describe the included studies in adequate detail?

The description of subjects, interventions, controls, outcomes, design, analysis and settings of the studies should be provided. The detail should be sufficient for an appraiser, or user, to make judgments about the extent to which the studies were appropriately chosen (in relation to the PICO structure) and whether the study populations and interventions were relevant their own practice or policy. The descriptors also provide a framework for studying heterogeneity in intervention effects (e.g. by dose, age range, clinical setting etc.)

Item 9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

This is a crucial part of the appraisal of any systematic review, particularly those that include non-randomized studies of interventions (NRSI). The key appraisal question is whether review authors have taken account of the risk of bias when summarising and interpreting the results.

When the review is confined to randomized controlled trials (RCTs) we recommend that you consult the Cochrane Handbook to determine whether the review authors have made an adequate assessment of ROB with individual RCTs. This section is concerned with the challenge posed by RoB in non-randomised studies.

Review authors should have used a systematic approach to ROB assessment, preferably with a properly developed rating instrument. If they have used a non-standard instrument you should be satisfied that it was capable of detecting serious methodological flaws. Several ROB instruments (for individual studies) are in common use, including the Newcastle Ottawa Scale, SIGN, and the Mixed Methods Appraisal Tool (MMAT). The most comprehensive assessment instrument is the recently introduced Cochrane instrument, ROBINS-I. It is appreciated that this instrument may not have been available at the time a review was performed.

In developing AMSTAR 2 we drew on the Cochrane RoB instruments for RCTs: (http://handbook.cochrane.org/chapter_8/8_5_the_cochrane_collaborations_tool_for_assessing_risk_of_bias.htm) and NRSI: www.riskofbias.info. In both cases the domain appraisal items are drawn from these instruments. Whatever instrument was used by the review authors, appraisers should be satisfied that it addresses the items listed in item 9 of the instrument.

Please note that the guidance given here is not comprehensive – AMSTAR 2 addresses only the most commonly recognised domains of bias. A deeper assessment of risk of bias requires specialist input. In assessing how RoB has been assessed by review authors you should seek methods and content expert advice, if that is not included in your team. Advisors should be asked to provide specific advice on which confounders are important, how to identify selection and measurement biases that are likely, to be relevant to the review under consideration. In addition, you should seek guidance on what adjustment techniques for confounding would be appropriate.

The following list of domains of bias has been selected from the ROBINS-I/ACROBAT-NRSI instrument as being the most relevant to systematic reviews that include NRSI:

Confounding. Confounding occurs when the effects of two associated interventions or exposures (e.g. smoking and alcohol consumption) have not been separated during analysis. This can result in an effect being attributed to one variable when it is due to the other. In the study of interventions confounding may also be related to the indication for treatment, for instance when one drug is given preferentially to patients with higher rates of co-morbidities than the comparator drug and where these co-morbid conditions are associated with the outcome of interest. These assessments are typically quantified in the baseline data reported in the individual study. Potential baseline confounding can be addressed in several ways, including design (eg matching by propensity score), adjustment (e.g. logistic regression) and other techniques such as instrumental variable analysis and the inclusion of 'tracer' exposures. It is common to assume that even sophisticated techniques will not adjust completely for all confounders, meaning weak associations, even if statistically significant, should be interpreted cautiously.

Sample selection bias. This occurs when subjects are sampled in a biased way that directly distorts the true relationship between exposure and outcome. It requires no third factor, as is the case with confounding. For instance, you should not study the association between smoking and heart disease by recruiting subjects referred to a smoking cessation clinic. The selection of subjects with the exposure of interest should be unrelated to their outcome. Likewise, selection of subjects with the outcome should be unrelated to their exposure status. The timing of selection can be important. If subjects have been using a drug for some time before enrolment (prevalent users) they will be a tolerant group with a lower risk of adverse outcomes. For this reason, contemporary pharmaco-epidemiological studies recruit 'new users' of medications (analogous to starting treatment in a RCT). Other temporal sampling biases (immortal time bias and inception bias) are sometimes important. It is recommended that users refer to ROBINS-I guidance document for more information.

Bias in measurement of exposures and outcomes: measurement of an exposure or treatment may be misclassified if there is no accurate recording made in real time. Typically, modern pharmaco-epidemiological studies use prescriptions or dispensing records as a surrogate for consumption. But adherence to dispensed treatment will not be 100% so actual consumption will be miss-classified by this method. If this error is non-differential it will be a bias to the null. However, in some fields of research investigators rely on recall (e.g. ultraviolet exposure and melanoma). This may lead to differential misclassification. For instance, parents of a child who has died of SIDS may have heightened recall of any medications they administered to the baby prior to the event. Measurement of outcomes can also be affected by misclassification and if this is non- differential it will usually be a bias to the null. However, non-differential misclassification can introduce bias. For instance, if leg

ultrasound is performed frequently in women with swollen painful legs who are taking an oral contraceptive, selection of individuals from an ultrasound clinic may bias studies of the association between DVT and oral contraceptives.

Selective reporting of outcomes and analyses: large observational studies may analyse population databases that record many outcomes occurring in a defined population. If outcomes are not pre-specified (preferably in a registered protocol) investigators may be tempted to analyse multiple outcomes and selectively report those that appear to be different between exposed and non-exposed individuals. In addition, there are usually several potential methods for analysing a non-randomized dataset (including, for example, different ways of categorising the intervention, or different multi-variable adjustment models). If the analytical protocol is not specified in advance of the study it may be possible to select one set of analyses that appears to show a significant statistical difference that is not apparent in the other analyses. Reviewers should determine whether study authors pre-specified outcomes and analyses. This will become easier as more studies are registered before being conducted.

Item 10: Did the review authors report on the sources of funding for the studies included in the review?

Several investigations have shown that commercially sponsored studies are more likely to have findings that favour a sponsor's product than independently funded studies. It is valuable for review authors to document the funding sources for each study included in the review or to record that the information was not provided in the study reports. Depending on this information it may be possible to analyse separately the results from commercially funded and independently funded studies.

Item 11: If meta-analysis was justified did the review authors use appropriate methods for statistical combination of results? (Only complete this item if meta-analysis of other data synthesis techniques were reported)

Review authors should have stated explicitly in the review protocol the principles on which they based their decision to perform meta-analysis of data from the included studies. These include the desire to obtain a single pooled effect (for instance from a number of compatible but underpowered studies) and the extent to which the studies are compatible (in terms of populations controls and interventions) and therefore capable of being combined.

Where meta-analysis was considered appropriate authors should have explained their decisions to use fixed or random effects models in the case of RCTs, and set out the methods they intended to use to investigate heterogeneity.

With NRSI study populations vary greatly in size from small cohorts (of tens or hundreds of participants) to studies of hundreds of thousands of individuals and thousands of events. If these results, are going to be combined with those from smaller RCTs the pooled estimates of effect will be dominated by the data from the non-randomized studies. In addition, the results from NRSI may be affected by a range of biases (see above), meaning that the overall pooled estimates may be precise but biased.

Review authors should report pooled estimates separately for the different study types. In the case of NRSI, pooling may result in a very precise and 'statistically significant', but biased, estimate of effect. However, the confidence interval is calculated on the assumption that there is no bias (i.e. the estimates are as accurate as if obtained from a high quality RCT with the same number of participants). It is rare for a NRSI to have as low risk of bias as a high quality RCT of the same research question and confidence intervals for NRSI (and pooled estimates based on NRSI) should be viewed with caution. This issue is important when considering the varying risk of bias, and uncertainty about the risk of bias across NRSI.

Heterogeneity is an important issue in any meta-analysis. It is particularly important in a review of NRSI because of the more diverse methods that are likely to have been used across different studies. In addition to the usual sources of heterogeneity [different comparators, variations in baseline risk of outcomes or other characteristics of the study population, differing interventions (e.g. dose effects, context/setting, practitioner experience) and different definitions of outcomes], it is important to consider heterogeneity in source of participants, completeness of data, methods of data management and analysis. Statistical adjustment of intervention effects for confounders may result in estimates that are quite different from the unadjusted estimate derived from the raw data.

Generally, when combining the results of NRSI review authors should pool the fully adjusted estimates of effect, not the raw data. If they do the latter there should be a clear justification. However, different studies are very likely to report treatment effects that have been adjusted for different sets of covariates (or covariates measured or fitted in different ways); this diversity represents another source of potential heterogeneity.

Item 12: If meta-analysis was performed did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

In cases where review authors have chosen to include only high quality RCTs there may be little discussion of the potential impact of bias on the results. But where they have included RCTs of variable quality they should assess the impact of this by regression analysis, or by estimating pooled effect sizes with only studies at low ROB. In the case of NRSI they should estimate pooled effect sizes while including only studies at low or moderate risk of bias, and/or only those at low ROB (if there are any). If meta-analyses (or other data synthesis techniques such as regression analysis) were not performed the authors should still provide some commentary on the likely impact of ROB on individual study results.

Item 13: Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

Even if meta-analyses were not conducted review authors should include discussion of the impact of ROB in the interpretation of the results of the review. This is always important, but especially when reviews include RCTs with variable ROB, and with any review that includes NRSI. This discussion should not be limited to the impact of ROB on the pooled estimates (see above), but should also consider whether it may account for differences between the results of individual studies. The authors should make an explicit consideration of ROB if they make any recommendations that are likely to have an impact on clinical care or policy.

Item 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

There are many potential causes of heterogeneity in the results of NRSI than in RCTs. Many factors considered in this instrument, including different study designs, different methods of analysis, different populations and differing intensities of the intervention(s) – dosages in the case of drugs. Both the PICO elements and the domains of bias listed in Item 9 should also be considered as important potential sources of heterogeneity in the results. Review authors should explore these possibilities and discuss the impact of heterogeneity on the results conclusions and any recommendations

Item 15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

This is a very important issue, but can be difficult for review authors and appraisers to resolve completely. Typically, statistical tests or graphical displays are used and if they are positive then it indicates the presence of PB. However, negative tests are not a guarantee of the absence of PB as the tests are insensitive. To some extent the importance of PB depends on context and setting. For instance, a series of apparently methodologically sound industry-sponsored studies (e.g. drugs, devices, putative toxins) might be more likely to be affected by PB than similar studies conducted independently of industry. The key issues are whether the authors have done their best to identify PB through deeper and intensive literature searches (as needed and according to the setting), shown an awareness of the likely impact of PB in their interpretation and discussion of the results and performed a sensitivity analyses to determine how many missing 'null' studies would be needed to invalidate the results they obtained.

Item 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

As noted above (under ROB), individual studies funded by vested interests may generate results that are more likely to favour the intervention than do independent studies. The same assumption applies to systematic reviews and authors should report their direct funding sources. Journals generally will require this. But assessment of the reviewers' conflicts of interest doesn't stop there. They should report their other ties. The review may be independently funded, but the authors have ties to companies that manufacture products included in the systematic review. Professional conflicts of interest are powerful, but harder to discern as they are seldom reported. When investigators have a career-long investment in a field of research, a review that conflicts with their long-held beliefs can be confronting. Potential conflicts of interest of this type will be hard to assess, but may be inferred from the fact that the reviewers have published extensively in the field being reviewed and their studies are included in the systematic review. While it can be argued that the effects of competing interests might manifest as flaws in the other domains of bias we believe that this item should always be rated separately.

Appendix E: ROBIS

ROBIS: Tool to assess risk of bias in systematic reviews

Phase 1: Assessing relevance (Optional)

ROBIS is designed to assess the risk of bias in reviews with questions relating to interventions, aetiology, diagnosis and prognosis. State your overview/guideline question (target question) and the question being addressed in the review being assessed:

Intervention reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Intervention(s):		
Comparator(s):		
Outcome(s):		

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Exposure(s) and comparator(s):		
Outcome(s):		

For DTA reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients):		
Index test(s):		
Reference standard:		
Target condition:		

For prognostic reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients:		
Outcome to be predicted:		
Intended use of model:		
Intended moment in time:		

Does the question addressed by the review match the target question?	YES/NO/UNCLEAR

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding methods used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review Rationale for risk:	RISK: LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Appendix F: Identification of Primary Relevant Studies (PRS)

Identification of Primary Relevant Studies (PRS), Overlap Between Systematic Reviews, and Frequency of Inclusion in Systematic Reviews

PRS Identification	Frequency of Inclusion of PRS (Total)	Systematic review identification							
		Balmori (2022)	Beranger (2013)	Brecken-kamp (2003)	Calvente (2010)	Karipidis (2021)	Kashani (2023)	Lim (2023)	Safari-Variani (2019)
Eger et al. (2004)	1	1							
Wolf & Wolf (2004)	1	1							
Groves et al. (2002)	3			1		1			1
Degrave et al. (2009)	2					1			1
Dabouis et al. (2016)	2					1			1
Walschaerts et al. (2007)	3		1			1			1
Grayson (1996)	2					1			1
Ha et al. (2007)	3				1		1	1	
Merzenich et al. (2008)	2				1			1	
Baumgardt-Elms et al. (2002)	3		1			1			1
Hayes et al. (1990)	2		1			1			
Li et al. (2012)	2	1						1	
Morgan et al. (2000)	1			1					
Finkelstein (1998)	2			1		1			
Lagorio et al. (1997)	1			1					
Tynes (1996)	1			1					
Szmigielski (1996)	1			1					
Muhm (1992)	1			1					
Tynes et al. (1992)	1			1					
Milham (1988)	1			1					
Robinette et al. (1980)	2			1		1			
Davis & Mostofi (1993)	1					1			
De Roos et al. (2001)	1					1			
Fabbro-Peray et al. (2001)	1					1			
Hardell et al. (1998)	1					1			
Holly et al. (1996)	1					1			
La Vecchia et al. (1990)	1					1			
Santana et al. (1999)	1					1			
Stang et al. (2001)	1					1			
Elliot et al. (2010)	1							1	
Hauri et al. (2014)	1							1	

Note: This table lists only the PRS identified by our UR as relevant based on the information provided in the SRs. For example, Elliot et al. (2010) is not included in Balmori (2022) as it lacked sufficient detail to be identified as relevant by the UR.