



The effect of exposure to radiofrequency fields on cancer risk in the general and working population: A systematic review of human observational studies – Part I: Most researched outcomes

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ABSTRACT

Background: The objective of this review was to assess the quality and strength of the evidence provided by human observational studies for a causal association between exposure to radiofrequency electromagnetic fields (RF-EMF) and risk of the most investigated neoplastic diseases.

Methods: Eligibility criteria: We included cohort and case-control studies of neoplasia risks in relation to three types of exposure to RF-EMF: near-field, head-localized, exposure from wireless phone use (SR-A); far-field, whole body, environmental exposure from fixed-site transmitters (SR-B); near/far-field occupational exposures from use of hand-held transceivers or RF-emitting equipment in the workplace (SR-C). While no restrictions on tumour type were applied, in the current paper we focus on incidence-based studies of selected “critical” neoplasms of the central nervous system (brain, meninges, pituitary gland, acoustic nerve) and salivary gland tumours (SR-A); brain tumours and leukaemias (SR-B, SR-C). We focussed on investigations of specific neoplasms in relation to specific exposure sources (i.e. E-O pairs), noting that a single article may address multiple E-O pairs. **Information sources:** Eligible studies were identified by literature searches through Medline, Embase, and EMF-Portal.

Risk-of-bias (RoB) assessment: We used a tailored version of the Office of Health Assessment and Translation (OHAT) RoB tool to evaluate each study’s internal validity. At the summary RoB step, studies were classified into three tiers according to their overall potential for bias (low, moderate and high).

Data synthesis: We synthesized the study results using random effects restricted maximum likelihood (REML) models (overall and subgroup meta-analyses of dichotomous and categorical exposure variables), and weighted mixed effects models (dose–response meta-analyses of lifetime exposure intensity).

Evidence assessment: Confidence in evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results: We included 63 aetiological articles, published between 1994 and 2022, with participants from 22 countries, reporting on 119 different E-O pairs. RF-EMF exposure from mobile phones (ever or regular use vs no or non-regular use) was not associated with an increased risk of glioma [meta-estimate of the relative risk (mRR) = 1.01, 95 % CI = 0.89–1.13], meningioma (mRR = 0.92, 95 % CI = 0.82–1.02), acoustic neuroma (mRR = 1.03,

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95 % CI = 0.85–1.24), pituitary tumours (mRR = 0.81, 95 % CI = 0.61–1.06), salivary gland tumours (mRR = 0.91, 95 % CI = 0.78–1.06), or paediatric (children, adolescents and young adults) brain tumours (mRR = 1.06, 95 % CI = 0.74–1.51), with variable degree of across-study heterogeneity ($I^2 = 0\%$ –62 %). There was no observable increase in mRRs for the most investigated neoplasms (glioma, meningioma, and acoustic neuroma) with increasing time since start (TSS) use of mobile phones, cumulative call time (CCT), or cumulative number of calls (CNC). Cordless phone use was not significantly associated with risks of glioma [mRR = 1.04, 95 % CI = 0.74–1.46; $I^2 = 74\%$] meningioma, (mRR = 0.91, 95 % CI = 0.70–1.18; $I^2 = 59\%$), or acoustic neuroma (mRR = 1.16; 95 % CI = 0.83–1.61; $I^2 = 63\%$). Exposure from fixed-site transmitters (broadcasting antennas or base stations) was not associated with childhood leukaemia or paediatric brain tumour risks, independently of the level of the modelled RF exposure. Glioma risk was not significantly increased following occupational RF exposure (ever vs never), and no differences were detected between increasing categories of modelled cumulative exposure levels.

Discussion: In the sensitivity analyses of glioma, meningioma, and acoustic neuroma risks in relation to mobile phone use (ever use, TSS, CCT, and CNC) the presented results were robust and not affected by changes in study aggregation.

In a leave-one-out meta-analyses of glioma risk in relation to mobile phone use we identified one influential study. In subsequent meta-analyses performed after excluding this study, we observed a substantial reduction in the mRR and the heterogeneity between studies, for both the contrast Ever vs Never (regular) use (mRR = 0.96, 95 % CI = 0.87–1.07, $I^2 = 47\%$), and in the analysis by increasing categories of TSS (“<5 years”: mRR = 0.97, 95 % CI = 0.83–1.14, $I^2 = 41\%$; “5–9 years”: mRR = 0.96, 95 % CI = 0.83–1.11, $I^2 = 34\%$; “10+ years”: mRR = 0.97, 95 % CI = 0.87–1.08, $I^2 = 10\%$).

There was limited variation across studies in RoB for the priority domains (selection/attrition, exposure and outcome information), with the number of studies evenly classified as at low and moderate risk of bias (49 % tier-1 and 51 % tier-2), and no studies classified as at high risk of bias (tier-3). The impact of the biases on the study results (amount and direction) proved difficult to predict, and the RoB tool was inherently unable to account for the effect of competing biases. However, the sensitivity meta-analyses stratified on bias-tier, showed that the heterogeneity observed in our main meta-analyses across studies of glioma and acoustic neuroma in the upper TSS stratum ($I^2 = 77\%$ and 76%), was explained by the summary RoB-tier. In the tier-1 study subgroup, the mRRs (95 % CI; I^2) in long-term (10+ years) users were 0.95 (0.85–1.05; 5.5 %) for glioma, and 1.00 (0.78–1.29; 35 %) for acoustic neuroma.

The time-trend simulation studies, evaluated as complementary evidence in line with a triangulation approach for external validity, were consistent in showing that the increased risks observed in some case-control studies were incompatible with the actual incidence rates of glioma/brain cancer observed in several countries and over long periods. Three of these simulation studies consistently reported that RR estimates > 1.5 with a 10+ years induction period were definitely implausible, and could be used to set a “credibility benchmark”. In the sensitivity meta-analyses of glioma risk in the upper category of TSS excluding five studies reporting implausible effect sizes, we observed strong reductions in both the mRR [mRR of 0.95 (95 % CI = 0.86–1.05)], and the degree of heterogeneity across studies ($I^2 = 3.6\%$).

Conclusions: Consistently with the published protocol, our final conclusions were formulated separately for each exposure-outcome combination, and primarily based on the line of evidence with the highest confidence, taking into account the ranking of RF sources by exposure level as inferred from dosimetric studies, and the external coherence with findings from time-trend simulation studies (limited to glioma in relation to mobile phone use). For near field RF-EMF exposure to the head from mobile phone use, there was moderate certainty evidence that it likely does not increase the risk of glioma, meningioma, acoustic neuroma, pituitary tumours, and salivary gland tumours in adults, or of paediatric brain tumours.

For near field RF-EMF exposure to the head from cordless phone use, there was low certainty evidence that it may not increase the risk of glioma, meningioma or acoustic neuroma.

For whole-body far-field RF-EMF exposure from fixed-site transmitters (broadcasting antennas or base stations), there was moderate certainty evidence that it likely does not increase childhood leukaemia risk and low certainty evidence that it may not increase the risk of paediatric brain tumours. There were no studies eligible for inclusion investigating RF-EMF exposure from fixed-site transmitters and critical tumours in adults.

For occupational RF-EMF exposure, there was low certainty evidence that it may not increase the risk of brain cancer/glioma, but there were no included studies of leukemias (the second critical outcome in SR-C).

The evidence rating regarding paediatric brain tumours in relation to environmental RF exposure from fixed-site transmitters should be interpreted with caution, due to the small number of studies. Similar interpretative cautions apply to the evidence rating of the relation between glioma/brain cancer and occupational RF exposure, due to differences in exposure sources and metrics across the few included studies.

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1. Introduction

1.1. Rationale

Radiofrequency (RF) electromagnetic fields (EMF) are part of the non-ionizing radiation region of the electromagnetic spectrum, which

means that there is not sufficient energy in a single quantum of RF energy to ionize an atom or a molecule (Barnes et al., 2019). There is currently no established mechanism underpinning the potential carcinogenicity of RF-EMF at exposure levels below international standards (ICNIRP, 2020a; IEEE, 2019). The capacity of RF-EMF to induce genetic damage or other cancer-related effects (Smith and Guyton, 2020) has

been assessed in a number of experimental studies (Miyakoshi, 2019; Wood, 2017). A meta-analysis of 225 studies of genetic damage in mammalian cells exposed to RF-EMF *in vitro* found no dose–response, and inverse correlations between effect size and study quality (Vijayalaxmi and Prihoda, 2019). A systematic review is in progress evaluating the effects of RF-EMF on cancer in experimental animal studies (Mevisen et al., 2022).

Independently of the pathogenesis, if exposure to RF-EMF increased the risk of cancer, then this would have serious public health consequences and require population-level preventive strategies, including a revision of the threshold-based limitation principle currently applied to non-ionizing radiation in the radiofrequency range (ICNIRP, 2020b).

RF-EMF was classified by IARC as possibly carcinogenic to humans (group 2B), based on limited evidence in humans, limited evidence in experimental animals, and weak support from mechanistic studies (IARC, 2013). The evaluation was driven by two large case-control studies showing positive associations between glioma and acoustic neuroma and wireless phone use (Baan et al., 2011). The IARC panel also examined studies of brain tumours, leukaemia/lymphoma, or other malignancies in relation to occupational or environmental RF exposure, and judged this evidence inadequate to formulate conclusions (IARC, 2013).

The IARC Monograph on RF-EMF covers the literature issued by mid-2011. Many new relevant studies have been made available since then.

Several expert panels performed updated reviews of this body of evidence (AGNIR, 2012; ANSES, 2013, 2016; ARPANSA, 2014; CCARS, 2017; Demers et al., 2014; FDA, 2020; HCN, 2016; ICHENF, 2018; SCENIHR, 2015; SCHEER, 2023; SSM, 2013, 2014, 2015, 2016, 2018, 2019, 2020, 2021, 2022). Eighteen meta-analyses (plus a relevant correction letter) addressing mobile phone use and head tumour risks were published since 2012 (Bielsa-Fernandez and Rodriguez-Martin, 2018; Bortkiewicz, 2017; Bortkiewicz et al., 2017; Carlberg and Hardell, 2017; Chen et al., 2021; Choi et al., 2020; de Siqueira et al., 2017; Gong et al., 2014; Lagorio and Roosli, 2014; Prasad et al., 2017; Repacholi et al., 2012; Roosli et al., 2019; Safari Variani et al., 2019; Vijayan and Eslick, 2023; Wang et al., 2018; Wang and Guo, 2016; Yang et al.,

2017; Yoshikawa et al., 2023), often arriving at conflicting conclusions (Ioannidis, 2018).

None of these evidence syntheses complies in full with the recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER) (Whaley et al., 2020), and only one protocol (Mao et al., 2013) of a meta-analysis later published in Chinese (Gong et al., 2014) was preregistered in PROSPERO.

The need for a structured updated appraisal of this body of evidence is widely recognised. Non-ionising radiation (radiofrequency) is among the agents recommended with high priority for re-evaluation by the Advisory Group for the IARC Monographs during 2020–2024 (Marques et al., 2019), and again in 2025–2029 (Berrington de Gonzalez et al., 2024). Two registered systematic reviews of epidemiological studies on RF-EMF and cancer are underway, focusing on exposures experienced by the general population (Farhat et al., 2020) and workers (Modenese et al., 2020).

2. Objectives

The overall aim of the planned systematic review was to assess the quality and strength of the evidence provided by human observational studies for a causal association between exposure to RF-EMF and risk of neoplastic diseases. The specific objectives were: (i) identify the relevant epidemiological literature; (ii) assess risk-of-bias for individual studies; (iii) synthesize the evidence on the exposure-outcome relationship (in terms of magnitude of effects and shape of exposure–response gradients) and evaluate heterogeneity in results across studies; (iv) rate confidence in the body of evidence.

No epidemiological study to date has investigated the risk of neoplastic diseases in relation to individual exposure to RF-EMF from all exposure sources and settings (AGNIR, 2012; ARPANSA, 2014; FDA, 2020; IARC, 2013). Therefore, we separately reviewed three bodies of evidence, addressing neoplasia risk in the general population in relation to RF exposure from near-field (SR-A) or far-field (SR-B) sources, and in working age individuals in relation to occupational RF exposures (SR-C). The scientific questions expressed as PECO statements (Morgan et al.,

Table 1
PECO statements.

SR-A. Systematic review of studies on RF-EMF exposure from wireless phone use	
Population	Humans (members of the general population), without restriction based on sex, age, or other individual characteristics.
Exposure	Definition: Near-field RF exposure from personal use of mobile or cordless phones, occurring prior to outcome, and based on indirect measures (subscriber status, self-reported history of mobile phone or cordless phone use), traffic data, or modelling. Classification: Ever exposed; time since first exposure; cumulative exposure level.
Comparator	No or low-level exposure (never or non-regular users of wireless phones).
Outcomes	Critical [†] : (incidence-based) glioma/brain cancer in adults; paediatric brain tumours*; meningioma; acoustic neuroma; pituitary gland tumours; salivary gland tumours. Important [†] : Any other neoplasm investigated in relation to the exposure of interest.
SR-B. Systematic review of studies on RF-EMF exposure from environmental sources	
Population	Humans (members of the general population), without restriction on sex, age, or other individual characteristics.
Exposure	Definition: Far-field RF exposure from radio-television transmitters, base stations or any other fixed-site transmitter, occurring prior to outcome, and based on environmental measures, modelling, or geocoded distance to the sources (the latter limited to broadcast transmitters). Classification: Ever exposed; duration of exposure or time since first exposure; average or cumulative exposure level.
Comparator	No or low-level exposure from environmental sources of RF-EMF.
Outcomes	Critical [†] : (Incidence-based) childhood leukaemia, paediatric brain tumours*, glioma/brain cancer in adults, and leukaemia in adults. Important [†] : Any other neoplasm investigated in relation to the exposure of interest.
SR-C. Systematic review of studies on occupational exposures to RF-EMF	
Population	Occupationally active individuals, with no further restriction on sex, age, or other individual characteristics.
Exposure	Definition: Near- or far-field RF exposure from professional use of hand-held transceivers or RF-emitting equipment in the workplaces, occurring prior to outcome, and based on measurements, estimates of exposure level from job- or source-exposure matrices (JEM, SEM), or indirect measures such job title or task (option limited to studies explicitly aimed at assessing the effect of exposure to well-characterized sources and types of RF-EMF). Classification: Ever exposed; exposure frequency; exposure duration or time since first exposure; average or cumulative exposure level.
Comparator	No or low-level occupational exposure to RF-EMF.
Outcomes	Critical [†] : (Incidence-based) glioma/brain cancer, leukaemia. Important [†] : Any other neoplasm investigated in relation to the exposure of interest.

Table 1 footnote: RF-EMF = radiofrequency electromagnetic fields; *Brain tumours in children, adolescents and young adults; [†] See Section 3.1.4.1.

2018) are reported in Table 1.

3. Methods

The methods for this systematic review and meta-analysis are described in detail in the published protocol (Lagorio et al., 2021), and summarised below. The amendments to the protocol are reported within the text in each relevant section, and later listed in § 6.2. Findings from the systematic review are reported in accordance with the updated PRISMA-2020 guidelines for reporting systematic reviews (Page et al., 2021b).

3.1. Eligibility criteria

3.1.1. Types of populations

SR-A and SR-B focused on members of the general populations, and SR-C on occupationally active individuals. No restrictions on sex, age, or other individual characteristics were applied.

3.1.2. Types of exposures

Given the lack of a known biological mechanism for a potential carcinogenic effect of RF-EMF, it is unknown which aspect of the exposure may be biologically relevant. Therefore, the choice of the exposure metrics of priority interest was informed by contextual evidence relevant for the types of RF exposure considered in each component of the systematic review, summarized below.

3.1.2.1. RF exposure from wireless phone use. Mobile phones are the most common type of wireless phones and their use is now universal, with 8.6 billion subscriptions in 2022, corresponding to 108 subscriptions per 100 inhabitants (ITU, 2022). Given the short time period since the introduction of 5G technology, which operates at higher frequencies, we did not expect to identify studies addressing the association between 5G mobile phone use and neoplasia risk. However, epidemiological studies of radar workers exposed to RF-EMF > 6 GHz have been conducted (Karipidis et al., 2021), and were considered for inclusion in SR-C.

The exposure of interest for tumours in the head region consists of RF-EMF energy emitted by handheld mobile phones during voice calls, with the device in contact with the head. Communication and data transfer from/to devices is established and regulated by base stations. The periodic signals for location update and possible traffic occurring when the device is in stand-by mode (Mild et al., 2012; Urbinello and Roosli, 2013) are not relevant for exposure to the head because the phone would usually not be held next to it (AGNIR, 2012).

This systematic review summarizes the evidence for the exposure variables most commonly used in the scientific literature: ever use of mobile phones, time since start of mobile phone use (TSS; also called time since first use), cumulative hours of mobile phone use (also called “cumulative call time”, CCT), and cumulative number of calls (CNC).

The variable TSS is a crude measure, but it takes into consideration the tumour latency, which may vary between tumour types, and allows an appropriate assessment of the external validity when comparing results of the analytical studies with incidence time-trend studies of the investigated tumours.

The variables CCT, and CNC provide better estimates of the total amount of mobile phone use, but are more greatly affected by recall bias (Vrijheid et al., 2009) because past intensity of use is more difficult to recall than current use, especially as mobile phone habits have changed considerably over time.

The preferred side of the head for mobile phone use is an important exposure determinant but, when assessed retrospectively through self-report, is affected by substantial misclassification and recall bias (Goedhart et al., 2015a; Goedhart et al., 2018; Goedhart et al., 2015b; Inyang et al., 2010; Kiyohara et al., 2018; Kiyohara et al., 2016), as also

indicated by concurrent observations of increased risk for ipsilateral mobile phone use and protective effect for contralateral use; i.e. in certain studies with no overall association, there was an increased risk with ipsilateral use which was compensated by a decreased risk with contralateral use, indicating a bias (Schuz, 2009). Due to such a poor validity, self-reported laterality of mobile phone use is not included among the exposure metrics and contrasts examined in SR-A (Table 1).

Cordless phones are another source of near-field exposure to RF-EMF. The most common technology is Digital Enhanced Cordless Communication (DECT), which uses time sharing and pulse modulated signals. DECT phones have a peak power of 250 mW, operate with 400 µs bursts every 10 ms (4 % duty factor), and have an average output power of 10 mW (SCENIHR, 2015). The transmission power of cordless phones is 1–2 orders of magnitude lower than that of 1G-2G mobile phones (Lauer et al., 2013), but similar to average transmission power for 3G and 4G network calls. RF-exposure from cordless phones can only be assessed based on indirect measures from interviews or questionnaires (prevalence, amount and duration of use), and there are no objective sources of data against which self-reported information can be validated.

3.1.2.2. Environmental RF exposure from fixed-site transmitters. In SR-B, we included studies addressing neoplasm risks in relation to RF exposure from radio and television masts, base stations or any other fixed-site transmitter. In principle, the average or cumulative whole-body specific absorption rate (SAR) is the exposure measure of interest. As the SAR cannot be directly measured, epidemiological studies have usually relied on measured or modelled levels of electric fields, magnetic fields or power density at the subjects’ residence (less often also at schools), or on crude exposure proxies such as distance to the exposure source.

For a given transmitter, the electric field decreases in the beam with 1/distance from the source. Provided that the distance is objectively recorded (e.g., derived from geocodes), distance from the source may be informative for antennas with a roughly isotropic transmission pattern. This is usually the case for large broadcast transmitters, although special care must be taken when different transmitters are included in the same study (Schmiedel et al., 2009). On the contrary, distance from a base station is a poor indicator of exposure to RF-EMF indoors, due to the complex propagation characteristics of emissions from base station antennas, including shielding effects and multiple reflections from house walls and other buildings (Frei et al., 2010).

We restricted eligibility for inclusion to studies based on objective exposure indicators, such as measurements, modelling, or geocoded distance to a broadcast transmitter (but not to a mobile phone base station). Studies based on self-estimated distance to an antenna were not included, as self-reported distance to transmitters is strongly affected by risk perception (Martens et al., 2017) and cannot be considered a reliable exposure indicator. The preferred exposure index was the E field strength in V/m, which is the unit used by the International Commission on Non-Ionizing Radiation Protection to express reference values (ICNIRP, 2020a). Other exposure units such as the magnetic field strength in ampere per metre (H, A/m) or the incident power density (S, in W/m²) can be easily converted to V/m applying the plane-wave model ($S = EH = E^2/377 = 377H^2$), which is valid for far field exposure situations. We focused on differences in exposure level (using categorical or continuous exposure data), and according to exposure duration.

3.1.2.3. Occupational RF exposures. Most epidemiological studies conducted so far used job-titles as exposure surrogates. Previous reviews of the relevant publications have considered the evidence uninformative, due to inconsistent results across studies affected by severe limitations in exposure assessment, and uncontrolled confounding (AGNIR, 2012; IARC, 2013). Bias in study identification due to selective mention of RF exposures for occupations found at increased cancer risk, was an

Table 2
Neoplasms of primary interest: ICD-10 (WHO, 2016) and ICD-O-3 (Fritz et al. 2013) codes.

	Neoplasm	ICD-10*	ICD-O-3	
			Site	Histology / behaviour
Central nervous system (CNS) neoplasms	Brain, malignant [†] (syn. brain cancer)	C71	C71	8020/3, 8440/3, 8680/3, 8693/3, 8963/3, 9060/3, 9061/3, 9064/3, 9065/3, 9070/3, 9071/3, 9072/3, 9080/3, 9081/3, 9082/3, 9083/3, 9084/3, 9085/3, 9100/3, 9101/3, 9364/3, 9380/3, 9381/3, 9382/3, 9390/3, 9391/3, 9392/3, 9393/3, 9400/3, 9401/3, 9410/3, 9411/3, 9420/3, 9421/1, 9423/3, 9424/3, 9425/3, 9430/3, 9440/3, 9441/3, 9442/3, 9450/3, 9451/3, 9460/3, 9470/3, 9471/3, 9472/3, 9473/3, 9474/3, 9480/3, 9490/3, 9500/3, 9501/3, 9502/3, 9505/3, 9508/3, 9522/3, 9523/3
	Brain, non-malignant [†] (syn. brain tumours)	D33.0- D33.2		8440/0, 8680/1, 8681/1, 8690/1, 8693/1, 9080/0, 9080/1, 9084/0, 9363/0, 9390/1, 9383/1, 9384/1, 9394/1, 9412/1, 9413/0, 9444/1, 9442/1, 9490/0, 9492/0, 9493/0, 9505/1, 9506/1, 9509/1
	Brain, uncertain or unknown behaviour	D43.0- D43.2		–
	<u>Gliomas</u> [§]	C71	C71	<u>9380–9384, 9391–9460</u>
	– Astrocytomas, low-grade (I-II)			– 9384, 9400, 9421, 9424, 9425
	– Astrocytoma, anaplastic (III)			– 9401
	– Glioblastoma (IV)			– 9440, 9441
	– Oligoastrocytomas (II-III)			– 9382
	– Oligodendroglioma (II-III)			– 9450, 9451
	– Other gliomas (I-II)			– 9431, 9444
	– Glioma, malignant NOS			– 9380
	Meningioma, malignant (rare)	C70	C70	9530/3, 9538/3
	Meningioma, non-malignant [†]	D32.0		9530/0, 9530/1, 9531/0, 9532/0, 9533/0, 9534/0, 9535/0, 9537/0, 9538/1, 9539/1
	Cerebral Meninges, uncertain or unknown behaviour	D42.0		–
	Acoustic neuroma (syn. vestibular schwannoma)	D33.3	C72.4	9560
Pituitary gland, malignant (rare)	C75.1	C75.1	8272/3	
Pituitary gland, benign	D35.2		8272/0	
Salivary glands (incl. Parotid), malignant	C07-C08	C07-	8272/0, 8561/0 ^{††}	
Salivary glands (incl. Parotid), benign	D11	08	8272/3, 8430/3 ^{††}	
<u>Leukaemias</u>	<u>C91-C95</u>	C42.1	<u>9800–9948</u>	
– Lymphoid leukaemias	C91		9811–9837	
– Myeloid leukaemias	C92		9840–9931	
– Other leukaemias of specified cell type	C93-		9940–99489800	
– Leukaemia of unspecified cell type	94C95			

*The ICD-10 classification of neoplasms is based on site and behaviour categories: malignant (C00-C97), in situ (D00-D09), benign (D10-D36), uncertain/unknown behaviour (D37-D48). The ICD-10 terms D42.0, D43.0-D43.2 have no equivalent codes in ICD-O-3.

[†]Paediatric brain tumours include histotypes uncommon in adults, such as germ cell tumours (8020, 8440, 9060–9061, 9064, 9065, 9070–9072, 9080–9085, 9100–9101), pilocytic astrocytoma (9421, 9425), ependymal tumours (9383, 9391–9394), embryonal tumours (8963, 9364, 9470–9474, 9480, 9490, 9500–9502, 9508), medulloblastoma (9470–9472, 9474), and primitive neuroectodermal tumours (9473).

[§]The main subtypes of gliomas are reported, with the WHO grade for neoplasms of the central nervous system (Louis et al. 2007) in brackets. Grade I are the least aggressive and grade IV the most aggressive tumours.

^{††}Major histotypes.

additional concern identified in these reviews. More recently, some studies improved on exposure characterization by using expert assessment and job- or source-exposure matrices (JEM, SEM). Existing JEMs of occupational RF exposure (Kauppinen et al., 1998; Migault et al., 2019; Siemiątycki and Lavoue, 2018) provide exposure estimates often based on a small number of measurements per source and/or job, and may not be informative about the probability of exposure per occupation, the typical exposure of workers in specific jobs, and the variability of exposure levels by task, working practices, and over time. A consequential option would have been to restrict inclusion in the current review to occupational studies with exposure assessment based on RF-EMF measurements at the individual level. In order to avoid a drastic reduction of the examined dataset, as well as the exclusion of potentially informative longitudinal studies of occupational groups (i.e., with high probability and/or intensity of RF-exposure, and limited co-exposures to

established carcinogens), we extracted the source-related activities with a yearly cumulative exposure $\geq 250 \text{ W/m}^2 \text{ hour}$ from a large Israeli measurement survey (Hareuveny et al., 2015), and the job titles with an exposure probability $> 20 \%$ from the INTEROCC JEM (Migault et al., 2019), trying to match the two series of data. We concluded that, for most occupations considered in both data sources, relying on job titles as the only exposure surrogate would be uninformative to the aim of the current review, due to either a low exposure probability (e.g., occupations possibly entailing exposure from industrial heating equipment or broadcast transmitters, and physiotherapists); a low level of over-background exposure to RF-EMF (e.g., ships' deck officers and pilots, and air traffic controllers); or common and relevant co-exposure to known or suspected carcinogens, in spite of a high probability and intensity of RF exposure (e.g., firefighters, or police officers). Therefore, we decided to include studies investigating neoplasia risk in relation to

exposure to RF-EMF from professional use of hand-held transceivers, or from RF-emitting equipment in the workplace, with exposure assessment based on measurements or estimates of exposure level derived from JEM or SEM. We also considered eligible for inclusion studies with indirect measures of exposure (job title or task), provided that the assessment of the effect of RF-EMF exposure was a predefined research objective, the exposure was well characterized in terms of source and type (equipment/device, frequency band, power), and the requirements concerning the exposure contrasts were met. We excluded studies based on self-reported exposure only (i.e., without information on job, task and/or exposure source). We also excluded studies addressing occupations where exposures to electric and magnetic fields between 0 Hz and 10 MHz were dominant compared to the co-occurring exposure to RF-EMF (e.g., MRI machine operators, arc-welders, or electricity production and distribution workers), or with dominant exposures to established carcinogens, without reliable assessment of RF-exposure and appropriate confounding control. The priority exposure classifications were ever vs never exposed, exposure frequency, exposure duration or time since first exposure, average or cumulative exposure level.

3.1.3. Types of comparators

To be eligible for inclusion, studies must have compared the occurrence of the outcome between exposed and unexposed subjects, or between at least two groups with different exposure frequency, intensity, duration, time since first exposure, average or cumulative exposure level.

3.1.4. Types of outcomes

3.1.4.1. Critical and important outcomes. While no eligibility restriction on tumour type was applied, in this paper we focus on six neoplasms, comprising five subgroups of central nervous system (CNS) tumours [brain tumours (including glioma and other histotypes) in adults and in children); meningioma; acoustic neuroma; pituitary tumours]; salivary gland tumours; and leukaemias (including several subtypes). In the lack of guiding biological hypotheses, the choice of these “critical” outcomes relied on contextual evidence: type of exposure (near-field, far-field), knowledge about exogenous risk factors for specific neoplasms (favouring tumours with poorly understood aetiology), and available study data (prioritizing tumours most commonly investigated in relation to RF-EMF, based on previous reviews). Actually, the tumours reviewed in this paper represent the most investigated outcomes in the relevant scientific literature.

We will describe findings from the systematic review of epidemiological studies on RF exposure and risk of any other (“important”) neoplasms in a separate article.

Table 2 reports the standard nomenclature and codes of the tumours of interest for the current review according to the ICD-10 and ICD-O-3 classifications. These details are given for illustrative purposes, reminding that clinical and aetiological disease definitions often diverge (Olsen, 2012).

3.1.4.2. Diagnostic methods and measures of occurrence. Eligibility for inclusion in the critical outcome subset was restricted to studies including newly diagnosed (incident) cases of the diseases of interest, either histology-confirmed or based on unequivocal diagnostic imaging (the latter criterion only applies to CNS tumours), ascertained through cancer registries, hospitals, or other sources with adequate coverage of the study base during the observation period. We excluded studies based on self-reported outcomes, as well as on hospital admissions only (due to uncertainties about the date of diagnosis). Information from death certificates was considered the least valid basis of diagnosis for neoplasms (Jensen et al., 1991). Studies based on cancer-related causes of death were eligible for inclusion in the “important” outcome subset, conditional on the study design (see 3.1.5.1), and will be described in a

separate article as mentioned earlier.

3.1.5. Types of studies

3.1.5.1. Inclusion criteria. Eligibility for inclusion was restricted to aetiological studies (i.e. studies investigating whether RF-EMF is causing or contributing to cancer occurrence) of cohort and case-control design, comprising all related typologies (Gail et al., 2019). We assessed compliance with the eligibility criteria based on standard definitions (Elwood, 2017; Porta, 2016), rather than on the terminology used by the article authors. If the measures of effect were based on cancer mortality, eligibility for inclusion was further restricted to cohort and cohort-nested case-control studies; population-based case-control studies restricted to deceased cases and controls were not included, because this study design renders the identification of the study base difficult or impossible.

3.1.5.2. Exclusion criteria. Case reports and case series were ineligible for inclusion due the lack of a control group. We also excluded comparative studies such as ecological studies (geographical correlation and time-trend analyses), cross-sectional studies, and case-case analyses of case-control studies, because these study designs do not allow calculating the intended measures of effect.

3.1.5.3. Complementary evidence. In line with the triangulation approach (Arroyave et al., 2021; Lawlor et al., 2016; Steenland et al., 2020), we systematically searched for and included three categories of complementary evidence: (a) studies aimed at estimating the amount and direction of exposure measurement errors or other distortions (termed “bias studies”), conducted in the framework of included studies, or directly relevant to the investigated exposure-outcome pairs; (b) source-specific RF dose-modelling; and (c) simulation studies based on incidence time trends of specific types of CNS tumours.

Findings from exposure validation and other bias studies were considered in the risk of bias assessment when applicable to individual studies, and findings from source-specific RF dose-modelling were considered at the final stage of quality of evidence assessment. The intended uses of data from simulation studies of incidence time trends, in line with COSTER recommendation 7.8 to interpret the external validity of the overall body of evidence (Whaley et al., 2020), is described below. Monitoring of incidence rates over time allows investigating changes in disease patterns that affect specific birth cohorts, vary with age, or exhibit calendar effects (which can occur if exposures are localized in time and affect large segments in the population at once), and has substantially contributed to current knowledge about environmental causes of cancer (Olsen, 2012). Regarding the possible carcinogenicity of RF-radiation at exposure levels below international guidelines, analyses of cancer incidence time trends are considered informative owing to the steep increase in mobile phone use (and related changes in prevalence and level of RF exposure to the head) since mid-1990s, along with the limited number of known competing environmental risk factors for glioma and other intracranial tumours (Olsen, 2012; Roosli et al., 2019; WHO, 2010). The availability of high-quality registry data with virtually complete tumour registration over long time periods, is a prerequisite for conducting these studies.

Time-trend analyses of CNS tumours are prone to bias. “Apparent” changes in incidence rates over time (i.e., not reflecting true changes in incidence) may result from demographic changes, and/or changes in sensitivity and accessibility of imaging techniques, in histologic classification, and in registration procedures (Ostrom et al., 2020). The latter is especially applicable to the collection of non-malignant brain tumours, meningioma and other benign CNS tumours (Dolecek et al., 2015; Withrow et al., 2021). Detection bias is an additional concern in time-trend analyses of acoustic neuroma incidence rates (Reznitsky et al., 2019). On these grounds, we only considered “simulation studies”,

purposely planned to assess the external plausibility of findings from analytical studies of specific CNS tumour risks in relation to mobile phone use, by comparing predicted and observed time-trends of incidence rates. To date, studies of this type have been conducted for all malignant brain tumours (Chapman et al., 2016; Sato et al., 2019); for gliomas (de Vocht, 2016; 2017; 2019; Deltour et al., 2012; Deltour et al., 2022; Karipidis et al., 2018, 2019a; b; Little et al., 2012; Villeneuve et al., 2021); for glioma subtypes [astrocytoma (Little et al., 2012); glioblastoma multiforme (de Vocht, 2016; 2019)]; and for multiple histotypes of malignant and benign tumours in the temporal lobe (de Vocht, 2019). We intended to use findings from these studies to set a range of “implausible sizes” for the measures of effect reported by the glioma/brain cancer studies considered in SR-A. These “credibility benchmarks” would be defined for RR estimates either above or below the null, at increasing intervals of time since first use and at increasing amount of use, overall and within specific time-windows.

We assessed comparability of findings across simulation studies in terms of:

- Setting (country, population demographics, time period);
- Risk scenarios (measures of effect and related effect size; latency periods; effect modifiers);
- Exposure (source of data used to model changes in mobile phone use in the target population);
- Outcome (anatomical site, histology, grade);
- Statistical methods;
- Predicted events (number of cases, incidence rates, percent rate changes, others).

If feasible, we planned to standardize to a common metric and meta-analyse the results of multiple simulation studies per brain tumour type. The study classification based on the external plausibility of the observed RR point estimate, would serve three purposes: (i) to validate the capacity of our customized RoB to distinguish studies at high and low risk of directional biases; (ii) to assess the influence of studies reporting implausible measures of effect on the main meta-analyses’ results; (iii) to inform the appraisal of the evidence strength.

3.1.5.4. Years considered. No restriction on publication date was applied.

3.1.5.5. Publication language. We did not exclude any article based on language, but the search queries included English terms only. During screening articles for inclusion, publications in languages other than the ones spoken by the reviewers (English, French, German, Greek, Italian, Portuguese) were translated into English using Google Translate. We did not find potentially relevant articles where we were in doubt about inclusion after automatic translation, and the intervention of a human translator was not necessary.

3.1.5.6. Publication types. We included peer-reviewed journal articles reporting original data from eligible study types. We considered indexing in Medline as evidence of peer-review status. We excluded reviews, meta-analyses, conference proceedings, editorials, comments and letters, with the exception of correspondence related to the included studies (such as letters by the authors reporting errors in the published analysis, providing more detailed or extended data analyses, or discussing study strengths and biases).

3.1.6. Types of effect measures

We focused on studies reporting incidence-based estimates of the relative risk of disease conditional on the exposure: rate ratio (RR) or hazard ratio (HR) in cohort studies, and odds ratios (OR) in case-control studies. Because of the rarity of the neoplasms of interest, the HR and the OR can be considered equivalent to a RR (Higgins et al., 2021a).

Moreover, possible meta-analyses were performed on log-transformed measures of effect and confidence limits (CLs).

3.2. Information sources and search strategy

Eligible studies were identified by literature searches through Medline and Embase. We also consulted the EMF Portal (<https://www.emf-portal.org/en>), a dedicated database of the scientific literature on the health effects of exposure to electromagnetic fields, with documented high coverage of the topic (Drießen et al., 2017). The search timeframe (as in-print publication) extended from the database inception dates (1946 for Medline; 1947 for Embase) to 11 March 2021 (i.e., the date of the actual literature searches).

To comply with the MECIR requirement and COSTER recommendation 2.7 to update the searches within 12 months before publication of the review (Higgins et al., 2020; Whaley et al., 2020), we conducted repeated selective monitoring of the EMF-Portal up to December 2022 to identify recent relevant studies. This was an amendment to the protocol, which envisaged to update the searches through all main databases (see §6.2 *Amendments to the protocol*, point 1), introduced because the precision [1-(excluded record / total retrieved)] of EMF-Portal was much greater than that of the other two sources (0.34 vs 0.05 for Medline, and 0.04 for Embase).

The Medline and Embase queries are reported in Annex 1 (§ 2–3). The search on EMF-Portal took advantages of the in-built facilities; to identify cohort, case-control and simulation studies, we toggled “Epidemiological studies” (as Topic), and “Radio frequency (≥10 MHz)” OR “Mobile communications” (as Frequency range), with “cancer” OR “tumour” as keywords; for exposure validation and dosimetry studies, we selected “Technical/dosimetric studies” and the above frequency ranges.

As an additional source, we used a library of over 400 “seed” studies (see Annex 1, § 1, Table 1), taken from the reference lists of 19 recent comprehensive reviews (AGNIR, 2012; ANSES, 2013, 2016, ARPANSA, 2014; CCARS, 2017; Demers et al., 2014; FDA, 2020; HCN, 2016; IARC, 2013; ICHENF, 2018; ICNIRP, 2020a; SCENIHR, 2015; SSM, 2013, 2014, 2015, 2016, 2018, 2019; WHO, 2014). We used this library to calibrate and assess the performance of draft Medline queries, intentionally designed to privilege sensitivity over precision (0.89 vs 0.09, in the final version of queries; Annex 1, § 1, Table 2).

As secondary sources of unidentified relevant articles, we also hand-searched the reference lists of included studies and consulted the authors’ own archives.

Unpublished studies were not sought. We did not search grey literature, defined as “all types of material not published commercially” (Alberani et al., 1990; The New York Academy of Medicine, 2016). We acknowledge that this might have resulted in a “grey literature bias”, whereas studies yielding smaller and/or statistically nonsignificant effects might be less likely to be published and only available in PhD theses, conference proceedings, books, personal communications, and other forms of grey literature (Song et al., 2010). By definition, it is doubtful that systematic reviews can ever get a complete or representative set of this literature. More importantly, while the common occurrence of grey literature bias was fully supported by a meta-research study of over 3000 meta-analyses from a wide range of scientific disciplines, the estimated effect size was very small [−0.092 (−0.143, −0.041)], and far below the impact of the “small study effects” [0.197 (0.133, 0.264)], acting in the opposite direction (Fanelli et al., 2017). Part of the possibly relevant grey literature was covered by the literature search through Embase, that includes over 3.6 million conference abstracts (Elsevier, 2020).

3.3. Selection process

EndNote 20 was used for the assemblage of the results of the literature searches, duplicate removal, and data management during the

study selection process (Bramer et al., 2017; Peters, 2017). We categorized all identified records by coherence with the subject of the systematic review and other features relevant to assess compliance with the predefined inclusion/exclusion criteria. This categorization occurred at the title/abstract or full-text screening levels of the review, as appropriate. Two reviewers (DB, MSP) independently assessed the relevance of the identified articles, and their eligibility for inclusion in any of the three systematic reviews. Then, both reviewers shared their EndNote libraries with two other team members (KK, SL) who revised and finalized the study selection. All four reviewers, provided with written instructions on categorization scheme, variable coding, and treatment of multiple publications per study, participated in a pilot testing of the study selection procedures undertaken on a small subset of the references retrieved.

3.3.1. Selection of eligible articles

Full-text articles were retrieved for all records classified as certainly or possibly relevant. Eligible article types (original studies and related correspondence) were further categorized by study design, setting/source of exposure to RF-EMF (mobile phone and/or cordless phone use; environmental sources; occupational sources), and investigated neoplasm(s). Eligibility for inclusion was then assessed based on compliance with the predefined inclusion/exclusion criteria. At completion of this stage, all identified articles were divided into four groups: (i) irrelevant; (ii) relevant but ineligible for inclusion, with reason(s) for exclusion specified (recording “various” and specifying which, if more than one applied); (iii) relevant and eligible for inclusion in one of the three systematic reviews (or in more than one, if multiple types of RF-EMF exposure were investigated); (iv) included as complementary evidence (or in both the aetiological and complementary evidence group, when appropriate).

3.3.2. Selection of eligible studies

We classified all the included articles by the investigated exposure (s), and outcomes(s), and our definition of the term “study” corresponds to each identified homogeneous exposure-outcome pair (i.e., articles addressing multiple exposure-outcome pairs had multiple corresponding studies).

3.3.2.1. Multiple publications per study. Multiple publications with overlapping data from the same study were identified by examining study acronym, author affiliations, study design, enrolment criteria, and enrolment dates. We included all articles relating to a given study (i.e. exposure-outcome pair), providing information relevant for each neoplasm and exposure contrast prioritized for our systematic reviews, selected one to use as the primary record for data extraction and risk of bias assessment, and considered the others as secondary publications with annotation as being related to the primary record. We considered as primary records the latest published follow-up/update for cohort and nested case-control studies, and the earliest article for case-control studies. We emphasize that more than one article per study can qualify for the role of primary record, depending on availability of information relevant for the various exposure-outcome pairs of interest. In the cases where exactly the same set of data from a primary study was reported in multiple articles (duplicate data), we kept the first publication and excluded subsequent articles.

3.3.2.2. Pooled analyses of primary studies. Pooled analyses of individual data from relevant primary studies (not to be confused with meta-analyses, which use published risk estimates as input data) were eligible for inclusion in our review. This was an a-priori choice, motivated by our knowledge of the available epidemiological studies on mobile phone use and risk of CNS tumours, and of the bias affecting many previous meta-analyses (i.e., improper study aggregation, resulting in multiple counting of individual data) which often included

primary studies and pooled analyses of the former (Roosli et al., 2019).

Where a quantitative synthesis of results was feasible, we avoided combining results from primary studies and pooled analyses with overlapping populations. That is, we created more than one dataset per neoplasm (e.g., one including primary studies only and others made of combinations of pooled analyses and non-overlapping primary studies). The main neoplasm-specific meta-analyses were based on one of these datasets, while the others were used in sensitivity analyses.

In practice, we sought to transform a complex feature of the body of evidence into an asset, which would allow us to assess the robustness of the meta-analyses findings to variations in study aggregation.

3.3.3. Disagreement between reviewers

Disagreements between reviewers involved in article and study selection (including decisions on between-study overlap) were resolved by discussion; if no consensus could be reached, a final decision was made by the two reviewers in charge of the study selection for each line of evidence.

3.3.4. Reporting of information flow

We documented the selection process in a study flow diagram based on the PRISMA-2020 reporting guidelines (Page et al., 2021b).

3.4. Data extraction process

For each included study, a standard set of details was extracted from the relevant publications (Table 3). The study design is reported in brackets when data refer to either cohort or case-control studies (including variants thereof); lack of specification means relevance for both main study designs.

For all prioritized exposure contrasts, we extracted from each neoplasm-specific study the most (appropriately) adjusted measure of effect and 95 % confidence interval per exposure category.

From the entire dataset of included studies, six subsets of equivalent size were assigned to as many team members (DB, CB, CN, KK, TL, MSP) who extracted and recorded the relevant data in the predefined templates (Study Key-Feature tables, and Summary of Findings tables). Three reviewers (CB, KK, SL) merged and checked the extracted information for completeness and accuracy as a quality control measure. Information inferred, converted, or estimated after data extraction, was recorded in the analytical datasets, and annotated with a rationale.

3.4.1. Missing data

We requested missing data considered important for the review (e.g., study key-features, and/or data required to conduct a meta-analysis) from the corresponding author by email, using the contact details available from the study report. We made two attempts of contact, two weeks apart. In case of no response within one month of the second, we considered the attempt unsuccessful.

3.5. Risk of bias assessment

3.5.1. Risk of bias in studies

To assess the study’s internal validity, or risk of bias (RoB), we followed the method developed by the National Toxicology Program – Office of Health Assessment and Translation (NTP-OHAT, 2019). As per the OHAT’s approach, we created a version of the OHAT RoB tool (NTP-OHAT, 2015) tailored to the topic of our review, focussing on the bias questions applicable to the study designs eligible for inclusion. The bias domains of relevance for observational cohort and case-control studies were: confounding; selection bias; attrition/exclusion/missing data bias; confidence in the exposure characterization; confidence in the outcome assessment; selective reporting; and appropriateness of statistical methods. In the sections addressing selection and outcome-information biases, the RoB tool developed by the Office of the Report on Carcinogens (NTP-ORoC, 2015) was also referred to. Detailed information on

Table 3

Data extraction elements.

Topic	Items
Article	First author and publication year, full reference
Study	Study design: cohort; nested case-control study; population-based case-control study hospital-based case-control study; other design variants (specify) Study acronym (if any)
Subjects	Study population (description) Geography (country, region, state, etc.) Dates of study and sampling time frame (period of case ascertainment) Demographics (sex; age or lifestage at exposure and at outcome assessment) Number of subjects (target, enrolled, number per group in analysis) Person-years of observations, length of follow-up and follow-up rates per exposure group [cohort] Participation rates of cases and controls (possibly for exposed and unexposed separately, in each series) [case-control]
Methods	Inclusion/exclusion criteria and recruitment strategy Case ascertainment: cancer register; hospital-based; other source (specify) Case type: incident cases; cases alive at enrolment; deceased cases Reference group description [cohort] Control type: population based (source and sampling method); hospital based (type of diagnoses); other types (specify) [case-control] Proportion of proxies interviewed among cases and controls [case-control] Outcome type(s): one or more of the following: glioma, brain tumours (when only topography available), paediatric brain tumours*, meningioma, acoustic neuroma, pituitary tumour, salivary gland tumours; childhood leukaemias; adult leukaemias; other type (specify) Outcome assessment: diagnostic methods (histology-based, %; imaging-based, %; cause of death only; not given) Exposure assessment timing: prospective vs retrospective (i.e., before vs after outcome occurrence, diagnosis or ascertainment) Exposure assessment methods (self-administered questionnaire, personal interview; computer assisted personal interview, network-operator customer lists; measurements, modelling, geocoded distance to a broadcast transmitter; JEM, SEM; occupational sector, job title, task) Exposure variables used in the analyses (e.g., ever vs never exposed; length of exposure; time since first exposure; exposure frequency; exposure level; cumulative exposure; others – specifying the variable unit and type: dichotomous/categorical/continuous) Statistical methods (specify)
Results	Mean/median exposure value within each exposure interval (for all relevant metrics) Number of cases and persons-years or total number of subjects per exposure level, including unexposed [cohort]; Number of cases and controls per exposure level, including unexposed [case-control]; Type of relative risk estimate (OR, HR, IRR, SMR) Measures of effect and confidence limits (CI) for each prioritized exposure contrast Confounders or modifying factors and how they were considered in analysis (i.e., list of factors included in final model, or considered for inclusion but found to have little or no impact on the measures of effect and therefore not included in the final model)
Funding	Funding source

Table 3 footnotes: *Usually referring to diagnoses in the age range 0–19 years; †Usually referring to diagnoses in the age range 0–14 years.

the customization process, along with the tailored bias rating instructions and answer option forms, are provided in the annexed RoB protocol (Annex 2).

During protocol development, all assessors participated in a pre-pilot aimed at assessing and thereby improving the comprehensibility and ease of application of a preliminary version of the tailored RoB tool (see Annex 2, § I.6 for details). The final RoB assessment form (Annex 2, § I.7, Table 5) was prepared taking into account the comments of the team members involved in the pre-pilot.

We performed the RoB assessment at the exposure-outcome level, as many studies eligible for inclusion in the current review reported on different neoplasms and multiple types/sources/settings of exposure to RF-EMF. This was in line with the Cochrane approach (Higgins et al., 2021b; Sterne et al., 2021), COSTER recommendation 5.2 (Whaley et al., 2020), and other guidance on conducting systematic reviews of observational studies of aetiology and risks from environmental or occupational exposures (Arroyave et al., 2021; Dekkers et al., 2019; Radke et al., 2019).

The potential for bias of each neoplasm-specific study and related exposure-outcome contrasts was rated in duplicate by two assessors. The number of studies to be rated were divided approximately equally amongst three assessor pairs (DB-TL, MSP-KK, KK-CB). No assessor evaluated studies that they co-authored. All assessors were trained in two working sessions, and a pilot-study (based on five studies per rater pair) was undertaken right after completion of the study selection, rather than at the protocol stage as suggested by COSTER recommendation 1.4.7 (Whaley et al., 2020), to be able to select a sample of studies representative of the review datasets.

The task of solving possible inter-rater disagreements was assigned to four adjudicators (MB, ME, SL, MR), avoiding that a given adjudicator

arbitrated studies that he/she co-authored.

Contrary to the original plan (see § 6.2. *Amendments to the protocol*, point 2), managing the RoB through the Health Assessment Workplace Collaborative (HAWC) platform (Shapiro et al., 2018) proved unfeasible; we used ad hoc paper forms for the ratings (Annex 2, § 1.7, Table 5) and Excel for the production of the heat maps.

One team member (SL), blind to the raters' identity, carried out a consistency check between the preliminary findings and the instructions provided in the RoB protocol; incoherent ratings were then amended and summarized in a final heat map.

3.5.2. Summary assessments of risks of bias

We applied the OHAT's 3-level tiering of the quality of individual studies, based on summary assessments of risk of bias for the domains most relevant to the specific systematic review (NTP-OHAT, 2019). This tiering differs from scaling and is consistent with the Cochrane's overall risk-of-bias judgement (Higgins et al., 2021b; Sterne et al., 2021). We focused on four key-items including selection/attrition biases, and exposure/outcome information biases.

The choice of the exposure information bias and the selection/attrition bias as key-domains for the tiering, was driven by the expected features of the dataset, as known from previous reviews on the topic at the stage of the protocol drafting, and confirmed after performing the review.

The large majority of included studies is of case-control design and, with reference to the largest exposure-subset (SR-A, RF exposure from wireless phone use), all but one case-control studies were based on self-reported exposure information collected after diagnosis. These studies are inherently prone to random, systematic and especially differential errors, as shown in several validation studies. Differential exposure

Table 4
Included incidence-based aetiological studies of “critical” neoplasms: 119 exposure-outcome (E-O) pairs from 63 articles.

Evidence Body	RF-Exposure Type, Source, Setting	Neoplasm	Article	Design	E-O Pairs	Total
SR-A	Mobile phones	Paediatric Brain Tumours	(Aydin et al. 2011; Castano-Vinyals et al. 2022; Feltbower et al. 2014)	CaCo	3	82
		Glioma Brain cancer	(Auvinen et al. 2002; Baldi et al. 2011; Christensen et al. 2005; Coureau et al. 2014; Hardell and Carlberg 2015; Hardell et al. 2006; Hardell et al. 2013a; Hardell et al. 2002b; Hardell et al. 1999; Hepworth et al. 2006; Hours et al. 2007; Inskip et al. 2001; Interphone SG 2010; Klaeboe et al. 2007; Lahkola et al. 2008; Lonn et al. 2005; Momoli et al. 2017; Muscat et al. 2000; Schuz et al. 2006a; Spinelli et al. 2010; Takebayashi et al. 2008; Turner et al. 2016b; Yoon et al. 2015)	CaCo	25	
		Meningioma	(Frei et al. 2011; Schuz et al. 2022)	Cohort		
			(Auvinen et al. 2002; Baldi et al. 2011; Carlberg and Hardell 2015; Carlberg et al. 2013; Christensen et al. 2005; Coureau et al. 2014; Hardell et al. 2005; Hardell et al. 2002a; Hardell et al. 1999; Hours et al. 2007; Inskip et al. 2001; Interphone SG 2010; Klaeboe et al. 2007; Lahkola et al. 2008; Lonn et al. 2005; Momoli et al. 2017; Schuz et al. 2006a; Takebayashi et al. 2008)	CaCo	20	
		Acoustic Neuroma	(Frei et al. 2011; Schuz et al. 2022)	Cohort		
			(Baldi et al. 2011; Christensen et al. 2004; Corona et al. 2012; Han et al. 2012; Hardell et al. 2005; Hardell et al. 2013b; Hardell et al. 2002a; Hardell et al. 1999; Hours et al. 2007; Inskip et al. 2001; Interphone SG 2011; Klaeboe et al. 2007; Lonn et al. 2004; Momoli et al. 2017; Muscat et al. 2002; Pettersson et al. 2014; Schlehofer et al. 2007; Schoemaker et al. 2005; Takebayashi et al. 2006)	CaCo	23	
		(Schuz et al. 2006b; Schuz et al. 2022; Schuz et al. 2011)	Cohort			
		Pituitary tumours	(Hardell et al. 2002a; Schoemaker and Swerdlow 2009; Shrestha et al. 2015; Takebayashi et al. 2008)	CaCo	5	
		Salivary gland tumours	(Schuz et al. 2022)	Cohort		
			(Auvinen et al. 2002; Duan et al. 2011; Hardell et al. 2004; Lonn et al. 2006; Momoli et al. 2017; Sadetzki et al. 2008; Soderqvist et al. 2012)	CaCo	8	
			(Schuz et al. 2006b)	Cohort	[10 behaviour-specific RR estimates per eligible expo metric]	
SR-A	Cordless phones	Paediatric Brain Tumours	(Aydin et al. 2011; Castano-Vinyals et al. 2022)	CaCo	2	23
		Glioma Brain cancer	(Hardell and Carlberg 2015; Hardell et al. 2006; Hardell et al. 2013a; Hardell et al. 2002b; Lonn et al. 2005; Schuz et al. 2006a)	CaCo	6	
		Meningioma	(Carlberg and Hardell 2015; Carlberg et al. 2013; Hardell et al. 2005; Hardell et al. 2002a; Lonn et al. 2005; Schuz et al. 2006a)	CaCo	6	
		Acoustic Neuroma	(Han et al. 2012; Hardell et al. 2005; Hardell et al. 2013b; Hardell et al. 2002a; Lonn et al. 2004; Pettersson et al. 2014)	CaCo	6	
		Pituitary tumours	(Hardell et al. 2002a)	CaCo	1	
		Salivary gland tumours	(Hardell et al. 2004; Soderqvist et al. 2012)	CaCo	2	
SR-B	Broadcast Transmitters	Paediatric Brain Tumours	(Ha et al. 2007)	CaCo	2	6
		Childhood Leukemias	(Hauri et al. 2014)	Cohort		
			(Ha et al. 2008; Ha et al. 2007; Maskarinec et al. 1994; Merzenich et al. 2008)	CaCo	4	
			(Hauri et al. 2014)	Cohort		
SR-B	Base Stations	Paediatric Brain Tumours	(Elliott et al. 2010; Li et al. 2012)	CaCo	2	4
		Childhood Leukaemias	(Elliott et al. 2010; Li et al. 2012)	CaCo	2	
SR-C	Occupational exposures (Multiple sources-JEM)	Glioma Brain cancer	(Grayson 1996)	CaCo-nested	3	3
		Leukaemias	(Grayson 1996; Karipidis et al. 2007; Vila et al. 2018)	CaCo	0	
Total E-O pairs for critical outcomes						119

Table 4. Footnotes

CaCo = Case-control. CaCo-nested = cohort-nested case-control. E-O pairs = exposure-outcome pairs.

Cells highlighted in blue consist of neoplasm-specific groups including primary studies and partially or fully overlapping pooled analyses of the former; to avoid multiple counting of individual data, we created multiple analytical datasets for glioma, meningioma, and acoustic neuroma (details on the study aggregation are provided in Table 5 below); all other (white) cells include independent primary studies.

Mobile phones & Glioma or Brain Cancer = Twelve of the 25 studies [11 CaCo (Christensen et al. 2005; Hardell and Carlberg 2015; Hardell et al. 2006; Hardell et al. 1999; Hepworth et al. 2006; Inskip et al. 2001; Lahkola et al. 2007; Lonn et al. 2005; Muscat et al. 2000; Schuz et al. 2006a; Takebayashi et al. 2008) and 1 Cohort (Schuz et al. 2022)] also report measures of effect for one or more glioma subtypes, not considered in this review.

Mobile phones & Salivary gland tumours = Two studies (Lonn et al. 2006; Sadetzki et al. 2008) report separate and independent measures of effect for malignant and benign salivary tumours, which were included as such in the meta-analyses.

Cordless phones & Glioma or Brain Cancer = One of the five studies (Hardell et al. 2006) also reports measures of effect for several glioma subtypes, not considered in this review.

Broadcast Transmitters & Childhood leukaemias = Two of the four studies, (Hauri et al. 2014) and (Ha et al. 2008; Ha et al. 2007), also report RRs leukaemia subtypes [Acute Lymphoblastic Leukaemia – ALL (Hauri et al. 2014); Lymphocytic Leukaemia and Myelocytic Leukaemia (Ha et al. 2008; Ha et al. 2007), not considered in this review; Hauri et al. 2014 = In data synthesis we focus on the main analyses of this cohort (time-to-event proportional hazard models), and do not consider the secondary analyses (incidence density based on Poisson regression); (Ha et al. 2008; Ha et al. 2007) = Ha et al. 2008 is an authors' response with relevant findings from amended leukaemia analyses.

Broadcast Transmitters & paediatric brain tumours = One of the two (Ha et al. 2007) also reports measures of effect separately for Neuroepithelial brain cancer and non-Neuroepithelial brain cancer, not considered in this review; Hauri et al. 2014 = In data synthesis we focus on the main analyses of this cohort (time-to-event proportional hazard models), and do not consider the secondary analyses (incidence density based on Poisson regression).

misclassification cannot occur in cohort studies with prospective exposure assessment independent of the outcome.

Furthermore, compared to cohort studies with exhaustive case ascertainment independent of the exposure, the case-control design is much more susceptible to selection/attrition bias via several mechanisms (e.g., differential participation, and differential missing data at enrolment or at the analysis stage, just to quote the major ones). The reasons why we considered selection and attrition biases (as per the OHAT RoB tool) as essentially equivalent in terms of bias structure are provided in our systematic review protocol (Lagorio et al., 2021).

Regarding the issues specific to the topic of our systematic review, within the exposure information bias we also considered reverse causation. Structurally speaking, reverse causation is a form of confounding by the disease itself. In studies of mobile phone use and tumours of the head region, reverse causation arises because prodromal symptoms (e.g., epilepsy, or cognitive impairment), which may precede the diagnosis of several years, make the “cases to be” less likely to start use of mobile phone, or more likely to reduce the amount of use, compared to healthy subjects of similar sex, age, and region. This kind of reverse causation is typically a downward bias, and can affect both cohort and case-control studies. Support in favour of the occurrence of reverse causation is provided by a multicentre follow-up study of glioma cases which observed a paradoxical better survival among mobile phone users than in non-users (Olsson et al., 2019). It can also explain the reduced risk of glioma and other brain tumours observed in several cohort and case-control studies in the lowest categories of time since start use. Reverse causation (which is a real phenomenon, rather than a distortion) is “artificially” concealed in case-control studies restricting eligibility at inclusion to cases alive at enrolment in the study, whereby the exposure distribution among cases from the source population is misrepresented.

The outcome information bias was considered as an additional key-bias item for the following reasons. Firstly, with special reference to studies of acoustic neuroma in relation to wireless phone use, detection bias is of concern; it is a form of differential misclassification of the outcome, with easily predictable upward direction, possibly occurring (in both cohort and case-control studies) because mobile phone use can raise awareness about the unilateral hearing loss that is an early symptom of the disease, facilitating or anticipating the diseases diagnosis; furthermore, physicians or otorhinolaryngologists, suspecting that mobile phone use causes acoustic neuroma, may monitor patients using mobile phones more closely than non-users (or low-users). Secondly, for all central nervous tumours (some of which, like glioblastoma, are characterized by particularly poor survival, and all – independent on the behaviour – involve a cognitive decline), rapid case-ascertainment is essential to minimize the occurrence of several biases (exposure information, and selection/attrition). Thirdly, as we included mortality-based cohort studies (most of which investigated the association between occupational RF-exposure and many different neoplasms that will be examined in a subsequent paper), we considered these studies as possibly liable to errors in outcome ascertainment, especially for non-rapidly fatal neoplasms.

Tier-1 comprised studies with definitely or probably low risk of bias for all key-items and most of other items; tier-3 included studies with definitely or probably high risk of bias for all key-items and most of

other items; and studies not meeting the above criteria were classified as tier-2. We used this ranking to assess the overall potential for bias in the body of evidence at the stage of quality of evidence assessment (Annex 3).

We also considered using the tiering results in data synthesis (see § 3.6.2 below) although, as anticipated in the systematic review protocol (Lagorio et al., 2021), the possibility to perform meaningful analyses by bias-tiers depended on the variability of proneness to influential biases in the dataset, and on the possibility to isolate the impact of one bias from those of competing biases (Savitz et al., 2019).

3.6. Synthesis methods

We summarized the main features of all included studies in tables grouped and ordered by exposure type/setting/source (SR-A, SR-B, and SR-C), neoplasm, and study design. Templates of the key study characteristic tables for cohort and case-control studies, as well as for the summary of findings tables, were provided in the online annexes to the published protocol (Lagorio et al., 2021).

The outcome, the exposure, and age at diagnosis are the most relevant factors affecting comparability between studies eligible for inclusion in our review. We did not combine exposure-outcome pairs of different tumours (in terms of ICD-O-3 main site or histology groups), neoplasm-specific risks from different exposure types and metrics, or risk of a specific tumour in relation to a given exposure type/metric in adult and paediatric populations (0–19 years).

For homogenous datasets (in terms of outcome, exposure type/metric, and subjects' lifestage), we set a minimum size requirement for amenability to a meta-analysis (i.e., at least 3 independent measures of effect). This was a deviation from the protocol whereby, to address concerns about the large uncertainty in heterogeneity statistics from meta-analyses based on few studies (Fu et al., 2008; Ioannidis et al., 2007), we had planned to calculate the confidence intervals of the I^2 statistics. However, this was not done because the I^2 statistic is considered more a descriptive measure of heterogeneity than a quantity on which to make statistical inference, such as a confidence interval (see § 6.2. Amendments to the protocol, point 3). We also assessed the heterogeneity in findings across studies (in terms of direction and magnitude of effects), to decide whether averaging individual measures of effect would produce meaningful results. Possible causes of inconsistency (e.g., design features) were explored through subgroup meta-analyses. In the presence of substantial unexplained heterogeneity, reporting of overall meta-risk estimates was considered inappropriate, and confidence in the body of evidence was reduced (see section 3.7).

The synthesis of findings from the study subsets not meeting the requirements for inclusion in a meta-analysis was based on a structured tabulation of results and visual displays, i.e., forest plots, with no overall meta-risk estimates and related statistics (Anzures-Cabrera and Higgins, 2010; McKenzie and Brennan, 2021).

We summarize below the pre-planned meta-analyses of studies included in SR-A. A similar approach would have been followed if a quantitative synthesis of data from other lines of evidence (SR-B, SR-C) had been considered feasible.

Table 5

List of studies potentially amenable to meta-analysis of effect measures in relation to ever and time since start use of wireless (mobile or cordless) phones by neoplasm, exposure source, and datasets with non-overlapping populations.

Study	Design	Type	Mobile Phones		Cordless Phones		Neoplasm					Dataset						
			Ever	TSS	Ever	TSS	PBT	G	M	N	P	S	MA1	MA2	MA3	MA4	MA5	
Aydin et al. 2011b	Ca-Co	1	✓	–	[✓]	–	✓	–	–	–	–	–	–	1	0	0	0	0
Feltbower et al. 2014	Ca-Co	1	✓	–	–	–	✓	–	–	–	–	–	–	1	0	0	0	0
Castano-Vinyals et al. 2022	Ca-Co	1	✓	[✓]	[✓]	[✓]	✓	–	–	–	–	–	–	1	0	0	0	0
Frei et al. 2011 Men	Cohort	1	✓	–	–	–	–	✓	✓	–	–	–	–	1	1	1	1	1
Frei et al. 2011 Women	Cohort	1	✓	✓	–	–	–	✓	✓	–	–	–	–	1	1	1	1	1
Schuz et al. 2006b*	Cohort	1	✓	–	–	–	–	–	–	✓	–	–	–	1	1	1	1	1
Schuz et al. 2011 Men*	Cohort	1	–	✓	–	–	–	–	–	✓	–	–	–	1	1	1	1	1
Schuz et al. 2022 Women	Cohort	1	✓	✓	–	–	–	✓	✓	–	–	–	–	1	1	1	1	1
Hardell et al. 1999	Ca-Co	1	✓	–	–	–	–	✓	✓	✓	–	–	–	1	1	1	1	1
Hardell et al. 2002b	Ca-Co	1	✓	✓	✓	✓	–	✓	–	–	–	–	–	1	1	0	0	0
Hardell et al. 2002a	Ca-Co	1	✓	–	✓	–	–	–	✓	✓	–	–	–	1	1	0	0	0
Hardell et al. 2005	Ca-Co	1	✓	✓	✓	✓	–	–	✓	✓	–	–	–	1	1	0	0	0
Hardell et al. 2006	Ca-Co	1	✓	✓	✓	✓	–	✓	–	–	–	–	–	1	1	0	0	0
Carlberg et al. 2013	Ca-Co	1	✓	✓	✓	✓	–	–	✓	–	–	–	–	1	1	0	0	0
Hardell et al. 2013a	Ca-Co	2	✓	✓	✓	✓	–	✓	–	–	–	–	–	1	1	0	0	0
Hardell et al. 2013b	Ca-Co	2	✓	✓	✓	✓	–	–	–	✓	–	–	–	0	0	1	0	1
Carlberg and Hardell 2015	Ca-Co	2	✓	✓	✓	✓	–	–	✓	–	–	–	–	0	0	1	0	1
Hardell and Carlberg 2015	Ca-Co	2	✓	✓	✓	✓	–	✓	–	–	–	–	–	0	0	1	0	1
Christensen et al. 2004	Ca-Co	1	✓	✓	–	–	–	–	–	✓	–	–	–	1	0	1	0	0
Lonn et al. 2004	Ca-Co	1	✓	✓	✓	–	–	–	–	✓	–	–	–	1	0	1	0	0
Christensen et al. 2005	Ca-Co	1	✓	–	–	–	–	–	✓	✓	–	–	–	1	0	1	0	0
Lonn et al. 2005	Ca-Co	1	✓	✓	✓	–	–	–	✓	✓	–	–	–	1	0	1	0	0
Hepworth et al. 2006	Ca-Co	1	✓	–	–	–	–	–	✓	–	–	–	–	1	0	1	0	0
Schuz et al. 2006a	Ca-Co	1	✓	✓	✓	✓	–	–	✓	✓	–	–	–	1	0	1	1	0
Takebayashi et al. 2006	Ca-Co	1	✓	✓	–	–	–	–	–	✓	–	–	–	1	0	1	1	0
Hours et al. 2007	Ca-Co	1	✓	✓	–	–	–	–	✓	✓	✓	–	–	1	0	1	0	0
Klaeboe et al. 2007	Ca-Co	1	✓	✓	–	–	–	–	✓	✓	✓	–	–	1	0	1	0	0
Schlehofer et al. 2007	Ca-Co	1	✓	✓	–	–	–	–	–	✓	–	–	–	1	0	1	1	0
Takebayashi et al. 2008	Ca-Co	1	✓	✓	–	–	–	–	✓	✓	–	–	–	1	0	1	1	0
Momoli et al. 2017	Ca-Co	1	✓	–	–	–	–	–	✓	✓	✓	–	–	1	0	1	0	0
Schoemaker et al. 2005	Ca-Co	2	✓	–	–	–	–	–	–	✓	–	–	–	0	0	0	1	0
Lahkola et al. 2007	Ca-Co	2	✓	–	–	–	–	–	✓	–	–	–	–	0	0	0	1	0
Lahkola et al. 2008	Ca-Co	2	✓	–	–	–	–	–	✓	–	–	–	–	0	0	0	1	0
Turner et al. 2016	Ca-Co	2	✓	–	–	–	–	–	✓	–	–	–	–	0	0	0	1	0
Interphone SG 2010	Ca-Co	2	✓	–	–	–	–	–	✓	✓	–	–	–	0	1	0	0	1
Interphone SG 2011	Ca-Co	2	✓	–	–	–	–	–	–	–	✓	–	–	0	1	0	0	1
Muscat et al. 2000	Ca-Co	1	✓	✓	–	–	–	–	✓	–	–	–	–	1	1	1	1	1
Inskip et al. 2001	Ca-Co	1	✓	✓	–	–	–	–	✓	✓	✓	–	–	1	1	1	1	1
Auvinen et al. 2002	Ca-Co	1	✓	–	–	–	–	–	✓	✓	–	–	–	1	1	1	1	1
Muscat et al. 2002	Ca-Co	1	✓	✓	–	–	–	–	–	–	✓	–	–	1	1	1	1	1
Spinelli et al. 2010	Ca-Co	1	✓	–	–	–	–	–	✓	–	–	–	–	1	1	1	1	1
Baldi et al. 2011	Ca-Co	1	✓	–	–	–	–	–	✓	✓	✓	–	–	1	1	1	1	1
Corona et al. 2012	Ca-Co	1	✓	✓	–	–	–	–	–	–	✓	–	–	1	1	1	1	1
Han et al. 2012	Ca-Co	1	✓	✓	✓	✓	–	–	–	–	✓	–	–	1	1	1	1	1
Coureau et al. 2014	Ca-Co	1	✓	✓	–	–	–	–	✓	✓	–	–	–	1	1	1	1	1
Pettersson et al. 2014	Ca-Co	1	✓	✓	✓	✓	–	–	–	–	✓	–	–	1	1	1	1	1
Yoon et al. 2015	Ca-Co	1	✓	✓	–	–	–	–	✓	–	–	–	–	1	1	1	1	1
Schuz et al. 2022 Women	Cohort	1	✓	✓	–	–	–	–	–	–	✓	–	–	1	0	0	0	0
Hardell et al. 2002a	Ca-Co	1	✓	–	[✓]	[✓]	–	–	–	–	✓	–	–	1	0	0	0	0
Takebayashi et al. 2008	Ca-Co	1	✓	✓	–	–	–	–	–	–	✓	–	–	1	0	0	0	0
Schoemaker and Swerdlow 2009	Ca-Co	1	✓	–	–	–	–	–	–	–	–	✓	–	1	0	0	0	0
Shrestha et al. 2015	Ca-Co	1	✓	–	–	–	–	–	–	–	–	✓	–	1	0	0	0	0
Schuz et al. 2006b Malignant	Cohort	1	✓	–	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Auvinen et al. 2002 Malignant	Ca-Co	1	✓	–	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Hardell et al. 2000 mostly Malignant	Ca-Co	1	✓	✓	[✓]	[✓]	–	–	–	–	–	–	✓	1	0	0	0	0
Lonn et al. 2006 Malignant	Ca-Co	1	✓	✓	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Lonn et al. 2006 Benign	Ca-Co	1	✓	✓	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Sadetzki et al. 2008 Malignant	Ca-Co	1	✓	✓	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Sadetzki et al. 2008 Benign	Ca-Co	1	✓	✓	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Duan et al. 2011 Malignant	Ca-Co	1	✓	✓	–	–	–	–	–	–	–	–	✓	1	0	0	0	0
Soderqvist et al. 2012 Malignant	Ca-Co	1	✓	✓	[✓]	[✓]	–	–	–	–	–	–	✓	1	0	0	0	0
Momoli et al. 2017 Any behaviour	Ca-Co	1	✓	–	–	–	–	–	–	–	–	–	✓	1	0	0	0	0

Table 5- Footnotes.

Design: CaCo = Case-Control; **Wireless device:** MP_h = mobile phone; CP_h = cordless phone; **Neoplasm:** PBT = Paediatric brain tumours; G = Glioma, M = Meningioma, N = Acoustic Neuroma; P = Pituitary tumours; S = Salivary gland tumours. **Type:** 1 = Primary study, 2 = Pooled analysis of primary studies. **Dataset:** MA1-Glioma = Primary studies only (Auvinen et al. 2002; Baldi et al. 2011; Christensen et al. 2005; Coureau et al. 2014; Frei et al. 2011; Hardell et al. 2006; Hardell et al. 2013a; Hardell et al. 2002b; Hardell et al. 1999; Hepworth et al. 2006; Hours et al. 2007; Inskip et al. 2001; Klaeboe et al. 2007; Lonn et al. 2005; Momoli et al. 2017; Muscat et al. 2000; Schuz et al. 2006a; Schuz et al. 2022; Spinelli et al. 2010; Takebayashi et al. 2008; Yoon et al. 2015); MA1-Meningioma = Primary studies only (Auvinen et al. 2002; Baldi et al. 2011; Carlberg et al. 2013; Christensen et al. 2005; Coureau et al. 2014; Frei et al. 2011; Hardell et al. 2005; Hardell et al. 2002a; Hardell et al. 1999; Hours et al. 2007; Inskip et al. 2001; Klaeboe et al. 2007; Lonn et al. 2005; Momoli et al. 2017; Schuz et al. 2006a; Schuz et al. 2022; Takebayashi et al. 2008); MA1-Acoustic Neuroma = Primary studies only (Baldi et al. 2011; Christensen et al. 2004; Corona et al. 2012; Han et al. 2012; Hardell et al. 2005; Hardell

et al. 2002a; Hardell et al. 1999; Hours et al. 2007; Inskip et al. 2001; Klæboe et al. 2007; Lonn et al. 2004; Momoli et al. 2017; Muscat et al. 2002; Pettersson et al. 2014; Schlehofer et al. 2007; Schuz et al. 2006b; Schuz et al. 2022; Schuz et al. 2011; Takebayashi et al. 2006); **MA2-Glioma** = Interphone international analyses (Interphone SG 2010), plus all other non-overlapping primary studies ((Auvinen et al. 2002; Baldi et al. 2011; Coureau et al. 2014; Frei et al. 2011; Hardell et al. 2006; Hardell et al. 2013a; Hardell et al. 2002b; Hardell et al. 1999; Inskip et al. 2001; Muscat et al. 2000; Schuz et al. 2022; Spinelli et al. 2010; Yoon et al. 2015)); **MA2-Meningioma** = Interphone international analyses (Interphone SG 2010), plus all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Carlberg et al. 2013; Coureau et al. 2014; Frei et al. 2011; Hardell et al. 2005; Hardell et al. 2002a; Hardell et al. 1999; Inskip et al. 2001; Schuz et al. 2022); **MA2-Acoustic Neuroma** = Interphone international analyses (Interphone SG 2011), plus all other non-overlapping primary studies (Baldi et al. 2011; Corona et al. 2012; Han et al. 2012; Hardell et al. 2005; Hardell et al. 2002a; Hardell et al. 1999; Inskip et al. 2001; Muscat et al. 2002; Pettersson et al. 2014; Schuz et al. 2006b; Schuz et al. 2022; Schuz et al. 2011); **MA3-Glioma** = Hardell-Series of intracranial tumour (ICT) 1st primary study (Hardell et al. 1999), plus Hardell-Series pooled analyses of primary ICT studies 2nd-3rd-4th (Carlberg and Hardell 2015; Hardell and Carlberg 2015; Hardell et al. 2013b), plus all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Coureau et al. 2014; Frei et al. 2011; Inskip et al. 2001; Muscat et al. 2000; Schuz et al. 2022; Spinelli et al. 2010; Takebayashi et al. 2008; Yoon et al. 2015); **MA3-Meningioma** = Hardell-Series of ICT 1st primary study (Hardell et al. 1999), plus Hardell-Series pooled analyses of primary ICT studies 2nd-3rd-4th (Carlberg and Hardell 2015), plus all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Coureau et al. 2014; Frei et al. 2011; Hours et al. 2007; Inskip et al. 2001; Momoli et al. 2017; Schuz et al. 2006a; Schuz et al. 2022; Takebayashi et al. 2008); **MA3-Acoustic Neuroma** = Hardell-Series of ICT 1st primary study (Hardell et al. 1999), plus Hardell-Series pooled analyses of primary ICT studies 2nd-3rd-4th (Hardell et al. 2013b), plus all other non-overlapping primary studies (Baldi et al. 2011; Corona et al. 2012; Han et al. 2012; Hours et al. 2007; Inskip et al. 2001; Momoli et al. 2017; Muscat et al. 2002; Pettersson et al. 2014; Schlehofer et al. 2007; Schuz et al. 2006b; Schuz et al. 2022; Schuz et al. 2011; Takebayashi et al. 2006); **MA4-Glioma**: Pooled analyses of two Interphone data-subsets (Lahkola et al. 2007; Turner et al. 2016), plus Interphone local studies from Germany and Japan (Schuz et al. 2006a; Takebayashi et al. 2008), and all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Coureau et al. 2014; Frei et al. 2011; Hardell et al. 2006; Hardell et al. 2013a; Hardell et al. 2002b; Hardell et al. 1999; Inskip et al. 2001; Muscat et al. 2000; Schuz et al. 2022; Spinelli et al. 2010; Yoon et al. 2015); **MA4-Meningioma** = Pooled analyses of the Interphone data-subset (Lahkola et al. 2008), plus Interphone local studies from France, Canada, Germany, and Japan (Hours et al. 2007; Momoli et al. 2017; Schuz et al. 2006a; Takebayashi et al. 2008), plus all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Carlberg et al. 2013; Coureau et al. 2014; Frei et al. 2011; Hardell et al. 2005; Hardell et al. 2002a; Hardell et al. 1999; Inskip et al. 2001; Schuz et al. 2022); **MA4-Acoustic Neuroma** = Pooled analyses of the Interphone data-subset (Schoemaker et al. 2005), plus Interphone local studies from France, Canada, Germany, and Japan (Hours et al. 2007; Momoli et al. 2017; Schuz et al. 2006a; Takebayashi et al. 2006), and all other non-overlapping primary studies (Baldi et al. 2011; Corona et al. 2012; Han et al. 2012; Hardell et al. 2005; Hardell et al. 2002a; Hardell et al. 1999; Inskip et al. 2001; Muscat et al. 2002; Pettersson et al. 2014; Schuz et al. 2006b; Schuz et al. 2022; Schuz et al. 2011); **MA5-Glioma (main meta-analyses)** = Interphone international analyses (Interphone SG 2010), plus Hardell-Series of ICT 1st primary study (Hardell et al. 1999), plus Hardell-Series pooled analyses of primary ICT studies 2nd-3rd-4th (Hardell and Carlberg 2015), and all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Coureau et al. 2014; Frei et al. 2011; Inskip et al. 2001; Muscat et al. 2000; Schuz et al. 2022; Spinelli et al. 2010; Yoon et al. 2015); **MA5-Meningioma (main meta-analyses)** = Interphone international analyses (Interphone SG 2010), plus Hardell-Series of ICT 1st primary study (Hardell et al. 1999), plus Hardell-Series pooled analyses of primary ICT studies 2nd-3rd-4th (Carlberg and Hardell 2015), and all other non-overlapping primary studies (Auvinen et al. 2002; Baldi et al. 2011; Coureau et al. 2014; Frei et al. 2011; Inskip et al. 2001; Schuz et al. 2022); **MA5-Acoustic Neuroma (main meta-analyses)** = Interphone international analyses (Interphone SG 2011), plus Hardell-Series of ICT 1st primary study (Hardell et al. 1999), plus Hardell-Series pooled analyses of primary ICT studies 2nd-3rd-4th (Hardell et al. 2013b), and all other non-overlapping primary studies (Baldi et al. 2011; Corona et al. 2012; Han et al. 2012; Inskip et al. 2001; Muscat et al. 2002; Pettersson et al. 2014; Schuz et al. 2006b; Schuz et al. 2022; Schuz et al. 2011).

* The measures of effect for acoustic neuroma in the Danish subscriber cohort were extracted from the 2nd follow for ever mobile phone use (Schuz et al. 2006b), and from the 3rd follow-up for long-term use (Schuz et al. 2011).

✓ = The study reports effect measure for cordless phone use, but a quantitative synthesis is clearly inappropriate (one or two neoplasm-specific studies available).

3.6.1. Meta-analyses of studies on wireless phone use and risk of neoplasms in the head region

The meta-analyses were neoplasm- and exposure-specific, performed separately for glioma, meningioma, acoustic neuroma, pituitary tumours, salivary gland tumours, and paediatric brain tumours, in relation to usage of each type of wireless phone (mobile or cordless).

We used the natural logarithms of the most (appropriately) adjusted point estimates of relative risk (RR, HR, OR), and related 95 % CIs, extracted from the relevant articles as input for the meta-analyses, focussing on the exposure metrics and contrasts below.

- a. For the binary exposure variable “ever vs never” (regular) use, we performed meta-analyses stratified on study design and based on random-effects restricted likelihood (REML) models, using the I^2 statistic (Higgins et al., 2003) to assess the statistical heterogeneity in results across studies. To describe the degree of heterogeneity detected via the I^2 index, we tried to be consistent with the Cochrane’s guidance (Deeks et al., 2021), whereby: 0 % to 40 %: might not be important; 30 % to 60 %: may represent moderate heterogeneity; 50 % to 90 %: may represent substantial heterogeneity; and 75 % to 100 %: considerable heterogeneity. Differences between cohort and case-control studies were assessed using the test for group differences (Q_b statistics).
- b. For the categorical variable “time since start of use” (TSS), the across-study variability in cutpoints was dealt with by aligning (to the possible extent) the original categories to a “standard” classification, namely into short-term (<5 years), mid-term (5–9 years), and long-term use (≥ 10 years). When needed, we combined the original measures of effect for adjacent categories using the inverse variance weighting method (IVWA, fixed effects model). We performed meta-

analyses stratified on category of TSS vs no exposure, based on REML models, using the Q_b statistic to assess the homogeneity in results across TSS subgroups (<5, 5–9, 10+ years). Note that this was a deviation from the protocol, whereby we had planned to perform a meta-regression, assigning increasing numerical values to the three levels of this categorical variable (short-term = 1; mid-term = 2; long-term = 3), in order to approximate an analysis of trend by latency (see § 6.2 *Amendments to the protocol*, point 4). We did carry out neoplasm-specific meta-regressions using a quality of exposure assessment score as moderator variable, but realized that the related findings were more difficult to interpret, compared to those from the subgroup meta-analyses. Therefore, results from the latter are reported in the main paper, while findings from the former are included in the [supplemental online material](#).

- c. We conducted dose–response meta-analyses (DRM) of glioma, meningioma, and acoustic neuroma risks in relation to mobile phone CCT and CNC using weighted mixed effects models (Crippa et al., 2019; Orsini, 2021). The dependent variable was the study-specific estimates of the log transformed (ln) odds ratio. The independent variable was the midpoint exposure value assigned to each interval. For an upper open-ended category, the assignment was its lower bound plus the width of the previous (second-to-highest) interval (Ilyasova et al., 2005). Weights for correlated study-specific ORs were derived from the confidence intervals (variances) and crude counts using the Hamling’s method (covariances). Restricted cubic splines with 3 knots at fixed percentiles of the exposure distribution were used to estimate a smooth shape (Orsini, 2021; Orsini and Spiegelman, 2020). The statistical heterogeneity of dose–response gradients across studies was taken into account by using random-effects for the regression coefficients of the exposure

transformations using a two-stage approach. A Wald-type test (w) at 5 % confidence level for the hypothesis of overall no summary exposure effect on neoplasm risks was conducted with reference to a χ^2 distribution with degrees of freedom equal to the number of regression coefficients being tested. Point and interval (95 %) estimates for the dose–response relationship (odds ratio) for the average study is shown graphically up to the 95th percentile of the exposure distribution using the 50th percentile (median) exposure as referent.

3.6.2. Secondary analyses

For glioma, meningioma, and acoustic neuroma, we assessed the sensitivity of results to variations in the dataset composition. As previously noted, for the above-mentioned neoplasms, we included primary studies and partially or completely overlapping pooled analyses of the former, and we created multiple datasets (MA1–MA5) per neoplasm to avoid multiple counting of individual data. For Ever vs Never and TSS mobile phone use, we performed our main analyses on the neoplasm-specific dataset including the largest overall number of exposed cases (MA5), and sensitivity analyses on four other datasets (MA1–MA4). We then conducted subgroup meta-analyses to assess the heterogeneity of findings within each dataset, and differences in results across datasets. For the DRM of risk estimates by CCT and CNC, we performed the main analyses on the dataset with the largest number of observations (MA1), and sensitivity analyses on those with more exposed cases (MA4 and MA5).

To assess changes over time in the summary measures of effect for the neoplasms most commonly investigated (glioma, meningioma, and acoustic neuroma) in ever and long-term users, we performed cumulative meta-analyses (i.e. added studies sequentially in the meta-analyses) on the dataset of studies ordered by the upper bound of the cases diagnosis' range of dates. We performed these analyses on the MA1 and MA2 datasets (including the greatest number of individual studies). The results of these analyses, focussing on the exposure contrasts Ever vs Never and Long-term (10+ years) use of mobile phones, are reported in cumulative forest plots (Anzures-Cabrera and Higgins, 2010), where each meta-RR is the pooled estimate of past studies and the more recent one.

We considered whether the additional sensitivity meta-analyses envisaged in our protocol (Lagorio et al., 2021) were worthwhile doing, taking into account the results of the main meta-analyses, as well as the findings from the summary RoB assessment (see § 4.3.1 and § 4.3.2 below), and the feasibility of creating credibility benchmarks from the incidence time trend simulation studies (see § 4.3.3).

Based on a *post-hoc* decision, we performed leave-one-out meta-analyses of the effect measures for glioma, meningioma, and acoustic neuroma in relation to Long-term (10+ years) mobile phone use (see § 6.2. Amendments to the protocol, point 5).

The analyses were performed using the meta-analysis software developed in Stata 18 (Palmer and Sterne, 2016), and the *drmeta*-Stata command (Orsini, 2021).

3.6.3. Reporting bias assessment

Reporting bias, or “meta-bias” (Shamseer et al., 2015), comprises several kinds of distortions due to missing data in a synthesis (Page et al., 2021a; Sedgwick, 2015). We attempted to minimize language bias by including studies in any language. We used both funnel plots and the Egger's test to examine funnel plot asymmetry.

3.7. Certainty assessment

We assessed the confidence in the evidence per critical outcome, by category of exposure addressed in each component of our systematic review (SR-A, SR-B, SR-C), and across multiple exposure types and related endpoints, as described in the predefined protocol (see Annex 3 for details).

In brief, we followed the OHAT GRADE-based method (NTP-OHAT,

2019). Based on this approach, the level of confidence in the exposure-outcome association was classified according to four descriptors:

- **High** (++++): The true effect is highly likely to be reflected in the apparent relationship.
- **Moderate** (+++): The true effect may be reflected in the apparent relationship.
- **Low** (++): The true effect may be different from the apparent relationship.
- **Very Low** (+): The true effect is highly likely to be different from the apparent relationship.

The process consisted of three steps. At first, we assigned an initial rating of “moderate” confidence to all aetiological studies included in our systematic review. This is in line with the GRADE approach which foresees that an initial “high confidence” rating is assigned to studies complying with 4 criteria (controlled exposure, exposure prior to outcome, individual outcome data, and use of a comparison group).

During the second step, we considered four possible downgrading factors (unexplained inconsistency; indirectness; imprecision; publication bias), and three possible upgrading factors (large magnitude of effect; dose response; residual confounding or other factors counter to the observed effect).

In the third step, we assessed the confidence in evidence across multiple exposure types for specific neoplasms, and across multiple outcomes for specific exposures.

In formulating our overall conclusions, we took into account the exposure-outcome specific confidence in evidence ratings, the internal coherence of the original study findings (based on ranking of RF sources by exposure level as inferred from dosimetric studies) and, limited to glioma in relation to mobile phone use, the external coherence with findings from time-trend simulation studies.

Four team members (MB, KK, SL, TL) prepared a preliminary version of the confidence in evidence ratings and overall conclusions, submitted it for revision to the other team members, and finalized the collectively agreed assessment.

To enhance clarity in conveying findings from our systematic review, we formulated our conclusive statements in line with the wording suggested by the GRADE guidelines 26 (Santesso et al., 2020); this was not originally envisaged (see § 6.2. Amendments to the protocol, point 6).

4. Results

4.1. Study selection

From the searches through Medline (2068 records), Embase (2752 records), and EMF-Portal (240 records) we identified 5060 records, of which 1193 were duplicates, leaving 3867 records for screening. In addition, 42 records were retrieved from the previously mentioned “seed-study” library ($n = 18$), citation searching ($n = 6$), selective monitoring of EMF-Portal up to December 2022 ($n = 16$), and the team members' archives ($n = 2$). Details about the study identification and screening process are provided in Fig. 1.

4.1.1. Excluded articles

The 3867 records identified through the main literature databases were pre-screened using EndNote scripts supplemented by human revision. This process excluded 1877 records, leaving 1990 records plus the 42 records identified via other sources (total of 2032 records) for title/abstract screening. The title/abstract screening excluded 1393 records, leaving 639 articles for full-text screening. Finally, the full-text screening excluded 492 articles, leaving 147 articles for inclusion in our systematic review.

In total 3764 records were excluded, comprising retracted articles ($n = 5$), studies of irrelevant topics ($n = 3319$), ineligible publication types ($n = 250$), studies of ineligible design ($n = 95$), plus 93 articles reporting

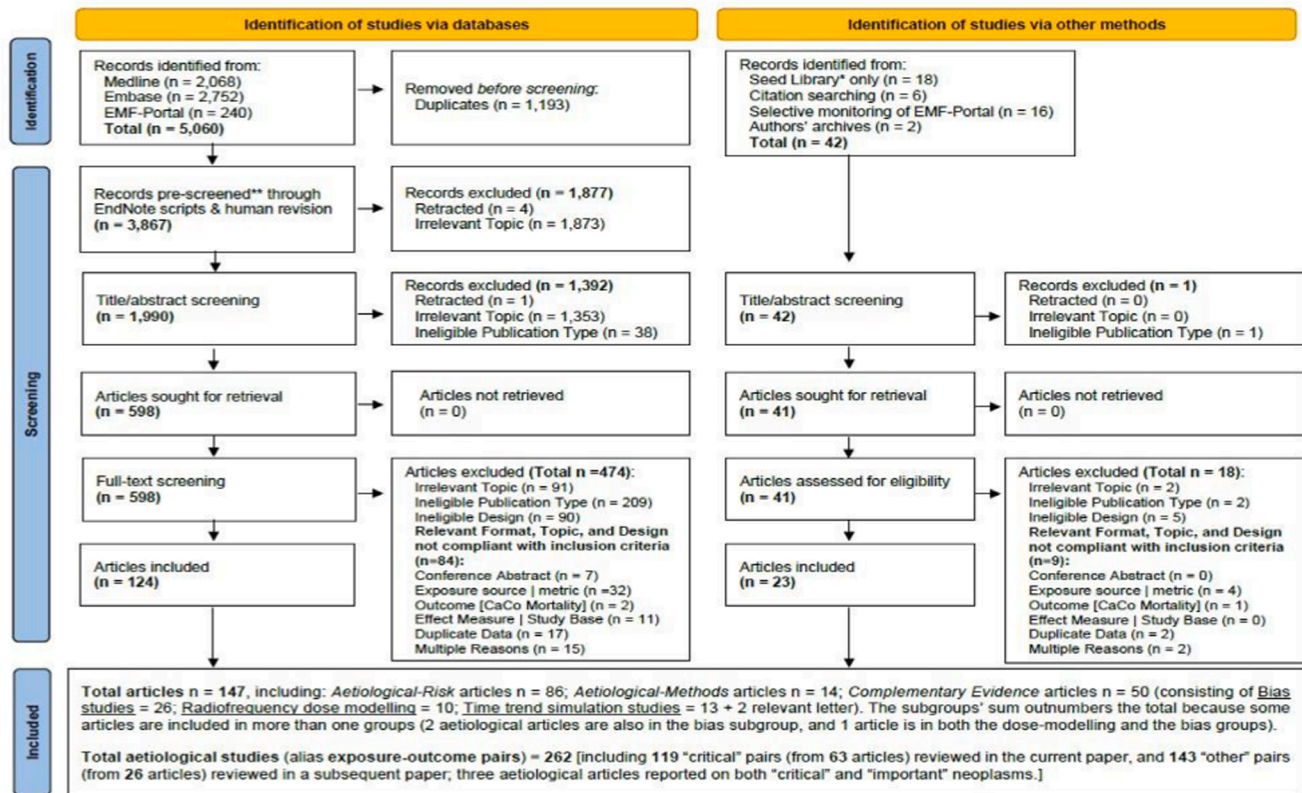


Fig. 1. PRISMA-2020 flow-diagram. **Fig. 1** footnotes: **Exposure source/metric** = the excluded article deals with an ineligible exposure source (e.g., medical exposure) or report analyses based on ineligible exposure metric (e.g., only analysis per unit increase in mobile phone amount of use). **Effect measure/study base** = the excluded article does not report risk estimates, or reports ineligible measure of effect (e.g., survival; prevalence-OR), or the study base is unidentifiable (that is, the reported RR is by default an unreliable estimate of the effect of exposure).

on studies not compliant with our additional predefined inclusion criteria. The list of studies from the latter group, with reasons for exclusion, is provided in [Annex 4, Table S1](#). Note that [Table S1](#) consists of 96 records; 93 of these relate to the excluded articles, while 3 records are exposure-specific data not meeting our inclusion criteria in SR-B and/or SR-C from two studies included in SR-A ([Baldi et al., 2011](#); [Spinelli et al., 2010](#)).

Several articles were excluded because they presented findings included in previous publications (meeting our definition of "duplicate data", n = 19), the study base was not identifiable (n = 11), the measure of outcome occurrence was cause-specific mortality (n = 3), or due to the publication type (conference abstracts, n = 7, all identified through Embase). Many articles were excluded due to ineligible exposure assessment methods, ineligible exposure metrics, or because exposures to RF and other types of EMFs were not discernible (n = 36 in total); the exposure-related exclusions were particularly common among articles potentially eligible for inclusion in SR-C.

4.1.2. Total included articles

In total, independently of the type of outcome (critical or important) and the exposure source/setting (SR-A, SR-B, SR-C), we considered eligible for inclusion 147 articles.

Of these articles, 86 reported on 262 distinct aetiological "studies", alias "Exposure-Outcome combinations" (E-O pairs), investigating the association between RF-EMF exposure from wireless phone use, fixed-site transmitters, or workplace sources, and either "critical" outcomes (63 articles, and 119 E-O pairs) addressed herein, or other "important" outcomes (26 articles, and 143 E-O pairs), which will be the subject of a separate subsequent paper.

Regarding non-aetiological articles, we identified and included 14 articles reporting on methodological aspects of a number of included

aetiological studies (SR-A = 11 articles, and SR-C = 3 articles; see [Annex 4 – Table S2](#)). Additionally, we included 50 articles in the "Complementary Evidence" dataset used to support this review, dealing with topic-relevant bias studies (n = 26); RF-dose modelling (n = 10); and simulation studies of glioma incidence rate time trends (n = 13, plus 2 relevant letters); these articles are listed in [Annex 4 – Tables S3-S5](#).

Please note that the detailed figures per group outnumber the total included articles because some articles reported on more than one topic or E-O pair: two articles were assigned to both the aetiological and bias-studies groups; one article was included in both the dose-modelling and the bias-studies groups; and three aetiological articles reported on studies investigating critical and important neoplasms.

4.1.3. Included studies of critical outcomes

The 119 E-O pairs from the 63 aetiological articles reporting on "critical outcomes" are shown in [Table 4](#).

In SR-A we included 82 studies investigating risks of selected tumours in the head region (paediatric brain tumour, glioma, meningioma, acoustic neuroma, pituitary gland tumours and salivary gland tumours) in relation to use of mobile phones, along with 23 studies reporting on a subset of the above-mentioned neoplasms in relation to use of cordless phones.

In SR-B, we considered 10 studies on risk of childhood neoplasms from far-field exposure to fixed-site transmitters (childhood leukaemia and broadcast antennas or base stations = 4 and 2 E-O pairs, respectively; paediatric brain tumour in relation to broadcast antennas or base stations = 2 studies for each E-O pair).

Only 3 studies of brain cancer/glioma risk among occupationally exposed workers were eligible for inclusion in SR-C.

Among the included aetiological studies, we identified those potentially amenable to the meta-analyses of effect measures in relation to

Table 6

List of studies potentially amenable to dose–response meta-analyses by neoplasm (glioma, meningioma, and acoustic neuroma in adults), RF source (mobile phone and/or cordless phone) and exposure metric (cumulative call time, or cumulative number of calls).

MA1 Dataset											
Study	Design	Group	Type	Country	G	M	N	MPh	CPh	CCT	CNC
Muscat et al. 2000	CaCo	3	1	US	✓	–	–	✓	–	✓	–
Inskip et al. 2001	CaCo	3	1	US	✓	✓	✓	✓	–	✓	–
Muscat et al. 2002	CaCo	3	1	US	–	–	✓	✓	–	✓	–
Christensen et al. 2004	CaCo	2	1	DK	–	–	✓	✓	–	✓	✓
Lonn et al. 2004	CaCo	2	1	SE	–	–	✓	✓	–	✓	✓
Christensen et al. 2005	CaCo	2	1	DK	✓	✓	–	✓	–	✓	✓
Lonn et al. 2005	CaCo	2	1	SE	✓	✓	–	✓	–	✓	✓
Hardell et al. 2006	CaCo	1	1	SE	✓	–	–	✓	✓	✓	–
Hepworth et al. 2006	CaCo	2	1	UK	✓	–	–	✓	–	✓	✓
Schuz et al. 2006a	CaCo	2	1	DE	✓	✓	–	✓	–	✓	✓
Takebayashi et al. 2006	CaCo	2	1	JP	–	–	✓	✓	–	✓	–
Hours et al. 2007	CaCo	2	1	FR	✓	✓	✓	✓	–	✓	✓
Klaeboe et al. 2007	CaCo	2	1	NO	✓	✓	✓	✓	–	✓	✓
Schlehofer et al. 2007	CaCo	2	1	DE	–	–	✓	✓	–	✓	✓
Takebayashi et al. 2008	CaCo	2	1	JP	✓	✓	–	✓	–	✓	–
Carlberg et al. 2013	CaCo	1	1	SE	–	✓	–	✓	✓	✓	–
Hardell et al. 2013a	CaCo	1	1	SE	✓	–	–	✓	✓	✓	–
Coureau et al. 2014	CaCo	3	1	FR	✓	✓	–	✓	–	✓	✓
Pettersson et al. 2014	CaCo	3	1	SE	–	–	✓	✓	✓	✓	✓
Yoon et al. 2015	CaCo	3	1	KR	✓	–	–	✓	–	✓	–
Momoli et al. 2017	CaCo	2	1	CA	✓	✓	✓	✓	–	✓	–
MA2 Dataset											
Study	Design	Group	Type	Country	G	M	N	MPh	CPh	CCT	CNC
Muscat et al. 2000	CaCo	3	1	US	✓	–	–	✓	–	✓	–
Inskip et al. 2001	CaCo	3	1	US	✓	✓	✓	✓	–	✓	–
Muscat et al. 2002	CaCo	3	1	US	–	–	✓	✓	–	✓	–
Hardell et al. 2006	CaCo	1	1	SE	✓	–	–	✓	✓	✓	–
Interphone SG 2010	CaCo	2	2	W13	✓	✓	–	✓	–	✓	✓
Interphone SG 2011	CaCo	2	2	W13	–	–	✓	✓	–	✓	✓
Carlberg et al. 2013	CaCo	1	1	SE	–	✓	–	✓	✓	✓	–
Hardell et al. 2013a	CaCo	1	1	SE	✓	–	–	✓	✓	✓	–
Coureau et al. 2014	CaCo	3	1	FR	✓	✓	–	✓	–	✓	✓
Pettersson et al. 2014	CaCo	3	1	SE	–	–	✓	✓	✓	✓	✓
Yoon et al. 2015	CaCo	3	1	KR	✓	–	–	✓	–	✓	–
MA3 Dataset											
Study	Design	Group	Type	Country	G	M	N	MPh	CPh	CCT	CNC
Muscat et al. 2000	CaCo	3	1	US	✓	–	–	✓	–	✓	–
Inskip et al. 2001	CaCo	3	1	US	✓	✓	✓	✓	–	✓	–
Muscat et al. 2002	CaCo	3	1	US	–	–	✓	✓	–	✓	–
Christensen et al. 2004	CaCo	2	1	DK	–	–	✓	✓	–	✓	✓
Lonn et al. 2004	CaCo	2	1	SE	–	–	✓	✓	–	✓	✓
Christensen et al. 2005	CaCo	2	1	DK	✓	✓	–	✓	–	✓	✓
Lonn et al. 2005	CaCo	2	1	SE	✓	✓	–	✓	–	✓	✓
Hepworth et al. 2006	CaCo	2	1	UK	✓	–	–	✓	–	✓	✓
Schuz et al. 2006a	CaCo	2	1	DE	✓	✓	–	✓	–	✓	✓
Takebayashi et al. 2006	CaCo	2	1	JP	–	–	✓	✓	–	✓	–
Hours et al. 2007	CaCo	2	1	FR	✓	✓	✓	✓	–	✓	✓
Klaeboe et al. 2007	CaCo	2	1	NO	✓	✓	✓	✓	–	✓	✓
Schlehofer et al. 2007	CaCo	2	1	DE	–	–	✓	✓	–	✓	✓
Takebayashi et al. 2008	CaCo	2	1	JP	✓	✓	–	✓	–	✓	–
Hardell et al. 2013b	CaCo	1	2	SE	–	–	✓	✓	✓	✓	✓
Carlberg and Hardell 2015	CaCo	1	2	SE	–	✓	–	✓	✓	✓	✓
Hardell and Carlberg 2015	CaCo	1	2	SE	✓	–	–	✓	✓	✓	✓
Coureau et al. 2014	CaCo	3	1	FR	✓	✓	–	✓	–	✓	✓
Pettersson et al. 2014	CaCo	3	1	SE	–	–	✓	✓	✓	✓	✓
Yoon et al. 2015	CaCo	3	1	KR	✓	–	–	✓	–	✓	–
Momoli et al. 2017	CaCo	2	1	CA	✓	✓	✓	✓	–	✓	–
MA4 Dataset											
Study	Design	Group	Type	Country	G	M	N	MPh	CPh	CCT	CNC
Muscat et al. 2000	CaCo	3	1	US	✓	–	–	✓	–	✓	–
Inskip et al. 2001	CaCo	3	1	US	✓	✓	✓	✓	–	✓	–
Muscat et al. 2002	CaCo	3	1	US	–	–	✓	✓	–	✓	–
Schoemaker et al. 2005	CaCo	2	2	5NE	–	–	–	✓	–	✓	–
Hardell et al. 2006	CaCo	1	1	SE	✓	–	–	✓	✓	✓	–

(continued on next page)

Table 6 (continued)

MA1 Dataset											
Study	Design	Group	Type	Country	G	M	N	MPh	CPh	CCT	CNC
Schuz et al. 2006a	CaCo	2	1	DE	✓	✓	–	✓	–	✓	✓
Takebayashi et al. 2006	CaCo	2	1	JP	–	–	✓	✓	–	✓	–
Hours et al. 2007	CaCo	2	1	FR	–	✓	✓	✓	–	✓	✓
Lahkola et al. 2007	CaCo	2	2	5NE	–	–	–	–	–	–	–
Schlehofer et al. 2007	CaCo	2	1	DE	–	–	✓	✓	–	✓	✓
Lahkola et al. 2008	CaCo	2	2	5NE	–	–	–	–	–	–	–
Takebayashi et al. 2008	CaCo	2	1	JP	✓	✓	–	✓	–	✓	–
Carlberg et al. 2013	CaCo	1	1	SE	–	✓	–	✓	✓	✓	–
Hardell et al. 2013a	CaCo	1	1	SE	✓	–	–	✓	✓	✓	–
Coureau et al. 2014	CaCo	3	1	FR	✓	✓	–	✓	–	✓	✓
Petterson et al. 2014	CaCo	3	1	SE	–	–	✓	✓	✓	✓	✓
Yoon et al. 2015	CaCo	3	1	KR	✓	–	–	✓	–	✓	–
Turner et al. 2016	CaCo	2	2	5OC	✓	–	–	–	–	✓	✓
Momoli et al. 2017	CaCo	2	1	CA	–	✓	✓	✓	–	✓	–

MA5 Dataset											
Study	Design	Group	Type	Country	G	M	N	MPh	CPh	CCT	CNC
Muscat et al. 2000	CaCo	3	1	US	✓	–	–	✓	–	✓	–
Inskip et al. 2001	CaCo	3	1	US	✓	✓	✓	✓	–	✓	–
Muscat et al. 2002	CaCo	3	1	US	–	–	✓	✓	–	✓	–
Interphone SG 2010	CaCo	2	2	W13	✓	✓	–	✓	–	✓	✓
Interphone SG 2011	CaCo	2	2	W13	–	–	✓	✓	–	✓	✓
Hardell et al. 2013b	CaCo	1	2	SE	–	–	✓	✓	✓	✓	✓
Coureau et al. 2014	CaCo	3	1	FR	✓	✓	–	✓	–	✓	✓
Petterson et al. 2014	CaCo	3	1	SE	–	–	✓	✓	✓	✓	✓
Carlberg and Hardell 2015	CaCo	1	2	SE	–	✓	–	✓	✓	✓	✓
Hardell and Carlberg 2015	CaCo	1	2	SE	✓	–	–	✓	✓	✓	✓
Yoon et al. 2015	CaCo	3	1	KR	✓	–	–	✓	–	✓	–

Table 6 Footnotes.

Type: 1 = Primary study, 2 = Pooled analysis of primary studies.

Country: 5NE = Pooled analyses of Interphone data-subset of five North European countries; 5OC = Pooled analyses of Interphone data-subset of other five countries (not from northern Europe); CA = Canada; DE = Germany; DK = Denmark; FR = France; JP = Japan; KR = Republic of Korea; NO = Norway; SE = Sweden; UK = United Kingdom; US = United States of America; W13 = International pooled analyses of Interphone data-from all 13 participating countries.

Neoplasm: G = Glioma; M = Meningioma; N = Acoustic neuroma.

RF source: MPh = Mobile phone use; CPh = Cordless phone use. **Exposure metric:** CCT = cumulative call time (hours); CNC = Cumulative number of calls (calls).

“Ever (regular) use” and TSS use of wireless (mobile or cordless) phones by neoplasm, exposure source, and datasets with non-overlapping populations (Table 5).

Table 6 enumerates the studies that were possible candidates for inclusion in the DRM of the most investigated neoplasm risks (glioma, meningioma, acoustic neuroma) in adults, in relation to wireless phone cumulative call time (CCT) and cumulative number of calls (CNC). All studies listed in Table 6 are of case-control design, and most of them provided analyses by self-reported lifetime intensity of mobile phone use, with only a few studies investigating cumulative use of cordless phones. It is worth noting that there is exposure overlap (and therefore multiple counting of individual data) in all studies reporting findings for exposures from mobile and cordless phones.

Few studies reported measures of effect for use of any wireless phone (either mobile or cordless) and selected neoplasms: one of paediatric brain tumours, three of brain cancer in adults (two primary studies and one pooled analyses including the former), three of meningioma (again, two primary studies and one pooled analyses including the former), two of acoustic neuroma (one primary study and one pooled analysis including the former), and two of salivary gland tumours; the findings from these studies are described in Annex 5 – Table S7.13; but were not considered amenable to quantitative syntheses.

4.2. Study characteristics

Detailed information about the main characteristics of all included aetiological studies is provided in Annex 5, Tables S6.1 to S6.5 (Study Key-Features tables).

4.3. Results of the assessment of risk of bias

4.3.1. Risks of bias in studies

Ratings agreed upon by the assessor pairs which were incoherent with the instructions provided in the RoB protocol and answer-options were identified by the consistency check in 52 study-forms (44 %). These were discussed with the rater pairs and amended. The RoB assessment forms for all examined studies are provided in Annex 6, where information on the rating rationale for each study can be found. The final RoB heat map is displayed in Table 7 below. At the individual study level, the most critical issue was exposure characterization, followed by susceptibility to selection bias. Outcome assessment and statistical methods were considered at low risk of bias in almost all studies.

4.3.2. Summary risk of bias (study tiering)

In the summary RoB assessment, focussed on the predefined most relevant biases (i.e., selection/attrition, exposure and outcome information), there was an approximately equal number of studies that were classified at low risk (tier-1; n = 58, 49 %) and moderate risk (tier-2; n = 61, 51 %), and none at high risk (tier-3) (Table 7, last column).

Based on the results of the summary RoB, we replaced the planned sensitivity analyses excluding tier-3 studies, with subgroup meta-analyses stratified on bias-tier (see § 6.2. Amendments to the protocol, point 7).

4.3.3. External coherence with results of time trend simulation studies

We included and examined 13 time-trend simulation studies (Chapman et al., 2016; Choi et al., 2021; de Vocht, 2016; 2017; 2019; Deltour et al., 2012; Deltour et al., 2022; Elwood et al., 2022; Karipidis

Table 7
Heat map illustrating the risk of bias assessment results.

SR-A Mobile phones	Selection	Attrition	Exposure	Outcome	Confounding	Selective reporting	Statistical methods	Summary bias tier
Paediatric Brain Tumours								
Aydin et al. 2011b	(+)	(++)	(+)	(++)	(+)	(++)	(++)	1
Feltbower et al. 2014	(+)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Castano-Vinyals et al. 2022	(+)	(++)	(+)	(++)	(+)	(++)	(++)	1
Gliona								
Hardell et al. 1999	(NR)	(--)	(NR)	(++)	(NR)	(++)	(++)	2
Muscat et al. 2000	(+)	(+)	(NR)	(++)	(+)	(+)	(++)	1
Inskip et al. 2001	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Auvinen et al. 2002	(+)	(++)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2002b	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Christensen et al. 2005	(++)	(+)	(+)	(++)	(+)	(++)	(++)	1
Lonn et al. 2005	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2006	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Hepworth et al. 2006	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2006a	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Hours et al. 2007	(+)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Klaeboe et al. 2007	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Lahkola et al. 2007	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Takebayashi et al. 2008	(+)	(+)	(+)	(+)	(+)	(+)	(++)	1
Interphone SG 2010	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Spinelli et al. 2010	(NR)	(NR)	(--)	(++)	(--)	(+)	(++)	2
Baldi et al. 2011	(++)	(++)	(--)	(+)	(+)	(++)	(++)	2
Frei et al. 2011	(++)	(+)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2013a	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Coureau et al. 2014	(+)	(NR)	(-)	(++)	(+)	(++)	(++)	2
Hardell and Carlberg 2015	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Yoon et al. 2015	(--)	(NR)	(--)	(NR)	(+)	(+)	(++)	2
Turner et al. 2016	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Momoli et al. 2017	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2022	(+)	(+)	(++)	(++)	(+)	(+)	(++)	1
Meningioma								
Hardell et al. 1999	(NR)	(--)	(NR)	(++)	(NR)	(++)	(++)	2
Inskip et al. 2001	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Auvinen et al. 2002	(+)	(++)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2002a	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Christensen et al. 2005	(++)	(+)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2005	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Lonn et al. 2005	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2006a	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Hours et al. 2007	(+)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Klaeboe et al. 2007	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Lahkola et al. 2008	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Takebayashi et al. 2008	(+)	(+)	(+)	(+)	(+)	(+)	(++)	1
Interphone SG 2010	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Baldi et al. 2011	(++)	(++)	(--)	(+)	(+)	(++)	(++)	2
Frei et al. 2011	(++)	(+)	(+)	(++)	(+)	(++)	(++)	1
Carlberg et al. 2013	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Coureau et al. 2014	(+)	(NR)	(-)	(++)	(+)	(++)	(++)	2
Carlberg and Hardell 2015	(NR)	(NR)	(--)	(++)	(+)	(++)	(++)	2
Momoli et al. 2017	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2022	(+)	(+)	(++)	(++)	(+)	(+)	(++)	1

(continued on next page)

Table 7 (continued)

Acoustic Neuroma								
Hardell et al. 1999	(NR)	(--)	(NR)	(++)	(NR)	(++)	(++)	2
Inskip et al. 2001	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2002a	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Muscat et al. 2002	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Christensen et al. 2004	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Lonn et al. 2004	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2005	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Schoemaker et al. 2005	(+)	(++)	(+)	(++)	(+)	(+)	(++)	1
Schuz et al. 2006b	(+)	(+)	(+)	(++)	(-)	(+)	(++)	1
Takebayashi et al. 2006	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Hours et al. 2007	(+)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Klaeboe et al. 2007	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schlehofer et al. 2007	(+)	(+)	(+)	(++)	(++)	(+)	(++)	1
Baldi et al. 2011	(++)	(++)	(--)	(+)	(+)	(++)	(++)	2
Interphone SG 2011	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2011	(++)	(++)	(+)	(++)	(+)	(+)	(++)	1
Corona et al. 2012	(++)	(NR)	(+)	(++)	(NR)	(++)	(++)	2
Han et al. 2012	(+)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Hardell et al. 2013b	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Pettersson et al. 2014	(++)	(+)	(+)	(+)	(+)	(+)	(++)	1
Momoli et al. 2017	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2022	(+)	(+)	(++)	(++)	(+)	(+)	(++)	1
Pituitary tumours								
Hardell et al. 2002a	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Takebayashi et al. 2008	(+)	(+)	(+)	(+)	(+)	(+)	(++)	1
Schoemaker and Swerdlow 2009	(+)	(++)	(+)	(++)	(+)	(+)	(++)	1
Shrestha et al. 2015	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Schuz et al. 2022	(+)	(+)	(++)	(++)	(+)	(+)	(++)	1
Salivary gland tumours								
Auvinen et al. 2002	(+)	(++)	(+)	(++)	(+)	(++)	(++)	1
Hardell et al. 2004	(NR)	(NR)	(--)	(++)	(+)	(++)	(++)	2
Lonn et al. 2006	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1
Schuz et al. 2006b	(+)	(+)	(+)	(++)	(-)	(+)	(++)	1
Sadetzki et al. 2008	(+)	(NR)	(+)	(++)	(+)	(+)	(++)	2
Duan et al. 2011	(++)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Soderqvist et al. 2012	(+)	(NR)	(--)	(++)	(+)	(+)	(++)	2
Momoli et al. 2017	(+)	(+)	(+)	(++)	(+)	(++)	(++)	1

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Table 7 (continued)

SR-A Cordless Phones	Selection	Attrition	Exposure	Outcome	Confounding	Selective reporting	Statistical methods	Summary bias tier
Paediatric Brain Tumours								
Aydin et al. 2011b	(++)	(++)	(NR)	(++)	(+)	(++)	(++)	2
Castano-Vinyals et al. 2022	(+)	(++)	(+)	(++)	(+)	(++)	(++)	1
Glioma								
Hardell et al. 2002b	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Lonn et al. 2005	(+)	(+)	(NR)	(++)	(+)	(++)	(++)	2
Hardell et al. 2006	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Schuz et al. 2006a	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Hardell et al. 2013a	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Hardell and Carlberg 2015	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Meningioma								
Hardell et al. 2002a	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Hardell et al. 2005	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Lonn et al. 2005	(+)	(+)	(NR)	(++)	(+)	(++)	(++)	2
Schuz et al. 2006a	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Carlberg et al. 2013	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Carlberg and Hardell 2015	(NR)	(NR)	(--)	(++)	(+)	(++)	(++)	2
Acoustic Neuroma								
Hardell et al. 2002a	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Lonn et al. 2004	(+)	(+)	(NR)	(++)	(+)	(++)	(++)	2
Hardell et al. 2005	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Han et al. 2012	(+)	(NR)	(+)	(++)	(+)	(++)	(++)	2
Hardell et al. 2013b	(--)	(--)	(--)	(++)	(+)	(++)	(++)	2
Pettersson et al. 2014	(++)	(+)	(+)	(+)	(+)	(++)	(++)	1
Pituitary tumours								
Hardell et al. 2002a	(NR)	(--)	(--)	(++)	(NR)	(++)	(++)	2
Salivary gland tumours								
Hardell et al. 2004	(NR)	(NR)	(--)	(++)	(+)	(++)	(++)	2
Soderqvist et al. 2012	(+)	(NR)	(--)	(++)	(+)	(+)	(++)	2
SR-B Broadcast Transmitters								
Paediatric Brain Tumours								
Ha et al. 2007	(+)	(+)	(-)	(+)	(++)	(+)	(++)	2
Hauri et al. 2014	(+)	(+)	(+)	(+)	(+)	(+)	(++)	1
Childhood Leukemias								
Maskarinec et al. 1994	(-)	(NR)	(--)	(+)	(-)	(+)	(++)	2
Ha et al. 2008; Ha et al. 2007	(+)	(+)	(-)	(+)	(++)	(+)	(++)	2
Merzenich et al. 2008	(+)	(+)	(+)	(+)	(+)	(+)	(++)	1
Hauri et al. 2014	(+)	(+)	(+)	(+)	(+)	(+)	(++)	1
SR-B Base Stations								
Paediatric Brain Tumours								
Elliott et al. 2010	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Li et al. 2012		(NR)	(NR)	(-)	(+)	(+)	(++)	2
Childhood leukemias								
Elliott et al. 2010	(+)	(+)	(+)	(++)	(+)	(+)	(++)	1
Li et al. 2012	(+)	(NR)	(NR)	(-)	(+)	(+)	(++)	2
SR-C Occupational Exposures								
Glioma								
Grayson 1996	(+)	(NR)	(--)	(+)	(-)	(+)	(++)	2
Karipidis et al. 2007	(+)	(NR)	(-)	(+)	(-)	(+)	(++)	2
Vila et al. 2018	(NR)	(-)	(-)	(+)	(-)	(+)	(++)	2

Table 7 footnotes: (++) = Definitely Low; (+) = Probably Low; (-) or (NR) = Probably High; (--) = Definitely High.

et al., 2018, 2019a,b; Little et al., 2012; Sato et al., 2016; Sato et al., 2019; Villeneuve et al., 2021), all of which assessed the credibility of the increased risks of brain cancer/glioma reported by some case-control studies, comparing predicted and observed time-trend incidence rates (**Annex 4, Table S4**).

The studies were conducted in 12 countries from four continents (Asia, Europe, North America, and Oceania), and covered different time periods [duration range = 17 to 37 years; recency (period upper bound) = 2005 to 2020]. The published outcomes are a mix of annual percent changes (APC) and predicted incidence rates. The parameters used for the simulations varied across studies. Although all studies used odds ratios from case-control studies reporting risk increases [with only two studies assessing the plausibility of risk deficits (Deltour et al., 2012; Little et al., 2012)], some explored scenarios including latency (Chapman et al., 2016; Choi et al., 2021; de Vocht, 2016; 2019; Deltour et al., 2012; Deltour et al., 2022; Elwood et al., 2022; Karipidis et al., 2018, 2019b; Little et al., 2012), most considered heavy users but differed as to definition and associated relative risks (Chapman et al., 2016; Choi et al., 2021; de Vocht, 2016; 2019; Deltour et al., 2012; Deltour et al., 2022; Elwood et al., 2022; Karipidis et al., 2018, 2019b; Little et al., 2012; Sato et al., 2016; Sato et al., 2019; Villeneuve et al., 2021), mainly based on cumulative exposure (Chapman et al., 2016; Choi et al., 2021; de Vocht, 2016; 2019; Deltour et al., 2012; Deltour et al., 2022; Elwood et al., 2022; Karipidis et al., 2018, 2019b; Little et al., 2012; Sato et al., 2016; Sato et al., 2019; Villeneuve et al., 2021), or mean daily call time duration in one study (Sato et al., 2019). Moreover, three studies present simulation results in figures only (de Vocht, 2016; 2019; Villeneuve et al., 2021), and three other studies report partial data either in the text or in the supplementary materials (Chapman et al., 2016; Elwood et al., 2022; Sato et al., 2016).

The time-trend simulation studies generally showed stable or very small increases or decreases in the brain cancer incidence rates over the last three decades. Increasing trends were often observed among the elderly or in morphological or site-specific brain cancer sub-types, accompanied by decreases in brain cancers of unspecified site and/or morphology. This suggests improvements in diagnostic techniques as the reason for increasing trends in certain brain cancer sub-types. There have also been shifts in classifying sub-types in updated editions of the WHO classification of tumours of the central nervous system; for example, the WHO 2000 classification induced a shift from anaplastic astrocytoma to glioblastoma (Kleihues et al., 2002). Reclassification of unclassified or overlapping brain cancers has been shown to reduce increased trends in morphological or topological sub-types (Choi et al., 2021; Karipidis et al., 2018).

Further, the time-trend simulation studies were very consistent in showing that the increased risks observed in some case-control studies were incompatible with the actual incidence rates of brain cancer observed in several countries and over long periods (up to over 30 years since handheld devices became available). The overestimation in the predicted incidence rates varied across the time-trend simulation studies given the different statistical methodologies and risk scenarios used, but it was as much as 86 % higher than the observed rates (Villeneuve et al., 2021).

The variability in explored scenarios, statistical methods, outcome indicators, and completeness of reporting, precluded the possibility to calculate combined “credibility benchmarks” based on the whole available dataset. However, three simulation studies consistently reported that relative risk estimates > 1.5 with a 10+ years induction period were definitely implausible (Deltour et al., 2012; Deltour et al., 2022; Little et al., 2012). Based on these findings, we carried out the planned sensitivity meta-analyses of glioma risk in relation to long-term mobile phone use (10+ years) excluding studies reporting implausible effect sizes.

4.4. Effects of the exposure

4.4.1. Results of individual studies

The whole set of findings extracted from the included cohort and case-control studies is provided in **Annex 5, Tables S7.1 to S7.18**. (Summary of findings tables).

4.4.2. Data synthesis

We present below findings from the meta-analyses of the studies included in SR-A, focused on risks of selected histological types of CNS tumours (glioma, meningioma, acoustic neuroma, pituitary tumours, paediatric brain tumours), and salivary gland tumours.

As anticipated, for three neoplasms (glioma, meningioma, and acoustic neuroma), we included both primary studies and fully or partially overlapping pooled analyses of the former. This concerned two study subsets: the Hardell series of intracranial tumours (ICT) case-control studies, and the studies belonging to the Interphone group.

The four primary ICT studies by Hardell and co-workers were conducted in subsequent time periods, in terms of case-diagnosis: 1994–1996 (Hardell et al., 1999); 1997–mid 2000 (Hardell et al., 2002a; Hardell et al., 2002b); mid 2000–2003 (Hardell et al., 2005; Hardell et al., 2006); 2007–2009 (Carlberg et al., 2013; Hardell et al., 2013a), using the same case ascertainment, control selection, and exposure assessment methods, while the statistical approach and data reporting changed over time. All primary study results were published, with the single exception of the fourth acoustic neuroma study. We also included the more recently published, fully overlapping, pooled analyses of the second, third, and fourth ICT studies from the Hardell series (Carlberg and Hardell, 2015; Hardell and Carlberg, 2015; Hardell et al., 2013b).

The Interphone multicentre case-control study, coordinated by the IARC, with cases diagnosed in 2001–2004, was concurrently carried out by 16 research centres in 13 countries, based on a common core protocol, including an identical computer-assisted personal interview (CAPI) created in English, translated into the local centre languages, and back-translated in English for consistency check. There were minor differences in case-ascertainment and control selection methods across countries, due to local specificities. The international Interphone analyses (Interphone SG 2010; 2011) included cases and matched controls aged 30–59 years. Most local Interphone centres which also published their own results extended the eligible age range (Christensen et al., 2005; Christensen et al., 2004; Hepworth et al., 2006; Klæboe et al., 2007; Lonn et al., 2004; Lonn et al., 2005; Schlehofer et al., 2007; Schuz et al., 2006a; Takebayashi et al., 2006; Takebayashi et al., 2008), and/or the eligible neoplasms (Lonn et al., 2006; Sadetzki et al., 2008; Schoemaker and Swerdlow, 2009; Shrestha et al., 2015; Takebayashi et al., 2008). Therefore, these studies included study populations larger than the country-specific contribution to the Interphone international analyses, and the same applies to the pooled analyses of some of these studies (Lahkola et al., 2007; Lahkola et al., 2008; Schoemaker et al., 2005). On the contrary, the Interphone international analyses included all study subjects from the published French and Canadian Interphone studies (Hours et al., 2007; Momoli et al., 2017), as well as the pooled analysis of data from these countries and other unpublished local Interphone studies (Turner et al., 2016a).

To avoid multiple counting of individual data, we created five different datasets each of whom consists of studies with non-overlapping populations. The main meta-analyses of findings related to the exposure contrasts Ever vs Never use and TSS use of mobile phones, were carried out on the MA5 dataset (Table 5) characterized by the greatest number of exposed cases. However, we performed secondary quantitative syntheses on all other four datasets (Tables 8, 10, and 12).

Note that four studies of mobile phone use and risk of glioma, meningioma, acoustic neuroma, and pituitary tumours, described in two articles (Hardell et al., 2002a; Hardell et al., 2002b) did not report the number of exposed cases for five exposure metrics in total; the same

Table 8

Sensitivity to changes in the dataset composition of the meta-analyses of glioma risk in relation to ever and time since start mobile phone use.

Neoplasm	Exposure Contrast	Dataset	Studies	E ⁺ Cases	mRR	95 % LCL	95 % UCL	I ² (%)	
Glioma	Ever or Regular Use vs No or non-Regular	MA1	22	4292	1.01	0.91	1.11	58.56	
		MA2	15	4635	1.06	0.93	1.20	69.69	
		MA3	20	4287	0.97	0.89	1.07	48.88	
		MA4	18	4580	1.04	0.92	1.16	64.02	
		MA5	13	4630	1.01	0.89	1.13	61.76	
	Test of group differences: Q_b = $\chi^2(4) = 1.20$, p = 0.88								
	TSS = <5 years vs No or non-Regular	MA1	18	1228	0.97	0.85	1.10	53.88	
		MA2	12	1362	1.04	0.89	1.22	55.01	
		MA3	16	1349	0.93	0.82	1.05	48.13	
		MA4	15	1279	1.02	0.90	1.16	46.09	
		MA5	10	1483	0.99	0.85	1.14	49.98	
	Test of group differences: Q_b = $\chi^2(4) = 1.79$, p = 0.775								
	TSS = 5–9 years vs No or non-Regular	MA1	18	1297	1.05	0.90	1.23	60.42	
		MA2	12	1470	1.12	0.92	1.36	68.33	
		MA3	16	1329	1.01	0.87	1.17	57.39	
		MA4	15	1493	1.07	0.90	1.26	66.37	
		MA5	10	1502	1.05	0.88	1.26	66.38	
	Test of group differences: Q_b = $\chi^2(4) = 0.72$, p = 0.95								
	TSS = 10+ years vs No or non-Regular	MA1	11	1271	1.22	0.94	1.58	80.23	
		MA2	8	1406	1.27	0.95	1.71	86.01	
MA3		10	1288	1.11	0.91	1.36	69.93		
MA4		10	1408	1.28	0.99	1.66	82.08		
MA5		7	1423	1.13	0.91	1.41	77.34		
Test of group differences: Q_b = $\chi^2(4) = 1.17$, p = 0.88									

Table 8 Footnotes. Dataset: MA1 = Primary studies only; MA2 = Interphone international analyses plus all other non-overlapping primary studies; MA3 = Hardell-Series IC 1st primary study, plus Hardell-Series pooled analyses of primary studies 2–3–4, plus all other non-overlapping primary studies; MA4-Glioma = Pooled analyses of Interphone data-subsets (5NE and 5OC), plus Interphone local DE and JP, plus all other non-overlapping primary studies; MA5 (main meta-analyses for glioma, meningioma, and acoustic neuroma) = Interphone international analyses, plus Hardell-Series IC 1st primary study, plus Hardell-Series pooled analyses of primary studies 2–3–4, plus all other non-overlapping primary studies. Obs = number of study-specific measures of effect. E⁺ Cases = total number of exposed cases (records with unavailable values not counted). mRR = meta-estimates of the relative risk, obtained using a random effects REML models. 95 % LCL, 95 % UCL = lower and upper confidence limits of the mRR; I² (%) = heterogeneity statistics (percentage of variation in the effect size across studies due to between-study differences rather than to sampling variation).

Table 9

Leave-one-out meta-analysis of long-term mobile phone use and glioma risk (MA5 dataset; REML random effects model; studies ordered by standard error of the log-transformed effect measure).

Omitted study	mRR	95 % Confidence Interval	P value
Schuz et al. 2022 _{Women}	1.21	0.95–1.53	0.12
Hardell and Carlberg 2015	0.97	0.87–1.08	0.58
Frei et al. 2011 _{Men}	1.16	0.89–1.51	0.28
Interphone SG 2010	1.17	0.91–1.51	0.23
Frei et al. 2011 _{Women}	1.14	0.90–1.45	0.27
Coureau et al. 2014	1.10	0.87–1.39	0.42
Yoon et al. 2015	1.14	0.90–1.45	0.27
Overall mRR	1.13	0.91–1.41	0.27

Table 9 Footnotes: mRR = meta-estimate of the relative risk.

information was unavailable for eight exposure metrics from seven neoplasm-specific studies on cordless phone use from four articles (Hardell et al., 2002a; Hardell et al., 2002b; Lonn et al., 2004; Lonn et al., 2005) (Annex 5 – Table S8).

Also note that the articles related to two primary intracranial tumour (ICT) studies of the Hardell series (Hardell et al., 2005; Hardell et al., 2006; Hardell et al., 2002a; Hardell et al., 2002b) provided measures of effect for users of analogue and digital mobile phones separately, but not for mobile phone use overall. However, a relevant proportion of mobile phone users claimed to have used both types of mobile phones: e.g., 37 % of all ICT cases and 29 % of controls (Hardell et al., 2005; Hardell et al., 2006). In these instances, to avoid double counting of individual data and minimize possible bias due to differential missing data (i.e., uneven distribution of unreported phone type by case-control status), we included in the meta-analyses the RR estimate based on the largest number of exposed cases, or, when the number of exposed cases and controls was missing, the estimate with the narrowest confidence interval as in (Hardell et al., 2002a; Hardell et al., 2002b). In practice, for

the “Ever (regular) use” exposure metric, we selected the RR estimate relating to digital phone use because stopping mobile phone use is unusual, and very likely most users of analogue phones were also included in the stratum of digital phone users; for the upper category of TSS, we chose the effect measures relating to analogue phone use, since analogue phones operating on 1G networks were introduced earlier than digital phones operating on 2G – GSM networks, and few long-term users of digital phones only were also included in the analogue long-term use subsets.

Analyses by TSS were unavailable for 15 E-O pairs from seven articles (Auvinen et al., 2002; Hours et al., 2007; Inskip et al., 2001; Muscat et al., 2002; Muscat et al., 2000; Takebayashi et al., 2006; Takebayashi et al., 2008) which, however, reported risk estimates for increasing duration of mobile phone use; in these instances, we extracted and included in the statistical datasets the measures of effect for categories of mobile phone length of use (Annex 5 – Table S9).

Preliminary data transformations, consisting of combination of measures of effects for adjacent exposure categories (or histological subtypes of glioma, in one instance) using inverse variance weighted average (IVWA) fixed effects models, yielded 50 calculated relative risk (RR) estimates, including 37 relating to SR-A studies, 11 from SR-B studies, and two from SR-C studies (Annex 5 – Table S10).

All the studies amenable to the DRM were of case-control design. The exposure metrics used in these analyses (CCT and CNC) were available from a congruous number of studies only for glioma, meningioma, and acoustic neuroma in relation to mobile phone use. We performed the main DRM on the MA1 dataset (including the greatest number of studies; Figs. 6, 9, and 13), and secondary DRM on the MA4 and MA5 datasets (Annex 7, Figures S2–S4).

We report below the main findings from the quantitative syntheses performed, separately for each investigated exposure-outcome pair.

4.4.2.1. SR-A – Mobile phone use and risk of tumours in the head region

Table 10
Sensitivity to changes in the dataset composition of the meta-analyses of meningioma risk in relation to ever and time since start mobile phone use.

Neoplasm	Exposure Contrast	Dataset	Studies	E ⁺ Cases	mRR	95 % LCL	95 % UCL	I ² (%)	
Meningioma	Ever or Regular Use vs No or non-Regular	MA1	18	2070	0.90	0.82	0.99	13.40	
		MA2	12	2779	0.91	0.82	1.02	26.20	
		MA3	16	2281	0.91	0.83	1.00	14.00	
		MA4	16	2362	0.90	0.82	1.00	25.73	
		MA5	10	2990	0.92	0.82	1.02	29.21	
	Test of group differences: $Q_b = \chi^2(4) = 0.06, p = 1.00$								
	TSS = <5 years vs No or non-Regular	MA1	14	627	0.84	0.74	0.96	8.45	
		MA2	9	1039	0.91	0.79	1.06	16.93	
		MA3	13	747	0.84	0.73	0.95	15.21	
		MA4	12	754	0.86	0.75	0.98	20.54	
		MA5	8	1159	0.89	0.79	1.02	14.38	
	Test of group differences: $Q_b = \chi^2(4) = 1.25, p = 0.87$								
	TSS = 5–9 years vs No or non-Regular	MA1	14	629	0.94	0.81	1.09	16.98	
		MA2	9	896	0.95	0.79	1.14	42.89	
		MA3	13	690	0.93	0.80	1.08	20.35	
		MA4	12	746	0.94	0.81	1.10	27.28	
		MA5	8	957	0.93	0.77	1.12	46.17	
	Test of group differences: $Q_b = \chi^2(4) = 0.03, p = 1.00$								
	TSS = 10+ years vs No or non-Regular	MA1	9	713	1.00	0.89	1.14	0.00	
		MA2	7	800	0.98	0.87	1.10	0.00	
MA3		8	731	1.03	0.91	1.15	0.00		
MA4		8	768	0.99	0.88	1.12	0.00		
MA5		6	818	1.00	0.90	1.12	0.00		
Test of group differences: $Q_b = \chi^2(4) = 0.35, p = 0.99$									

Table 10 Footnote – Dataset: MA1 = Primary studies only; MA2 = Interphone international analyses, plus all other non-overlapping primary studies; MA3 = Hardell-Series IC 1st primary study, plus Hardell-Series pooled analyses of primary studies 2–3–4, plus all other non-overlapping primary studies; MA4-Meningioma = Pooled analyses of Interphone data-subset 5NE+Interphone local CA, DE, FR, and JP, plus all other non-overlapping primary studies; MA5 (main meta-analyses for glioma, meningioma, and acoustic neuroma) = Interphone international analyses, plus Hardell-Series IC 1st primary study, plus Hardell-Series pooled analyses of primary studies 2–3–4, plus all other primary studies. Obs = number of study-specific measures of effect. E⁺ Cases = total number of exposed cases (records with unavailable values not counted). mRR = meta-estimates of the relative risk, obtained using a random effects REML model. 95 % LCL, 95 % UCL = Lower and Upper confidence limits of the mRR. I² (%) = heterogeneity statistics (percentage of variation in the effect size across studies due to between-study differences rather than to sampling variation).

Table 11
Leave-one-out meta-analysis of long-term mobile phone use and meningioma risk (MA5 dataset; REML random effects model; studies ordered by standard error of the log-transformed effect measure).

Omitted study	mRR	95 % Confidence Interval	P value
Schuz et al. 2022 _{Women}	1.00	0.84–1.19	0.98
Carlberg and Hardell 2015	0.95	0.83–1.09	0.47
Interphone SG 2010	1.03	0.91–1.16	0.63
Frei et al. 2011 _{Men}	1.01	0.90–1.13	0.88
Frei et al. 2011 _{Women}	1.00	0.9–1.12	0.94
Coureau et al. 2014	1.00	0.89–1.11	0.93
Overall mRR	1.00	0.9–1.12	0.97

Table 11 Footnotes: mRR = meta-estimate of the relative risk.

4.4.2.1.1. *Ever vs Never (regular) use of mobile phones and glioma risk.* The main meta-analysis of mobile phone use and risk of glioma, stratified on design and performed on the MA5 dataset, included data from 3 cohort and 10 case control studies, with a total of 4630 exposed cases (1293 from cohort studies and 2907 from case-control-studies) with available information on the exposure contrast “Ever or Regular” use vs “No use” (Fig. 2). The design-weighted meta-relative risk (mRR) was 1.01 (95 % CI = 0.89 – 1.13), with substantial heterogeneity (I² = 62 %) across studies. No differences between cohort and case-control-studies were found (p = 0.68).

4.4.2.1.2. *Time since start use (TSS) of mobile phones and glioma risk.* For the analyses by TSS use of mobile phones, all three cohort studies had sufficient data, while three case-control studies (Baldi et al., 2011; Hardell et al., 1999; Spinelli et al., 2010) were excluded because no analyses based on this exposure metric were presented. The mRRs for the three exposure categories (<5 years, 5–9 years, 10+ years) were 1.00, 1.05 and 1.13 respectively, with all confidence intervals including the null value (Fig. 3). Among mid-term (5–10 years) and long-term (10+ years) mobile phone users we observed substantial and

considerable heterogeneity across studies, respectively.

Statistically significant trends of increasing glioma OR with increasing latency were reported in two articles (Coureau et al., 2014; Hardell and Carlberg, 2015), but not observed in any other studies. However, in our subgroup meta-analysis, no difference between TSS subgroups was detected.

The findings from the meta-regression support the absence of an overall increasing trend of the mRR as latency increases (Annex 5, Table S11.a), while there was a significant decreasing trend with quality improvement of the exposure assessment method.

The results of the secondary meta-analyses aimed at assessing possible differences in the quantitative synthesis due to varying combinations of non-overlapping primary studies and pooled analyses (Table 8) showed no major differences across datasets (MA1 to M5); all mRRs for Ever use of mobile phones, or for increasing categories of TSS, were close to 1.0, although small differences in the mRR point estimates were observed for the TSS category 10+ years (not significant, p = 0.88).

4.4.2.2. 4.4.2.1.c. *Cumulative meta-analysis of mobile phone use and glioma risk.* The cumulative meta-analysis of glioma risk among ever and long-term users showed that the combined meta-estimates (cmRRs) decreased and became more precise with accumulating evidence over time (see Annex 7 – Figures S1.a and S1.b, left panels, based on the MA1 and MA2 datasets respectively).

4.4.2.2.1. *Leave-one-out meta-analysis of long-term mobile phone use and glioma risk.* In the leave-one-out meta-analysis of glioma risk among long-term (10+ years) mobile phone users, performed on the MA5 dataset using the random effects models – REML method, we identified one influential study (Hardell and Carlberg, 2015), whereby the 95 % confidence interval of the mRR obtained excluding it (0.87–1.08) does not include the point estimate of the overall mRR (1.13) (Table 9).

Repeating the main meta-analyses of glioma risk in relation to mobile phone use after excluding the study by Hardell and Carlberg (2015),

Table 12

Sensitivity to changes in the dataset composition of the meta-analyses of acoustic neuroma risk in relation to mobile phone use (ever and by categories of time since start use).

Neoplasm	Exposure Contrast	Dataset	Studies	E ⁺ Cases	mRR	95 % LCL	95 % UCL	I ² (%)	
Acoustic Neuroma	Ever or Regular Use vs No or non-Regular	MA1	18	1152	0.95	0.82	1.09	20.67	
		MA2	11	1463	1.03	0.87	1.21	33.14	
		MA3	17	1300	0.96	0.82	1.13	39.36	
		MA4	15	1352	0.97	0.85	1.11	20.65	
		MA5	10	1610	1.05	0.86	1.27	52.44	
	Test of group differences: Q _b = $\chi^2(4) = 1.02$, p = 0.907								
	TSS = <5 years vs No or non-Regular	MA1	12	333	0.89	0.75	1.05	0.00	
		MA2	7	501	0.90	0.76	1.07	3.80	
		MA3	12	369	0.91	0.76	1.08	14.22	
		MA4	10	426	0.87	0.76	1.00	3.42	
		MA5	7	537	0.95	0.78	1.16	26.13	
	Test of group differences: Q _b = $\chi^2(4) = 0.54$, p = 0.97								
	TSS = 5–9 years vs No or non-Regular	MA1	13	457	1.10	0.87	1.39	39.55	
		MA2	8	591	1.28	0.98	1.68	51.29	
		MA3	13	511	1.12	0.86	1.45	56.94	
		MA4	11	541	1.12	0.87	1.43	49.63	
		MA5	8	645	1.34	1.00	1.79	64.78	
	Test of group differences: Q _b = $\chi^2(4) = 1.77$, p = 0.78								
	TSS = 10+ years vs No or non-Regular	MA1	7	299	1.20	0.97	1.48	0.00	
		MA2	6	351	1.08	0.85	1.36	28.42	
		MA3	7	350	1.32	0.93	1.86	65.86	
		MA4	6	330	1.14	0.94	1.38	0.00	
		MA5	6	402	1.22	0.86	1.74	75.85	
	Test of group differences: Q _b = $\chi^2(4) = 1.14$, p = 0.89								

Table 12 Footnotes – Dataset: MA1 = Primary studies only; MA2 = Interphone international analyses plus all other non-overlapping primary studies; MA3 = Hardell-Series IC 1st primary study, plus Hardell-Series pooled analyses of primary studies 2–3–4, plus all other non-overlapping primary studies; MA4-Acoustic Neuroma = Pooled analyses of Interphone data-subset 5NE, plus Interphone local CA, DE, FR, and JP, plus all other non-overlapping primary studies; MA5 (main meta-analyses for glioma, meningioma, and acoustic neuroma) = Interphone international analyses, plus Hardell-Series IC 1st primary study, plus Hardell-Series pooled analyses of primary studies 2–3–4, plus all other non-overlapping primary studies. Obs = number of study-specific measures of effect; E⁺ Cases = total number of exposed cases (records with unavailable values not counted). mRR = meta-estimates of the relative risk, obtained using a random effects REML model. 95 % LCL, 95 % UCL = Lower and Upper confidence limits of the mRR. I² (%) = heterogeneity statistics (percentage of variation in the effect size across studies due to between-study differences rather than to sampling variation).

we observed substantial reductions in the mRRs and in the between-study heterogeneity for both the contrast “Ever vs Never” use (mRR = 0.96, 95 % CI = 0.87–1.07, I² = 47 %), and in the analysis by increasing categories of TSS (“<5 years”: mRR = 0.95, 95 % CI = 0.81–1.12, I² = 43 %; “5–9 years”: mRR = 0.96, 95 % CI = 0.83–1.11, I² = 34 %; “10+ years”: mRR = 0.97, 95 % CI = 0.87–1.08, I² = 10 %).

4.4.2.2.2. Meta-analysis of glioma risk in long-term mobile phone users stratified on RoB tier. The summary risk of bias proved able to explain the considerable heterogeneity observed in the main meta-analysis of glioma risks in relation to Long-term (TSS = 10+ years) mobile phone use (Fig. 4). In the tier-1 study subgroup there were neither increased mRRs, nor heterogeneity across studies, in either the MA1 dataset [mRR 0.94 (95 % CI 0.85–1.05), I² = 4 %], or the MA5 dataset [mRR 0.95 (95 % CI 0.85–1.05), I² = 5.5 %]. Increased risks of glioma were observed in the tier-2 study subgroup [mRR 1.80 (95 % CI 1.15–2.82), I² = 65 %, MA1; mRR 1.63 (95 % CI 1.38–1.94), I² = 0 %, MA5]. Statistically significant differences between bias-tier subgroups [p (Q_b) ≤ 0.001] were observed in both datasets (Fig. 4).

The bias-tiering was less effective in explaining the heterogeneity in results across studies of glioma in relation to ever (regular) use of mobile phones. In the tier-1 study subgroup from the MA1 dataset, there were no exposure-outcome associations [mRR 0.92 (95 % CI 0.84–1.01), I² = 38 %], while increased risks of glioma were observed in the tier-2 study subgroup [mRR 1.24 (95 % CI 1.05–1.46), I² = 23 %]; the difference between bias-tier subgroups was statistically significant [p (Q_b) < 0.001]. In the tier-1 subgroup from the MA5 dataset, we observed no exposure-outcome associations [mRR 0.93 (95 % CI 0.82–1.06), with substantial heterogeneity I² = 61 %]; increased risks of glioma were observed in the tier-2 study subgroup [mRR 1.21 (95 % CI 1.05–1.39), I² = 0 %]; again, there was a statistically significant difference between bias-tier subgroups [p (Q_b) = 0.01].

4.4.2.2.3. Meta-analysis of glioma risk in long-term mobile phone users excluding studies with implausible effect size. Five case-control studies of glioma reported risk estimates > 1.5 among mobile phone users at TSS ≥ 10 years (Coureau et al., 2014; Hardell and Carlberg, 2015; Hardell et al., 2006; Hardell et al., 2013a; Schuz et al., 2006a).

Such effect sizes have been shown to be incompatible with the actual incidence time trends of glioma in three simulation studies (Deltour et al., 2012; Deltour et al., 2022; Little et al., 2012).

In the planned sensitivity meta-analyses excluding these studies (Fig. 5), performed on multiple datasets (MA1, MA4, and MA5), we observed no exposure-outcome associations, independently on the study aggregation (test of group differences Q_b = 0.08, p = 0.960). We omitted the MA2 and MA3 datasets because, due to exclusions made, they were identical to the MA5 and MA1 datasets, respectively.

4.4.2.2.4. Lifetime intensity of mobile phone use and glioma risk. Based on 14 studies included in the MA1 dataset (consisting of primary studies only), there was no strong indication against the hypothesis of no summary effect of CCT (w = 1.74, p = 0.42) on glioma risk (Fig. 6, left). Similarly, based on 7 studies in MA1, there was no strong indication against the hypothesis of no summary effect of CNC (w = 3.33, p = 0.18) on glioma risk (Fig. 6, right).

Secondary DRM carried out on MA4 and MA5 datasets provided analogous findings (Annex 7 – Figure S2.a, and S2.b).

4.4.2.2.5. Ever vs Never (regular) use of mobile phones and meningioma risk. The risk of meningioma from mobile phone use was investigated in three cohort studies including 621 exposed cases, and in seven case-control studies with 2369 exposed cases (Fig. 7).

The overall mRR was 0.92 (95 % CI = 0.82–1.02), not indicating an exposure-outcome association. No important heterogeneity in results across studies ($\tau^2 = 0.01$; I² = 29.21), and no difference in results between cohort and case-control studies (p = 0.57), were detected.

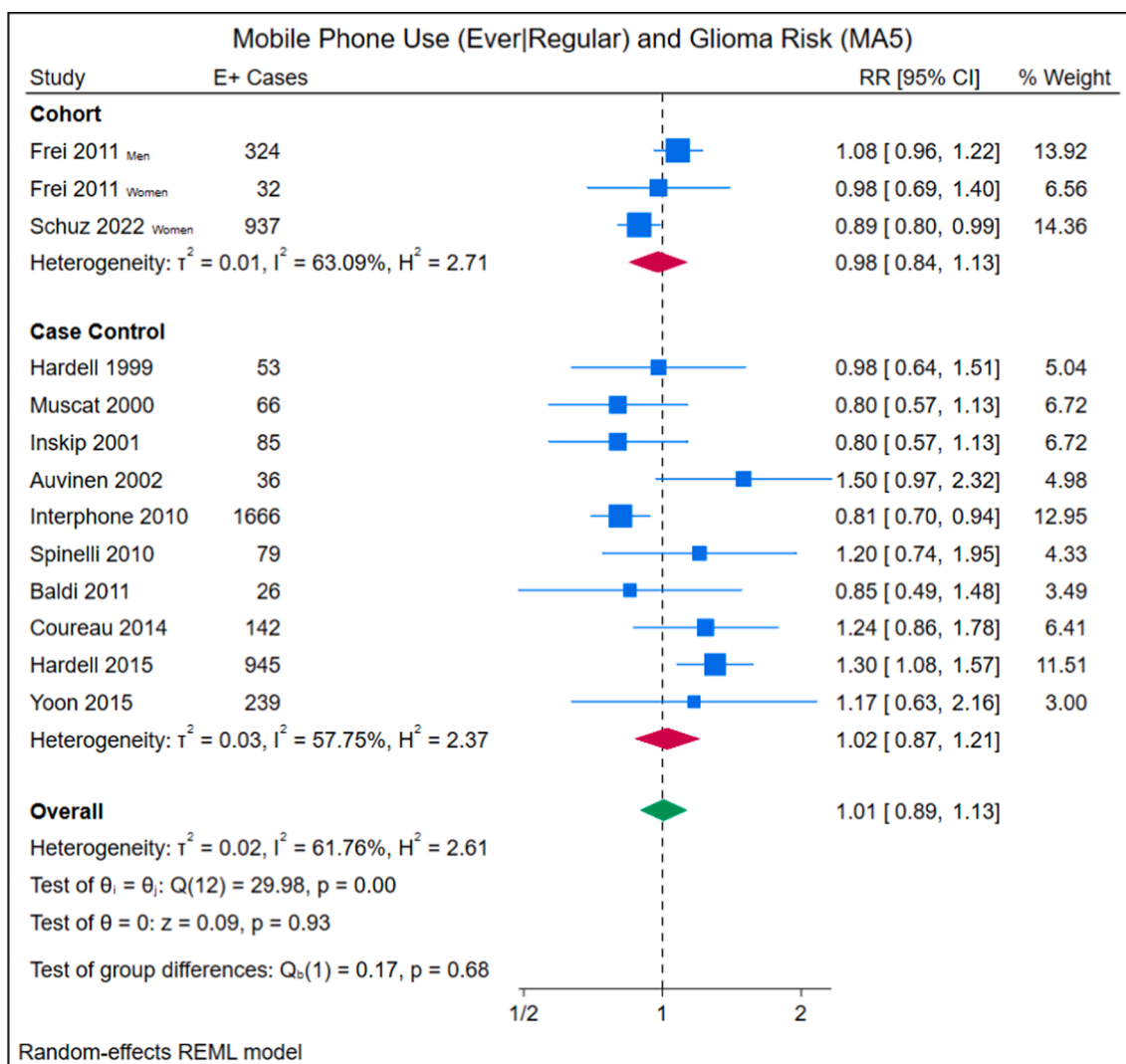


Fig. 2. Meta-analysis of mobile phone use (Ever or Regular) and glioma risk.

4.4.2.2.6. *Time since start use (TSS) of mobile phones and meningioma risk.* The results of the meta-analyses of meningioma risk by increasing categories of TSS are shown in Fig. 8. There are no indications of a risk increase with increasing TSS. The mRR is below or equal to 1 in all three categories, with no/not important heterogeneity across studies.

When different datasets were used (MA1 to MA4, Table 10) for the analyses of meningioma risk among Ever (Regular) users, the results were nearly identical (mRR between 0.90 and 0.92), with no indication of differences between datasets ($p = 1.00$). Similarly, there were no differences across datasets in findings from the meta-analyses of meningioma risk by increasing categories of TSS (Table 10), although it may be worth noting that the upper confidence limit of the mRR among short-term users (<5 years) was below the null in three of the other four datasets (MA1, MA3, and MA4).

4.4.2.2.7. *Cumulative meta-analysis of mobile phone use and meningioma risk.* The cumulative meta-analysis of meningioma for the contrast Ever vs Never use was characterized by a progressive reduction over time in the statistically significant decreased cmRRs observed among mobile phone users, and the cumulative meta-analysis of meningioma risk among long-term users showed a decreasing trend over time (Annex 7 – Figures S1.a and S1.b, central panels, based on the MA1 and MA2 dataset respectively).

4.4.2.2.8. *Leave-one-out meta-analysis of long-term mobile phone use and meningioma risk.* In the leave-one-out meta-analysis of meningioma

risk among long-term (10+ years) mobile phone users, based on six studies included in the MA5 dataset, no single influential study was identified (Table 11).

4.4.2.2.9. *Lifetime intensity of mobile phone use and meningioma risk.* Based on 10 studies in MA1, there was no strong indication against the hypothesis of no summary effect of CCT ($w = 4.68$, $p = 0.10$) on meningioma risk (Fig. 9, left). Based on 6 studies in MA1, there was a strong incompatibility with the hypothesis of no summary effect of CNC ($w = 12.63$, $p = 0.002$) on meningioma risk (Fig. 9, right). In particular, for exposure values above the median of 1440 CNC, the summary odds ratio was below one.

Similar findings were observed in the sensitivity DRM performed on MA4 and MA5 (Annex 7 – Figures S3.a and S3.b).

4.4.2.2.10. *Acoustic neuroma and ever vs never use of mobile phones.* The risk of acoustic neuroma in relation to mobile phone use was investigated in only two cohort studies (183 exposed cases), and nine case control studies (1431 exposed cases). There was no increased risk of acoustic neuroma in either design subgroup (Fig. 10); the overall mRR was 1.03 (95 % CI = 0.85–1.24), with moderate heterogeneity ($\tau^2 = 0.04$; $I^2 = 51\%$).

4.4.2.2.11. *Time since start use (TSS) of mobile phones and acoustic neuroma risk.* For the meta-analysis of acoustic neuroma by increasing TSS of mobile phone use, two cohort studies (one of which reporting on long-term use only) and seven case-control studies were available

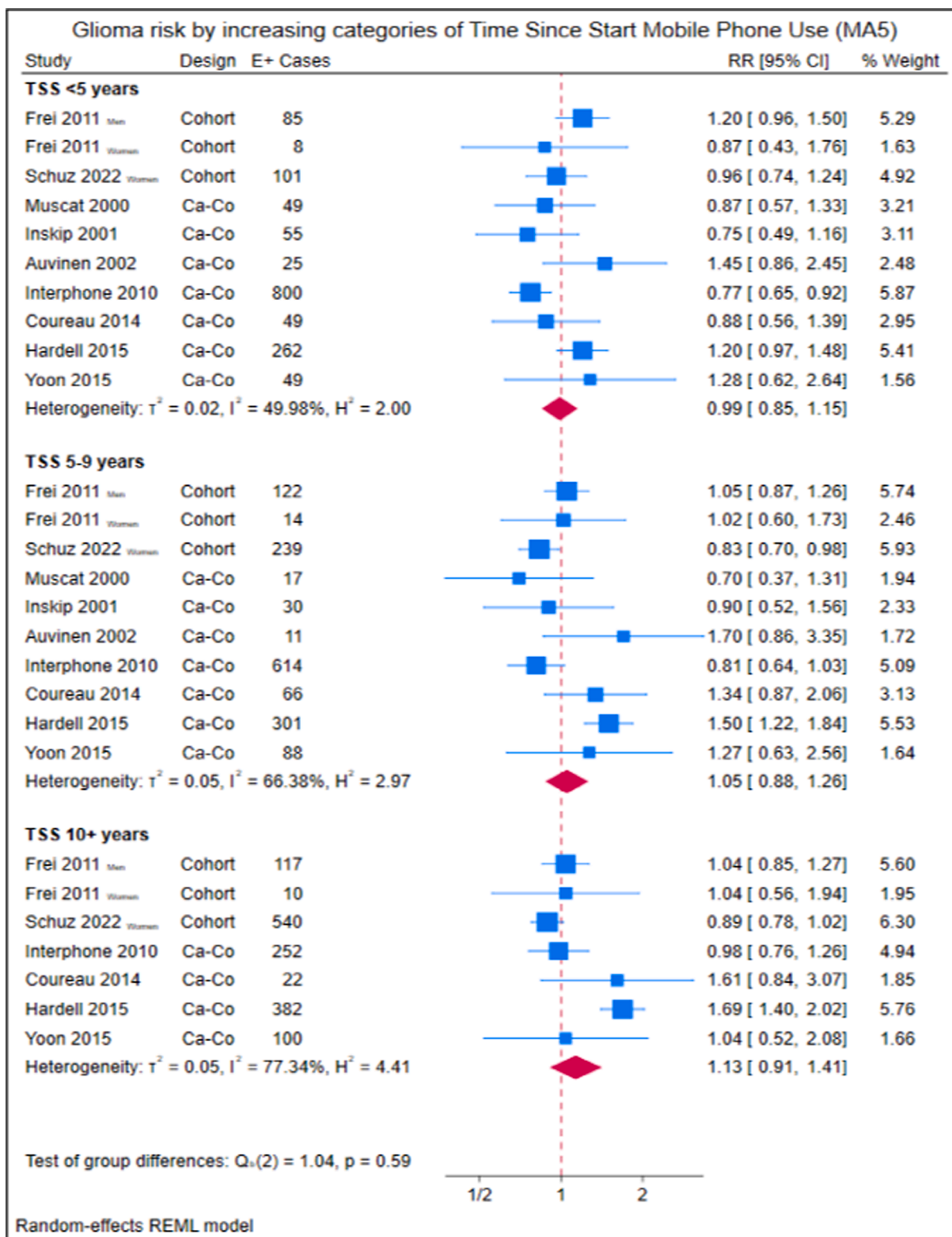


Fig. 3. Subgroup meta-analysis of mobile phone use and risk of glioma by time since start use (TSS; MA5 dataset).

(Fig. 11). There was no clear trend across increasing categories of TSS. For persons who started using mobile phones 5–9 years in the past, the mRR was slightly and borderline statistically significant elevated [mRR 1.34 (95 % CI = 1.00 – 1.79)], albeit there was substantial heterogeneity between studies ($I^2 = 65\%$). Among long-term users (TSS ≥ 10 years), the mRR was 1.22 (95 % CI = 0.86–1.74), with considerable between-study heterogeneity ($I^2 = 76\%$).

Changing the dataset composition (MA1 to MA5) had no noticeable impact on the findings (Table 12), and only in our main analyses on MA5 the lower limit of the confidence interval of the mRR for mid-term users (TSS = 5–9 years) reached 1.00.

4.4.2.2.12. Cumulative meta-analysis of mobile phone use and acoustic neuroma risk. The cumulative meta-analyses of acoustic neuroma in relation to Ever or Long-term use of mobile phones (Annex 7- Figure S1.

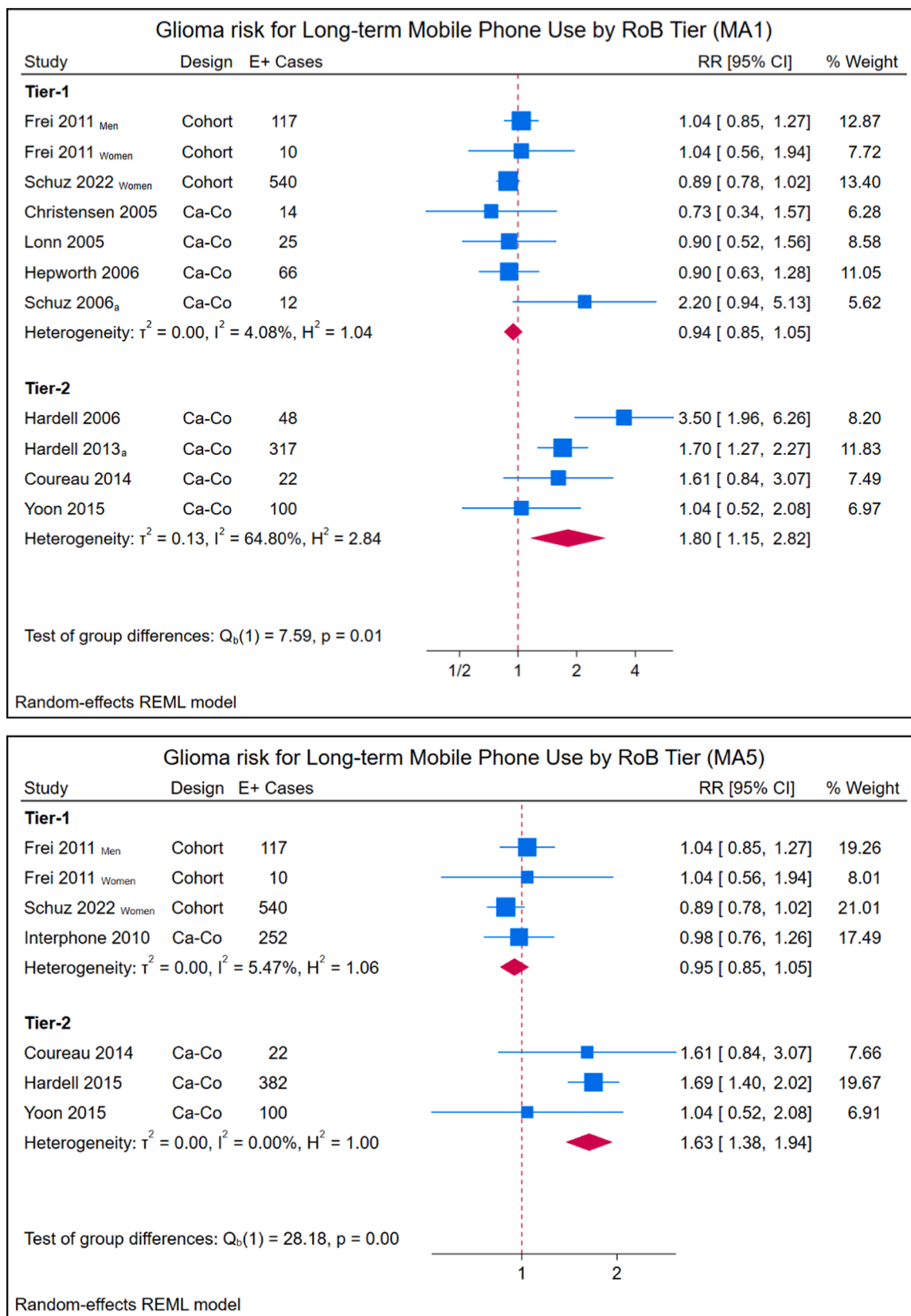


Fig. 4. Meta-analyses of glioma risk in Long-term (TSS 10+ years) mobile phone users stratified on bias-tier (MA1 and MA5 datasets).

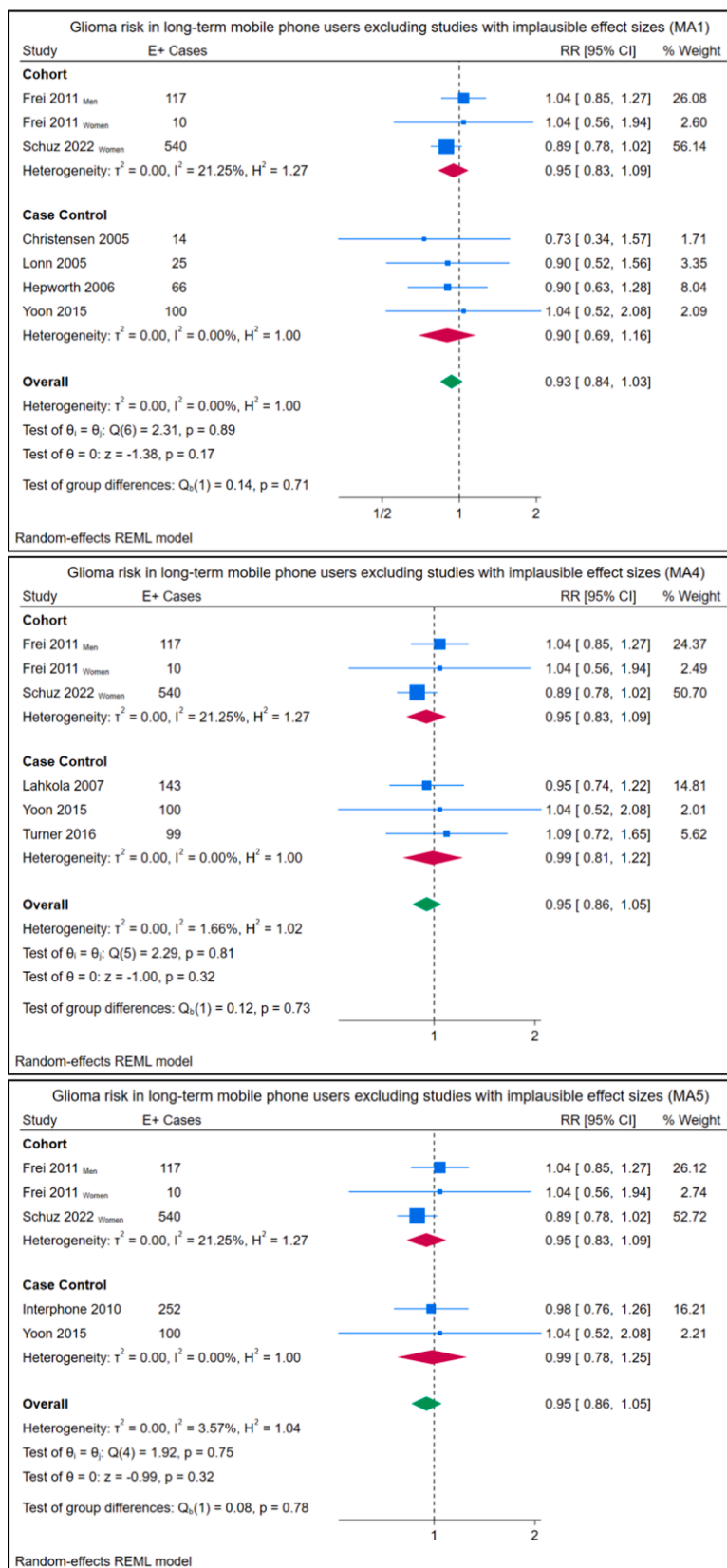


Fig. 5. Sensitivity meta-analyses of glioma risk in long-term mobile phone users excluding studies with implausible effect sizes ($RR \geq 1.5$) according to findings from simulation studies.

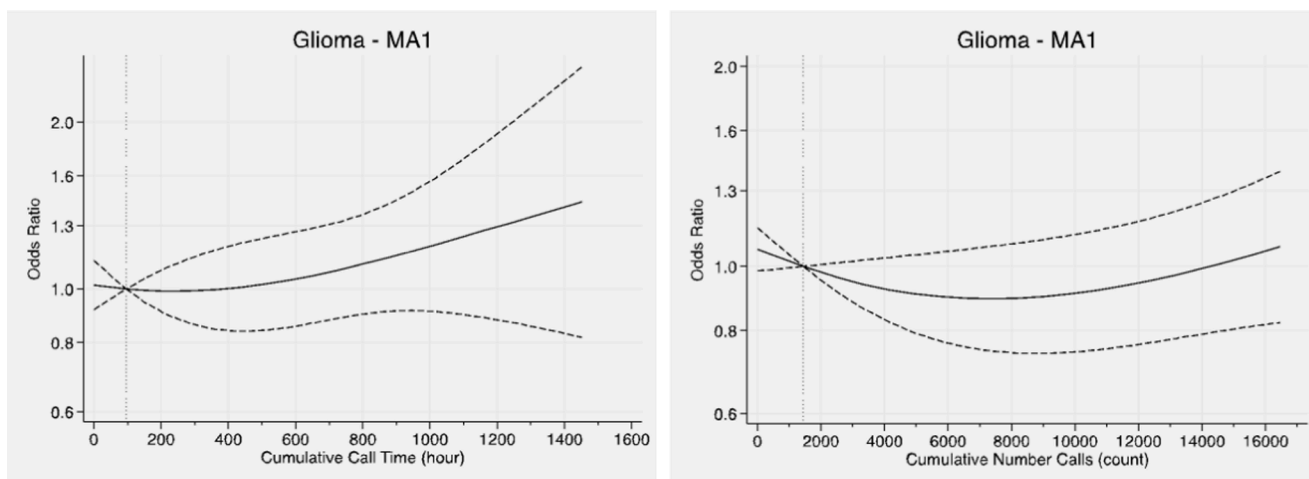


Fig. 6. Dose-response meta-analyses between glioma risk and mobile phone cumulative call time (CCT, left) or cumulative number of calls (CNC, right).

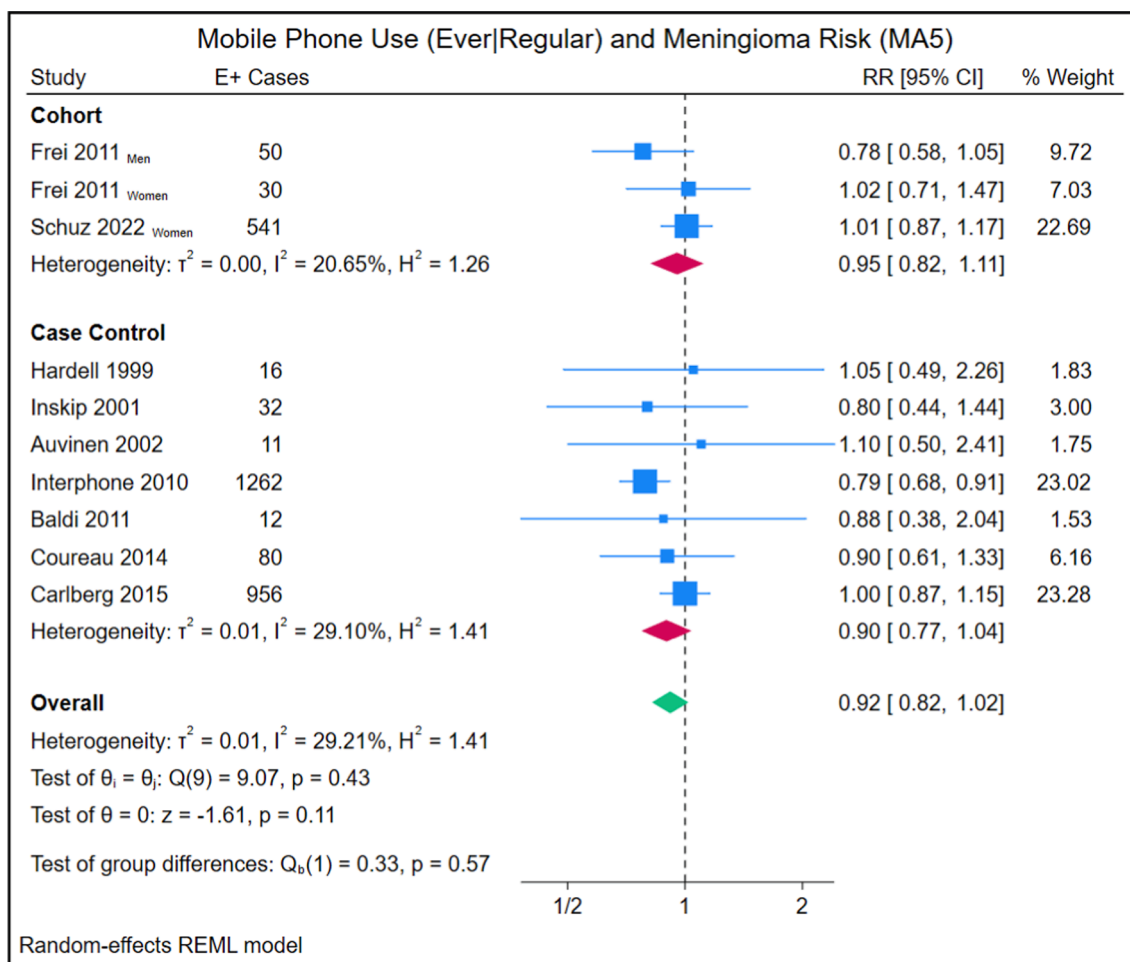


Fig. 7. Meta-analysis of mobile phone use (Ever or Regular) and meningioma risk.

a, and S1.b, right panels, based on MA1 and MA2 datasets respectively) showed patterns similar to the cumulative meta-analyses of glioma (decreasing and more precise cmRRs with accumulating evidence over time).

4.4.2.2.13. *Leave-one-out meta-analysis of long-term mobile phone use and acoustic neuroma risk.* In the leave-one-out meta-analysis of acoustic neuroma risk among long-term (10+ years) mobile phone users, based on six studies included in the MA5 dataset, no single influential study

was identified (Table 13).

4.4.2.2.14. *Meta-analysis of acoustic neuroma risk in long-term mobile phone users by RoB tier.* Similarly to glioma, we performed subgroup meta-analyses by RoB-tier to assess whether the latter might explain the heterogeneity observed in the main meta-analyses of acoustic neuroma risks among Ever (regular) mobile phone users (51 % or 52 % in the analyses stratified on design or not stratified, respectively), and especially long-term users (76 %).

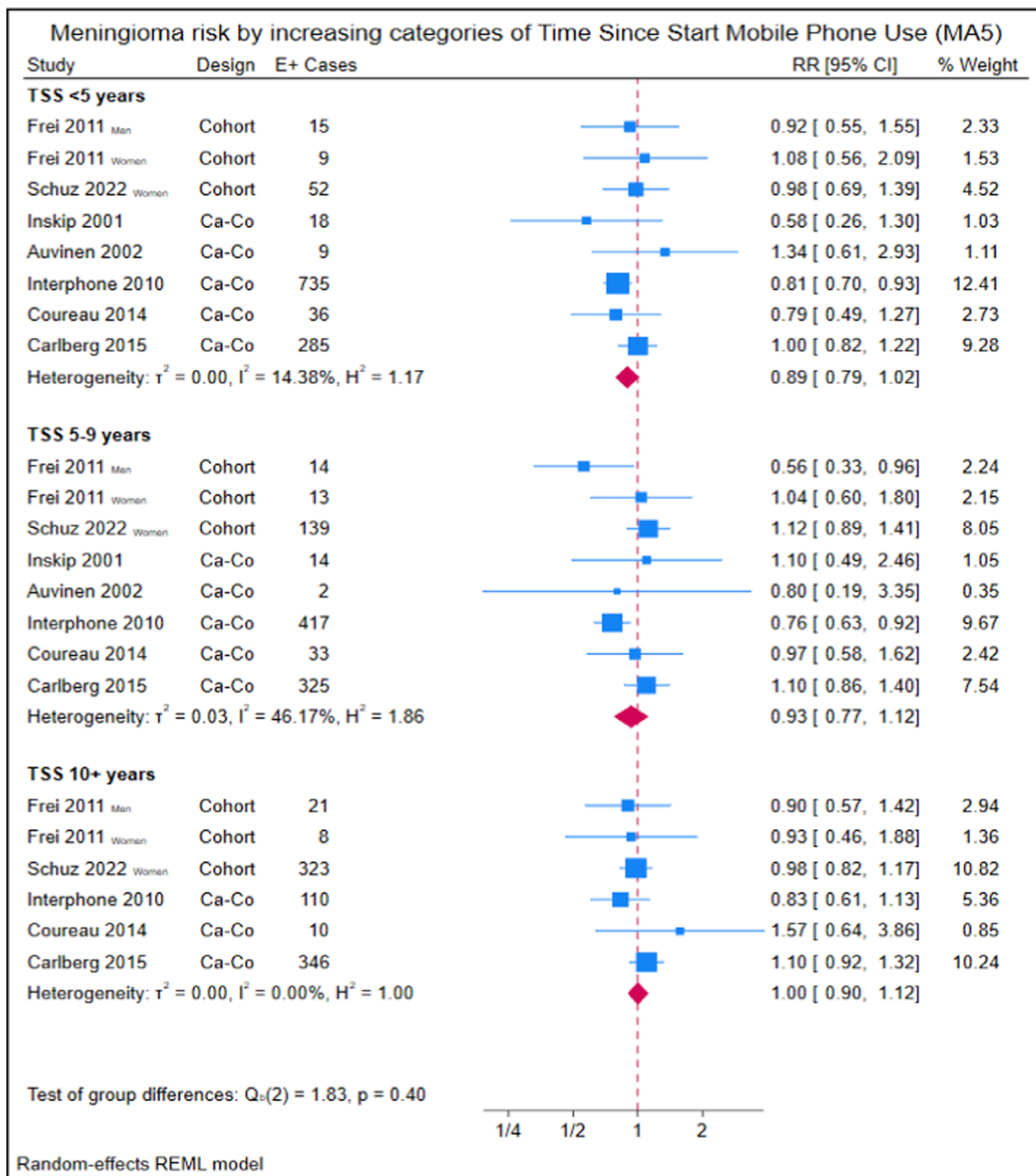


Fig. 8. Subgroup meta-analyses of mobile phone use and risk of meningioma by time since start use (TSS; MA5 dataset).

In the analyses focussed on the Ever/ Never (regular) use contrast, we observed no increased risk of acoustic neuroma in the tier-1 study subgroup from either the MA1 dataset [mRR = 0.90 (95 % CI 0.75–1.08), $I^2 = 30\%$], or the MA5 dataset [mRR = 0.96 (0.80–1.16), $I^2 = 42\%$]. No exposure-outcome associations and no across-study heterogeneity were observed in the tier-2 subgroup [mRR = 1.11 (95 % CI 0.85–1.45), $I^2 = 5.4\%$; MA1; mRR = 1.15 (95 % CI 0.76–1.72), $I^2 = 43\%$; MA5]. There were no statistically significant differences between tier-subgroups [$p(Q_b) = 0.19$ and 0.44 in the MA1 and MA5 datasets, respectively].

In the analyses relating to long-term use (Fig. 12), there were no increased risks of acoustic neuroma and no heterogeneity in the tier-1 study subgroup [mRR = 1.15 (95 % CI 0.85–1.44), $I^2 = 0\%$; MA1 dataset; mRR = 1.00 (0.78–1.29), $I^2 = 35\%$; MA5 dataset]. In the tier-2 subgroup, we observed a non-statistically significant increased risk of acoustic neuroma [1.58 (0.85–2.94), $I^2 = 16\%$] in the MA1 dataset, and a borderline significant risk increase in the MA5 dataset [mRR 1.89 (95

% CI 1.00–3.57), $I^2 = 69\%$, based on only two studies]. The Q_b test for differences between subgroup were 0.90 ($p = 0.34$), and 3.28 ($p = 0.07$) in the MA1 and MA5 datasets, respectively.

4.4.2.2.15. Lifetime intensity of mobile phone use and acoustic neuroma risk. Based on 9 studies in MA1, there was no strong indication against the hypothesis of no summary effect of CCT ($w = 1.48$, $p = 0.48$) on acoustic neuroma risk (Fig. 13, left). Similarly, based on 6 studies in MA1, there was no strong indication against the hypothesis of no summary effect of CNC ($w = 0.61$, $p = 0.74$) on acoustic neuroma risk (Fig. 13, right).

Similar results were observed in the sensitivity DRM carried out on MA4 and MA5 (see Annex 7 – Figures S4.a and S4.b).

4.4.2.2.16. Ever vs never use of mobile phones and risk of other tumours of the head region. For pituitary tumours, data from one cohort study with 175 exposed cases, and 4 case-control studies with 291 exposed cases (not counting cases from one study with missing data), were available. The overall mRR was 0.81 (95 % CI 0.61 – 1.06), without

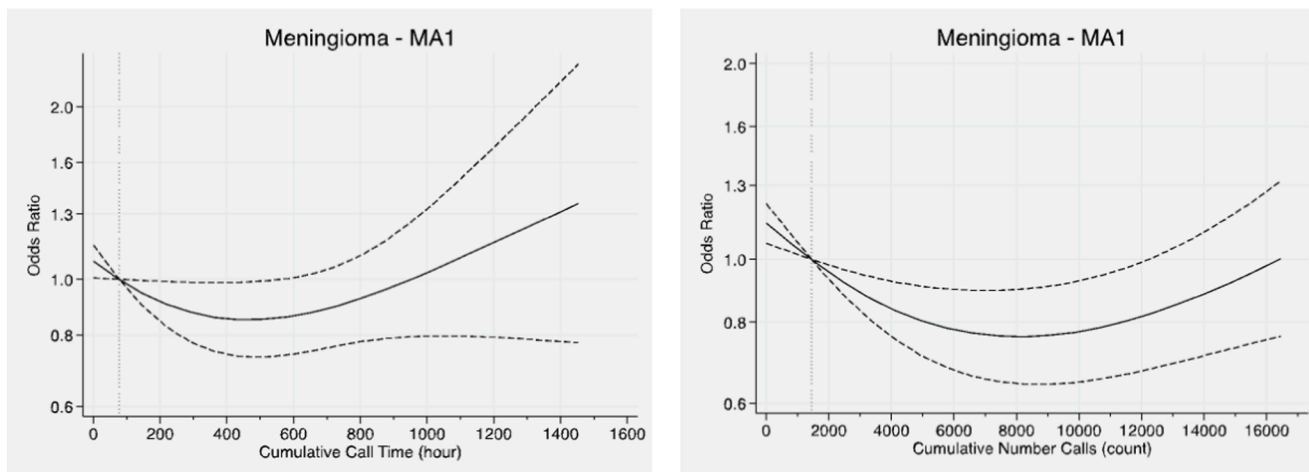


Fig. 9. Dose-response meta-analyses between meningioma risk and mobile phone cumulative call time (CCT, left) or cumulative number of calls (CNC, right).

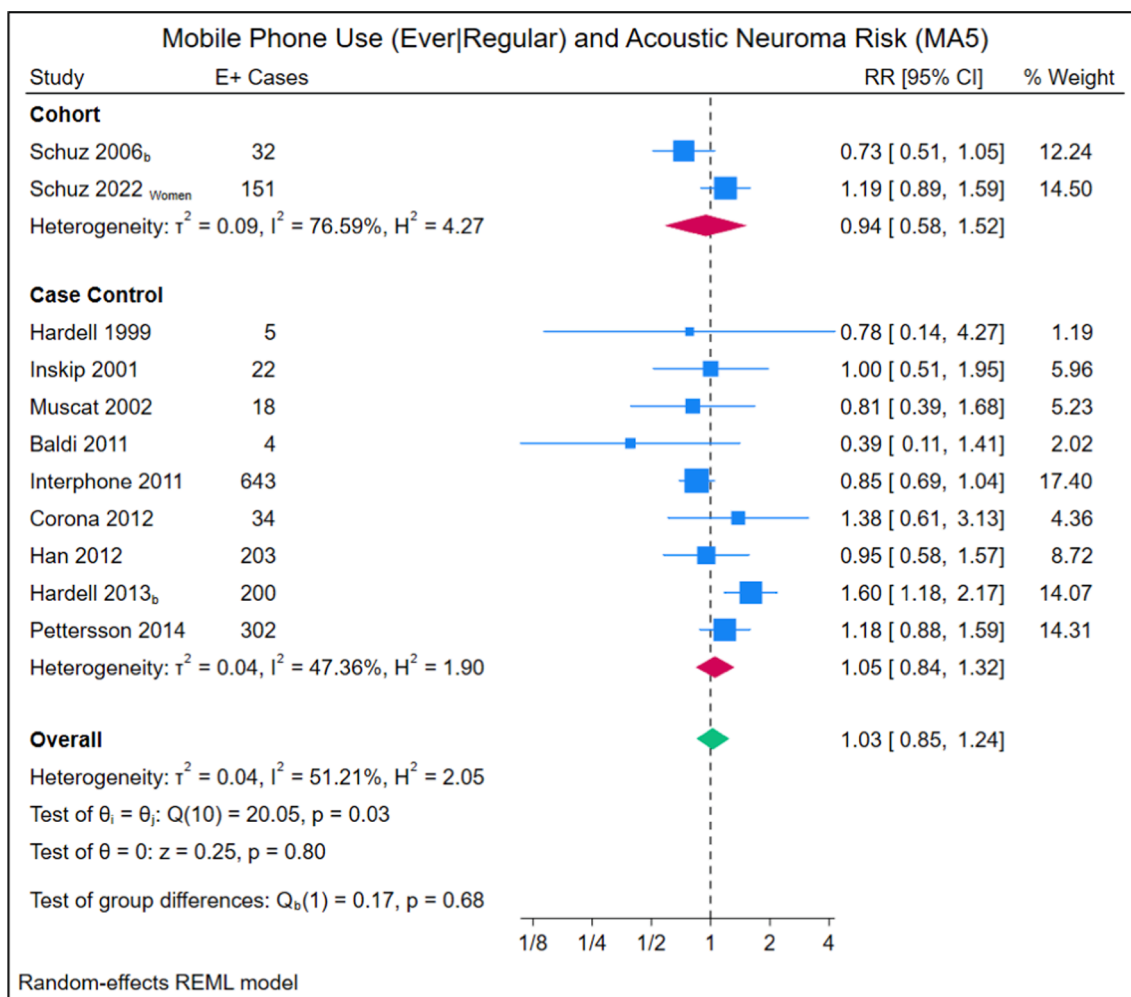


Fig. 10. Meta-analysis of mobile phone use (Ever or Regular) and acoustic neuroma risk.

major differences in results across studies (Fig. 14). The results of the meta-analyses of pituitary tumours risk by increasing categories of TSS mobile phone use are shown in Fig. 15. There are no indications of a risk increase with increasing TSS.

For salivary tumours, data from one cohort study (26 exposed cases) and 7 case-control studies contributing 9 independent measures of effects (585 exposed cases), were available. The overall mRR was 0.91 (95

% CI = 0.78 – 1.06), with $\tau^2 = 0.00$ and $I^2 = 0\%$, indicating similar results across studies (Fig. 16). The results of the meta-analyses of salivary tumours risk by increasing categories of TSS mobile phone use are shown in Fig. 17. There are no indications of a risk increase with increasing TSS.

For paediatric brain tumours, RR estimates for the contrast Ever vs Never (regular) mobile phone use were available from three case-control

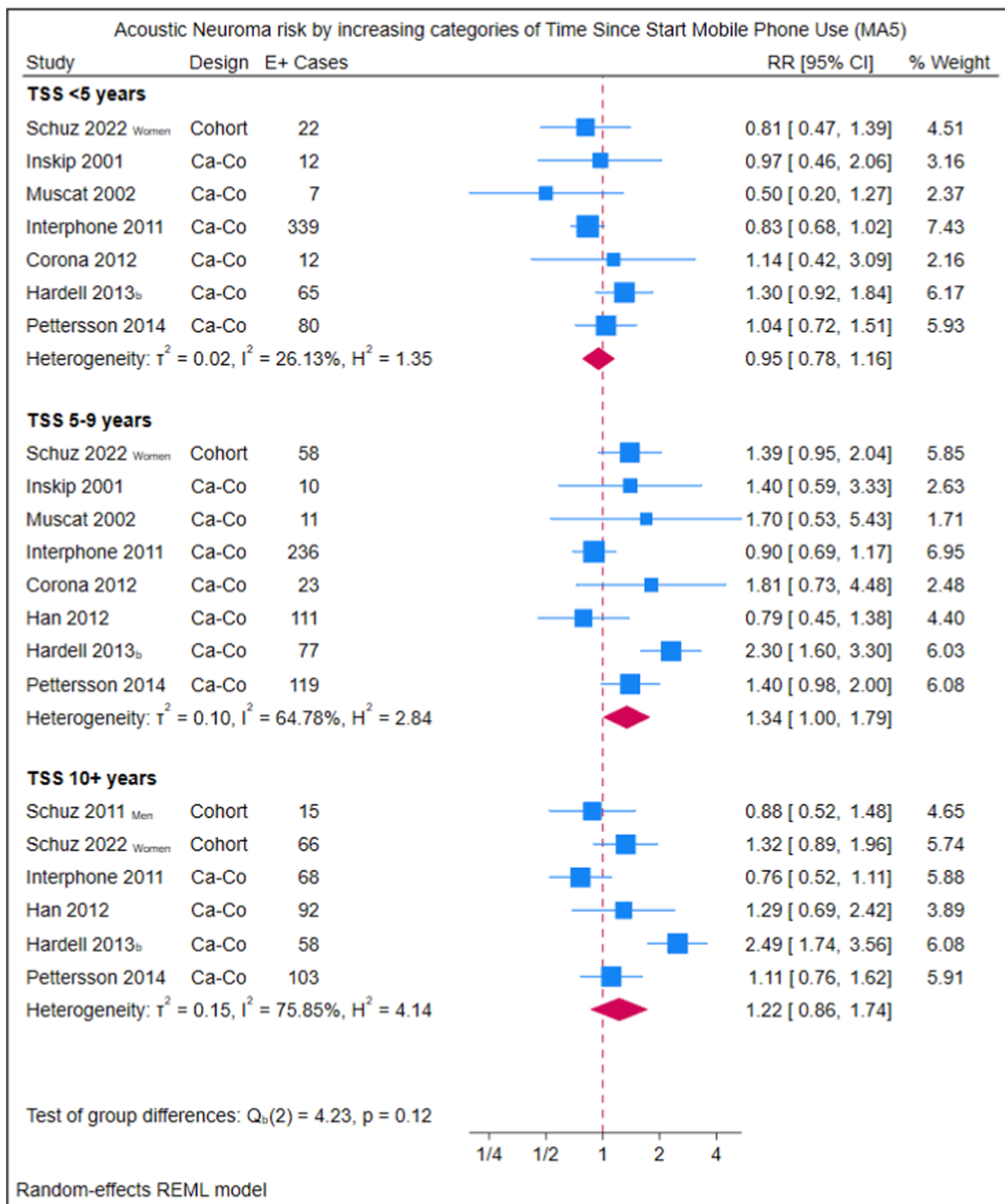


Fig. 11. Subgroup meta-analyses of mobile phone use and risk of acoustic neuroma by time since start use (TSS, MA5 dataset).

studies including 733 exposed cases (Fig. 18). The mRR was 1.06 (95 % CI = 0.74–1.51), and there were no indications of an increased risk, nor of heterogeneity in results across studies ($\tau^2 = 0.04$; $I^2 = 44.5\%$).

The subgroup meta-analysis of paediatric brain tumours by increasing TSS was not performed due to the paucity of studies, but no trend with increasing latency was observed in the studies with available

data (Aydin et al., 2011b; Castano-Vinyals et al., 2022), as shown in Annex 5 – Table S7.1.

4.4.2.3. SR-A – Cordless phone use and risk of tumours in the head region. Very few studies investigated the use of cordless phones; therefore, it was sufficient creating only two non-overlapping datasets (MA1 and

Table 13

Leave-one-out meta-analysis of long-term mobile phone use and acoustic neuroma risk (MA5 dataset; REML random effects model; studies ordered by standard error of the log-transformed effect measure).

Omitted study	mRR	95 % Confidence Interval	P value
Hardell et al. 2013b	1.03	0.82–1.30	0.78
Pettersson et al. 2014	1.24	0.81–1.92	0.32
Interphone SG 2011	1.36	0.95–1.95	0.10
Schuz et al. 2022 ^{Women}	1.20	0.78–1.85	0.41
Schuz et al. 2011 ^{Men}	1.29	0.87–1.93	0.21
Han et al. 2012	1.21	0.80–1.83	0.37
Overall mRR	1.22	0.86–1.74	0.27

Table 13 Footnotes: mRR = meta-estimate of the relative risk.

MA5). Less than 3 neoplasm-specific studies reported analyses by TSS use of cordless phones, and no quantitative synthesis was performed.

The forest plots from the meta-analyses of the measures of effect for Ever vs Never use of cordless phone use and risks of glioma, meningioma or acoustic neuroma are displayed in Fig. 19.

For glioma (Fig. 19, top), five case-control studies were available in MA1 and three in MA5. Focussing on MA1, the mRR shows a slightly increased risk (mRR = 1.23; 95 % CI = 0.87–1.74), with considerable heterogeneity between studies ($\tau^2 = 0.12$; $I^2 = 79\%$). There was no association when looking at the MA5 dataset (mRR = 1.04; 95 % CI = 0.74–1.46), also with considerable heterogeneity ($I^2 = 74\%$).

No association was found between use of cordless phones and meningioma risk (mRR = 0.99, 95 % CI = 0.81–1.21, for MA1, and mRR = 0.91, 95 % CI 0.70–1.18 for MA5). The forest plots suggest low or moderate heterogeneity (MA1 or MA5, respectively), albeit the confidence intervals for the individual studies were rather large (Fig. 19, middle).

For acoustic neuroma, the mRRs were compatible with the null hypothesis in MA1 (mRR = 1.09, 95 % CI = 0.85–1.38), and slightly elevated in MA5 (mRR = 1.16, 95 % CI = 0.83–1.61), with large confidence intervals in both datasets (Fig. 19, bottom).

The association between cordless phone and other neoplasms was assessed in less than three studies for paediatric brain tumours (Aydin et al., 2011; Castano-Vinyals et al., 2022), pituitary tumours (Hardell et al., 2002a), and salivary gland tumours (Hardell et al., 2004; Soderqvist et al., 2012), so that no quantitative synthesis was performed. The original results are presented in Annex 4, Tables S7.7 and 7.11–12, showing no statistically significant association between cordless phone use and any of the neoplasms.

4.4.2.4. SR-B – RF exposure from fixed-site transmitters and risk of childhood leukaemia. Few studies were eligible for inclusion in SR-B, and the relatively largest subset investigated the risk of childhood leukaemia in relation to far-field exposure from either broadcast transmitters (one cohort and two case-control studies), or base stations (two case-control studies). In accordance with our inclusion criteria, the exposure assessment in all these studies was based on modelled estimates of RF level at the children's residences, even though the methods and measurement units differed across studies. Therefore, we performed a subgroup meta-analysis by increasing categories of estimated exposure level (Fig. 20), without calculating the overall mRR. However, notwithstanding the differences in exposure source and methodological features, all study-specific measures of effect were close to the null. Further, there were neither heterogeneity, nor statistically significant differences, within and between exposure level subgroups, respectively.

From an additional meta-analysis, carried out on combined measures of effect for the contrast Exposed vs Unexposed calculated via IVWA fixed effect models, we obtained a mRR of 0.93 (95 % CI 0.85–1.03); $\tau^2 = 0.0034$; $I^2 = 28\%$.

4.4.2.5. SR-B – RF exposure from fixed-site transmitters and risk of paediatric brain tumours. The effect of RF exposure from broadcast

transmitters or base stations on paediatric brain tumour risk was investigated in two studies per source (one cohort, and three case-control). Overall, there was no exposure-outcome association (mRR = 0.97; 95 % CI 0.73–1.29), with considerable heterogeneity across studies ($I^2 = 80\%$), but no statistically significant differences between medium and high exposure level subgroups (Fig. 21).

4.4.2.6. SR-C – Occupational RF exposure and risk of glioma. We identified only three incidence-based studies of occupational exposure to RF-EMF and brain cancer/glioma risk eligible for inclusion in SR-C (one cohort-nested case-control study, and two population-based case-control studies). All studies used JEMs to estimate the cumulative individual exposure level, although the exposure assessment method, as well as the exposure sources, classification, and measurement units, varied across studies. To synthesize the findings, we used the same approach described in the preceding sections (§ 4.4.2.4 and § 4.4.2.5, relating to SR-B). That is, we performed a subgroup meta-analysis by increasing categories of exposure level, without presenting an overall mRR (Fig. 22). The results of the individual studies, along with the lack of heterogeneity within subgroups and of differences between subgroups, suggests lack of an exposure-outcome association. However, the subgroup-specific mRRs should be interpreted with caution, due to the differences in the exposure level definition across studies, and the few included studies.

On this small body of evidence also, we performed an additional meta-analysis of the effect measures for the contrast Exposed vs Unexposed calculated via IVWA fixed effect models, which suggested no statistically significant effect of the exposure on the outcome (mRR = 1.06; 95 % CI 0.72–1.54), even though the interpretation of this meta-estimate is very uncertain due to imprecision and considerable heterogeneity across studies ($\tau^2 = 0.082$; $I^2 = 86\%$).

4.4.3. Assessment of reporting bias

In the large majority of investigated exposure-outcome associations, there was no evidence of publication/small study bias (Annex 7, Figures S5.a to S5.i), with the single exception of the few studies of RF exposure from fixed site transmitters and risk of paediatric brain tumours in the exposed vs unexposed contrast (Egger test for small study bias = 3.66, $p = 0.0003$), as well as by increasing exposure level (Annex 7, Figure S5.h).

4.5. Confidence in evidence assessment

The results of the confidence in evidence assessment are shown in an Evidence Profile in Table 14. The considerations that emerged from the assessment are presented in the Discussion (section 5.1).

5. Discussion

5.1. Summary of the evidence and interpretation of the results

We performed an extensive review of epidemiological studies investigating neoplasia risks in relation to three types of RF exposure: near-field, head-localized, exposure from wireless phone use (SR-A); far-field, whole body, environmental exposure from fixed-site transmitters (SR-B); near/far-field occupational exposures from use of hand-held transceivers or RF-emitting equipment in the workplace (SR-C). While no restrictions on tumour type were applied, this paper focuses on selected "critical" neoplasms of the CNS (glioma, meningioma, acoustic neuroma, pituitary gland tumours) and salivary gland tumours (SR-A); brain tumours and leukaemias (SR-B, SR-C).

In total, we included 63 aetiological articles reporting on the association between RF exposure from different sources and risks of critical neoplasms, published between 1994 and 2022, with participants from 22 countries, investigating 119 different exposure-outcome pairs. The large majority of studies addressed the association between mobile

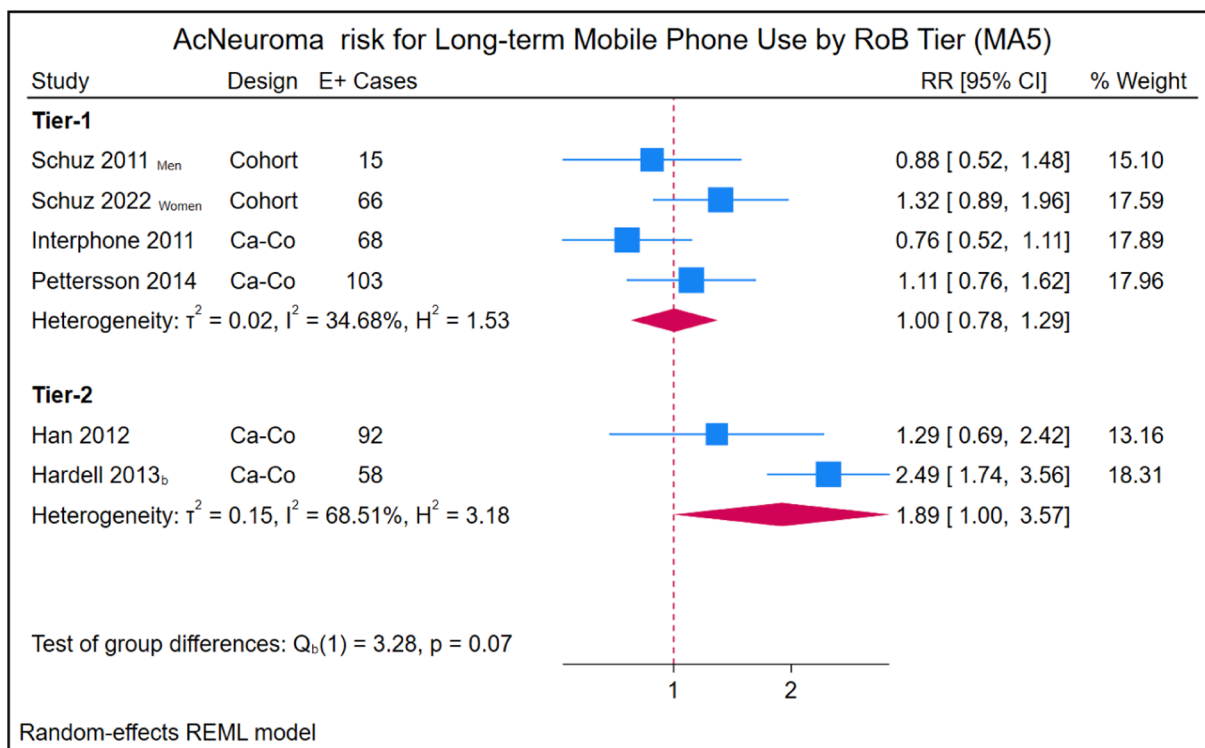
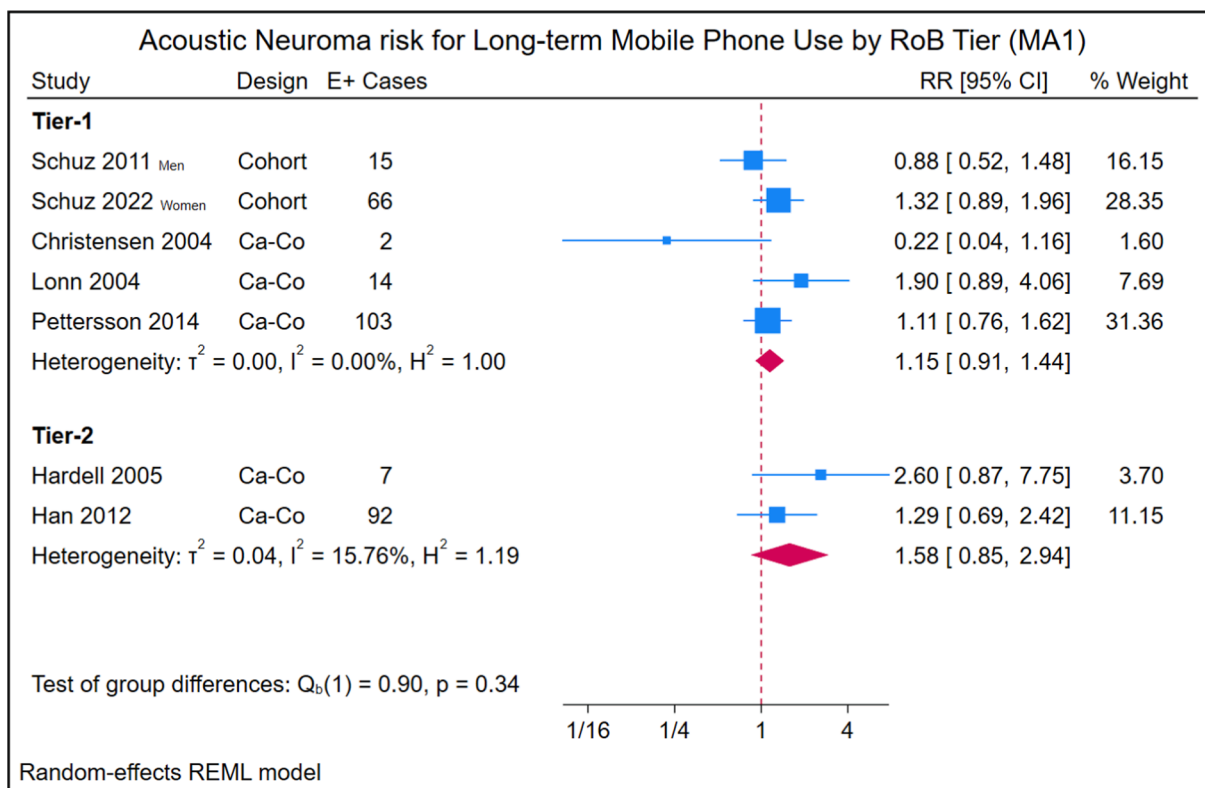


Fig. 12. Meta-analyses of acoustic neuroma risk in Long-term (TSS 10+ years) mobile phone users stratified on bias-tier (MA1 and MA5 datasets).

phone use and tumours in the head region (69 % of all E-O pairs), and a few of these studies also reported on risks of some neoplasms from cordless phone use (SR-A). Ten studies examined the effect of exposure from fixed-sites transmitters on risks of childhood leukaemia or paediatric brain tumours (SR-B), and only three studies concerned glioma incidence in relation to occupational RF exposure (SR-C). In total 114 E-O pairs were included in the quantitative synthesis.

In line with our protocol for the confidence in evidence assessment (Annex 3), in formulating our final conclusions we took into account the exposure-outcome specific confidence in evidence ratings, the ranking of RF sources by exposure level as inferred from dosimetric studies, and the external coherence with findings from time-trend simulation studies (only available for glioma/brain cancer in relation to mobile phone use).

In our main meta-analyses, RF exposure from mobile phones,

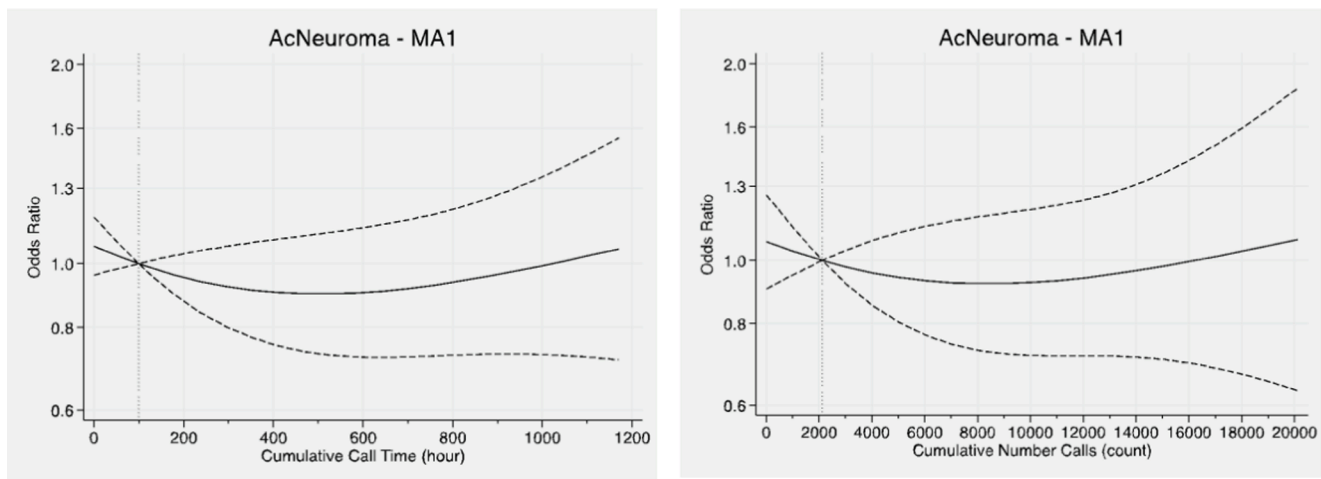


Fig. 13. Dose-response meta-analyses between acoustic neuroma risk and mobile phone cumulative call time (CCT, left) or cumulative number of calls (CNC, right).

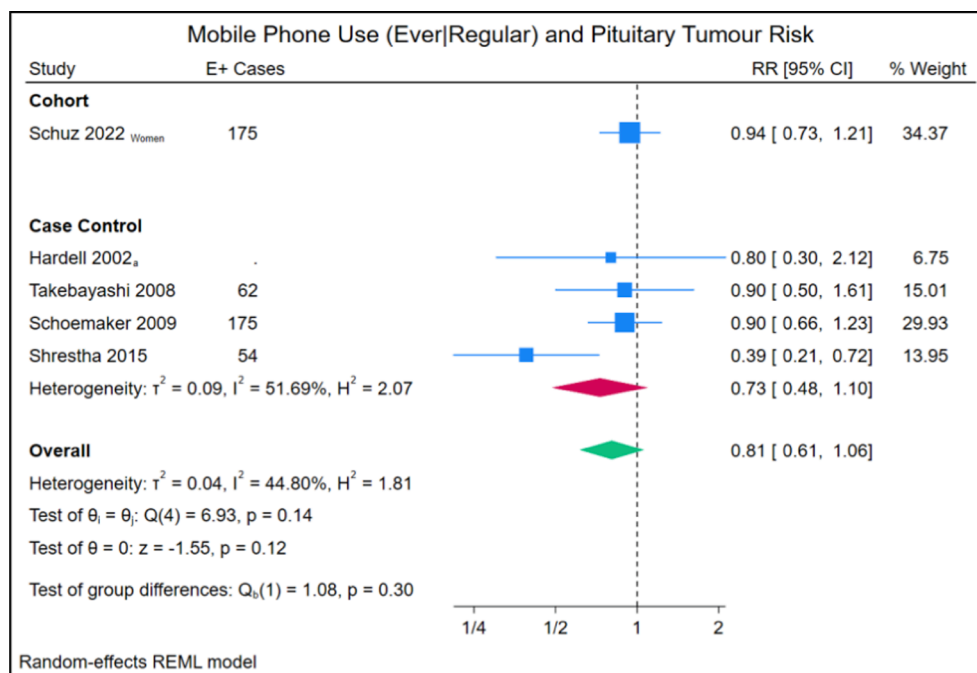


Fig. 14. Meta-analysis of mobile phone use (Ever or Regular) and risk of pituitary tumours.

measured as ever or regular use vs no or non-regular use, was not associated with risk of glioma (mRR = 1.01, 95 % CI 0.89–1.13; 13 studies and 4630 exposed cases; Fig. 2). There was some variation in the point estimates, overlapping confidence intervals in 10 out of 13 effect measures, and substantial heterogeneity across studies ($I^2 = 62\%$).

Similarly, there was no association between ever (regular) mobile phone use and acoustic neuroma (mRR = 1.03, 95 % CI 0.85–1.24; 11 studies and 1614 exposed cases; Fig. 8) with some variation in the point estimates, overlapping confidence intervals in most effect measures (7 of 11 studies), and moderate heterogeneity across studies ($I^2 = 51\%$).

The degree of heterogeneity observed in the meta-analyses of glioma and acoustic neuroma in relation to Ever vs Never (regular) mobile phone use, was driven by much larger across-study inconsistency of findings among long-term (10+ years) mobile phone users.

The leave-one-out meta-analyses identified one influential study investigating mobile phone use and glioma (Hardell and Carlberg, 2015). Repeating the meta-analyses of glioma risk in relation to mobile phone use after excluding this study, we observed substantial reductions

in the risk estimates and in the between-study heterogeneity for both the contrast “Ever vs Never” use (mRR = 0.96, 95 % CI = 0.87–1.07, $I^2 = 47\%$), and in the analysis by increasing categories of time since start use of mobile phones (“<5 years”: mRR = 0.97, 95 % CI = 0.83–1.14, $I^2 = 41\%$; “5-9 years”: mRR = 0.96, 95 % CI = 0.83–1.11, $I^2 = 34\%$; “10+ years”: mRR = 0.97, 95 % CI = 0.87–1.08, $I^2 = 10\%$).

Moreover, in the subgroup meta-analyses of the effect measures for glioma and acoustic neuroma in relation to long-term mobile phone use stratified on bias-tier, we observed no exposure-outcome associations and no across-study heterogeneity within the tier-1 study subgroup of either neoplasm. Therefore, we did not downgrade the evidence relating to mobile phone use and risk of glioma or acoustic neuroma for unexplained inconsistency.

The results of the sensitivity meta-analyses excluding five studies with implausible effect sizes (>1.5), as inferred from three time-trend simulation studies, although not considered in the confidence in evidence assessment, further strengthen the confidence in the lack of association between mobile phone use and glioma.

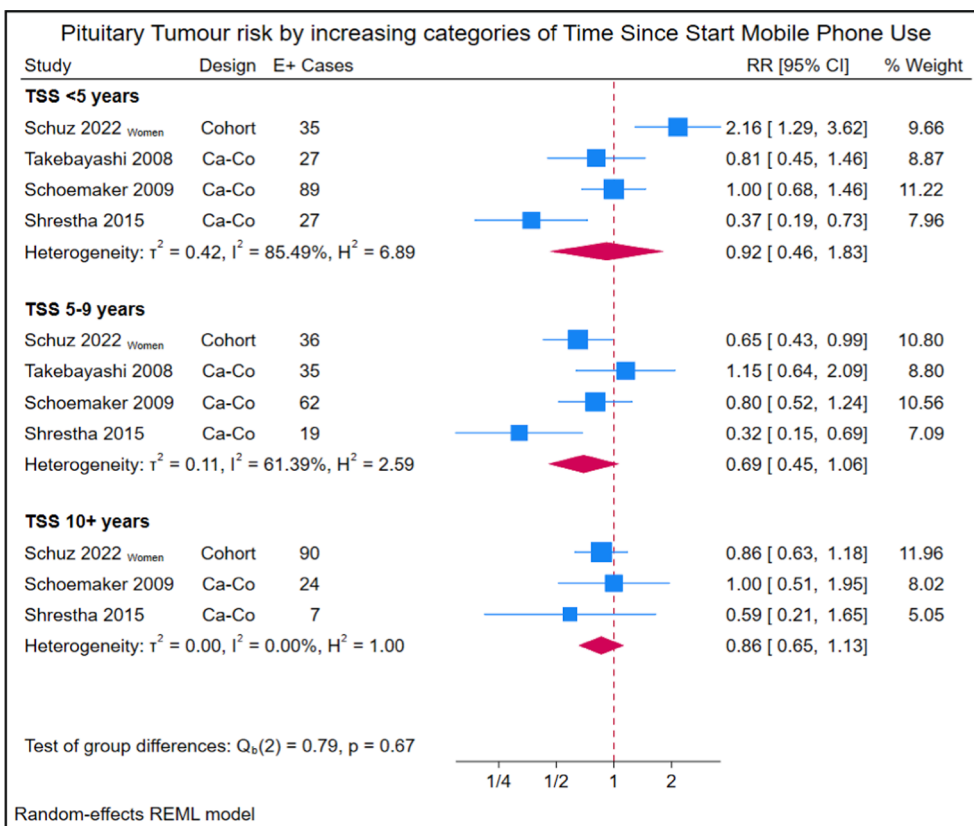


Fig. 15. Subgroup meta-analyses of mobile phone use and risk of pituitary tumours by time since start use (TSS).

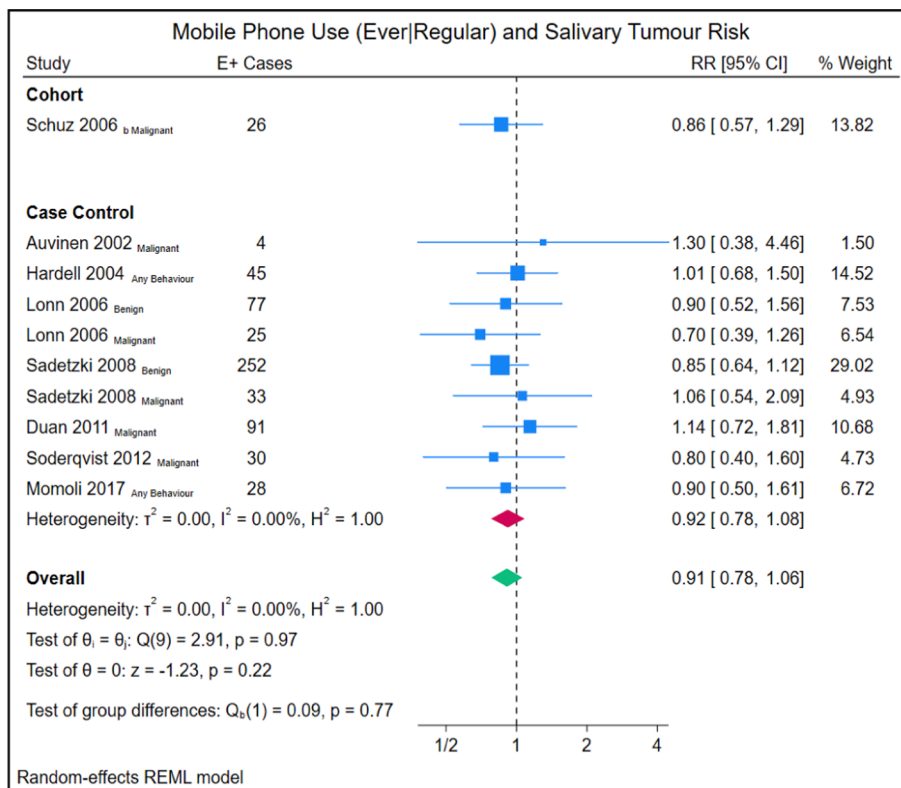


Fig. 16. Meta-analysis of mobile phone use (Ever or Regular) and risk of salivary gland tumours.

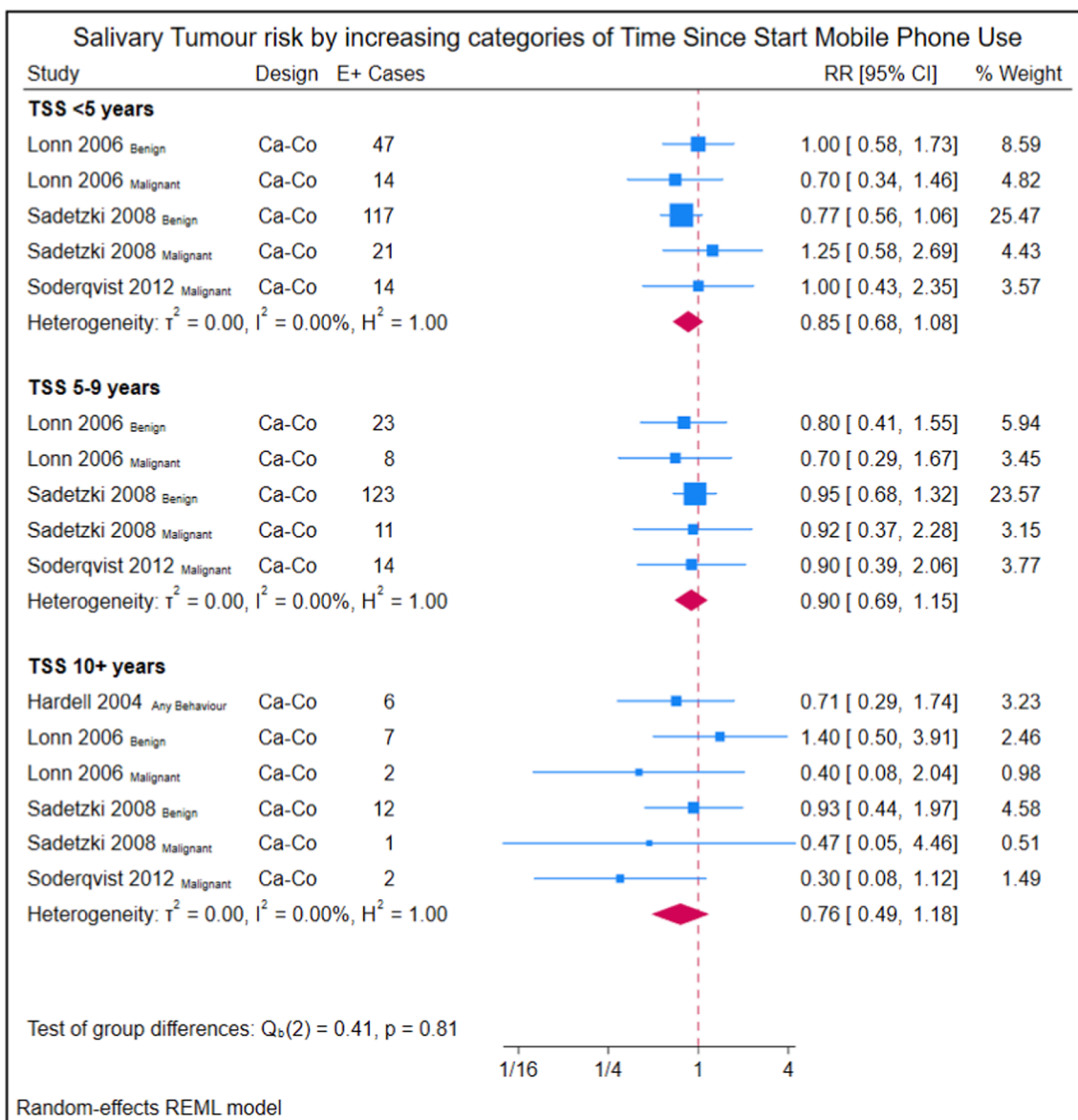


Fig. 17. Subgroup meta-analyses of mobile phone use and risk of salivary tumours by time since start use (TSS).

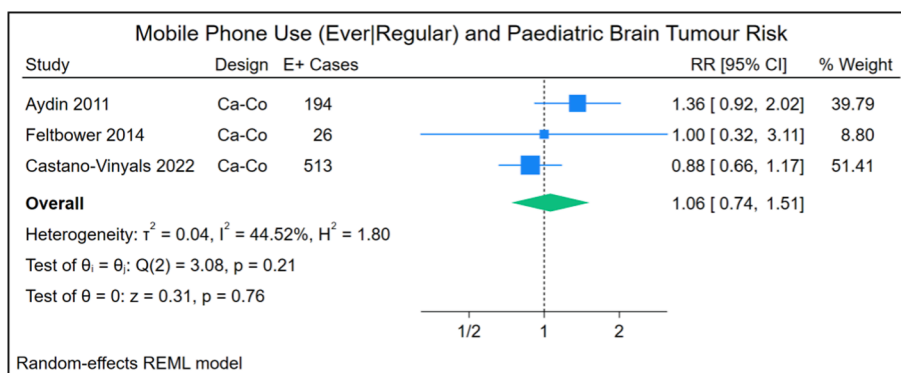


Fig. 18. Meta-analysis of mobile phone use (Ever vs Never) and risk of paediatric brain tumours.

RF exposure from mobile phones, measured as ever or regular use vs no or non-regular use, was also not associated with risks of meningioma (mRR = 0.92, 95 % CI 0.82–1.02; 10 studies and 2990 exposed cases; Fig. 7), pituitary tumours (mRR = 0.81, 95 % CI 0.61–1.06; 5 studies and

466 exposed cases, not counting missing data from 1 study; Fig. 14), salivary gland tumours (mRR = 0.91, 95 % CI 0.78–1.06; 10 studies and 611 exposed cases; Fig. 16), or paediatric brain tumours (mRR = 1.06, 95 % CI 0.74–1.51; three studies and 733 exposed cases; Fig. 18). There

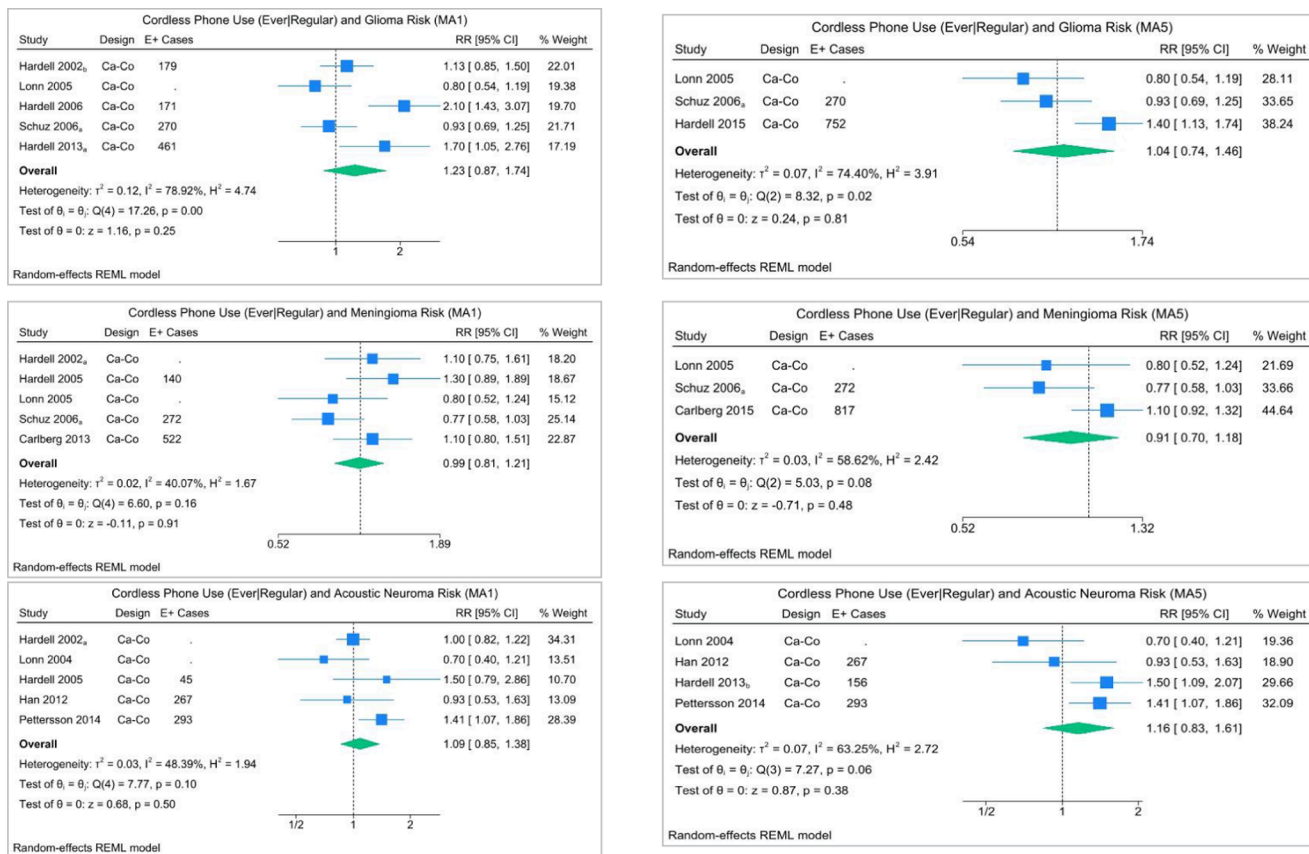


Fig. 19. Meta-analysis of cordless phone use and risks of glioma, meningioma and acoustic neuroma (MA1 and MA5 datasets).

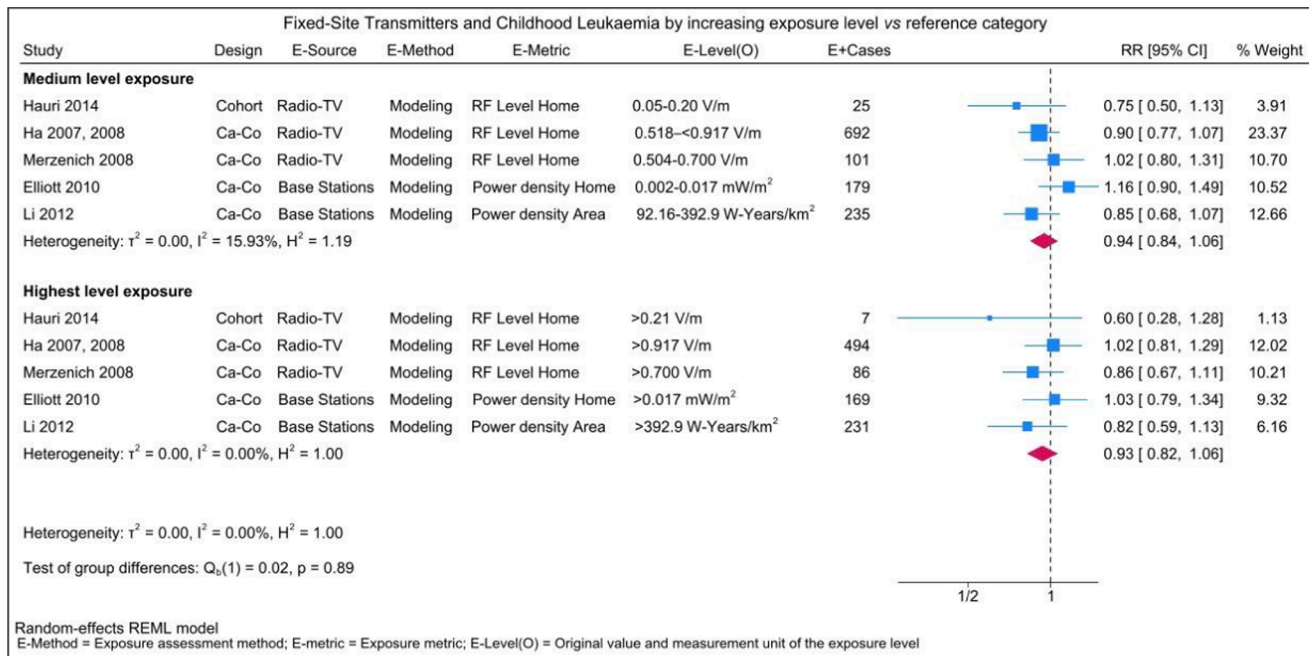


Fig. 20. Subgroup meta-analysis of RF exposure from fixed-site transmitters and childhood leukaemia, by exposure level.

were no factors which decreased or increased certainty in the evidence for any of these tumours, therefore, the certainty in the observed absence of association between mobile phone use and meningioma, pituitary tumours, salivary gland tumours or paediatric brain tumours was classified as moderate.

For the most investigated neoplasms (glioma, meningioma, and acoustic neuroma), we generally observed no tendency of increasing risk with increasing time since start use of mobile phones, cumulative call time, or cumulative number of calls.

For meningioma, we observed a statistically significant decreasing

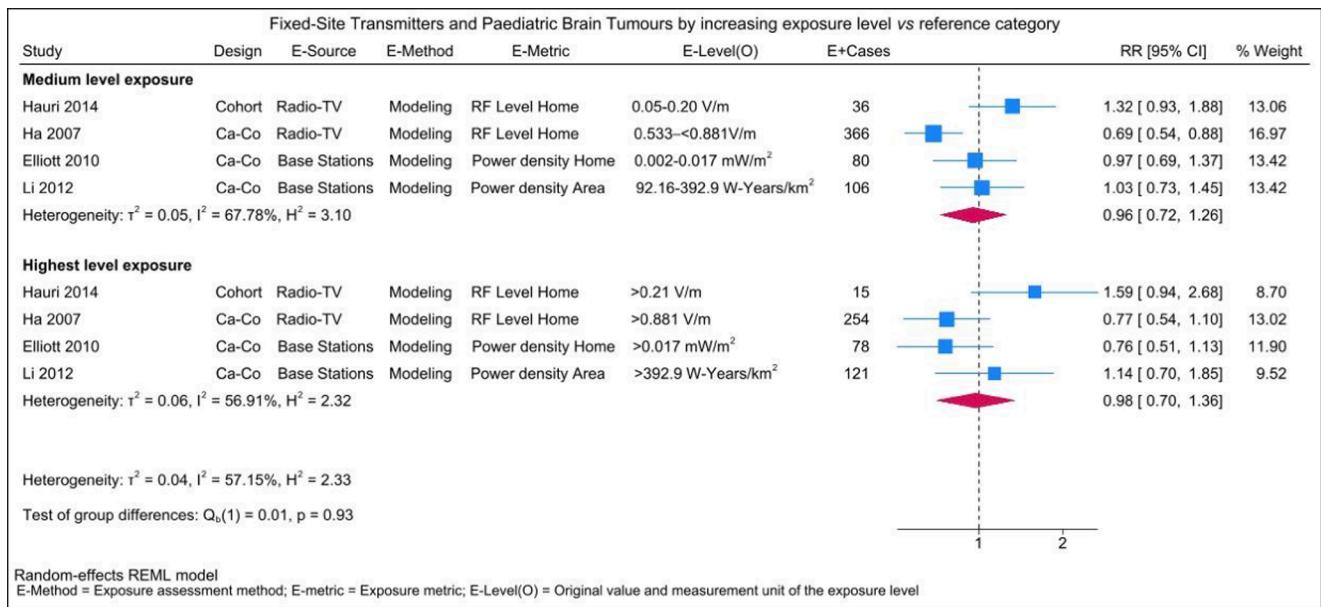


Fig. 21. Subgroup meta-analysis of RF exposure from fixed-site transmitters and paediatric brain tumours, by exposure level.

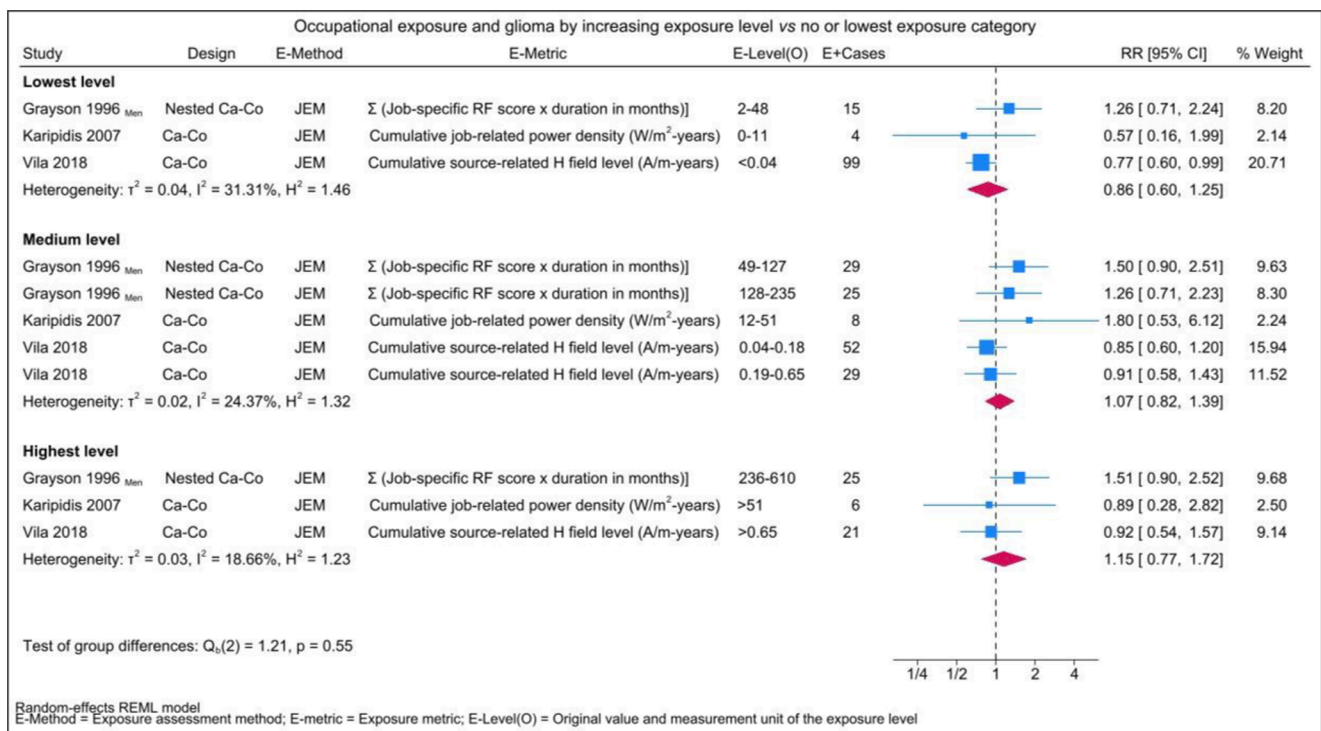


Fig. 22. Subgroup meta-analysis of occupational RF exposure and glioma risk, by exposure level.

trend in mRR with increasing lifetime intensity of mobile phone use (in particular, with increasing total number of calls). This finding may be attributable to reverse causation, whereas prodromal symptoms of the tumour (e.g., epilepsy) may be inversely associated with the prevalence and/or intensity of mobile phone use. Actually, in one Swedish study investigating the preclinical association between mobile phone use and primary adult intracranial tumours (Schwartzbaum et al., 2005), an increased risk of meningioma was observed among people discharged with epilepsy ≥ 11 years before the neoplasm diagnosis (OR 2.16; 95% CI 1.45–3.21).

For acoustic neuroma, in the main meta-analyses we detected a

borderline significantly increased mRR in the “5–9 years” category of TSS (mRR = 1.34, 95% CI = 1.00–1.79, $I^2 = 65\%$). This finding may be at least partly attributable to detection bias. In studies of acoustic neuroma, mobile phone use can raise awareness about the unilateral hearing loss that is an early symptom of the disease, and physicians or otorhinolaryngologists, suspecting that mobile phone use causes acoustic neuroma, may monitor patients using mobile phones more closely than non-users (or low-users), facilitating or anticipating the diseases diagnosis. Consequently, a differential measurement error of the outcome will occur in both cohort and case-control studies, wherein the exposure affects the likelihood of (an early) diagnosis (Savitz, 2004).

Table 14
Evidence profile.

Certainty assessment									Summary of findings		Final Confidence Rating	
Initial Confidence for Each Body of Evidence (# of Studies by design)		Factors decreasing confidence (“–” if no concern; “↓” if serious concern to downgrade confidence)					Factors increasing confidence (“–” if not present; “↑” if sufficient to upgrade confidence)					High (++++) Moderate (+++) Low (++) Very Low (+)
Moderate (+++)		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Confounding	No. of exposed cases	Effect (95% CI)	
Outcome: Glioma												
Near-field, head localized, exposure from wireless phones (SR-A): Mobile phones¹												
Ever vs Never use		–	↓ ²	–	–	–	–	–	–	4,200	mRR 1.01 (0.89–1.13)	Moderate
(MA5, 3 Coh and 10 CaCo)												
Near-field, head localized, exposure from wireless phones (SR-A): Cordless phones												
Ever vs Never use		–	↓ ³	–	–	–	–	–	–	> 1,022 ⁴	mRR 1.04 (0.74–1.46)	Low
(MA5, 3 CaCo)												
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters												
No eligible studies												
Near field/far-field occupational exposure (SR-C): Occupational exposures⁵												
Exposed vs Unexposed		–	↓ ⁶	–	–	–	–	–	–	313	mRR 1.06 (0.72–1.54)	Low
(3 CaCo)												
Outcome: Meningioma												
Near-field, head localized, exposure from wireless phones (SR-A): Mobile phones⁷												
Ever Vs Never use		–	–	–	–	–	–	–	–	2,990	mRR 0.92 (0.82–1.02)	Moderate
(MA5, 3 Coh and 7 CaCo)												
Near-field, head localized, exposure from wireless phones (SR-A): Cordless phones												
Ever Vs Never use		–	↓ ⁸	–	–	–	–	–	–	>1,089 ⁹	mRR 0.91 (0.70–1.18)	Moderate
(MA5, 3 CaCo)												
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters												
No eligible studies												
Near field/far-field occupational exposure (SR-C): Occupational exposures												
No eligible studies												

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Table 14 (continued)

Certainty assessment										Summary of findings		Final Confidence Rating					
Initial Confidence for Each Body of Evidence (# of Studies by design) Moderate (+++)										Factors decreasing confidence ("—" if no concern; "↓" if serious concern to downgrade confidence)	Factors increasing confidence ("—" if not present; "↑" if sufficient to upgrade confidence)			High (++++)	Moderate (+++)	Low (++)	Very Low (+)
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Confounding	No. of exposed cases	Effect (95% CI)							
Outcome: Acoustic Neuroma																	
Near-field, head localized, exposure from wireless phones (SR-A): Mobile phones ¹⁰																	
Ever Vs Never use (MA5, 2 Coh and 9 CaCo)	—	↓ ¹¹	—	—	—	—	—	—	1,614	mRR 1.03 (0.85–1.24)		Moderate					
Near-field, head localized, exposure from wireless phones (SR-A): Cordless phones																	
Ever Vs Never use (MA5, 4 CaCo)	—	↓ ¹²	—	—	—	—	—	—	>716 ¹³	mRR 1.16 (0.83–1.61)		Low					
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters																	
No eligible studies																	
Near field/far-field occupational exposure (SR-C): Occupational exposures																	
No eligible studies																	
Outcome: Pituitary tumours																	
Near-field, head localized, exposure from wireless phones (SR-A): Mobile phones ¹⁴																	
Ever Vs Never use (1 Coh and 4 CaCo)	—	—	—	—	—	—	—	—	> 466 ¹⁵	mRR 0.81 (0.63–1.06)		Moderate					
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters																	
No eligible studies																	
Near field/far-field occupational exposure (SR-C): Occupational exposures																	
No eligible studies																	
Outcome: Salivary gland tumours																	
Near-field, head localized, exposure from wireless phones (SR-A): Mobile phones ¹⁶																	
Ever Vs Never use (1 Coh and 9 CaCo)	—	—	—	—	—	—	—	—	611	mRR 0.91 (0.78–1.06)		Moderate					
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters																	
No eligible studies																	

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Table 14 (continued)

Certainty assessment						Summary of findings			Final Confidence Rating		
Initial Confidence for Each Body of Evidence (# of Studies by design) Moderate (+++)	Factors decreasing confidence ("—" if no concern; "↓" if serious concern to downgrade confidence)					Factors increasing confidence ("—" if not present; "↑" if sufficient to upgrade confidence)			No. of exposed cases	Effect (95 % CI)	High (++++) Moderate (+++) Low (++) Very Low (+)
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Confounding			
Near field/far-field occupational exposure (SR-C): Occupational exposures No eligible studies											
Outcome: Paediatric brain tumours Near-field, head localized, exposure from wireless phones (SR-A): Mobile phones Ever Vs Never use (MA5, 3 CaCo)											
	–	–	–	–	–	–	–	–	733	mRR 1.06 (0.74–1.51)	Moderate
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters ¹⁷ Exposed Vs Unexposed (1 Coh and 3 CaCo)											
	–	↓ ¹⁸	–	–	–	–	–	–	1056	mRR 0.97 (0.73–1.29)	Low
Near field/far-field occupational exposure (SR-C): Occupational exposures No eligible studies											
Outcome: Childhood leukemias Near-field, head localized, exposure from wireless phones (SR-A): Wireless phones No eligible studies											
Far-field, whole body, exposure from environmental sources (SR-B): Fixed-site transmitters ¹⁹ Exposed Vs Unexposed (1 Coh and 4 CaCo)											
	–	–	–	–	–	–	–	–	2219	mRR 0.93 (0.85–1.03)	Moderate
Near field/far-field occupational exposure (SR-C): Occupational exposures No eligible studies											

Table 14 footnotes

Coh = Cohort; CaCo = Case-Control.

Glioma: ¹ In addition to these results there was no increase in glioma risk with increasing time since start use of mobile phones, or cumulative mobile phone call time, or cumulative number of mobile phone calls; ² notwithstanding the $I^2 = 62\%$, we did not downgrade by one level because the observed heterogeneity, driven by the results in the upper category of TSS, was explained by the findings from the leave-one-out meta-analysis, as well as by the subgroup meta-analysis by RoB tier; ³ $I^2 = 74\%$, downgraded by one level; ⁴ No information on number of exposed cases for one study; ⁵ In addition to these results there was no increase in glioma risk with increasing exposure level; ⁶ $I^2 = 86\%$, downgraded by one level; **Meningioma:** ⁷ In addition to these results there was no increase in meningioma risk with increasing time since start use of mobile phones or cumulative mobile phone call time; there was a decrease in meningioma risk with cumulative number of mobile phone calls; ⁸ $I^2 = 59\%$, downgraded by one level; ⁹ No information on number of exposed cases for one study; **Acoustic neuroma:** ¹⁰ In addition to these results there was no increase in acoustic neuroma risk with increasing time since start use of mobile phones, or cumulative mobile phone call time, or cumulative number of mobile phone calls; ¹¹ notwithstanding the $I^2 = 51\%$, we did not downgrade by one level because the heterogeneity, driven by the results in the upper category of TSS, was explained by the findings from the subgroup meta-analysis by RoB tier in long-term mobile phone users; ¹² $I^2 = 63\%$, downgraded by one level; ¹³ No information on number of exposed cases for one study; **Pituitary tumours:** ¹⁴ In addition to these results there was no increase in pituitary tumours risk with increasing time since start use of mobile phones ¹⁵ No information on number of exposed cases for one study; **Salivary gland tumours:** ¹⁶ In addition to these results there was no increase in salivary gland tumours risk with increasing time since start use of mobile phones; **Paediatric brain tumours:** ¹⁷ In addition to these results there was no increase in paediatric brain tumour risk with increasing exposure level; ¹⁸ $I^2 = 80\%$, downgraded by one level; **Childhood leukaemias:** ¹⁹ In addition to these results there was no increase in childhood leukaemia risk with increasing exposure level.

The results of the SOTAN study (Pettersson et al., 2014), where the overall increased risk of acoustic neuroma in relation to both mobile and cordless phones was driven by findings observed in the subgroup of patients with small-size neoplasms diagnosed through imaging only (without histological confirmation because not operated), support the occurrence of this bias. Together with the increasing accessibility of neuroimaging resulting in higher rates of incidentally diagnosed acoustic neuroma and other benign CNS tumours (Cote and Laws, 2017), detection bias may also have contributed to the increasing incidence rate of acoustic neuroma accompanied by a parallel decrease in tumour size at diagnosis, observed in a 40-year time trend study in Denmark (Reznitsky et al., 2019).

The secondary analyses performed on alternative datasets consisting of different non-overlapping combinations of primary studies of glioma, meningioma, or acoustic neuroma and pooled analyses of the latter, indicated that the findings from the main meta-analyses are robust and independent of the study aggregation.

The association between cordless phone use and tumours in the head region was investigated in few studies (Fig. 19). In the meta-analyses performed on the MA5 dataset, there was no increased risk of glioma [mRR = 1.04, 95 % CI 0.74–1.46; 3 studies and over 1022 exposed cases (missing information from one study)] with considerable heterogeneity: $I^2 = 74\%$, meningioma (mRR = 0.91, 95 % CI 0.70–1.18; 3 studies and over 1089 exposed cases; $I^2 = 59\%$), or acoustic neuroma (mRR = 1.16; 95 % CI 0.83–1.61; 4 studies, over 716 exposed cases; $I^2 = 63\%$). No exposure-outcome associations were observed in the MA1 datasets, consisting of five studies for each E-O pair; herein, the heterogeneity in findings across studies of glioma was still substantial (79 %), while the results from the studies of meningioma and acoustic neuroma were consistently null ($I^2 = 40\%$ and 48 %, respectively).

Based on the more unfavourable scenario (MA5 dataset), the certainty in the evidence for the three neoplasms in relation to cordless phone use downgraded by one level due to unexplained inconsistency. However, in drawing our final conclusion we also accounted for dosimetric considerations. As already noted, the average output power of cordless phone is 1–2 order of magnitude less than that from 1G to 2G mobile phones (Lauer et al., 2013). In addition, findings from studies of modelled integrated “doses” of RF-EMF in children/adolescents and adults, indicate that mobile phone calls on 2G-GSM networks are an important contributor as long as 2G-GSM was operating (Birks et al., 2021; van Wel et al., 2021). The possibility of validating self-reported information on cordless phone use is hindered by the lack of objective data. The heterogeneity across studies of cordless phone use and glioma observed in current review, stems from the increased risks observed in Hardell’s series (Hardell and Carlberg, 2015; Hardell et al., 2006; Hardell et al., 2013a; Hardell et al., 2002b), in contrast to findings from a few other relevant studies (Lonn et al., 2005; Schuz et al., 2006a). For acoustic neuroma, increased risks in relation to cordless phone use were reported by both the Hardell studies (Hardell et al., 2005; Hardell et al., 2013b; Hardell et al., 2002a) and the SOTAN study (Pettersson et al., 2014). The inconsistency with dosimetric data can be appreciated in some studies of the Hardell series, where the findings are reported in comparable units (per 100 h of CCT) for mobile and cordless phone use. Similar effect sizes per unit increase in CCT were reported for glioma in relation to cordless phones (OR 1.013; 95 % CI 1.007–1.020) and mobile phones (OR 1.011; 95 % CI 1.006–1.015) (Hardell et al., 2013a), as well as for acoustic neuroma (2G mobile phones: OR 1.008; 95 % CI 0.998–1.018, and cordless phones: OR 1.007; 95 % CI 0.998–1.016) (Hardell et al., 2013b). In the pooled analysis of the second, third, and fourth study of meningioma, the OR per 100 h of CCT was 1.002; (95 % CI 0.996–1.007) for digital 2G-3G mobile phones, and 1.009 (95 % CI 1.004–1.013) for cordless phones (Carlberg and Hardell, 2015). In the SOTAN study, the effect size for cordless phone use was higher than that for mobile phone use (Pettersson et al., 2014). All in all, these findings are at odds with dosimetric data, and point to recall bias as a plausible explanation. This increases the credibility of the lack of association

between cordless phone use and risks of glioma, meningioma or acoustic neuroma.

The association between RF exposure levels from fixed site transmitters (broadcasting antennas or base stations) and childhood leukaemia was investigated in six studies. Five of these, characterized by good quality exposure assessment, and including 2219 exposed cases (1232 in the intermediate exposure level, and 987 in the highest exposure category), consistently showed lack of exposure-outcome association, independent of the level of the modelled RF exposure, notwithstanding cross-population and cross-study differences. For the contrast exposed vs unexposed, the mRR was 0.93 (95 % CI 0.85–1.03; $I^2 = 28\%$). There were no factors which decreased or increased certainty in the evidence, therefore, the certainty in the observed absence of association between RF exposure from fixed site transmitters (broadcasting antennas or base stations) and childhood leukaemia was defined as moderate.

The effect of exposure from broadcast transmitters or base stations and paediatric brain tumours was assessed in only two studies per source with 1056 exposed cases, also showing a lack of an association (for the contrast exposed vs unexposed the mRR was 0.97, 95 % CI 0.73–1.29). There was substantial heterogeneity across the studies ($I^2 = 80\%$), and the certainty in the evidence was downgraded by one level for inconsistency. There were no further factors which decreased or increased certainty in the evidence. Therefore, the certainty in the observed absence of association between fixed site transmitters (broadcasting antennas or base stations) and paediatric brain tumours was classified as low.

Glioma risk was not increased following occupational RF exposure in the three included studies (for the contrast exposed vs unexposed the mRR was 1.06, 95 % CI 0.72–1.54, 313 exposed cases), and no differences were detected between increasing categories of modelled cumulative exposure level. There was substantial heterogeneity across the studies ($I^2 = 86\%$) so the certainty in the evidence was downgraded by one level for inconsistency. There were no further factors which decreased or increased certainty in the evidence. Therefore, the certainty in the observed absence of association between occupational RF exposure and glioma was set to low.

There was limited variation in susceptibility to relevant biases in the dataset, with most studies classified in the tier-2 group, and no tier-3 studies. Therefore, in place of the planned sensitivity meta-analyses excluding tier-3 studies, we performed subgroup meta-analyses stratified on bias-tier. The results of these analyses were accounted for in our confidence in evidence rating, as previously mentioned.

The complementary evidence, collected in line with the triangulation approach, allowed us to deepen the interpretation of the systematic review results. The bias studies were helpful in the RoB assessment.

The time-trend simulation studies were very consistent in showing that the increased risks observed in some case-control studies were incompatible with the actual incidence rates of glioma/brain cancer observed in several countries and over long periods (up to over 30 years since handheld devices became available), and allowed us to account for external validity in assessing the certainty of evidence. In particular, based on findings from three simulation studies, we could define a credibility benchmark for the observed risk of glioma in relation to long-term mobile phone use, and perform sensitivity meta-analyses excluding studies reporting implausible effect sizes (>1.5) for this exposure contrast. In line with our confidence in evidence protocol, findings from these analyses were accounted for in our final conclusions.

The major strengths of this systematic review are the transparency and reproducibility of the detailed protocol, the extensive literature search, the clear definition of inclusion and exclusion criteria, and the detailed RoB assessment. A further asset is the creation of multiple neoplasm-specific datasets consisting of studies with non-overlapping populations, to avoid multiple counting of individual data, which allowed us to assess the robustness of findings to changes in the study aggregation.

Our conclusive statements, formulated in accordance with the GRADE guidelines 26 (Santesso et al., 2020), are provided below.

- For near field RF-EMF exposure to the head from mobile phones, there was moderate certainty evidence that it does not increase the risk of glioma, meningioma, acoustic neuroma, pituitary tumours, salivary gland tumours or paediatric brain tumours. For near field RF-EMF exposure to the head from cordless phones, there was low certainty evidence that it may not increase the risk of glioma, meningioma or acoustic neuroma. The credibility of the observed lack of association between mobile phone use and risk of glioma is reinforced by the external coherence with incidence time-trend simulation studies. The observed lack of association between cordless phone use and risks of glioma, meningioma, and acoustic neuroma, is strengthened by dosimetric considerations.
- For whole-body far-field RF-EMF exposure from fixed-site transmitters (broadcasting antennas or base stations), there was moderate certainty evidence that it likely does not increase childhood leukaemia risk, and low certainty evidence that it may not increase the risk of paediatric brain tumours. We could not assess the confidence in evidence for environmental exposure from transmitters and risk of critical neoplasms in adults due to lack of studies eligible for inclusion.
- For occupational RF-EMF exposure, there was low certainty evidence that it may not increase the risk of brain cancer/glioma, while there were no included studies of leukemias (the second critical outcome in SR-C).

The certainty in evidence rating regarding paediatric brain tumours in relation to environmental exposure from fixed-site transmitters should be interpreted with caution, due to the small number of studies. Similar interpretative cautions apply to the evidence rating of the relation between glioma/brain cancer and occupational RF exposure, due to differences in exposure sources and metrics across the few included studies.

5.1.1. Comparison between the current systematic review and the IARC evaluation

As mentioned in the Introduction, IARC in its 2011 evaluation classified RF-EMF as possibly carcinogenic to humans (group 2B), largely based on the positive associations between mobile phone use and risk of glioma and acoustic neuroma observed in two case-control studies: Interphone and the pooled analyses of the second and third ICT studies from the Hardell series (Baan et al., 2011). These findings were considered as consistent by the majority of the working group, with a disagreeing statement expressed by a minority of the panellists (IARC, 2013). IARC found the evidence related to RF exposure from environmental and occupational exposure sources to be inadequate (IARC, 2013).

Due to the extended time coverage, our systematic review is based on a much larger dataset compared to that examined by IARC. Our main datasets for glioma, meningioma, and acoustic neuroma relied on the updated follow-up of the Danish subscriber cohort (Frei et al., 2011; Schuz et al., 2011), the UK million-women cohort study (Schuz et al., 2022), the fourth primary studies of the Hardell series (Carlberg et al., 2013; Hardell et al., 2013a), and the pooled analyses of the Hardell's second, third, and fourth studies (Carlberg and Hardell, 2015; Hardell and Carlberg, 2015; Hardell et al., 2013b), and other new case-control studies (Corona et al., 2012; Coureau et al., 2014; Han et al., 2012; Pettersson et al., 2014; Yoon et al., 2015). Comparing our MA5 dataset and the dataset available to the IARC working group, there was a substantial increase in the number of cases in the highest category of TSS use of mobile phones (≥ 10 years): 1423 glioma cases (*vs* ~ 350); 818 meningioma cases (*vs* 192); 402 acoustic neuroma cases (*vs* 87).

Only one study of paediatric brain tumours and wireless phone use had been published at the time of the IARC evaluation (Aydin et al.,

2011), while our systematic review includes two additional articles: a small UK pilot study (Feltbower et al., 2014), and the large multicentre Mobi-Kids study (Castano-Vinyals et al., 2022).

A few new studies were also available for RF-exposure from environmental fixed-site transmitters investigating risks of childhood leukaemia and paediatric brain tumours: one case-control study (Li et al., 2012), and the only cohort study ever performed on the topic (Hauri et al., 2014). Compared to the IARC evaluation, only one (but important) additional study of glioma in relation to occupational RF-exposure was available to us: the large INTEROCC multicentre case-control study (Vila et al., 2018).

At the time of the IARC assessment, several time-trend studies of brain cancer or other tumours in the head region had been conducted; however, the 13 simulation studies included in our systematic review were all published since 2012 onwards.

Compared to the IARC assessment of the epidemiological studies, our systematic review was based on stricter inclusion criteria regarding:

- The measure of outcome occurrence (we did not include mortality-based case-control studies);
- The exposure metrics (we selected those deemed more reliable based on findings from pertinent exposure validation studies).

Unlike IARC, we did not review analyses of tumour side in relation to mobile phone use. This can be considered a limitation. The underlying rationale was that most of these analyses were available from case-control studies, and prone to recall bias. One Interphone case-only study of glioma, published after the IARC evaluation, showed no differences in distances to the closest ear between regular users and non-users when only imaging data (and no self-reported information) were relied upon [(Grell et al., 2016), Fig. 3]. In the available cohort studies (immune to recall bias) no increased risks of glioma in the temporal and parietal lobes, located closest to the ear (Frei et al., 2011; Schuz et al., 2022), were observed.

While the IARC performed a hazard assessment, based on an extensive review of relevant human, animal, and mechanistic studies available at that time, we conducted a systematic review of epidemiological studies, and evaluated the certainty of this line of evidence only.

In terms of other features, we performed formal risk of bias and confidence in evidence assessments using the OHAT approach, while the IARC followed the agency's own method described in the Preamble of the Monograph 102 (IARC, 2013). In our certainty of evidence assessment, we accounted for the study summary risk of bias. Although we have identified studies with increased RR for long-term mobile phone use, almost all of them were tier-2 studies, and we trusted this data much less than findings from the tier-1 studies (none of which showed increased risk estimates).

5.2. Limitations in the evidence

We believe that the study identification was complete, with little evidence that we missed major investigations. The funnel plots and the Egger tests did not detect publication bias. Moreover, we identified seven relevant conference abstracts (excluded, due the publication type), and only one of them (Bozinovic and Randjelovic, 2011) was apparently never published; it was a small hospital-based case-control study (including 113 glioma cases, 51 meningioma cases, 22 acoustic neuroma cases, and 250 controls), where no exposure-outcome associations were observed.

In the RoB assessment performed at the individual study level, the most critical issue was exposure characterization, followed by susceptibility to selection bias. Outcome assessment and statistical methods were considered at low risk of bias in almost all studies.

The reviewed bodies of evidence are likely affected by common limitations of epidemiological studies. Given the low incidence rates of all investigated neoplasms, the large majority of studies was of case-

control design, with retrospective exposure assessment based on self-reported information, inherently susceptible to any types of information bias (random misclassification, systematic errors, and differential errors), and to various sources of selection bias. Most articles discuss such drawbacks in detail, and some studies also estimated the impact of exposure measurement errors, and differential participation rates on the study findings through side validation studies.

The original analyses by lifetime intensity of mobile phone use, in terms of cumulative call time and cumulative number of calls, were presented for categories varying widely across the available epidemiological studies. This hampered the preliminary standardization of results required to perform meaningful meta-analyses of findings from the published categorical analyses. For this reason, for mobile phone cumulative call time and cumulative number of calls, we performed dose–response meta-analyses (a statistical method developed to deal with such a problem).

Another exposure metric commonly used in studies of mobile phone use and risk of CNS tumours is the preferred side of the head for mobile phone use assessed retrospectively through self-reports, which is affected by substantial misclassification and recall bias. Due to such a poor validity, self-reported laterality of mobile phone use was not included among the exposure metrics and contrasts examined in our systematic review.

Inadequate adjustment for confounding variables may be an additional limitation. Most studies controlled for critical confounders (age, sex), but few studies had detailed and accurate information on socioeconomic status, and exposure to occupational and lifestyle risk factors. However, residual confounding may not be a major issue because, except ionizing radiation, no strong risk factors for the investigated neoplasms are known. For further details on potential critical confounders see [Annex 2](#), § III.1, pp. 30–33. Uncontrolled confounding was a major concern only in the occupational study subset.

5.3. Limitations in the review process

Regarding the assessment of publication bias, we note that interpretation of funnel plot and Egger's test was challenging, as it is difficult to identify whether an association between study size and reported exposure/treatment effect is due to true heterogeneity, biases in individual studies, selective reporting, publication bias, or a combination of these ([Hartwig et al., 2020](#); [Sterne et al., 2011](#)).

The scientific literature relevant to the planned systematic review spanned four decades. Recency of publication is likely to be a strong determinant of both the quality of reporting, and the possibility to obtain unpublished information. For early studies, we expected the chance of obtaining missing data to be low for substantive reasons, regardless of the number of contact attempts. Relevant information was missing in several articles by one particular research team ([Hardell et al., 2005](#); [Hardell et al., 2006](#); [Hardell et al., 2004](#); [Hardell et al., 2002a](#); [Hardell et al., 2002b](#)). The missing data consisted of key-study features, such as number of exposed cases and controls, details on the control selection procedures, response rates among controls (overall, and by reason) and other important pieces of information. Although we made two subsequent attempts to obtain additional information for these studies, we were not provided with the requested data. We also asked for the number of cases exposed to cordless phones not reported in two articles from the Swedish Interphone study ([Lonn et al., 2004](#); [Lonn et al., 2005](#)), but the raw data were no longer available since it has been almost twenty years after their publication.

Treatment of multiple articles of the same study is a neglected quality item of systematic reviews ([Hennessy and Johnson, 2020](#)). Multiple publication bias occurs because of the increasing likelihood of a study being identified and included in a meta-analysis if its results are published more than once. When studies with shared populations are included in a meta-analysis, multiple counting of the same individual data will result in biased meta-risk estimates (“study aggregation” bias).

Our predefined inclusion strategy and analysis plan were aimed at maximizing the size of the available dataset while avoiding multiple publication and study aggregation biases.

We share the opinion that the a-priori downgrading of human observational studies is the most challenging feature of evidence assessment methods adapted from clinical epidemiology, because the cohort or case-control designs may be the only feasible or ethical option to provide evidence on environmental health hazards ([Arroyave et al., 2021](#); [Krewski et al., 2022](#); [Steenland et al., 2020](#)).

Finally, the finalization of the current paper was a lengthy process (spanning 4 years, from the protocol drafting to the publication of results). A drawback common to this and other systematic reviews, is the risk of becoming obsolete already before being published.

Our conclusions would have been further strengthened if we had included the aetiological studies published after the end-date of our literature searches (see § 6.3. below).

In the first analyses of cancer risk in the COSMOS prospective cohort study, including over 260,000 participants, no increased risks of intracranial tumours (glioma, meningioma, or acoustic neuroma) with increasing cumulative call time were observed ([Feychting et al., 2024](#)). The exposure assessment in COSMOS was based on information reported at baseline (prior to case diagnosis/ascertainment) and combined with operator data, therefore immune to recall bias. Furthermore, there was a consistent lack of association between mobile phone use and glioma risk at TSS of 10+ years in the meta-analysis of data from COSMOS and previous cohort studies, with a mRR of 0.94 (95 % CI = 0.84–1.04), based on 764 exposed cases [([Feychting et al., 2024](#)), [Supplemental Table S9](#)]. Due to the still short follow-up period (median 7.2 years) and the low incidence rates of CNS neoplasms, relatively few cases (especially of acoustic neuroma) were available for the first analyses of cancer risk in COSMOS; that notwithstanding, the study is very informative, because about one third of participants had started mobile phone use \geq 15 years before baseline ([Feychting et al., 2024](#)).

Furthermore, two additional studies (both based on data from the UK Biobank cohort) did not find associations between mobile phone use and risk of benign salivary gland tumours ([Gao et al., 2024](#)) or brain/CNS cancer ([Zhang et al., 2024](#)).

It is also worth noting that a recent bias simulation study, based on the Interphone glioma case-control study, showed that the larger variance in exposure recall errors among cases than among controls, combined with the control participation bias, fully explained the J shaped exposure–response relationship observed in the analyses by cumulative call time, under the null hypothesis ([Bouaoun et al., 2024](#)).

5.4. Implications of practice and policy

In the largest and most informative line of evidence reviewed (SR-A: mobile phone use and risk of CNS and salivary gland tumours), we did not observe an adverse effect of the exposure on the investigated outcomes, neither overall, nor among long-term (10+ years) or with increasing CNC or CCT. It is also worth noting that most participants in the reviewed studies had used mobile phones operating on 1G-2G networks, and mobile phones of newer technology (3G-4G) have substantially lower average output power ([Iyare et al., 2021](#); [van Wel et al., 2021](#)). Thus, notwithstanding the intrinsic limitations of the reviewed body of evidence, the exposure from mobile phones evaluated in the included studies is presumed to have been below the exposure limits of the current international RF exposure guidelines ([ICNIRP, 2020a](#)). It is important to note however that the purpose of this systematic review was not to investigate the validity of the ICNIRP guidelines.

5.5. Implications for research

The exposure assessment is the most critical issue in the body of evidence examined in this systematic review. Substantial improvements have been made in the COSMOS multicentre cohort study ([Reedijk et al.,](#)

2023; Reedijk et al., 2024); as previously mentioned, the first results on risks of CNS tumours among over 250,000 participants with a long mobile phone use history already at baseline, and an average follow-up of about 7 years, have just been published (Feychting et al., 2024), and additional valuable information will be provided in the future. As it is unlikely that similar improvements may be introduced in studies relying on retrospective self-reported exposure information, further case-control studies on this topic are not recommended. Additional prospective cohort studies, similar to the COSMOS study, that pay particular attention to the assessment of exposure to assist in future dose–response analyses, have been recommended (ARPANSA, 2017; SCENIHR, 2015). Given that wireless communications have only recently started to use RF frequencies above 6 GHz there are no epidemiological studies investigating 5G mobile networks directly as yet, but it is envisaged that future prospective cohort studies should cover this and other future planned technologies.

Possible risk of bias, and the expected impact of individual and competing distortions on the study findings, remains an issue in epidemiological studies investigating RF-EMF and cancer. Well-designed side validation studies should be planned in any new epidemiological study (Fox and Lash, 2017; Lash and Ahern, 2012; Lash et al., 2009; Lash et al., 2016), and this is a high-priority issue for those investigating the exposure-outcome associations examined in the current review. Multiple bias simulation studies, such as that performed using Interphone data (Bouaoun et al., 2024), may be valuable contributions to the interpretation of the epidemiological evidence from previous aetiological studies.

6. Other information

6.1. Registration and protocol

The protocol has been registered in PROSPERO (CRD42021236798), and published [(Lagorio et al., 2021), DOI <https://doi.org/10.1016/j.envint.2021.106828>].

6.2. Amendments to the protocol

There were seven amendments to the published protocol (Lagorio et al., 2021):

1. Instead of updating the literature searches on all main databases (Medline, Embase and EMF-Portal), we carried out periodic searches of relevant aetiological studies on EMF-Portal only, because the precision [1-(excluded record / total retrieved)] of this topic-specific literature database was much greater than that of the other two sources (0.34 vs 0.05 for Medline, and 0.04 for Embase).
2. We assessed the risk of bias (RoB) using paper forms, and Excel to produce the related heat maps, because the envisaged management through the HAWK platform (Shapiro et al., 2018) proved unfeasible due to the complexity of our tailored question–answer forms.
3. For homogenous datasets (in terms of outcome, subjects' lifestage, and exposure type/metric), we did set a minimum size requirement for amenability to a meta-analysis (at least 3 independent measures of effect). Following on from this we did not provide a confidence in evidence rating where the evidence consisted of less than three studies. Moreover, contrary to what was envisaged, we did not calculate the confidence intervals of the I^2 statistics using the Stata heterogi module, because the I^2 statistic is considered more a descriptive measure of heterogeneity, rather than a quantity on which to make statistical inference, such as a confidence interval.
4. To assess possible increasing trend in risks of critical outcomes with increasing TSS use of mobile phones, we performed subgroup meta-analyses with formal test of differences between TSS categories (<5, 5–9, and 10+ years), because the planned meta-regression provided not easily interpretable results (see [Annex 5 – Tables S11](#))

5. We decided *post-hoc* to perform leave-one-out meta-analyses of glioma, meningioma, and acoustic neuroma risks among long-term users of mobile phones. In addition, as we did identify one influential study in the leave-one-out meta-analysis of glioma, we repeated the main meta-analyses of glioma risk in relation to Ever vs Never mobile phone use and by TSS after excluding the “outlier” study.
6. The statements to convey findings from our systematic review were formulated in accordance with the wording suggested by the GRADE guidelines 26 (Santesso et al., 2020).
7. In place of the sensitivity analyses restricted to best quality studies (unfeasible due to lack of tier-3 studies), we performed subgroup meta-analyses stratified on RoB-tier of glioma and acoustic neuroma measures of effect for long-term use of mobile phones.

6.3. New relevant studies issued after the literature search end date

At the last selective monitoring of EMF-Portal, performed on 17 May 2024, we identified the following relevant articles, potentially or definitely eligible for inclusion in our systematic review:

1. Aetiological studies (meeting our inclusion criteria)
 - Mobile phone use and brain tumour risk – COSMOS, a prospective cohort study (Feychting et al., 2024).
 - Mobile Phone Use and Risks of Overall and 25 Site-Specific Cancers: A Prospective Study from the UK Biobank Study (Zhang et al., 2024).
 - Impact of Radiofrequency Exposure from Mobile Phones on the Risk of Developing Brain Tumors in Korean and Japanese Adolescents: A MOBI-Kids Case-Control Study (Kojimahara et al., 2024).
 - Modifiable factors for benign salivary gland neoplasms: A Mendelian randomization study (Gao et al., 2024).
2. Complementary evidence – RF dose modelling (meeting our inclusion criteria)
 - Modelling of daily radiofrequency electromagnetic field dose for a prospective adolescent cohort (Eeftens et al., 2023).
 - Dosimetric assessment in the brain for downlink EMF exposure in Korean mobile communication networks (Lee and Choi, 2023).
3. Complementary evidence – Time trend and simulation studies
 - Changes in incidence trends of meningioma in Finland, 1990–2017: analysis of Finnish Cancer Registry data (Ekqvist et al., 2023).
 - Incidence and Mortality of Malignant Brain Tumors after 20 Years of Mobile Use (Uddin et al., 2023).
4. Complementary evidence – Exposure assessment (not meeting our inclusion criteria, but very relevant because to our knowledge it is the first personal measurement survey in the workplace)
 - Personal exposure to radiofrequency electromagnetic fields in various occupations in Spain and France (Turuban et al., 2023).
5. Complementary evidence – Multiple bias modelling (meeting our inclusion criteria)
 - Effects of recall and selection biases on modelling cancer risk from mobile phone use: Results from a case-control simulation study (Bouaoun et al., 2024).

6.4. Support

This project was commissioned and partially funded by the World Health Organization (WHO), and this review was partially funded by the WHO radioprotection programme. Co-financing was provided by the New Zealand Ministry of Health; the Istituto Superiore di Sanità in its capacity as a WHO Collaborating Centre for Radiation and Health; and ARPANSA as a WHO Collaborating Centre for Radiation Protection.

7. Availability of other material

Data, analytic codes, or other materials will be made available upon request addressed to the corresponding author (ken.karipidis@arpana.gov.au), specifying the intended use, and provided that the request is approved by the co-leaders (SL and MB) along with the other team members.

CRedit authorship contribution statement

Ken Karipidis: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition. **Dan Baaken:** Writing – review & editing, Project administration, Investigation, Data curation. **Tom Loney:** Writing – original draft, Methodology, Investigation. **Maria Blettner:** Writing – original draft, Methodology, Conceptualization. **Chris Brzozek:** Resources. **Mark Elwood:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Clement Narh:** Writing – review & editing, Investigation. **Nicola Orsini:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Martin Rösli:** Writing – review & editing, Methodology, Conceptualization. **Marilia Silva Paulo:** Writing – review & editing, Investigation, Data curation. **Susanna Lagorio:** Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ken Karipidis as part of his employment is involved in the provision of advice to the Australian Commonwealth Government, Australian States and Territories and the general public on the risks and health effects of exposure to ionising and non-ionising radiation. He is also a member of the International Commission on Non-Ionizing Radiation Protection where he contributes in the development and dissemination of science-based advice on limiting exposure to non-ionizing radiation.

Mark Elwood has given expert advice on topics in electromagnetic fields and health, and on the objective interpretation of epidemiological and other scientific information, over many years to individuals and groups, including government ministries, environmental regulators, community groups, commercial organisations, and formal inquiries by government and professional groups including parliamentary and legal proceedings. Some of this work has been financially supported, by universities, health care organisations, research bodies, or by government, professional or commercial groups. Some work has been reported ‘blind’, with the client being unidentified.

Susanna Lagorio was principal investigator (April 2019 – March 2020) of the research project “BRiC 2018/06 - Systematic reviews of exposure to radiofrequency fields and cancer”, supported by the Italian Workers’ Compensation Authority, a public no-profit entity (grant code I85B19000120005). Her employment duties involved provision of advice on health hazards from exposure to RF-EMF to the Italian Ministry of Health and Higher Health Council (she retired on August 1st, 2023).

Martin Rösli’s research is entirely funded by public entities or not for profit foundations. He has served as advisor on potential health effects of exposure to non-ionizing radiation to several national and international public advisory and research steering groups, including the World Health Organization, the International Agency for Research on Cancer, the International Commission on Non-Ionizing Radiation Protection, the Swiss Government (member of the working group “Mobile phone and radiation” and chair of the expert group BERENIS), the German Radiation Protection Commission (member of the committee Non-ionizing Radiation (A6) and member of the working group 5G (A630)) and the Independent Expert Group of the Swedish Radiation Safety Authority. From 2011 to 2018, M.R. was an unpaid member of the

foundation board of the Swiss Research Foundation for Electricity and Mobile Communication, a non-profit research foundation at ETH Zurich. Neither industry nor nongovernmental organizations are represented on the scientific board of the foundation.

Chris Brzozek as part of his employment is involved in the provision of advice to the Australian Commonwealth Government, Australian States and Territories and the general public on the risks and health effects of exposure to ionising and non-ionising radiation.

The other authors declare that they have no known conflicts of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108983>.

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