

Mobile phone use and risk of brain tumours: a systematic review of association between study quality, source of funding, and research outcomes

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Abstract Mobile phones emit electromagnetic radiations that are classified as possibly carcinogenic to humans. Evidence for increased risk for brain tumours accumulated in parallel by epidemiologic investigations remains controversial. This paper aims to investigate whether methodological quality of studies and source of funding can explain the variation in results. PubMed and Cochrane CENTRAL searches were conducted from 1966 to December 2016, which was supplemented with relevant articles identified in the references. Twenty-two case control studies were included for systematic review. Meta-analysis of 14 case-control studies showed practically no increase in risk of brain tumour [OR 1.03 (95% CI 0.92–1.14)]. However, for mobile phone use of 10 years or longer (or >1640 h), the overall result of the meta-analysis showed a significant 1.33

times increase in risk. The summary estimate of government funded as well as phone industry funded studies showed 1.07 times increase in odds which was not significant, while mixed funded studies did not show any increase in risk of brain tumour. Metaregression analysis indicated that the association was significantly associated with methodological study quality ($p < 0.019$, 95% CI 0.009–0.09). Relationship between source of funding and log OR for each study was not statistically significant ($p < 0.32$, 95% CI 0.036–0.010). We found evidence linking mobile phone use and risk of brain tumours especially in long-term users (≥ 10 years). Studies with higher quality showed a trend towards high risk of brain tumour, while lower quality showed a trend towards lower risk/protection.

Keywords Mobile phones · Risk · Brain tumour · Metaregression · Meta-analysis

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Background

Mobile phones are now an integral part of modern telecommunication. The use of mobile phones is globally widespread with high prevalence among almost all age groups in the population, posing a potential public health concern. The use of mobile phones has increased rapidly in recent years.

At the end of 2015, there were 4.7 billion unique mobile subscribers globally, equivalent to 63% of the world's population. By 2020, almost three-quarters of the global population will have a mobile subscription, with around 1 billion new subscribers added over the period [1].

Mobile phones emit electromagnetic energy waves, which are classified as possibly carcinogenic to humans by the International Agency for Research on Cancer [2]. This has raised concern of health risks, primarily an increased risk

for brain tumours, since the brain is the target organ for radiation exposure during mobile phone calls.

Several studies have reported the relationships between the use of mobile phones and malignant or benign tumours of brain [3–16], head, and neck [9, 17–19] non-Hodgkin's lymphoma [20, 21] and testicular cancer [22, 23]. An increased risk of brain tumours especially was evident in few studies [3, 6–8, 17, 24, 25], whereas others have failed to find such an association [4, 5, 9, 11, 12, 14, 15, 26]. While some studies have shown possible increased odds of brain tumours in mobile phone users for a duration longer than 10 years or >1640 h [6, 8, 15, 25, 27, 28], others have failed to find such an association. Even many cohort studies found no evidence for the association among short-term or long-term users [29–32]. The results of various studies on the possible association between mobile phone use and brain tumour have been conflicting.

Some reports have attempted to explore the reasons for discrepant results across various studies, and suggest that source of funding and quality of studies explain the discrepancy, at least in part [33–35]. Several meta-analyses have appeared in the literature [34–38], and few have reported no association or slightly increased risk [36–39], whereas others found possible evidence linking mobile phone use to an increased risk of tumours [33–35]. No meta-analysis until date has explored the association of methodological quality and funding source with research outcome.

Given the large number of mobile phone users, it is important to investigate reasons for discrepant results across various studies that range from lack of standardization, biases, and errors in studies population characteristics, funding, and quality of studies [33–35]. It is, therefore, vital to understand the reasons of the conflicting data. Our aim was to investigate whether methodological quality of study (risk of bias) and/or sources of funding explain the inconsistencies in the results of the reported studies in this updated meta-analysis.

Methods

Search strategy

PubMed and Cochrane CENTRAL database were comprehensively searched from 1966 to December 2016, to identify all relevant studies. The following keywords were applied: 'mobile phones', 'cell phones', and 'brain tumours'. Manual searches of the reference lists of retrieved articles and pertinent reviews were also conducted. No language restrictions were imposed.

Criteria for considering studies

Inclusion criteria

Study design: Case-control investigated the associations between the use of mobile phone and brain tumours, reported outcome measures with odds ratios and 95% CIs, or values in cells of a 2 × 2 table (from which odds ratios could be calculated).

Exclusion criteria

Where editorials, letters, news, reviews, expert opinions, case report, and study without original data, shared identical population, were included totally or partially in another article.

If data were duplicated or shared in more than one study, the study published later or the more comprehensive report was included in the analysis.

The protocol for selection of relevant studies and data collection has been explained in Supplementary Appendix I.

Assessment of funding source

The source of funding [40] of the studies was categorized as follows:

1. Government funded: if the funding source was:
 - (a) A national, provincial, or regional government body.
 - (b) Tax payers of a country.
 - (c) Foundation/philanthropists, for example, Orebro Cancer Fund.
2. Industry funded: if the funding source was a company manufacturing/selling mobile phones, either partially or fully.
3. Mixed funded: Studies with funding from phone industry, government, the International Union against Cancer (UICC), and Mobile Manufacturers Forum & GSM Association were categorized as mixed funded studies.

The details of the funding sources have been enlisted in Supplementary Table I and Table II and Supplementary Appendices II and IV.

Assessment of methodological quality

The quality of studies was assessed using the scores proposed by modified Newcastle–Ottawa Quality Assessment Scale (NOS) [41] (Supplementary Table III).

Statistical analyses

The RevMan 5.2 software was used for data treatment and statistical analysis. Measure of association used was Odds Ratio. The effect sizes and 95% CIs were calculated to test the results of different studies. Random-effects model was used to calculate the summary odds ratio. The heterogeneity among studies was evaluated by the Chi-square test, tau-squared, and *I*-squared statistics. Studies included in the meta-analysis fall into five data streams which have been explained in Supplementary Appendix ID. These data were used to conduct different types of meta-analyses. Metaregression was also performed to investigate heterogeneity. Odds ratios and 95% CIs were calculated using the study level Log OR and the Standard Error (SE) of the estimate by constructing univariate random-effects (RE) metaregression model in STATA 13.0 using the *metareg* command. A plot of ORs was done against NOS Scores to determine if there was a linear relationship between methodological quality of the studies and their results. Similar plot was done to explore relationship between source of funding and study results. Both the analysis were done separately for 'if ever use of mobile phone' and 'mobile phone use for 10 years or more'.

Results

The flowchart for selection of relevant studies is explained in Fig. 1.

Characteristics of studies included in the final analysis: In the 22 case–control studies, a total of 48,452 participants (17,321 patient cases and 31,131 controls) were identified, with the mean age of 46.65 years (range 18–90 years). Data for ipsilateral use and temporal lobe location could not be retrieved from the papers. However, data for long-term use of mobile phones (more than 10 years) were extracted from 12 studies out of 22 studies (Tables 1, 2).

Assessment of methodological quality

The quality scores of studies ranged from 8 to 5; 8 ($n = 1$); 7 ($n = 6$); 6 ($n = 11$); and 5 ($n = 4$) (Supplementary Table IV). Only seven studies gave the definition of controls [4, 5, 7, 9, 17, 25, 42]. 17 studies had controls matched for two potential confounders. Blinding during ascertainment of exposure was done in only four studies, all conducted by Hardell et al. Two studies [3, 8] had the same non-response rate for the two groups.

Meta-analysis: mobile phone use and risk of brain tumour

Overall use of mobile phones and risk of brain tumour

22 case–control studies reported the results for the risk of brain tumour. Interphone study 2010 [27] and Interphone study 2011 [28] included the data from studies [7, 10–14, 26, 43] conducted in different countries which were part of Interphone Group. 8 out of 22 studies were part of Interphone study 2011 and Interphone study 2010; therefore, data from 14 studies were included in the meta-analysis and a total of 30,421 participants (12,426 cases and 19,334 controls) were identified.

Data from 14 case control studies were included in for meta-analysis. We identified a total of 30,421 participants (12,426 cases and 19,334 controls). In Fig. 2, the study with quality sum of 8 shows that there is 1.64 times increase in odds of having brain tumour with mobile phone use. In the hierarchical meta-analysis of studies with progressively lower quality scores of 7, 6, and 5, the odds ratio progressively decreased to 1.08, 0.98, and 0.81, respectively. Therefore, the overall result [OR 1.03 (95% CI 0.92–1.14)] shows a statistically insignificant increase in odds of risk of brain tumour.

Mobile phone use of 10 years or longer and risk of brain tumour

12 out of the 22 case control studies reported the results for risk of brain tumours with mobile phone use of more than or equal to 10 years. 5 out of these 12 studies were part of Interphone study 2011 and Interphone study 2010; therefore, data from seven studies were included in the meta-analysis and a total of 17,972 participants (7583 cases and 10,389 controls) were identified.

In Fig. 3, the study with quality sum of eight shows that there is 2.58 times increase in odds of having brain tumour with mobile phone use of more than 10 years duration. In the meta-analysis, studies with progressively lower quality score of 7 and 6 show a progressively lower risk of brain tumour with odds ratio 1.44 and 1.13, respectively. However, the overall result of the meta-analysis shows a significant 1.33 times increase in odds of having risk of brain tumours with mobile phone use.

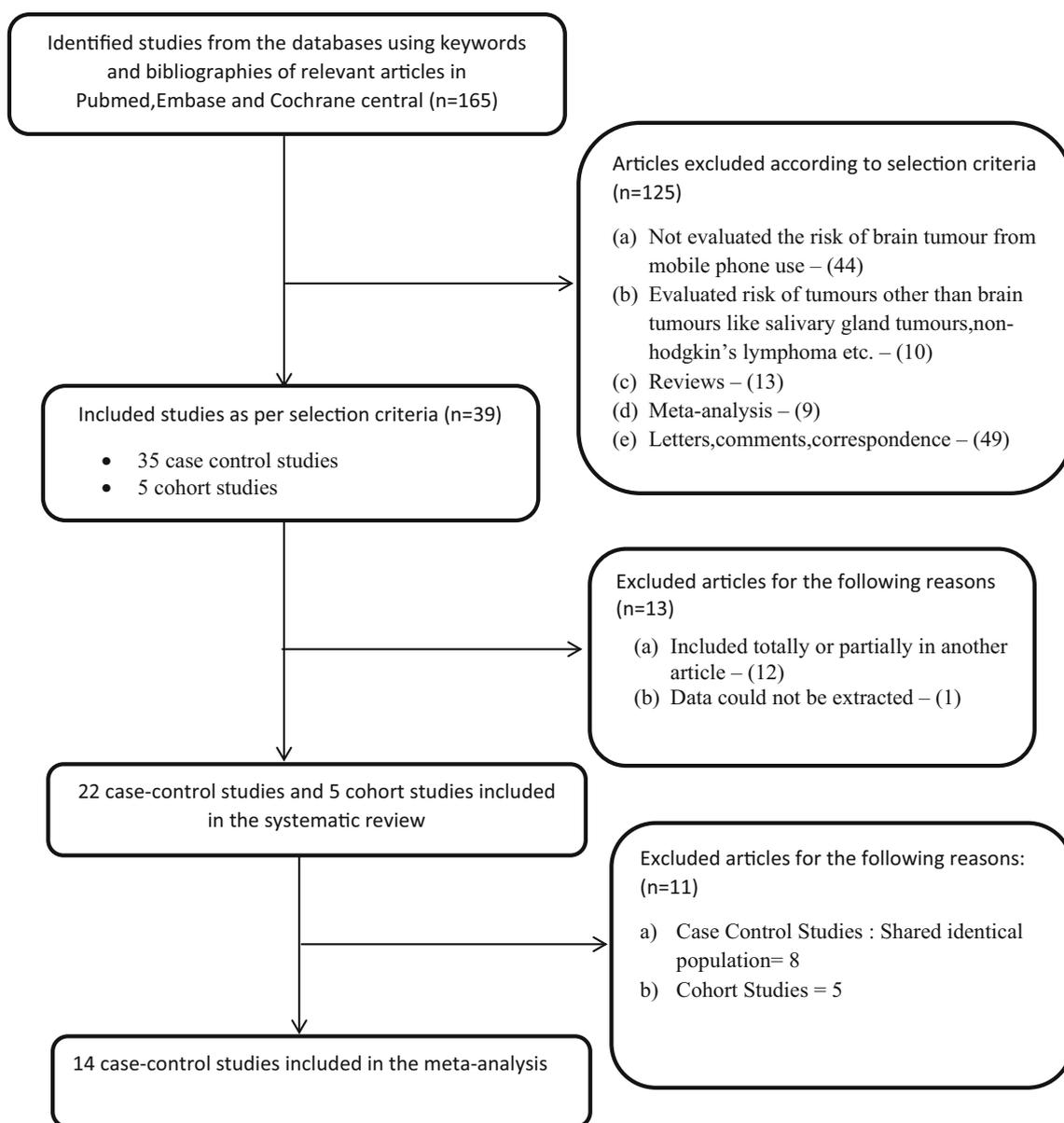


Fig. 1 Selection of relevant studies

Meta-analysis: on the basis of funding source

The studies of Government Funded, Phone Industry Funded, and Mixed Funded were 10, 3, and 7 in number, respectively. A total of 20 studies were included in for the analysis based on funding sources. Interphone 2010 and Interphone 2011 included data from various studies with different funding sources; therefore, both these studies were not included in this analysis; instead, data from individual studies which were part of Interphone Group were included. The studies were divided into different categories as per their funding sources (Supplementary Appendix II and Supplementary Table III).

Mobile phone use and risk of brain tumour

Stratified meta-analysis according to sources of funding shows divergent results (Supplementary Figures I, II, and III). While summary estimate of government funded studies shows statistically non-significant 7% increase in odds of risk brain tumour with mobile phone use, phone industry funded studies show non-significant 7% increase in odds and mixed funded studies show significant 10% decrease in odds of brain tumour with mobile phone use (the results are not significant enough to explain the association between the funding source of study and its research outcome). The following observations can also be made:

Table 1 Characteristics of included case–control studies

S. no.	Study ID (sorted by year of publication)	Country (type of funding)	Age range (years)	Type of tumour investigated	Participation rate		Overall results (OR, 95% CI) (if ever used)	Overall results (OR, 95% CI) (>10 years use)	Comments
					Cases	Controls			
1.	Hardell [3]	Sweden (G)	20–80	M, G, AN	90%	91%	0.98 (0.69–0.41)	1.20 (0.56–2.59)	No overall increased risk of brain tumours associated with exposure to cellular phones
2.	Muscat [4]	USA (P)	18–80	G	82%	90%	0.85 (0.6–1.2)	–	Use of handheld cellular telephones is not associated with risk of brain cancer
3.	Inskip [5]	USA (M)	18+	M, G, AN	80%	NM	Gliomas 1.0 (0.7–1.4) Meningiomas 0.8 (0.5–1.2) Acoustic neuromas 0.8 (0.5–1.4)	–	The data is not sufficient to evaluate the risks among long-term, heavy users and for potentially long induction periods
4.	Auvinen [17]	Finland	20–69	M, G	NM	NM	Analogue 1.6 (1.1–2.3) Digital 0.9 (0.5–1.5)	–	Cellular phone use was not associated with brain tumours, but there was a weak association between gliomas and analogue cellular phones
5.	Hardell [16]	Sweden	20–80	M, G, AN	88%	91%	1.3 (1.02–1.6)	1.8 (1.1–2.9)	Use of analogue cellular telephones was associated with increased risk of brain tumours
6.	Warren [9]	USA	Not stated	AN	–	–	Handheld cellular telephone 0.6 (0.2–1.9) Regular cellular telephone 0.4 (0.1–2.1)	–	Regular cellular telephone use does not appear to be associated with a higher risk of brain tumour development
7.	Hardell [6]	Sweden	18–74	M, AN	89%	84%	Meningiomas Analogue 1.7 (0.97–3.0) Digital 1.3 (0.9–1.9) Cordless 1.3 (0.9–1.9) Acoustic neuromas Analogue 4.2 (1.8–10) Digital 2 (1.05–2.8) Cordless 1.5 (0.8–2.9)	Meningiomas Analogue 2.1 (1.1–4.3) Digital 1.5 (0.6–3.9) Cordless 1.9 (0.97–3.6) Acoustic neuromas Analogue 2.6 (0.9–8) Digital 0.8 (0.1–6.7) Cordless 0.3 (0.03–2.2)	The study showed an increased risk for acoustic neuromas associated with analogue phone use, regarding meningioma, a somewhat increase risk was found

Table 1 continued

S. no.	Study ID (sorted by year of publication)	Country (type of funding)	Age range (years)	Type of tumour investigated	Participation rate		Overall results (OR, 95% CI) (if ever used)	Overall results (OR, 95% CI) (>10 years use)	Comments
					Cases	Controls			
8.	Lonn [10] ^b	Sweden	20–69	G, M	Meningiomas 74%	85%	Meningiomas 0.7 (0.5–0.9)	Meningiomas 0.7 (0.3–1.6)	The data do not support the hypothesis that mobile phone use is related to an increased risk of glioma or meningioma
					Gliomas 71%	85%	Gliomas 0.8 (0.62–1.0)	Gliomas 0.9 (0.5–1.6)	
9.	Schoemaker [7] ^{a, c}	Denmark, Finland, Norway, Sweden, UK	18–69	AN	84%	61%	0.9 (0.7–1.2)	1.8 (1.1–3.1)	The study suggests that an increase in risk of brain tumour after long-term use or after a longer lag period could not be ruled out
10.	Hardell [8]	Sweden	20–80	G	88%	84%	2.6 (1.5–4.3)	3.5 (2.0–6.4)	The study showed an increased risk for malignant brain tumours associated with the use of analogue and digital cellular telephones and cord-less phones
11.	Schuz [15]	Denmark	30–69	M, G	Meningiomas 88.4%	79.6%	Meningiomas 0.84 (0.62–1.13)	Meningiomas 1.09 (0.35–3.37)	The elevated risk of glioma after 10 or more years of cellular phone use needs to be confirmed by other studies
					Gliomas 62.7%	79.6%	Gliomas 0.98 (0.75–1.29)	Gliomas 2.20 (0.94–5.11)	
12.	Takebayashi [11] ^a	Japan	30–69	AN	84.2%	52.4%	0.73 (0.43–1.23)	–	The results suggest that there is no significant increase in the risk of acoustic neuroma in association with mobile phone use
13.	Hours [12] ^a	France	30–59	M, AN, G	–	–	1.15 (0.65–2.05)	–	The results suggest the possibility of an increased risk among the heaviest users
14.	Lahkola [13] ^{b, d}	Denmark, Finland, Sweden, Norway, UK	18–69	G	60%	50%	0.78 (0.68–0.91)	0.95 (0.74–1.23)	The overall results do not indicate an increased risk of glioma in relation to mobile phone use
15.	Schlehofer [43] ^a	Germany	30–69	AN	89%	55%	0.67 (0.38–1.19)	–	Exposure to ionizing radiation or to radio frequency electromagnetic fields eg. from mobile phones, did not increase the risk of brain tumours
16.	Lahkola [14] ^b	Denmark, Finland, Norway, Sweden, UK	18–69	M	74%	50%	0.76 (0.65–0.89)	0.85 (0.57–1.26)	The result do not provide support for an association between mobile phone use and risk of meningioma

Table 1 continued

S. no.	Study ID (sorted by year of publication)	Country (type of funding)	Age range (years)	Type of tumour investigated	Participation rate		Overall results (OR, 95% CI) (if ever used)	Overall results (OR, 95% CI) (>10 years use)	Comments
					Cases	Controls			
17.	Takebayashi [26] ^b	Japan	30–69	M, G	–	51.2%	1.22 (0.63–2.37)	–	No increase in overall risk of glioma or meningioma in relation to regular mobile phone use
18.	Hardell [25]	Sweden	20–80	G	75%	67%	1.0 (0.6–1.7)	2.4 (1.4–4.1)	An increased risk for malignant brain tumours for use of mobile phones was seen. The risk increased with latency and was statistically significant in the more than 10 years latency group
19.	Interphone study group [27]	13 countries	30–59	M, G	Meningiomas 78%	64%	Gliomas 0.81 (0.70–0.95)	Gliomas 0.83 (0.61–1.14)	No increase in risk of gliomas or meningiomas with use of mobile phone
					Gliomas 53%	64%	Meningiomas 0.79 (0.68–0.91)	Meningiomas 0.89 (0.76–1.26)	
20.	Interphone Study Group (29)	13 countries	30–59	AN	82%	53%	0.85 (0.69–1.04)	0.83 (0.58–1.19)	No increased risk of acoustic neuroma with ever regular use of mobile phone or for users who began regular use 10 years or more
21.	Aydin [24]	Denmark, Sweden, Norway, Switzerland	7–19	G	83.2%	71.1%	1.36 (0.92–2.02)		Brain tumour risk was related to the time elapsed since the start of mobile phone subscriptions but was not related to the amount of use
22.	Coureau [42]	France	16 years and above	M, G	73%	45%	Gliomas 1.11 (0.82–1.50)	2.08 (1.07–4.05)	The study provides data on the relationship between mobile phone use and brain tumours. An increased risk appears among the heaviest users, often with occupational use and especially of gliomas
							Meningiomas 0.87 (0.62–1.24)		

13 countries: Australia, Canada, Denmark, Finland, France, Italy Germany, Japan, New Zealand, Sweden, Norway, UK

G gliomas, M meningiomas, AN acoustic neuromas

^a Part of data in Interphone study 2011. Not included while updating the meta-analysis

^b Not included in meta-analysis because already part of data in Interphone study 2010

^c Schoemaker et al. includes data of studies (meningiomas and acoustic neuromas) by Christensen [48], Christensen [49], Lonn [50], and Klæboe [51]

^d Lakhola et al. includes data of studies (gliomas) by Christensen [49], Hepworth [52] and Klæboe [51]

1. While six of nine government funded studies have a quality score of 7 or 8, all studies funded by phone industry and mixed sources have a score of 5 or 6.
2. Most of the government funded studies have a high-quality score of 7, and one has 8.
3. In subgroup meta-analysis on the basis of quality scores, no significant heterogeneity is seen within a

Table 2 Characteristics of included cohort studies

S. no.	Study ID (sorted by year of publication)	Country	Type of tumour investigated	Sample size	Age range (years; at first subscription)	Overall results	Comments
1.	Morgan [29]	USA	All brain cancers	195,775	–	SMR 0.53 (0.21–1.09)	The result do not support an associated between occupational radiofrequency exposure and brain cancers
2.	Johansen [30] ^a	Denmark	M, AN, G	420,095	18–70	SIR 0.95 (0.81–1.12)	The result do not support the hypothesis of an association between use of telephones and tumours of the brain
3.	Schuz [31] ^a	Denmark	M, AN, G	420,095	–	SIR brain tumours (0.97) Acoustic neuromas (0.73) >10 years 0.66 (0.44–0.95)	No evidence for an association between tumour risk and cellular telephone use among either short-term or long-term users
4.	Frei [32]	France	M, G	358,403	–	IRR >10 years Glioma 1.04 (0.85–1.26) in men 1.04 (0.56–1.95) in women Meningioma 0.90 (0.57–1.42) in men 0.93 (0.46–1.87) in women	No increased risks of tumours of the central nervous system, providing little evidence for a causal association
5.	Schuz [53] ^a	Denmark	AN	29,000,000	–	RRE 0.87 (0.52–1.46)	No evidence was found that mobile phone use is related to the risk of acoustic neuromas

G gliomas, M meningiomas, AN acoustic neuromas

^a Part of data in Frei 2011

group as compared to heterogeneity across different quality score groups.

4. Studies with higher quality score show a trend towards harm, while lower quality score studies show a trend towards protection.

Mobile phone use of 10 years or longer and risk of brain tumour

Stratified meta-analysis according to sources of funding shows a consistent increase in risk of brain tumour with mobile phone use of more than 10 years. While summary estimate of government funded studies shows 1.64 times increase in odds (Supplementary Figure IV), mixed funded

studies show 1.05 times increase in odds of risk of brain tumours, but the results were not statistically significant (Supplementary Figure V). The data for more than 10 years of use were not available for phone industry funded studies.

Metaregression analysis

If ever use of mobile phone

A total of 20 studies were included for random-effects metaregression. The data on a whole from INTERPHONE 2010 and INTERPHONE 2011 were not included in the analysis; instead, data from individual studies which were

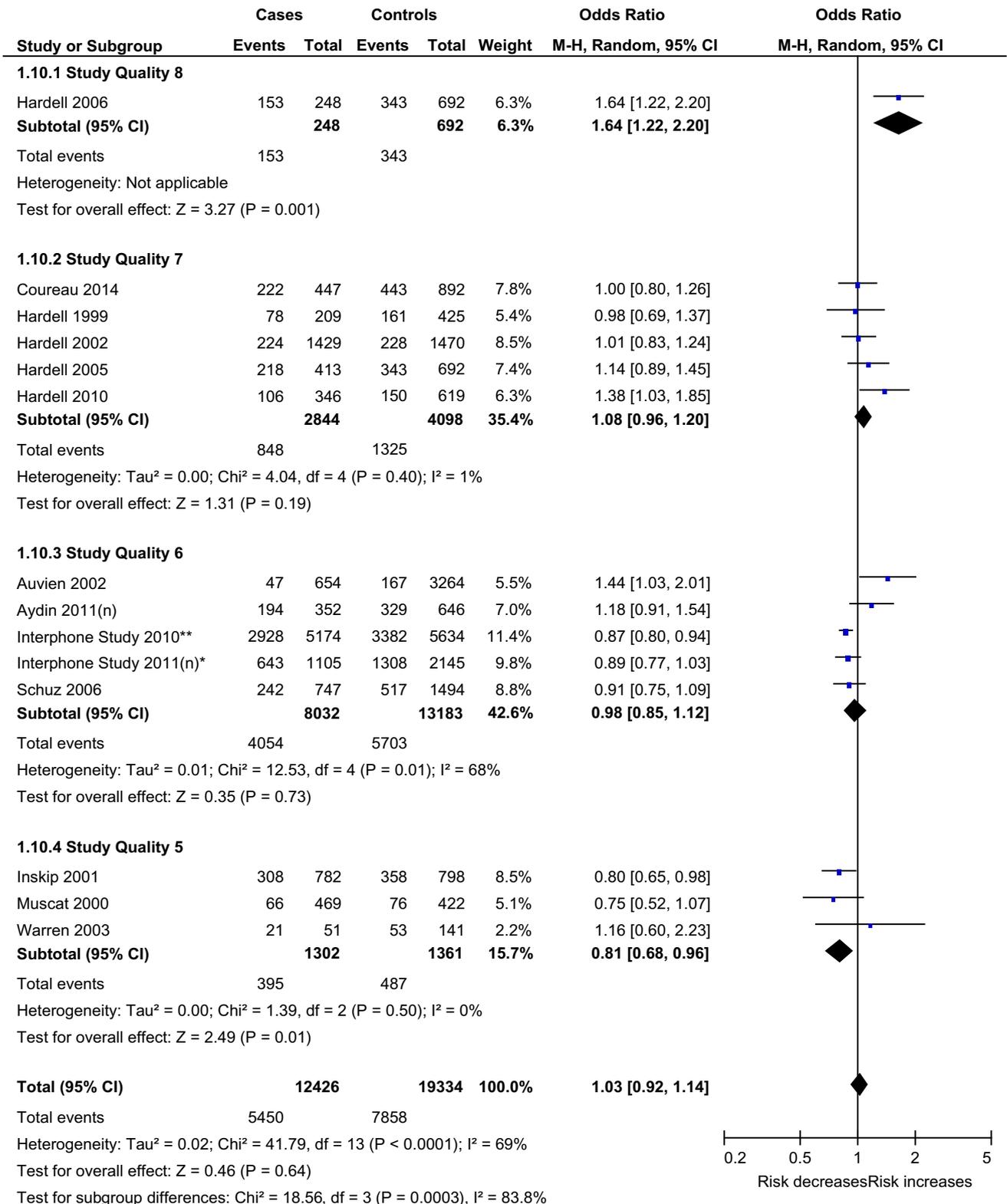


Fig. 2 Risk of brain tumour (if ever use of mobile phone). *Asterisk* includes the data of Schoemaker 2005, Takebayashi 2006, Hours 2007 (acoustic neuromas data only), and Schlehofer 2007. *Double*

asterisks includes the data of Lonn 2005, Hours 2007 (gliomas and meningiomas data only), Lakhola 2007, Lakhola 2008, and Takebayashi 2008

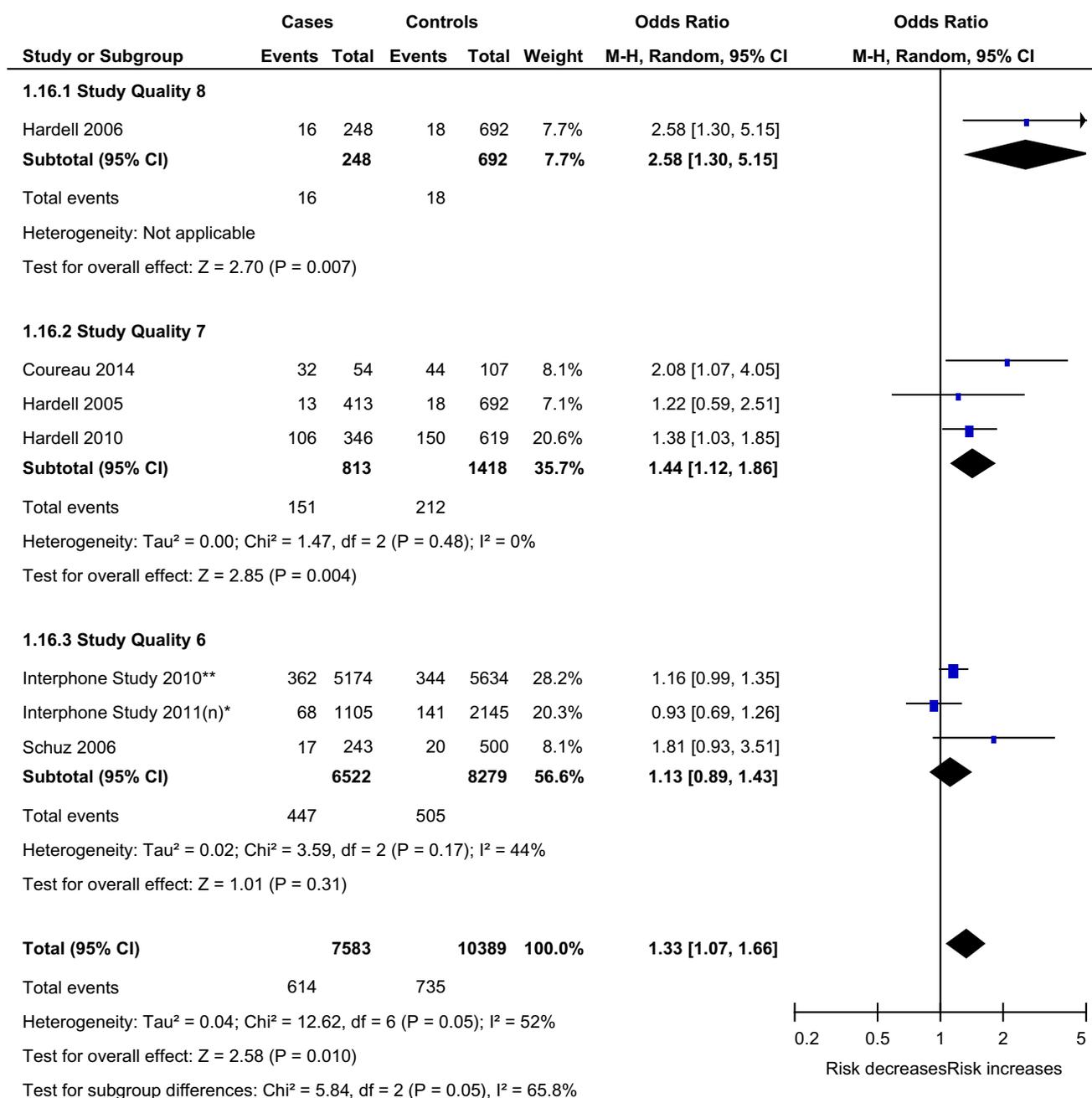


Fig. 3 Risk of brain tumours (more than or equal to 10 years). *Asterisk* includes the data of Schoemaker 2005, Takebayashi 2006, Hours 2007 (acoustic neuromas data only), and Schlehofer 2007.

Double asterisks include the data of Lonn 2005, Hours 2007 (gliomas and meningiomas data only), Lakhola 2007, Lakhola 2008, and Takebayashi 2008. (*n*) additional study

part of Interphone Group were included as different studies have different funding sources. The association between the study quality and log OR for each study showed a positive and statistically significant linear relation ($p < 0.01$, 95% CI 0.009–0.09). Relationship between source of funding and log OR for each study was not statistically significant ($p < 0.32$, 95% CI 0.036–0.010). The results are shown in Fig. 4 and Table 3a.

Mobile phone use for 10 years or more

A total of ten studies were included for random-effects metaregression, and results are shown in Fig. 4 and Table 3b. It showed a statistically insignificant relationship between log OR and source of funding ($p < 0.167$, 95% CI 0.193–0.942), as well as for log OR and study quality ($p < 0.291$, 95% CI 0.185–0.543).

Fig. 4 Metaregression analysis. **a** Relationship between study quality and log odds ratio of risk of brain tumour (if ever use of mobile phone). **b** Relationship between source of funding and log odds ratio of risk of brain tumour (if ever use of mobile phone). **c** Relationship between study quality and log odds ratio of risk of brain tumour (mobile phone use for 10 years or more). **d** Relationship between source of funding and log odds ratio of risk of brain tumour (mobile phone use for 10 years or more). *Log_{ES}* log odds ratio

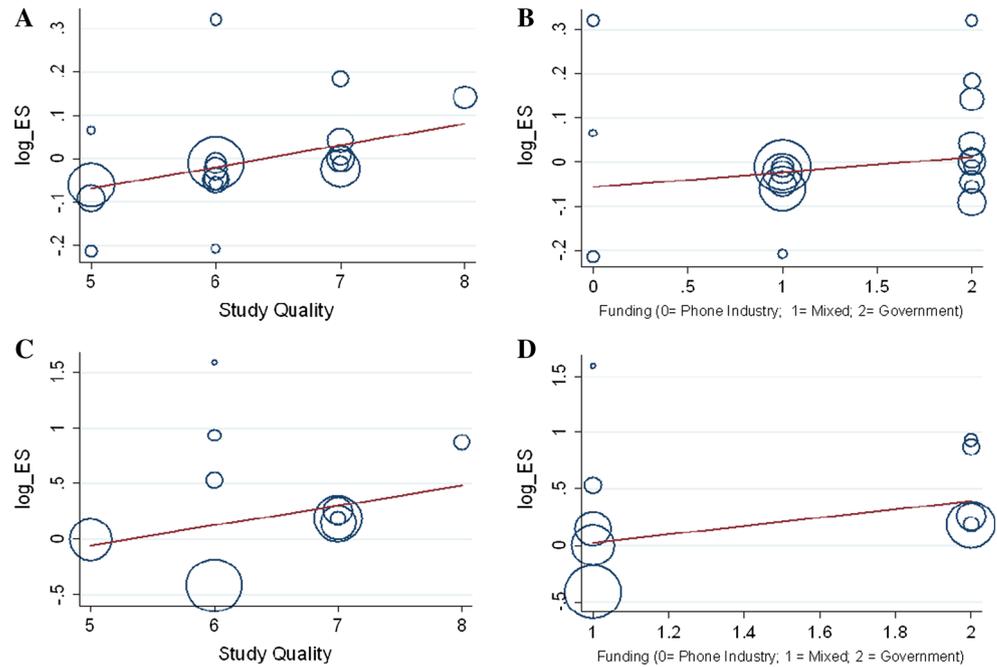


Table 3 Results for metaregression analysis

Variable	Exp(<i>b</i>)/coefficient	Standard error	<i>t</i>	<i>p</i> value	<i>p</i> > <i>t</i>	95% CI
(a) Risk of brain tumour and if ever use of mobile phone						
Funding	0.034	0.033	1.02	0.322		0.036–0.104
Study quality	0.049	0.019	2.58	0.019		0.009–0.090
(b) Risk of brain tumour and mobile phone use (use of 10 years or more)						
Funding	0.374	0.246	1.52	0.167		0.193–0.942
Study quality	0.179	0.158	1.13	0.291		0.185–0.543

Mobile phone use and risk of gliomas

14 studies gave the results for the risk of gliomas with mobile phone use. Three of these studies were part of Interphone study 2010. Therefore, 11 studies were included in the meta-analysis and a total of 16,309 (6272 cases and 10,037 controls) participants were identified.

The study with quality sum of eight showed that there is 1.64 times increase in odds of having brain tumour with mobile phone use. In the meta-analysis of studies with progressively lower quality scores of 7, 6, and 5, the odds ratio progressively decreased to 1.16, 1.07, and 0.82, respectively. Therefore, the overall result [OR 1.08 (95% CI 0.94–1.25)] showed practically no increase in odds (Supplementary Figure VI).

Mobile phone use and risk of meningiomas

For Meningiomas, results were obtained from 11 studies. Three of these were part of Interphone study 2010. A total of 11,637 participants (4401 cases and 7236 controls) were identified. The analysis gave a decreased risk for Meningiomas (odds ratio 0.84; 95% CI 0.746–0.93) (Supplementary Figure VII).

Mobile phone use and risk of acoustic neuromas

Regarding acoustic neuromas, ten studies were recognized. Four of these studies were part of Interphone study 2011. A total of 5455 participants (1508 cases and 3947 controls) were included in the meta-analysis of six studies. Results of the meta-analysis show no increase in odds of having acoustic neuroma with mobile phone use (odds ratio 1.04, 95% CI 0.82–1.33) (Supplementary Figure VIII). There was acceptable heterogeneity (Tau squared 0.03, *I* squared 38%)

Overall assessment of our results was done using Bradford–Hill's criteria [44], which has been mentioned in Supplementary Appendix IIIa.

Discussion

The meta-analysis of case–control studies found that there is a significant positive correlation between study quality and risk of brain tumour associated with use of mobile phones. Higher quality studies show a statistically significant association between mobile phone use and risk of brain tumour, but adding poor quality studies leads to loss

of significance. We found that Government funded studies were generally of higher methodological quality than phone industry funded or mixed funded.

However, one qualitatively similar finding in both government funded as well as mixed funded studies is that long-term use (>10 years or >1640 h) is associated with increased risk of brain tumour.

Our analysis based on study quality also explains why the results of various meta-analyses differ in their conclusions [34–39, 45]. Meta-analyses that did not take into account the methodological quality of the studies showed no overall increase in risk of brain tumours [39, 45], whereas those which took this into consideration showed results similar to that of our meta-analysis [34, 35].

The issue of associations between mobile phone use and risk of brain tumour is beset with controversies and our paper, as well as those of Myung et al. [35], Hardell et al. [34], and Levis et al. [33] provide insights into the underlying reasons for the controversy and help deduce some findings which are reasonable with the currently available body of data. There should be no controversy that methodological quality is important and poor quality means high risk of bias.

Biases (participation bias, recall bias, and lack of blinding) compromise our ability to detect an association, if present. Our data and that of Myung et al. show that poor quality studies have varying but significant biases that tend to pull the odds ratio in favor of protection against brain tumour with mobile phone use—a biologically implausible finding. High-quality studies tend to control these biases and show the finding of increased risk which is biologically plausible.

Levis et al. [33] stated that blind protocols, free from errors, bias, and financial conditioning factors give positive results. Similarly, Valentini et al. [46] identified that the heterogeneity of results may be due to striking differences in methodology and interpretation criteria along with a sponsorship bias, which may seriously impair correct understanding of the actual phenomenon. However, our analysis for effect of funding sources on the study outcome did not reveal any significant association.

Future research particular care should be dedicated to both methodological and statistical control, the most relevant criteria in this research field. Establishment of an international body to harmonise and minimize these issues is warranted.

Our analysis of risk of types of tumours (gliomas, meningiomas, and acoustic neuromas) is informative, but also entails inadequacy of power as all studies do not provide the tumourwise break-up of data. It seems clear that increase in risk is only for gliomas, not meningiomas and acoustic neuromas but does not reach 0.05 level of statistical significant because of inadequate sample size.

The systematic review of Repacholi et al. [39] also showed a trend (OR 1.4) of increased risk of gliomas, though it did not reach statistical significance. The estimate was 1.4 for all gliomas without consideration of laterality or lobar location. They did not conduct analyses of laterality citing that recall bias was likely to unduly affect the results.

In view of the data presented, mobile phone use and electromagnetic radiation effects in humans are of relevance, as attested by the ad hoc WHO programme [46]. Mobile Phone-Electromagnetic Fields (MP-EMF) may influence normal brain physiology through changes in cortical excitability, and several studies have investigated on dependent variables (e.g., regional cerebral blood flow, rCBF; spectral power of electroencephalogram, EEG; evoked potentials, EP, etc) through different experimental protocols (double vs. single blind) and highly variable EMF parameters (frequency, power, distance to the electromagnetic sources, etc) [47]. Future studies should address electrophysiological and neuro-metabolic effects of MP-related EMF on neurologically intact children and adults. A precautionary approach is also recommended as widespread substantial exposure of mobile phone use could have important public health consequences.

Conclusion

In our review of the literature and meta-analysis of case-control studies, we found evidence linking mobile phone use and risk of brain tumours especially in long-term users (>10 years). We also found a significantly positive correlation between study quality and outcome in the form of risk of brain tumour associated with use of mobile phones. Higher quality studies show a statistically significant association between mobile phone use and risk of brain tumour. Even the source of funding was found to affect the quality of results produced by the studies. As mobile phone use certainly continues, our findings are pertinent to warrant application of precautionary measures aimed at reducing its adverse effects. Furthermore, well-designed studies embedded with prospective cohorts are required to provide a higher level of evidence.

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Author contributions KP supervised the study. MP and PK screened the papers on inclusion and exclusion criteria followed by data extraction. They also appraised the methodological quality of the retrieved studies. Data analysis was carried out by KP, PK, MP, and AK. Drafting of manuscript was done by KP, PK, and MP. PN, PK, and MP were involved in the formulation of tables. They were also involved in reviewing the manuscript and revising it critically for

important intellectual content. All authors read the final manuscript, and approval was given by KP.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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