Author's response to reviews

Title: Meningioma patients diagnosed 2007-2009 and the association with use of mobile and cordless phones: a case-control study

Authors:

Michael Carlberg (michaelrita@yahoo.se)
Lennart Hardell (lennart.hardell@orebroll.se)
Fredrik Söderqvist (fredrik.soderqvist@ltv.se)
Kjell Hansson Mild (kjell.hansson.mild@radfys.umu.se)

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Author's response to reviews: see over
Comments, editorial team:

As for the formatting, the title should include the study design e.g. A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study.

Now added “:a case-control study” to the title.

Please remove the email addresses after the addresses and list under the heading Email addresses as author's initials:email address e.g. JS:joe.shmoe@university.edu below the Corresponding author information.

OK – done.

For the Corresponding author information, please remove the colon and all the text after it.

OK – done.

All the text in the manuscript should be double spaced.

OK – done.

In the Abstract remove the colon and move the text below the headings.

OK – done.

Please delete the subheadings in the Discussion.

OK – done.

The first three sentences of the Conclusions need to be rephrased so that it is clear to the reader exactly what is meant. Also, the Conclusions in the Abstract need to clarify the key message from this study.

The Conclusions have now been rephrased. However, we can’t see how the Conclusions in the Abstract can be further clarified.

For the tables, all horizontal lines should be visible.

OK – done.

Please also ensure that your revised manuscript conforms to the journal style (http://www.ehjournal.net/info/instructions/). It is important that your files are correctly formatted.
Referee #1:

Minor Essential Revisions -
The Methods section of the Abstract and the Statistical Methods section both use the term "matched" or "matching variables" and then note that unconditional logistic regression and "adjustment/stratification" was used. If the matching was pairwise, then conditional logistic regression would have been preferred. If not, then the authors might use the term "frequency matching" to describe the method and justify unconditional logistic regression.

The motivation for use of unconditional logistic regression has been described in "Statistical Methods":

"This was possible since adjustment/stratification was made for the matching variables (gender, age within 5 years, and year of diagnosis)."

In "Discussion" we further explain:

"In the unconditional logistic regression analysis all controls, both to cases with malignant and benign brain tumour, were used so as to maximise the statistical power. This was possible since adjustment was made for the matching variables age, gender, and year of diagnosis."

We have now also added:

“Analysis using conditional logistic regression yielded overall for wireless phones OR = 1.1, 95% CI = 0.7-1.6 versus OR = 1.0, 95% CI = 0.7-1.5 using unconditional logistic regression (see Table 3). Similar differences were seen for the different phone types, i.e. similar estimates using both methods, although with slightly wider confidence intervals in the conditional logistic regression.”

Discretionary Revisions -
In the Strengths and Limitations section, third paragraph (p. 17), the authors comment of the response rate in controls from another study (the Interphone study). This is a tangential comparison that might be moved to the section called "Results from Other Studies" or left out altogether.

We would like to have this unchanged since it is discussed in relation to the response rate in our study.

Minor Issues not for Publication-
In the Background section, first paragraph, the term "well-demarked" should be "well-demarcated."

OK – changed.

In the section on Wireless technology, second paragraph, the phrase "very common overtaking telephones" should be "very common and are overtaking telephones. . ."
In the section on Inclusion criteria, first paragraph, the phrase "and the whole Sweden" should be "the whole of Sweden. . ."

OK – changed.

In the same paragraph, the phrase "Sweden contains of six administrative . . ." should be "Sweden contains six administrative . . ."

OK – changed.

In the Results section, final paragraph, the phrase "statistically significant per year. . ." should be "statistically significantly per year. . ."

OK – changed.

In the Strengths and limitations section, final paragraph, the word "technique" or "techniques" should be "technology" or "technologies" in referring to the changing transmission systems.

OK – changed.

In the Conclusions paragraph, the phrase "taking the long latency periods" might be clearer if it was "considering the long latency periods. . ."

OK – changed.
Referee #2:

This manuscript reports about a very important investigation that would for the first time allow a meaningful analysis of the potential association between mobile and cordless phone use and meningioma. Earlier studies were compromised by two short periods of use of these devices. Due to the long latencies of meningioma and the slow growth an effect could only be detected, if it exists, if a substantial proportion of cases have used a wireless phone for 15 years or longer. In this study more than 20% of cases had usage durations exceeding 15 years. However, there are some problems with the analysis that make it difficult to decide whether or not there is an association. Detailed comments are given below.

Page 3, second paragraph: The study by Korhonen et al. (2006) has been mentioned as indicating that sex hormones cannot fully explain the differences in incidence between males and females. However, what the study actually shows is that the hormone receptor status does not differ between male and female meningioma. The interpretation by Korhonen et al. is not in line with the evidence. Obviously, since women have higher levels of circulating estrogen this will cause a larger growth rate and consequently a higher incidence of meningioma.

OK-changed

Page 7, last paragraph: The method used for selection of controls should be described in greater detail. 1. Because cases were reported in different intervals for the regions of Sweden at which time the population register was contacted to provide controls?

All controls were recruited from the same source population as the cases as soon as the treating physician had permitted inclusion of the respective case.
Now added.

2. It is stated that cases were recruited from the same population source; does this mean that they were obtained from the same region? This should be clarified.

The whole country was used for retrieving controls (Gothenburg region excluded 2007).
Now added.

3. As it would take time to contact the physician once a case is reported, was the population registry contacted before or after eligibility of the case was established?

See above.

A table, similar to Table 1 or included in Table 1, with participation of controls should be provided with details of contacted controls and refusals (if possible also reason for refusal).

We think that this is described under Results, first paragraph and that a table would not be necessary.
There is also another issue that needs to be addressed in this section or in statistical analysis section: Since controls were selected matched to cases according to gender, age (and region?) it is stated that they were assigned year of diagnosis as cutoff for assessment of exposure. But because controls for malignant brain tumors were included in this analysis as well this is insufficiently correcting for time of diagnosis. I suggest performing a re-matching. This will consist of a selection of all suitable controls for each case (that could be more than one) and assigning all controls the same cutoff date as the case. A conditional logistic regression analysis should then be conducted with varying sizes of matched sets (which is actually no big problem).

For technical reasons, a re-matching could not be performed. We have however added a comparison with conditional logistic regression in "Discussion":

"Analysis using conditional logistic regression yielded overall for wireless phones OR = 1.1, 95% CI = 0.7-1.6 versus OR = 1.0, 95% CI = 0.7-1.5 using unconditional logistic regression (see Table 3). Similar differences were seen for the different phone types i.e. similar estimates using both methods, although with slightly wider confidence intervals in the conditional logistic regression."

Page 8, first paragraph: Please specify how many cases and controls needed to be contacted over the phone for supplementary information. Also explain how interviews were done to keep case status blinded.

Now added:

“There was no difference regarding supplementary interviews according to being a case (74 % supplemented) or a control (70 % supplemented). Adjusting for whether or not a supplementary interview was performed did not change the results of the logistic regression analysis.”

Page 8, 2nd paragraph: Has ear mostly been used during calls been inquired separately for mobile and cordless phones? Please clarify!

Now clarified: “The ear that had mostly been used during calls was assessed by separate questions for mobile and cordless phones; > 50 % of the time for one side, or equally much for both sides.”

Page 8, last paragraph: It would be interesting to specify (maybe by expanding Table 1) participating cases by diagnosis (if this is available from cancer registry).

Histopathology is presented in Table 2.

Page 9: There is a fundamental problem with the analysis related to the different type of age-incidence function for meningioma. In contrast to that for glioma, it is a power function of age. If we assume, as authors mention on page 10 (2nd paragraph), there is an effect of mobile phone use on promotion then, necessarily, the odds ratio for mobile phone use must depend on age! Of course this effect cannot be removed by including age as a covariate in the analysis. The expected odds ratio for an effect on growth rate resulting in an earlier
diagnosis is \((\text{age}+m)/\text{age}\)^b, where \(m\) is the shift in years due to earlier
diagnosis and \(b\) is the exponent of the power function (a value between 2 and 3).
For a sample with an equal number of years of mobile phone use the logistic
regression with mobile phone use as the predictor variable will result in a
parameter estimate \(\beta = b \cdot \ln(1+m/\text{age})\). Since \(m\) will be much smaller than age we
can approximate the logarithm by \(m/\text{age}\) yielding \(\beta \approx b \cdot m/\text{age}\).

Hence the effect of mobile phone use is biased depending on age. This bias
cannot be removed unless the shift parameter \(m\) is known. It can be shown that
this bias is always towards the null.

This is a theoretical discussion beyond the scope of this article and cannot be further analysed
based on our data. Adjustment for age was made in all analyses.

There is another problem related to the development of mobile phone
technology. As the figures in Table 3 demonstrate, almost all analogue phone
users have later used a 2G or 3G phone and likewise 3G phone users have
previously used 2G and/or analogue phones. Cordless phones have mostly been
used concomitantly with mobile phones. Hence the analyses of amount and
duration of use of these types of phones are not independent and the analyses
presented are therefore misleading. For hours of use, which is additive, a
multivariate approach would be possible

\(\beta_{\text{analogue}} \cdot d_{\text{analogue}} + \beta_{2G} \cdot d_{2G} + \beta_{3G} \cdot d_{3G} + \beta_{\text{DECT}} \cdot d_{\text{DECT}}\),

with \(d_x\) hours of use of phone type \(x\). But years of use (‘latency’) is not additive due to
overlapping periods of use (especially of mobile and cordless phones) and hence
cannot be modeled in the same way. However, in separate analyses of the
different phone types years of use of any mobile or cordless phone prior to using
the respective type can be used as a covariate.

We have now added in “Results” regarding Table 6:

“In a multivariate analysis including all phone types (i.e. analogue, 2G, 3G and cordless
phone) a statistically significant result was found for cordless phone only (OR = 1.010, 95 %
CI = 1.005-1.016; data not in table).

“These results did not change if years of use of any mobile or cordless phone prior to the
respective type was included as a covariate in each analysis of the individual phone types
(data not in table).”

Page 11, 1st paragraph: SEI has been categorized into 4 groups. It is unclear
whether ‘no work’ indicates unemployment, retirement, living on returns etc. It
can thus indicate a very high or very low SEI. Clarify!

Now added.

Page 11, 2nd paragraph: Analysis of tumor volume is not a very good idea
without referring to the location. Meningiomas grow to a size that depends on the
location. If pressure of the tumor induces symptoms (e.g. seizures) it might soon
be detected and at a smaller volume than in areas where symptoms might easily
remain unnoticed or not being related to a tumor for a long time (e.g. headaches). It has also to be noted that if mobile phone use increases tumor growth rate this will not be associated with a larger volume but with earlier diagnosis. However, it is possible that mobile phone use increases the area occupied by the tumor which would not necessarily result in an earlier diagnosis. Therefore, I suggest adding an analysis of the tumor area (i.e. omitting the third axis).

Now added in "Discussion".

Page 13, 2nd paragraph: In the legend to Table 4 it is stated that ipsilateral was assigned if >50% of the time the phone was held to the side where the tumor occurred while in the methods section it is stated the both side users were included among ipsilateral users (as would be reasonable). It seems, comparing figures for ‘All’ that both side users were omitted. I suggest including them among ipsilateral users as stated in the methods section.

≥50% use on the same side was indeed included in the ipsilateral group; this has now been corrected in the legend to Table 4. Thank you for pointing this out. As stated in “Statistical methods” not all cases/controls were included in the analysis since laterality was not available for all cases (e.g. midline tumours).

Furthermore, due to a possible effect of symptoms on side of use it would be important to clarify whether change of the side of use was addressed in the questionnaire. I also suggest to do the laterality analysis only for latencies above 5 years to overcome this problem (if laterality was specified separately for the current and earlier use).

We have no data on laterality change.

Page 14, 3rd paragraph: The smaller tumor volume in wireless phone users could be due to an awareness bias or a consequence of the different tumor locations. Meningioma in the temporal lobe are often associated with memory loss and also with problem of coordination that are quite distinct and often lead to an early diagnosis with volumes of 10 cm³ or less. Therefore, as mentioned above location must be considered.

Addressed, see above.