Title: Validation of exposure assessment and assessment of recruitment methods for a prospective cohort study of mobile phone users (COSMOS) in Finland

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Author’s response to reviews: see over
We thank reviewers for their valuable comments on our manuscript.

Reviewer: Maria Blettner
Reviewer’s report:

1. There may be some doubt whether a cohort study is needed to further investigate health effects of mobile phone use. As the authors state (page 3) no biological mechanisms has been identified for RS-Fields. So it remains unclear whether a large cohort study is needed. However, this is not the scope of this paper. Overall, the introduction can be shortened and should emphasize on what is the scope of the paper.
Response: The introduction has been revised and the scope of the paper has been sharpened.

2. Methods: First paragraph is not needed. It should be made clear, how the main study and the validation study are associated.
Response: The first paragraph of the methods section has been excluded. In the pilot phase, the methods were similar to the original study proposal for the full cohort. Similar approach has been used in the main study.

3. It is not clear how the persons were selected for this validation study.
Response: Selection criteria are now described more clearly in the beginning of the Methods section.

4. The statistical analysis should be described in the method section.
Response: Corrected. Statistical analyses have now been described in more detail in the Methods section.

5. Results: Response rates and participation rates are unclear. At one point authors talk about 17 % of persons that responded to the invitation while 2.4 % refuse to participate. This is confusing.
Response: The proportions of subjects giving consent and those supplying both consent and questionnaire have now been clarified in the paper in the methods section. A total of 124 persons (2% of the study subjects and 14% of the responders) informed the study personnel that they refuse to participate in the study. These subjects are now called informed decliners in Figure 2.

6. I also do not understand what the “overall participation proportion” is.
Response: This has now been clarified. The overall participation proportion is calculated for the entire material i.e. both questionnaires (short and long) and recruitment approaches (one- and two-phase procedure).

7. Results: Percentages all in the text and in the tables are given without any confidence intervals. The analysis is based on correlation coefficient. If two measurements are compared, this is not a valid statistical method. Bland Altman methods should be used. Neither Spearman rank correlation nor mean difference of the two values are sufficient to evaluate the validation of the answers of the persons.
Response: The referee makes a good point. The association between the self-reported and operator-derived data is now illustrated also with the Bland Altman plot. The percentages are still given without confidence intervals since they are primarily given for descriptive purposes.

8. The last paragraph (Based on…) is not a part of the study and is not belongs to the result section.
Response: This is true. This paragraph has been omitted.
9. The discussion is quite extensive, but did not in taken to consideration the problem of low response rate and measurement errors for the cohort study.  
Response: The discussion has been sharpened. Problems of low response rate and measurement errors of the cohort study have been discussed.

10. The conclusion “a prospective cohort study seems to be feasible is not justified by the results of this paper: response rate is low, measurement error is high, nothing is said about the power of the study (the author state “internal comparisons will be made”), however, selection bias may still be a problem.  
Response: The procedures evaluated could be carried out in Finnish circumstances. Substantially better accuracy of exposure assessment is obvious and data on the outcomes are available. In our view these findings support the feasibility. Low response proportion is mainly resource concern requiring a large number of subjects to be approached for the study. Statistical power was not an issue in this feasibility study. Power calculations show that a study with some 250 000 cohort members would give sufficient power for the most outcomes of interest.  
For a cohort study with internal comparisons we see no fundamental concern for selection bias. We will compare outcomes between exposure groups of those who participated in the study. The study participants will not need to represent all mobile phone users with respect to their mobile phone use and risks of diseases.  
If we have some overlap in demographic characteristics across exposure groups, incomplete balance can be adjusted for in the analyses.

Reviewer: Peter D Inskip  
Reviewer’s report:  
1. The stated aim of this study is the evaluation of the validity of exposure information in the context of a pilot study assessing the feasibility of a cohort study on mobile phone use. The content of the paper is broader than implied by the title and stated aim, as it addresses other aspects of feasibility as well. Indeed, of the three tables and one figure, only the figure addresses the comparison of self-reported and operator-derived exposure information. The authors might consider providing more detail concerning the validation objective.  
Response: The referee makes a good point. The title has been changed to cover the full range of topics addressed in the manuscript.

2. I assume the planned cohort study will collect exposure information both prospectively and retrospectively with respect to the date of enrollment. Do the authors know about the availability of historical records from the operators (e.g., 10+ years in the past)?  
Response: Cohort study will collect exposure information both prospectively and retrospecively. Since historical operator records are not available, retrospective exposure information can be based on self-reported use only. However, we will validate the exposure assessment between self-reported and operator-derived data for the study subjects in the main cohort study. Retrospective exposure assessment will then be based on self-reported mobile phone use corrected for subject-specific factors. This is now mentioned in the manuscript.

3. The use of mobile phones registered under corporate accounts strikes me as an important issue. The authors acknowledge this as a challenging issue in the second-to-last paragraph of the background section, but it is not clear how they propose to address it. Did the questionnaire try to collect information for personal phones and business phones separately? If not, might this be a reason for the apparent overestimation for self-reported use? As the authors note in the discussion, failure to account for use of company phones might lead to serious under-ascertainment of use for heavy business users.
Response: The questionnaire is used to collect information on all mobile phone use, regardless of whether personal or corporate subscription. To avoid the apparent overestimation for self-reported use, we present the self-reported and operator-derived estimates of call duration only for those study subjects with only one mobile phone.

We have made an effort to take heavy users with company phones into account in the main study. The questionnaire elicits information separately for each mobile phone. This way we can take, at least to some extent, the exposure due to company phones into account.

4. The time interval for which operator data were obtained systematically preceded the interval for which interview data were collected. For this to be a true validation study requires an assumption of stability in use over time.
Response: This is true: this assumption is now discussed clearer in the discussion section. We tried to match the three month period for self-derived and operator-derived data. In the questionnaire study participant was asked to evaluate her/his mobile phone use during the preceding three months. We asked the operator data for a period which would make the best match for an average study participant. This assumption is now also validated with the sensitivity analysis in the Results section.

5. Do the authors anticipate a one-time questionnaire or periodic updates regarding manner of use of mobile phones? How confident are the authors that questions concerning manner of use will adequately get at the issue of intensity of exposure, to be used as an adjunct to operator data concerning frequency/duration of use?
Response: Questionnaire will be repeated regularly and will be revised with changes in manners of mobile phone use. Intensity of use will be assessed primarily based on annual data downloads from the operators. Repeated questionnaire also covers mobile phone numbers in use, well-being and symptoms, for example.

6. The first paragraph of the results states that the subscriber could be assumed to also be the user of the phone since age and sex as defined by the operator matched that on the consent form. Could this be a self-fulfilling result; i.e., if the subscriber assumed that he or she was the person of concern?
Response: Yes, this could potentially be a self-filling result to some extent. However, it is quite common for a parent buy a subscription to his/her child or an adult to acquire a subscription for an elderly parent. Since the network operators only record the owner and not the user of the subscriptions, user of the phone can well change in a family. We actually expected to have worse match for age and sex.
By collecting mobile phone numbers, name, date of birth and sex, we always check whether a person who got an invitation was the same as a person who agreed to participate in the study. Requests on operator data are based on mobile phone numbers given by study participants (persons who agreed to participate in the study).

7. In the full cohort study, how will the matter of changes in network operator/mobile phone numbers be handled?
Response: Current network operator of each mobile phone number can be retrieved from an internet service which is offered and maintained by Finnish network operators. Information on changes in mobile phone numbers are obtained from repeated questionnaires. All the three major operators (providing >95% coverage of the market) have promised access to customer data for the full cohort study.

8. The authors conclude that a prospective cohort study of mobile phone users and health appears to be feasible in Finland based on the pilot study, but there are additional questions I would want answered before I would be confident in this conclusion.
Response: We hope the information provided in our responses above is sufficient convince the reviewer

Reviewer: Martha Linet
Reviewer's report:
The manuscript entitled "Validation of exposure assessment for a prospective cohort study of mobile phone users (COSMOS) in Finland" provides useful new information, but major revisions are needed to clarify the objectives of this pilot study and more clearly explain the different components and phases. In addition, the authors should underscore the novel contribution(s) of this study, briefly describe the methods for the planned cohort investigation that will follow this pilot study, and explain what will be done with the results of this pilot study.
Response: The manuscript has been revised substantially in accordance with the detailed comments made by the four highly esteemed reviewers and we hope the revised version addresses these three general points.

The title of the manuscript suggests that the focus is on validation of exposure assessment, but several other important methodologic components are described that were evaluated by assessing participation. The authors should revise the title to reflect the additional components (something like "Validation of exposure assessment and assessment of methods to improve participation in a planned prospective study of mobile phone users (COSMOS) in Finland").
Response: The referee raised a good point. The title of the manuscript has been changed.

The Abstract should reflect more accurately the nature of the pilot study with: a more precise statement of the study objectives; a clearer statement of the approach (e.g. targeted population, data sources and methods for data collection, methods of analysis); a reorganization of the Results starting with the overall response rate, followed by the availability of operator data, then the results of the exposure assessment, then the other study results; and Conclusions that do not replicate the results but focus on the several implications of the results for the planned cohort study.
Response: The structure of the Abstract has been revised.

The Background should be shorter and more focused on the RELEVANT background. One needs to understand why this pilot study was carried out. The authors should briefly describe the planned methods for the proposed cohort study so the goals of the pilot study are more clear. From the Background as is, it was not clear how the new cohort study will overcome the limitations of case-control studies (since the plan is to use questionnaires with self-report), other than the idea that the cohort study will also utilize operator records (which have their own limitations). The Background should provide information about what is novel about the pilot study.
Response: We have shortened the background section and focused it on the justification of the pilot validation and the strengths of the cohort study.

The Methods would be clearer if the authors provide a flow chart to show the two major different components, and the two approaches within the second component along with participation rates.
Response: Figures 1 and 2 have now been included to clarify the major components and the time line of the study.

The rationale for obtaining additional operator data for 2008 and 2009 was not explained.
Response: The rationale was to evaluate the changes in usage patterns over time, more specifically to assess if tracking i.e. stability of the grouping by amount of use over time. This has now been explained on pages…
The Results should be completely quantitative. For example in the first paragraph in the section on Validation, the authors should describe reasons for not receiving mobile phone data for 17% of the subjects from the operators.  
Response: A change of the network operator or errors in mobile phone numbers were the most probable reasons for not receiving mobile phone data. However we cannot quantify the proportion of missing data due to each these reasons since they both caused the same outcome (no operator data were retrieved from operators’ records).

The authors state "The amount of mobile phone use differed slightly between the period preceding the start of the study and the first monitoring period." What was the length of the interval between the start of the study and the first monitoring period? What do the authors mean by 'differed slightly'?  
Response: This has been clarified in the manuscript as the six month periods for which the operators based their assessment for the amount of mobile phone use have now been given. The changes in usage categories are provided in more quantitative terms.

In the second paragraph in the Validation section, it was not clear why the authors collected mobile phone data for successive years.  
Response: See the earlier comment and response on operator data for 2008 and 2009. To reiterate, we evaluated the changes over time in mobile phone usage and assessed whether those who were heavy users initially remained in the high usage group over time and vice versa.

The Discussion needs substantial revision. Paragraph one should also summarize the participation rates overall and by method of data collection.  
Response: Participation rates are now summarized in Figure 2. Discussion has been restructured and the first paragraph includes discussion of participation rates.

In Discussion: Paragraph two should eliminate the description of non-differential random errors, since it is not relevant. What the authors found is systematic bias. Paragraph three ends with a comment about the uncertainties inherent in retrospective exposure assessment based on interviews. However, the self-report planned for the cohort study will have the same inherent problems, particularly for those subjects for whom operator records cannot be obtained.  
Response: This is true and is now mentioned in Discussion.

In Discussion: Paragraph five states that "for the full study, however, call data will be obtained for a three-month period each year". This critically important statement is buried in the Discussion, but should have been describe in the Background section of the manuscript so the reader could understand more about the ultimate validation approach for the proposed cohort study.  
Response: This is true. The annual download of objective operator data of a three-month period is now mentioned in the Background section.

In Discussion: Interpretation of the pilot study validation is substantially affected by knowing that the cohort study data collection will involve only 3 months of operator records. The authors acknowledge that phone use varies within and over time. Limitations of the Results of the pilot study are not described.  
Response: The comments on validation have been broadened in the Discussion section. The Results section includes now sensitivity analysis of the validation.

In Discussion: In addition, the last paragraph seems to gloss over the very low participation rate and the implications for the planned cohort study. A more measured conclusion would be appropriate.
Response: we have revised the conclusion and hope the reviewer finds it less hermetic

Reviewer: Martin Röösli

Reviewer’s report:
- Major Compulsory Revisions
  This analysis is well conducted and described and merits publication. No major compulsory revisions suggested.
- Minor Essential Revisions
  Background, 1st paragraph: “low participation of controls who do not use mobile phones”. One should mention that this statement refers to the Interphone study but not to all mobile phone studies in general.
  Response: This sentence has been modified.

  Background, 4th paragraph: No references are given for this statement: “A handful of studies have demonstrated only moderate consistency between self-reported amount of mobile phone use and recorded estimates (obtained from operator databases and software modified phones), with overestimation by a factor up to more than two.
  Response: References are now given.

  Discussion: First sentence of 1st and 2nd paragraph are not clear and should be rephrased.
  Response: These sentences have been rephrased.

- Discretionary Revisions
  It is quite difficult for a reader to get an overview about the data situation of this study. I suggest adding a graph which shows all the data that has been collected and the mailings that have been made. For instance a time bar indicating the time period of the operator data that was used for study participant recruitment and for validation, as well as indicating all mailings. There is some fuzziness about the agreement between the period for which the study subjects estimated their mobile phone use at recruitment and the period of the operator data that has been used for validation. Apparently (see discussion) these periods are not perfectly matched in all subjects and this should be better described and mentioned as a reason for disagreement.
  Response: This is a good idea. The upper half of Figure 1 now shows the time line of the study recruitment and the lower half the three-month periods (and their range) for which operator-derived and self-derived data were obtained.

  Table 1 is not very reader friendly. To me, most important is the comparison of the participation rate in the various strata (two phase vs. one phase, short vs. long questionnaire). Thus, I suggest sorting the data according to these strata resulting in 7 columns including “all” (or 14 if the % columns are counted separately).
  Response: This is true. Table 1 has now been replaced by Figure 2 to simplify the description of the study population.

  Is there any explanation why the participation rate was somewhat higher in the 1st stage compared to the 2nd stage? Was the 1st stage accompanied with media reports?
  Response: We don’t know. It might be that media release had positive effect on the participation. The 1st stage occurred just before the Christmas. It might also be that during the Christmas vacation people had more time and good will to concentrate on the study material and to post the signed informed consent form.

  The authors do not discuss the fact that operator data may not perfectly represent personal use of mobile phones. There are a number of limitations: study participants may use other people’s phone (or vice versa), participants may forget phone numbers and thus operator data cannot be
retrieved, operator data may be wrongly linked or not accessible for various reasons, etc. This aspect should be discussed. One could also point out which problems are less relevant for prospective data collection (e.g. forgetting phone numbers).

Response: This issue is now discussed in Discussion.

In my view ensuring a balanced distribution with respect to sex and age in the exposure strata is not crucial. It would maximize the power of the study for a given sample size. However, if the strata are imbalanced this can be considered in the statistical analysis. Moreover, the paper clearly demonstrates that the distribution will not stay balanced in a longitudinal study as more than a third (157/418) changed their original usage category between autumn 2006 and spring 2007.

Response: The referee has a good point. It is important to achieve some degree of overlap in demographic characteristics across exposure groups so that incomplete balance can be adjusted for in the analyses. This is now mentioned in Discussion.

In the discussion was written that the actual user cannot always be identified for corporate subscriptions. This is certainly true for retrospective data collection. However, in a prospective study, this should be feasible. If not, this should be explained.

Response: Operator-derived data cannot only be released without the subject’s consent. As study subject does not legally own her/his corporation subscription he/she can neither give legal permissions concerning that subscription. There can be country-specific variation is this issue but in Finland operators’ lawyers were strict on this issue. A sentence has been added in Discussion.