Author’s response to reviews

Title: Maternal cell phone use in early pregnancy and child's language, communication and motor skills at 3 and 5 years: The Norwegian Mother and Child Cohort Study (MoBa)

Authors:

Eleni Papadopoulou (eleni.papadopoulou@fhi.no)
Margaretha Haugen (margaretha.haugen@fhi.no)
Synnve Schjølberg (Synnve.Schjolberg@fhi.no)
Per Magnus (per.magnus@fhi.no)
Gunnar Brunborg (Gunnar.Brunborg@fhi.no)
Martine Vrijheid (mvrijheid@isglobal.cat)
Jan Alexander (jan.alexander@fhi.no)

Version: 1 Date: 30 May 2017

Author’s response to reviews:

The authors' response letter has been included as a supplementary file.

Manuscript reference: PUBH-D-16-03406

Title: Maternal cell phone use in early pregnancy and child's language, communication and motor skills at 3 and 5 years: The Norwegian Mother and Child Cohort Study (MoBa)

From the authors: Please note that the line and page numbers are referring to the revised manuscript with marked changes.

Response to reviewers’ comments

Reviewer reports:

Valborg Baste (Reviewer 1): Maternal cell phone use in early pregnancy and child's language, communication and motor skills at 3 and 5 years: The Norwegian Mother and Child Cohort Study (MoBa)

The study has a large sample with information on cell phone use collected at time of exposure and years before the self-reported outcome; the child's language, communication and motor skills
at 3 and 5 years. These two conditions are a strength of the study. But, the information about cell
phone exposure and utilization of data from the MoBa study is not gratifying and must be
improved.

Major compulsory revisions:

Comment 1: Maternal cell phone use during pregnancy (page 4): The exposure from maternal
cell phone use is essential. In this paragraph, maternal cell phone use, is (so called) categorized
into 4 groups, the only thing done is changing of the words of the original categories - why? For
instance "daily" is changed to "average", average in this situation says nothing about the use of
the cell phone.

Our response: We would like to thank the reviewer for this comment. it is true that we revised
the original labels of the fixed answers from “Seldom/never; A few times per week; Daily; On
average more than 1 hour per day” to “No use; Low use; Average use; High use” for the
convenience of the reader, as the original labels were very long. In addition, this study was
performed at the same time as a meta-analysis from Birks et al.[1], which also draws on
resources from the MoBa study. In this meta-analysis, the same exposure variable was used as in
our study with the labelling: “No use; Low use; Medium use; High use”. To be consistent with
the meta-analysis and due to the reviewers comment, we have now renamed the category of
“Average use” to “Medium use” throughout the manuscript, including tables and figures in the
main manuscript and in the supplemental material.

Comment 2: Further, the MoBa study also included question on duration of the call this is not
mentioned in the manuscript. Duration of the call is important when assessing the mother's
exposure of cell phone and should not be ignored. In an article from 2015, regarding maternal
and paternal cell phone use and reproductive outcome, based on data from the Norwegian
Mother and Child Cohort Study, a combined variable of the two questions was created. Why are
not both questions, or a combination of these questions (for instance like the 2015 article) used in
the current study?

Our response: We would like to thank the reviewer for this comment and we understand that the
reviewer has deep knowledge of the MoBa study as she was the author of the article referred to
above. According to the Baste et al.[2], study the combination of the two variables assessing
frequency of mobile phone use and duration of mobile phone calls, can be as follows:

(table is in the point by point response to reviewers uploaded in supplementary file)
Of the 45,389 mother-child pairs in our study, 241 mothers did not answer the duration of calls question and of those who answered, 35% replied “never”, 54% replied “seldom” and 12% replied “often”. The combination of the questions as used in the Baste et al., article, resulted in the categorization of 28% of the mothers as low users, 60% of the mothers as medium users and 12% of the mothers as high users. We have performed and presented in Table 1 below, the adjusted exposure-outcome statistical analysis using the combined variable of frequency of use and duration of calls:

Table 1. Adjusted association between maternal combined frequency of use and duration of calls from mobile phones in pregnancy and offspring’s neurodevelopmental outcomes.

The associations of the combined variable for mobile phone use and neurodevelopmental outcomes are very similar as those presented in the manuscript. The main difference is the significant association with the risk of low communication skills at 3 years only for children born to medium mobile phone users (OR=1.36, 95%CI=1.10, 1.68).

Nevertheless, we did not include any of this information in the main manuscript, as we want to provide comparable results and be consistent with the exposure variable used in the meta-analysis by Birks et al.[1]

Comment 3: Child language, communication and motor skills at 3 and 5 years (page 4): Language developments, what is the rationale behind assess 'the risk of low sentence complexity, by grouping any ratings below six'.

Our response: In the original paper by Dale P.S et al [3], they use the scale as a proxy for sentence complexity related to mean length of utterance. The scale is described as a quick and crude measure of affected language development. As we are not expecting severe language delay in our study population, we have used a cut-off for capturing children with inflated language scores, i.e. children who score lower than the typical developing groups. In the original paper by Dale P.S et al [3], 89% of their typical sample children scored highest, and 11% scored ≤5. In their early language delayed sample, 46% of these children scored ≤5. We have therefore used this cut-point to capture potentially late language development. The following text has been added in the methods section (lines 92-96, page 3):

“We used this cut-off to capture potentially late language development, basing the rationale on the publication by Dale P.S. et al, where 11% of the typical children and 46% of the early language delay children scored ≤5 [3]. As we do not expect children with severe language delay
in our study population, we used this cut-off for capturing children with inflated language scores, i.e. children who score lower than the typical developing groups.”

Comment 4: Low Motor skills were defined as the lowest tertile. The cutoff value for both ASQ at 3 year and CDI at 5 year must be given. How can the lowest tertile be calculated for the included study sample, include 23%? Why is not the ASQ cutoff-point for low motor skills at 3 year used?

Our response: We would like to thank the reviewer for this comment. Children with motor skills score ≤30 (score range 0-40) and with scores ≤10 were categorised as with low motor skills at 3 and 5 years respectively. This information has now been included in the revised manuscript (lines 109-110, page 4).

Only 23% of the 5 year-olds and not 33% were categorised in the low tertile for motor skills score, because of the skewed distribution of the score. If the cut-off was at 11 points of the score then 43% of the children would have been categorised as having low motor skills. We have tried to clarify this issue in the revised manuscript (lines 107-108, page 4).

Regarding the identification of children with low motor skills as those scoring at the lower tertile rather than the suggested cut-off of 2 or 3SD below the mean, we need to clarify that the ASQ items included to assess motor development at 3 years are a subset of the original ASQ questionnaire (Supplemental Table 3a). Hence, the manual’s cut-off could not be used. This was also the case at 5 years, where a subset of the original CDI questionnaire was used to assess motor skills. Hence, we created a study specific cut-off point for a comparison across the age spans involved, considering the population distributions.

Comment 5: Other characteristics (page 5): P6/L 21-24: Year of delivery was used in ’ … sensitivity analyses included stratified analysis by year of birth (1999-2004, 2005-2006, 2007-2009) to study the potential effect of changes in cell phone technology.’ There are no references or arguments for choice of the three time periods.

Our response: We would like to thank the reviewer for this comment. Several studies have shown an exponential increase of mobile phone users from the mid to late 1990s’ in the Nordic countries as well [4-6]. Around the mid-2000s’ smartphones were widely available and around 2007-2008 the iPhone was introduced. In addition, around 2003, mobile operators in Europe deployed UMTS networks (3G), which were later upgraded to HSPA starting in 2006 and then HSPA+ in 2008. These investments have led to a 4400 fold increase in data transmission rates [7]. Hence, we have stratified our analyses by these periods to investigate possible time trends in cell phone use. In addition, this categorisation provided groups with similar numbers of mother-
Comment 6: In the MoBa study paternal questionnaire was distributed to the expectant fathers around week 15 of gestation. But, the question about paternal cell phone use, was regarding used 6 months before conception. And there were two different versions of the questionnaire, one with four response categories concerning cell phone use, and one with five response categories. None if these conditions are mentioned in the manuscript. How was paternal cell phone use defined? It is not clear why it is included in the manuscript, and why as an exposure in Supplementary table 8?

'Paternal use of cell phones during pregnancy was also assessed, but only 20,424 (45%) of the fathers provided information,' - This must be clarified, 75 200 fathers participated, 'provide information' about what?

Our response: As the reviewer is describing the fathers were asked to answer their frequency of use of mobile phones in the period of 6 months before the beginning of the pregnancy and this was assessed around 15th weeks of gestation. There is also this issue with the two different versions of the questionnaire, in one questionnaire the fathers were asked to report how often they were using their mobile phones the last half a year by choosing one of the fixed answers: “Seldom/never; A few times per week; Daily; On average more than 1 hour per day”, which are the same as the ones the mothers answered. In the other version of the questionnaire the given frequency option were “Less than once a week; 1-2 times/week; 3-6 times/week; 1-4 times/week; More than 5 times/week”. In total, 35,612 fathers answered any question on frequency of mobile phone use but for consistency and comparability reasons, we have used only the information assessed by the first questionnaire (n=20,424 fathers). This information has now been included in the manuscript (lines 138-145, page 4-5).

Comment 7: Statistics: The presentation of statistical methods is not fully described. What model was used in general and how was the cluster of siblings within the mother accounted for.

Our response: We have described in the statistical analysis section that we have used crude and multiple logistic regression models to explore the association between the exposure and the outcomes. The siblings were considered clusters of children within the same mother and in Stata there is the extension “vce(cluster)” of the command “logit” for the logistic regression that specifies that there is inter-correlation within clusters.

Results and supplementary tables/figures:
Comment 8: The chapter should be more succinct. Especially the two first paragraphs can be shortened. Figure 2A and 3A can be omitted, only mentioned gender in the text. Figure 1A and 1B could be merged, with each outcome grouped and for each outcome the OR for the three levels of exposures (instead of grouping the level of exposure and OR for each outcome). Similar could be done for Figure 2B and 3B.

Supplementary table 7 and 8 can be omitted, Table 7 due to same results as not taking into account siblings, and Table 8 because the paternal cell phone exposure is inadequate (see above comment).

Table 2: The n noted for the model is not the sum of the n given for the categories, and the % given in the table, cannot be calculated from the numbers given. Further, why is not the % given for 'Any use' (regards also table 3 and 4).

Our response: According to the reviewer’s suggestion we have now shorten and collapsed the two first paragraphs of the results section in the revised manuscript (lines 197-223, page 6).

According to the reviewer’s suggestion, we have now merged Supplementary figures 1A and 1B into one (Supplementary figure 1). Regarding Supplementary Figures 2A, 2B and 3A, 3B we tried to merge them as suggested, but the result is confusing, hence we would prefer to keep them as is. The labels of maternal phone use in pregnancy have been also revised in the supplemental figures (from “average use” to “medium use”). Finally, we did not delete any of the Supplementary figures.

Regarding the supplementary table 7, in which the association between maternal cell phone use and risk for lower sentence complexity and low motor skills at 3 years are presented, after taking into account the clusters of siblings, we would like to keep this table in the Supplemental material as we think some readers will be interested to see the estimates.

Regarding the association between paternal mobile phone use and risk for lower sentence complexity and low motor skills at 3 years (supplementary table 8), we have described in details the variable used for paternal mobile phone use in the methods section of the revised manuscript. We would like to keep this sensitivity analysis in the supplemental information as we think it adds valuable information for the association of maternal use of cell phone and child’s neurodevelopment.

Regarding Table 2, we would like to apologize for the mistake with the number of women in each cell phone use category. This has now been corrected. As it is explained in the footnote of tables 2, 3 and 4 the percentage is given for the exposure variable with 4 categories and the reason was not to overcrowd the table and also to avoid any confusions of what the percentage represents. Nevertheless, according to the reviewer’s suggestion we have now added the percentage of cases within the “any use” category in tables 2, 3 and 4.
Discussion:

Comment 9: It is unclear what possible mechanism of the RF-EMF field from the cell phone exposure could have in this study. Is it through the maternal head exposure or the possible exposure of the fetus through the abdomen?

Our response: We would like to thank the reviewer for this very interesting comment on a complicated issue. The estimation of fetus radiofrequency (RF) exposure induced by wireless communication systems is highly complex because the exposure depends on many parameters (source, usage, frequency, posture, age of fetus). It has been suggested by specific absorption models that the fetus is exposed to various RF-EMF from the mother holding her cell phone close to her head or her body, depending on the position of the fetus, the pregnancy week and where the mother carries her phone [8]. We have added the following text in the discussion section (lines 336-341, page 9):

“To add to the complexity of the issue, the estimation of fetus RF exposure induced by wireless communication systems is highly complex because the exposure depends on many parameters (source, usage, frequency, posture, age of fetus). Specific absorption models showed that the fetus is exposed to various RF-EMF from the mother holding her cell phone close to her head or her body, depending on the position of the fetus and the pregnancy week[8].”

Comment 10: The argument that the span of the recruitment years can be considered as a strength of the study, could rather be argued as a limitation. Changes in technology does not mean that everyone is changing at the same time, so it would have been easier to assess cell phone exposure in a period where the technology was more homogeneous. In the time period the cell phone use has increasing while the RF-fields have been reduced with newer technology.

Our response: We have now considered this issue and added the following text in the discussion section (lines 361-365, page 10):

“On the other hand, changes on cell phone use overtime can be considered a limitation as well, as they can introduce bias in our analysis. Nevertheless, when restricting to children born earlier (1999-2004), between 2005-2006 and later (2007-2009) when cell phone use may have been more homogenous, similar results were found.”

Comment 11: The authors claim that the main limitation is reporting exposure and outcome, however, this is years apart and together with lots of possible exposures and outcomes. How could the misclassification bias influence the results?
Our response: We would like to note that we have now revised this sentence and have focused on the self-reported cell phone use. The misclassification of the exposure due to errors in self-reports of cell phone use would be non-differential (ie, the same degree of misclassification to both mothers of children with and without low language, communication, motor skills), because this was a cohort study and use of cell phones was assessed long before the neurodevelopmental assessment of the child. Non-differential bias leads to attenuation of observed associations, meaning that without such misclassification the observed associations could have been stronger [9]. We have now added this text in the discussion section (lines 366 and lines 370-375, page 10).

Comment 12: The conclusion in the abstract, '...which might be explained by enhanced maternal-child communication among cell phone users.' There was no association with communication skills, and it has not been shown an enhanced maternal-child communication among cell phone users.

Our response: We understand that this sentence might be confusing and we have revised as follows (line 20, page 1):

“We reported a decreased risk of low language and motor skills at three years in relation to prenatal cell phone use, which might be explained by enhanced maternal-child communication interaction among cell phone users.”

Minor comments:

Comment 13: The language could be more succinct, for instance exclude confusing extra words:

P3/L12; 'In spite of' (the findings have nothing to do with the numbers of studies)
P3/L57; 'Now' (the study enrollment ended 9 years ago)
P4/L11; 'included'
P5/L34,' We note that even though'
P13/L38 'Nevertheless, and similar …'

Insufficient information on abbreviation; OR, CI.

Our response: All the above-mentioned sentences have now been revised (line 28, page 2; line 63, page2; line 74, page 3; line 136, page 4; line 292, page 8; line 295, page 8).
Comment 14: P3/L 35-39: One of the background arguments, interventions and monitoring of maternity and antenatal health care is weak; it refers to two articles concerning use of text messaging, which generates minimal RF fields. The references should either be deleted or commented in a relevant way.

Our response: We would like to clarify that the argument here is not that the use of cell phone during a text-based intervention per se will expose the fetus to this minimal RF fields and this is why we need to study prenatal exposures due to cell phone use. Our argument is based on explaining the two sides of the coin, which is cell phone use in pregnancy. Nowadays, cell phone use is so abundant that cell phone based interventions are becoming more and more popular for public health promotion especially in underprivileged populations, in which maternity and antenatal health care is challenging. In order to make our argument clear, we have now revised this paragraph (lines 48-52, page 2).

Comment 15: P5: A lot of possible confounders are listed; some of them seem odd, for instance folic acid supplement, BMI. Include women with an extrovert personality as one of the confounders rather than write 'We hypothesized …'.

Our response: Folic acid supplements use during pregnancy has an established association with offspring’s neurodevelopment, and maternal pre-pregnancy BMI has an established association with pregnancy complications, birth outcomes and other health outcomes that may be related with restricted neurodevelopment. Since their association with cell phone use is not known we have included them in the potential confounders list. However, as the reviewer is pointing out, these two variables were not confounders of the associations under study.

Regarding our elaborative explanation of the maternal personality score inclusion, we consider that this information is important for the reader. Since the maternal personality traits related to cell phone use are unknown, the extrovert personality does not have a straightforward association with cell phone use. Hence, we needed to explain that this is a hypothesis.

Comment 16: P 13: The two first sentences belong to the method section.

Our response: These sentences from page 13 have now been moved to the statistical analyses subsections of the methods section (lines 190-193, page 6).

Comment 17: P 13/L 38: School aged children, 5 years? and 'similar' referring to a Spanish study regarding 6 and 18 months?

Our response: We have now revised these sentences as follows (lines 291-292, page8):
“…, while our study also includes pre-school children (5 years). Nevertheless, in the Spanish study cell phone users had children who scored higher in the Bayley mental scale…”

CARSTEN OBEL (Reviewer 2): This study aim to test the association between maternal cell phone use during pregnancy and early development measures and finds an association suggesting a protective link. The paper is well written, data are analyzed well and the discussion is balanced and provides an adequate conclusion on findings. The study is based on unique data and overall well done. The only thing that may be considered is to provide subanalyses comparing estimates based on the different combinations of maternal and paternal exposure. This kind of analyses may provide a contribution to the discussion of the underlying cause of this finding.

Our response: We would like to thank the reviewer for the positive feedback and for the interesting comment on combined parental cell phone use. We have combined maternal and paternal cell phone use as follows: both parents non-users, mother user & father non-users, mother non-user & father user and both parents users, and explored the association with child’s neurodevelopment, using non-users as the reference. We found lower OR for language delay and low motor skills at 3 years when both parents were using cell phones and the effect estimates were very similar to those reported for maternal non-use vs. any use, as reported in the manuscript.

(table is in the point by point response to reviewers uploaded in supplementary file)

As discussed in the manuscript the above shown association demonstrates the effect of unmeasured confounding rather than a causal relationship.

Nevertheless, we would not want to include this additional analysis in the manuscript since the main reason of including paternal cell phone use was to use it as a negative control of exposure. Negative controls of exposure are commonly used in epidemiological studies to detect confounding and other bias [10]. The essential purpose of a negative control (paternal exposure) is to reproduce a condition that cannot involve the hypothesized causal mechanism, but is very likely to involve the same sources of bias that may have been present in the original association (maternal exposure) [11]. In our study we hypothesized that in the presence of a true biological intrauterine effect, maternal cell phone use during pregnancy would be associated with offspring’s neurodevelopment, whereas paternal cell phone use wouldn’t or the association would be of smaller magnitude. An association of similar magnitude for both maternal and paternal exposures, as the one we observed, would be attributed to shared familial confounding factors.
References


