Author's response to reviews

Title: Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in adolescence. A historically matched cohort study.

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Version: 2 Date: 19 December 2013

Author's response to reviews: see over
Reviewer 1, Peter Gerard Gibson

The methods are well described but there are inadequacies, such as the failure to account for childhood exposure variables that might have influenced the outcomes assessed.

Several perinatal variables are included and described in methods section and tables, i.e. list of variables. To improve the overview of the covariates included, we have specified these in the statistics section in the revised version. We have included covariates that might be confounders in the relationship between maternal preeclampsia and outcomes related to atopy, and covariates that are design variables, see page 8 in manuscript (…) including the covariates gender, birthweight z-score for gestational age, being firstborn, maternal smoking during pregnancy, maternal age at birth, caesarean section, gestational age, maternal BMI and maternal asthma. Paternal asthma was not included as a covariate due to low response rate and due to missing data, matching was not included in the analyses, but the matching variables were adjusted for. We could not find other childhood exposure variables that might be confounders in the relationship between preeclampsia and outcomes related to atopy.

There is a low follow-up at FU2.

We agree. The discussion of this limitation has been extended in the revised version. See page 13 in manuscript: One limitation of the study is the rather low rate of participation, especially in FU2. It is not known whether there was a difference in prevalence of asthma or atopy between those who consented and those who didn’t consent to overall follow-up. Especially for the outcomes of asthma, there was a rather low response rate which increases the risk of a type 2 error.

The data do not make biological sense, as there is an increased risk of one allergic disease (rhinoconjunctivitis), no risk of another (eczema) and a reduced risk of asthma. This seems biologically implausible

It is not correct that there was a reduced risk of asthma. As shown in tables 2 and 3, there was no significant relationship between maternal preeclampsia and offspring asthma ever, or current asthma. Moreover, it may not be biologically implausible that the results differ between allergic rhinoconjunctivitis and eczema/asthma, as discussed in the manuscript: the pathophysiology of asthma and atopic dermatitis is more multifactorial than the specific allergy driven rhinoconjunctivitis. This is thoroughly discussed in the manuscript page 12.

Reviewer 2, Franca Rusconi

However, biological plausibility, as the authors also agree, is not so clear, so we need to be cautious before considering such an association as a causal one.

We fully agree. This is discussed in the discussion section page 12: as this is an observational study, the possibility of residual confounding cannot be excluded.
I am particularly worried about the fact that the authors possibly selected adolescents with allergic symptoms (mothers/adolescents who are atopic could be more willing to participate) and that in the analysis they do not correct for maternal atopy.

We agree that there may be a possibility of selection bias. However, when consenting to the first follow-up, the mothers and adolescents were not aware of the contents of the questionnaire or a second follow-up with lung function testing and allergy testing. Later, most of the participants of the first follow-up consented to participation in the second follow-up. The difference in known characteristics between those who consented to both and those who only consented to first follow-up has been described in the results section page 10. There were more children with atopic dermatitis who consented to FU1 than to both FU1 and FU2, but no difference in participation in the two follow-ups in the amount of asthma ever or allergic rhinoconjunctivitis. The question regarding maternal atopy is discussed below.

1. In the Introduction the authors should better discuss the topic of the relationship between preeclampsia, BPD, and childhood wheezing, not as an inflammatory problem. I would suggest to delete the phrase starting with “Both wheezing and asthma…inflammation”; this could be substituted with “Preeclampsia has been also associated to an increased risk of RDS and BPD in preterm infants and to recurrent wheezing in a general population of pre-school children”. I would further discuss how the pathophysiology of these conditions could be due either to an increased soluble antiangiogenic factor (this has been demonstrated for BPD, as correctly stated by the authors) or by a congenital reduction in airways calibre/compliance in particular in IUGR/SGA infants.


Finally, I would delete also phrases on the short/long term effect of BPD which are not important for the topic at hand, starting from “These are also inflammatory conditions”..to “….irrespective to neonatal disease”.

We appreciate these comments. We have revised the manuscript accordingly, which in our opinion improves the introduction. See page 4-5: Preeclampsia has also been associated with an increased risk of RDS and BPD in preterm infants and to recurrent wheezing in a general population of pre-school children [14]. This association might either be due to an increased soluble antiangiogenic factor [15], or a congenital reduction in airways calibre and compliance in particular in infants with intrauterine growth restriction [16].

2. Do the authors know if among mothers who had preeclampsia and who decided not to participate/or whose offspring decided not to, there was a lower prevalence of asthma or atopic diseases in comparison with those who participated?

We regret that we do not know this, the information on asthma and atopy were retrieved for consenting participants only, during follow-up.
If the authors do not have these data I think: a) they should tell us the reason for not participation;

The only information available comparing participation with not participation is shown in table 1 and there were no differences between groups for those variables.

b) They should discuss this point as a possible limitation.

This has been added to the discussion page 14: One limitation of the study is the rather low rate of participation, especially in FU2. It is not known whether there was a difference in prevalence of asthma or atopy between those who consented and those who didn’t consent to overall follow-up. Especially for the outcomes of asthma, there was a rather low response rate which increases the risk of a type 2 error. Furthermore, adolescents who participated in FU1 but not in FU2 had a higher BMI and more atopic dermatitis. This may have biased our results, as both overweight and atopic dermatitis may be associated with allergic sensitization and other atopic disease.

3. The analyses should have been adjusted for maternal atopy, but I suspect that the authors do not have this information. If they have it I would suggest to use a combined variable as a confounder (maternal asthma or atopy); if they do not have data on maternal atopy this is to be acknowledge as a limitation in the discussion.

We agree that the maternal atopy should have been included as a variable and adjusted for in the analyses. However, when the “Stavanger Study” was planned several years ago, this question was not included. In the revised version we have added this information to discussion page 14: The only data on family atopy available were on maternal and paternal asthma, and the limitation is discussed.

4. – The authors adjust for some variables (birth weight z-score for gestational age, gestational age, caesarean section, and respiratory distress syndrome) which are in fact intermediate between maternal preeclampsia and outcome. For instance, maternal preeclampsia reduces birthweight (increases small for gestational age infants and reduces birthweight z-scores); if smaller infants have a greater likelihood of developing asthma, adjusting for birthweight z-score will “overadjust” and will reduce/eliminate the contribution of preeclampsia to asthma. It is generally believed that one should not adjust for intermediate variables in analysis (e.g. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology 1992;3:143-155). I would suggest to perform multivariable analyses without these variables.

This is an important issue which has been thoroughly discussed in our group including a statistician. We acknowledge the problem of intermediate covariates, but also consider that there may be different solutions in this case. The variables GA and birthweight z-score may be influenced by other factors than preeclampsia, and therefore possibly not fully intermediate. The reviewer is concerned about the possibility of “overadjusting”; however, also the opposite may be possible. Preeclampsia may reduce GA, however in our analyses; increasing GA is a risk factor for allergic sensitization even in the final analysis. There is also no interaction between GA and preeclampsia. We therefore prefer including this variable in the analyses. Excluding mode of delivery or birth weight z-score does not alter the conclusions of the analyses. We therefore prefer keeping these variables in the analyses, but
this may be considered if the reviewer or editor still has a different opinion. The covariate IRDS may be excluded.

In addition in the final analysis I would keep important potential confounders such as: maternal asthma/atopy, gender, maternal smoking in pregnancy.

We agree, and have included maternal asthma and gender in the final analyses. Maternal smoking was not always significant in the fully adjusted model, and there were some missing values, the variable was therefore not included in the final model (unless significant) to avoid a lower number of included participants in the last step.

5. Another limitation the authors need to discuss is the very low number of subjects in the analyses; this could be a problem in particular for ever and current asthma, for which the authors did not find an association with preeclampsia. This needs to be acknowledged in the discussion.

We agree that this is a limitation. This was already discussed, but the discussion has been extended in the revised version page 13: It is not known whether there was a difference in prevalence of asthma or atopy between those who consented and those who didn’t consent to overall follow-up. Especially for the outcomes of asthma there was a rather low response rate which increases the risk of a type 2 error.

For ever asthma another point is that the authors did not investigate wheezing disorders in the first few years of life. As they state correctly, these have been related to preeclampsia in previous works; the present study therefore does not contradict previous results, and this should be stressed in the discussion.

We agree that our conclusion on this could have been stated otherwise. We have therefore made additions to discussion page 13: Our results do not contradict this. Although we could not find any association between preeclampsia and asthma ever, current asthma or lung function in adolescence, we did not investigate wheezing disorders in the first years of life. However, the present study had a longer follow-up than in the studies mentioned above, and may therefore be better suited to exclude any long time effect of preeclampsia on asthma and lung function in adolescence.

It is not clear to me if the LR-p the authors report refers to the whole model (exposure + covariates), or if it refers to the exposure only (i.e., if the LR-P tests the joint hypothesis “mild preeclampsia OR=1 AND severe preeclampsia OR=1”); the test relevant for the reader is this last one.

The LR-p refers to each exposure variable, not to the whole model. This has been clarified in the statistics section and in table 3 of the revised version.

Reviewer 3, Bernt Alm:
In the paper, the term “adolescence” is used of the study population. However, the follow-up ages were all below 13 years of age, while the definition of an adolescent is >13 years, according to MeSH.

We agree that perhaps another term would be better used according to MeSH. However, the term “adolescence” has been used in previous articles from the same study, and the participants were close to 13 years. Hence, we suggest continuing using this term.

On p. 5: The follow-up studies seem to be done at very strange ages, i.e. at 10.8 years for girls and 11.8 years for boys. A second follow-up at 12.8 years was also done. Why these ages? Are they means? If so, some measure of dispersion should be given.

The study is a part of the main “Stavanger study”, and the ages were chosen due to research questions related to puberty. The ages were therefore target ages. We agree that this was not fully explained. We have now clarified this in the manuscript, and also given the ages as mean with SD. The text has been changed in methods section page 5: (These ages were chosen due to research questions related to atopy in the “Stavanger Study” [17]) and in results section page 9: At FU1 the age of the girls was 10.8 (+0.22) years (mean, SD); and for boys the age was 11.8 (+0.18) years. At FU2 the age for both genders was 12.8 (+0.19) years.

P 7: The questionnaire is said to be “modified from the International Study of Asthma and Allergies in Childhood (ISAAC)”. Modified, how? It would be useful to give the exact wording of the questions asked.

We regret that this was not appropriately stated, the ISAAC questions were used as they are, but translated to Norwegian. This has now been changed in manuscript page 7. At FU2, the adolescents answered a questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC) translated into Norwegian [20].

On p 8, end of para 1, it is said, “…analyses, but the matching variables were adjusted for SPSS for Windows (version 18.0.0, Chicago, Ill., USA) was used for all analyses. …”. Something seems to be missing in this sentence.

We appreciate the comment; these were two sentences which are now separated: Due to missing data, matching was not included in the analyses, but the matching variables were adjusted for. SPSS for Windows (version 18.0.0, Chicago, Ill., USA) was used for all analyses.

P. 12: “We found no association with any atopic sensitization or disease if the mother had mild or moderate preeclampsia, only if the mother had severe preeclampsia. This suggests that an increasing severity of the maternal preeclampsia increases the risk of atopic disease in the child.” What the authors say here is that there is no biological gradient, or dose-response relationship. This is, according to the Hill criteria, rather speaking against a causal relationship than in favor of.

We regret that this was not appropriately stated; this has been changed in the revised version page 12: There was a trend of an increased risk of atopic disease in the child by an increasing severity of the maternal preeclampsia.
P. 20: Why did the age at FU1 differ between boys and girls?

The target age at FU1 was related to the onset of puberty. This has been clarified in the methods section of the revised manuscript page 5: These ages were chosen due to research questions related to puberty in the “Stavanger Study” [17]

On p 21, in table 1, Gosset's t-test is mentioned, but not in the Methods. Although it is commendable to reveal the real name of the pseudonym "Student", I suspect that this will puzzle many readers. In any case, it should be stated in the Methods.

We acknowledge that this was not presented in the methods section and is now added in the statistics section. We think it educational to name the inventor of “Student’s t-test”. See page 8 in manuscript: Groups were compared with Pearson’s chi-square exact test for the dichotomous outcomes and independent t-tests (Gosset’s t-test) and one way analysis of variance for the continuous outcomes.

P 23, Table 3: It is not clear what the difference between model “a” and “b” is. On the whole, table 3 is very cluttered and hard to read.

We agree that this table is hard to read, but this is a summary of several tables. “a” and “b” are footnotes and explained under the table. An alternative way of presenting the results of table, would be 6 tables containing multiple logistic regression analyses with all covariates included, and in addition, 3 tables with multiple linear regression analyses with all covariates included (instead of table 4). This would be too many tables, and including too many details. Tables 3 and 4 are therefore compressed information of 9 tables into 2 tables.

In the revised manuscript we have explained better in the top texts how to read the tables. It is not unusual to present a summary of several regression analyses this way (e.g.: Sevelsted A, Bisgaard H. Neonatal size in term children is associated with asthma at age 7, but not with atopic dermatitis or allergic sensitization. Allergy 2012; 67: 670–675).

Why adjust for maternal asthma only and not for paternal or for family history of other allergic manifestations?

We have commented on this by changes in the manuscript page 8: The covariate paternal asthma was not included in analyses due to low response rate and page 14: Further, our only data on family atopy available were on maternal and paternal asthma. Paternal asthma was not considered to be a possible confounder for the relationship between maternal preeclampsia and subsequent atopy or lung function in offspring, and there was a low response rate on the question so the variable was not included in statistical analyses.

It would also be interesting to see which variables in the model were still significant after the stepwise procedure. Also, whether the variable maternal asthma had large influence on the point estimate.

As also stated above, the analyses included 9 preliminary tables with results from multiple regression analyses, but as the aim of this study was to study the possible association between maternal preeclampsia and outcomes, only main outcomes are presented. However, footnotes under tables 3 as well as text in the results section, explain which covariates remained in the
models also in the cases where preeclampsia as a variable remained until the final model. The covariates gender and maternal asthma are now added to all final models, as suggested by reviewer no. 2.