Reviewer's report

Title: Influence of advanced age of maternal grandmothers on Down syndrome

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Reviewer: Bendix Carstensen

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General remarks
The paper has improved much, but is still too long considering the simple, but very
relevant and important message. Such an important message as is carried in this paper
deserves to be delivered more succinctly than the case is now.

2 Tables
There should only be two tables, one describing the data material and one describing the results of
the logistic regression.
Thus only table 1 and 4 should be in the paper:
Table 1 should only contain number of cases and controls subdivided by mother’s age,
father’s age and grandmother’s age, describing the data. The means are irrelevant in table
1. Cases and controls should be in adjacent lines for each of the three classifications, so as to make
it clear that it is the entire material that is tabulated in three different ways.
It would help if a “Total” category were added to the age-categories. All the tests are irrelevant, they
are taken care of in the logistic regression analysis.
Table 4 should be the only other table. As I see it, it is a bit overkill to report all models; in my opinion
it would suffice to give marginal and joint estimates in a simple table as I suggested in my previous
review.

3 Specific comments
The following suggestions only cover the major flaws in the language and formulations.
The authors must carefully review every sentence of the paper and consider whether it is essential
and accurate for the description of the study and its results.
The following examples should make it clear that this has not been done so far.
In general, the term “logistic regression” is sufficient, “binary” is superfluous.
p. 3, l. 4: Replace “The age of . . . nondisjunction. Therefore” by: “Besides the known risk factors,
mother’s age, father’s age”. Replace “of high number of DS children.” by: “of Down’s syndrome.”
p. 5, l. 5 from bottom: Delete “Age of the . . . years and above”.
p. 5–6: Replace: “Age of the mother, father and grandmother at birth of the child” by:
“Age of the mother, father at birth of the child as well as age of the grandmother
at the birth of the mother . . . ”.
p. 6, l. 13–14: Replace with “. . . father and grandmother as well as an indicator of
consanguineous marriage as covariates. Results are reported as odds-ratios from
models with one variable at a time as well from a model with all four variables
simultaneously.”
p. 7, l. 4: Delete from “In the controls, . . . ” to ”. . . in the production of DS children”.
Everything in that paragraph is covered elsewhere, particularly in the results from
the logistic regression.
p. 7–8: Delete from “Table 2 reveals . . . ” to “. . . aged 30 years and above”.
p. 8, l. 8: Change to “Table 2 shows the results of the logistic . . . ”.
p. 8, l. 10: Change to: “. . . confidence intervals for the effect of age of . . . ”.
p. 8, l. 12: Delete from “and also . . . ” to “. . . maternal grandmother age”).
p. 9, l. 11 ff: Replace by: “. . . present study, the logistic regression analysis using all
four covariates have shown that when these covariates are considered together the
effects of mother’s and father’s age as well as consanguineous marriage were diluted but still of clinical relevance, albeit not statistically significant. However, the effect of age of the maternal grandmother was not diluted, showing an increase in odds by 30% per extra year. If we look into the pedigree of these families it is clear that whenever . . . ”.
p. 11, l. 1: Delete first sentence.
p. 11, “Conclusions”: The time direction of effects is turned upside down. Replace paragraph by: “Age of the maternal grandmother at the time of birth of the mother is a risk factor for the occurrence of Down’s syndrome, as is the age of the mother and the father and consanguineous marriage as previously established.”