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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1 General remarks
The paper has been reduced in length, but it would still improve if it was clearly stated that the purpose (aim) of the study was to quantify the effect of maternal and paternal age as well as grand-maternal age on the occurrence of Down’s syndrome. The problem as stated is really a case-control study problem, and it should be approached and analysed as such. In particular it seems important that the gathered information on the age of the grandmother is used properly, as this appear to quite a unique piece of informations that is rarely available in such studies.

2 Specific remarks
2.1 Data
What should be done is to form a proper case-control-dataset, by taking the 69 cases of Down’s syndrome and one randomly selected control from each of the 200 control families. For each of these 269 persons in the case-control dataset the following variables should be used:
- Case-control status.
- Consanguinity of marriage (yes/no)
- Age of mother at birth of the child.
- Age of father at birth of the child.
- Age of grandmother at the birth of the mother.
Thus the basis should be a dataset with 260 observations and 5 variables.
Note that ‘age’ is not a well-defined term, it must refer to some point in time, in this case the birth date of the child (or the mother). This should be observed in the description of the data.
2.2 Statistical methods
These variables should be used in a logistic regression with case-control-status as response variable and the other four variables as explanatory variables.
My knowledge of Down’s syndrome is limited so I would not know whether sex of the child is a variable that one should stratify on, i.e. make sure that the proportion of girls is the same among cases as among controls. If this is done, sex should be included in the analysis too. The results would be odds ratios for a Down’s syndrome birth:
- comparing consanguineous and non-consanguineous marriages.
- comparing mothers say 5 years apart in age.
- comparing fathers say 5 years apart in age.
- comparing grand-mothers say 5 years apart in age.
This way the study would produce estimates of the effects of the prespecified covariates. As the number of cases is only 69 it is not advisable to include more covariates in the analysis.

2.3 Note
The above is merely an outline of how data should be processed and analysed. It that can only be used if sufficient knowledge of practical epidemiological data-processing and -analysis is available.