Author's response to reviews

Title: Maternal and neonatal risk factors for childhood type 1 diabetes: a matched case-control study

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Author's response to reviews: see over
We thank the peer reviewers for their comments and appreciate the opportunity of revising our manuscript. We have addressed the reviewers’ comments in a revised manuscript with all amendments highlighted with tracked changes. We provide below responses to the reviewers’ individual concerns.

We look forward to your decision on our manuscript.
Reviewer 1: Thomas Waldhoer

Reviewer’s report:

I would like to see a reference for a recent meta-analysis concerning the effect of maternal age using individual data included into the paper. (Cardwell CR, et al. Maternal age at birth and childhood type 1 diabetes: a pooled analysis of 30 observational studies. Diabetes 2009(Epub);PMID:19875616.)

We thank the reviewer for bringing this recent article to our attention. References to the recent meta-analysis on the effect of maternal age (Cardwell et al. 2010) together with another recent meta-analysis on the effect of birth weight (Cardwell et al. 2010) have now been included in the Introduction and Discussion sections (see page 4, paragraph 2 and page 13 paragraphs 2 and 4).


What is the reason you have chosen only 1083 controls and not all children (~139,000) without diabetes and using unconditional logistic regression? I am aware that this approach will not dramatically increase the power but in light of somewhat “weak” p-values for the effect of smoking it may corroborate these findings. Furthermore, this approach has been chosen in quite a few other papers (see e.g. the Cardwell reference).

When we started designing this study in 2007, we considered various different study designs, including the one suggested. We decided to adopt a matched case-control study with three controls per case, as we felt that having additional controls per case would not dramatically increase the power (Taylor, 1986) but would have certain practical implications. Coupled with our a priori sample size calculation, we felt we would have sufficient power to detect clinically meaningful effects. In retrospect, we accept that our study size could be underpowered to detect the very small effects shown in recent meta-analyses and have added comments relating to this in the Discussion section (page 11, paragraph 2). However, this evidence of such small effects was not available at the design stage of our study. At that time, the reported effects of maternal age on the risk of type 1 diabetes ranged from an odds ratio of 1.34 (Stene 2001) to 2.43 (Patterson 1994) comparing maternal age ≥35 with younger age groups.

Taylor JM. Choosing the number of controls in a matched case-control study, some sample size, power and efficiency considerations. Statistics in Medicine 1986;5:29-36.


“Continuous variables were grouped into categories for analysis.” Using categories is used very often because it allows simple description of the effect. Nevertheless, have you tried including continuous variables as continuous and thereby avoiding artificial group boundaries? Even if the results are same, this could be included into section results just by one sentence stating that both type of models coincide. Furthermore, continuous variables allow easier inclusion of interaction terms.

We have performed the analysis using continuous variables and results are similar to that already reported. We have amended the Methods and Results sections accordingly (see page 7, paragraph 3 and page 10, paragraph 2).

Reviewer 2: Chris Patterson

Reviewer's report:

1 Introduction
   a) There are two recent publications describing meta analyses for maternal age and birth weight (Cardwell et al, Diabetes 2009 and Cardwell et al, Diabetologia 2010) which could usefully be cited and summarised somewhere in the manuscript. Together with the Caesarean section meta analysis (reference 11), these indicate that perinatal risk factors show significant but only rather modest associations with childhood type 1 diabetes.

We thank the reviewer for bringing these recent articles to our attention. References to these two recent publications have now been included in the Introduction and Discussion sections (see page 4, paragraph 2 and page 13 paragraphs 2 and 4).

2 Methods
   a) Among the 611 cases a surprisingly large number (241 or ~40%) were excluded as ‘outwith AMH’. The authors should document these exclusions in greater detail. How many were:
      • born outside the time period 1972-2002?
      • Home deliveries?
      • Resident in Aberdeen but delivered in a different hospital?
      • Inward migrants who were born outside Aberdeen?
We agree that further details of the characteristics of the cases excluded would be informative. Of the 241 excluded cases, 15 (6%) were born outside 1972-2002. We have no information about whether the remaining excluded cases were home delivered, delivered in another Grampian hospital or inward migrants who were born outside Aberdeen. However, there were relatively few home births in Aberdeen and Aberdeenshire, about 7 per 1,000 births in 1998 (Scottish Executive, 2001). The proportion of live births in Grampian recorded in other maternity units in 2005 was 22% (ISD, 2008). This information has been added to the Results and Discussion sections (see page 8, paragraph 1 and page 11, paragraph 3).


b) Was any attempt made to include outward migrants (cases diagnosed in other parts of Scotland but born in Aberdeen) which, judging from the ~40% above, may have been quite numerous but could have been identified in the SSGCYD register and included in the study? Migrants are typically not representative of the population as a whole, so this is a potential source of bias which might have been overcome to some degree by ensuring that selected controls were also still resident in the Aberdeen area when the case was diagnosed.

We were unable to link the whole of the SSG Register (covering Scotland) with the Aberdeen Maternity Neonatal Database due to prohibitive costs and administration issues. We accept that bias might be introduced as a result of this, as we have already stated in the Discussion section on page 12, paragraph 2. However, there is evidence of geographical stability among Aberdonians (Batty 2004). This cohort study found that 73% of individuals born in Aberdeen between 1950 and 1956 who took part in the Aberdeen Child Development Survey, remained in the Grampian region in 1998 (Batty 2004).


b) The methodology used for estimating sample size in a matched case-control design should be cited.

A reference has been cited for the methodology used for estimating sample size (see page 7, paragraph 1).
The power calculation assumes 10% of births in controls have maternal age >35 yr versus 20% in cases, giving an odds ratio of 2.25. This is rather unrealistically large since the best evidence available from meta-analysis (Cardwell et al. Diabetes 2009) estimates an odds ratio of only 1.10 (95%CI 1.01-1.20) for this >35 yr group relative to 25-29 yr group.

In 2007, when we performed this power calculation, the reported effects of maternal age on the risk of type 1 diabetes ranged from an odds ratio of 1.34 (Stene 2001) to 2.43 (Patterson 1994) comparing maternal age ≥35 with younger age groups and we felt that 10% was the minimum difference that was clinically important. With hindsight, we accept a difference of 10% was unrealistically large. Since the recent publication of a meta-analysis estimating an odds ratio of only 1.10, we acknowledge that our study may not have sufficient power to detect such small differences. We have changed our Discussion section accordingly (see page 11, paragraph 2).


c) The use of subgroup analyses to compare the risk factors for early (<5 years) and later onset (5-14 years) type 1 diabetes is not ideal, and instead tests for interaction in the logistic model should be used.

We agree that tests for interactions are more powerful than subgroup analyses and should be performed instead when possible. However, tests for interactions can only be performed when both cases and controls have the characteristic of interest. Since controls do not have an age of diagnosis, it is not possible to perform tests for interactions between age of onset of diabetes and the risk factors being investigated. Therefore, we have made no changes to the subgroup analyses.

3 Results
a) Table 1 seems unnecessary since the information in the top half is included in Table 2, and most of the variables in the bottom half have a trivial number of missing values that need hardly be documented. Perhaps the main points in Table 1 could be stated in a sentence near the start of the Results.

We have removed Table 1 and added information regarding missing values in the Results section as suggested (see page 8, paragraph 2).
b) Para 4 states 'After adjusting for ..., the overall association between maternal smoking and type 1 diabetes was no longer significant (P=0.13). However, there was a suggestion of a reduced risk ..., with an adjusted OR of 0.67 with 95% CI (0.45, 0.99). Judging by this 95%CI not including 1.00, is this adjusted odds ratio not significant (i.e. P<0.05 rather than P=0.13)? The latter P value seems to be from a test which also includes the Unknown group (Table 2).

The overall P value of 0.14 does indeed include the unknown group. The adjusted odds ratio of 0.67 with 95% CI (0.46, 0.99) is from the same analysis and merely suggests a reduced risk in children whose mothers smoked compared to children whose mothers did not smoke. We then performed a sensitivity analysis making different assumptions about the Unknown smoking status. This sensitivity analysis produced similar adjusted odds ratios and confidence intervals with P-values ranging from 0.05 to 0.10. We have clarified the statement in the Results to make this more clear (see page 9, paragraph 2). (Please note the minor changes to these adjusted results are due to the reclassification of mode of delivery to differentiate between elective and emergency Caesarean sections.)

c) In Table 2 the ‘No (reference category)’ for Previous abortions is missing. Also in the Mode of Delivery there is no entry to show n(%) for CS.

We thank the reviewer for bringing these omissions to our attention. We have now included these missing results regarding previous abortions and mode of delivery in the table.

The section comparing Elective and Emergency CS is rather difficult to interpret; unlike all other analyses in the table it does not include all subjects. Instead both ought to be compared using either SVD or no CS as reference category.

We have amended the categories for mode of delivery to include spontaneous vaginal delivery, assisted delivery, elective Caesarean section, and emergency Caesarean section. We have repeated the analyses using this new mode of delivery variable and amended the table of results (page 20) accordingly.

4 Discussion
a) The only positive finding is of an inverse association between type 1 diabetes and maternal smoking, particularly for those diagnosed at older ages, does seems to have some support in the literature albeit from studies where the design may not be perfect. However, some additional consideration should be given in the Discussion to the possible bias through omission from the study of outward migrants, especially if large in number. Also, given the rather large number of statistical tests performed (~20 unadjusted analyses in Tables 2 and 3), there must be some possibility that this result is a type 1 error.
We accept the possible bias due to omission of cases born in Aberdeen Maternity Hospital, but diagnosed outwith Grampian (as already stated in the Discussion section, page 12, paragraph 2) and the possibility of a type 1 error. We have amended the Discussion section to reflect these possibilities (see page 13, paragraph 1).

b) The authors should include some mention about the possible lack of power of their study to identify the sorts of small differences currently being described in meta analyses of perinatal risk factors. So, for example, this is a likely explanation for failure of their study to confirm the Caesarean section association (para 7) as significant. The authors’ finding of an OR=1.16 (95%CI 0.82, 1.66) is actually completely consistent with the meta analysis findings of a 20% increase in risk.

The possible lack of power to detect small differences currently being described in recent meta-analyses has been included in the Discussion section (see page 11, paragraph 2; page 13, paragraph 2 and 3).