Author's response to reviews

Title: Maternal and perinatal factors associated with hospitalised infectious mononucleosis in children, adolescents and young adults: record linkage study

Authors:

Imran Mahmud (imran.mahmud@stcatz.ox.ac.uk)
Omar Abdel-Mannan (omar.abdel-mannan@sjc.ox.ac.uk)
Clare J Wotton (clare.wotton@dphpc.ox.ac.uk)
Michael J Goldacre (michael.goldacre@dphpc.ox.ac.uk)

Version: 2 Date: 17 September 2010

Author's response to reviews:

Maternal and perinatal factors associated with hospitalised infectious mononucleosis in children, adolescents and young adults: record linkage study

Responses to reviewer’s comments

Reviewer 1: Dorothy Crawford

Essential revisions:
The working hypothesis should be stated ie why was the study undertaken and what did the authors expect to find?

WE HAVE NOW ADDED A SECTION TO THE INTRODUCTION (PAGE 5) TO EXPLAIN THE RATIONALE BEHIND THE STUDY.

The IM/EBV references used are old and in many cases have been superseded. For example, reference 1 is used to show a 50% IM rate from late infections, but the incidence of IM is changing and the paper quoted is a hypothesis from the US published in 1982. The most recent and largest study was carried out in the UK and showed a 25% rate of IM from delayed primary EBV infections. This study generated several papers including Crawford et al JID 186: 731-6. 2002, Crawford et al CID 43: 276-82. 2006, Higgins et al JID 195: 474-82. 2007, Macsween et al CID 50: 699-706. 2010. Also, our knowledge of the epidemiology of HD and its association with EBV has moved on since reference 5 was published in 1980. More recent work by RF Jarrett and others would be worth quoting.

REFERENCES HAVE NOW BEEN UPDATED, AND IN PARTICULAR, THE RECENT LARGE STUDY PERFORMED IN THE UK THAT SHOWS A 25% RATE OF IM FROM DELAYED PRIMARY EBV HAS BEEN INCLUDED INSTEAD OF THE PAPER WE REFERENCED ORIGINALLY – OPENING PARAGRAPH OF INTRODUCTION.

The reference Lindberg 1991 is in the text but not the reference list.
NOW REMOVED FROM THE TEXT AS WELL

Page 7, Results, para 1, the authors state that the age profile of IM contrasts with that of primary EBV infection, but IM is a form of primary EBV infection – this needs rewording.

THIS HAS NOW BEEN REWORDED.

Page 9, Discussion, it is important to know how the IM was diagnosed in the hospitalised patients - were IgM anti VCA levels always measured?

WE HAD TO ACCEPT A CODED DIAGNOSIS OF IM ON THE HOSPITAL DISCHARGE ABSTRACT, AS CURRENT PRIVACY REGULATIONS PRECLUDE CHECKING THE ACTUAL MEDICAL RECORDS OF THE PATIENTS FOR FURTHER DETAIL. WE NOW SAY SO IN THE TEXT (3RD PARAGRAPH OF DISCUSSION).

The discussion should be more wide ranging including information on the biology of EBV, HD and MS, for example the recent findings that the risk of development of both IM and HD is related to genetic factors that influence the immune response to EBV during primary infection. Twin studies on HD would also be worth a exploring. The inclusion of these studies may suggest possible explanations for the results found in the present study.

A PARAGRAPH REFLECTING SOME OF THE BIOLOGY HAS NOW BEEN ADDED TO THE DISCUSSION UNDER ‘DELAYED EBV INFECTION, IM HD AND MS’. HOWEVER, WE WRITE FROM AN EPIDEMIOLOGICAL PERSPECTIVE AND HESITATE TO GO INTO BIOLOGICAL/IMMUNOLOGICAL DETAIL FOR FEAR OF GETTING OUT OF OUR DEPTH.

The conclusion in the abstract is very negative. Once the risk factors for IM and HD are explored in more depth this could perhaps be revised.

AS OUR FINDINGS WERE MOSTLY NEGATIVE, WE ARE A BIT CONSTRAINED. HOWEVER, WE HAVE RE-WORDED THE CONCLUSION TO COVER OUR FINDINGS MORE CLOSELY, RATHER THAN WRITING A NEGATIVE GENERALITY.

Reviewer 2: Sally Glaser

This paper evaluates perinatal and maternal predictors of IM requiring hospitalization in children in the period 1970 through 1999. IM is well-established in its associations with subsequent chronic diseases and malignancies, and as such, deserves to be better understood epidemiologically. In addition, the dataset the authors analyze is, indeed, strong in its prospective nature. However, the research question and the discussion of the study findings in this paper are not as strong. The authors essentially justify the study on the established associations of IM with MS and various cancers, particularly Hodgkin lymphoma. While the relation of EBV infection in general, and IM in particular, to these later conditions is important, the authors present no evidence about why maternal and
perinatal factors might be suspected to impact IM development itself, which should be the essential research question. Also, if the authors are going to cite the importance of IM to MS and cancers as a justification for their study, they should indicate why an impact of maternal and perinatal factors on IM specifically might be expected to affect an IM-determined risk of these secondary outcomes. In addition, the paper does not address several potential limitations of its findings, as laid out below. Thus, the complexities around timing and severity of primary EBV infection, and its recognition by the medical community, go undiscussed.

WE HAVE NOW ADDED A PARAGRAPH TO THE BACKGROUND SECTION, PAGE 5, TO EXPLAIN THE RATIONALE BEHIND THE STUDY.

Background
1. Page 4: EBV is not only associated with Burkitt’s lymphoma, it was discovered in it.

WE HAVE NOW ALTERED THE SENTENCE TO REFLECT THIS.
2. Page 4: The association of IM with Hodgkin lymphoma could use a more recent citation to reflect the body of research in this area.

A RECENT REFERENCE (DIEPSTRA ET AL, 20050 HAS NOW BEEN ADDED.

3. Page 4: As stated above, the authors’ primary justification for this paper—“If any perinatal factors are associated with an increased risk of IM, they may also have some relevance to the epidemiology of MS and HD”—is not really adequate evidence to prompt this analysis. Rather, the authors should indicate why we might expect perinatal and maternal factors to impact IM and then how those influences might in turn affect risk of MS and cancers.

NOW ADDRESSED IN THE SECTION ON PAGE 5, AS MENTIONED ABOVE.

Methods
1. Page 5: The term “day case care” should be defined.

DAY CASE CARE IS NOW DEFINED.

Results
1. It would be useful if Table 1 included relative frequency distributions.

NOW ADDED TO TABLE

2. Table 1 suggests gender differences in IM cases by age. The authors might mention this. It is also potentially relevant for whether IM in children has different predictors than IM in young adulthood.

WE NOW MENTION THE APPARENT GENDER DIFFERENCES SUGGESTED IN TABLE 1 IN THE 1ST PARAGRAPH OF RESULTS. THERE WAS NO STATISTICALLY SIGNIFICANT DIFFERENCE.

3. How was social class determined? This should be described in the Methods.
Also, there should be labels for the social class categories in Table 2.

THERE IS NOW A SECTION IN METHODS – BOTTOM OF PAGE 6, TOP OF PAGE 7 – TO EXPLAIN HOW SOCIAL CLASS WAS DEFINED AND MEASURED. WE HAVE LABELLED THE SOCIAL CLASS PART OF TABLE 2.

Discussion

1. Page 9: Before the authors call for meta-analyses, it would be important to better justify why perinatal and maternal factors might be important for IM requiring hospitalization. Perhaps such cases are, in fact, the most interesting to the development of other chronic diseases, if by being symptomatic enough to lead to hospitalization, they reflect particularly poor host management of primary EBV infection. However, this is not discussed. In general, the Discussion would benefit substantially from some thoughts about how the study findings impact primary EBV infection and its manifestation as IM in young people.

WE HOPE THAT THE NEW SECTION ON PAGE 5, COVERING THE REASONS WHY (AT LEAST IN THEORY) PERINATAL FACTORS MIGHT BE IMPORTANT IS NOW SUFFICIENT TO JUSTIFY OUR COMMENT ABOUT ‘FURTHER WORK’ AND, IF WARRANTED, META-ANALYSIS. THERE IS NOW ALSO A PARAGRAPH AT THE END OF THE ‘STRENGTHS AND LIMITATIONS’ SECTION OF THE DISCUSSION ADDRESSING THE USE OF HOSPITAL ADMISSION DATA.

2. Page 9: The Discussion would be greatly enhanced by a thorough discussion of the generalizability of the findings, given that they are based on hospitalization for a typically mild disease. There are three issues to address: 1) are hospitalized IM cases likely to be representative of all IM cases, and if not, how might the difference impact the study findings? 2) is IM in children different than IM in adolescents, particularly where the need for hospitalization is involved? and 3) have hospitalization and diagnostic practices for IM changed during the study period and, if so, how might that have biased the findings?

AS ABOVE; AND WE HAVE NOW GIVEN DATA ABOUT HOSPITAL ADMISSION RATES SHOWING THAT THEY HAVE CHANGED VERY LITTLE IN THE PERIOD COVERED BY THE STUDY. THIS SUGGESTS – THOUGH WE HAVE NO WAY OF PROVING IT – THAT HOSPITALISATION AND DIAGNOSTIC PRACTICES PROBABLY HAVEN’T CHANGED

3. Page 10: If there has been an increase in hospitalizations for IM, as the authors state, has there been an increase in IM in general?

WE HAVE NOW CHANGED THIS PARAGRAPH, AND HAVE GIVEN HOSPITAL ADMISSION TRENDS BASED ON THE ORLS DATASET USED FOR THE MAIN ANALYSES. IN FACT, HOSPITALISATION RATES HAVE CHANGED VERY LITTLE – WE NOW MAKE THIS CLEAR.

How do the authors reconcile the association in their data of younger maternal
age and IM with both the observation that IM admissions are increasing over time, and yet the shift to a later age at first birth over time?


4. Page 10: The authors should try to explain findings in the Discussion, not just repeat them (e.g., third full paragraph regarding pre-eclampsia and forceps delivery).

THE ASSOCIATIONS WITH PRE-ECLAMPSIA AND FORCEPS DELIVERY WERE NOT SIGNIFICANT AFTER MULTI-VARIATE ANALYSES, SO IT SEEMS UNLIKELY THAT THERE WAS ANY TRUE ASSOCIATION. WE NOW SAY THIS.

5. Page 10: The discussion of twins raises the question of sibship and birth order in general on findings. The authors should address this. 6. Page 10: As above, the dataset presumably lacks information about birth order and sibship size for IM patients, and one wonders whether the maternal age finding is confounded by sibship size, with mothers’ age being correlated with the patients’ birth order. The authors should address this. In general, the complex sociologic issues of marital status, social class, and sibship size, as well as the extent to which this complex might have changed over the study period, complicate the interpretation of these findings in a way that is not really discussed.

WE DO NOT HAVE INFORMATION ON BIRTH ORDER OR SIBSHIP SIZE PER SE, BUT WE DO HAVE INFORMATION ON PARITY. WE HAVE GIVEN A NEW TABLE, TABLE 3, SHOWING THE PARITY DATA IN GREATER DETAIL. IT CAN STAND PROXY FOR BIRTH ORDER (IE IT SHOWS FIRST-BORN, SECOND-BORN, ETC). THERE IS REMARKABLY LITTLE EFFECT OF PARITY/BIRTH ORDER. PARITY CAN ALSO BE CONSIDERED AS A PROXY FOR OLDER SIBLINGS. MULTI-VARIATE ANALYSIS ADJUSTED FOR ANY CONFOUNDBING BETWEEN PARITY AND MATERNAL AGE – WE NOW MAKE THIS CLEAR IN THE LAST PARAGRAPH OF PAGE 9.