Reviewer's report

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

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**Reviewer:** Sally Glaser

**Reviewer's report:**

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.

Specific observations follow.

**Background**

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

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.

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.

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

Results

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

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.

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.

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.

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?

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? 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).

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.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.