Author’s response to reviews

Title: Space-time clustering of childhood central nervous system tumours in Yorkshire, UK

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Version: 2 Date: 6 December 2011

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POINT-BY-POINT RESPONSES TO REVIEWERS’ COMMENTS

We thank the reviewers for their most constructive and helpful comments. Full point-by-point responses are given below.

REPORT FROM FAITH DAVIS

Major

General Comments

1. The hypothesis has now been amended to include any transient aetiological agent. The background and discussion have been enhanced to include additional literature. Additional narrative ties the methods back to the hypothesis, gives the logic involved in the analytic decision and addresses the strengths and limitations of the different methods used. This study has the following merits: (i) it is much more up to date than the previous analyses from the whole of GB; (ii) two distance metrics were used: fixed geographical distance thresholds and variable nearest neighbour (NN) thresholds, allowing an assessment to be made to determine whether clustering is more likely to have arisen from a geostationary or an infective process (this was not done in the previous studies from GB [12, 13]); (iii) the full set of diagnostic groups were analyzed; and (iv) full diagnostic case review was performed consistently by a single experienced neuropathologist. [Text added – Background, Hypothesis & Discussion].

Specific Comments
Methods
2. Para 2 - The case review was conducted by a single neuropathologist. [Text Added – Methods, Study Subjects, Final Sentence].

Discussion
3. Para 1 – This paragraph has been made consistent with the abstract and the results section. The main results are for overall space-time clustering (based on the K-function method). The secondary results concern the identification of individual clusters (based on Kulldorff’s method) – see page 11, paragraph 3, lines 3-5 [Text amended – this paragraph].

Minor Essential
Background
4. We now include seasonality studies and case-control studies that have looked at the infectious disease hypothesis, as well as other environmental exposures. [Text added – Background, paragraphs 1 & 2].

Prior Hypothesis
5. We have changed the first hypothesis to state that: “a primary factor influencing geographical or temporal heterogeneity of incidence of childhood CNS tumours was related to a transient environmental agent” and omit any mention of infections at this point. [Text amended – Prior Hypotheses, line 3].

Methods
6. There were two separate sets of analyses. First, the K-function method (supplemented by the Knox method) was used to test for overall space-time clustering. Second, Kulldorff’s scan statistic was used to identify individual clusters and to test for differences between cases within and not within clusters (using a case-control method). This is now made clear in the background section. [Text added – Background, final paragraph & Statistical Methods section].

Results
7. Para 4 – The rationale for the analysis of time periods has now been moved into the methods section & the explanation in the discussion has been correspondingly reduced. [Text added – page 11, paragraph 2].

Discretionary
Statistical Methods
8. An interpretation of the interactions is now provided on page 12. [Text added – Pages 12 & 13].

10. Page 14 para 3. The results of pairs of cases with one male and with one female are now only stated once. [Text amended – Page 15, final two lines].

11. Page 17 – top – We agree that this discussion about transient agents is appropriate and doesn’t overstate the link to infectious processes. [No changes made].

12. The paper has been rewritten so that the reader can understand more clearly what each statistic is telling them with respect to the hypothesis, how these regional data add to the previous national and related literature on the topic and how the results fit within the larger body of literature on infectious agents and other transient environmental exposures. [Changes made throughout the manuscript].

REPORT FROM MICHAEL SCHEURER

General Comment

The central hypothesis has been amended to test the involvement of a transient environmental agent in aetiology. [Changes made throughout the manuscript].

Major Compulsory Revisions

1. We have changed the primary hypothesis to posit that “a primary factor influencing geographical or temporal heterogeneity of incidence of childhood CNS tumours was related to a transient environmental agent”. We have made changes throughout the manuscript. We acknowledge that clustering could be related to various transient exposures including infections and pollution. However, such patterning would not be consistent with a factor related to socioeconomic position as this would convey a persistent (and not a transient) environmental influence. [Changes made throughout the manuscript].

2. The main results are based on the K-function method, which has two versions, one based on the fixed geographical distance metric and the other based on the variable NN metric. If clustering is identified only by the fixed geographical distance threshold in a heterogeneous population, this could suggest that it has occurred purely as an artefact of variations in population density. However, if clustering has arisen due to a geostationary exposure, then this could lead to detection only by the fixed geographical distance threshold. Alternatively, if clustering has arisen due to an infective process, then this could lead to detection only by the variable NN threshold. In the study both metrics gave significant results for PNET (see Table 4). Therefore, it is not possible to distinguish between the two possible types of transient exposure. The abstract and main text have been amended for clarity [Text added – Abstract, Discussion, paragraph 3, second sentence & elsewhere throughout the manuscript].

Minor Essential Revisions

1. All CNS tumours, except intracranial germ cell tumours, are captured by the ICCC IIIa-f codes. Benign tumours included cases of ependymoma, other
gliomas, other specified intracranial and intraspinal neoplasms and unspecified intracranial and intraspinal neoplasms. [Text Added – Methods, Study Subjects, End of Paragraph 3].

2. We now state upfront that the analyses are based on both the address at birth and the address at diagnosis. [Text Added – Background, Paragraph 3, Second Sentence].

3. An exact geographically based match to the underlying population distribution was not available. Thus we used the case distribution as a proxy for the underlying population distribution to test whether population density was associated with space-time clustering. [Text Added – Statistical Methods, Page 10, Paragraph 2, Second and Third Sentences].

4. We have now added the interaction based on “time at birth and place at diagnosis” [Text Added, page 12 & 13 & New Table].