Author’s response to reviews

Title: Late onset depression after stroke could be related to small vessel disease: Mood After Stroke: a cross-sectional case control study.

Authors:

Kausik Chatterjee (kausik.chatterjee@coch.nhs.uk)
Susan Fall (susan.fall@ghnt.nhs.uk)
David Barer (david.barer@ghnt.nhs.uk)

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Author’s response to reviews:

Angelina Ilievska
c/o Lisa Martin
BMC Editorial Admin
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Dear Ms Ilievska / Ms Martin


Thank you for asking us to revise this manuscript in the light of the reviewers’ comments. I apologise for the delay but neither Dr Chatterjee nor I have had any time to spend on it until this week. Thank you for granting a 3 day extension in recognition of this.

I have attempted to address the reviewers’ points under the following headings (changes to the m/s indicated in italics):

Title and Aims of Study

I am afraid I cannot understand how the initial phrase “Late onset depression after stroke could be related to small vessel disease:” came to be incorporated into the title and apologise for the error. As well as being grammatically inappropriate it has clearly given the misleading impression that our sole purpose was to test a specific hypothesis about the relationship between cerebral small vessel disease and post stroke depression (PSD). In fact we tested a range of factors and I have amended the title to make this clear.

We deliberately avoided discussion of particular aetiological theories in our short
Background section. In particular in our analysis of neuro-imaging factors, we focused on chronic changes as the study was not designed to examine the possible link between PSD and the location of the index stroke lesion. I have added a short phrase near the end of the Background section to make this clear.

We are aware of interesting work distinguishing affective from apathetic components of mood disorder after stroke, but unfortunately we did not collect data on this and so feel it would be inappropriate to comment on this issue in this paper.

We feel that the primary purpose of a paper like this should be describe the study as planned and report the findings, rather than to produce a clear message in support of or against a particular theory, though we have devoted several paragraphs in the Discussion to the ‘vascular depression hypothesis’.

Study Design

We are sorry if some key features of the study design were not clear. It was a cross-sectional case-control study, aiming to identify risk factors for development of PSD, so both cases and controls were stroke survivors. As far as possible we wanted to eliminate the influence of post stroke disability, which is likely to overwhelm other effects, and of age, which is complex and nonlinear, so we tried to match for these variables. Group frequency matching was the only practical procedure, so a method of analysis designed for matched pairs, such as McNemar’s test, would not have been appropriate.

We excluded minor depressive disorder, according to DSM-IV criteria, as we wanted to maintain a clear separation between cases and controls. If we had not done this, we could easily have recruited many more subjects but possible causal effects might have become blurred.

I have added brief comments in the text which I hope will help to clarify these points.

Specific Points Raised

We are grateful to the reviewers for spotting several errors or omissions, for which we apologise

ABSTRACT

• Line 4 of the Methods section in the Abstract should begin: “socio-economic factors” rather than “psychosocial factors”. The measures used are outlined under ‘Methods’ / ‘Interview’ / paragraph 2. Some psychosocial factors (such as negative life events) were recorded, as they could have acted as confounders for biological PSD risk factors, but since we found no important effects in analysis, only minimal details are given. Social participation and quality of life scores were also measured but it is more logical to regard these as consequences rather than
potential causes of PSD.

• I have removed reference to frequency matching at the end of the Abstract, but emphasised that it was a cross-sectional study.

METHODS

• Because of its key importance, I have brought forward the section on Case and Control Categorisation and included it within the Interview section (since the categorisation was performed at interview). I have emphasised that both cases and control subjects were stroke survivors.

• In addition to assessing the pre-stroke Rankin score, we also asked about pre-stroke mobility and urinary continence, graded along similar lines to these items in the Barthel. I have clarified this in the Methods section under ‘Other Assessments’.

RESULTS

Para 2.

• The DSM-IV manual does sub-classify episodes of major depression into ‘mild, moderate and severe’ (I have attached the relevant section from the manual to my email). Although it may not be used widely in clinical practice, it is a recognised research classification and I have added a citation to the DSM-IV manual.

• This was a cross-sectional study and it is important to understand that the cases with PSD and non-depressed control subjects were identified and interviewed at least 9 months (average over 2 years) post stroke. Thus it is perfectly reasonable (and reassuring) that the majority of the cases had already been diagnosed and that many of them were already on treatment for post-stroke depression (I have added a note to emphasise that depression was diagnosed and treated after the stroke). Since our aim was to study the aetiology of PSD, it only mattered that the cases satisfied the criteria for major depression, whether or not they were on treatment. On the other hand, it was important to ensure that control subjects did not even have mild depression, so we excluded anyone who had been treated for depression within the last 6 months. We feel that the rigorous selection of cases with clinically confirmed major depression and controls without depressive symptoms (but with similar levels of physical function) is one of the main strengths of this study, in comparison with other studies, which have relied on the responses to depression screening questionnaires to define ‘cases’.

Para 3.

• We would have been disappointed if cases and controls had differed significantly in terms of age and Barthel scores, after we had matched for these
variables! Nevertheless we felt it was important to show that, despite the matching, there were slight differences, which had to be adjusted for in analysis to avoid confounding.

- Mobility and urinary continence: please see under METHODS above.

- We apologise for using an unexplained abbreviation: ‘ADL’ does indeed refer to activities of daily living and was measured using the Barthel Index. In the Methods section, I have made it clear that the Barthel was the main measure of functional status, used for group frequency matching, but that we also used the FAI to measure instrumental ADL and social participation.

Para 5 and Neuro-imaging section.

- I agree it is confusing to refer to the location of the index stroke lesion in both Tables 1 and 3. Whereas all cases and controls are included in Table 1, the data in Table 3 are from the subset of participants for whom we had full CT brainscan information, so the numbers are smaller and the results are presented in different ways (Table 1 takes account of clinical as well as neuro-imaging information). I have checked the results in both tables and they are correct, but to avoid confusing the reader I have removed the ‘lesion location’ section from Table 1.

- Since Table 1 now contains only data from clinical and interview assessments, it is logical to keep the order within the Results section (remembering that the Neuro-imaging section focuses on chronic changes rather than the acute stroke lesion).

Neuro-imaging section, Para 2.

- I have moved the word ‘however’ into the middle of the sentence.

Multivariate Analysis section, Para 3.

- I have turned these two sentences around to emphasise that smoking and ‘history of hypertension’ were eliminated from the multivariate model after adjustment for other factors. I hope the meaning is now clearer, but there is inevitably a lot of difficult technical detail in this section.

DISCUSSION

- As requested, I have begun this section with a summary of the main findings. We are not convinced that this is best, as we feel the role of the Discussion should be to qualify the study findings and to put them in context, rather than to emphasise a particular ‘message’. Although the ‘vascular depression hypothesis’ was one of the central issues in this study, we felt there was already enough emphasis on it in the Discussion. There is also some overlap with the Conclusions section. Nevertheless we hope that beginning the section with a brief summary of findings makes it easier for the reader.

- Although case-control studies use powerful methodology, they are subject to
numerous potential biases and it is important to discuss these carefully. Nevertheless I have shortened the Discussion by omitting some of the less important points.

- We appreciate that the Discussion is still quite long but feel this is necessary to explore the complex theoretical and empirical relationships between factors such as blood pressure, homocysteine, cognitive impairment, different patterns of subcortical changes on CT and depression, and to propose directions for future research.

The changes have been seen and approved by Dr Chatterjee, the first author. We hope the reviewers feel that these changes have addressed their concerns and that the paper is now acceptable for publication.

Yours sincerely

David Barer
Prof. / Cons. In Stroke Medicine