Author's response to reviews

Title: Exposure to General Anesthesia and Risk of Alzheimer's Disease: A Systematic Review and Meta-Analysis

Authors:

Dallas P. Seitz (seitzd@providencecare.ca)
Prakesh S. Shah (pshah@mtsinai.on.ca)
Nathan Herrmann (nathan.herrmann@sunnybrook.ca)
Joseph Beyene (beyene@mcmaster.ca)
Naveed Siddiqui (naveed.siddiqui@uhn.on.ca)

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Author's response to reviews: see over
Editorial Board  
BMC Geriatrics

Dear members of the BMC Geriatrics Editorial Board:

Thank you for your comments dated August 24, 2011 on our manuscript MS-1988426194561308 “Exposure to General Anesthesia and Risk of Alzheimer’s Disease: A Systematic Review and Meta-Analysis” submitted as a Research Article in BMC Geriatrics. We appreciate the suggestions made to improve our manuscript. Below are our responses to the requests made by the reviewers. We have highlighted the changes in our manuscript using the Track Changes feature of Word.

Reviewer 1:  
This is an important and novel piece of research. There remains a perception despite evidence to the contrary that GA is associated with cognitive decline and or disease. This well presented and methodologically sound meta-analysis is an important counterpoint to that perception.

- We thank Reviewer 1 for highlighting this aspect of our manuscript.

1. In the background, I would like to see a sentence or two summarising the meta-analysis / systematic reviews with regards to these papers conclusions of POD and POC (References 13-17).

- We have added the following statement to the introduction. “Most reviews found that there was limited evidence to suggest any difference between general anesthesia and regional anesthesia on the incidence of post-operative delirium or POCD [13, 15-17]. One exception was a review on anesthesia for hip fracture surgery which found a reduction in acute postoperative confusion for regional anesthesia compared to GA [14].”

2. In the abstract results section – I would add that no cohort studies were identified as I was surprised at the emphasis on case-control studies and wondered if this was a methodological flaw that only case-control studies had been sought. This addition would put that concern to bed straight away.

- We have modified the results section of the abstract to now read: “A total of 15 case-control studies were included in the review. No cohort studies were identified that met inclusion criteria.”
3. There could also have been greater clarity in the methods section about the acceptance of control groups that were either no surgery or surgery but no GA. This wasn’t always clear and I have concluded this from the results section.

- We have modified the methods section to clarify this issue. The primary comparison for exposure to GA was not having any surgery under GA. The methods section now reads: “Exposure to GA was defined as any reported history of surgery under GA when compared to no history of surgery under GA.”. The next statement in the methods outlines that a secondary comparison was the risk of Alzheimer’s disease associated with GA when compared to regional anesthesia: “Where information was available, the following information was also recorded: history of exposure to GA when compared to regional anesthesia (RA)....”

4. There were several typos and other grammatical errors in the manuscript – especially in the background and discussion – I suggest that the authors proof read again before copy editing.

- We have proofread and corrected any spelling errors identified in the previous manuscript.

Reviewer 2:
Undertaking epidemiological meta-analyses are very hard to undertake well and in general the authors have done a good review here.

- We thank reviewer 2 for highlighting this aspect of our study.

There are a few points that make some of their results less generalisable than they discuss. In general what is presented is a good systematic review of the narrow hypothesis mentioned by the authors. I find this somewhat disappointing that a very clear and good quality review systematic is let down by the quality of the original question. However it appears as though the original question is not really the question at all. There is a difference between AD and dementia though the authors appear to interchange and swap the two.

- Our review was focussed on the association between exposure to general anesthesia and the development of Alzheimer’s disease. We have now used the term Alzheimer’s disease instead of dementia to avoid any confusion caused by using these terms interchangeably.

Major compulsory revision
1. The use of terms for epidemiological investigations traditionally are poorly coded within the Bibliographic databases and can therefore lead to the exclusion of good epidemiological investigations. This may well be the case here.

- The search terms utilized in our study were broad and designed to be sensitive. Although our research question was narrowly defined, our search of electronic databases resulted in retrieval of over 1,300 citations which were reviewed for potential inclusion in the review. Our handsearch of reference lists identified other potentially relevant articles. Our search strategy identified observational studies that assessed the relationship between anesthesia and Alzheimer’s (e.g. Zuo, 2010; Bohnen, 1994) and other studies that evaluated exposure to general anesthesia only as secondary outcomes as part of larger studies examining risk factors for Alzheimer’s (e.g. Heyman, 1984; Kokmen, 1991, and
2. The other factor is the use of just AD and the definition of AD used by the authors will be
enormously restrictive of some of the largest epidemiological studies that have been used over a
number of years. However many of the studies are just not AD but dementia. This needs to be
clearer. It appears as though dementia was used, but AD is the hypothesis.

- The definition of Alzheimer’s used to include studies in our review included studies that
used a case definition of Alzheimer’s which were consistent with current clinical
diagnosis of AD. Some of the earlier publications included in our review pre-date the
commonly utilized standard AD criteria such as the NINDS-ADRDA criteria. All of the
included studies examined the outcome of dementia consistent with Alzheimer’s disease.
To investigate the possible effect of differing diagnostic criteria on the association
between general anesthesia and AD we included an additional subgroup analyses
comparing the method of determining dementia diagnosis (standard criteria vs. other
criteria). “Criteria for Defining Dementia: Eight studies used standardized criteria for
diagnosing AD [27,28,30-35] and seven studies used clinical criteria or other methods for
diagnosing AD [24-26,29,36,38,39]. The OR for exposure to GA and development of AD
in studies that used standard criteria was 1.06 (95% CI: 0.84 – 1.33, p=0.63) and the OR
for GA and AD in the remaining studies was 1.05 (95% CI: 0.90 – 1.22, p=0.53). There
was no significant difference in the OR for these subgroups (Q=0.13, p =0.72.).”

3. I do not understand all their results. Some a quoted as being calculated from the exposed
cases and controls but they do not agree with the papers themselves. Why have the authors
changed the results? This is particularly worrying where their results are now attenuated from
the original papers. They have additionally highlighted odds ratios that agree with their ideas
above other ones presented that do not. Why did the authors not discuss with the original study
authors the best results to use?

- The observational studies included in our review often reported odds ratios derived from
both crude and adjusted estimates. In our methods section we described that we only
included studies that controlled for the crucial variables of both age and gender, be that
through matching on these variables or statistical adjustment using multivariate
regression. In the results table we presented both the number of exposed cases and
controls and the odds ratio that was determined to be the least biased estimate of the
association between the anesthesia and Alzheimer’s disease for the purposes of our study.

4. Do any of the bibliographical databases mentioned by the authors cover the PsychInfo sets of
journals, that include some very important papers that are not generally in Medline. [I’m afraid
I do not know the google scholar reach].

- We cannot comment on the degree of overlap between Medline, EMBASE and
PsychInfo. The number of journals contained in Medline (>5,500 journals;
http://www.nlm.nih.gov/tsd/serials/lji.html) and EMBASE (>7,500 journals;
http://www.embase.com/info/what-is-embase/coverage) covers the vast majority of
clinically oriented journals. We supplemented these electronic database searches with
additional handsearches of reference lists and searches of Google scholar which does not
have any limitations on the journals searched using this interface and includes conference
proceedings, theses, and other potential sources of information (http://scholar.google.com/intl/en/scholar/about.html). In addition, we repeated the search strategy in PsychINFO and found no additional studies that were overlooked in our initial search. We are therefore confident that we have not missed any other important papers. However, to address the reasonable concerns of the Reviewer, we proceeded with the following analysis:

- To estimate the impact of potentially having missed some articles with our search strategy we have included the following sensitivity analysis: “To investigate the potential effect that additional studies would have had on our results, we calculated the Orwin’s failsafe N to determine the number of studies of a given effect size that would be required to change the observed OR by a given amount. We selected a mean observed OR for a hypothetical group of missing studies to be 1.3 based on the observed upper range of the ORs in the studies identified in our review. Assuming a minimal clinically significant OR of 1.2 for the association between GA and AD, an additional 25 studies, each with a mean observed OR of 1.3, would be needed to arrive at an statistically significant OR of 1.2.”

Minor Essential revisions
5. The discussion of AD is simplistic at best and is not really the most up to date literature on AD that have been recently reviewed in a systematic way.
   - Presumably this is a comment on the description of AD provided in the introduction section of the manuscript. Our introduction provides a brief, focused, and accurate, description of the impact and pathophysiology of Alzheimer’s disease providing enough context to justify examination of the association between GA and AD. Should the Editor feel that a more detailed, general description of AD would be appropriate for the Journal readership, we would be happy to provide one.

6. There is obviously a problem with individuals who are already well on a cognitive decline pathway who may not be offered the same opportunity for GA as individuals who are of normal cognition and this needs to be considered within the analysis.
   - We agree with the Reviewer, and this is a potential limitation of our study. We have included the following sentence in the discussion to reflect this point: “Finally, some individuals with early cognitive impairment or dementia may be less likely to be offered surgical procedures which may have reduced the apparent observed risk of AD associated with GA in our review.”

Discretionary revisions
7. It is difficult to understand how a randomised controlled trial could be undertaken in this area. The risk of AD is low and the patient group that could be randomised is small.
   - We agree that a randomized controlled trial using a clinical diagnosis of Alzheimer’s as endpoint would not be feasible; however, in the discussion we suggested other potential endpoints such as biomarkers or neuroimaging that may be possible to utilize to examine the effects of general anesthesia on Alzheimer’s disease pathology, as changes in some neuroimaging modalities or biomarkers may precede the clinical manifestations of AD by several years.
Thank you for considering our manuscript for publication in *BMC Geriatrics* and we hope that you find our revised manuscript suitable for publication.

Sincerely,

Dallas Seitz MD FRCPC