16-Apr-2019

Dear Dr. Sanders

Manuscript ID BMJ-2019-049203 entitled "Effect of Major Surgical and Medical Admissions on Cognitive Trajectory: 19-year follow-up of the Whitehall II Longitudinal Prospective Cohort Study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Jose Merino
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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (chair), Tim Cole (statistician), Elizabeth Loder, Helen Macdonald, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- We were interested in the question. The possible effect of general anesthesia on cognition has been widely studied and remains controversial. Can the authors say something about anesthesia in their ' major surgery' category ? Is that the essential factor, as minor surgery did not show any cognitive decline ?

- The statistical analysis is complex but very well described. Our statistician did not have major concerns but did have two questions that you may address in the methods: why two constants in the regression equation? Why include diabetes and smoking in the models?

- One of our editors wanted additional clarifications. Were the patients planned surgical admissions? Did they undergo emergency surgery?

- The strength of the association is difficult to appraise, as these psychometric scores are not easily translated into an intuitive QoL or disability score. Could you provide more information on the magnitude and clinical importance of the decline?

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

To Editors
While this manuscript addresses a clinically important issue, I worry that a sizeable proportion of the "major" surgeries likely represent relatively minor procedures, which would not be expected to have much effect on cognition. Also, the population is relatively young, so susceptibility to the deleterious effects of major surgery will be diminished. The statistical modeling is very complex, so the manuscript should be carefully reviewed by a biostatistician with expertise in longitudinal analyses.

To Authors
This is a well-written manuscript that presents results from a longitudinal analysis of data from the Whitehall II study to determine whether incident major surgical admissions induce long-term changes in cognitive trajectory. The authors found that major surgery is associated with a small, long-term change in the cognitive trajectory that is less pronounced than that for major medical admissions. The manuscript has several strengths, including: its large size and duration of follow-up, assessments of cognition before and after hospitalizations, and translation of effect estimates to equivalent years of cognitive aging.

Major Comments

1. The authors used a very low bar for defining a major surgery, namely an overnight hospital stay coupled to an ICD-10 code. There is no requirement that the surgical procedure occurred in an operating room. It is highly likely that a sizeable proportion of the "major" surgeries represented relatively minor procedures. The authors should use a more conservative definition of major surgery that includes only procedures that occurred in the operating room, as recommended by: Kwok AC, Semel ME, Lipsitz SR, Bader AM, Barnato AE, Gawande AA, et al. The intensity and variation of surgical care at the end of life: a retrospective cohort study. Lancet. 2011;378(9800):1408-13. The authors should also provide a complete listing of the ICD-10 codes used to identify major surgery.

2. It is very odd that the number of hospitalizations for "major" surgery is so much larger than the number of hospitalizations for other medical conditions (2932 vs. 2114). The opposite is true in the US.

This raises serious concerns about the authors' ascertainment of hospitalizations and/or use of ICD-10 codes.

3. The study population was relatively young, with a mean age of only 55.5. Susceptibility to the adverse consequences of major surgery and other hospitalizations will be much greater in an older population. At the very least, the authors should repeat their analyses in the subgroup of participants who were 65 years or older.

4. The statistical modeling is very complex, so the manuscript should be carefully reviewed by a biostatistician with expertise in longitudinal analyses.

5. Table 1 is very difficult to understand, and the right column of results is particularly unclear. The categories are rather nonspecific, with the vast majority of surgeries listed as "Other".

6. Figure 1 does not provide sufficient details. Specifically, the authors do not indicate the timing of the hospital admissions relative to the cognitive assessment intervals. It is likely that some of these intervals included more than 1 hospitalization and potentially both surgical and medical hospitalizations. How were the authors able to distinguish the effects of these different hospitalizations within a single interval?

7. Figure 3 is also very difficult to understand, with rather unusual color patterns and discontinuity between the left and right sides of the figure.

Minor Comments

1. Table 2: p-values should not be reported < 0.001.

2. More complete details should be provided for the Framingham cardiovascular disease risk score.

3. What do the authors mean by "baseline": "… baseline adjustments for numbers of surgical admissions, medical admissions, and stroke admissions (including events that occurred after cognitive follow-up but during the range of years analyzed), …"

4. Information should be provided about the amount of missing da

Additional Questions:
Please enter your name: Thomas M. Gill, M.D.

Job Title: Professor of Medicine

Institution: Yale School of Medicine

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
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HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-co
mpeting-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Mervyn Maze

University of California, San Francisco, Department of Anesthesia and Perioperative Care

GENERAL COMMENTS:
The authors are to be congratulated on applying their well-honed expertise in the area of Perioperative
Cognitive Disorders (PND) to the Whitehall II database, one that has been validated for reliability of the
cognitive assessment because "556 subjects underwent retesting within 3 months of their initial
assessment with good test-retest reliability." In particular the authors seem to have overcome some of
the major methodological issues that have plagued the reports from previous observational studies of
defined databases. In particular the very large cohort size, the use of "stroke" as a positive control, and
the prolonged duration of follow-up overcome limitations in previous studies.
The use of the "step-change" in their choice of a Bayesian model is appropriate because the events that
precipitate and follow a hospital admission for a major medical condition or major surgical procedure do
impose a "new condition" (possibly inflammation-based) capable of impairing function.
The choice to quantify the disorder in terms of an enhanced age-related cognitive trajectory decline has
been used in past Whitehall II database interrogations. However, as the "additional months/years" of
decline apply to an average patient at age 67.4 years, I am not sure how meaningful using these data
would be in explaining possible surgical risk to an 80 year-old. As this is not the typical manner in which
prevalence of the PND conditions (± interventions) are reported, I would ask the authors to also cater to
the existing PND field in which a binary outcome is used that describes the likelihood of crossing a
threshold to having the new condition. However, the problem with this "usual PND investigational
approach" is that there is lack of uniformity regarding the diagnosis of the PND conditions apart from
delirium whose features are listed in the DSM V. While I understand the authors' choice to consider the
entire spectrum of cognitive assessment and not reduce it to a binary outcome, I would have benefitted
further with an additional description of the outcome using the binary approach. By also reporting on the
binary outcome the authors' may discover that they have sufficient granularity to comment on risk
factors that modulate the incidence of the PND disorders.While I appreciate that additional work that will
be needed, I do think that it will make this report more meaningful to those working in the field.
SPECIFIC COMMENTS
Abstract/Participants:
While it is stated that one could have up to 5 cognitive assessment, was there a minimum # of cognitive
assessments that an enrolled pat could have?

Abstract/Participants:
"to" missing following "linkage" and prior to "Health Episode…"

Abstract/Results:
Define "Minor surgery"

Introduction:

For those concerned about Perioperative Neurocognitive Decline, it is definitely the "step-change" in cognitive trajectory (worsening of the expected cognitive decline either through an early inflection point or a change in the trajectory). In the Introduction, there needs to be more about the "binary" nature of the condition (presence of a > 2SD change of the cognitive score).

I appreciated the discussion on limitations of existing observational studies that report on the interrogation of an already collected database to elicit the longitudinal changes that are then linked to a medical or surgical "incident." When flaws of previous studies are highlighted it is important to demonstrate how the existing study avoided these flaws without creating any new ones.

In the following sentence there is a lack of punctuation between the main and dependent clauses. "Longer life expectancy implies increasing number of surgeries in older adults hence better understanding of the extent of any cognitive "hit" following surgery is urgently required."

Methods/Exposures
It is stated that
"To limit effects of intrahospital transfers, we linked together any admissions within 14 days."
How would the data be handled if a patient had a major surgical procedure but was discharged and then re-admitted within the 14-day period with a postop complication, e.g., sepsis and/or stroke? As stated above it appears that the effect of the medical complication of a surgical complication is now lumped together with the major surgical procedure.

From the following sentence, I presume that every subject had a minimum of one cognitive assessment. "Admissions during the study period but without cognitive follow-up were retained for use in adjusting baseline cognitive scores."

Are data captured from Whitehall II subject that are admitted to hospitals outside of the NHS for England and Wales i.e., private or Scotland, Ireland or rest of EU?

To whom did the discarded HES linkages refer if not to the 7532 subjects?
"Out of 43,692 HES entries during the study period (for 7,532 subjects), 35,099 remained after linkage."

Based upon
5,110 HES entries occurred after the first cognitive assessment and prior to the last cognitive assessment in the study (2,932 surgeries, 2,114 medical admissions, and 64 strokes).
I assume that 3,872 (i.e. 8982-5110) HES admissions were in subjects that had NO cognitive assessments and had no global cognitive score. If so, were these included in the analysis?

How many HES entries did you link to subjects that had 2 or more cognitive assessments prior to the hospital admission?

Methods/Outcomes
The Whitehall database has in the past used an "offset in age-related cognitive trajectory" to provide context to their outcome findings (see Ref #22). This is not the way that most PND studies have been explored and reported. They set up a threshold effect describing whether subject had/had not experience sufficient decline to indicate that they had developed a new condition of postoperative cognitive decline. This binary outcome is the most common method of describing the impact of an intervention. Surely, you can use a cohort (n = 4,916) that had at least 4 cog assessments and was used for sensitivity analysis in order to determine the binary of effect/no effect null hypothesis.

Methods/Covariates
From the sentence below it is still not clear whether there are patients with NO cognitive assessments.

"We also included the number of cognitive assessments for each participant as a covariate"

Statistical Model
In defending their use of Bayesian statistics, the authors state that the binary methods are
"…not most useful or informative statistic in the context we study.."
Almost all the results that are reported from prospective RCT for interventions to prevent one or other aspect of the spectrum of PNDs are binary. Therefore, a "throw-away" line stating binary methods is not the most useful or informative requires further elaboration. Note that a binary outcome has been used in studies involving the Whitehall II database and cognitive assessment (for MMSE in Ozawa et al PMID: 26874911).

Reference needed for
"We separated medical admissions for stroke events due to the expected substantial cognitive impact following stroke."

Results
Including subjects with only one cognitive assessment appears meaningless because one could not establish their individual cognitive trajectory except through the use of population statistics.

Discussion

Concerning the following sentences it seems that there are more than one "Schulte et al" studies. In this case please provide the citation for the other.
"More recently, Schulte et al. found that incident surgery was associated with a non-statistically significant cognitive decline using 4 waves of data over 8 years (n=431). In a larger cohort they suggested that surgery in the prior 20 years was associated with cognitive decline over the subsequent 8 year period32."

Regarding the following statement
"Fourth, all events occurred over the same period as the cognitive assessments allowing us to test how incident admissions affect
cognition."
I understand that this can apply to patients that have bot a pre and postop assessments but from the methods it is not clear that this was the case. Can you please resolve the confusion for me.

Figure 3:
This was difficult to interpret. I cannot view the label on the ordinate because the line marker numbering occludes this.

Additional Questions:
Please enter your name: Mervyn Maze

Job Title: Tenured Professor

Institution: UCSF

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Sanders worked in my laboratory between 2001 and 2009 at Imperial College. Apart from concluding
and reporting on work performed during that period we have not formally collaborated on research
projects since that time. I was not aware of this research project prior to my receiving this manuscript to
review.