## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The Relationship between Executive Dysfunction and Post-Stroke Mortality- a Population-based Cohort Study |
| **AUTHORS** | Bernice Wiberg, Lena Kilander, Johan Sundström, Liisa Byberg and Lars Lind |

## VERSION 1 - REVIEW

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| **REVIEWER** | Gary Ford, Jacobson Chair of Clincial Pharmacology, Newcastle University, UK |
| **REVIEW RETURNED** | 03/02/2012 |

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| **THE STUDY** | Introduction line 21. Age is also known to be a major influence on outcome for 30 day survival following stroke.<br><br>It is not clear whether baseline measures of executive function were similar to executive function immediately prior to stroke.<br><br>Methods. The study had a 27% loss to follow up. Such a high drop out rate may have produced significant bias. As a minimum the authors should report the baseline characteristics and cognitive function in drop outs compared to those who were included in the study. |
| **RESULTS & CONCLUSIONS** | This manuscript describes the association of pre-stroke executive cognitive performance with mortality after first ever stroke/TIA a prospective cohort of 919 Swedish men of which 155 experienced first ever stroke/TIA. Mortality was increased in those with worse executive cognitive performance on Trail Making tests.<br><br>The results are of some interest but as the cause of death is not reported and data on the mortality rate in the 764 patients who did not experience first ever stroke are not reported these data do not describe the extent to which stroke/TIA increase the mortality rate in patients with executive dysfunction i.e. the influence of executive dysfunction on mortality may be the same in those who do not experience stroke or TIA.<br><br>Abstract results. The authors consider the association is strong but the hazard ratio is less than 2. |

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| **REVIEWER** | Peter Appelros, MD, PhD<br>Neurology Department<br>University Hospital<br>Örebro<br>Sweden<br><br>I was dr. Wiberg's opponent when she defended her doctoral thesis. |

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| | A previous version of the present manuscript was a part of that thesis |
| **REVIEW RETURNED** | 08/02/2012 |

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| **THE STUDY** | A STROBE checklist is supplied.<br><br>Regarding Methods:<br><br>Study Sample: 2nd paragraph: “In the whole ULSAM cohort... 232 men had experienced a first stroke, and 586 had died, before the planned date of cognitive function tests.” Are they the patients who “were not available”, according to the previous paragraph?. Please clarify.<br><br>When was the cognitive testing performed in relationship to the “baseline examination” (which, I suppose, was the examination that was performed when the patients were 69-75 years old). This must have done some time after, because 11 patients had a stroke before this testing could be performed.<br><br>Follow-up: The patients were followed up for 11 to 15 years. With respect to stroke and subsequent death, I suppose? |
| **GENERAL COMMENTS** | This is a well-designed and interesting cohort study. Using this study design, it was possible to do the cognitive evaluation before the stroke. It is also interesting that the authors used TMT, not only MMSE, when testing the cognitive performance in these probands.<br><br>I have only a few comments and questions.<br><br>How well suited are the Swedish Hospital Discharge Register and Cause of Death Register to identify stroke? If possible, comment on that in the Discussion.<br><br>Conclusion: It might be added that the often-used MMSE only gives a limited information of cognitive performance in stroke patients.<br><br>See also a few items above, regarding Methods. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: Gary Ford, Newcastle University

Introduction line 21. Age is also known to be a major influence on outcome for 30 day survival following stroke.
Answer: Yes. I mention that in the previous line and have made this clearer by starting the sentence ‘Other known prognostic factors for 30-day survival…..’

It is not clear whether baseline measures of executive function were similar to executive function immediately prior to stroke.
Answer: General baseline measures were carried out 1991-1995 and the subsequent baseline cognitive testing were performed 1993-1996. I have added the years in a sentence, line five, in Methods. I hope this will make it clearer.

Methods. The study had a 27% loss to follow up. Such a high drop out rate may have produced significant bias. As a minimum the authors should report the baseline characteristics and cognitive function in drop outs compared to those who were included in the study.

Answer: We have a 73% participation rate based on eligible participants invited to the age 70-investigation. This number refers to those participating in the age 70 investigation and aims to give an idea on the bias from recruitment from our population-based sample. In our study regarding the follow-up from the investigations at the age of 70 there were no loss to follow-up since we scrutinized the medical records of those registered in the national patient registry as having a stroke. This is also noted in the section 'Follow-up'. Unfortunately we do not have information on the cognitive function among those who did not participate in the age 70-investigation.

This manuscript describes the association of pre-stroke executive cognitive performance with mortality after first ever stroke/TIA a prospective cohort of 919 Swedish men of which 155 experienced first ever stroke/TIA. Mortality was increased in those with worse executive cognitive performance on Trail Making tests.
The results are of some interest but as the cause of death is not reported and data on the mortality rate in the 764 patients who did not experience first ever stroke are not reported these data do not describe the extent to which stroke/TIA increase the mortality rate in patients with executive dysfunction i.e. the influence of executive dysfunction on mortality may be the same in those who do not experience stroke or TIA.
Answer: We have studied mortality rate after stroke according to pre-stroke cognitive function where we see an independent association. Please see Methods, Study sample. We have not studied mortality in general and the association to results from cognitive testing.

Abstract results. The authors consider the association is strong but the hazard ratio is less than 2.
Answer: Yes that is to exaggerate. We have deleted the word strong.

Reviewer: Peter Appelros, MD, PhD
Neurology Department
University Hospital
Örebro
Sweden

I was dr. Wiberg's opponent when she defended her doctoral thesis. A previous version of the present manuscript was a part of that thesis.

Regarding Methods:

Study Sample: 2nd paragraph: "In the whole ULSAM cohort... 232 men had experienced a first stroke, and 586 had died, before the planned date of cognitive function tests." Are they the patients who "were not available", according to the previous paragraph? Please clarify.
Answer: Yes they were but also others that because of different reasons took part in the investigation at age 50 but not in the one at age of 70. Of the 2322 men participating at age 50, 586 had died before the planned date of cognitive function. Please see Methods, Study sample.

When was the cognitive testing performed in relationship to the "baseline examination" (which, I suppose, was the examination that was performed when the patients were 69-75 years old). This must have done some time after, because 11 patients had a stroke before this testing could be performed.
Answer: Yes that's right. The general baseline examination took place 1991-1995 and the subsequent cognitive testing 1993-1996. This is stated in the Methods, Study sample 'In subsequent tests…

Follow-up: The patients were followed up for 11 to 15 years. With respect to stroke and subsequent death, I suppose?
Answer: Good point. The whole sample was followed from baseline (Aug 1991-May1995) to Dec 31st

2006 as is stated in Methods, Follow-up. In Results, third line the word after should be changed to to. The mistake is now corrected.

This is a well-designed and interesting cohort study. Using this study design, it was possible to do the cognitive evaluation before the stroke. It is also interesting that the authors used TMT, not only MMSE, when testing the cognitive performance in these probands.

I have only a few comments and questions.

How well suited are the Swedish Hospital Discharge Register and Cause of Death Register to identify stroke? If possible, comment on that in the Discussion.
Answer: Good point. The accuracy of the SHDR and the CDR has been shown to be high regarding the stroke diagnosis. We have added a sentence about that and a reference in the Discussion. In our study all medical records from the hospitalization of those suffering a stroke/TIA were reviewed as is mentioned in Methods, Study sample.

Conclusion: It might be added that the often-used MMSE only gives limited information of cognitive performance in stroke patients.
Answer: It's now done in Methods, cognitive Function Tests.

See also a few items above, regarding Methods.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Peter Appelros, MD, PhD<br>Neurology Department<br>University Hospital<br>Örebro<br>Sweden |
| **REVIEW RETURNED** | 15/02/2012 |

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| **GENERAL COMMENTS** | The changes made to the manuscript are fine. I have no further comments to the authors. |

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| **REVIEWER** | Gary Ford, Jacobson Chair of Clincial Pharmacology, Newcastle University, UK |
| **REVIEW RETURNED** | 02/03/2012 |

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| **GENERAL COMMENTS** | The data are of interest and the reviewers had adequately addressed the points reaised by myself and the other reviewer. As previously commented it would be of interest to know the impact of executive dysfunction on mortality in the group without stroke/TIA from the same cohort in comparison - although this would require addtioanal work and analysis as a separate study. |