ANSWERING REVIEWERS

Title: Predictors of future stroke in adults 60-64 years living in the community

Author: Nicolas Cherbuin, Leeanne Carey, Moyra Mortby, Kaarin J Anstey

Name of Journal: *World Journal of Neurology*

ESPS Manuscript NO: 19656

We thank the reviewers and the editorial team for their constructive comments and suggestions which we have addressed point by point and in full below.

Reviewer 1

Point 1:
This manuscript is well written and form part of series of manuscript derived from: The Path Through Life Project, specifically, in this manuscript the identified predictors of incident stroke; high systolic blood pressure and smoking are very know, and the sensosimotor performance is new, and is interesting, however, in the discussion sections the explanation for this finding is weak.
Response:
As pointed out by this reviewer the discussion of sensorimotor factors in stroke was somewhat limited. We have edited and expanded our explanation of possible mechanisms underlying this effect (page 14) as follows:
"The novel and possibly most significant finding of this study is the demonstration of an association between poorer sensorimotor skill and increased risk of stroke. Despite extensive search, we are not aware of any previous study reporting such a finding. The pegboard task is timed, visually guided and involves dexterous coordinated movements of both hands. Performance on this task is therefore likely mediated by circuits involving the basal ganglia [27] and lesions in these brain regions would be expected to be associated with deteriorating performance. Consistent with this hypothesis are findings from previous research indicating that lacunar and non-lacunar strokes occur in 7 to 18% of cases in the basal ganglia [28]. Moreover, microbleeds in the basal ganglia and other deep brain regions have been found to be specifically associated with hypertensive arteriopathy and more generally greater prevalence of microbleeds is associated with poorer motor performance [29]. Taken together this evidence suggests that cerebro-vascular disease and its risk factors, particularly hypertension, may lead in some instances to the development of striatal microbleeds thus impairing fine motor control. Consequently, a possible interpretation of our findings is that impaired sensorimotor performance is indicative of the presence or development of silent lacunar strokes which predict and foreshadow the future occurrence of a major stroke."

Point 2:
I think that other limitation is the high % of the lost of follow-up patients.
Response:
Indeed, as in many other prospective studies, loss to follow-up is a limitation. To acknowledge this point the following statement has been made in the limitation section (page 15):

"Finally, participants lost to follow-up was relatively high and this may have somewhat biased the reported estimates"

Reviewer 2

The autors investigate predictors of incident stroke in 1774 participants from the PATH Through Life Project over an 8-year follow up and identified systolic blood pressure, smoking and sensorimotor skills as variables associated with increased risk of cerebrovascular disease. This is an interesting study and this suggestions are intended to improve the paper.
Thank you

Point 1:
The study identified an incidence rate of 197 per 100.000 individuals per year. It would be also interesting to know the incidence by gender (men and women) and compare the results with a recent epidemiologic study published in Catalonia (Spain) on acute stroke, and add a comment in the Introduction (see data in Rev Esp Cardiol 2007; 60; 573-580). In this study the cumulative incidence rate of cerebrovascular diseases per 100,000 population was 218 (95% CI, 214-221) in men and 127 (95% CI, 125-128) in women.
Response:
We appreciate this reviewer's suggestions. We have now made reference to the suggested paper (page 5):
"For example, Marrugat et al.[3] reported incidence rates per 100,000 people of 218 in men and 127 in women in Spain which is consistent with Australian estimates (157 for men and 123 for women)[4] and those of other western countries with a recent meta-analysis reporting an incidence rate 33% higher in men than women[5].
We also reported gender specific incidence rates as requested (page 11)
"This is equivalent to an annual incidence rate of 197 (161 for women and 230 for men) per 100,000 individuals"

Point 2:
It would be suitable to add a comment about other limitation of the present study: authors did not include the "Emerging vascular risk factors", that is, sleep-related breathing disorders, drug abuse, oral contraceptive use, inflammatory markers, etc. These could open new research lines (World J Clin Cases 2015; 3: 418-429). A reference to this study can be included.
Response:
As suggested we have now added this point to study limitations and made reference to the suggested article. (page 16)

Point 3:
Authors point to the possibility that silent strokes in basal ganglia/striatum may be associated with poorer sensorimotor skill. They shall note that silent strokes are often lacunar strokes. A study comparing patients with dysarthria-clumsy hand syndrome versus patients with other lacunar syndromes reported that internal capsule, thalamus and basal ganglia were the most frequent cerebral lacunar topographies (see data in J Neurol Neurosurg Psychiatry 2004; 75: 231-234).
Response:
We thank this reviewer for making us aware of this very relevant study. We have edited the discussion to make reference to this research (page 14)

"The pegboard task is timed, visually guided and involves dexterous coordinated movements of both hands. Performance on this task is therefore likely mediated by circuits involving the basal ganglia [27] and lesions in these brain regions would be expected to be associated with deteriorating performance. Consistent with this hypothesis are findings from previous research indicating that lacunar and non-lacunar strokes occur in 7 to 18% of cases in the basal ganglia [28]."

Point 4:
Check reference #15
Response:
We have checked that the reference used was the correct one and that it was accurately reported based on its pubmed entry. We could not find any problem as per details provided on pubmed (20th Oct 2015) below:
Goldberg D, Bridges K, Duncan-Jones P, Grayson D. Detecting anxiety and depression in general medical settings. BMJ. 1988 Oct 8; 297 (6653): 897-9. PubMed PMID: 3140969; PubMed Central PMCID: PMC1834427.