PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Permanent work disability before and after ischemic heart disease or stroke event: A nationwide population-based cohort study in Sweden
AUTHORS	Ervasti, Jenni; Virtanen, Marianna; Lallukka, Tea; Friberg, Emilie; Mittendorfer-Rutz, Ellenor; Lundström, Erik; Alexanderson, Kristina

VERSION 1 – REVIEW

REVIEWER	Aravind Ganesh Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford
REVIEW RETURNED	05-Jun-2017

GENERAL COMMENTS	The authors have provided a complete analysis including pre-morbid data on disability pensions in Swedish patients with IHD and stroke. I only have a couple of minor points that need to be addressed in the Methods and Discussion: 1. I am not convinced that a Poisson Regression is indicated for this analysis as the main outcome (whether or not disability pension was claimed) is binary - sticking with logistic regression would help keep the results section consistent. A statistical reviewer's input would be helpful here. 2. The Discussion section merits some discussion about how the Swedish welfare system compares with other Western countries (e.g. the UK). The system is unusually generous, so such a discussion would help readers better interpret the generalisability of the results.

REVIEWER	Kiviniemi, Tuomas Turku University Hospital and University of Turku, Heart Center
REVIEW RETURNED	10-Jun-2017

GENERAL COMMENTS	Authors sought to assess the risk of permanent work disability pension before and after ischemic heart disease or stroke event, the burden of stroke compared to IHD, and which factors predicted disability pension after either event. This is an important study because of its potentially important aspects on quality of life as well as economical consequences in the society. Some issues remain: 1) In the strengths section authors state that there were no lost to

	follow-up. How were duplicates handled? It seems possible that the same patients could enter study as the first event, then end up in permanent work disability pension, have a new event etc. This needs to be explained in detail. 2) "percutaneous transluminal angioplasty" is nowadays "percutaneous coronary intervention". Please revise. 3) "Female sex, older age, lower education, economic inactivity, immigrant status, living in rural areas, and having comorbid conditions were all risk factors for disability pension after cardiovascular events, which corresponds to previous studies". This manuscript provides in fact little new information of the causes of PWD. 4) Administrative registry-based setting is the main limitation of the paper. For instance, many assumptions need to be taken such as "Medical procedure can be viewed as a proxy for the severity of the event." This variable prone to bias in the analysis. 5) Lack of information on quality and outcome of post-event care, individuals' health behaviours or workplace psychosocial factors - as pointed out by authors in the limitations section - pose major bias in the data. 6) Discussion sections lacks an important factor for permanent work disability, namely health care providers presumptions. Some may have a general attitude that patients who have had MI are considered sick enough for permanent work disability pension even if the the revascularization was complete and there was no heart failure or other imminent reasons for pension. Please discuss.

REVIEWER	Susan Xu Houston Methodist Research Institute, USA
REVIEW RETURNED	27-Jun-2017

GENERAL COMMENTS	This is a well-written manuscript. I have a couple of questions: 1. The authors stated that logistic regression with a logit link function was used to assess the risk of new disability pension during the first year after the event. If it is logistic regression model, then there is no logit link function with it. Same for the Poisson regression procedure with a log link function to produce relative risks (RR). Did the authors mean generalized linear model with a logit link function? 2. The authors also stated that least square means adjusted for all predictor variables were produced using Poisson regression analysis. Why didn't the authors use the same generalized linear model with a logit link function?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Aravind Ganesh
Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford Please state any competing interests or state 'None declared': None declared
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The authors have provided a complete analysis including pre-morbid data on disability pensions in Swedish patients with IHD and stroke. I only have a couple of minor points that need to be addressed in the Methods and Discussion:
POINT 1. I am not convinced that a Poisson Regression is indicated for this analysis as the main outcome (whether or not disability pension was claimed) is binary - sticking with logistic regression would help keep the results section consistent. A statistical reviewer's input would be helpful here.
OUR RESPONSE: Poisson regression can be used to model data with binary outcomes. This method is suggested especially when the outcome is frequent. Poisson regression produces relative risks, which are seen as easier to interpret than odds ratios, again, especially when the outcome prevalence is high. References regarding this are for instance:
Greenland S. Am J Epidemiol. 2004;160:301-5. https://www.ncbi.nlm.nih.gov/pubmed/15286014
Zou G. Am J Epidemiol. 2004;159:702-6. https://www.ncbi.nlm.nih.gov/pubmed/15033648
We have now inserted these references in the revised manuscript, and made changes to the description of statistical analysis. As also pointed out by Reviewer 3, our description about statistical modelling was rather ambiguous, and we have now clarified and corrected the text as follows (p. 8-9):

“The cumulative incidence trend in disability pension five years before and five years after the event was calculated with frequencies (percentage of individuals on disability pension each year, with 95% confidence intervals [CI]). Between-group differences in disability pension were tested with Chi2 tests. To assess the risk of new disability pension during the first year after the event (outcome incidence 3%), we used generalized linear model with binary distribution and logit link function, which produced odds ratios (OR) with 95% CI. To examine the differences between the predictors of disability pension for IHD and stroke cases, we tested the effect modification (interaction) of event type (IHD/stroke) and each of the predictors. When a statistically significant ($p<0.05$) interaction effect was observed, we performed stratified subgroup analyses. The relative and absolute differences in disability pensioning by these subgroups were illustrated with least square means adjusted for all predictor variables. These adjusted means were produced using Poisson distribution due to conversion problems with binary logistic models.
In sensitivity analyses, we used generalized linear model with Poisson distribution and log link function to produce relative risks (RR) with 95% CI to estimate predictors of disability pension by the fifth year after the cardiovascular event (outcome incidence 18%). Different regression methods were used for the fifth and the first post-event year since OR is not a good approximation of risk ratio when outcome prevalence is above 10%.[15-17] SAS 9.4 was used for all analyses.”

POINT 2. The Discussion section merits some discussion about how the Swedish welfare system compares with other Western countries (e.g. the UK). The system is unusually generous, so such a discussion would help readers better interpret the generalisability of the results.
OUR RESPONSE: As suggested, we have now added discussion about welfare system in Sweden (i.e., the Scandinavian/Nordic/Social democratic system) in comparison to other systems, as follows (p. 22):
“Finally, the high employment frequency in higher ages and among women in Sweden as well as the universal coverage with relatively high benefit levels might limit the generalizability of the results.[32]”

Reviewer: 2
Kiviniemi, Tuomas
Turku University Hospital and University of Turku, Heart Center Please state any competing interests or state ‘None declared’: None declared.

Authors sought to assess the risk of permanent work disability pension before and after ischemic heart disease or stroke event, the burden of stroke compared to IHD, and which factors predicted disability pension after either event. This is an important study because of its potentially important

aspects on quality of life as well as economical consequences in the society.
Some issues remain:
POINT 3: In the strengths section authors state that there were no lost to follow-up. How were duplicates handled? It seems possible that the same patients could enter study as the first event, then end up in permanent work disability pension, have a new event etc. This needs to be explained in detail.
OUR RESPONSE: By no loss to follow up we mean that all included people could be followed through end of follow up. We do not have any 'duplicates', that is, this is a study of individuals with a first IHD or stroke - not of events of IHD/stroke. The latter might have led to people being included more than once. Here, our focus was on individuals with a first event. As you state, all analyses are based on information from T0, that is, the time of inclusion (IHD or stroke event). We do not have information about other type of events, nor about possible changes during the follow-up in family status, type of living area, comorbidity, etc. From inclusion, we have no information on different types of health events, such as recurring IHD or stroke - nor about other diseases or injuries. We included only the first event of each individual, and started the follow-up from that event (minus 5 years and plus 5 years): "First event dates in 2006, 2007, and 2008 were included, except for cases in which death occurred within 30 days of the event. This resulted in a sample of 28 374 cases. The data on cumulative disability pension were gathered five years prior to the event date, and five years after the event. People with both IHD and stroke were excluded (n=144), resulting in 18 480 cases of IHD and 9750 stroke cases."(P. 6)
Patients having a second event after ending up on disability pension did not affect our analysis, because disability pension was our outcome of interest, i.e., anything that happened after that was considered irrelevant in this study. However, as regards our sensitivity analysis with five-year follow-up, it is possible that an individual could have had the first event and continue working and then have a second event which lead to disability pension. In these cases, the time until disability pension would have been from the first event onwards, thus, irrespective of the recurrent event. This means that confounding due to recurrent event was not accounted for in the sensitivity analysis. However, this did not affect our main analysis. We have added the following sentence under study limitations (p. 22): "In future studies, also recurrent events could be included."

POINT 4: "percutaneous transluminal angioplasty" is nowadays "percutaneous coronary intervention". Please revise.
OUR RESPONSE: Thank you! This has now been corrected throughout the text.

POINT 5: "Female sex, older age, lower education, economic inactivity, immigrant status, living in rural areas, and having comorbid conditions were all risk factors for disability pension after cardiovascular events, which corresponds to previous studies". This manuscript provides in fact little new information of the causes of PWD.
OUR RESPONSE: While the observed risk factors for disability pension after cardiovascular event were similar to those observed previously, we showed that similar characteristics and pre-existing conditions were associated with disability pension before the event, as well as after the event (Table 1).

Previous studies have focused on the predictors of disability pension after ischemic heart disease, so we added findings on the predictors of disability pension after stroke. Moreover, our study adds an important finding that in Sweden, large part of working-age people who have a CVD event, are already on long-term disability benefits before the event (Fig 1). We also add knowledge about differences between ischemic heart disease and stroke cases (Table 2, Fig 2). Thus, we claim that we have provided new information as regards the association between cardiovascular disease and permanent work disability at a more detailed level.

POINT 6: Administrative registry-based setting is the main limitation of the paper. For instance, many assumptions need to be taken such as "Medical procedure can be viewed as a proxy for the severity of the event." This variable prone to bias in the analysis.
OUR RESPONSE: We agree that having undergone a medical procedure is not the same as event severity, and that it would be better if we had had a direct measure of event severity, as proxy measures are less accurate. We have now included this notion to the limitations section (p. 22: “We also did not have direct measure of event severity, but used medical procedure as a proxy measure”). Nevertheless, we found that having had medical procedure related to the event was associated with disability pension shortly after a stroke event, which supports using medical procedure as a proxy for the severity of the event.

POINT 7: Lack of information on quality and outcome of post-event care, individuals’ health behaviours or workplace psychosocial factors - as pointed out by authors in the limitations section - pose major bias in the data.
OUR RESPONSE: We agree that this is a limitation, which causes residual confounding. We reflect this limitation against previous studies as follows (p. 22): “The register data also have some limitations: we were only able to include information that was available in administrative registers. This meant that we had no information on quality and outcome of post-event care, or on individuals’ health behaviours or workplace psychosocial factors, which are typically collected in surveys, and have previously been linked to disability pension in general populations.[30] However, a recent study among Finnish public sector employees demonstrated that the contribution of health behaviours and workplace psychosocial factors to the risk of disability pension was relatively small compared to the contribution of comorbidity, especially mental comorbidity.[7] The use of self-reported information regarding health behaviour and psychosocial factors would also have involved both recall bias and loss to follow-up. Regarding post-event care, men were more likely to enrol in disease management program than women after coronary heart disease in Germany.[31]”

POINT 8: Discussion sections lacks an important factor for permanent work disability, namely health care providers’ presumptions. Some may have a general attitude that patients who have had MI are considered sick enough for permanent work disability pension even if the revascularization was complete and there was no heart failure or other imminent reasons for pension. Please discuss.
OUR RESPONSE: This is an interesting hypothesis, which warrants further studies. This type of influence could, as you mention, take place either through attitudes within healthcare or within the Social Insurance Office, or both. In Sweden, at least one physician and often other health professionals, are involved in the assessments of the disease the patient has, the functional limitations the disease have led to and to what extent those limitations actually might influence the work capacity of the patient and for how long. These assessments are sent to the Social Insurance Agency, where an officer evaluates and decides whether the patient (= claimant) should be granted disability pension or not, and if so, to what extent (part- or full-time). That is, it is not the physician who takes the decision on granting disability pension or not. There are so far only a few studies based on this hypothesis and they mainly concern sickness absence rather than disability pension. In 2010, a systematic review was published in Swedish (will soon be published in English also) regarding evidence on physician factors that might influence sick-leave certification/practices.

Based on the identified studies there was no evidence whatsoever on that physician attitudes, gender, age, or specialty affects their sick-leave certification practices. The results from the few studies have been controversial, and most studies involved general practitioners only. That is, more studies are definitely warranted on this. In sum, it might be that disability pensions are granted on an “easier grounds” if the claimant has IHD or stroke, rather when having long-term back pain, for example. However, the above mention review regarding sickness absence did not find evidence for that. Other types of studies are warranted to shed light on these aspects - and maybe this explorative study can inspire such studies.

Reviewer: 3
Susan Xu
Houston Methodist Research Institute, USA Please state any competing interests or state 'None declared': None
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This is a well-written manuscript. I have a couple of questions:
POINT 9: The authors stated that logistic regression with a logit link function was used to assess the risk of new disability pension during the first year after the event. If it is logistic regression model, then there is no logit link function with it. Same for the Poisson regression procedure with a log link function to produce relative risks (RR). Did the authors mean generalized linear model with a logit link function?
OUR RESPONSE: Thank you for alerting us on this imprecision in the manuscript! We have now modified the text regarding statistical analyses, as follows (p. 8-9):
"The cumulative incidence trend in disability pension five years before and five years after the event was calculated with frequencies (percentage of individuals on disability pension each year, with 95% confidence intervals [CI]). Between-group differences in disability pension were tested with Chi2 tests. To assess the risk of new disability pension during the first year after the event (outcome incidence 3%), we used generalized linear model with binary distribution and logit link function, which produced odds ratios (OR) with 95% CI. To examine the differences between the predictors of disability pension for IHD and stroke cases, we tested the effect modification (interaction) of event type (IHD/stroke) and each of the predictors. When a statistically significant ($p<0.05$) interaction effect was observed, we performed stratified subgroup analyses. The relative and absolute differences in disability pensioning by these subgroups were illustrated with least square means adjusted for all predictor variables. These adjusted means were produced using Poisson distribution due to conversion problems with binary logistic models.
In sensitivity analyses, we used generalized linear model with Poisson distribution and log link function to produce relative risks (RR) with 95% CI to estimate predictors of disability pension by the fifth year after the cardiovascular event (outcome incidence 18%). Different regression methods were used for the fifth and the first post-event year since OR is not a good approximation of risk ratio when outcome prevalence is above 10%.[15-17] SAS 9.4 was used for all analyses."

POINT 10: The authors also stated that least square means adjusted for all predictor variables were produced using Poisson regression analysis. Why didn't the authors use the same generalized linear model with a logit link function?
OUR RESPONSE: This was due to conversion problems with binary logit model. SAS did not calculate least square means with general linear modelling (dist=binary, link=logit), so we changed to Poisson with log link function. We acknowledge that it would be more elegant to have both the relative and absolute risk estimates from the same model, but as the OR (binary logistic) and RR (Poisson) risk estimates are very close to one another when the outcome is rare (here outcome incidence was 3%), we don't see this having particular effect to results or conclusions.

VERSION 2 – REVIEW

REVIEWER	Aravind Ganesh 1. Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, United Kingdom 2. Department of Clinical Neurosciences, University of Calgary, Canada
REVIEW RETURNED	28-Jul-2017

GENERAL COMMENTS	The authors have adequately addressed the comments raised in my original review.

REVIEWER	Tuomas Kiviniemi Heart Center, Turku University Hospital, Finland
REVIEW RETURNED	02-Aug-2017

GENERAL COMMENTS	POINT 3: Authors have responded well regarding the inclusion of the first-ever event of patients. Yet, no comment is given on patients moving abroad. How these patients were identified and were they excluded? POINT 8: Authors have discussed relevant literature regarding possible healthcare professionals' attitudes on patients being sick enough for permanent work disability pension. However, no comment in the revised manuscript was made. I think that clinical implication of these findings need to be better presented in the revised manuscript. This would made manuscript more valuable and useful for potential physician readers of the Journal. To shed more insight into this topic, you might find the following publication useful. A recent contribution found that "despite excellent overall survival after coronary revascularization in patients under 50 years old, the rate of PWD was fairly high. At 5 years follow-up, every third patient after CABG and every seventh patient after PCI were on PWD. The rates of cardiac PWD were markedly higher than in the general population (a third of both CABG and PCI patients with PWD). Strikingly, there was discrepancy in the high rate of PWD compared to low post-CABG rates of repeat revascularization, stroke, or congestive heart failure, which would have been the imminent reasons for cardiac PWD. This may reflect a general attitude that patients who have undergone CABG are considered sick enough for PWD even if the operation is successful and leads to complete revascularization. This is supported by the finding that the median time to PWD after CABG was equal to the maximum time of sickness benefit in the country (330 days) suggesting that these patients fail to return to work at all after CABG." (Eur Heart J Qual Care Clin Outcomes (2017) 3 (2): 101-106.)

REVIEWER	Susan Xu Houston Methodist Research Institute Houston Methodist Research Institute
REVIEW RETURNED	26-Jul-2017

GENERAL COMMENTS	The authors have adequately addressed my previous comments. I have no any further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Kiviniemi, Tuomas
Turku University Hospital and University of Turku, Heart Center Please state any competing interests or state 'None declared': None declared.

POINT 1: Authors have responded well regarding the inclusion of the first-ever event of patients. Yet, no comment is given on patients moving abroad. How these patients were identified and were they excluded?
OUR RESPONSE: We thank the reviewer for alerting us on this impreciseness in the manuscript. If an individual was not living in Sweden at the end of December in two consecutive years and thus not having any information in the population register (LISA) for these two years and this was not due to death the individual was censored (labelled as emigrated) at the last date of the first of those two years.
That is, they were not excluded from the analyses, they contributed with person time in the analyses during the time living in Sweden, in the same way as people who died contributed with person time until death.
As people moving abroad cannot be reached through register data after their emigration, the individuals moving abroad after IHD or stroke were censored similarly as those who died, i.e., they were excluded in the analyses from the emigration year and onwards. In the analyses, we did not separate those who died from those who emigrated. However, the proportion of people moving out from Sweden after a serious cardiac event, such as IHD or stroke, is likely to be very small (at least during the first post-event year). We have corrected the manuscript as follows (p. 7):

"Those who died or moved abroad were excluded from the death/emigration year onwards. This resulted in a final sample of 20 498 individuals for analyses of the onset of disability pension during the first post-event year (185 individuals died or moved abroad during the first year), and 19 771 for analysis of the onset of disability pension in the fifth post-event year (912 individuals died or moved abroad during the five follow-up years)."

POINT 2: Authors have discussed relevant literature regarding possible healthcare professionals' attitudes on patients being sick enough for permanent work disability pension. However, no comment in the revised manuscript was made. I think that clinical implication of these findings need to be better presented in the revised manuscript. This would made manuscript more valuable and useful for potential physician readers of the Journal.
To shed more insight into this topic, you might find the following publication useful. A recent contribution found that "despite excellent overall survival after coronary revascularization in patients under 50 years old, the rate of PWD was fairly high. At 5 years follow-up, every third patient after CABG and every seventh patient after PCI were on PWD. The rates of cardiac PWD were markedly higher than in the general population (a third of both CABG and PCI patients with PWD).

Strikingly, there was discrepancy in the high rate of PWD compared to low post-CABG rates of repeat revascularization, stroke, or congestive heart failure, which would have been the imminent reasons for cardiac PWD.

This may reflect a general attitude that patients who have undergone CABG are considered sick enough for PWD even if the operation is successful and leads to complete revascularization. This is supported by the finding that the median time to PWD after CABG was equal to the maximum time of sickness benefit in the country (330 days) suggesting that these patients fail to return to work at all after CABG." (Eur Heart J Qual Care Clin Outcomes (2017) 3 (2): 101-106.)
OUR RESPONSE: We thank the reviewer also about this very useful reference. We have now added the following text to the Discussion section (p. 22-23):

"In a recent study, disability pensioning five years after percutaneous coronary intervention or coronary artery bypass crafting was fairly common (15-35%) among young (≤50 years) IHD patients.[33] The fact that even after successful surgery and complete revascularization, these patients often ended up on disability pension lead the authors to speculate that disability pensioning may be partly explained by patients' and healthcare professionals' attitudes towards recovery and

return to work.[33] In Sweden, at least one physician and often other health professionals, are involved in the assessments of the disease the patient has, the functional limitations the disease have led to, and to what extent those limitations actually might influence the work capacity of the patient and for how long. These assessments are sent to the Social Insurance Agency, where an officer evaluates and decides whether the patient (=claimant) fulfills the criteria for being granted disability pension or not, and if so, to what extent (part- or full-time). However, other type of studies are warranted to shed light on these processes, and perhaps this explorative study can inspire such studies."

VERSION 3 – REVIEW

REVIEWER	Tuomas Kiviniemi Heart Center, Turku University Hospital
REVIEW RETURNED	17-Aug-2017

GENERAL COMMENTS	Authors have responded to all queries adequately.