Author's response to reviews

Title: Working and hypertension: Gaps in employment not associated with increased risk in 13 European countries, a retrospective cohort study.

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Version: 2
Date: 8 May 2014

Author's response to reviews: see over
Thank you to the Editor and to all the reviewers for assessing the paper and for your helpful feedback. **Amended text is in bold in the revised manuscript.**

**Editorial comments**

Title page: Please included the email addresses of all the authors in the title page.

_Thank you Editor, email addresses have been added._

**Reviewer 1: Ricardo Pagan**

The article analyses an important question from a health, social and economic perspective. The authors explore the contribution of breaks in employment to the development of hypertension. Most of the previous studies on this issue have been cross-sectional, as the authors mentioned. Overall, the paper is well written and has the conventional structure. However, I have found some important limitations and drawbacks in the paper that make its contribution very limited. In addition, some of them have been pointed out by the own authors in the last section of the paper.

1) The main contributions of the paper must be improved by the authors and included in the introduction. The results obtained in the paper are similar to others found in the literature and have little impact on the study of the relationship between hypertension and breaks in employment. In addition, I have missed more discussion on the possible existence of reverse causality in the paper and its effects on the results shown by the authors.

_Thank you very much for your comments and feedback. The issue of reverse causality is an interesting one, and we carefully considered its impact when designing our study and interpreting the results._

_Firstly, we deliberately chose to focus on a condition that was highly prevalent and largely asymptomatic to minimize the risk of this bias. That is, hypertension is a condition present in a substantial proportion of the population, yet the majority of these people continue to function successfully and maintain long working lives._
Second, we considered the possibility of hypertension in itself causing breaks employment (for example as a result of a hemorrhagic cerebrovascular event). However, the relative impact of this bias is likely to be minimal – hypertension is usually asymptomatic (as evidenced by the substantial rates of undiagnosed disease), and secondly, significant health events due to hypertension within the working life would be comparatively low, compared to their peak incidence in the 7th and 8th decades.

2) The authors use an interesting database (SHARE), which contains information on many socioeconomic variables. However, the authors do not use some explanatory variables in the multivariable analysis that may have impact on the likelihood of having hypertension. For example, job responsibility, industry, firm size, type of contract of the past job positions before being unemployed, household composition, etc.

Thank you for the comment on model selection. We carefully selected our covariates, drawing both on theoretical frameworks and the evidence from the published literature. Although the SHARE database contains a wealth of data, the majority of the variables were measured at the time of interview only, with no historical information available. For example, despite BMI data present in the database (obtained at time of interview), this value could not be used to infer historical BMI values without the risk of substantial error; similarly we could not infer smoking status over time. As such, because of the time-dependent nature of potential confounders, we were not able to include in the model many of these variables. However, we did investigate the role of the included covariates individually (age at interview, age at visit, gender, socio-economic position, country), as well as others available in the dataset (such as marital status), and found that the impact of confounders on the estimates of the principal findings in our models were minimal.

3) Furthermore, a selection problem in the sample can exist due to the fact that some individuals are more likely to have hypertension than others. This lack of control leads to consider the results shown in Table 2 as very preliminary. The authors must take into account this important selection problem.

Thank you for this comment. We agree, it is possible that some individuals may be more at risk of this condition than others, for example due to their gender and age. For this reason, we have included key confounders (such as socio-economic position, age at interview – to account for a
cohort effect, age at visit, gender, education, and country) in our model. However, as noted above, we found that ultimately confounding had little impact in our data.

4) The conclusions are very poor and must include some public policy recommendations. We appreciate this comment. This paper provides useful information to contribute to our understanding of the interplay between employment and chronic disease, as well as reassurance to individuals or communities who may be more likely to experience breaks in paid employment. Also, we respectfully suggest that not all research must directly inform policy, and that policy implications may be more suited to in-depth discussion in other fora, such as commentaries (Editorial. Epidemiology 12; 4 p371-372). That said, there is an indication for future research in this area, to address some of the methodological limitations of our data, and to better understand the role of mediation and confounding in the association between unemployment and hypertension. The final paragraph has been expanded to better portray these thoughts; this is given below (Reviewer 2, point 4).

Reviewer 2: Kirsten Fiest

In this study, the effect of gaps in employment on the development of hypertension is assessed in a sample of 9985 European's over 50 years of age. The introduction is well organized and sufficiently covers the literature. The paper is well written and organized. I have concerns with the statistical methodology of this paper, which limit this paper considerably.

Major Compulsory Revisions

1) My greatest concern is with the statistical model selected by the authors for data analysis. They state that the data is panel in nature, yet they do not use a method that takes this into account. The analysis does not take time into account, though they mention their model takes into account "time varying covariates". Please consider using a model that adequately takes into account the longitudinal nature of the dataset.

Thank you for your time and effort in reviewing this paper, and for your comments. To elaborate on our methods:
In preparing the data we created a discretized dataset, where each year between age 18 and censoring was determined as a ‘visit’.

At each visit, the presence or absence of the exposure (‘Not working’, NW) and the outcome (diagnosis of hypertension) was noted in the dataset.

The model then estimated the odds of hypertension diagnosis against NW at each visit, combining these multiple estimates in a pooled odds ratio.

This is the approach recommended in this situation, as noted in Robins JM, Hernán MA, Estimation of the causal effects of time-varying exposures (In: Fitzmaurice G, Davidian M, Verbeke G, et al., editors. Longitudinal Data Analysis. New York, NY: Chapman and Hall; 2008. p. 553-599). It is a technique commonly used to account for time-varying covariates and to ensure the temporality between the exposure and outcome is maintained. This approach minimizes this form of systematic error and allows the investigation of causation.

We have edited the text in the manuscript to clarify this point, it now reads:

“Pooled logistic models compared the odds of hypertension according to the exposure NW. That is, at each visit for each individual, the odds of hypertension with respect to employment state were modeled, and these multiple estimates then combined into one pooled estimate.

We have also added the reference above to this paragraph, as support for our statistical model.

2) Please explain how you assessed for confounding (an adjusted model is mentioned).

To adjust for confounding, we included terms for age (at time of interview – time-fixed confounder), age at each visit (time-varying), gender (time-fixed), age finished full-time education (time-fixed), childhood socio-economic position (time-fixed), and country (time-fixed). This explanation is noted in the final paragraph of page 7, under ‘Statistical analysis’.

3) Before confounding is assessed, effect measure modification should be assessed, as it is certainly plausible that the measures of effect could differ based on levels of age, sex, etc...

Thank you for this comment. We adjusted for variables such as age and gender as ‘pure confounders’, reflecting their placement in theoretical frameworks of the published literature.
We also gave the issue of interaction substantial thought, and investigated the model in a
number of ways and with a variety of terms and combinations thereof. However, with all the
manipulation and additional analyses, the findings were consistently null.

Minor Essential Revisions
4) The directions for future research are week, please explore this point further.

Thank you for this suggestion. We have expanded the final paragraph to address this point, it
now reads:

This study contributes to the growing research base around the interplay between
employment and health. However, there are several pathways for future research. For
example, there is an indication for methodologically-focused studies to explore the role of
mediators and time-dependent confounders, and the extent of their impact. Additionally,
prospective studies may be useful to obtain more precise information on the timing and
impact of gradually progressive conditions, such as increases in blood pressure or weight, with
respect to transitions in employment.