Reviewer’s report

Title: Unemployment and ill health: a connection through inflammation?

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Reviewer: Nicolas Rohleder

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The aim of the study presented here is to test the hypothesis that unemployment, as a potent social stressor, is associated with low-grade inflammation.

To test their hypothesis, the authors recruited n=225 participants (mean age 52) from the general population. N=19 of those were unemployed. Inflammatory molecules IL-6 and CRP were measured and participants with IL-6 and CRP concentrations greater than the median were categorized as having low-grade inflammation (n=72). Unemployed participants had an increased odds ratio of being in the “inflammatory” category.

This is a very important question and a valid rationale. I’m not convinced by the methodological approach, particularly by the statistical strategy (see below):

Major Compulsory Revisions

1 General methodological point: the authors measure IL-6 and CRP in plasma and dichotomize participants into having low-grade inflammation or not based on specific cut-offs. No attempt is made to use continuous values of IL-6 and CRP. And the number of participants who are unemployed AND in the “inflammatory” group is never given.

This raises 2 questions: why cut-offs, and why these? The authors cite two papers (Capuron and Yaffe) that have successfully used median splits. However, when taking a closer look at these papers, it appears that none of the authors have gone as far as the authors of this study, which is to completely and solely rely on this categorization. In contrast, both use regression approaches in addition. Another problem that came to my attention is that using the median leads to very different cut-off levels (Capuron: CRP=1.34 mg/L; IL-6=1.66 pg/mL; Yaffe: CRP=2 mg/L; IL-6=2 pg/mL ). These values are markedly higher than those of the present study (CRP= 1.49 mg/L; IL-6= .97 pg/mL).

This might be explained by the age of the sample (Yaffe: 70-79 yrs., Capuron: 55yrs; this study: 52 yrs.); but this is a problem nonetheless: While in Yaffe’s study, cut-off levels are closer to established cut-offs for cardiovascular risk (3 mg/l for CRP), the cut-offs in this study are much lower than these cut-offs for clinically relevant inflammation. The authors need to thoroughly think about and discuss the implications of this. The main question is: Is their statistical cut-off clinically meaningful? Are participants categorized as “inflammatory” using these cut-offs really in a state of low-grade inflammation? Depending of the outcome,
the authors might want to come up with an alternate or additional analysis strategy.

In summary, while I agree that the strategies by Yaffe and Capuron are a valid approach, and might be used on this sample, I disagree that it is sufficient to do so. By relying solely on their definition of inflammation, too much valuable data points are just lost. Therefore I strongly suggest to add analyses using the full range of IL-6 and CRP data.

we first need a description of the distribution of IL-6 and CRP. Is it normally distributed? Are there individuals with extremely high values, that might be indicative of acute inflammation? Should these be excluded?

What is the relation between IL-6 and CRP?

What is the relation between IL-6 or CRP and other variables assessed here (age, BMI, smoking, depression, etc)? Is one of those (e.g. Economical hardship) a better predictor of inflammation than unemployment alone? Or is the effect of unemployment mediated by economical hardship? Or depression?

Then, it could be tested what the mean IL-6 and CRP concentration is in each group; is it significantly different? Does it differ if covariates are used?

Also, I would suggest testing established cut-offs for CRP (and check if any exists for IL-6).

It might turn out that the authors’ approach is better suited, but I think it is absolutely necessary to use the continuous distribution of the inflammatory variables.

2 Methods - IL-6 is measured using a multiplex assay. Usually, multiplex assays do not have a sensitivity high enough for detecting unstimulated plasma concentrations of IL-6; or if they do, they yield strangely elevated levels. This is problematic because data from this study are compared with other studies that uniformly use high-sensitivity ELISAs, which usually are better suited and yield lower concentrations than multiplex assays. This is a limitation that needs to be thoroughly discussed, particularly in relation to the problem of the cut-offs mentioned in my earlier comment. Ideally, the authors would provide a validation by re-analyzing a subgroup of results with a high-sensitivity ELISA.

Minor Essential Revisions

3 P4 - I would remove the bracketed (March 2009) from the first line of the background section. You could say “In March 2009, approximately…”

4 P5 - is the sole paragraph on top of page 5 a summary of the literature summarized previously? Or is it a hypothesis? Please make that more clear.

5 P6, second paragraph - I suggest rephrasing “…were assessed to have…”;

6 P6/7 - it would help the reader if the structure of the methods section would be improved: the paragraph describing measurement of BMI and blood draw should be moved to the beginning, measurement of IL-6 and CRP should follow, and after that would I suggest describing the cut-offs and categorization of
participants into groups; I would also suggest moving the questionnaire part to the front of the methods section (before biochemical analyses are described).

7 P7 - specify the units of CVs (percentages?)

Summary - this is a very promising preliminary study linking unemployment with inflammation, thereby providing the basis for larger follow-up studies. I am not happy with the analysis strategy, but I believe that this is easily addressable, although a major change to the manuscript.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests