PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The influence of family history on prognosis of spinal pain and the role of leisure time physical activity and body mass index: a prospective study using family-linkage data from the Norwegian HUNT Study.
AUTHORS	Amorim, Anita; Ferreira, Paulo; Ferreira, Manuela; Lier, Ragnhild; Simic, Milena; Pappas, Evangelos; Zadro, Joshua; Mork, Paul Jarle; Nilsen, Tom

VERSION 1 – REVIEW

REVIEWER	Arthur Eumann Mesas State University of Londrina, Brazil.
REVIEW RETURNED	12-Apr-2018

GENERAL COMMENTS	This is an interesting prospective analyses based on data from the HUNT study. The authors proposed to evaluate in offsprings if the risk of recovering from spinal pain symptoms and also from activity limiting spinal pain could be partially explained by the presence of this same pain condition in their parents. Moreover, physical activity and excess body weight were explored as potential effect modifiers. 1) My major concern relates to the use of only baseline information about lifestyle and health conditions, which could be importantly changed over the 10y of follow-up and influence the studied outcomes. For instance, on the website of the HUNT study it can be found that in the HUNT3-Q1, questions 32 to 35 were related to exercise at the end of follow-up. Thus, the availability of these data suggests that the authors could examine if the study associations varied according to changes in leisure-time physical activity during the follow-up. If available, other change variables could be also interesting to test as confounder or interaction variables, as the depressive symptoms score and the recovery from spinal pain in their parents. 2) Which was the value considered as the cut-off for statistical significance? This is important and should be clearly stated in Methods, because the authors had different interpretations regarding this. For example, in Table 3, the adjusted RR of recovery from spinal pain was significant lower [0.78 (0.62-0.98), p<0.05] for those whose both parents had the same problem only in the active group, but not in the inactive group [0.98 (0.71-1.35), p>0.05]. Althought this is possibly a quantitative and not a qualitative interaction and the p for interaction was 0.037 (i.e., <0.05), the authors stated that there was no interaction. On the other hand, in Table 4, for the first outcome, the RR in normal weight offsprings are very similar to those observed in the overweights, but the authors emphasyzed that the study association was particularly clear in oveweight offsprings. 3) In the Results section, the values presented in the text are different from those observed in Table 1 and should be correted or

	justified (in case that they refer to a subsample). 4) To be consistent with the manuscript proposal, Table 3 should include the results for the association between the main exposure and the second outcome (recovery from activity limiting spinal pain) stratified by physical activity (at baseline and, if possible, by the change of PA over the follow-up).

REVIEWER	Paul Campbell Keele University, UK.
REVIEW RETURNED	04-May-2018

GENERAL COMMENTS	Many thanks for the invitation to review this paper. This is a report of a very interesting study that looks to investigate the influence of parental chronic pain on adult child offspring within a longitudinal dataset. This is a well written paper and I only have a few comments that may improve the overall clarity and the authors have touched on some of the issues I have highlighted within their discussion. 1. I thought the introduction may have mentioned more about the genetic influences of pain (e.g. for more specific types of conditions such as disk prolapse, disk degeneration etc), and also the behavioural influences (e.g. parents level of catastrophizing linking to child reports of pain etc). 2. How reliable is the linkage between family members, is it linked by name and address, is there other indicators, just trying to get a sense of misclassification here, for example what about single parents, parents who are not married and have different names etc 3. Were only trios (mother, father, child) analysed, did this mean removal of potential dyad linkages, if so how many single parent relationships were removed, would this have any implications? 4. Was nice to see RERI used as well as statistical interactions 5. It is such a long time between data points (11 years), it is hard to be sure this recovered cohort had anything to do with factors 11 years previously, is recovery the right term, it would have been better to have “persistence” and look at increase in risk, but I do understand that changing would not be feasible. Perhaps highlight the limitation on the time elapsed?

VERSION 1 – AUTHOR RESPONSE

Reviewer’s comments:

Reviewer #1: This is an interesting prospective analyses based on data from the HUNT study. The authors proposed to evaluate in offspring if the risk of recovering from spinal pain symptoms and also from activity limiting spinal pain could be partially explained by the presence of this same pain condition in their parents. Moreover, physical activity and excess body weight were explored as potential effect modifiers.

Author’s response: We thank the reviewer for the valuable comments and suggestions. They have been addressed in the revised manuscript.

1. My major concern relates to the use of only baseline information about lifestyle and health conditions, which could be importantly changed over the 10y of follow-up and influence the studied outcomes. For instance, on the website of the HUNT study it can be found that in the HUNT3-Q1, questions 32 to 35 were related to exercise at the end of follow-up. Thus, the availability of these data suggests that the authors could examine if the study associations varied according to changes in leisure-time physical activity during the follow-up. If available, other change variables could be also interesting to test as confounder or interaction variables, as the depressive symptoms score and the recovery from spinal pain in their parents.

Author's response: We agree with the reviewer that the lengthy follow-up is a limitation of the study and we have expanded on this in the limitations section of the manuscript (page 18). However, including information on leisure-time physical activity or possible confounders from the follow-up measures would violate the prospective design of this study, and could bias the results due to reverse causation. We would therefore prefer to not include such change variables in the analyses of the revised manuscript, and hope this is satisfactory.

Page 18: "Information on chronic spinal pain was only reported at baseline and at follow-up 10-11 years later, with no information on possible changes in the status of chronic spinal pain during the follow-up period. Consequently, a person could have recovered from spinal pain at some time-point between the surveys, but still report pain at follow-up. However, if parental pain reflects an underlying heritable frailty, this may have an impact also on long-term recurrence and recovery from pain. Likewise, information on leisure time physical activity and BMI was only assessed at baseline, with no information on possible changes during the follow-up period."

2. Which was the value considered as the cut-off for statistical significance? This is important and should be clearly stated in Methods, because the authors had different interpretations regarding this. For example, in Table 3, the adjusted RR of recovery from spinal pain was significant lower [0.78 (0.62-0.98), $p<0.05$] for those whose both parents had the same problem only in the active group, but not in the inactive group [0.98 (0.71-1.35), $p>0.05$]. Although this is possibly a quantitative and not a qualitative interaction and the p for interaction was 0.037 (i.e., <0.05), the authors stated that there was no interaction. On the other hand, in Table 4, for the first outcome, the RR in normal weight offsprings are very similar to those observed in the overweight, but the authors emphasized that the study association was particularly clear in overweight offsprings.

Author's response: We understand the reviewer's confusion about this which was due to a typo in the reported p-value - this should read 0.11. We thank the reviewer for pointing this out. We realized that we reported erroneous p-values from the interaction analyses, and this has now been corrected in the revised manuscript (page 12). In line with recommendations for reporting results from medical studies,[1, 2] we have emphasised the estimating of the magnitude and precision (95% confidence intervals) and not on hypothesis testing and the use of strict cut-offs for statistically significance (e.g. p-value <0.05).

3. In the Results section, the values presented in the text are different from those observed in Table 1 and should be corrected or justified (in case that they refer to a subsample).

Author's response: We thank the reviewer for pointing this out. We have now corrected the values in the results section (page 10) and have highlighted the changes in the revised manuscript.

Page 10: "Most offspring were physically active (63.9%), and nearly half of the offspring (42.3%) were classified as overweight or obese. About one third (33.1%) of the offspring were current smokers, and just a small portion of offspring (20.7%) reported having a higher education degree. A small proportion

(10.4%) of offspring had symptoms of depression according to the Hospital Anxiety and Depression Scale."

4. To be consistent with the manuscript proposal, Table 3 should include the results for the association between the main exposure and the second outcome (recovery from activity limiting spinal pain) stratified by physical activity (at baseline and, if possible, by the change of PA over the follow-up).

Author's response: Based on how we have created the outcome "activity limiting spinal pain" as described in the methods section (pages 7 and 8), people with activity limiting spinal pain are likely to have limited engagement in leisure and work activities. Therefore, it was not reasonable to analyse the second outcome (activity limiting spinal pain) stratified by physical activity. This has been clarified in the methods section (page 8) of the revised manuscript.

Page 8: "We did not conduct analyses stratified by physical activity status on the outcome 'activity limiting spinal pain', since people with activity limiting spinal pain are likely to have limited engagement in leisure and work activities."

Reviewer #2: Many thanks for the invitation to review this paper. This is a report of a very interesting study that looks to investigate the influence of parental chronic pain on adult child offspring within a longitudinal dataset. This is a well written paper and I only have a few comments that may improve the overall clarity and the authors have touched on some of the issues I have highlighted within their discussion.

Author's response: We thank the reviewer for the valuable comments and suggestions. They have been addressed in the revised manuscript.

1. I thought the introduction may have mentioned more about the genetic influences of pain (e.g. for more specific types of conditions such as disk prolapse, disk degeneration etc), and also the behavioural influences (e.g. parents level of catastrophizing linking to child reports of pain etc).

Author's response: As suggested by the reviewer and to further highlight the genetic and behavioural influences on pain we have included the following information in the introduction section (page 4) of the revised manuscript.

Page 4: "Family studies have suggested that chronic pain aggregates in families,[3, 4] with the parent-offspring transmission of chronic pain explained by genetic heritability[5, 6] and shared environment factors.[7-10] The mean heritability of chronic low back pain is 67%,[6, 11] suggesting that a substantial proportion of the risk of developing chronic spinal pain is driven by genetics. However, families also share similar lifestyles and express similar health behaviours and beliefs. This suggests shared environmental factors[4, 12] could also have an important influence on the prognosis of spinal pain.[13, 14]"

2. How reliable is the linkage between family members, is it linked by name and address, is there other indicators, just trying to get a sense of misclassification here, for example what about single parents, parents who are not married and have different names etc.

Author's response: As described in the methods section (page 6), the link between parents and offspring in the HUNT Study was obtained from the national Family Registry in Norway using the unique 11-digit personal identification number of all Norwegian citizens. The registry give information on parents that are registered as legal parents at birth. This means that some parents could be registered as legal parents without being a biological parent [e.g. due to adoption or non-paternity (i.e. not the biological father)]. Such misclassification could potentially attenuate the observed associations of the current study, and we have included this as a limitation in the revised manuscript (page 18).

Page 18: "Although the Norwegian Family registry was used to identify family relations between parents and offspring, misclassification of biological family relations in the registry due to adoptions and non-paternity is possible. Although the influence on our results is likely to be small, such misclassification could give attenuated parent-offspring associations. Moreover, we had no information on whether the offspring shared environment with none, one or both of their biological parents during childhood. Finally, residual confounding due to unmeasured or unknown factors cannot be ruled out."

3. Were only trios (mother, father, child) analysed, did this mean removal of potential dyad linkages, if so how many single parent relationships were removed, would this have any implications?

Author's response: As the reviewer correctly suggest, we based the analyses on trios (mother, father and child) who all had participated in a HUNT survey. This was preferred instead of dyads to be able to take into account the other parent's pain status, although selecting parent-offspring pairs would have given a larger sample size. We have clarified this in the methods section of the manuscript (page 6). The possibility for selection bias is mentioned as a possible limitation in the discussion section (page 18).

Page 6: "The unique 11-digit personal identification number held by all Norwegian citizens was used to link each participant's record to information from the Family Registry at Statistics Norway, and there by establish a link between parents and offspring who participated in one or both of HUNT2 and HUNT3. The Family Registry provide data on persons registered as legal parents, either as biological parents or through adoption."

Page 18: "A premise for inclusion into this study was that the mother, father and offspring all had to participate in the health survey. To some extent, this may have resulted in a selected and more health conscious sample than the general population. Nevertheless, it is questionable whether representativeness is a prerequisite for making valid risk assessments in epidemiological studies."

4. Was nice to see RERI used as well as statistical interactions.

Author's response: Your encouraging comment is greatly appreciated.

5. It is such a long time between data points (11 years), it is hard to be sure this recovered cohort had anything to do with factors 11 years previously, is recovery the right term, it would have been better to have "persistence" and look at increase in risk, but I do understand that changing would not be feasible. Perhaps highlight the limitation on the time elapsed?

Author's response: We agree with the reviewer that the term recovery and the lengthy follow-up is a limitation of the study and we have expanded on this in the limitations section of the manuscript (page 18). However, we have chosen to keep the term "recovery", as we believe the term "persistence" will have the same limitations regarding fluctuating pain, as displayed in the text below extracted from the manuscript:

Page 18: “Information on chronic spinal pain was only reported at baseline and at follow-up 10-11 years later, with no information on possible changes in the status of chronic spinal pain during the follow-up period. Consequently, a person could have recovered from spinal pain at some time-point between the surveys, but still report pain at follow-up. However, if parental pain reflects an underlying heritable frailty, this may have an impact also on long-term recurrence and recovery from pain. Likewise, information on leisure time physical activity and BMI was only assessed at baseline, with no information on possible changes during the follow-up period.”

VERSION 2 – REVIEW

REVIEWER	Paul Campbell Keele University, UK
REVIEW RETURNED	27-Jun-2018

GENERAL COMMENTS	The authors have successfully addressed my initial concerns within this revised draft, and from my perspective addressed the views of Reviewer 1, therefore I am recommending acceptance of this well written and interesting paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2 comment to Author:

- The authors have successfully addressed my initial concerns within this revised draft, and from my perspective addressed the views of Reviewer 1, therefore I am recommending acceptance of this well written and interesting paper.

Author’s response: We would like to thank the reviewers for their detailed comments and suggestions for the manuscript. The revised manuscript has benefitted from an improvement in the

overall presentation and clarity.