Reviewer’s report

Title: Neuromuscular exercise reduces low back pain intensity and improves physical functioning in nursing duties among female healthcare workers; secondary analysis of a randomised controlled trial

Version: 1 Date: 20 May 2019

Reviewer: Remco Arensman

Reviewer's report:

Point-by-point comments to the Reviewer 1 (Remco Arensman):

We wish to thank Reviewer 1 for deepening not only to the manuscript, but also to the protocol article(1), reliability article of the measure methods(2) and to the main article of the results of the NURSE RCT in 4-arm setting (3).

"In the introduction the authors write that exercise is most frequently recommended for the treatment of patients with LBP, but that it remains unclear which form of exercise therapy is most effective. The reasoning for NME as a treatment strategy appears to be based on assumptions based on findings from primarily cross-sectional studies, but are presented as longitudinal data."

The references considering exercise for LBP in the Background session are reviews, systematic reviews or meta-analysis. In the Background session, we discuss potential risk factors for LBP, namely movement or postural control, and level of physical fitness.

References 20-24 in the manuscript refer to deficiencies in movement or postural control among people with LBP, and yes, they are based on cross-sectional data. Also references 25-28, which discuss associations between low physical fitness and LBP are based on cross-sectional data. We don't understand, how a reader gets an impression that we present them as longitudinal data. And finally, in the section where we discuss the treatment strategy for neuromuscular exercise (NME), our references are 2 Cochrane reviews, 1 systematic review and 3 RCT studies. Sorry, we don't understand the reviewer's argument. Could the Reviewer 1 specify more exactly, which section of the Background should be revised with different references?

Reviewer 1's response:

After rereading my comment, I understand the confusion. I was unable to adequately present my concerns regarding the rationale of the study. My concerns are that the assumption that impairments in postural and/or movement control are causes or risk factors for LBP or persistence of LBP are based on findings from cross-sectional studies. In the abstract of the 2015
study by Babiolakis and colleagues cited by the authors it is even stated that "It is unclear whether poor lumbopelvic control is causal or adaptive in RInj nurses and may require further investigation." (reference 14) References 20 through 24 are indeed all cross-sectional and as a result do not provide information on impairments in postural and/or movement control as a cause for LBP or persistence of LBP. It is as likely that the impairments found are adaptive and way for patients with LBP to move with as little pain as possible. Similarly, the associations between low physical fitness and LBP could be due to the decreased activity levels in patients with LBP because of the pain. Furthermore, line 85 (Spinal stability... back health.) references the 2003 work of Punjabi based on similar assumptions. Although the use of reference 29 is justified, I cannot find this in reference 30. Reference 30 only mentions "One factor that has been proposed as important in the genesis and persistence of nonspecific LBP is stability and control of the spine.", which was referenced from the same 2003 paper from Punjabi.

While it is true that the references for the intervention are reviews and RCTs, the rationale for the intervention is based on inferences of causality from data from cross-sectional studies. "Patients with LBP show differences in spinal movement (control) compared to healthy controls, therefore reducing or removing these differences reduces LBP."

Unsurprisingly, after more than 20 years of research on movement control exercises, and to a lesser extent Pilates exercises, as a treatment for LBP the most recent Cochrane reviews on both interventions conclude that there is no conclusive evidence of superiority over any other form of exercise, which is supported by the literature referenced by the authors.

"...one would expect the contents of a treatment strategy for people with acute LBP to contain advice to remain active and education, with the addition of exercise therapy and cognitive behavioural therapy for people with persistent LBP" and "When reading the eligibility criteria for potential participants, it remains unclear what the exact definition of recurrent LBP is the authors have used. To my understanding, a recurrent LBP episode is defined as return of LBP with a minimum duration of 24 hours since recovery (a minimum duration of 4 weeks pain-free). (Vet, Heymans, Dunn, & Pope, 2002) Similarly, the definition used for subacute LBP is not clarified, although this is generally the period of 4-12 weeks after onset of LBP. (Foster et al., 2018) LBP persisting for more than 12 weeks would then be chronic LBP. When using these definitions and reading the eligibility criteria, the only criteria related to LBP mentioned are >2 pain score on an NRS (0-10) in the preceding four weeks and the presence of chronic LBP (defined as LBP persisting for 7 months or longer). With these criteria healthcare workers with first time ever acute LBP with a duration of less than 4 weeks or with first time ever LBP persisting for up to 7 months are eligible for participation.
Although the definition of chronic LBP is debatable, the eligibility criteria used allow inclusion of patients with acute, sub-acute and chronic complaints (unless chronic LBP was diagnosed by a physician).

If we understood right, one of the major concerns of the Reviewer 1 was that we used the term "recurrent LBP" or "recurrent NSLBP" to describe the study sample, which also reflects to Reviewer 1's opinion of the treatment strategies that we used in the neuromuscular exercise (NME) intervention.

LBP is reported to run a recurrent course in majority of patients. In a systematic review, Stanton et al. (4) presented, that there is a large variation in definitions of term "recurrent LBP" in the literature, and it is used in different ways by researchers and clinicians. The most commonly feature in defining recurrent LBP is according to frequency of pain episodes, and the criteria range from "at least one episode over past year" (5) to "pain twice weekly" (6). More recently, Macedo et al. (7) present that the differentiation between people with fluctuating pain and those with episodic LBP should be made. The former would be people who have pain with levels that fluctuate over time, while the latter would be those with episodic/recurrent LBP who recover from an episode, but then experience a recurrence (8). Because there are different definitions of recovery and recurrence, identifying those with episodic or recurrent LBP is challenging (7).

Research using e-mail and SMS answers by mobile phone to record back pain intensity levels on daily basis has broadened the understanding of the fluctuating nature of LBP in the recent years: majority of back pain sufferers experience pain episodes of and on over an extended span of time (9-11). Proposal by VET et al. 2002 about defining recurrent LBP was made long before recent knowledge (via SMS reporting) about the fluctuating nature of LBP.

Due to difficulties in definitions, in this manuscript and in all other articles of the NURSE RCT (1-3, 12, 13) term "recurrent LBP" is used and it covers both episodic and fluctuating low back pain. The term" Fluctuating LBP" is also difficult to define and it is not a term of established practice. In the Method section of the manuscript (Study design and participants), we have described the study sample in page 7, rows 132-136 as "Most of the study subjects (82%) experienced LBP on some or most days of the week, but not daily" (row 133-134). If majority of the study sample had pain-free days in between and were generally able to work (in physically demanding work), we cannot talk about chronic, persistent LBP. A sentence "Duration of LBP was less than 3 months for 65% (12)" (row 136) as well as "Althoug term "recurrent LBP" lacks consensus (4), we use it to describe the study subjects, most of whom had a recurring pain behavior (12)" was added to the end of the paragraph (row 139-140). Also, the term "or" (in subacute or recurrent LBP) was added to the manuscript.

In the baseline-analysis of the current study sample (12), which we also refer in the manuscript, more precise description of the duration and frequency of the participants' LBP is given. The time span between screening and beginning of the group-based intervention (with baseline measurements in between) exceeded 4 weeks for most, nearly for all of the participants. On the
other hand, there were 7 persons out of 219, whose duration of daily LBP exceeded 6 months during the waiting time from measurements to the beginning of the group-based interventions (12).

Reviewer 1's response:

The authors provide a clear rationale for the selection of the term "recurrent LBP". The extensive explanation highlights the importance of defining the terms the manuscript with the current lack of widely used definitions for acute-, subacute, recurrent and persistent LBP. The information added to the manuscript by the authors indeed addresses my points on the selection of participants in relation to the research question and the definitions of recurrent and sub-acute LBP.

"Following this line of reasoning and the findings from Foster and colleagues, one would expect the contents of a treatment strategy for people with acute LBP to contain advice to remain active and education, with the addition of exercise therapy and cognitive behavioural therapy for people with persistent LBP. (Foster et al., 2018)" We are very aware of the fact that advice to remain active is recommended in acute LBP, and it was included in back care counselling intervention in a 4-arm setting of the NURSE RCT. To avoid any contamination with the counselling, all advice considering life style was avoided in the NME intervention.

Reviewer 1's response:

Based on the author's response I would recommend the addition of a modified version of the last sentence to the description of the NME intervention.

"Surprisingly, the current analysis focusses on exercise vs no exercise. If the aim was to test the effects of NME therapy with the knowledge that currently no evidence showing superiority of one form of exercise exists, one would expect a trial investigating NME therapy compared to general exercise" In the original NURSE RCT with a 4-arm setting, the purpose was to examine effects of combined NME+ counselling or either alone vs. controls with no intervention. The present study combined NME+counselling and NME only to be "exercisers" and counselling only + controls to be "no exercisers", and all the analysis were adjusted for counselling. In that way we were able to get two groups with more than 100 study subjects. We agree with the Reviewer 1, that adding a group of general exercisers would have broadened the understanding of which type of exercise is the most effective for persons with physically demanding work and LBP. But intervention studies are expensive and demanding to carry out, and we did not have resources for additional personnel and/or locations. In the original NURSE RCT, we had already 4 study arms, and it took us 3 years the recruit a sufficient sample size. The more study arms you
have, the more subjects you need. General exercise was advised to the participants of the counselling intervention among other advices of managing LBP and its consequences.

We have reported two earlier intervention studies among males with chronic LBP (14) or healthy back (15) including combined exercise and counseling. Together with NURSE RCT, all three studies applied the same biomechanical principles of maintenance of the lumbar neutral zone in all exercises and utilizing exercises with high muscular activity (16, 17) and reasonable compressive force (16).

Reviewer 1’s response:

I understand fully that adding an additional arm to the trial would have increased the resources required to complete it. However, I do not ask the authors to perform a trial of this magnitude. However, when the authors write in the background that there is currently no evidence of superiority of pilates or movement control exercises over other forms of exercise they raise the expectation that the current trial will attempt to demonstrate the superiority.

I don't understand the relevance of the last paragraph.

"…with the current understanding of LBP treatment, the results from this study are unlikely to contribute significantly to the literature on the effects of (any form of) exercise therapy on pain and disability in people with LBP."

We agree with the reviewer, that this study is unlikely to contribute significantly to the literature of exercise and LBP. Very seldom any single study does. But we dare to argue, that it casts some light on the field of this research. Because our study subjects expose their back for harmful loading at work (frequent flexion-extension, working in stooped position and/or heavy loading with high compressive and shearing moment in lifting and transferring patients), and already have back pain, we do not consider that whatever exercise with maybe additional harmful loading to spinal structures would have been beneficial.

For example, Kjaer et al. (18) presented very recently a structured exercise program for LBP, based on current knowledge and evidence. Exercises in that program are very similar to those, that we had in the current NURSE study with interventions conducted in 2012-2014. We conducted a modified Pilates-based NME program with focus on controlling the lumbar spine posture, according to Pilates principals to a group of healthcare workers, who have a physically demanding work, who still are at work, and whose LBP is not yet chronic, but many of them are on the verge to chronicity due to several risk factors, which we presented in the baseline article (12). Corresponding research is still scarce.

Reviewer 1’s response:
Based on the response by the authors, I understand their work adds to the literature on the treatment of healthcare workers. As the work duties of healthcare workers puts them at higher risk of LBP and developing persistent LBP (because of both the physical and mental stress of the work), they are as a group most likely different from the general population. Highlighting this difference between healthcare workers with LBP a group and patients from the general population might improve the rationale.

"…recurrence of LBP is not one of the eligibility criteria. Therefore, I am not convinced that the included sample of healthcare workers is suitable to test the main hypothesis.

We hope that we have convinced the Reviewer 1, that the screening was conducted adequately. Our hypothesis was, that "NME reduces LBP intensity and pain interfering with work, and improves lumbar movement control, fitness levels, and work-related factors more than non-exercise". Contradictory to Reviewer 1's opinion, we think that managing to get a study sample with non-chronic (sub-acute or recurrent) LBP and physically heavy work is one of the strengths of the NURSE RCT.

Reviewer 1's response:

My concerns regarding the included sample have been adequately addressed in previous responses.

"Another point of discussion for the eligibility criteria is the age restriction. In both the protocol article and this manuscript, the rationale for the age range of 30-55 years remains unclear."

We wanted that the study subjects had exposed their back for physically loading work for some years. When we started to plan the NURSE RCT, the mean age for retirement was 56 years for assistant nurses in Finland. The main reason for early retiment was musculoskeletal disorders, LBP being the leading cause. A sentence "Age range was set in order to get a study sample, who have been exposed to physically demanding work, and who would still be working during the 24 months' follow up (in NURSE RCT)" was added to page 7, rows 128-130.

Reviewer 1's response:

I agree with the added sentence.

"The main difference between the analysis in the manuscript and the previously published results by Suni et al. 2018 is that the combined exercise and back care counseling and exercise alone group were combined to form the exercise group and that the counselling only and control
groups were combined to form the non-exercise group in this study. Two of the main outcomes remain the same, namely intensity of LBP measured with a Visual Analog scale and pain interfering with work. Of the outcomes selected for the secondary analysis it is notable that the results of the test battery regarding movement control impairment are presented, where in the paper by Suni et al. 2018 the authors write: "Contrary to the original plan of the NURSE-RCT, the results of the test battery regarding movement control impairment are not included in the present paper due to the poor reliability of several test items assessed as part of the first sub-study." In this manuscript the authors do not provide a rationale as to why the results from the MCI test battery are used as an outcome, when these same results were dismissed by Suni and colleagues because of poor reliability. Only after reading the repeatability article of the MCI test battery and its supplement, it becomes clear that the 2 tests with kappa values of 0.31 and 0.16 have been omitted from the original test MCI battery. The explanation and a short discussion on this is located in the discussion. However, it would be more appropriate to move this paragraph to the methods so that the reader is well aware of the changes made to the MCI battery before reading the results. The question as to why the MCI battery of 4 tests was used as an outcome when Suni and colleagues chose to omit them remains.

The main outcome measure of the NURSE-RCT is the intensity of low back pain, according to which the sample size calculations were (1, 3). In addition, in the main article (3), effectiveness on fear avoidance beliefs were studied as well the cost- effectiveness in terms of days of sickness absence and quality of life. In the main article of the NURSE-RCT (3), movement control impairment (MCI) test battery was rejected from primary outcomes due to results of the repeatability study, that we conducted in the first sub-study in 2011 (2). Due to poor repeatability, two measurements (Rocking forwards and backwards and One leg stance) were removed from the original test battery of 6 tests, but remaining four MCI test were repeatable enough to study the effects of an exercise intervention, which was targeted to "reduce pain-induced disturbances of movement control". Reviewer's suggestion to move the paragraph considering MCI tests from Discussion to Method -section was very good, we thank for that. A sentence "From the original MCI test battery of 6 tests (19) two tests with poor repeatability (rocking forwards and backwards and 1-leg stance) were removed (Table 1.) has been added to Measurements; page 8, rows 159-161, and the text in Discussion (Limitations of the study) has been shortened.

Reviewer 1's response:

I agree with the changes made.

"The last point of concern for the measurements chosen is that although the authors claim that LBP is often recurrent, presence and duration of pain free episodes were not recorded. Since the
measurements were taken after 6 and 12 months, it is possible for the LBP to have resolved completely and recurred in the month before the follow up measurement."

Very often in intervention studies measurements are conducted at baseline, immediately after the intervention (in this case 6 months) and after a period of follow-up time (in this case 12 months). The question of pain frequency was asked at at the screening point, at baseline measurements, and in 6, 12 and 24 months follow-up in

NURSE RCT, but we did not analyze this measurement in this manuscript due to already one primary outcome and 7 secondary outcomes. Our purpose is to present those results in a future article.

The development of LBP frequency (at baseline, 6 and 12 months) is presented in the following table:

<table>
<thead>
<tr>
<th>Frequency of LBP; n (%)</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NME, n=110</td>
<td>no NME, n=109</td>
<td>missing (m)</td>
</tr>
<tr>
<td>Daily</td>
<td>16 (17)</td>
<td>36 (43)</td>
<td>27 (37)</td>
</tr>
<tr>
<td>Most days of the week</td>
<td>10 (10)</td>
<td>29 (30)</td>
<td>42 (44)</td>
</tr>
<tr>
<td>A few days a week</td>
<td>40 (42)</td>
<td>4 (5)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Recovered from LBP (from screening)</td>
<td>16 (19)</td>
<td>24 (29)</td>
<td>11 (15)</td>
</tr>
</tbody>
</table>

Yes, it is possible that for persons with LBP, pain or pain intensity levels fluctuate, flare up, or resolve during the intervention. That happens also without any intervention as well. In non-specific LBP, we can very seldom point out a specific reason either for pain or recovery from pain. The fluctuation of pain is individual, and we can not presume, that it would happen systematically, neither in the NME nor in the control group.
Reviewer 1's response:

I'm afraid that the formatting of the table is missing. I accept the explanation by the authors.

In regards to the contents of the exercise programme, the general principles of the neuromuscular exercises have been criticized elsewhere. (Lederman, 2010) In his narrative review, Lederman (2010) criticizes emphasizing / focusing on activating m. transversus abdominis, not the training principles that we had in our NME program.

Focusing on any special, single deep muscle was not in our focus in this modified Pilates-based NME program, although that principle is emphasized in many Pilates schools and in many other NME programs, which are called "motor control exercise" or "stabilizing exercises". We explain that in the Background-session, page 5, rows 90-92.

Especially functional squatting exercises (with arm and trunk movements and controlling the neutral spine posture) recruit the whole kinetic chain. We added a Supplement with exercises to the manuscript (see following answer).

"Furthermore, in the introduction the authors write that healthcare workers are exposed to physically heavy work duties and in the protocol article one of the aims of NME is to increase muscle strength (and endurance) needed in heavy nursing tasks. However, the only strength related exercises described in the supplementary materials of the protocol article are functional squatting exercises. As the NME program aims to improve strength for healthcare workers who perform heavy lifts and patient transfers, it is questionable when the program contains only exercises performed without weights and aimed only at the lower extremities."

In the Supplement material of the protocol article (1) Training principles and specific objectives of the key (not all) exercises were presented. We consider for example Modified curl up, Bird dog, Side bridge, Single leg stretch, and 1-leg Shoulder Bridge to be core muscle strength or endurance exercises for persons, who were previously not engaged in NME-type training. Exercises are described more precisely in a new, additional Supplement. A sentence: "The exercises are presented in Additional file 1".

Was added on page 9, rows 189-190, and the Supplement 1. has been added as attachment. Also, a sentence "The individual depicted in the images in Additional file 1. provided her written informed consent for the publication of these identifiable images" was added under subheading Consent for publication (page 22, 465-466) Functional 1-leg squatting exercises are muscle strength training for lower extremities (especially when keeping in mind that 60% of study subjects were overweight or obese (12). In the baseline measurements, results of the fitness tests were only modest with a wide range. For people with subacute or recurring LBP, it is important
to have exercises, which minimize the load to spinal structures but induce high muscular activity (16).

During progression (from level I to level II and from II to III) several participants had difficulties in managing either the exercises or targeted amount of repetitions. The fact that we gained increased fitness level only in abdominal strength, not in other fitness components can be due to 1) only moderate exercise compliance (average of 1.1 times/week, which generally allows to maintain the existing strength level, but not increasing muscular strength), 2) deficiencies in measurement selection or 3) as the Reviewer 1 suggests, that exercises were not demanding enough regarding to muscular strength and endurance. We discuss the two first mentioned arguments in Discussion, Limitation section. Unfortunately, we did not have access to weights in the locals, were we instructed the group-based NME sessions. And we definitely do not know, if adding more weights to the NME program would have increased the exercise compliance.

Reviewer 1’s response:

I would like to thank the authors for adding the additional file. This clears up a lot of the confusion regarding the specific contents of the NME program. My reference to Lederman (2010) was mainly aimed at the points he made on core stability and training in relation to motor learning and training issues and teaching patients to move in the "correct" way. Which is that the effects of exercises which are not similar to the work the patient has to do (for instance heavy lifting in the case of the nurses) generally transfer poorly to real life situations. Furthermore, teaching patients to keep their spine in a neutral position during their work and general movement may cause bracing or unwanted co-contractions in trunk muscles or even give the patient the idea that flexing the spine is bad.

As stated in my comments on the eligibility criteria, recurrence of LBP was neither a criterion for eligibility nor recorded for the enrolled healthcare workers, and it remains unclear how the authors define sub-acute. Additionally, the duration of the episode of LBP the healthcare workers were suffering from when they were enrolled in the study was not reported in the manuscript. As a result, I do not think the authors can claim that their study was performed in healthcare workers with sub-acute recurrent LBP (written as NSLBP in first sentence of the discussion).

We have described the study sample more precisely in the baseline article(12), which we refer to in the current manuscript. We hope that the reviewer accepts our description with those insertions that we explained earlier.

Reviewer 1’s response:

I accept the authors previously mentioned additions.
In a large part of the discussion the authors build a case for the importance of lumbar movement control. However, there are two issues the authors do not address in sufficient detail. The first is that claims on the effectiveness of lumbar control exercises or NME focusing on control of the lumbar spine are exclusively based on trials with "no exercise" as controls. As was the case in the current analysis.

The reason why we did not refer to other intervention studies comparing lumbar movement control exercises to other exercise is the lack of existing studies. Luomajoki et al. published very recently (autumn 2018) the first systematic review and meta-analysis comparing effectiveness of movement control exercise to other interventions(20). According to that systematic review, "Based on the available studies, it is difficult to assess the relative effectiveness of MVCE (=movement control exercise) treatment compared to other interventions offered to people with NSLBP and MCI." We did not refer to Luomajoki et al. (20) in the first version of the manuscript due to differences either in study populations or treatment protocol (for example individual, direction-specific MVCE). After this critic by Reviewer 1 we added this systematic review to references with the following paragraph in Discussion, page 17, rows 346-350: Among general population with LBP, lumbar movement control exercises appear to be more effective in reducing pain in short term, and in improving disability in long term. However, the quality of evidence varies from very low to moderate. Based on the available studies, it is difficult to assess the relative effectiveness of lumbar movement control exercises compared to other interventions offered to people with LBP (20).

Thus, in the Discussion of the revised version of the manuscript, we first discuss other exercise studies conducted among healthcare personnel with LBP, then studies focusing on controlling the neutral spine posture conducted among other study samples with physically heavy work and LBP (railroad workers and conscripts in the military), and finally lumbar movement exercises vs. other interventions among general population with LBP.

Reviewer 1's response:

I accept the additions made.

The authors state in the background that currently there is no evidence for the superiority of one type of exercise over another and write in the discussion that they cannot say that the NME intervention is superior to any other exercise type. Therefore, I would like the authors to clarify why or when a clinician should choose NME over any other form of exercise.

This was a good idea. We added a sentence: …NME program.. was feasible and easy to modify into other kind of exercise training. It can be recommended specially for those who are interested in Pilates- or yoga-type NME. to page 19, rows 398-400.
Reviewer 1's response:

I agree with the changes made. However, I recommend adding the importance of tailoring exercise recommendations to the preferences of the patient to improve adherence. Pilates- and or yoga-type NME can be recommended to those who are interested in them to improve adherence.

The second issue is that many of the assumptions cited in the discussion are based on cross-sectional studies. This makes cause-effect claims difficult. This makes lines 339 to 363 redundant, as the assumed mechanisms of exercise on LBP are either not specific to the NME intervention, based on cross-sectional data or based on assumptions on how findings from the cited studies transfer to real life situations.

Indeed, reading the discussion without these paragraphs detracts nothing from the findings and implications of the current study.

In the revised manuscript the corresponding rows are 350-374. We removed one sentence and reference (21). Otherwise we consider important to discuss about the pain-reducing mechanisms of exercising or risks for lumbar pain caused by mechanical loading (due to exercise). Although this discussion is partly theoretical and/or based on cross-sectional studies, it was a rationale for us in exercise selection and can be beneficial also for clinical practitioners. But if the Reviewer 1 insists, we are ready to remove that part of the manuscript.

Reviewer 1's response:

My personal preference is to have the rationale for the intervention and study in the background, as it is often the result of an analysis of the existing literature and combining important pieces to form a meaningful theory. This appears to be the case for the mentioned paragraphs (reflected by the presence of a reference after almost every sentence). However, if the authors feel that this theoretical analysis of the literature has a place in the discussion of the manuscript, I can agree with that.

References (by Reviewer 1):


**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

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