Journal of Clinical and Translational Research
Peer review process file 05.2020S4.002

Early physical activity and clinical outcomes following pediatric sport-related concussion

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Review timeline:

Received: 3 December, 2019
Editorial decision: 27 January, 2019
Revision received: 17 February, 2020
Editorial decision: 16 March, 2020
Published online: 16 April, 2020

1st editorial decision

27-Jan-2019

Ref.: Ms. No. JCTRes-D-19-00036
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Dear Dr. Howell,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Feb 26, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Nicholas G Murray, Ph.D.
Editorial Board Member
Journal of Clinical and Translational Research

Reviewers' comments:

Dr. Howell -

Thank you for submitting to JCTR for our special issue. Please respond to the below reviewer comments and please tighten up the overall casual language found throughout the manuscript.

Let me know if you have questions.

Nic Murray

Reviewer #1:

Intro:
- Overall the intro was very well done and set up the study nicely. I do recommend being a little more specific with your literature review in regards to the patient populations studied in the various references. Given the disparity in outcomes between youth, adolescents, and adults it would be nice to see how PA impacts these various groups in the current literature.
- Along the same lines, making mention of your target age range in somewhere in the last paragraph would be helpful for the reader.

Methods:
- Well done describing excluded participants.
- A minor comment, but given your data collection time period, it is impossible that all patients were diagnosed in accordance with the Berlin guidelines as referenced on page 7, line 9.
- Do you have any thoughts on the reliability and validity of your PA question(s)? I realize this was probably just one question in a larger battery, but any information on how accurate self-reported PA was would be very useful.
- Page 8, line 24: Did the reported symptom burden have to be 0 before you considered the patient symptom free, or was there some range around a 0 score given the fact that some people never report 0 symptoms, regardless of concussion?
- Clinical tests: Given there were likely many raters, do you have any inter-rater reliability data, especially pertaining to the BESS?

- Were any of your participants instructed to begin light PA after the initial visit but before any follow up visits? If so, how would they be categorized?

Results:
- Table 1: For the sport category, percentages would be useful given the large sample size disparity between groups.
- Table 3: Please be specific in the table title regarding which time point these data are from. I'm assuming initial visit but it is not clear.
- Given the large variability in your outcomes, which was to be expected, I appreciated the effect sizes reported in figure 1. Please consider adding an effect size column to table 3 as well.

Discussion:
- The first sentence is worded oddly, please consider a revision for clarity.
- Given the focus on using the word "pediatric" in the Discussion, you may consider defining this term in the Methods. Given you sample went up to age 18, many would consider your cohort to be a mix of pediatric and adolescent populations.
- I appreciate the first paragraph statement about not being able to determine if PA positively affected clinical characteristics given your study design, well done.
- Page 18, line 14: Please consider that am important confounder is that the people in the non-PA group might have had more severe concussions, thereby limiting their ability to do PA and also increasing their recovery time. I'm not suggesting you did anything wrong by not accounting for severity, given there is no good way to clinically account for this, but I do think it is important to bring up in the Discussion. Here, you are starting to get at this point, but I'm not sure you go far enough.
- Page 19, paragraph beginning line 14: Well done with this paragraph. I do think you should consider expanding a bit on the idea of dosage. Obviously we don't know how much PA is good or bad, but there is likely a fine line between good and bad. Thus, I think it is important that clinicians administer PA very carefully in well-supervised conditions. Clinicians who cannot closely monitor PA may consider not prescribing it without in-depth counseling given too much PA could have serious adverse effects. Overall, I think some text about very careful clinical discretion is warranted and the decision to recommend early PA should be made on a case-by-case basis at this point.
- Limitations: Please include some text about limitations around your clinical assessments from a reliability standpoint. Especially given the relatively small between group BESS differences, it is possible there were actually no clinically meaningful differences on some of these statistically significant clinical assessments.
- Conclusion: While I agree, I do think you should temper the final sentence a bit given my previous comment about the potential negatives of unsupervised PA, especially in younger patients.

Reviewer #2:
General:
This manuscript explores the relationship between early physical activity following a sport-related concussion and clinical outcomes. The manuscript clearly conveys the goals,

methodology and findings of this investigation. However, there are a number of items of concern with this manuscript as written. The largest concern pertains to the congruency of the methodology and the interpretation of findings. Given the methods employed, it is suggested that the framing of the research findings in the Discussion be modified to better reflect the nature of this study with specific emphasis on the inability of this method to determine a cause-effect relationship between these variables.

Introduction:
There is a significant amount of literature now that supports the use of low intensity physical activity to enhance recovery from concussion. However, there is a dearth of literature regarding the dose-response relationship in individuals with concussion. This is an important aspect of your study as the volume and intensity of physical activity remains unknown. It would be beneficial to have that highlighted in your introduction given that you make comments relating to this in your Discussion.

You should identify the "normal" delay between concussion injury and reporting to a clinic in the general population. This is important as your introduction (purpose statement) and methods have you include participants that report for INITIAL evaluation with 21 days post-concussion.

The hypothesis statement beings my concerns for the language used in this manuscript. The language is ambiguous as to whether this is an "association" or an effect. It would benefit the reader to have you identify that early PA would be "associated with" better clinical presentations. This aids in identifying not only the perspective of the relationship of PA with clinical outcomes, but also identifies the statistical methods that will be used.

Methods
The 21-day inclusion period should be justified. Why 21 days? Why not within 7 days or 10 days given that this seems to be a retrospective review of existing data. This would likely reduce your sample size and negatively affect your regression-based analyses. However, justification is warranted. Is it based on symptom presentation, normal time-course of concussion injury in pediatric patients?

It needs to be explicitly stated that this study was a retrospective investigation of clinical records OR that patient consent and parental assent was obtained prior to being included in this study.

While the BESS and ROMBERG are clinically used and viable tests of postural stability, their inherent limitations have been well identified and published. These limitations in reliability should be identified in the manuscript (either in the Methods or more likely in the Discussion).

Were balance tests performed by the same ATC's? Again, reliability is a concern.

Statistical analysis: "for normally distributed data". No tests of normality are listed in the statistical analysis. How was normality determined? This is an important aspect of the Methods as it determines the assessments used and assumptions made in the statistical tests.

The use of $p < 0.20$ for co-variates should be justified in the text. The references identified at the end of this sentence are not statistical papers justifying this p-value.

Results
Tables throughout the manuscript: if there is a significant effect, bold the p-value such that it is easier to visually identify.

Table 1. Justify 0.15 as significant.

It is important to identify clearly and to re-state that there was a difference in the time to initial clinical evaluation between the groups. The no PA group arrived earlier than the early PA group, but the early PA group still came suggesting that they were still symptomatic to the point of seeking medical care.

The presentation of headache may be associated with concussion-induced neurometabolic crisis. This suggests that those with less headache may have had less neurometabolic crisis and were therefore able to do early PA.

It is suggested to present not only p-values but also effect sizes to support interpretation of findings. For example, the statistical assessment of time from injury to initial evaluation has a highly significant p-value, but a moderate effect size (Cohen's d).

Discussion
First line - remove the semi colon. Incomplete sentence.

The presentation of the findings of this study as written are overstated. The language used in the Discussion implies a cause-effect relationship that cannot be established by this study's methodology. In the case of this study, those that participated in self-paced early PA (without a clinical evaluation) performed better on clinical assessments and symptomology. This is an important finding; however, we cannot identify from this study that the early PA is responsible for these outcomes. Suggested reviions of the language to indicate the associative (rather than causative) nature of these variables. This is the major concern with the current manuscript (presentation of findings).

Paragraph 3: "These past studies focused mainly" - this differentiation from previous studies should be highlighted not only in the Discussion, but identify the hole in the literature in the Introduction as well.

Also highlight more effectively the use of the parent-report as a corroborating factor.

Be careful of using language that insinuates causal relationships.

The findings and interpretations of the regression model could be better presented.

Additional statements regarding the lack of information regarding the dose-response relationship could be beneficial to the readership.

Author's rebuttal

Article Title: Early physical activity and clinical outcomes following pediatric sport-related concussion

Article Number: JCTRes-D-19-00036

We would like to thank the reviewers for their critique of our manuscript submitted to the Journal of Clinical and Translational Research. We have carefully responded to each of the points raised in bold font within this document and made revisions to the manuscript corresponding to the reviewer comments. As a result, we believe that the quality of the manuscript has improved substantially. All changes within the revised manuscript have been noted using tracked changes, and all page numbers refer to the revised manuscript, unless otherwise noted.

Reviewer #1:

Intro:

- Overall the intro was very well done and set up the study nicely. I do recommend being a little more specific with your literature review in regards to the patient populations studied in the various references. Given the disparity in outcomes between youth, adolescents, and adults it would be nice to see how PA impacts these various groups in the current literature.

Author response: Thank you for pointing this out. We agree, and we have updated our introduction to specify the age range within the studies we have referenced. We have updated the following sections of our introduction:

Pages 5-6:

> ***This evolution in concussion care is based upon studies which have found that PA does not negatively impact recovery[12,13], and prolonged or complete rest may actually be harmful[14] among children and adolescents. In addition, regular aerobic exercise below the level of symptom exacerbation appears to be beneficial for symptom reduction among children and adolescents with persistent concussion symptoms,[15–18] although the efficacy of exercise on other functional capabilities has not yet been clearly delineated.***
>
> ***However, additional work is needed to clarify whether children or adolescents can begin PA on their own without medical supervision or exercise prescription and still receive similar benefits. In addition, clinical outcomes among children or adolescents who present for their first evaluation to a sports concussion clinic who have already begun exercising are not known. This information would be beneficial for clinicians who see children or adolescents in acute and sub-acute phases of injury to better determine appropriate management and set recovery expectations.***

- Along the same lines, making mention of your target age range in somewhere in the last paragraph would be helpful for the reader.

Author response: We agree with this point. We have added this information to our purpose statement.
Page 6:

> ***Therefore, the purpose of our investigation was to evaluate if initial post-concussion clinical outcomes vary between children and adolescents (8-18 years of age) who engaged in early PA post-injury relative to those who had not resumed PA when reporting to a sports concussion clinic for initial evaluation within 21 days of injury.***

Methods:
- Well done describing excluded participants.

Author response: Thank you.

- A minor comment, but given your data collection time period, it is impossible that all patients were diagnosed in accordance with the Berlin guidelines as referenced on page 7, line 9.

Author response: We appreciate this observation and agree. Patients were diagnosed in accordance with the most recent international guidelines available at the time of diagnosis. We have amended this section to also include the citation from the Zurich meeting to better describe which guidelines were available throughout our study period.
Page 7:

> ***Concussion was defined among the treating physicians consistent with the most recent international consensus guidelines for concussion in sport available at the time of assessment.[2,10]***

- Do you have any thoughts on the reliability and validity of your PA question(s)? I realize this was probably just one question in a larger battery, but any information on how accurate self-reported PA was would be very useful.

Author response: Our clinical registry asks patients to report whether or not they are currently doing any activity/exercise, and if so, asks for a description. The treating provider reviews patient-reported responses with the patient and family before final entry into the clinical registry. Our study design did not allow for comparison of self-reported data with objective measurements for physical activity, so we are unable to comment on the reliability and validity of this question. However, a recent study in high school and college athletes with concussion found moderate correlation between objective and subjective reports of physical activity (Huber DL, Thomas DG, Danduran M, Meier TB, McCrea MA, Nelson LD. Quantifying Activity Levels After Sport-Related Concussion Using Actigraph and Mobile (mHealth) Technologies. Journal of Athletic Training 2019;54(9):929-938.). Thus, it is reasonable to expect that our patients

answered this question with a moderate level of accuracy. This is addressed as a limitation of our study in the discussion:
Page 20:

> ***Furthermore, PA grouping was based on self-reported data, and not validated with activity or heart rate monitors, so it is possible that patients may have under- or over-reported their PA level.***

- Page 8, line 24: Did the reported symptom burden have to be 0 before you considered the patient symptom free, or was there some range around a 0 score given the fact that some people never report 0 symptoms, regardless of concussion?

Author response: We appreciate this concern and agree that this information is critical for readers to understand. Consistent with past studies, we instructed patients to rate their symptoms as only those that started at the time of injury and were still present at the time of assessment. Thus, symptom free was defined as an HBI score of 0. We have added this information to our revised methods section.
Page 8:

> ***As patients returned for follow-up care through recovery, we also calculated the total symptom duration time, as the time elapsed (days) from injury until the patient no longer reported the presence of any concussion symptoms. Consistent with other studies of child and adolescent patients seen in specialty care concussion clinics,[12,27,28] we instructed patients to rate only those symptoms that began at the time of injury and were still present within one day of the assessment. Thus, we defined symptom-free as an HBI score of zero.***

- Clinical tests: Given there were likely many raters, do you have any inter-rater reliability data, especially pertaining to the BESS?

Author response: Yes, there were many raters for the BESS. We do not have any inter-rater reliability, unfortunately. We have added this as a limitation to our study.
Page 20:

> ***In addition, we did not have inter-rater reliability data for our assessments. Given the small between-group differences for the BESS outcomes, the clinical significance is likely low.***

- Were any of your participants instructed to begin light PA after the initial visit but before any follow up visits? If so, how would they be categorized?

Author response: Thank you for this question. At the time this study was performed, our Concussion program providers recommended return to symptom-limited daily activity for patients who were still symptomatic from their concussion, so this would not

be expected to vary among included patients after entry to our clinic. We instead focused our study on what patients reported doing prior to entry to our program, where initial care may have been more diverse.

Results:
- Table 1: For the sport category, percentages would be useful given the large sample size disparity between groups.

Author response: Thank you for this suggestion. We agree, and we have listed percentages for each sport, in addition to the number included.

- Table 3: Please be specific in the table title regarding which time point these data are from. I'm assuming initial visit but it is not clear.

Author response: We have updated the table title to now specify the time point the data are from. We now state:

> ***Table 3. Comparisons of headache, sleep disturbance, balance, vestibular, and oculomotor function at the initial post-concussion visit between early PA and no PA groups.***

- Given the large variability in your outcomes, which was to be expected, I appreciated the effect sizes reported in figure 1. Please consider adding an effect size column to table 3 as well.

Author response: Thank you for this suggestion. We have added odds ratios and 95% confidence intervals for the dichotomous outcome variables, and Cohen's d effect sizes for continuous outcome variables in Table 3.

Discussion:
- The first sentence is worded oddly, please consider a revision for clarity.

Author response: Thank you for this constructive comment. We agree, and have deleted this sentence to the manuscript.

- Given the focus on using the word "pediatric" in the Discussion, you may consider defining this term in the Methods. Given you sample went up to age 18, many would consider your cohort to be a mix of pediatric and adolescent populations.

Author response: Thank you for this suggestion. We have revised our discussion to specify "adolescent and child" patients rather than pediatric given the ambiguity surrounding this term.

Page 17:

> ***In our study, child and adolescent patients who engaged in early PA prior to the initial evaluation in a sports concussion clinic had shorter symptom recovery times than those who did not.***

Page 20:

> ***In addition, further investigation into the effectiveness of self-initiated PA compared to individualized exercise prescription is also relevant, especially within the child and adolescent population, where patients may be more likely to engage in free play during recovery.***

Page 21:

> ***Future methodologically stronger research is needed to definitively determine the causal role of exercise in outcomes after child or adolescent concussion.***

Page 21:

> ***In conclusion, within the first 3 weeks of sport-related concussion, participation in early PA is associated with shorter symptom recovery times, fewer overall symptoms, and better postural control in child and adolescent patients.***

- I appreciate the first paragraph statement about not being able to determine if PA positively affected clinical characteristics given your study design, well done.

Author response: Thank you.

- Page 18, line 14: Please consider that am important confounder is that the people in the non-PA group might have had more severe concussions, thereby limiting their ability to do PA and also increasing their recovery time. I'm not suggesting you did anything wrong by not accounting for severity, given there is no good way to clinically account for this, but I do think it is important to bring up in the Discussion. Here, you are starting to get at this point, but I'm not sure you go far enough.

Author response: We appreciate your concern, and certainly agree that this is an important consideration that is a challenging clinical factor. We agree that our discussion could include more detail, and we have added this to our revised discussion.

Page 18:

> ***This may be due to factors such as a more severe concussion in the no PA group, although this is a concept that does not have a quantifiable outcome. However, it should be considered as a potential confounding variable, as those who were more symptomatic or affected by the injury were likely limited in their ability to do***

physical activity and perhaps independently or as a result, required a longer time to recover.

- Page 19, paragraph beginning line 14: Well done with this paragraph. I do think you should consider expanding a bit on the idea of dosage. Obviously we don't know how much PA is good or bad, but there is likely a fine line between good and bad. Thus, I think it is important that clinicians administer PA very carefully in well-supervised conditions. Clinicians who cannot closely monitor PA may consider not prescribing it without in-depth counseling given too much PA could have serious adverse effects. Overall, I think some text about very careful clinical discretion is warranted and the decision to recommend early PA should be made on a case-by-case basis at this point.

Author response: We greatly appreciate the reviewer bringing up this point. We agree with the assertions made, and feel that this paragraph is the appropriate place to bring up these issues.
Pages 19-20

The clinical implications of our study, as well as other recent research and evidence-based guidelines,[2,3,11,20,21] suggest that health care providers should consider encouraging early PA under well-supervised conditions in order to facilitate better outcomes sooner after injury, rather than perpetuating the historic convention of rest until symptom-free.[10] To date, the majority of the literature supports physician-supervised, individualized aerobic exercise prescription to facilitate concussion recovery, but additional information regarding the optimal exercise "dosage" (intensity, frequency, duration) is needed.[22] However, clinicians should administer PA recommendations with careful clinical discretion on a case-by-case basis, as potential harmful effects of unsupervised PA after concussion have not yet been reported. In addition, further investigation into the effectiveness of self-initiated PA compared to individualized exercise prescription is also relevant, especially within the child and adolescent population, where patients may be more likely to engage in free play during recovery.

- Limitations: Please include some text about limitations around your clinical assessments from a reliability standpoint. Especially given the relatively small between group BESS differences, it is possible there were actually no clinically meaningful differences on some of these statistically significant clinical assessments.

Author response: We agree with this point raised, and have added the requested text to our limitations section.
Page 20:

In addition, we did not have inter-rater reliability data for our assessments. Given the small between-group differences for the BESS outcomes, the clinical significance is likely low.

- Conclusion: While I agree, I do think you should temper the final sentence a bit given my previous comment about the potential negatives of unsupervised PA, especially in younger patients.

Author response: We thank the reviewer for this perspective, and agree that in light of the point raised previously, we should temper our conclusions. We have modified the text accordingly.

Page 21:

> ***In children and adolescent populations, however, closer supervision may be required to avoid potential harmful effects from over-exertion. Further investigations into proper exercise dosage during concussion recovery are needed.***

Reviewer #2:

General:

This manuscript explores the relationship between early physical activity following a sport-related concussion and clinical outcomes. The manuscript clearly conveys the goals, methodology and findings of this investigation. However, there are a number of items of concern with this manuscript as written. The largest concern pertains to the congruency of the methodology and the interpretation of findings. Given the methods employed, it is suggested that the framing of the research findings in the Discussion be modified to better reflect the nature of this study with specific emphasis on the inability of this method to determine a cause-effect relationship between these variables.

Author response: We thank the reviewer for these comments. We agree, and we have modified our manuscripts so that our methodology and interpretation are more congruent. In particular, we have modified the framing of our findings to better reflect the cross-sectional study design. Related to these primary concerns, we have made the following changes.

Page 17:

> ***Given our study design, we cannot determine the causal nature of why patients engaged in early PA (e.g., perhaps due to lower symptom burden at the time of assessment) or whether early PA actually positively affects clinical characteristics. Our results suggest that there is an association between early PA after concussion and better post-injury outcomes, although causality must be determined through more rigorous prospective study designs.***

Pages 18-19

Our data indicate that early PA was associated with better postural control outcomes.

Pages 19-20

> ***The clinical implications of our study, as well as other recent research and evidence-based guidelines,[2,3,11,20,21] suggest that health care providers should consider encouraging early PA under well-supervised conditions in order to facilitate better outcomes sooner after injury, rather than perpetuating the historic convention of rest until symptom-free.[10] To date, the majority of the literature supports physician-supervised, individualized aerobic exercise prescription to facilitate concussion recovery, but additional information regarding the optimal exercise "dosage" (intensity, frequency, duration) is needed.[22] However, clinicians should administer PA recommendations with careful clinical discretion on a case-by-case basis, as potential harmful effects of unsupervised PA after concussion have not yet been reported.***

Introduction:

There is a significant amount of literature now that supports the use of low intensity physical

activity to enhance recovery from concussion. However, there is a dearth of literature regarding the dose-response relationship in individuals with concussion. This is an important aspect of your study as the volume and intensity of physical activity remains unknown. It would be beneficial to have that highlighted in your introduction given that you make comments relating to this in your Discussion.

Author response: We agree that bringing up the unknown dose-response relationship as it relates to physical activity after concussion should be acknowledged in the introduction. We have made this addition, as suggested.
Page 5:

> ***In addition, regular aerobic exercise below the level of symptom exacerbation appears to be beneficial for symptom reduction among children and adolescents with persistent concussion symptoms,[15–18] although the efficacy of exercise on other functional capabilities has not yet been clearly delineated. Further work suggests that it is also safe to perform aerobic exercise in the first week after injury[19] and early PA initiation is associated with faster recovery time,[20,21] although the dose-response relationship between PA intensity, timing, and frequency and concussion recovery needs further investigation.[22]***

You should identify the "normal" delay between concussion injury and reporting to a clinic in the general population. This is important as your introduction (purpose statement) and methods have you include participants that report for INITIAL evaluation with 21 days post-concussion.

Author response: We included patients who were seen with a concussion up to 21 days after sustaining a concussion in order to analyze an appropriately sized sample of participants who were at varying stages of recovery, as shown in Table 2, and consistent with other studies from similar clinical care settings. This was done so that we could best answer our stated purpose of evaluating if clinical outcomes varied among those who did and did not engage in PA prior to their initial assessment.

According to recent work from a similar practice setting as ours, the typical delay from concussion injury to reporting to a clinic was approximately 9-15 days (Desai, N., Wiebe, D. J., Corwin, D. J., Lockyer, J. E., Grady, M. F., & Master, C. L. [2019]. Factors Affecting Recovery Trajectories in Pediatric Female Concussion. Clinical Journal of Sport Medicine, 29[5]), a similar time as our observation, as our subjects were seen for initial evaluation between 8-12 days post-injury, on average. We are unaware of any studies investigating this delay in the general population, although we would expect differences between our setting and that of an Emergency Department, for example.

We have added this information and citation to our revised methodology.
Page 7:

> ***We selected a cutoff of 21 days from injury to initial clinical presentation to examine a sample of participants who were at varying stages of recovery and***

consistent with previous studies among children and adolescents with concussion.[12,23]

Page 8:

Consistent with other studies of child and adolescent patients seen in specialty care concussion clinics,[12,27,28] we instructed patients to rate only those symptoms that began at the time of injury and were still present within one day of the assessment. Thus, we defined symptom-free as an HBI score of zero.

The hypothesis statement beings my concerns for the language used in this manuscript. The language is ambiguous as to whether this is an "association" or an effect. It would benefit the reader to have you identify that early PA would be "associated with" better clinical presentations. This aids in identifying not only the perspective of the relationship of PA with clinical outcomes, but also identifies the statistical methods that will be used.

Author response: We appreciate this point, and attempted to avoid any language that inferred a causal effect, but appreciate the opportunity to clarify this further. We agree that it would be beneficial for the reader to have an early identification that we sought to identify associations, not effects. We have modified our hypothesis, as suggested, to reflect this point.

Page 6:

We hypothesized that early PA (i.e. beginning PA prior to the initial evaluation) would be associated with fewer symptoms and better performance on vestibular, ocular, and balance tests.

Methods

The 21-day inclusion period should be justified. Why 21 days? Why not within 7 days or 10 days given that this seems to be a retrospective review of existing data. This would likely reduce your sample size and negatively affect your regression-based analyses. However, justification is warranted. Is it based on symptom presentation, normal time-course of concussion injury in pediatric patients?

Author response: We agree that further justification is required to provide rationale for a 21 day inclusion period. Recovery from concussion in children and adolescents can take longer than that of adults (Harmon et al., American Medical Society for Sports Medicine position statement on concussion in sport. British Journal of Sports Medicine 2019; 53:213-225); thus, we felt that inclusion of patients presenting during this time period was reasonable.

Page 7:

We selected a cutoff of 21 days from injury to initial clinical presentation to examine a sample of participants who were at varying stages of recovery and consistent with previous studies among children and adolescents with concussion.[12,23]

It needs to be explicitly stated that this study was a retrospective investigation of clinical records OR that patient consent and parental assent was obtained prior to being included in this study.

Author response: Thank you for pointing this out. This was a retrospective investigation of clinical records. We now explicitly state this in our revised methods.
Page 6:

> ***Patients were seen at the [redacted] for evaluation of concussion and were enrolled in a prospective clinical registry. We conducted a retrospective investigation of existing clinical records among patients evaluated between January 1, 2015 and August 31, 2017.***

While the BESS and ROMBERG are clinically used and viable tests of postural stability, their inherent limitations have been well identified and published. These limitations in reliability should be identified in the manuscript (either in the Methods or more likely in the Discussion).

Author response: We agree with this point, and recognize their limitations. In line with our revisions made in response to Reviewer 1's comments, we have added this as a limitation in our revised Discussion.
Page 20:

> ***In addition, we did not have inter-rater reliability data for our assessments. Given the small between-group differences for the BESS outcomes, the clinical significance is likely low.***

Were balance tests performed by the same ATC's? Again, reliability is a concern.

Author response: The balance tests were conducted across a network-of-care, involving multiple clinical practice locations. Thus, the balance tests were performed by a variety of different Athletic Trainers. However, we do not have any information about reliability between testers. As a result, we have added this as a limitation to our revised discussion.
Page 20:

> ***In addition, we did not have inter-rater reliability data for our assessments. Given the small between-group differences for the BESS outcomes, the clinical significance is likely low.***

Statistical analysis: "for normally distributed data". No tests of normality are listed in the statistical analysis. How was normality determined? This is an important aspect of the

Methods as it determines the assessments used and assumptions made in the statistical tests.

Author response: Thank you for identifying this omission on our part. We used Shapiro-Wilks tests to quantify data normality. We have added this information to our revised methods.

Page 10:

Normality was assessed for continuous variables using Shapiro-Wilks tests.

The use of $p < 0.20$ for co-variates should be justified in the text. The references identified at the end of this sentence are not statistical papers justifying this p-value.

Author response: We appreciate this need for more rigor in our references. We have added a reference from a paper specifying that a $p < 0.15$ level is appropriate for retention of significant covariates. We have implemented this methodology, and the covariates included remain the same as our original analysis.

Page 10:

The characteristics (Table 1) that demonstrated a potential difference between groups (defined as $p < 0.15$) were then included as covariates in subsequent multivariable models.[37] These included time from injury to evaluation and history of pre-existing headaches.

Results

Tables throughout the manuscript: if there is a significant effect, bold the p-value such that it is easier to visually identify.

Author response: Thank you for this suggestion. We have bolded those p-values that are significant throughout the tables.

Table 1. Justify 0.15 as significant.

Author response: Thank you for the opportunity to clarify. We did not intend to indicate 0.15 as significant, but rather meant to visually identify those variables for which $p < 0.15$ and therefore were retained as covariates in multivariable models. Given the rounding effect, this variable (History of pre-existing headaches) met inclusion as a covariate in multivariable models ($p=0.149$) and was identified as such. To reduce confusion with the asterisk indicating significance in our figures, however, we have instead denoted those variables that met criteria for inclusion in the multivariable models with a "†".

It is important to identify clearly and to re-state that there was a difference in the time to initial clinical evaluation between the groups. The no PA group arrived earlier than the early PA group, but the early PA group still came suggesting that they were still symptomatic to the point of seeking medical care.

Author response: We agree that this should be stated explicitly for better context. We have added this point to our revised discussion.
Page 17:

> ***Our results align with others who found that engaging in early PA after concussion is associated with shorter recovery times.[20,21] However, we also observed that the no PA group was assessed approximately four days earlier than the early PA group. After adjusting for this in our multivariable model, we observed that participation in early PA was associated with a symptom duration that was approximately one week less than no reported PA.***

The presentation of headache may be associated with concussion-induced neurometabolic crisis. This suggests that those with less headache may have had less neurometabolic crisis and were therefore able to do early PA.

Author response: We agree with the concept that headache may be related to concussion-induced neurometabolic crisis effects. However, we have no way of measuring this within the framework of our current study. Therefore, we believe that any comment on the levels of ionic shifts, neuronal architecture, inflammatory chemical concentrations, neurotransmitter release, or energy availability within the brain would be speculative and outside the scope of this manuscript. If the reviewer and editor feel strongly that we should include this type of information in our manuscript, we will happily make further revisions related to these concepts in a subsequent revision.

In line with the reviewer's concern regarding headache, we have revised our discussion to comment further.
Page 18:

> ***A particular strength of our study was that symptom burden was measured not only by self-report but by parent-report as well. In those reporting early PA engagement, both patients and parents rated total symptomatology at the time of the initial clinic evaluation as significantly less compared to those who did not engage in early PA. In addition, a smaller proportion of the early PA group reported headaches at initial clinical presentation, which may have various explanations. This may be due to factors such as a more severe concussion in the no PA group, although this is a concept that does not have a quantifiable outcome. However, it should be considered as a potential confounding variable, as those who were more symptomatic or affected by the injury were likely limited in their ability to do physical activity and perhaps independently or as a result, required a longer time to recover.***

It is suggested to present not only p-values but also effect sizes to support interpretation of findings. For example, the statistical assessment of time from injury to initial evaluation has a highly significant p-value, but a moderate effect size (Cohen's d).

Author response: We agree. Within table 3, we have added effect size (Cohen's d) results for continuous variables and odds ratio results for dichotomous variables.

Discussion
First line - remove the semi colon. Incomplete sentence.

Author response: Thank you for this constructive comment. We agree, and have deleted this sentence from the manuscript.

The presentation of the findings of this study as written are overstated. The language used in the Discussion implies a cause-effect relationship that cannot be established by this study's methodology. In the case of this study, those that participated in self-paced early PA (without a clinical evaluation) performed better on clinical assessments and symptomology. This is an important finding; however, we cannot identify from this study that the early PA is responsible for these outcomes. Suggested reviions of the language to indicate the associative (rather than causative) nature of these variables. This is the major concern with the current manuscript (presentation of findings).

Author response: We agree with the reviewer that the language used must be associative, rather than causal, throughout the discussion so we do not over-state our findings. We attempted to ensure this in our original submission, but appreciate the opportunity to clarify and reword to improve our manuscript. We have revised the discussion to reflect this point and to remove areas that suggested a cause-effect (beneficial) relationship.

Abstract, page 3:

> ***However, as early PA was associated with better post-injury outcomes, clinicians may consider supervised and structured early PA programs as a method to improve clinical outcomes following concussion.***

Page 17:

> ***Given our study design, we cannot determine the causal nature of why patients engaged in early PA (e.g., perhaps due to lower symptom burden at the time of assessment) or whether early PA actually positively affects clinical characteristics. Our results suggest that there is an association between early PA after concussion and better post-injury outcomes, although causality must be determined through more rigorous prospective study designs.***

Pages 18-19

Our data indicate that early PA was associated with better postural control outcomes.

Pages 19-20

> ***The clinical implications of our study, as well as other recent research and evidence-based guidelines,[2,3,11,20,21] suggest that health care providers should consider encouraging early PA under well-supervised conditions in order to facilitate better outcomes sooner after injury, rather than perpetuating the historic convention of rest until symptom-free.[10] To date, the majority of the literature supports physician-supervised, individualized aerobic exercise prescription to facilitate concussion recovery, but additional information regarding the optimal exercise "dosage" (intensity, frequency, duration) is needed.[22] However, clinicians should administer PA recommendations with careful clinical discretion on a case-by-case basis, as potential harmful effects of unsupervised PA after concussion have not yet been investigated.***

Paragraph 3: "These past studies focused mainly" - this differentiation from previous studies should be highlighted not only in the Discussion, but identify the hole in the literature in the Introduction as well.

Author response: We appreciate this point and agree. We have added this point to our introduction.
Page 5:

> ***In addition, regular aerobic exercise below the level of symptom exacerbation appears to be beneficial for symptom reduction among children and adolescents with persistent concussion symptoms,[15–18] although the efficacy of exercise on other functional capabilities has not yet been clearly delineated.***

Also highlight more effectively the use of the parent-report as a corroborating factor.

Author response: Thank you for the opportunity to clarify. Patients completed the clinical registry questionnaire with assistance from their parent or guardian as needed. In addition, parents/guardians completed their own rating of the patient's symptoms. Previous work suggests that there is generally good agreement between parent and child HBI ratings, although some discrepancies may exist, and may be clinically relevant (Patsimas T, Howell DR, Potter MN, Provance AJ, Kirkwood MK, Wilson JC. Concussion symptom rating agreement between pediatric patients and their parents. *Journal of Athletic Training* February 2020, e-pub ahead of print); thus, we have included both parent and child ratings in our study. We have clarified this rationale in the manuscript.
Page 8:

Discrepancies between parent-child HBI reports may be clinically relevant, thus, both measures were included in our study.[26]

Be careful of using language that insinuates causal relationships.

Author response: We appreciate the reviewer's feedback and as mentioned above, have revised the discussion to remove areas that suggested a cause-effect relationship between early PA and improved clinical outcomes after concussion.

Abstract, page 3:

However, as early PA was associated with better post-injury outcomes, clinicians may consider supervised and structured early PA programs as a method to improve clinical outcomes following concussion.

Page 17:

Given our study design, we cannot determine the causal nature of why patients engaged in early PA (e.g., perhaps due to lower symptom burden at the time of assessment) or whether early PA actually positively affects clinical characteristics. Our results suggest that there is an association between early PA after concussion and better post-injury outcomes, although causality must be determined through more rigorous prospective study designs.

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The findings and interpretations of the regression model could be better presented.

Author response: We appreciate this feedback and have attempted to present the results from our regression model in a transparent and easy to understand format. Along with convention, this includes presenting the adjusted odds ratio or beta coefficient (for

logistic or linear regression, respectively), standard error, 95% confidence interval, and p value. We have noted that we adjusted for the effect of covariates that met inclusion (injury to presentation time and pre-existing headache history). We believe that these are all of the required elements for readers to fully understand the results we are presenting. We are open to suggestions on a better method to present the results from each model transparently for readers to understand the associations found. If the reviewer has specific recommendations about other types of information that we should include in the presentation of our results, we will happily consider them within a future revision of this manuscript.

Additional statements regarding the lack of information regarding the dose-response relationship could be beneficial to the readership.

Author response: We agree, and as a result, we have added additional language to our revised discussion about the lack of information regarding dose-response for early PA after concussion.
Pages 19-20

> ***The clinical implications of our study, as well as other recent research and evidence-based guidelines,[2,3,11,20,21] suggest that health care providers should consider encouraging early PA under well-supervised conditions in order to facilitate better outcomes sooner after injury, rather than perpetuating the historic convention of rest until symptom-free.[10] To date, the majority of the literature supports physician-supervised, individualized aerobic exercise prescription to facilitate concussion recovery, but additional information regarding the optimal exercise "dosage" (intensity, frequency, duration) is needed.[22] However, clinicians should administer PA recommendations with careful clinical discretion on a case-by-case basis, as potential harmful effects of unsupervised PA after concussion have not yet been investigated.***

2nd Editorial decision

16-Mar-2020

Ref.: Ms. No. JCTRes-D-19-00036R1
Early physical activity and clinical outcomes following pediatric sport-related concussion
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Nicholas G Murray, Ph.D.
Editorial Board Member
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: Nice work on the revisions.