Author's response to reviews

Title: Clinical Attributes for the Conservative Gait Pattern in Diabetes

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Author's response to reviews: see over
Dear Dr. Menz:

Thank you for forwarding the reviewers’ critiques of our paper and permitting us to respond. We will address the reviewers’ concerns sequentially.

Dr. Raspovic’s major compulsory revision:
1. “Does this really add to the body of work in this area?” We believe it does due to the statistical power available, depth & breadth of clinical measures, and multivariate techniques applied. “Has this assessment been validated?...0.43 acceptable reliability?” We haven’t found reliability testing reported for this specific aspect of visual gait analysis. There are isolated aspects from visual gait analysis that suggest moderate to substantial reliability in this area. We have rewritten this section of the methods specific to this aspect of the gait cycle. We also provide a supportive reference for interpreting kappas and intraclass correlation coefficients. The 25% slower walking speed and 18% decreased stride length are around the range of clinical effect sizes the clinicians view as being relevant.
2. “Pooling data” In our previous manuscripts from this data set, we performed two levels of analysis to account for the lack of independence of the data. The results were quite similar. If you compare the new analysis with the previous submission, you will find this to be the case with this paper as well. We changed our analytic approach in the following way, “Since the observations were not entirely independent, a generalized linear model was created using sandwich robust variance estimator and assuming Poisson errors and a log link to estimate relative risk for dichotomous errors.” Our team has worked with a statistician, Michael Beach, MD, PhD, in a past publication using this approach.[1] I will include the output from STATA.
3. “Summary: apropulsive gait could be adopted for many reasons—no dynamic measures—and the conclusions are not supported from work in this study.” Thank you for this very important critique. We have provided more discussion on possible clinical implications. We have reworded the conclusion as not to overreach what was supported in our study.
4. “Limitations section-- power analysis for Post Hoc approach—selection bias.” We have included a more thorough limitations section including selection bias, and power analysis for each measure. Our power ranged from 0.65-1.0 (insensitivity to monofilament =0.92 and Romberg’s sign =0.85). Incidentally, selection bias as it relates to generalizability of results should be dutifully acknowledged; however, its importance to an audience of JFAR should be questioned as the patient populations could be similar. Nonetheless, we will make the acknowledgement in particular to gender representation.

Dr. Raspovic’s minor compulsory revisions:
1. “Clarify neuropathy in abstract.” We added this.
2. “Many people with diabetes adopt more conservative gait strategy is speculative and misleading.” Since there are no large scale epidemiological studies to support this qualification, we stated “people with diabetes sometimes...”
3. We have attempted to re-phrase our conclusions and clinical discussion of the findings to help address this concern.

4. “More inclusive methods section regarding measures.” We have added a more complete list.

5. “Define conservative gait pattern.” We added this definition.

6. We have changed the analysis plan and described it in the paper.

7. We changed the decimal points here and elsewhere.

8. We changed the conclusion to reflect the paper.

9. “Gait changes not associated with neuropathy—background literature needs more description”. Yes, thank you for this critique. It is worth highlighting for those not familiar with the study that neuropathy was diagnosed from electrophysiology. We have described these findings in greater detail.

10. “Expand on rationale and aims to justify knowledge gained” Thank you for this critique. We have expanded upon this.

11. “More specifics on study population.” We did exclude patients with foot injury. I am fairly but not entirely certain that we did not have patients with Charcot or PTTD. I would not feel comfortable including this language. I performed another analysis stratified by foot type. The prevalence of conservative gait by normal foot and flat foot were 13% and 17% respectively. We were underpowered at 0.13 to show this difference.

12. Yes, we have changed norm to methods. Thank you.

13. We have described ankle joint ROM in more detail.

14. “Provide figure with error in degree units for ICC.” The data file I have for the reliability section is corrupt and I can’t open it on my PC. I suspect this may have occurred during our transition from Mac to PC. I’m unable to reanalyze this data to produce the requested figure.

15. “Describe how stride length was measured.” The current description is “Walking speed was assessed by measuring the time taken to walk a 10M distance following a 3M pre-distance to assure constant velocity. Stride length was determined by measuring the distance a foot travels from initial heel contact to heel contact for the next stride of the same foot using a tape measure on the floor. The average of three trials was taken and the patient was coached to walk at their regular walking speed.”

16. “Describe the statistical analysis to provide more information to clinicians. Explain rationale for multiple tests on the same data.” We submitted this work to JFAR because it might appeal to clinician-scientists in this field. This level of modeling is not intuitive to the clinician. We did our best to describe the rationale for this approach. Clinician scientists should easily recognize this is a secondary analysis of an existing data set and understand the inherent limitations and strengths of analyzing a relatively large data base. We have included an introductory sentence in the statistical analysis section.

17. The analysis approach was described.

18. We welcome a critique on our statistical analysis approach.

19. “Discuss clinical significance.” We have included this in the limitations section. Again, my perception of the JFAR readership is largely clinician scientists that
understand most large database research report many statistically significant
associations that require interpretation of clinical significance.
20. “Add standard deviations to table.” We have done this.
21. “Do not draw conclusions not supported by the data.” Thank you for this critique.
   We have rephrased the discussion which typically allows speculation on
   interpretation within the context of other studies.
22. A limitations section is provided.
23. “Clarify, model building strategies.” This is language we use for the model
   building process, “The multivariate model was built using a forward stepwise
   logistic regression with the criterion for removal being a p-value<0.1.”

Dr. Raspovic’s discretionary revisions:
1. “Abstract wording neuropathy significantly higher reads strangely.” Previous
   revisions have addressed this.
2. “Depressive symptoms are not the only reason gait unsteadiness is clinically
   meaningful.” Agreed. This distinction is highlighted to emphasize to a
   biomechanical-anchored readership that gait unsteadiness is indeed more
   clinically significant because it has an additional contribution to a patient’s
   morbidity other than a fearful gait and increased risk of falling. Unrecognized or
   untreated depression may also partially explain non-adherence.
3. “Change adopted to had or presented with.” We changed it.
4. “Fearless sounds melodramatic.” This was changed.
5. “Add overviewed below” This was added.

Dr. Rao’s major revisions:
1. Push-off power is continuous—lack of blinding” Thank you for this critique. We
   have rewritten this section of the methods to hopefully address some of these
   concerns. We haven’t found reliability testing reported for this specific aspect of
   visual gait analysis. There are isolated aspects from visual gait analysis that
   suggest moderate to substantial reliability in this area. We have re-written this
   section of the methods specific to this aspect of the gait cycle. We also provide a
   supportive reference for interpreting kappas and interclass correlation
   coefficients. The 25% slower walking speed and 18% decreased stride length are
   around the range of clinical effect sizes the clinicians view as being relevant. The
   study was actually blinded by the temporal frame used to conceive this secondary
   analysis. Neither examiner was aware that a study would be done regarding the
   conservative gait strategy.
2. “Absence of hypothesis testing” Likelihood ratios and confidence intervals.” I am
   unclear on why a multivariate approach with candidate measures defined A Priori
   is not considered to be a valid aim. We have included a power analysis to help in
   interpretation of the effects of sample size contribution to SE and confidence
   intervals.
3. “Conclusions overstated” Thank you for this important and accurate critique. We
   have addressed it based on suggestions from Dr. Raspovic.
4. “Ankle at push-off is proportional to plantar loading—not observed in this data—
   the strategy maybe utilized as a method of unloading” We were truly excited
   about this observation. Dr. Rao is quite correct that effort to improve mobility
using physical modalities or surgically may lead to increase in peak plantar pressure. This has historically been viewed as a negative outcome. We have presented abstracts in this area and have a paper in preparation (on different patient populations) that addresses this topic on two levels. We have also added more discussion on the clinical implications based on suggestions from Dr. Raspovic.

Dr. Rao’s minor revisions:
1. “Reorganize paragraph one—should DMPN demonstrate increased unsteadiness or adopt conservative gait pattern as compensation?” We have reorganized the paragraph to be clear regarding demonstration of this finding.
2. “Fall risk and gait instability better elucidated” We wanted to describe the literature as it pertained to fall risk due to diabetes, gait, and balance measures. We also wanted to describe the conservative gait pattern literatures as it pertained to diabetes and neuropathy. We did not want to extrapolate our findings to the fall literature.
3. “Which dependent variables are used as predictors?” We described our A Priori candidate variables and the model building strategy for selecting candidate variables.
4. “Were A Priori covariates independent of each other?” The neuropathy measures were not entirely independent of each other; however, they are clinically important measures of severity of neuropathy. Oddly enough, the mobility measures did not demonstrate a significant correlation ($r=0.02; p=0.74$) or linear relationship. However, they may be considered conceptually independent measures of preserving forward momentum in gait, thus potentially independent contributors to conservative gait.[2]
5. “Power analysis” We added table 3 as a power analysis table.
6. “No direct relationship apropulsive gait and fall risk” Our intention was not to describe a causal link. It is inferred from the literature we described. However, the tenets of clinical epidemiology dictate there should be biologic plausibility, dose-response, replication of findings across designs, and a large effect to begin inferring causality. It would be up to the reader to come to this conclusion. Based on our citations, there appears to be a preliminary basis for this. Again, our lab is pursuing this line of investigation for the quality of activity in the home where we can simultaneously determine this gait strategy and a fall.
7. “Mueller citation misleading.” Thank you for this critique. We have included language to make it clear on where the findings agree and disagree.

We appreciate Dr. Raspovic and Rao thorough critiques. Addressing their concerns has improved the quality and clarity of the paper. Thank you again for your consideration.

Best regards,
Jim
References

Analysis
```
. glm gait age romaj callus, family(poisson) link(log) robust cluster(subjectn) eform
Iteration 0:   log pseudolikelihood = -110.02058
Iteration 1:   log pseudolikelihood = -103.05713
Iteration 2:   log pseudolikelihood = -103.03
Iteration 3:   log pseudolikelihood = -103.02998
Iteration 4:   log pseudolikelihood = -103.02998

Generalized linear models                          No. of obs      =       304
Optimization     : ML                              Residual df     =       300
Scale parameter =         1

Deviance        =  128.0599682                     (1/df) Deviance =  .4268666
Pearson         =  250.2800535                     (1/df) Pearson  =  .8342668

Variance function: V(u) = u                        
Link function    : g(u) = ln(u)                    

Log pseudolikelihood = -103.0299841                BIC             = -1587.048
(Std. Err. adjusted for 304 clusters in subjectn)

|       |       IRR | Std. Err. |      z  |    P>|z|    |    [95% Conf. Interval] |
|-------|----------|-----------|--------|--------|-------------------------|
| age   |  1.093396 | .0176086  |  5.54  |  0.000 |  1.059422                |  1.128458 |
| romaj | .8549979  | .0380782  | -3.52  |  0.000 | .7835306                 | .9329839 |
| callus|  1.809476 | .4978795  |  2.16  |  0.031 |  1.055222                |  3.102859 |
```

```
. glm gait age romaj sw, family(poisson) link(log) robust cluster(subjectn) eform
Iteration 0:   log pseudolikelihood = -111.15642
Iteration 1:   log pseudolikelihood = -103.96683
Iteration 2:   log pseudolikelihood = -103.94455
Iteration 3:   log pseudolikelihood = -103.94454
Iteration 4:   log pseudolikelihood = -103.94454

Generalized linear models                          No. of obs      =       304
Optimization     : ML                              Residual df     =       300
Scale parameter =         1

Deviance        =  129.8890827                     (1/df) Deviance =  .4329636
Pearson         =  243.6650641                     (1/df) Pearson  =  .8122169

Variance function: V(u) = u                        
Link function    : g(u) = ln(u)                    

Log pseudolikelihood = -103.9445414                BIC             = -1585.219
(Std. Err. adjusted for 304 clusters in subjectn)
```
| gait | Robust IRR | Std. Err. | z    | P>|z| | [95% Conf. Interval] |
|------|------------|-----------|-----|-----|----------------------|
| age  | 1.095109   | .0196295  | 5.07| 0.000| 1.057304 1.134266  |
| romaj| .8694171   | .036438   | -3.34| 0.001| .8008546 .9438494 |
| sw   | 1.438083   | .4085745  | 1.28| 0.201| .8240407 2.509685  |