

Referee report for “Hypothesis tests for multiple responses regression: effect of probiotics on addiction and binge eating disorder”

Summary of contributions

The authors propose using Wald tests for testing linear restrictions in multivariate covariance generalized linear models, a class of models for regressions with several response variables of (potentially) different types. The authors study the properties of the tests using simulations and apply the tests in a relevant data example.

Review

I agree with the authors that, in general, testing is one aspect of modeling regressions with responses of different types that warrant additional attention. The data example nicely illustrates this point. My main concern is that, for a journal like *Statistics in Medicine*, the statistical contributions in the article are limited. A primary objective of the article is, according to the authors, “to propose the use of the Wald test to carry out tests of general hypotheses on regression and dispersion parameters of McGLMs...”. Given that McGLMs have been introduced in other work and that Wald tests are quite well understood in relatively general parametric models, this proposition does not in itself appear to be a substantial enough contribution.

The contribution could be strengthened if, for example, there are particular issues with using Wald tests in McGLMs that the authors can address, or if some theoretical properties of interest can be given.

I list some additional questions and comments below (not in order of importance).

1. In the application, It was not clear to me how the responses were transformed to unit range, why they were transformed, and how that affected the choice of distribution in the McGLM.
2. Reference [13] is incorrectly formatted (the name is not St).
3. The description of hypothesis testing on p.2, approximately lines 32–34, is somewhat confusing.
4. P.5: What is a standard link function?
5. P.5: Two definitions of Σ_r are given, depending on which type a variable is. Is there something specific about the mentioned variable types that makes them compatible with the framework while other variable types are not? If so, what?
6. Related to the previous point, it appears that a count variable must have a covariance matrix of the second form, but if the count can be divided by a total to give a proportion, then it must have a covariance matrix of the first form. Is this a misunderstanding? If not, that appears strange. Some comments on why certain variable types must have certain structures could be helpful.
7. Is the bold Σ_R overloaded in the notation on p.5? It appears on the left-hand side of the definition of generalized Kronecker product, and its Cholesky root appears on the right-hand side in what seemed to me an unexpected way. Is the notation correct?
8. P6. Typo: spplit

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9. P.7: The authors say ``...the generalization of the Wald test statistic to verify the validity of a hypothesis..'' but it's not made clear of what, and in what way, this test-statistic is a generalization.
10. P.7: It is stated that W has a particular asymptotic distribution – has this been proven somewhere? If so, a reference would be in order. Overall I found the discussion of which parts of classical asymptotic theory can be expected to hold for the Wald tests in this setting lacking. For example, many classical results assume the parameter is identifiable, but I would be surprised if the parameters in McGLMs are identifiable in general. Either way, some comments would be helpful.
11. In the abstract, the authors mention proposing a strategy for multiple comparisons, but in the manuscript, they recommend Bonferroni corrections for multiple comparisons. Since Bonferroni corrections are well-known, I suspect they may have intended to propose something else. A clarification would be useful.