Author's response to reviews

Title: Restless legs syndrome and functional limitations among American elders in the Health and Retirement Study

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Version: 3 Date: 16 March 2012

Author's response to reviews: see over
RE: MS: 1200095748633776

March 16, 2012

Dear Dr. Pura:

We had provided a response for our initial review of the manuscript “Restless legs syndrome and functional limitations among American elders in the Health and Retirement Study” (dated 1/27/12). However, the comments from our second reviewer were not initially included. We were notified of this oversight and would like to respond with the following changes and clarifications. Please refer to the previous email for the responses to the first reviewer.

Of note, we apologize for not previously submitting the tables according to the template, and we changed our tables to fit the guidelines. Portrait layout for Tables 4 and 5 does not optimally show the data, so we may need to discuss removing columns that are less informative as the Tables are important to the discussion and should not be changed to appendices.

Reviewer #2 (Hanlon): “Transparency in data analysis is essential to any peer review publication. It is not entirely clear which set of independent predictors are used for each set of models (as listed in Table 1?), as well as their type and categorization.

Response: We agree and have tried to ensure that the models are reproducibly described in the text and in the Table captions. For all of the potential covariates, we described the categorization of the variables in the methods section, predominantly in the second and third paragraphs. We did detect an error on the cutoffs for the income quartiles, which has been corrected in Table 1. Several variables were more clearly defined, including self-reported falls (0, 1, 2+); pain (None, mild to moderate, or severe / interferes with activity); chronic medication use (0, 1, 2, or 3+), and provider visits in the previous 2 years (0-3, 4-7, 8-11, and 12+). Self-reported health status was initially measured as a five-item response scale, which was collapsed into three categories (“Excellent” and “Very Good” were combined and “Fair” and “Poor” were combined). Age was analyzed with previously defined risk categories (64 or younger, 65-79, and 80+). Age and other continuous variables were tested in various manners (linear, polynomial, ordinal, or nominal categorical), with selection of best fitting relationship based on AIC. A statement to this point has been added to the Methods section.

Reviewer #2 (Hanlon): Additionally, please make it clear in the methods section that RLS is defined by having all three criteria, versus at least one of the three criteria.

Response: We have updated the description of the case definition. The statement now reads: “The operational definition of RLS required all three criteria:”.
Reviewer #2 (Hanlon): Please indicate whether or not multicollinearity in predictors was examined; and if not, please revise the analysis to include this.

Response: The correlated predictors were added initially based on their performance in incrementally improving AIC, so correlated candidate variables were unlikely to perform well. However, in order to fully evaluate this, we did explore the condition indices from each final regression model, and there were no outlier eigenvalues and all condition indices were small (less than 12, although we used 30 as a more accepted threshold). The following statement was added to the Methods section under Statistical analysis:

“Continuous independent variables were tested in various manners (linear, polynomial, ordinal, or nominal categorical), with selection of best fitting relationship based on AIC. Correlation among predictors was evaluated based on eigenvalues derived from principal component analysis of the predictor variables. Variables were selected so that each variable contributed uniquely to total variance (i.e., condition indices associated with individual predictor variables were $\leq 30$), while maximizing AIC [21].”

Reviewer #2 (Hanlon): Table 1 would provide more clarity with columns representing the distribution of characteristics by RLS (Y/N), and overall. The statistic used should be identified (rather than chi or exact) -- perhaps using Fisher’s Exact for all categorical comparisons would simplify things and be the most appropriate. A test of trend should be used for ordinal variables. The most powerful comparisons would include those variables measured on a continuum, if available.

Response: Initially only the total sample and the cases of RLS were shown in Table 1 due to space concerns. The additional columns were added. No categorical variables required Fisher’s exact test, so this was simplified in the text and the caption for Table 1. The methods section now includes a statement: “Ordinal variables were evaluated for trend.”

Reviewer #2 (Hanlon): Table 2 -- for RLS sx at night, were comparisons made for the overall distribution by gender, for example -- rather than within each level of frequency? The former is appropriate, but the superscripts indicative of significance suggest multiple tests within the RLS sx distributions. Removing race from the table would make it more readable, although it makes sense to mention in the results that there were no significant differences by race.

Response: Based on the recommendation, we removed the columns reporting the frequencies by racial group and now included a statement in the results section: “There were no associations with race (data not shown).” The “symptoms at night” question does show a significant trend by gender, with females having more frequent symptoms. The dagger symbol was moved to the row with the question name in order to clarify that this was a comparison for the trend. However, the associations with age group were not significant for trend, but the middle age group (65-79) had the most distinct differences and the categorical Chi-square test was significant. An explanation was added to the table caption.
**Reviewer #2 (Hanlon):**  *Table 4 -- were these separate Cox models, with adjustment for all variables in table 3? Again, please address the question of multicollinearity.*

**Response:** Each outcome presented represents the dependent variable in our Cox regression models. The covariates include all significant factors from Table 3, and this is indicated in the Table caption. This is also listed in the results section labelled “RLS and Concurrent Disability.” In Tables 4 and 5, the predictors other than RLS are not shown, as these are meant to be control variables and we do not wish to estimate their individual contributions to each outcome. For the analyses, we formally evaluated for multicollinearity and added the text to the methods section as indicated above.

**Reviewer #2 (Hanlon):**  *Table 5 -- again, were these separate models? If so, perhaps the heading for the first column should say “outcome variable” or “dependent variable”. Multicollinearity again should be addressed.*

**Response:** The table headings for both Table 4 and Table 5 have been changed to reflect that these are the outcome variables. The issue of multicollinearity was addressed as above.

Please feel free to contact us with any further questions or needed clarifications. We appreciate the thoughtful comments by the reviewers.

Sincerely,

Dominic J. Cirillo