Authors′ Responses to the Reviewers′ Comments – Revision 1

World Journal of Psychiatry - Manuscript ID: 76431

Title: Development of Parkinson's Dementia Prediction Model Using Regression with Optimal Scale

We appreciate the editor, who gave opportunity to revise our work. Also, we would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We carefully considered your comments as well as those offered by the reviewers. We agree with most of them, and the manuscript has been revised thoroughly according to the reviewer′s advice. We hope that these revisions improve the paper such that you and the reviewers now deem it worthy of publication in World Journal of Psychiatry. Also, we hope our revision meet your approval. We next detail our responses to each reviewer′s concerns and comments.

Our response follows (the reviewer′s comments and editor′s comments are in italics).

Editor

1) We are pleased to inform you that, after preview by the Editorial Office and peer review as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 76431, Case Control Study) basically meet the publishing requirements of the World Journal of Psychiatry. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision.

Upon our receipt of your revised manuscript, we will send it for re-review. We will then make a final decision on whether to accept the manuscript or not, based upon the

reviewers′comments, the quality of the revised manuscript, and the relevant documents.

Please follow the steps outlined below to revise your manuscript to meet the requirements for final acceptance and publication.

We appreciate the editor, who gave opportunity to revise our work. We carefully considered your comments as well as those offered by the reviewers. We agree with most of them, and the manuscript has been revised thoroughly according to the reviewer′s advice. We hope that these revisions improve the paper such that you and the reviewers now deem it worthy of publication in World Journal of Psychiatry. Also, we hope our revision meet your approval.

Reviewer #1

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

1. Equation are not in mathematical notation, I suggest the authors should be experienced enough in writing out the equations

We appreciate the reviewer′s detailed evaluations and positive comments. We appreciate the positive feedback. Also, we appreciate you very much for giving us the opportunity to revise our paper. We modified functions (1), (2), (3), (4) to reflect the reviewer's suggestions.

$$Y_i = \alpha + \beta X\_i + \epsilon\_i$$

$$Y_i = \text{dependent variable}$$

$$X_i = \text{independent variable} \qquad \text{(Equation 1)}$$

$$\epsilon_i = \text{error term}$$

When the assumptions for the error term, such as "the expected value of the error term shall be 0" and "it shall follow a normal distribution and all observations shall have the same variance", parameters are estimated by using the least-squares and other methods to determine the relationship between the independent and dependent variables. The least-squares method is used to obtain parameter estimates ($\hat{\alpha}$ and β) that minimize the sum-of-squared residuals, where the residual (ϵ_i) is equal to the difference between the actual observations (Y_i) and the predicted values of the dependent variables ((Y_i) ($\hat{Y}_i$) = $\hat{\alpha} + \beta X_i$)).

In this study, regression with optimal scaling consisted of three stages. The first is the data transformation stage. After normalizing k categorical indicators for the nth variable by vectorizing them, all of the variables are treated as numeric variables. Subsequently, they are optimized repeatedly by using the calculated categorical quantification values and regression coefficients. The second stage is updating the categorical quantification vector by considering the scale level (i.e., whether the variables are nominal, ordinal, or numeric) and calculating the regression coefficient vector. The third stage is to establish convergence by repeatedly calculating the categorical quantification vector and the regression coefficient vector until they satisfy the predetermined convergence condition [19].

Regression with optimal scaling transforms each variable appropriately by considering its scale in the generalized linear regression model. When dependent variable Y is transformed to $\theta(Y)$ and independent variable X to $\sigma(X)$, the resulting parameters are the intercept and slope of a linear regression equation formed by minimizing the sum-of-squares (SSQ) of the error [19] as follows:

$$minSSQ(\theta(Y) - \beta\sigma(X)) \; (Equation\; 2)$$

The conversion variable has a standardization constraint. Minimizing the SSQ error is achieved by least-squares regressing the transformed variables ($e.g.,\; \theta(Y),\; \sigma_1(X_1),\; ...,\; \sigma_n(X_n)$). The categorical regression analysis with standardization constraints is written as

$$minSSQ(\theta(Y) - \sum_{i=1}^{n} \beta_i\, \sigma_i(X_i)). \; (Equation\; 3)$$

$$T = \frac{\sum_{i=1}^{R} n_{i1}(R_i - \bar{R})}{(n\ (1-n\ )\sigma^2} s^2 = \sum_{i=1}^{R} n_{i.}(R_i - \bar{R})^2 \; (Equation\; 4)$$

2. If a parameter is given in italic in equations, then it should be italic in text if you mean the same parameter. 2.

We appreciate the reviewer's detailed evaluations and positive comments.
We appreciate the positive feedback. Also, we appreciate you very much for

giving us the opportunity to revise our paper. We modified functions (1), (2), (3), (4) to reflect the reviewer's suggestions.

We appreciate you very much for giving us the opportunity to revise our paper. Also, we hope our revision meet your approval.

Reviewer #2

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

1. *Introduction seems to be well prepared and extensive. Editor might like to decide to shorten it, depending on the overall approach of the Journal to prepare manuscripts.*

   We appreciate the reviewer′s detailed evaluations and positive comments. We appreciate the positive feedback. Also, we appreciate you very much for giving us the opportunity to revise our paper. We agree with most of them, and the manuscript has been revised thoroughly according to the reviewer′s advice. Our changes have been marked in black font and highlight in the revised manuscript. We hope that these revisions improve the paper such that reviewers now deem it worthy of publication in World Journal of Psychiatry. Also, we hope our revision meet your approval.

2. *In contrary, Most of the materials and section description is rather brief. In my humble opinion, tools that have been used are rather well known in the world of psychiatry, so there is no need for extensive description. The only problem that I have noticed in this section is in ″Regression with Optimal Scale″ subsection.*

   You have wrote „Although a general linear regression model can be used if all of the variables used in the analysis are numeric, this is not the case for ordinal or nominal variables because they do not meet the assumptions for regression and error terms″ I do not understand what do You mean here by „if all of the variables″. Do You mean „All of the dependent variables″? In my humble

opinion, one can add ordinal variable as a independent factor In the linear regression model, am I right? While using ordinal logistic regression, ordinal variable could serve as a dependent variable. Then You wrote „Therefore, analysis can be˝ could You be more specific here? What kind of analysis? What is the purpose of the analysis here? I suppose that optimal scaling applied in Your study might be a suitable method in overall, however the implementation of this particular model should be better justified in the first sentences of this paragraph. I suppose that ordinal independent variables could be analysed using linear regression methods, but maybe some practical difficulties might occur in implementation of such models?

We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we appreciate you very much for giving us the opportunity to revise our paper. We agree with the reviewers' comments. In response to a reviewer's suggestion, we've added (or changed) the following text to the Methods section:

The following paragraphs have been deleted: Although a general linear regression model can be used if all of the variables used in the analysis are numeric, this is not the case for ordinal or nominal variables because they do not meet the assumptions for regression and error terms. Therefore, analysis can be conducted by deriving an optimized linear regression equation for transformed variables by repeatedly performing optimal scaling based on the alternating least-squares method. The estimated general linear regression model is presented as follows [19]:

The following paragraph has been added: If all the variables (e.g. Independent variables, dependent variables, and confounding variables) used in the analysis are numeric variables, the general linear regression model can be used. However, if it is an ordinal or nominal variable, it is difficult to use the general linear regression model because these variable types do not meet the assumptions of the regression models and error terms. Therefore, analysis can be con-ducted by deriving an optimized linear regression equation of transformed variables by repeatedly performing optimal scaling based on the alternating least squares method.
  It is a way to estimate parameters for the linear relationship between independent and dependent variables using data on each variable. The estimated general linear regression model is presented as follows [19]:

3. *Results:"The results of chi-squared tests" information about particular methods of analysis should be described In the last section of materials and methods. In the results section, only results from those methods should be described, not methods itself.*

> We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we appreciate you very much for giving us the opportunity to revise our paper. We agree with the reviewers' comments. However, we felt that moving the statistical test results to the Methods section would be misleading to readers. Therefore, we presented the results of our chi-square test in the Results section. However, some sentences have been added to Methods section to reflect the reviewer's suggestion.

> (page 10) Regression with optimal scale was used to identify the independent relationship between each neuropsychological test and PDD. The analysis results were presented with a regression coefficient, standard error by bootstrap (n=1,000), quantification index, odds ratio, and 95% CI. General characteristics of the subjects and the prevalence of dementia were analyzed using the Chi-square test.

4. *"ADL were not significantly different between PDD and PD-MCI" How it was analyzed? Could You describe it In the materials and methods section? Could You calculate the effect size for this between group comparison?"*

We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we appreciate you very much for giving us the opportunity to revise our paper. We agree with the reviewers' comments. We indicated the significance level in Table 2 reflecting the reviewer's suggestion.

Table 2 General characteristics of the subjects based on PDD, n (%).

Variables	PD-MCI (n=179)	PDD (n=110)	p
Age			0.168
60-74	117 (65.0)	63 (35.0)	
75+	62 (56.9)	47 (43.1)	
Sex			0.550
Male	78 (63.9)	44 (36.1)	
Female	101 (60.5)	66 (39.5)	
Education level			0.072
Middle school graduate and below	110 (58.2)	79 (41.8)	
High school graduate and above	69 (69.0)	31 (31.0)	
Family history of the Parkinson's disease			0.600
No	144 (64.3)	80 (35.7)	
Yes	12 (70.6)	5 (29.4)	
Family history of the Alzheimer's disease			0.285
No	130 (63.4)	75 (36.6)	
Yes	8 (80.0)	2 (20.0)	
Carbon monoxide poisoning			0.743
No	158 (62.5)	95 (37.5)	
Yes	10 (66.7)	5 (33.3)	
Traumatic brain injury			0.277
No	158 (62.0)	97 (38.0)	
Yes	10 (76.9)	3 (23.1)	
Diabetes			0.508
No	144 (64.0)	81 (36.0)	
Yes	35 (59.3)	24 (40.7)	
Hypertension			0.304
No	110 (65.5)	58 (34.5)	

5. "P for trend" please rephrase "

We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we

appreciate you very much for giving us the opportunity to revise our paper. We agree with the reviewers' comments. We fixed the error.

(Page 11) The results of the Cochran-Armitage Trend test show a significant relationship (P for Trend <0.001) between the increase in OR and the K-MMSE score (optimal categories score).

6. *"Figure 1 A" description − could You explain what does „test 4", „test5" etc.*

   Stands for?

   We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we appreciate you very much for giving us the opportunity to revise our paper. We added a legend.
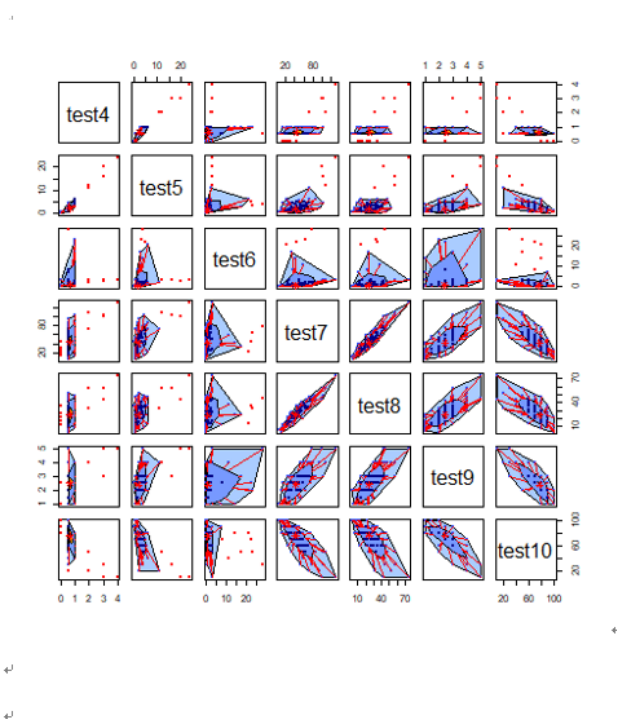
   Figure Legends

Figure 1 A bagplot that visualizes the location, spread, skewness, and outlier of the test results

Test 4=Global CDR score; Test 5=Sum of boxes in CDR; Test 6=K-IADL; Test 7=UPDRS (Total UPDRS score); Test 8=UPDRS (Motor UPDRS score); Test 9= H&Y staging; Test 10= Schwab & England ADL

7. *K-MMSE and H&Y staging could independently differentiate PDD from PD-*

MCI even after adjusting for all of the Parkinson′s motor symptom and neuropsychological test results.″ In my humble opinion it is not perfectly clear that such results could be drawn from the above study. What about the possibility that (as You stated in the further part of discussion) that patients with former PD-MCI converted into PDD as disorder progressed, and therefore there is the relationship with H and Y? "

> We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we appreciate you very much for giving us the opportunity to revise our paper. We have revised some sentences in the Discussion section to reflect the reviewer's comments.
>
> (Page 14) Consequently, it is believed that clinical application will be easy. Additional longitudinal studies are required to prove the effectiveness of the optimal scale for distinguishing PDD from PD-MCI proposed in this study.
>
> (Page 14) Third, the results of this study cannot be interpreted as a causal relationship because it was conducted using secondary data and the Parkinson's Disease with Dementia Epidemiologic Data, the source data of this study, was designed as a cross-sectional survey. Further longitudinal studies are needed to prove the causality of the results of this study.

8. *One thing that I would add to the discussion: from Your results MMSE showed higher utility in diagnosis than MoCA test, what is rather in contrary to the wave from literature from the last years, what showed higher utility of MocA in MCI diagnosis. Could you add a sentence or two on this result to the discussion? Could You refer to the longitudinal studies on older people with MMSE, MoCA, TMT B (or other widely used cognitive test)?*

> We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Also, we appreciate you very much for giving us the opportunity to revise our paper. MocA was developed for the sensitive differentiation of Alzheimer's mild cognitive impairment. Because this study was for Parkinson's disease mild cognitive impairment, the results of previous studies may differ. Direct comparison

with previous studies was difficult in the discussion because there were few longitudinal studies that identified the predictive performance of diagnostic tests for Parkinson's mild cognitive impairment. We made some sentences in the Conclusion section to reflect the reviewers' suggestions.

(Page 15) Further longitudinal studies are required to confirm the performance of neuropsychological tests such as K-MMSE and MoCA in predicting the progression of PD-MCI to PDD.

Also, reference number 32 has been added.

32. Chin J, Park J, Yang SJ Yeom J, Ahn Y, Baek MJ, Ryu HJ, Lee BH, Han NE, Ryu KH, Kang Y. Re-standardization of the Korean-Instrumental Activities of Daily Living (K-IADL): clinical usefulness for various neurodegenerative diseases. Dement Neurocogn Disord 2018;17: 11-22. [PMID: 30906387 DOI: 10.12779/dnd.2018.17.1.11]

We appreciate you very much for giving us the opportunity to revise our paper. Also, we hope our revision meet your approval.