Author's response to reviews

Title: Association between Psychiatric Disorders and Iron Deficiency Anemia among Children and Adolescents: A Nationwide Population-Based Study

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Author's response to reviews:

Dear Editors:

Thank you for reviewing our article and we appreciated your good comments very much. Our point-to-point responses to the editor’s and reviewers’ comments are listed in the following pages. We also revised our manuscript according to these suggestions and comments. We hope that now this article will be found suitable for publication in the “BMC psychiatry”.

Sincerely Yours

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Reply to Reviewers 1’ Comments

1. This is a study to investigate the association between iron deficiency anemia and psychiatric disorders. This is a well writing manuscript with clear organization.
   Ans: Thanks for your comment.

2. What is the age of the control group? The authors should add the age distribution of the control group and compute the statistical analysis in Table 2 to demonstrate that there is no age difference between IDA patients and controls.
   Ans: Thanks for your comment. In our study, age-/gender-matched controls were randomly picked so there was no difference of age between case and control groups. We added the age in the Table 2.
3. This is an age- and gender-matched study design. What is the reason for adjusting for age and gender in statistical analysis?

Ans: Thanks for your good comment. We removed the variables of age and gender from the regression model and revised our results accordingly. The results were still consistent.

4. Although the authors have excluded major physical illnesses when recruiting the control group, how can they determine that the control group really has no iron-deficiency problem? That is, can subjects without major physical illnesses be equal to subjects without any iron-deficiency problem?

Ans: Thanks for your good comment. All subjects who were ever diagnosed as having iron deficiency anemia (ICD-9-CM code: 280) were excluded from our control group. However, those subjects who were not diagnosed ever but possibly had iron deficiency problem could not be noted in our dataset. In addition, no diagnostic code of iron deficiency was available by ICD-9-CM. We added this possible bias in our limitation part.

Page 12 line 5: Second, those subjects who were not diagnosed as having IDA ever but had iron deficiency problem cannot be detected in our study. The clinical study would be required to elucidate the possible association between psychiatric disorders and iron deficiency or subthreshold IDA.

5. The National Health Insurance database in Taiwan has recorded the timing of IDA and psychiatric diagnosis. What is the temporal sequence of IDA and psychiatric diagnosis because it may contribute to the understanding of underlying cause relationship?

Ans: Thanks for your good comment. In our study, we investigated the association between IDA and psychiatric disorders first. Reviewer’s comment was very good for us. We also planned to investigate the possible causal relationship of IDA with psychiatric disorders in the future studies.

6. The subjects with IDA may receive treatment for iron deficiency. Is there treatment effect on the association between IDA and psychiatric disorders in the authors’ data?

Ans: Thanks for your good comment. In our study, we would investigate the association between IDA and psychiatric disorders first. Reviewer’s comment was very good for us. The possible medication effect of IDA treatment with psychiatric disorders would be investigated in our future study.

Reply to Reviewers 2’ Comments

1. The following sentence is not clear to me..please rephrase: "IDA is more severe form of ID that level of ID reaches the threshold causing clinical awareness or symptoms.

Ans: Thanks for your comment. We rephrased our sentence.

Page 3 line 6: IDA is characterized by a defect in hemoglobin synthesis owing to significant ID, resulting in the reduced capacity of the red blood cells to deliver
oxygen to body cells and tissues, and many clinical symptoms, such as pale conjunctiva, shortness of breath, dizziness, and lethargy.

2. Please provide a clear definition ID and IDA.
Ans: Thanks for your comment. We added more details about the ID and IDA.

Page 3 line 4: ID, defined by two or more abnormal measurements (serum ferritin, transferrin saturation, erythrocyte protoporphyrin), is insidious and uneasily detected by patients themselves and may not develop significant clinical symptoms [1-4]. IDA is characterized by a defect in hemoglobin synthesis owing to significant ID, resulting in the reduced capacity of the red blood cells to deliver oxygen to body cells and tissues, and many clinical symptoms, such as pale conjunctiva, shortness of breath, dizziness, and lethargy [1-4].

3. Regarding ADHD, I would stress that, given the mixed findings from the literature (please cite studies that did and did not find a significant association between ADHD and serum ferritin levels) large studies like this one are needed to better understand the possible relationship between ADHD and ID/IDA.
Ans: Thanks for your good comment. We cited the studies that did and did not find a significant association between ADHD and serum ferritin levels.

Page 4 line 6: Some clinical studies supposed that brain ID involved in the pathophysiology of attention deficit hyperactivity disorder (ADHD) [32] and ferritin level was related to behavioral symptoms in ADHD patients [33]. But, Millichap et al disclosed no significant difference in severity of ADHD symptoms between children with ADHD who had the lower serum ferritin levels (<20 ng/mL) and those who had the higher levels (>60 ng/mL) [34].

4. The study hypotheses are not stated.
Ans: Thanks for your comment. We added the study hypotheses in our introduction part.

Page line: We hypothesized that children and adolescents with ADHD exhibited the higher risk of having a psychiatric disorder.

5. Controlling for confounding factors as ulcer, methrorrhaggia etc is a particular strength of this study.
Ans: Thanks for your comment.

6. The first two sentences are not necessary…this has already been written in the introduction…I would start the discussion with “The results of…”
Ans: Thanks for your comment. We deleted these two sentences.

Reply to Editor’s comment
1. Data availability: Please document within the Methods section of your manuscript as to whether the data used for the study is openly available or as to whether you received permission (and by who) to use this.
Ans: Thanks for your comment. NHIRD was an anonymous dataset and was audited and released by NHI for the research. We added the IRB information
about our permission to use this dataset.

Page 4 line 26: Our study was approved by Institutional Review Board of Taipei Veterans General Hospital (2012-04-012BC).