Author's response to reviews

Title: Increased risk of major depression subsequent to a first-attack and non-infection caused urticaria in adolescence: A nationwide population-based study

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Version: 4  Date: 30 June 2014

Author's response to reviews:

Dear Editor

Enclosed is our revised manuscript (MS: 8558458611197573; Increased risk of major depression subsequent to a first-attack and non-infection caused urticaria in adolescence: A nationwide population-based study). We appreciate your comments regarding our submission to “BMC Pediatrics”, and we have made revisions to this manuscript.

Below are our replies to your comments:

Editorial Comments

1. Abstract: Please ensure that your Abstracts are correct and identical on both the submission system and in the main body of your manuscript.

Answer: Yes, we have checked the Abstracts on both submission system and manuscript.

2. Tables: Please include a heading in each of your tables. For more information see: http://www.biomedcentral.com/bmcpediatr/authors/instructions/researcharticle#preparing-tables.

Answer: Yes, we have included a heading in each table.

3. STROBE: Please include a statement in your manuscript confirming that your research has adhered to the STROBE guidelines as outlined here: http://www.strobe-statement.org/. Please upload a completed checklist as an additional file with your revised submission.

Answer: Yes, we have included a statement in this manuscript confirming that
this research has adhered to the STROBE guidelines. Please see the section of Method (Page 6, line 21). In addition, the checklist was also uploaded.

Additional formatting request

1. Title Page: Please include the email addresses of all authors on the title page. Please ensure that it is the same with the one entered on the submission system.

Answer: Yes, we have included the email addresses of all authors on the title page.

2. Authors Contributions: For manuscripts with more than one author, all BMC Series journals require an Authors’ Contributions section to be placed after the Competing Interests section. An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. We suggest the following format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. Contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

Answer: Yes, the authors' contributions has described as your suggestion.

3. Acknowledgements: By way of a section ?Acknowledgements?, please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible. The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We
thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Answer: Yes, the Acknowledgements have been added. All authors agree the Acknowledgements.

4. List of abbreviations: If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Answer: Yes, we have added the list of abbreviations.

We hope that you will find the revised manuscript suitable for publication in BMC Pediatrics. We look forward to hearing from you.

Best regards,

Han-Ping Wu, M.D., Ph.D.
Shinn-Ying Ho, Ph.D.
Yan-Ren Lin, M.D., Ph.D.

Dear Dr. Lun-De Liao:

Enclosed is our revised manuscript (MS: 8558458611197573; Increased risk of major depression subsequent to a first-attack and non-infection caused urticaria in adolescence: A nationwide population-based study). We appreciate your constructive comments regarding our submission to “BMC Pediatrics”, and we have revised this manuscript.

Below are our replies to your comments:

1. The manuscript only focuses on non-infection urticaria; however, other recurrent skin disorders may result in similar conclusions. I suspect that other chronic skin disorders like psoriasis or atopic dermatitis should be included.

Answer: We appreciate your comment. We agree that some recurrent skin disorders may result in similar conclusions. Because of two major reasons, we did not include these two common skin diseases (psoriasis or atopic dermatitis) in our primary outcomes. First, the associations between the two diseases and depression have been well demonstrated (J Rheumatol. 2014; 41:887-96 and J Psychosom Res. 2004; 57:195-200.). Second, urticaria has never been suspected to be a risk factor of depression in adolescence. Therefore, our study attempted to provide novel information regarding this potential risk. Moreover, as we discussed in the introduction section, in adolescents with urticaria, simple infections have been associated with the majority of acute episodes. However, the stress and urticarial symptoms caused by simple infections are usually transient, particularly when patients are protected from the source of infection. Thus, this study focused on non-infection urticaria.

2. The author should consider other psychosis disorder in your primary outcome.

Answer: We appreciate your comment. During the study preparation, we
attempted to include different forms of depression. In this study, we excluded depressive and affective disorders because the principles of their diagnoses and their clinical presentations are different compared with major depression. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV) published by the American Psychiatric Association, major depressive syndrome or episode manifests with five or more of the following nine symptoms: depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, or recurrent thoughts about death or suicide; the symptoms must present most of the day nearly every day for a minimum of two consecutive weeks. At least one symptom must be either depressed mood or loss of interest or pleasure. In contrast, depressive disorder is marked by the presence of two to four of the nine symptoms during the same two-week period. The primary difference between major depression and depressive disorder is the number of symptoms. Major depression causes clear clinical distress and psychosocial impairment; therefore, this is the reason that we only included major depressive disorder. Finally, affective disorder may include manic (e.g., elevated, expansive, or irritable mood with hyperactivity, pressured speech, and inflated self-esteem) or depressive (e.g., dejected mood with disinterest in life, sleep disturbance, agitation, and feelings of worthlessness or guilt) episodes and often combinations of the two. Because affective disorder may include manic symptoms, it is difficult to clearly identify periods of depressive symptoms; therefore, we excluded affective disorder from this study. We have summarized the reasons we excluded depressive and affective disorders in the methods section.

On page 8 line 4: Bipolar depression, affective disorder substance-related depression, postpartum depression and depressive disorder were also not included as our primary outcomes because the principles of their diagnoses and their clinical presentations are different compared with major depression. Affective disorder may include manic attacks, and depressive disorder has only some of the same symptoms as major depression.

3. The structure of discussion should be revised to focus your main finding.

Answer: We appreciate your comment. The structure of the discussion has been revised. Moreover, according to other reviewer’s suggestion, we have added the associations of depression with autoimmune and allergic diseases in the families. Please see the discussion.

On page 15 line 18: In addition, affective disorders have been demonstrated to be increased by chronic autoimmune/allergy conditions that increase life stress, social phobia or even chronic central nerve inflammatory reactions.[40-42] For example, autoimmune diseases (including atopic dermatitis and systemic lupus erythematosus) and allergic diseases (including allergic rhinitis and asthma) could increase the risk of depression or bipolar disorders.[28, 30, 31, 43] Because these autoimmune/allergy diseases are strongly genetic in origin and have been demonstrated to potentially develop as heritable diseases[44], identifying the family history is important. Identification of autoimmune/allergy diseases in parents might help family physicians in the early detection of children
with silent symptoms. The risks of suffering from affective disorders might be decreased by the early control of their chronic autoimmune/allergy conditions.

4. The section discussed about the severity of major depression should be deleted.
Answer: We have deleted all information regarding the severity of depression.

We hope that you will find the revised manuscript suitable for publication in BMC Pediatrics. We look forward to hearing from you.

Best regards,

Han-Ping Wu, M.D., Ph.D.
Shinn-Ying Ho, Ph.D.
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