PEER REVIEW HISTORY

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pre-existing hyperlipidemia increased the risk of new-onset anxiety disorders after traumatic brain injury - A 14-year population-based study
AUTHORS	Kuo, Jinn-Rung; Ho, Chung-Han; Hsieh, Kuang-Yang; Liang, Fu-Wen; Li, Chia-Jung; Wang, Jhi-Joung; Chio, Chung-Ching; Chang, Chin-Hung

VERSION 1 - REVIEW

REVIEWER	Rajkumar Ramamoorthy National University of Singapore, Singapore
REVIEW RETURNED	11-Apr-2014

GENERAL COMMENTS	Abstract: 1. Anxiety disorders are Strengths and limitations of the study: 2. "The claims data obtained from ICD-9-CM diagnosis may exist misclassification"- reframe the sentence. Introduction 3. It is important to have some statistics on TBI in Asian, European and may be the world population. 4. Page 4, Paragraph 3: commas between the reference citations are missing. 5. Page 4: Hypertension can be abbreviated as HTN here. 6. "Furthermore, it has been reported that taking anti-hyperlipidemia drugs treatment, such as Statins, could restore anxiety-like deficits after TBI in an animal model". It is suggested to use 'anxiety-like' instead of 'anxiety' when referring to animal models. 7. Page 5: 'So far' would sound better than 'Up to now'

	Study selection 8. "Patients with a psychiatric disorder (ICD-9-CM codes: 295, 296, 297, 300, and 301) before TBI were excluded."- It would be good to mention here the disorders excluded, since it leaves a doubt in the mind of the reader if he is not aware of the codes. 9. Data- analysis : Please remove the hyphen. This section can be fused with the previous section and headed as Study Details (instead of study selection). Results 10.Page 8: " The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years." it differs from the figure mentioned in the abstract - "The overall incidence rate of new-onset ADs for TBI patients with hyperlipidemia is 102.43 per 10,000 person-years" 11."In addition, female TBI patients with hyperlipidemia had a higher incidence rate (292.32 per 10,000 person-years) than males (142.12 per 10,000 person-years)." mentioned in the result does not sync with the statement in the abstract "The incidence rates of ADs for males and females with hyperlipidemia, respectively, were 225.27 and 363.21 per 10,000 person-years, which were higher than those without hyperlipidemia (142.12 and 292.32 per 10,000 person-years, respectively)." I strongly recommend a double checking of these figures and reframing of the sentences for the want of clarity. Discussion 12. Page 11: "In the general population, in addition to hyperlipidemia,20 several studies have demonstrated that CAD,14 15 hypertension,16 17 DM,16 18 and TBI6 10 11 are risk factors for the development of ADs" - It is redundant to what is mentioned in the introduction page 4, paragraph 3. The sentence can be removed or further information from all or some of these references, which supports the present data can be showcased. 13. Page 12: Clarify 'psycho pharmacokinetic' 14. " Because natural menopause is thought to occur due to the exhaustion of ovarian follicles at a mean age of 51 years,40 the suddenly reduced hormone may effect anxiety." - Reframe the sentence 15. The format of Figure 1 is too light and unclear.

REVIEWER	George J. Demakis University of North Carolina Charlotte
REVIEW RETURNED	10-Apr-2014

GENERAL COMMENTS	Despite yes responses to the questions above, I think this ms remains too narrow as it only addresses anxiety disorders. It does not do justice to the full range of even more common psychological issues post-TBI. This is potentially important study, identifying hyperlipidemia as a risk factor for the development of anxiety disorders (AD) in individuals with traumatic brain injury (TBI). Individuals with hyperlipedemia were 1.6 times more likely to develop an anxiety disorder than individuals without hyperlipedemia, even after a variety of possibly confounding variables were controlled. These findings were based on data obtained from the National Health Research Insurance Database in Taiwan between 1997 and 2010. In my view, there are three main flaws to this work that seriously limit my enthusiasm. First, the TBI variable is very crude and doesn't specify the type of injury or, more problematically, the severity of the injury. Psychological effects of a mild injury can be different than a more severe injury—paradoxically these individuals sometimes have worse outcomes. This can be traced to increased over-reporting or even exaggeration in those with mild injuries to poor awareness in more severe injuries (i.e., anosognosia). Related to this aggregation of multiple severities, there are many, many different types of TBIs grouped into a single TBI variable, again making interpretation and application of findings difficult. Second, I am concerned that authors only examined anxiety after TBI—why not other psychological issues that are even more common, such as depression? There are other psychological issues as well such as impulsivity, irritability, aggression, etc. Examination of only anxiety provides a narrow glimpse into psychological functioning post-TBI. I should not that authors' introduction seems to acknowledge the reality of broad psychiatric difficulties in the first half of p. 4—it is not until the middle of that page that anxiety disorders are addressed. At minimum, authors should address hyperlipidemia as a risk factor for depression as well as anxiety to provide a more comprehensive and useful picture of new-onset psychological issues after TBI. Authors describe an enormous change in AD onset after TBI from 1997 to 2010—from 7.85 to 431.1 per 10,000—yet don't describe possible reasons. I know that this was not the main purpose of study, but if authors are going to include they need to explain these findings. Given such enormous changes, I wonder about possible errors in data entry or analyses or possible changes in diagnostic practices. Would we really expect such enormous changes over such a short time period? Minor points 1. On p. 6, please specify why a 1:2 age- and gender-matched cohort was selected beyond just to "avoid potential confounders." I am suspecting that this might affect prevalence rates obtained in this study, but it difficult to know with the provided information. 2. On p. 6, I couldn't find reference to ICD-9-CM code 300.04—this was the diagnosis that was excluded. Please identify it. 3. On p. 10, line 3, I don't think it accurate to characterize this work as a "14-year longitudinal study" as it appears to use a cross-sectional design. In other words, the same individuals are not

	tracked over a period of time, as required for a longitudinal design. 4. On p. 10, line 21, I am not sure it best to characterize patients with hyperlipidemia as having a “trait to develop AD.” What would this be anyway? Perhaps better just to say that these individuals are at increased risk for AD. 5. On p. 10, line 43, why note only that the neurosurgeon should “expect to see more TBI patients”—what about other specialties? It is Important to note too that the vast majority of TBIs are mild and these patients are not likely to see a neurosurgeon. 6. On p. 10, line 49, I wouldn’t consider TBIs as “episodes.”

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Rajkumar Ramamoorthy
Institution and Country National University of Singapore, Singapore
Please state any competing interests or state ‘None declared’: None declared

Abstract:

1. Anxiety disorders are
λ Thanks for reviewer pointing this grammar error out. We have fixed it.
Strengths and limitations of the study:

2. "The claims data obtained from ICD-9-CM diagnosis may exist misclassification"- reframe the sentence.
λ We have reframed the sentence. "In the claims data, disease was recorded using ICD-9-CM which may be misclassified."
Introduction

3. It is important to have some statistics on TBI in Asian, European and may be the world population.
λ We all agree the reviewer's comment that the information of TBI in different area is important. We add the description " From the global estimation, 57 million people may have been hospitalized with TBIs and about 1.5 million die.1 The annual incidence of TBI is ~1.7 million in the United States.2 The yearly incidence of TBI is estimated at 235 per 100,000 people in European Union 3, and about 160 to 344 per 100,000 people in Asia.4, 5"
4. Page 4, Paragraph 3: commas between the reference citations are missing.
λ Thanks for reviewer pointing out this error, we have fixed it.
5. Page 4: Hypertension can be abbreviated as HTN here.
λ We have checked all paper and changed the Hypertension as HTN.
6. "Furthermore, it has been reported that taking anti-hyperlipidemia drugs treatment, such as Statins, could restore anxiety-like deficits after TBI in an animal model". It is suggested to use 'anxiety-like' instead of 'anxiety' when referring to animal models.
λ Thanks for reviewer's reminder, we have changed it.
7. Page 5: 'So far' would sound better than 'Up to now'
λ Thanks for reviewer's reminder, we have changed it.
Study selection

8. "Patients with a psychiatric disorder (ICD-9-CM codes: 295, 296, 297, 300, and 301) before TBI were excluded."- It would be good to mention here the disorders excluded, since it leaves a doubt in the mind of the reader if he is not aware of the codes.
λ Thanks for reviewer's suggestion, we add the description" Patients with a psychiatric disorder such

as schizophrenic disorders (ICD-9-CM codes: 295); episodic mood disorders (ICD-9-CM codes: 296); delusional disorders (ICD-9-CM codes: 297); anxiety, dissociative and somatoform disorders (ICD-9-CM codes:300); and personality disorders (ICD-9-CM codes:301) before TBI were excluded. "
9. Data- analysis : Please remove the hyphen. This section can be fused with the previous section and headed as Study Details (instead of study selection).
λ Thanks for reviewer's reminder, we have changed it.

Results

10.Page 8: " The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years." it differs from the figure mentioned in the abstract - "The overall incidence rate of new-onset ADs for TBI patients with hyperlipidemia is 102.43 per 10,000 person-years"
λ Thanks for reviewer point out this typo. The incidence rate of new-onset ADs for TBI patients with hyperlipidemia is 142.03 per 10,000 person-years. We had modified typo in the abstract.

11."In addition, female TBI patients with hyperlipidemia had a higher incidence rate (292.32 per 10,000 person-years) than males (142.12 per 10,000 person-years)." mentioned in the result does not sync with the statement in the abstract "The incidence rates of ADs for males and females with hyperlipidemia, respectively, were 225.27 and 363.21 per 10,000 person-years, which were higher than those without hyperlipidemia (142.12 and 292.32 per 10,000 person-years, respectively)."
λ Thanks for reviewer point out this typo. We have changed the sentence in the abstract " The incidence rates of ADs for males and females with hyperlipidemia, respectively, were 142.12 and 292.32 per 10,000 person-years, which were higher than those without hyperlipidemia (93.03 and 171.68 per 10,000 person-years, respectively)."

I strongly recommend a double checking of these figures and reframing of the sentences for the want of clarity.

Discussion

12. Page 11: "In the general population, in addition to hyperlipidemia,20 several studies have demonstrated that CAD,14 15 hypertension,16 17 DM,16 18 and TBI6 10 11 are risk factors for the development of ADs" - It is redundant to what is mentioned in the introduction page 4, paragraph 3. The sentence can be removed or further information from all or some of these references, which supports the present data can be showcased.
λ Thanks for reviewer's suggestion, the sentence have been removed.
13. Page 12: Clarify 'psycho pharmacokinetic'
λ Psycho pharmacokinetic is the difference of absorption and distribution after specific anti-anxiety drug administration. We add " the difference of absorption and distribution after specific anti-anxiety drug administration (psycho pharmacokinetic) during the treatment of women with anxiety disorders, " in the paper.
14. " Because natural menopause is thought to occur due to the exhaustion of ovarian follicles at a mean age of 51 years,40 the suddenly reduced hormone may effect anxiety." - Reframe the sentence
λ We reframe the sentence to "Natural menopause usually occur at a mean age of 51 years, and the suddenly reduced hormone resulting from the exhaustion of ovarian follicles may affect anxiety."
15. The format of Figure 1 is too light and unclear.
λ Thanks for the reviewer's reminder, we have fixed it.

Reviewer: 2
Reviewer Name George J. Demakis
Institution and Country University of North Carolina Charlotte
Please state any competing interests or state ‘None declared’: None declared.

Despite yes responses to the questions above, I think this ms remains too narrow as it only addresses anxiety disorders. It does not do justice to the full range of even more common psychological issues post-TBI.
λ Thanks for reviewer's comment, we understand that the post-TBI psychological symptoms are not only AD but also including more. The main limitation of this study is that we can just observe the outcomes for the anxiety disorders. Thus, the future research we will consider other psychological issues risk post-TBI.
This is potentially important study, identifying hyperlipidemia as a risk factor for the development of anxiety disorders (AD) in individuals with traumatic brain injury (TBI). Individuals with hyperlipedemia were 1.6 times more likely to develop an anxiety disorder than individuals without hyperlipedemia, even after a variety of possibly confounding variables were controlled. These findings were based on data obtained from the National Health Research Insurance Database in Taiwan between 1997 and 2010.
In my view, there are three main flaws to this work that seriously limit my enthusiasm. First, the TBI variable is very crude and doesn’t specify the type of injury or, more problematically, the severity of the injury. Psychological effects of a mild injury can be different than a more severe injury—paradoxically these individuals sometimes have worse outcomes. This can be traced to increased over-reporting or even exaggeration in those with mild injuries to poor awareness in more severe injuries (i.e., anosognosia). Related to this aggregation of multiple severities, there are many, many different types of TBIs grouped into a single TBI variable, again making interpretation and application of findings difficult.
λ Thanks for reviewer's comments, we agree the different types / severity level of TBI may lead to different psychological information, but our database did not include the variables for the TBI severity level. Thus, we add the describe in the limitation " Finally, some potential risk factors of TBI, such as the severity level and types, were not in the database. However, these potential risk factors may lead to different psychological effects. Therefore, in the future research, validating our findings with these potential risk factors is necessary."
Second, I am concerned that authors only examined anxiety after TBI—why not other psychological issues that are even more common, such as depression? There are other psychological issues as well such as impulsivity, irritability, aggression, etc. Examination of only anxiety provides a narrow glimpse into psychological functioning post-TBI. I should not that authors’ introduction seems to acknowledge the reality of broad psychiatric difficulties in the first half of p. 4—it is not until the middle of that page that anxiety disorders are addressed. At minimum, authors should address hyperlipidemia as a risk factor for depression as well as anxiety to provide a more comprehensive and useful picture of new-onset psychological issues after TBI.
λ Thanks for reviewer's suggestion, and we will do this in the future research. The current goal of our study was focus on the relationship between hyperlipidemia and ADs after TBI. We understand a lot of psychological issues will be presented post-TBI, and the depression and ADs were similar but a little bit different. Thus, we believe the cause-related effects between depression, ADs, and hyperlipidemia were interesting, and it will be worth to understand the association in the future research.
Authors describe an enormous change in AD onset after TBI from 1997 to 2010—from 7.85 to 431.1 per 10,000—yet don’t describe possible reasons. I know that this was not the main purpose of study, but if authors are going to include they need to explain these findings. Given such enormous changes, I wonder about possible errors in data entry or analyses or possible changes in diagnostic practices.

Would we really expect such enormous changes over such a short time period?

λ Thanks for reviewer's comments. We think it could be a good question for the future research. The below listed the possible reasons of this enormous changes:
1. At beginning of national health insurance program, most patients did not understand their rights of insurance for seeking medical diagnosis.
2. The behaviors of health seeking was still based on the old concepts, all medical treatment is expensive.
3. Because of culture or social issues, most patients in Taiwan reject to visit psychiatrists for appropriate treatment. A study used the Taiwan's national health insurance research database in 2000 and indicated the prevalence rates of psychiatric disorders in this database at that time is lower.6 From our results, we think the situation is changing now.
Thus, for illustrating the changes of prevalence rates of ADs in TBI patients, we add the describe" Although, at beginning of national health insurance program, the behaviors of health-seeking and culture or social issues may affect the lower prevalence rate of ADs in TBI patients,6 our finding indicated that the situation is changing, which could be from the improvement of health insurance program or the change of health-seeking behaviors. "

Minor points

1. On p. 6, please specify why a 1:2 age- and gender-matched cohort was selected beyond just to "avoid potential confounders." I am suspecting that this might affect prevalence rates obtained in this study, but it difficult to know with the provided information.
λ Thanks for reviewer's constructive suggestions. From the lecture review, the hyperlipidemia were often in men above 35 years of age and postmenopausal women7. The age- and gender-matched method was applied to control the potential bias among the age and gender. Thus, we will add the describe before the sentence, " Since hyperlipidemia was often in men aged older than 35 and women older than 557, a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected for avoiding potential confounders."
2. On p. 6, I couldn't find reference to ICD-9-CM code 300.04—this was the diagnosis that was excluded. Please identify it.
λ Thanks for reviewer point out this typo. It should be the ICD-9-CM code 300.4, dysthymic disorder.
3. On p. 10, line 3, I don't think it accurate to characterize this work as a "14-year longitudinal study" as it appears to use a cross-sectional design. In other words, the same individuals are not tracked over a period of time, as required for a longitudinal design.
λ Thanks for reviewer's comment, we will change it to "14-year population-based study."
4. On p. 10, line 21, I am not sure it best to characterize patients with hyperlipidemia as having a "trait to develop AD." What would this be anyway? Perhaps better just to say that these individuals are at increased risk for AD.
λ Thanks for reviewer's comment, we all agree to change it to " these individuals are at increased risk for AD"
5. On p. 10, line 43, why note only that the neurosurgeon should "expect to see more TBI patients"—what about other specialties? It is Important to note too that the vast majority of TBIs are mild and these patients are not likely to see a neurosurgeon.
λ Thanks for reviewer's comment. We add the describe" the caregivers and physicians, including neurosurgeon, critical care physician, psychiatrists, physiatrists, can expect to see more TBI patients"
6. On p. 10, line 49, I wouldn't consider TBIs as "episodes."
λ Thanks for reviewer's suggestion, we have changed the "episodes" to "event".

1. Murray CJ, Lopez AD, Kovacs L, Di Paola M, Mastrantonio M, Carboni M, et al. Global health statistics: A compendium of incidence prevalence and mortality estimates for over 200 conditions. GERONTOLOGIST. 1996;36:773-782

2. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the united states: Emergency department visits, hospitalizations, and deaths. Atlanta (ga): Centers for disease control and prevention. National Center for Injury Prevention and Control. 2010;2:1-9
3. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. The Lancet Neurology. 2008;7:728-741
4. Chiu WT, Yeh K, Li Y-C, Gan Y, Chen H-Y, Hung C. Traumatic brain injury registry in taiwan. Neurological research. 1997;19:261
5. Gururaj G, Sastry Koeluri V, Chandramouli B, Subbakrishna D. Neurotrauma registry in the nimhans. National Institute of Mental Health & Neurosciences, Bangalore, India. 2004
6. Chien I-C, Chou Y-J, Lin C-H, Bih S-H, Chou P. Prevalence of psychiatric disorders among national health insurance enrollees in taiwan. Psychiatric Services. 2004;55:691-697
7. Havel RJ, Rapaport E. Management of primary hyperlipidemia. The New England journal of medicine. 1995;332:1491-1498