Pre-existing hyperlipidemia increased the risk of new-onset anxiety disorders after traumatic brain injury - A 14-year population-based study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005269
Article Type:	Research
Date Submitted by the Author:	16-Mar-2014
Complete List of Authors:	Ho, Chung-Han; ChiMei medical center, Medica lresearch Hsieh, Kuang-Yang; ChiMei medical center, Psychiatry Liang, Fu-Wen; National Cheng Kung University, Public Health Wang, Jhi-Joung; ChiMei Medical center, medical research Chio, Chung-Ching; ChiMei Medical center, Neurosurgery Li, Chia-Jung; National Cheng Kung University, Psychiatry Kuo, Jinn-Rung; Southern Taiwan University of Science and Technology, Biotechnology; Chi-Mei Medical Center, Neurosurgery Chang, Chin-Hung; Chimei medical center, Neurosurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Epidemiology
Keywords:	Neurosurgery < SURGERY, PSYCHIATRY, Anxiety disorders < PSYCHIATRY

Title: Pre-existing hyperlipidemia increased the risk of new-onset anxiety disorders after traumatic brain injury - A 14-year population-based study

Running title: Hyperlipidemia and anxiety after brain injury

*Chung-Han Ho, PhD [a,e], *Kuang-Yang Hsieh, MD, PhD [b, f], Fu-Wen Liang, PhD [d], Jhi-Joung Wang, MD, PhD [a], Chung-Ching Chio, MD [a,c], Chia-Jung, Li, MD [g], Jinn-Rung Kuo, MD, PhD [a,c, f] , Chin-Hung, Chang, MD [a]

Departments of [a]Medical Research, [b]Psychiatry, [c]Neurosurgery, Chi-Mei Medical Center, Tainan, Taiwan

[d]Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[e]Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

[f]Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan

[g]Departments of Psychiatry, National Cheng-Kung University, Tainan, Taiwan

Corresponding author: Jinn-Rung Kuo, Department of Neurosurgery, Traumatic Brain Center, Chi-Mei Medical Center, #901, Jong-Hwa Road, Yung-Kung City, 710, Tainan, Taiwan

Telephone: +886-6-281-2811 ext. 9

Fax: +886-6-282-8928

E-mail: kuojinnrung@gmail.com

Word count: 2787

References number: 40

ABSTRACT

Objectives:

Anxiety disorders (ADs) is common after traumatic brain injury (TBI). However, the risk factors of new-onset ADs remain unclear. This study was aimed at evaluating the incidence and risk factors for new-onset ADs, including pre-existing hyperlipidemia and three major comorbidities (diabetes mellitus, hypertension, and cardiovascular disease), in TBI patients.

Setting: A matched longitudinal cohort study was conducted using the Taiwan Longitudinal Health Insurance Database between January 1997 and December 2010.

Participants: A total of 3822 subjects (1274 TBI patients with hyperlipidemia and 2548 age- and gender-matched TBI patients without hyperlipidemia).

Outcome measures: The incidence and hazard ratios (HR) for the development of new-onset ADs after TBI were compared between the two groups.

Results: The overall incidence rate of new-onset ADs for TBI patients with hyperlipidemia is 102.43 per 10,000 person-years. TBI patients with hyperlipidemia have a 1.60-fold incidence rate ratio (p<0.0001) and increased HR of ADs (1.58, 95% confidence interval: 1.24-2.02) compared with those without hyperlipidemia. 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). Stratified by age group, hyperlipidemia is a risk factor of ADs for TBI patients aged 65 years or younger.

Conclusions: Pre-existing hyperlipidemia is an independent predictor of new-onset ADs in TBI patients, even when controlling for other demographic and clinical variables. Female patients with pre-existing hyperlipidemia had significantly higher risk of new-onset ADs than males, especially between the ages of 35 and 65 years.

Key Words: Hyperlipidemia; traumatic brain injury; anxiety disorders; comorbidities; population-based

Strengths and limitations of this study

.To our knowledge, there are no published studies investigating the risk of new-onset anxiety in TBI patients with hyperlipidemia based on the population database.

.The information that hyperlipidemia is an independent risk factor of new-onset anxiety after TBI may play a role in preventive medicine.

.The claims data obtained from ICD-9-CM diagnosis may exist misclassification

. As a retrospective observational study, our results could be biased by unrecognised confounders which may influence the development of anxiety after TBI.

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability in humans. According to the Centers for Disease Control and Prevention, the annual incidence of TBI in the United States is ~1.7 million.[1] However, the assessment and treatment of TBI typically focus on physical and cognitive impairments, even though neuropsychiatric impairments represent significant causes of disability.[2] TBI can result in various neuropsychiatric disorders, including cognitive impairments, mood or anxiety disorders, and behavioral problems. These post-TBI neuropsychiatric impairments contribute to disability after TBI, which becomes a chronic problem for an estimated 3.17 million in the United States.[3] Therefore, evaluating the risk factors associated with the new-onset psychiatric problem after TBI is an important issue in the field of neuropsychiatry.

The risk of developing neuropsychiatric disorders after TBI ranges from 21% to 65%.[4-6] TBI patients with psychiatric disorders were associated with significantly greater costs (approximately 3.39 times) than TBI patients without psychiatric disorders; hence, TBI represents a major public health issue.[7] Anxiety disorders (ADs), one of the common psychiatric disorders, is defined as worrying about the future state of arousal with the feeling of a non-specific threat;[8] the prevalence of ADs is 11%–70% in patients with TBI.[6, 9-11] However, the risk factors of new-onset ADs after TBI remain unclear.

Beside TBI insults, age,[12] sex,[13]cardiovascular disease (CAD),[14 15] hypertension,[16 17] diabetes mellitus (DM),[16 18] and hyperlipidemia are risk factors associated with ADs.[19 20] Among these AD risk factors, hyperlipidemia was also related to the risk of CAD, DM,[16] and hypertension.[21] Furthermore, it has been reported that taking anti-hyperlipidemia drugs, such as Statin, could restore anxiety deficits after TBI in an animal model.[22] However, to the best of our knowledge, few studies have examined

the association between hyperlipidemia and the risk of new-onset ADs in TBI patients.

Up to now, the incidence and risk factors of new-onset AD symptoms in TBI patients with hyperlipidemia remain unclear. Therefore, the aim of this study was to evaluate the risk factors for developing ADs in TBI patients with or without previous hyperlipidemia using data from the nationwide database of the National Health Insurance (NHI) Program in Taiwan (1997–2010). We attempted to clarify the long-term effects of pre-existing hyperlipidemia on new-onset ADs among TBI patients. We propose that awareness of the incidence and risk factors for new-onset ADs in TBI patients can improve not only one's understanding of the sequelae of brain injury but also patient treatment and the rehabilitation protocol.

Methods

Data sources and researches

In this study, data were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan between January 1997 and December 2010. The NHIRD covers 99% of inpatient and outpatient medical benefit claims for Taiwan's 23 million residents. The database comprises detailed information regarding clinical visits for each insured subject, including diagnostic codes according to the clinical modification of the International Classifications of Disease-9 (ICD-9-CM) and prescription details.[23 24] For a population-base medical research purpose, the NHIRD has released a database of medical claims of 1,000,000 random subjects, approximately 4.3% of the population in various studies. All datasets can be interlinked through each individual's unique personal identification number.

Study selection

We accessed the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Subjects were selected from the partial sample of the 1 million

individuals. The study protocol was as follows: patients with a diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010 were selected. Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis. To avoid potential confounders, a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected. The event of ADs was defined as three times of outpatient visits or one inpatient admission with a AD diagnosis (ICD-9-CM code: 300.xx were included but 300.04 was excluded) between the date of TBI diagnosis and December 31, 2010. Patients with a psychiatric disorder (ICD-9-CM codes: 295, 296, 297, 300, and 301) before TBI were excluded. This method of selection has been used extensively in various published studies using the Taiwan NHIRD. [25-27] The baseline comorbidities prior to TBI, including hypertension (HTN; ICD-9-CM code: 401~405,437.2, and 362.11), diabetes mellitus (DM; ICD-9-CM code: 250, 357.2, 362.0, and 366.41), and cardiovascular disease (CAD; ICD-9-CM code: 410~414), were determined, as these diagnoses are important factors affecting episodes of mental disorders.

Data- analysis

To estimate the risk of ADs, demographic and clinical information, including age, sex, hyperlipidemia, DM, HTN, and CAD, were obtained directly from each subject's file in the NHI insurance database. Age was classified into four categories: ≦35, 35–50, 50-65 and ≥65 years old.

Statistical analysis

Pearson's chi-square test was used to analyze distribution differences in age group, gender, AD, HTN, DM, and CAD between TBI patients with and without hyperlipidemia. Student's t-test and the Wilcoxon rank-sum test were used to

compare age at first TBI diagnosis and time to ADs, respectively.

The incidence rate of ADs was calculated from the number of TBI patients with ADs divided by the total person-years as rates per 10,000 person-years of observation. The Poisson regression was applied to calculate the incidence rate ratios of ADs with 95% confidence intervals between TBI patients with/without Hyperlipidemia. In addition, the Kaplan-Meier failure plot was applied to describe the cumulative incidence rate of ADs; the log-rank test was used to compare the risk difference between two groups. The relative risks adjusted for potential confounding variables were estimated by the Cox regression. In the survival analysis, the subjects who died were considered censored, and the censoring date was their date of mortality. The statistical software, Statistical Analysis System (SAS) (version 9.3; SAS Institute, Inc, Cary, NC), was used to perform all statistical analyses. Kaplan-Meier curves were generated using STATA (version 12; Stata Corp. *College Station*, TX). All significance levels were set at *P*-value <0.05.

Results

Table 1 shows the distribution of demographical variables between TBI patients with and without hyperlipidemia. A total of 3822 adult patients were enrolled in this study. After matching by age and gender, group differences in comorbidity of HTN, DM, and CAD were determined. TBI patients with hyperlipidemia (10.75%) had significantly more ADs than TBI patients without hyperlipidemia (6.95%). TBI patients with hyperlipidemia developed new-onset ADs (median: 2.40 years, interquartile range [IQR]: 0.93-4.42) earlier than TBI patients without hyperlipidemia (median: 2.70 years, IQR: 0.91-4.81). The overall follow-up median time is 5.44 years (IQR: 2.20-9.07).

Figure 1 shows the prevalence of ADs for TBI patients with hyperlipidemia increased from 7.85 per 10,000 in 1997 to 431.71 per 10,000 in 2010. The estimated

prevalence of ADs among TBI patients without hyperlipidemia is consistently lower than those with hyperlipidemia.

The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years. Table 2 shows that TBI patients with hyperlipidemia have a 1.60-fold incidence rate ratio of ADs compared with TBI patients without hyperlipidemia. The TBI patients aged 35~65 years had a significant difference in the ADs incidence ratio between patients with/without hyperlipidemia. 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). There was no significant difference in the incidence rate of ADs in patients with comorbid HTN, DM, or CAD compared with those without the aforementioned comorbidities. TBI patients with hyperlipidemia have a 1.58-fold (95% CI: 1.24-2.02) risk of ADs compared with TBI patients without hyperlipidemia, even when controlling for age, sex, HTN, DM, and CAD. Females have a 1.84-fold (95% CI: 1.47-2.30) risk of ADs compared with male TBI patients.

In addition, TBI patients with hyperlipidemia were more likely to experience ADs than those without hyperlipidemia in any given month during the follow-up. The Kaplan-Meier plot (Figure 2) indicated that TBI patients with hyperlipidemia developed ADs more quickly than those without hyperlipidemia. The cumulative probability of ADs in hyperlipidemia patients was 3.00% (95% C.I.: 2.17%-4.14%) at one-year, 7.10 % (95% C.I.: 5.72%-8.79%) at three-years, 11.26% (95% C.I.: 9.43%-13.42%) at five-years, and 15.35% (95% C.I.: 12.98%-18.09%) at 10 years; in patients without hyperlipidemia, the cumulative probability of ADs was 1.92% (95% C.I.: 1.44%-5.26%) at one-year, 4.17% (95% C.I.: 3.41%-5.10%) at three-years, 6.83% (95% C.I.: 5.79%-8.05%) at five-years, and 10.83% (95% C.I.: 9.28%-12.62%) at 10 years.

As we stratified by age group (Table 3), the ratio of incidence rate was significantly different between TBI patients with and without hyperlipidemia for females aged 50~65 years. However, in the same age group, no significant difference was observed between male TBI patients with and without hyperlipidemia. Compared with TBI patients without hyperlipidemia, all age groups show the increased hazards for TBI patients with hyperlipidemia, but only patients between the ages of 50~65 were significantly different. Furthermore, females aged 35~50 years and 50~65 years had a 2.81-fold (95% C.I.: 1.73-4.58) and 2.44-fold (95% C.I.: 1.65-3.60) risk of ADs, respectively, compared with males.

Table 4 shows the adjusted hazard ratios of ADs for TBI patients with hyperlipidemia. Female TBI patients with hyperlipidemia presented a 1.97-fold (95% C.I.: 1.40-2.77) risk of ADs compared with males. Stratified by age group, females aged 35~50 and 50~65 years had an increased risk of ADs compared with males (HR: 2.53, 95% C.I.: 1.21-5.27, and HR: 2.97, 95% C.I.: 1.70-5.21, respectively). Further, the TBI females aged 50~65 years have a higher risk (2.04, 95% C.I.: 1.17-3.57) than older females (age>65).

Discussion

To the best of our knowledge, this is the first study to demonstrate that pre-existing hyperlipidemia, especially in females aged 35-65 years, is an independent risk factor for developing new-onset ADs after TBI. Because the NHIRD covers nearly 99% of inpatient and outpatient medical benefit claims for the 23 million residents in Taiwan, these results closely approximate the true distribution of ADs among TBI patients with pre-existing hyperlipidemia in Taiwan. This information is critical to alter the course of and prevent TBI-related disability.

Our findings were consistent with previous study that ADs are common in the general population and may be even more common in individuals with traumatic brain

injuries.[28] In our 14-year longitudinal study, we found that the prevalence of ADs in TBI patients with hyperlipidemia increased from 7.85 per 10,000 in 1997 to 431.71 per 10,000 in 2010. We also found the incidence of new-onset ADs in pre-existing hyperlipidemia after TBI is 10.75% and 189.43 per 10,000 person-years, the overall cumulative ADs rate is 17.62%, and approximately 43% of ADs cases occurred within two years after TBI, which were all significant when compared with TBI patients without hyperlipidemia ($p<.0001$). The incidence rate of ADs supports the validity of the high prevalence rate of ADs among TBI patients with pre-existing hyperlipidemia. These results imply patients with hyperlipidemia may have the trait to develop ADs after TBI and pre-existing hyperlipidemia may play an important role in the development of new-onset ADs after TBI.

In Taiwan, the prevalence of hyperlipidemia for adults ranged from 10.2% to 13.4%.[25] The incidence rate of TBI was 344 per 100,000 people in Taiwan.[29] To the best of our knowledge, this is the first study to show the prevalence of ADs for TBI patients with pre-existing hyperlipidemia. The fact that the prevalence of ADs for TBI patients continually increased over 14 years highlights the possible characteristics of ADs for TBI patients. Importantly, the prevalence of ADs in TBI patients with pre-existing hyperlipidemia was always higher than that in patients without hyperlipidemia. Therefore, the neurosurgeon can expect to see more TBI patients who have pre-existing hyperlipidemia in daily practice. At present, TBI is a major cause of death and neuropsychiatric disability in humans and remains a public health challenge. Whether the treatment of hyperlipidemia prior to a TBI episode helps improve post-traumatic new-onset ADs is worth exploring.

Furthermore, in a three year interventional study, the researchers found awareness of hyperlipidemia had no effect on anxiety.[30] In contrast, the other study indicated that simvastatin, an anti-hyperlipidemia drug, caused significant anxiolytic effects in

animals.[24]In the current study, we did not investigate the impact of anti-hyperlipidemia medications in pre-existing hyperlipidemic patients before TBI, as the data were unavailable. However, in our study, we emphasize that physicians should pay more attention on the plasma hyperlipidemia level of high-risk patients to prevent the occurrence of ADs after TBI in daily practice. Well-controlled hyperlipidemia may attenuate the risk of developing ADs if a TBI has occurred.

In the general population, in addition to hyperlipidemia,[20] several studies have demonstrated that CAD,[14 15] hypertension,[16 17] DM,[16 18] and TBI[6 10 11] are risk factors for the development of ADs. In our study, we further elucidated and provided novel findings that pre-existing hyperlipidemia is an independent risk factor for new-onset ADs after TBI, even when we controlled for DM, hypertension and CAD. Therefore, hyperlipidemia's neuropathological effects on the development of ADs after TBI should be investigated.

Vogelzangs et al. reported an elevation in the systemic inflammation biomarker C-reactive protein in individuals with a late-onset anxiety disorder.[31] Salim et al. also demonstrated that anxiety is associated with neuroinflammation.[32] Esmaillzadeh et al. showed a positive association between hyperlipidemia and markers of systemic inflammation and endothelial dysfunction.[33] Furthermore, inflammatory actions of the neuroimmune system may contribute to the development of anxiety disorders following TBI.[34] Taken together, we suppose that the inflammatory entity of hyperlipidemia could aggravate new-onset ADs developed after TBI. Despite our results, there remains insufficient evidence to conclude what the role of the neuropathological consequences of pre-existing hyperlipidemia may play in the development of new-onset ADs after TBI. However, we propose post-injury anti-inflammation therapy may be a clinically useful strategy to prevent new-onset ADs in humans. This hypothesis should be investigated in the future.

Our study found that hyperlipidemic women, specifically aged between 35 and 65 years, had an increased risk of new-onset ADs after TBI compared to men. In a two-year national general population survey of comorbidity, the researchers found that the lifetime prevalence rates for ADs were 30.5% for women and 19.2% for men; women were more likely to develop ADs in their lifetime compared with men.[35] The other studies reported the male to female prevalence ratios of ADs for 12-month and lifetime were 1:1.79 and 1:1.7, respectively.[36] The possible explanations as to the greater susceptibility of women to ADs may be multifactorial. For example, genetic or environmental factors,[37] psycho pharmacokinetic differences during the treatment of women with anxiety disorders,[38] and female reproductive hormones, such as estrogen, may play a protective role in the development of ADs in women.[1439] Thus, our results are consistent with previous reports which showed that TBI female patients with hyperlipidemia had a significantly higher risk for ADs than males. Using a subgroup analysis, we further found that TBI females with hyperlipidemia aged 35~50 years and 50~65 years have a significantly increased risk of new-onset ADs (HR: 2.53 and 2.97, respectively) than males. Further, when only females were considered, we found hyperlipidemic females aged 50~65 years have a significantly increased risk of new-onset ADs after TBI (HR: 2.04) than older females (age>65). 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. However, as estrogen levels were unavailable in our study, there is no sufficient evidence could conclude whether estrogen has anti-anxiety effects on the development of new-onset ADs after TBI patients with pre-existing hyperlipidemia. Therefore, we consider the role of estrogen and the interaction between estrogen and hyperlipidemia in ADs development after TBI as a critical issue to evaluate in the future.

There are several limitations to our study. First, the diagnoses, including ADs

and other comorbidities, all relied on the claims data and ICD-9-CM diagnosis codes; thus, some disease misclassifications may exist. Second, we did not evaluate socioeconomic status, which may influence the development of ADs after TBI. Finally, information regarding the severity of TBI and hyperlipidemia were unavailable, which may also intervene the occurrence of ADs.

Conclusions

Pre-existing hyperlipidemia is an independent predictor for new-onset ADs after TBI. Hyperlipidemic women, specifically aged between 35~65 years, had a significantly higher risk of new-onset ADs compared with men after TBI. Therefore, it is suggested that physicians should pay more attention to the plasma hyperlipidemia level of high-risk patients to prevent the development of ADs after TBI.

Acknowledgement

This study is based in part on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes.

Author Contributions

Conceived and designed the experiments: Chung-Han Ho, Jinn-Rung Kuo, and Kuang-Yang Hsieh. Performed the experiments: Chung-Han Ho, Kuang-Yang Hsieh, Jinn-Rung Kuo, and Chia-Jung, Li. Analyzed the data: Chung-Han Ho, Fu-Wen Liang, Jinn-Rung Kuo, Contributed reagents/materials/analysis tools: Jhi-Joung Wang, Chung-Ching Chio, and Chin-Hung, Chang. Wrote the paper: Chung-Han Ho, Jinn-Rung Kuo, Fu-wen Liang, and Kuang-Yang Hsieh.

Funding

No current external funding sources for this study.

Competing interests

The authors have declared that no competing interests exist.

Ethics approval

Institutional Review Board (IRB), Chi-Mei Medical Center, Tainan approved these surveys.

References

1. Faul M, Xu L, Wald MM, et al. 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.
2. Consensus conference. Rehabilitation of persons with traumatic brain injury. NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. JAMA. 1999/09/15 ed. pp. 974-83.
3. Zaloshnja E, Miller T, Langlois JA, et al. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil. 2008;23:394-400.
4. Bryant RA, O'donnell ML, Creamer M, et al. The psychiatric sequelae of traumatic injury. Am J Psychiatry. 2010;167: 312-20.
5. Fann JR, Burington B, Leonetti A, et al. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch Gen Psychiatry 2004;61: 53.
6. Whelan-Goodinson R, Ponsford J, Johnston L, et al. Psychiatric disorders following traumatic brain injury: their nature and frequency. The J Head Trauma Rehabil 2009;24: 324-32.
7. Rockhill CM, Jaffe K, Zhou C, et al. Health care costs associated with traumatic brain injury and psychiatric illness in adults. J Neurotrauma. 2012;29:1038-46.
8. Rosen JB, Schulkin J. From normal fear to pathological anxiety. Psychol Rev.1998;105:325-50.
9. Klonoff H. Factor analysis of a neuropsychological battery for children aged 9 to 15. Percept Mot Skills. 1971;32:603-16.

10. Moore EL, Terryberry-Spohr L, Hope DA. Mild traumatic brain injury and anxiety sequelae: a review of the literature. Brain Inj. 2006;20:117-32.

11. Rogers JM, Read CA.Psychiatric comorbidity following traumatic brain injury. Brain Inj. 2007;21:1321-33.

12. Byers AL, Yaffe K, Covinsky KE, et al. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. Arch Gen Psychiatry. 2010;67: 489-96.

13. Bromberger JT, Kravitz HM, Chang Y, et al. Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. Menopause. 2013;20:488-95.

14. Olafiranye O, Jean-Louis G, Zizi F, et al. Anxiety and cardiovascular risk: review of epidemiological and clinical evidence. Mind Brain. 2011;2:32-7.

15. Tully PJ, Cosh SM, Baune BT. A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. Psychol Health Med. 2013;18:627-44.

16. Huang C-J, Chiu H-C, Lee M-H, et al. Prevalence and incidence of anxiety disorders in diabetic patients: a national population-based cohort study. Gen Hosp Psychiatry. 2011;33:8-15.

17. Schmieder RE, Grassi G, Kjeldsen SE. Patients with treatment-resistant hypertension report increased stress and anxiety: a worldwide study. J Hypertens. 2013;31:610-5.

18. Smith KJ, Béland M, Clyde M, et al. Association of diabetes with anxiety: A systematic review and meta-analysis. J Psychosom Res. 2013;74:89-99.

19. van Reedt Dortland AK, Giltay EJ, Van Veen T, et al. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. Acta Psychiatr Scand. 2010;122:30-9.

20. van Reedt Dortland AK, Vreeburg SA, Giltay EJ, et al. The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression. Psychoneuroendocrinology. 2013;38:209-18.

21. Kawamoto R, Tabara Y, Kohara K, et al. Increased high-density lipoprotein cholesterol is associated with a high prevalence of pre-hypertension and hypertension in community-dwelling persons. Endocrine 2012;42:321-8.

22. Can ÖD, Ulupinar E, Özkay ÜD, et al. The effect of simvastatin treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet. Behav Pharmacol. 2012;23:582-92.

23. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. Health Aff (Millwood). 2003;22:61-76.

24. Cheng TM. Taiwan's national health insurance system: high value for the dollar. Six Countries, Six Reform Models: Their Healthcare Reform: Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan Hackensack, NJ: World Scientific: 2009;171-204.

25. Chang HY, Yeh WT, Chang YH, et al. Prevalence of dyslipidemia and mean blood lipid values in Taiwan: results from the Nutrition and Health Survey in Taiwan (NAHSIT, 1993-1996). Chin J Physiol. 2002;45:187-98.

26. Chen YC, Yeh HY, Wu JC, et al. Taiwan's National Health Insurance Research Database: administrative health care database as study object in bibliometrics. Scientometrics 2011;86:365-80.

27. Chung SD, Lin HC. Association between chronic prostatitis/chronic pelvic pain syndrome and anxiety disorder: a population-based study. PLoS One 2013;8:e64630.

28. Hiott DW, Labbate L. Anxiety disorders associated with traumatic brain injuries. NeuroRehabilitation 2002;17:345-55.

29. Chiu WT, Yeh K, Li YC, Gan Y, Chen H-Y, et al. Traumatic brain injury registry in Taiwan. Neurol Res. 1997;19:261-4.

30. Einvik G, Ekeberg O, Lavik JG, et al. et al. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. J Psychosom Res 2010;68:567-72.

31. Vogelzangs N, Beekman A, de Jonge P, et al. Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry. 2013;3: e249.

32. Salim S, Chugh G, Asghar M. Inflammation in anxiety. Adv Protein Chem Struct Biol 2012;88:1-25.

33. Esmaillzadeh A, Azadbakht L. Increased levels of inflammation among women with enlarged waist and elevated triglyceride concentrations. Ann Nutr Metab. 2010;57:77-84.

34. Hoge E, Brandstetter K, Moshier S, et al. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depress Anxiety. 2009;26:447-55.

35. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51:8-19.

36. McLean CP, Asnaani A, Litz BT, et al. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res.2011;45:1027-35.

37. Kendler KS, Neale MC, Kessler RC, et al. Generalized anxiety disorder in women: a population-based twin study. Arch Gen Psychiatry. Archives of General Psychiatry 1992;49:267-72.

38. Jensvold M, Halbreich U, Hamilton J, eds. Psychopharmacolgy and women: sex, gender, and hormones. Washington, DC: American Psychiatric Press; 1996.

39. Shear MK. Anxiety disorders in women: gender-related modulation of neurobiology and behavior. Semin Reprod Endocrinol. 1997;15:69-76.

40. Dratva J, Real FG, Schindler C, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. Menopause 2009;16: 385-94.

Figure Legends

Figure 1. Overall prevalence of new-onset anxiety disorders for traumatic brain injury patients with/without pre-existing hyperlipidemia.

Figure 2. Kaplan-Meier plot for traumatic brain injury patients with anxiety disorders by hyperlipidemia.

Tables

Table 1. Demographics and clinical characteristics of traumatic brain injury patients with and without pre-existing hyperlipidemia

Table 2. Incidence of anxiety disorders in traumatic brain injury patients with and without pre-existing hyperlipidemia

Table 3. Incidence of anxiety disorders in traumatic brain injury patients stratified by age group

Table 4. Adjusted hazard ratios for anxiety disorders in traumatic brain injury patients with hyperlipidemia

Table 1. Demographics and clinical characteristics of traumatic brain injury patients with and without pre-existing hyperlipidemia

	TBIs with hyperlipidemia (N=1274)	TBIs without hyperlipidemia (N=2548)	p-value*
Age (mean±SD)	59.45±15.37	59.45±15.37	0.9991
Age Group			
<=35	82(6.44)	164(6.44)	1.0000
35~50	274(21.51)	548(21.51)	
50~65	399(31.32)	797(31.28)	
>65	519(40.74)	1039(40.78)	
Gender			
Male	860(67.50)	1720(67.50)	1.0000
Female	414(32.50)	828(32.50)	
Hypertension			
Yes	557(43.72)	425(16.68)	<.0001
No	717(56.28)	2123(83.32)	
Diabetes mellitus			
Yes	446(35.01)	217(8.52)	<.0001
No	828(64.99)	2331(91.48)	
Cardiovascular disease			
Yes	201(15.78)	135(5.30)	<.0001
No	1073(84.22)	2413(94.70)	
Anxiety disorders			
Yes	137(10.75)	177(6.95)	<.0001
No	1137(89.25)	2371(93.05)	
Time to anxiety disorders (years)			
Median(IQR)	2.40(0.93-4.42)	2.70 (0.91-4.81)	0.3968

TBI= traumatic brain injury; SD= standard deviation; IQR= interquartile range.
*the p-value was determined by Student's t-test or Wilcoxon test for continuous variables and Pearson's chi-square test for categorical variables.

Table 2. Incidence of anxiety disorders in traumatic brain injury patients with and without pre-existing hyperlipidemia

	TBI with hyperlipidemia				TBI without hyperlipidemia				IRR* (95% CI)	Crude HR (95% CI)	Adjusted** HR (95% CI)
	N	ADs	PY	IR	N	ADs	PY	IR			
Total	1274	137	7217.41	189.82	2548	177	14890.15	118.87	1.60(1.28-2.00)□	1.58(1.27-1.98)□	1.58(1.24-2.02)□
Age											
<=35	82	7	651.46	107.45	164	8	1335.06	59.92	1.79(0.65-4.94)	1.00(ref.)	1.00(ref.)
35~50	274	29	1779.58	162.96	548	36	3657.26	98.43	1.66(1.02-2.70)$	1.47(0.84-2.58)	1.33(0.75-2.33)
50~65	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10(1.44-3.07)□	1.87(1.09-3.21)$	1.52(0.88-2.64)
>65	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22(0.86-1.75)	1.82(1.07-3.11)$	1.43(0.82-2.49)
Gender											
Male	860	70	4925.39	142.12	1720	93	9997.31	93.03	1.53(1.12-2.08)$	1.00(ref.)	1.00(ref.)
Female	414	67	2292.02	292.32	828	84	4892.85	171.68	1.70(1.24-2.35)$	1.90(1.52-2.37)□	1.84(1.47-2.30)□
Hypertension											
No	717	78	4517.91	172.65	2123	144	12891.99	111.70	1.55(1.17-2.04)$	1.00(ref.)	1.00(ref.)
Yes	557	59	2699.50	218.56	425	33	1998.16	165.15	1.32(0.86-2.03)	1.43(1.12-1.82)$	1.16(0.88-1.54)
Diabetes Mellitus											
No	828	95	4995.69	190.16	2331	164	13814.23	118.72	1.60(1.24-2.06)□	1.00(ref.)	1.00(ref.)
Yes	446	42	2221.72	189.04	217	13	1075.93	120.83	1.56(0.84-2.91)	1.14(0.85-1.52)	0.80(0.58-1.10)
Cardiovascular Disease											
No	1073	114	6119.97	186.28	2413	163	14189.06	114.88	1.62(1.28-2.06)□	1.00(ref.)	1.00(ref.)
Yes	201	23	1097.44	209.58	135	14	701.10	199.69	1.05(0.54-2.04)	1.47(1.05-2.08)$	1.20(0.83-1.75)

TBI= traumatic brain injury; ADs= anxiety disorders; PY=person-year; IR= incidence rate, per 10,000 person-years; IRR= incidence rate ratio; HR= hazard ratio; CI= confidence interval; ref.= reference group.

*Estimated with Poisson regression.

**The model was adjusted by age, gender, hypertension, diabetes mellitus, and cardiovascular disease.

□:P<.001; $: P<.05

Table 3. Incidence of anxiety disorders in traumatic brain injury patients stratified by age group

	TBI with Hyperlipidemia				TBI without Hyperlipidemia				IRR* (95% CI)	Adjusted** HR(95% CI)
	N	ADs	PY	Rate	N	ADs	PY#	Rate		
Age<35										
Total	82	7	651.46	107.45	164	8	1335.06	59.92	1.79(0.65-4.94)	2.63(0.58-4.71)
Male	72	7	591.77	118.29	144	8	1217.52	65.71	1.80(0.65-4.96)	1.00(ref.)
Female	10	0	59.69	0.00	20	0	117.53	0.00	N/A	N/A
Age: 35~50										
Total	274	29	1779.58	162.96	548	36	3657.26	98.43	1.66(1.02-2.70)$	1.42(0.82-2.47)
Male	208	16	1359.21	117.72	417	18	2751.44	65.42	1.80(0.92-3.53)	1.00(ref.)
Female	66	13	420.36	309.26	131	18	905.82	198.72	1.56(0.76-3.18)	2.81(1.73-4.58)□
Age: 50~65										
Total	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10(1.44-3.07)□	2.54(1.68-3.83)□
Male	249	20	1344.10	148.80	495	23	2752.23	83.57	1.78(0.98-3.24)	1.00(ref.)
Female	150	33	7847.11	420.86	302	30	1718.87	174.53	2.41(1.47-3.95)□	2.44(1.65-3.60)□
Age: >65										
Total	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22(0.86-1.75)	1.13(0.77-1.67)
Male	331	27	1630.31	165.61	664	44	3276.11	134.31	1.23(0.76-1.99)	1.00(ref.)
Female	188	21	1027.85	204.31	375	36	2150.63	167.39	1.22(0.71-2.09)	1.30(0.92-1.85)

TBI= traumatic brain injury; ADs= anxiety disorders; PY=person-year; IR= incidence rate, per 10,000 person-years; IRR= incidence rate ratio; HR= hazard ratio; CI= confidence interval; ref.= reference group; N/A= Not available.

*Estimated with Poisson regression.

**The model was adjusted by gender, hypertension, diabetes mellitus, and cardiovascular disease.

□:P<.001; $: P<.05

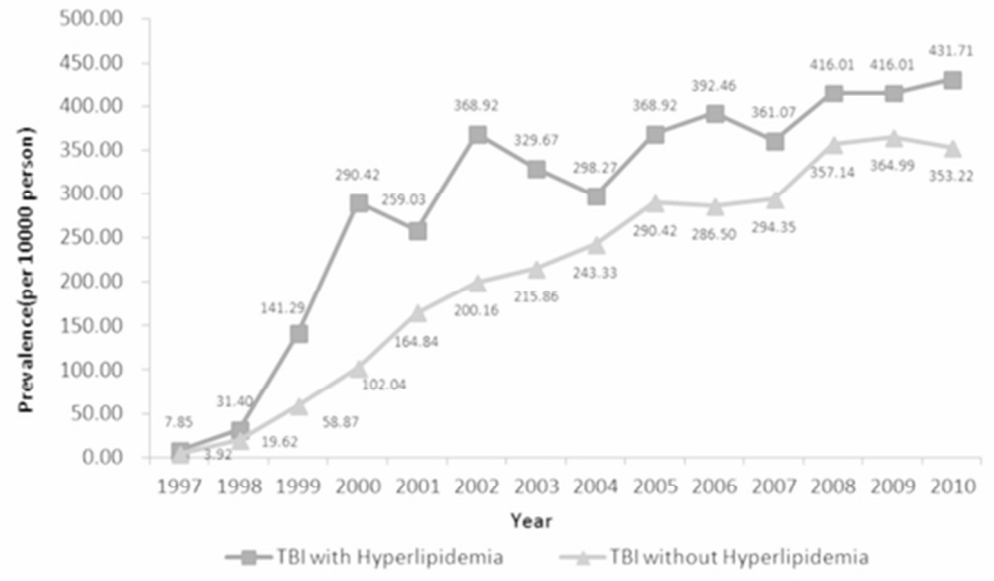
Table 4. Adjusted hazard ratios for anxiety disorders in traumatic brain injury patients with hyperlipidemia

Adjusted* HR (95% CI)	Overall	<=35 only	35~50 only	50~65 only	>65 only	Female only
Age Group						
<=35	1.00 (ref.)					--
35~50	1.27 (0.55-2.92)					1.65 (0.80-3.41)
50~65	1.62 (0.72-3.66)					2.04 (1.17-3.57)$
>65	1.12 (0.49-2.59)					1.00 (ref.)
Gender						
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
Female	1.97 (1.40-2.77)$	--	2.53 (1.21-5.27)$	2.97 (1.70-5.21)$	1.27 (0.72-2.26)	
Hypertension						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.14 (0.78-1.68)	11.73 (1.37-100.58)$	2.45 (1.08-5.55)$	0.61 (0.32-1.14)	1.39 (0.75-2.60)	1.17 (0.69-1.98)
Diabetes Mellitus						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.81 (0.55-1.19)	--	1.06 (0.47-2.42)	0.59 (0.30-1.14)	0.97 (0.54-1.76)	0.86 (0.50-1.47)
Cardiovascular disease						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.18 (0.73-1.90)	--	1.51 (0.44-5.21)	1.86 (0.80-4.37)	0.96 (0.50-1.85)	1.05 (0.50-2.22)

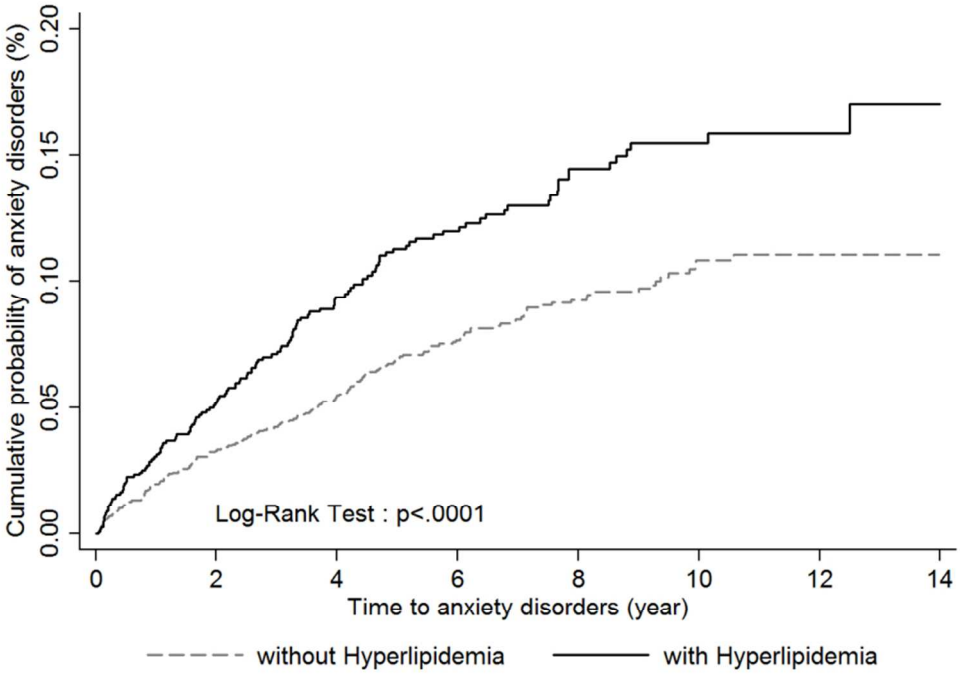
HR= hazard ratio; CI= confidence interval; ref.= reference group; N/A= Not available.

**The model was adjusted by hypertension, diabetes mellitus, and cardiovascular disease.

$p<0.05



46x27mm (300 x 300 DPI)



80x58mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract " Pre-existing hyperlipidemia increased the risk of new-onset anxiety disordersafter traumatic brain injury - A 14-year population-based study", **page1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found The abstract included objective, setting, participant, results, and conclusion in **page2-3**.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported All presented on the part of introduction, **Page4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses " the aim of this study was to evaluate the risk factors for developing ADs in TBI patients with or without previous hyperlipidemia ", **Page5**
Methods		
Study design	4	Present key elements of study design early in the paper "a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected", **page6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection All of the above criteria is in the part of "study selection", **Page5-6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up " data were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan between January 1997 and December 2010.", **page5** "The study protocol was as follows: patients with a diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010 were selected. Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis.", **Page6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed " a 1:2 age- and gender- matched ", **page6** & "A total of 3822 adult patients were enrolled in this study.", page8; "TBI with hyperlipidemia=1274 & TBI without hyperlipidemia=2548", **Table1, page21**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable "The diagnostic criteria was based on " the International Classifications of Disease-9 (ICD-9-CM)", **page5**; " diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010; Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis; The event of ADs was defined as three times of outpatient visits or one inpatient admission with a AD diagnosis (ICD-9-CM code: 300.xx were included but 300.04 was excluded) between the date of

		TBI diagnosis and December 31, 2010. The baseline comorbidities prior to TBI, including hypertension (HTN; ICD-9-CM code: 401~405,437.2, and 362.11), diabetes mellitus (DM; ICD-9-CM code: 250, 357.2, 362.0, and 366.41), and cardiovascular disease (CAD; ICD-9-CM code: 410~414)", **page5-6**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group " To estimate the risk of ADs, demographic and clinical information, including age, sex, hyperlipidemia, DM, HTN, and CAD, were obtained directly from each subject's file in the NHI insurance database. Age was classified into four categories: □35, 35–50, 50-65 and ≥65 years old.", **page6**
Bias	9	Describe any efforts to address potential sources of bias " To avoid potential confounders, a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected.", **page6**
Study size	10	Explain how the study size was arrived at " We accessed the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Subjects were selected from the partial sample of the 1 million individuals.", **page5-6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why " Age was classified into four categories: ≦35, 35–50, 50-65 and ≥65 years old.", **page6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding All of the above criteria is in the part of " Statistical analysis", **Page5-7**
		(*b*) Describe any methods used to examine subgroups and interactions None, there is no subgroups in this study.
		(*c*) Explain how missing data were addressed None. The missing data were excluded before selecting the enrolled subjects.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed " the subjects who died were considered censored, and the censoring date was their date of mortality.", **page7**
		(*e*) Describe any sensitivity analyses None

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed This study applied the clams dataset, so we did not have above information.
		(b) Give reasons for non-participation at each stage "The NHIRD covers 99% of inpatient and outpatient medical benefit claims for Taiwan's 23 million residents.", **page5.** In addition, this study applied the clams dataset, so we did not have above information.
		(c) Consider use of a flow diagram None.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders "Table 1 shows the distribution of demographical variables between TBI patients with and without hyperlipidemia. A total of 3822 adult patients were enrolled in this study. After matching by age and gender, group differences in comorbidity of HTN, DM, and CAD were determined. ", **page7.**
		(b) Indicate number of participants with missing data for each variable of interest None.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) " The overall follow-up median time is 5.44 years (IQR: 2.20-9.07)." , **page7**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time " TBI patients with hyperlipidemia (10.75%) had significantly more ADs than TBI patients without hyperlipidemia (6.95%).TBI patients with hyperlipidemia developed new-onset ADs (median: 2.40 years, interquartile range [IQR]: 0.93-4.42) earlier than TBI patients without hyperlipidemia (median: 2.70 years, IQR: 0.91-4.81).", **page7**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included " The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years.", **page8; "**TBI patients with hyperlipidemia have a 1.58-fold (95% CI: 1.24-2.02) risk of ADs compared with TBI patients without hyperlipidemia, even when controlling for age, sex, HTN, DM, and CAD.", **page8**
		(*b*) Report category boundaries when continuous variables were categorized None.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period All information presented on the part of results, **page7-9.**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses None.
Discussion		
Key results	18	Summarise key results with reference to study objectives " To the best of our knowledge, this is the first study to demonstrate that pre-existing

		hyperlipidemia, especially in females aged 35-65 years, is an independent risk factor for developing new-onset ADs after TBI.", **page9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias " There are several limitations to our study. First, the diagnoses, including ADs and other comorbidities, all relied on the claims data and ICD-9-CM diagnosis codes; thus, some disease misclassifications may exist. Second, we did not evaluate socioeconomic status, which may influence the development of ADs. Finally, information regarding the severity of TBI and hyperlipidemia were unavailable, which may also intervene the occurrence of ADs.", **page12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence All information presented on the part of discussion, **Page9-12**
Generalisability	21	Discuss the generalisability (external validity) of the study results " Pre-existing hyperlipidemia is an independent predictor for new-onset ADs after TBI. Hyperlipidemic women, specifically aged between 35~65 years, had a significantly higher risk of new-onset ADs compared with men after TBI. Therefore, it is suggested that physicians should pay more attention to the plasma hyperlipidemia level of high-risk patients to prevent the development of ADs after TBI.", **page13**.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based "No current external funding sources for this study.", **page14**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pre-existing hyperlipidemia increased the risk of new-onset anxiety disorders after traumatic brain injury - A 14-year population-based study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005269.R1
Article Type:	Research
Date Submitted by the Author:	13-Jun-2014
Complete List of Authors:	Ho, Chung-Han; ChiMei medical center, Medica lresearch Hsieh, Kuang-Yang; ChiMei medical center, Psychiatry Liang, Fu-Wen; National Cheng Kung University, Public Health Li, Chia-Jung; National Cheng Kung University, Psychiatry Wang, Jhi-Joung; ChiMei Medical center, medical research Chio, Chung-Ching; ChiMei Medical center, Neurosurgery Chang, Chin-Hung; Chimei medical center, Neurosurgery Kuo, Jinn-Rung; Southern Taiwan University of Science and Technology, Biotechnology; Chi-Mei Medical Center, Neurosurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Epidemiology
Keywords:	Neurosurgery < SURGERY, PSYCHIATRY, Anxiety disorders < PSYCHIATRY

Title: Pre-existing hyperlipidemia increased the risk of new-onset anxiety disorders after traumatic brain injury - A 14-year population-based study

Running title: Hyperlipidemia and anxiety after brain injury

*Chung-Han Ho, PhD [a,e], *Kuang-Yang Hsieh, MD, PhD [b, f], Fu-Wen Liang, PhD [d], Chia-Jung, Li, MD [g], Jhi-Joung Wang, MD, PhD [a], Chung-Ching Chio, MD [a,c], Chin-Hung, Chang, MD [a], Jinn-Rung Kuo, MD, PhD [a,c, f]

Departments of [a]Medical Research, [b]Psychiatry, [c]Neurosurgery, Chi-Mei Medical Center, Tainan, Taiwan

[d]Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[e]Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

[f]Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan

[g]Departments of Psychiatry, National Cheng-Kung University, Tainan, Taiwan

Corresponding author: Jinn-Rung Kuo, Department of Neurosurgery, Traumatic Brain Center, Chi-Mei Medical Center, #901, Jong-Hwa Road, Yung-Kung City, 710, Tainan, Taiwan

Telephone: +886-6-281-2811 ext. 9

Fax: +886-6-282-8928

E-mail: kuojinnrung@gmail.com

Word count: 2787

References number: 40

ABSTRACT

Objectives: Anxiety disorders (ADs) are common after traumatic brain injury (TBI). However, the risk factors of new-onset ADs remain unclear. This study was aimed at evaluating the incidence and risk factors for new-onset ADs, including pre-existing hyperlipidemia and three major comorbidities (diabetes mellitus, hypertension, and cardiovascular disease), in TBI patients.

Setting: A matched cohort study was conducted using the Taiwan Longitudinal Health Insurance Database between January 1997 and December 2010.

Participants: A total of 3822 subjects (1274 TBI patients with hyperlipidemia and 2548 age- and gender-matched TBI patients without hyperlipidemia).

Outcome measures: The incidence and hazard ratios (HR) for the development of new-onset ADs after TBI were compared between the two groups.

Results: The overall incidence rate of new-onset ADs for TBI patients with hyperlipidemia is 142.03 per 10,000 person-years. TBI patients with hyperlipidemia have a 1.60-fold incidence rate ratio ($p<0.0001$) and increased HR of ADs (1.58, 95% confidence interval: 1.24-2.02) compared with those without hyperlipidemia. 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). Stratified by age group, hyperlipidemia is a risk factor of ADs for TBI patients aged 65 years or younger.

Conclusions: Pre-existing hyperlipidemia is an independent predictor of new-onset ADs in TBI patients, even when controlling for other demographic and clinical variables. Female patients with pre-existing hyperlipidemia had significantly higher risk of new-onset ADs than males, especially between the ages of 35 and 65 years.

Key Words: Hyperlipidemia; traumatic brain injury; anxiety disorders;

comorbidities; population-based

Strengths and limitations of this study

.To our knowledge, there are no published studies investigating the risk of new-onset anxiety in TBI patients with hyperlipidemia based on the population database.

.The information that hyperlipidemia is an independent risk factor of new-onset anxiety after TBI may play a role in preventive medicine.

.In the claims data, disease was recorded using ICD-9-CM which may be misclassified.

. As a retrospective observational study, our results could be biased by unrecognised confounders which may influence the development of anxiety after TBI.

Introduction

Traumatic brain injury (TBI) remains high incidence rate and is a major cause of death and disability in humans. 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]

However, the assessment and treatment of TBI typically focus on physical and cognitive impairments, even though neuropsychiatric impairments represent significant causes of disability.[6] TBI can result in various neuropsychiatric disorders, including cognitive impairments, depression or anxiety disorders, and behavioral problems. These post-TBI neuropsychiatric impairments contribute to disability after TBI, which becomes a chronic problem for an estimated 3.17 million in the United States.[7] Therefore, evaluating the risk factors associated with the new-onset psychiatric problem after TBI is an important issue in the field of neuropsychiatry.

The risk of developing neuropsychiatric disorders after TBI ranges from 21% to 65%.[8-10] TBI patients with psychiatric disorders were associated with significantly greater costs (approximately 3.39 times) than TBI patients without psychiatric disorders; hence, TBI represents a major public health issue.[11] Anxiety disorders (ADs), one of the common psychiatric disorders, is defined as worrying about the future state of arousal with the feeling of a non-specific threat;[12] the prevalence of ADs is 11%–70% in patients with TBI.[9, 13-15] However, the risk factors of new-onset ADs after TBI remain unclear.

Beside TBI insults, age,[16] sex,[17] cardiovascular disease (CAD),[18, 19] hypertension (HTN),[20, 21] diabetes mellitus (DM),[20, 22] and hyperlipidemia are risk factors associated with ADs. [23, 24] Among these AD risk factors, hyperlipidemia was also related to the

risk of CAD, DM,[20] and HTN.[25] It has been reported that taking anti-hyperlipidemia drugs, such as Statin, could restore anxiety-like deficits after TBI in an animal model.[26] Furthermore, hyperlipidemia has been considered associated with depression in general condition. [27] However, to the best of our knowledge, few studies have examined the association between hyperlipidemia and the risk of new-onset ADs in TBI patients.

So far, the incidence and risk factors of new-onset AD symptoms in TBI patients with hyperlipidemia remain unclear. Therefore, the aim of this study was to evaluate the risk factors for developing ADs in TBI patients with or without previous hyperlipidemia using data from the nationwide database of the National Health Insurance (NHI) Program in Taiwan (1997–2010). We attempted to clarify the long-term effects of pre-existing hyperlipidemia on new-onset ADs among TBI patients. We propose that awareness of the incidence and risk factors for new-onset ADs in TBI patients can improve not only one's understanding of the sequelae of brain injury but also patient treatment and the rehabilitation protocol.

Methods

Data sources and researches

In this study, data were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan between January 1997 and December 2010. The NHIRD covers 99% of inpatient and outpatient medical benefit claims for Taiwan's 23 million residents. The database comprises detailed information regarding clinical visits for each insured subject, including diagnostic codes according to the clinical modification of the International Classifications of Disease-9 (ICD-9-CM) and prescription details.[28, 29] For a population-base medical research purpose, the NHIRD has released a database of medical claims of 1,000,000 random subjects, approximately 4.3% of the population in various studies. All datasets can be

interlinked through each individual's unique personal identification number. The Institutional Review Board of Chi-Mei Medical Center approved this study for exemption.

Study Details

We accessed the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Subjects were selected from the partial sample of the 1 million individuals. The study protocol was as follows: patients with a diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010 were selected. Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis. Since hyperlipidemia was often in men aged older than 35 and women older than 55,[30] a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected for avoiding potential confounders.

To avoid potential confounders, a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected. The event of ADs was defined as three times of outpatient visits or one inpatient admission with a AD diagnosis (ICD-9-CM code: 300.xx were included but 300.4 : dysthymic disorder was excluded) between the date of TBI diagnosis and December 31, 2010. 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. This method of selection has been used extensively in various published studies using the Taiwan NHIRD. [31-33] The baseline comorbidities prior to TBI, including HTN (ICD-9-CM code: 401~405,437.2, and 362.11), DM (ICD-9-CM code: 250, 357.2, 362.0, and 366.41), and CAD (ICD-9-CM code: 410~414), were determined, as these diagnoses are

important factors affecting episodes of mental disorders.

To estimate the risk of ADs, demographic and clinical information, including age, sex, hyperlipidemia, DM, HTN, and CAD, were obtained directly from each subject's file in the NHI insurance database. Age was classified into four categories: ≦35, 35–50, 50-65 and ≥65 years old.

Statistical analysis

Pearson's chi-square test was used to analyze distribution differences in age group, gender, AD, HTN, DM, and CAD between TBI patients with and without hyperlipidemia. Student's t-test and the Wilcoxon rank-sum test were used to compare age at first TBI diagnosis and time to ADs, respectively.

The incidence rate of ADs was calculated from the number of TBI patients with ADs divided by the total person-years as rates per 10,000 person-years of observation. The Poisson regression was applied to calculate the incidence rate ratios of ADs with 95% confidence intervals between TBI patients with/without Hyperlipidemia. In addition, the Kaplan-Meier failure plot was applied to describe the cumulative incidence rate of ADs; the log-rank test was used to compare the risk difference between two groups. The relative risks adjusted for potential confounding variables were estimated by the Cox regression. In the survival analysis, the subjects who died were considered censored, and the censoring date was their date of mortality. The statistical software, Statistical Analysis System (SAS) (version 9.3; SAS Institute, Inc, Cary, NC), was used to perform all statistical analyses. Kaplan-Meier curves were generated using STATA (version 12; Stata Corp. *College Station*, TX). All significance levels were set at *P*-value <0.05.

Results

Table 1 shows the distribution of demographical variables between TBI patients with and without hyperlipidemia. A total of 3822 adult patients were enrolled in this

study. After matching by age and gender, group differences in comorbidity of HTN, DM, and CAD were determined. TBI patients with hyperlipidemia (10.75%) had significantly more ADs than TBI patients without hyperlipidemia (6.95%). TBI patients with hyperlipidemia developed new-onset ADs (median: 2.40 years, interquartile range [IQR]: 0.93-4.42) earlier than TBI patients without hyperlipidemia (median: 2.70 years, IQR: 0.91-4.81). The overall follow-up median time is 5.44 years (IQR: 2.20-9.07).

Figure 1 shows the prevalence of ADs for TBI patients with hyperlipidemia increased from 7.85 per 10,000 in 1997 to 431.71 per 10,000 in 2010. The estimated prevalence of ADs among TBI patients without hyperlipidemia is consistently lower than those with hyperlipidemia.

The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years. Table 2 shows that TBI patients with hyperlipidemia have a 1.60-fold incidence rate ratio of ADs compared with TBI patients without hyperlipidemia. The TBI patients aged 35~65 years had a significant difference in the ADs incidence ratio between patients with/without hyperlipidemia. 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). There was no significant difference in the incidence rate of ADs in patients with comorbid HTN, DM, or CAD compared with those without the aforementioned comorbidities. TBI patients with hyperlipidemia have a 1.58-fold (95% CI: 1.24-2.02) risk of ADs compared with TBI patients without hyperlipidemia, even when controlling for age, sex, HTN, DM, and CAD. Females have a 1.84-fold (95% CI: 1.47-2.30) risk of ADs compared with male TBI patients.

In addition, TBI patients with hyperlipidemia were more likely to experience ADs than those without hyperlipidemia in any given month during the follow-up.

The Kaplan-Meier plot (Figure 2) indicated that TBI patients with hyperlipidemia developed ADs more quickly than those without hyperlipidemia. The cumulative probability of ADs in hyperlipidemia patients was 3.00% (95% C.I.: 2.17%-4.14%) at one-year, 7.10 % (95% C.I.: 5.72%-8.79%) at three-years, 11.26% (95% C.I.: 9.43%-13.42%) at five-years, and 15.35% (95% C.I.: 12.98%-18.09%) at 10 years; in patients without hyperlipidemia, the cumulative probability of ADs was 1.92% (95% C.I.: 1.44%-5.26%) at one-year, 4.17% (95% C.I.: 3.41%-5.10%) at three-years, 6.83% (95% C.I.: 5.79%-8.05%) at five-years, and 10.83% (95% C.I.: 9.28%-12.62%) at 10 years.

As we stratified by age group (Table 3), the ratio of incidence rate was significantly different between TBI patients with and without hyperlipidemia for females aged 50~65 years. However, in the same age group, no significant difference was observed between male TBI patients with and without hyperlipidemia. Compared with TBI patients without hyperlipidemia, all age groups show the increased hazards for TBI patients with hyperlipidemia, but only patients between the ages of 50~65 were significantly different. Furthermore, females aged 35~50 years and 50~65 years had a 2.81-fold (95% C.I.: 1.73-4.58) and 2.44-fold (95% C.I.: 1.65-3.60) risk of ADs, respectively, compared with males.

Table 4 shows the adjusted hazard ratios of ADs for TBI patients with hyperlipidemia. Female TBI patients with hyperlipidemia presented a 1.97-fold (95% C.I.: 1.40-2.77) risk of ADs compared with males. Stratified by age group, females aged 35~50 and 50~65 years had an increased risk of ADs compared with males (HR: 2.53, 95% C.I.: 1.21-5.27, and HR: 2.97, 95% C.I.: 1.70-5.21, respectively). Further, the TBI females aged 50~65 years have a higher risk (2.04, 95% C.I.: 1.17-3.57) than older females (age>65).

Discussion

To the best of our knowledge, this is the first study to demonstrate that pre-existing hyperlipidemia, especially in females aged 35-65 years, is an independent risk factor for developing new-onset ADs after TBI. Because the NHIRD covers nearly 99% of inpatient and outpatient medical benefit claims for the 23 million residents in Taiwan, these results closely approximate the true distribution of ADs among TBI patients with pre-existing hyperlipidemia in Taiwan. This information is critical to alter the course of and prevent TBI-related disability.

Our findings were consistent with previous study that ADs are common in the general population and may be even more common in individuals with traumatic brain injuries.[34] In our 14-year population-based study, we found that the prevalence of ADs in TBI patients with hyperlipidemia increased from 7.85 per 10,000 in 1997 to 431.71 per 10,000 in 2010. We also found the incidence of new-onset ADs in pre-existing hyperlipidemia after TBI is 10.75% and 189.43 per 10,000 person-years, the overall cumulative ADs rate is 17.62%, and approximately 43% of ADs cases occurred within two years after TBI, which were all significant when compared with TBI patients without hyperlipidemia (p<.0001). The incidence rate of ADs supports the validity of the high prevalence rate of ADs among TBI patients with pre-existing hyperlipidemia. These results imply these individuals are at increased risk for AD after TBI and pre-existing hyperlipidemia may play an important role in the development of new-onset ADs after TBI.

In Taiwan, the prevalence of hyperlipidemia for adults ranged from 10.2% to 13.4%.[33] The incidence rate of TBI was 344 per 100,000 people in Taiwan.[5] To the best of our knowledge, this is the first study to show the prevalence of ADs for TBI patients with pre-existing hyperlipidemia. The fact that the prevalence of ADs for TBI patients continually increased over 14 years highlights the possible characteristics of

ADs for TBI patients. 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,[35] 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. Importantly, the prevalence of ADs in TBI patients with pre-existing hyperlipidemia was always higher than that in patients without hyperlipidemia. Therefore, the physicians including neurosurgeon, critical care physician, psychiatrists, physiatrists, caregivers can expect to see more TBI patients who have pre-existing hyperlipidemia in daily practice. At present, TBI is a major cause of death and neuropsychiatric disability in humans and remains a public health challenge. Whether the treatment of hyperlipidemia prior to a TBI event helps improve post-traumatic new-onset ADs is worth exploring.

Furthermore, in a three year interventional study, the researchers found awareness of hyperlipidemia had no effect on anxiety.[36] In contrast, the other study indicated that simvastatin, an anti-hyperlipidemia drug, caused significant anxiolytic effects in animals.[26] In the current study, we did not investigate the impact of anti-hyperlipidemia medications in pre-existing hyperlipidemic patients before TBI, as the data were unavailable. However, in our study, we emphasize that physicians should pay more attention on the plasma hyperlipidemia level of high-risk patients to prevent the occurrence of ADs after TBI in daily practice. Well-controlled hyperlipidemia may attenuate the risk of developing ADs if a TBI has occurred.

In our study, we further elucidated and provided novel findings that pre-existing hyperlipidemia is an independent risk factor for new-onset ADs after TBI, even when we controlled for DM, HTN and CAD. Therefore, hyperlipidemia's neuropathological effects on the development of ADs after TBI should be investigated. Vogelzangs et al. reported an elevation in the systemic inflammation

biomarker C-reactive protein in individuals with a late-onset anxiety disorder.[37] Salim et al. also demonstrated that anxiety is associated with neuroinflammation.[38] Esmaillzadeh et al. showed a positive association between hyperlipidemia and markers of systemic inflammation and endothelial dysfunction.[39] Furthermore, inflammatory actions of the neuroimmune system may contribute to the development of anxiety disorders following TBI.[40] Taken together, we suppose that the inflammatory entity of hyperlipidemia could aggravate new-onset ADs developed after TBI. Despite our results, there remains insufficient evidence to conclude what the role of the neuropathological consequences of pre-existing hyperlipidemia may play in the development of new-onset ADs after TBI. However, we propose post-injury anti-inflammation therapy may be a clinically useful strategy to prevent new-onset ADs in humans. This hypothesis should be investigated in the future.

Our study found that hyperlipidemic women, specifically aged between 35 and 65 years, had an increased risk of new-onset ADs after TBI compared to men. In a two-year national general population survey of comorbidity, the researchers found that the lifetime prevalence rates for ADs were 30.5% for women and 19.2% for men; women were more likely to develop ADs in their lifetime compared with men.[41] The other studies reported the male to female prevalence ratios of ADs for 12-month and lifetime were 1:1.79 and 1:1.7, respectively.[42] The possible explanations as to the greater susceptibility of women to ADs may be multifactorial. For example, genetic or environmental factors,[43] the difference of absorption and distribution after specific anti-anxiety drug administration (psycho pharmacokinetic) during the treatment of women with anxiety disorders,[44] and female reproductive hormones, such as estrogen, may play a protective role in the development of ADs in women.[18, 45] Thus, our results are consistent with previous reports which showed that TBI female patients with

hyperlipidemia had a significantly higher risk for ADs than males. Using a subgroup analysis, we further found that TBI females with hyperlipidemia aged 35~50 years and 50~65 years have a significantly increased risk of new-onset ADs (HR: 2.53 and 2.97, respectively) than males. Further, when only females were considered, we found hyperlipidemia females aged 50~65 years have a significantly increased risk of new-onset ADs after TBI (HR: 2.04) than older females (age>65). 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.[46] However, as estrogen levels were unavailable in our study, there is no sufficient evidence could conclude whether estrogen has anti-anxiety effects on the development of new-onset ADs after TBI patients with pre-existing hyperlipidemia. Therefore, we consider the role of estrogen and the interaction between estrogen and hyperlipidemia in ADs development after TBI as a critical issue to evaluate in the future.

There are several limitations to our study. First, the diagnoses, including ADs and other comorbidities, all relied on the claims data and ICD-9-CM diagnosis codes; thus, some disease misclassifications may exist. Second, we did not evaluate socioeconomic status, which may influence the development of ADs after TBI. Third, information regarding the severity of hyperlipidemia was unavailable, which may also intervene the occurrence of ADs. 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.

Conclusions

Pre-existing hyperlipidemia is an independent predictor for new-onset ADs after TBI. Hyperlipidemic women, specifically aged between 35~65 years, had a

significantly higher risk of new-onset ADs compared with men after TBI. Therefore, it is suggested that physicians should pay more attention to the plasma hyperlipidemia level of high-risk patients to prevent the development of ADs after TBI.

Acknowledgement

This study is based in part on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes.

Author Contributions

Conceived and designed the experiments: Chung-Han Ho, Jinn-Rung Kuo, and Kuang-Yang Hsieh. Performed the experiments: Chung-Han Ho, Kuang-Yang Hsieh, Jinn-Rung Kuo, and Chia-Jung, Li. Analyzed the data: Chung-Han Ho, Fu-Wen Liang, Jinn-Rung Kuo, Contributed reagents/materials/analysis tools: Jhi-Joung Wang, Chung-Ching Chio, and Chin-Hung, Chang. Wrote the paper: Chung-Han Ho, Jinn-Rung Kuo, Fu-wen Liang, and Kuang-Yang Hsieh.

Funding

No current external funding sources for this study.

Competing interests

None declared.

Data Sharing Statement

No additional data available

Ethics approval

Institutional Review Board (IRB), Chi-Mei Medical Center, Tainan approved these study for exemption.

References

1. Murray CJ, Lopez AD, Kovacs L, 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. Gururaj G, Sastry Koeluri V, et al.Neurotrauma registry in the nimhans. *National Institute of Mental Health & Neurosciences, Bangalore, India*. 2004
5. Chiu WT, Yeh K, Li Y-C, Gan Y, et al.Traumatic brain injury registry in taiwan. *Neurological research*. 1997;19:261
6. Consensus conference. Rehabilitation of persons with traumatic brain injury. Nih consensus development panel on rehabilitation of persons with traumatic brain injury. *JAMA*. 1999;282:974-983
7. Zaloshnja E, Miller T, Langlois JA, et al. Prevalence of long-term disability from traumatic brain injury in the civilian population of the united states, 2005. *The Journal of Head Trauma Rehabilitation*. 2008;23:394-400
8. Fann JR, Burington B, Leonetti A, et al. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. *Archives of General Psychiatry*. 2004;61:53
9. Whelan-Goodinson R, Ponsford J, Johnston L, Grant F. Psychiatric disorders following traumatic brain injury: Their nature and frequency. *The Journal of Head Trauma Rehabilitation*. 2009;24:324-332
10. Bryant RA, O'donnell ML, Creamer M, et al.The psychiatric sequelae of traumatic injury. *American Journal of Psychiatry*. 2010;167:312-320
11. Rockhill CM, Jaffe K, Zhou C, et al. Health care costs associated with traumatic brain injury and psychiatric illness in adults. *Journal of Neurotrauma*. 2012;29:1038-1046
12. Rosen JB, Schulkin J. From normal fear to pathological anxiety. *Psychological review*. 1998;105:325
13. Klonoff H. Factor analysis of a neuropsychological battery for children aged 9 to 15. *Perceptual and motor skills*. 1971;32:603-616
14. Moore EL, Terryberry-Spohr L, Hope DA. Mild traumatic brain injury and anxiety sequelae: A review of the literature. *Brain Injury*. 2006;20:117-132
15. Rogers JM, Read CA. Psychiatric comorbidity following traumatic brain injury.

Brain Injury. 2007;21:1321-1333

16. Byers AL, Yaffe K, Covinsky KE, et al. High occurrence of mood and anxiety disorders among older adults: The national comorbidity survey replication. *Archives of General Psychiatry*. 2010;67:489
17. Bromberger JT, Kravitz HM, Chang Y, et al.Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. *Menopause*. 2013;20:488-495
18. Olafiranye O, Jean-Louis G, Zizi F, et al.Anxiety and cardiovascular risk: Review of epidemiological and clinical evidence. *Mind & brain: the journal of psychiatry*. 2011;2:32
19. Tully PJ, Cosh SM, Baune BT. A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. *Psychology, health & medicine*. 2013:1-18
20. Huang C-J, Chiu H-C, Lee M-H, et al.Prevalence and incidence of anxiety disorders in diabetic patients: A national population-based cohort study. *General hospital psychiatry*. 2011;33:8-15
21. Schmieder RE, Grassi G, Kjeldsen SE. Patients with treatment-resistant hypertension report increased stress and anxiety: A worldwide study. *Journal of hypertension*. 2013;31:610-615
22. Smith KJ, Béland M, Clyde M, et al. Association of diabetes with anxiety: A systematic review and meta-analysis. *Journal of psychosomatic research*. 2012
23. van Reedt Dortland AK, Giltay EJ, et al.Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *Acta Psychiatrica Scandinavica*. 2010;122:30-39
24. van Reedt Dortland AK, Vreeburg SA, Giltay EJ, et al.The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression. *Psychoneuroendocrinology*. 2013;38:209-218
25. Kawamoto R, Tabara Y, Kohara K, et al.Increased high-density lipoprotein cholesterol is associated with a high prevalence of pre-hypertension and hypertension in community-dwelling persons. *Endocrine*. 2012;42:321-328
26. Can ÖD, Ulupinar E, Özkay ÜD, et al.The effect of simvastatin treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet. *Behavioural Pharmacology*. 2012;23:582-592
27. Chien I, Lin C-H, Chou Y-J, et al.Increased risk of hyperlipidemia in patients with major depressive disorder: A population-based study. *Journal of psychosomatic research*. 2013;75:270-274

28. Cheng T-M. Taiwan's new national health insurance program: Genesis and experience so far. *Health Affairs*. 2003;22:61-76
29. Cheng T-M. Taiwan's national health insurance system: High value for the dollar. *Six Countries, Six Reform Models: Their Healthcare Reform: Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan. Hackensack, NJ: World Scientific*. 2009:171-204
30. Havel RJ, Rapaport E. Management of primary hyperlipidemia. *The New England journal of medicine*. 1995;332:1491-1498
31. Chung SD, Lin HC. Association between chronic prostatitis/chronic pelvic pain syndrome and anxiety disorder: A population-based study. *PloS one*. 2013;8:e64630
32. Chen Y-C, Yeh H-Y, Wu J-C, et al.Taiwan's national health insurance research database: Administrative health care database as study object in bibliometrics. *Scientometrics*. 2011;86:365-380
33. Chang H-Y, Yeh W-T, Chang Y-H, et al. Prevalence of dyslipidemia and mean blood lipid values in taiwan: Results from the nutrition and health survey in taiwan (nahsit, 1993-1996). *Chinese Journal of Physiology*. 2002;45:187-198
34. Hiott DW, Labbate L. Anxiety disorders associated with traumatic brain injuries. *NeuroRehabilitation*. 2002;17:345-355
35. Chien I-C, Chou Y-J, Lin C-H, et al. Prevalence of psychiatric disorders among national health insurance enrollees in taiwan. *Psychiatric Services*. 2004;55:691-697
36. Einvik G, Ekeberg O, Lavik JG, et al. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. *J Psychosom Res*. 2010;68:567-572
37. Vogelzangs N, Beekman A, de Jonge P, et al. Anxiety disorders and inflammation in a large adult cohort. *Translational psychiatry*. 2013;3:e249
38. Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv Protein Chem Struct Biol*. 2012;88:1-25
39. Esmaillzadeh A, Azadbakht L. Increased levels of inflammation among women with enlarged waist and elevated triglyceride concentrations. *Annals of Nutrition and Metabolism*. 2010;57:77-84
40. Hoge E, Brandstetter K, Moshier S, et al.Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depression and anxiety*. 2009;26:447-455
41. Kessler RC, McGonagle KA, Zhao S, et al.Lifetime and 12-month prevalence of dsm-iii-r psychiatric disorders in the united states: Results from the national comorbidity survey. *Archives of General Psychiatry*. 1994;51:8

42. McLean CP, Asnaani A, Litz BT, et al. Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of psychiatric research*. 2011;45:1027-1035
43. Kendler KS, Neale MC, Kessler RC, et al. Generalized anxiety disorder in women: A population-based twin study. *Archives of General Psychiatry*. 1992;49:267
44. Jensvold MF, Halbreich UE, Hamilton JA. *Psychopharmacology and women: Sex, gender, and hormones*. American Psychiatric Association; 1996.
45. Shear MK. Anxiety disorders in women: Gender-related modulation of neurobiology and behavior. *Seminars in reproductive endocrinology*. 1997;15:69
46. Dratva J, Real FG, Schindler C, et al. Is age at menopause increasing across europe? Results on age at menopause and determinants from two population-based studies. *Menopause*. 2009;16:385-394

Figure Legends

Figure 1. Overall prevalence of new-onset anxiety disorders for traumatic brain injury patients with/without pre-existing hyperlipidemia.

Figure 2. Kaplan-Meier plot for traumatic brain injury patients with anxiety disorders by hyperlipidemia.

Tables

Table 1. Demographics and clinical characteristics of traumatic brain injury patients with and without pre-existing hyperlipidemia

Table 2. Incidence of anxiety disorders in traumatic brain injury patients with and without pre-existing hyperlipidemia

Table 3. Incidence of anxiety disorders in traumatic brain injury patients stratified by age group

Table 4. Adjusted hazard ratios for anxiety disorders in traumatic brain injury patients with hyperlipidemia

Table 1. Demographics and clinical characteristics of traumatic brain injury patients with and without pre-existing hyperlipidemia

	TBIs with hyperlipidemia (N=1274)	TBIs without hyperlipidemia (N=2548)	p-value*
Age (mean±SD)	59.45±15.37	59.45±15.37	0.9991
Age Group			
<=35	82(6.44)	164(6.44)	1.0000
35~50	274(21.51)	548(21.51)	
50~65	399(31.32)	797(31.28)	
>65	519(40.74)	1039(40.78)	
Gender			
Male	860(67.50)	1720(67.50)	1.0000
Female	414(32.50)	828(32.50)	
Hypertension			
Yes	557(43.72)	425(16.68)	<.0001
No	717(56.28)	2123(83.32)	
Diabetes mellitus			
Yes	446(35.01)	217(8.52)	<.0001
No	828(64.99)	2331(91.48)	
Cardiovascular disease			
Yes	201(15.78)	135(5.30)	<.0001
No	1073(84.22)	2413(94.70)	
Anxiety disorders			
Yes	137(10.75)	177(6.95)	<.0001
No	1137(89.25)	2371(93.05)	
Time to anxiety disorders (years)			
Median(IQR)	2.40(0.93-4.42)	2.70 (0.91-4.81)	0.3968

TBI= traumatic brain injury; SD= standard deviation; IQR= interquartile range.
*the p-value was determined by Student's t-test or Wilcoxon test for continuous variables and Pearson's chi-square test for categorical variables.

Table 2. Incidence of anxiety disorders in traumatic brain injury patients with and without pre-existing hyperlipidemia

	TBI with hyperlipidemia				TBI without hyperlipidemia				IRR* (95% CI)	Crude HR (95% CI)	Adjusted** HR (95% CI)
	N	ADs	PY	IR	N	ADs	PY	IR			
Total	1274	137	7217.41	189.82	2548	177	14890.15	118.87	1.60(1.28-2.00)‡	1.58(1.27-1.98)‡	1.58(1.24-2.02)‡
Age											
<=35	82	7	651.46	107.45	164	8	1335.06	59.92	1.79(0.65-4.94)	1.00(ref.)	1.00(ref.)
35~50	274	29	1779.58	162.96	548	36	3657.26	98.43	1.66(1.02-2.70)$	1.47(0.84-2.58)	1.33(0.75-2.33)
50~65	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10(1.44-3.07)‡	1.87(1.09-3.21)$	1.52(0.88-2.64)
>65	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22(0.86-1.75)	1.82(1.07-3.11)$	1.43(0.82-2.49)
Gender											
Male	860	70	4925.39	142.12	1720	93	9997.31	93.03	1.53(1.12-2.08)$	1.00(ref.)	1.00(ref.)
Female	414	67	2292.02	292.32	828	84	4892.85	171.68	1.70(1.24-2.35)$	1.90(1.52-2.37)‡	1.84(1.47-2.30)‡
Hypertension											
No	717	78	4517.91	172.65	2123	144	12891.99	111.70	1.55(1.17-2.04)$	1.00(ref.)	1.00(ref.)
Yes	557	59	2699.50	218.56	425	33	1998.16	165.15	1.32(0.86-2.03)	1.43(1.12-1.82)$	1.16(0.88-1.54)
Diabetes Mellitus											
No	828	95	4995.69	190.16	2331	164	13814.23	118.72	1.60(1.24-2.06)‡	1.00(ref.)	1.00(ref.)
Yes	446	42	2221.72	189.04	217	13	1075.93	120.83	1.56(0.84-2.91)	1.14(0.85-1.52)	0.80(0.58-1.10)
Cardiovascular Disease											
No	1073	114	6119.97	186.28	2413	163	14189.06	114.88	1.62(1.28-2.06)‡	1.00(ref.)	1.00(ref.)
Yes	201	23	1097.44	209.58	135	14	701.10	199.69	1.05(0.54-2.04)	1.47(1.05-2.08)$	1.20(0.83-1.75)

TBI= traumatic brain injury; ADs= anxiety disorders; PY=person-year; IR= incidence rate, per 10,000 person-years; IRR= incidence rate ratio; HR= hazard ratio; CI= confidence interval; ref.= reference group.

*Estimated with Poisson regression.

**The model was adjusted by age, gender, hypertension, diabetes mellitus, and cardiovascular disease.

‡:P<.001; $: P<.05

Table 3. Incidence of anxiety disorders in traumatic brain injury patients stratified by age group

	TBI with Hyperlipidemia				TBI without Hyperlipidemia				IRR* (95% CI)	Adjusted** HR(95% CI)
	N	ADs	PY	Rate	N	ADs	PY#	Rate		
Age<35										
Total	82	7	651.46	107.45	164	8	1335.06	59.92	1.79(0.65-4.94)	2.63(0.58-4.71)
Male	72	7	591.77	118.29	144	8	1217.52	65.71	1.80(0.65-4.96)	1.00(ref.)
Female	10	0	59.69	0.00	20	0	117.53	0.00	N/A	N/A
Age: 35~50										
Total	274	29	1779.58	162.96	548	36	3657.26	98.43	1.66(1.02-2.70)$	1.42(0.82-2.47)
Male	208	16	1359.21	117.72	417	18	2751.44	65.42	1.80(0.92-3.53)	1.00(ref.)
Female	66	13	420.36	309.26	131	18	905.82	198.72	1.56(0.76-3.18)	2.81(1.73-4.58)ǂ
Age: 50~65										
Total	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10(1.44-3.07)ǂ	2.54(1.68-3.83)ǂ
Male	249	20	1344.10	148.80	495	23	2752.23	83.57	1.78(0.98-3.24)	1.00(ref.)
Female	150	33	7847.11	420.86	302	30	1718.87	174.53	2.41(1.47-3.95)ǂ	2.44(1.65-3.60)ǂ
Age: >65										
Total	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22(0.86-1.75)	1.13(0.77-1.67)
Male	331	27	1630.31	165.61	664	44	3276.11	134.31	1.23(0.76-1.99)	1.00(ref.)
Female	188	21	1027.85	204.31	375	36	2150.63	167.39	1.22(0.71-2.09)	1.30(0.92-1.85)

TBI= traumatic brain injury; ADs= anxiety disorders; PY=person-year; IR= incidence rate, per 10,000 person-years; IRR= incidence rate ratio; HR= hazard ratio; CI= confidence interval; ref.= reference group; N/A= Not available.

*Estimated with Poisson regression.

**The model was adjusted by gender, hypertension, diabetes mellitus, and cardiovascular disease.

ǂ:P<.001; $: P<.05

Table 4. Adjusted hazard ratios for anxiety disorders in traumatic brain injury patients with hyperlipidemia

Adjusted* HR (95% CI)	Overall	<=35 only	35~50 only	50~65 only	>65 only	Female only
Age Group						
<=35	1.00 (ref.)					--
35~50	1.27 (0.55-2.92)					1.65 (0.80-3.41)
50~65	1.62 (0.72-3.66)					2.04 (1.17-3.57)$
>65	1.12 (0.49-2.59)					1.00 (ref.)
Gender						
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
Female	1.97 (1.40-2.77)$	--	2.53 (1.21-5.27)$	2.97 (1.70-5.21)$	1.27 (0.72-2.26)	
Hypertension						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.14 (0.78-1.68)	11.73 (1.37-100.58)$	2.45 (1.08-5.55)$	0.61 (0.32-1.14)	1.39 (0.75-2.60)	1.17 (0.69-1.98)
Diabetes Mellitus						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.81 (0.55-1.19)	--	1.06 (0.47-2.42)	0.59 (0.30-1.14)	0.97 (0.54-1.76)	0.86 (0.50-1.47)
Cardiovascular disease						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.18 (0.73-1.90)	--	1.51 (0.44-5.21)	1.86 (0.80-4.37)	0.96 (0.50-1.85)	1.05 (0.50-2.22)

HR= hazard ratio; CI= confidence interval; ref.= reference group; N/A= Not available.

**The model was adjusted by hypertension, diabetes mellitus, and cardiovascular disease.

$p<0.05

Title: Pre-existing hyperlipidemia increased the risk of new-onset anxiety disorders after traumatic brain injury - A 14-year population-based study

Running title: Hyperlipidemia and anxiety after brain injury

*Chung-Han Ho, PhD [a,e], *Kuang-Yang Hsieh, MD, PhD [b, f], Fu-Wen Liang, PhD [d], Chia-Jung, Li, MD [g], Jhi-Joung Wang, MD, PhD [a], Chung-Ching Chio, MD [a,c], Chin-Hung, Chang, MD [a], Jinn-Rung Kuo, MD, PhD [a,c, f]

Departments of [a]Medical Research, [b]Psychiatry, [c]Neurosurgery, Chi-Mei Medical Center, Tainan, Taiwan

[d]Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[e]Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

[f]Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan

[g]Departments of Psychiatry, National Cheng-Kung University, Tainan, Taiwan

Corresponding author: Jinn-Rung Kuo, Department of Neurosurgery, Traumatic Brain Center, Chi-Mei Medical Center, #901, Jong-Hwa Road, Yung-Kung City, 710, Tainan, Taiwan

Telephone: +886-6-281-2811 ext. 9

Fax: +886-6-282-8928

E-mail: kuojinnrung@gmail.com

Word count: 2787

References number: 40

ABSTRACT

Objectives: Anxiety disorders (ADs) ~~is~~ are common after traumatic brain injury (TBI). However, the risk factors of new-onset ADs remain unclear. This study was aimed at evaluating the incidence and risk factors for new-onset ADs, including pre-existing hyperlipidemia and three major comorbidities (diabetes mellitus, hypertension, and cardiovascular disease), in TBI patients.

Setting: A matched ~~longitudinal~~ cohort study was conducted using the Taiwan Longitudinal Health Insurance Database between January 1997 and December 2010.

Participants: A total of 3822 subjects (1274 TBI patients with hyperlipidemia and 2548 age- and gender-matched TBI patients without hyperlipidemia).

Outcome measures: The incidence and hazard ratios (HR) for the development of new-onset ADs after TBI were compared between the two groups.

Results: The overall incidence rate of new-onset ADs for TBI patients with hyperlipidemia is 142.03~~102.43~~ per 10,000 person-years. TBI patients with hyperlipidemia have a 1.60-fold incidence rate ratio (p<0.0001) and increased HR of ADs (1.58, 95% confidence interval: 1.24-2.02) compared with those without hyperlipidemia. 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).~~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)~~. Stratified by age group, hyperlipidemia is a risk factor of ADs for TBI patients aged 65 years or younger.

Conclusions: Pre-existing hyperlipidemia is an independent predictor of new-onset ADs in TBI patients, even when controlling for other demographic and clinical

variables. Female patients with pre-existing hyperlipidemia had significantly higher risk of new-onset ADs than males, especially between the ages of 35 and 65 years.

Key Words: Hyperlipidemia; traumatic brain injury; anxiety disorders; comorbidities; population-based

Strengths and limitations of this study

.To our knowledge, there are no published studies investigating the risk of new-onset anxiety in TBI patients with hyperlipidemia based on the population database.

.The information that hyperlipidemia is an independent risk factor of new-onset anxiety after TBI may play a role in preventive medicine.

.~~The claims data obtained from ICD-9-CM diagnosis may exist misclassification~~ In the claims data, disease was recorded using ICD-9-CM which may be misclassified.

. As a retrospective observational study, our results could be biased by unrecognised confounders which may influence the development of anxiety after TBI.

Introduction

Traumatic brain injury (TBI) remains high incidence rate and is a major cause of death and disability in humans.

From the global estimation, 57 million people may have been hospitalized with TBIs and about 1.5 million die.[1] Tthe annual incidence of TBI is ~1.7 million in the United States ~~is ~1.7 million.~~[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]

However, the assessment and treatment of TBI typically focus on physical and cognitive impairments, even though neuropsychiatric impairments represent significant causes of disability.[62] TBI can result in various neuropsychiatric disorders, including cognitive impairments, depression~~mood~~ or anxiety disorders, and behavioral problems. These post-TBI neuropsychiatric impairments contribute to disability after TBI, which becomes a chronic problem for an estimated 3.17 million in the United States.[73] Therefore, evaluating the risk factors associated with the new-onset psychiatric problem after TBI is an important issue in the field of neuropsychiatry.

The risk of developing neuropsychiatric disorders after TBI ranges from 21% to 65%.[8-104-6] TBI patients with psychiatric disorders were associated with significantly greater costs (approximately 3.39 times) than TBI patients without psychiatric disorders; hence, TBI represents a major public health issue.[117] Anxiety disorders (ADs), one of the common psychiatric disorders, is defined as worrying about the future state of arousal with the feeling of a non-specific threat;[12;8] the prevalence of ADs is 11%–70% in patients with TBI.[9, 13-156, 9-11] However, the risk factors of new-onset ADs after TBI remain unclear.

Beside TBI insults, age,[1612] sex,[17] cardiovascular disease (CAD),[18, 1914, 15]

hypertension (HTN),[20, 21] diabetes mellitus (DM),[20, 22] and hyperlipidemia are risk factors associated with ADs.[23, 24] Among these AD risk factors, hyperlipidemia was also related to the risk of CAD, DM,[20] and hypertensionHTN.[25] Furthermore, It has been reported that taking anti-hyperlipidemia drugs, such as Statin, could restore anxiety-like deficits after TBI in an animal model.[26] Furthermore, hyperlipidemia has been considered associated with depression in general condition.[27] However, to the best of our knowledge, few studies have examined the association between hyperlipidemia and the risk of new-onset ADs in TBI patients.

So farUp to now, the incidence and risk factors of new-onset AD symptoms in TBI patients with hyperlipidemia remain unclear. Therefore, the aim of this study was to evaluate the risk factors for developing ADs in TBI patients with or without previous hyperlipidemia using data from the nationwide database of the National Health Insurance (NHI) Program in Taiwan (1997–2010). We attempted to clarify the long-term effects of pre-existing hyperlipidemia on new-onset ADs among TBI patients. We propose that awareness of the incidence and risk factors for new-onset ADs in TBI patients can improve not only one's understanding of the sequelae of brain injury but also patient treatment and the rehabilitation protocol.

Methods

Data sources and researches

In this study, data were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan between January 1997 and December 2010. The NHIRD covers 99% of inpatient and outpatient medical benefit claims for Taiwan's 23 million residents. The database comprises detailed information regarding clinical visits for each insured subject, including diagnostic codes according to the clinical modification of the International Classifications of Disease-9 (ICD-9-CM) and

prescription details.[28, 29~~23, 24~~] For a population-base medical research purpose, the NHIRD has released a database of medical claims of 1,000,000 random subjects, approximately 4.3% of the population in various studies. All datasets can be interlinked through each individual's unique personal identification number. The Institutional Review Board of Chi-Mei Medical Center approved this study for exemption.

Study Details ~~Study selection~~

We accessed the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Subjects were selected from the partial sample of the 1 million individuals. The study protocol was as follows: patients with a diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010 were selected. Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis. Since hyperlipidemia was often in men aged older than 35 and women older than 55,[30] a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected for avoiding potential confounders.

To avoid potential confounders, a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected. The event of ADs was defined as three times of outpatient visits or one inpatient admission with a AD diagnosis (ICD-9-CM code: 300.xx were included but 300.~~0~~4 : dysthymic disorder was excluded) between the date of TBI diagnosis and December 31, 2010. 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. ~~Patients with a psychiatric disorder (ICD-9-CM codes: 295, 296, 297, 300, and 301) before TBI were~~

~~excluded.~~ This method of selection has been used extensively in various published studies using the Taiwan NHIRD. [31-33][25-27] The baseline comorbidities prior to TBI, including ~~hypertension~~ HTN (ICD-9-CM code: 401~405,437.2, and 362.11), DM~~diabetes mellitus~~ (~~DM;~~ ICD-9-CM code: 250, 357.2, 362.0, and 366.41), and CAD~~cardiovascular disease~~ (~~CAD;~~ ICD-9-CM code: 410~414), were determined, as these diagnoses are important factors affecting episodes of mental disorders.

~~**Data analysis**~~

To estimate the risk of ADs, demographic and clinical information, including age, sex, hyperlipidemia, DM, HTN, and CAD, were obtained directly from each subject's file in the NHI insurance database. Age was classified into four categories: ≦35, 35–50, 50-65 and ≥65 years old.

Statistical analysis

Pearson's chi-square test was used to analyze distribution differences in age group, gender, AD, HTN, DM, and CAD between TBI patients with and without hyperlipidemia. Student's t-test and the Wilcoxon rank-sum test were used to compare age at first TBI diagnosis and time to ADs, respectively.

The incidence rate of ADs was calculated from the number of TBI patients with ADs divided by the total person-years as rates per 10,000 person-years of observation. The Poisson regression was applied to calculate the incidence rate ratios of ADs with 95% confidence intervals between TBI patients with/without Hyperlipidemia. In addition, the Kaplan-Meier failure plot was applied to describe the cumulative incidence rate of ADs; the log-rank test was used to compare the risk difference between two groups. The relative risks adjusted for potential confounding variables were estimated by the Cox regression. In the survival analysis, the subjects who died were considered censored, and the censoring date was their date of mortality. The statistical software, Statistical Analysis System (SAS) (version 9.3;

SAS Institute, Inc, Cary, NC), was used to perform all statistical analyses. Kaplan-Meier curves were generated using STATA (version 12; Stata Corp. *College Station*, TX). All significance levels were set at *P*-value <0.05.

Results

Table 1 shows the distribution of demographical variables between TBI patients with and without hyperlipidemia. A total of 3822 adult patients were enrolled in this study. After matching by age and gender, group differences in comorbidity of HTN, DM, and CAD were determined. TBI patients with hyperlipidemia (10.75%) had significantly more ADs than TBI patients without hyperlipidemia (6.95%). TBI patients with hyperlipidemia developed new-onset ADs (median: 2.40 years, interquartile range [IQR]: 0.93-4.42) earlier than TBI patients without hyperlipidemia (median: 2.70 years, IQR: 0.91-4.81). The overall follow-up median time is 5.44 years (IQR: 2.20-9.07).

Figure 1 shows the prevalence of ADs for TBI patients with hyperlipidemia increased from 7.85 per 10,000 in 1997 to 431.71 per 10,000 in 2010. The estimated prevalence of ADs among TBI patients without hyperlipidemia is consistently lower than those with hyperlipidemia.

The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years. Table 2 shows that TBI patients with hyperlipidemia have a 1.60-fold incidence rate ratio of ADs compared with TBI patients without hyperlipidemia. The TBI patients aged 35~65 years had a significant difference in the ADs incidence ratio between patients with/without hyperlipidemia. 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). There was no significant difference in the incidence rate of ADs in patients with comorbid HTN, DM, or CAD compared with those without the aforementioned comorbidities. TBI patients with

hyperlipidemia have a 1.58-fold (95% CI: 1.24-2.02) risk of ADs compared with TBI patients without hyperlipidemia, even when controlling for age, sex, HTN, DM, and CAD. Females have a 1.84-fold (95% CI: 1.47-2.30) risk of ADs compared with male TBI patients.

In addition, TBI patients with hyperlipidemia were more likely to experience ADs than those without hyperlipidemia in any given month during the follow-up. The Kaplan-Meier plot (Figure 2) indicated that TBI patients with hyperlipidemia developed ADs more quickly than those without hyperlipidemia. The cumulative probability of ADs in hyperlipidemia patients was 3.00% (95% C.I.: 2.17%-4.14%) at one-year, 7.10 % (95% C.I.: 5.72%-8.79%) at three-years, 11.26% (95% C.I.: 9.43%-13.42%) at five-years, and 15.35% (95% C.I.: 12.98%-18.09%) at 10 years; in patients without hyperlipidemia, the cumulative probability of ADs was 1.92% (95% C.I.: 1.44%-5.26%) at one-year, 4.17% (95% C.I.: 3.41%-5.10%) at three-years, 6.83% (95% C.I.: 5.79%-8.05%) at five-years, and 10.83% (95% C.I.: 9.28%-12.62%) at 10 years.

As we stratified by age group (Table 3), the ratio of incidence rate was significantly different between TBI patients with and without hyperlipidemia for females aged 50~65 years. However, in the same age group, no significant difference was observed between male TBI patients with and without hyperlipidemia. Compared with TBI patients without hyperlipidemia, all age groups show the increased hazards for TBI patients with hyperlipidemia, but only patients between the ages of 50~65 were significantly different. Furthermore, females aged 35~50 years and 50~65 years had a 2.81-fold (95% C.I.: 1.73-4.58) and 2.44-fold (95% C.I.: 1.65-3.60) risk of ADs, respectively, compared with males.

Table 4 shows the adjusted hazard ratios of ADs for TBI patients with hyperlipidemia. Female TBI patients with hyperlipidemia presented a 1.97-fold

(95% C.I.: 1.40-2.77) risk of ADs compared with males. Stratified by age group, females aged 35~50 and 50~65 years had an increased risk of ADs compared with males (HR: 2.53, 95% C.I.: 1.21-5.27, and HR: 2.97, 95% C.I.: 1.70-5.21, respectively). Further, the TBI females aged 50~65 years have a higher risk (2.04, 95% C.I.: 1.17-3.57) than older females (age>65).

Discussion

To the best of our knowledge, this is the first study to demonstrate that pre-existing hyperlipidemia, especially in females aged 35-65 years, is an independent risk factor for developing new-onset ADs after TBI. Because the NHIRD covers nearly 99% of inpatient and outpatient medical benefit claims for the 23 million residents in Taiwan, these results closely approximate the true distribution of ADs among TBI patients with pre-existing hyperlipidemia in Taiwan. This information is critical to alter the course of and prevent TBI-related disability.

Our findings were consistent with previous study that ADs are common in the general population and may be even more common in individuals with traumatic brain injuries.[34~~28~~] In our 14-year population-based ~~longitudinal~~ study, we found that the prevalence of ADs in TBI patients with hyperlipidemia increased from 7.85 per 10,000 in 1997 to 431.71 per 10,000 in 2010. [32]We also found the incidence of new-onset ADs in pre-existing hyperlipidemia after TBI is 10.75% and 189.43 per 10,000 person-years, the overall cumulative ADs rate is 17.62%, and approximately 43% of ADs cases occurred within two years after TBI, which were all significant when compared with TBI patients without hyperlipidemia (p<.0001). The incidence rate of ADs supports the validity of the high prevalence rate of ADs among TBI patients with pre-existing hyperlipidemia. These results imply ~~patients with hyperlipidemia may~~ these individuals are at increased risk for AD ~~have the trait to develop ADs~~ after TBI and pre-existing hyperlipidemia may play an important role in

the development of new-onset ADs after TBI.

In Taiwan, the prevalence of hyperlipidemia for adults ranged from 10.2% to 13.4%.[31] The incidence rate of TBI was 344 per 100,000 people in Taiwan.[5] To the best of our knowledge, this is the first study to show the prevalence of ADs for TBI patients with pre-existing hyperlipidemia. The fact that the prevalence of ADs for TBI patients continually increased over 14 years highlights the possible characteristics of ADs for TBI patients. 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,[35] 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. Importantly, the prevalence of ADs in TBI patients with pre-existing hyperlipidemia was always higher than that in patients without hyperlipidemia. Therefore, the physicians including neurosurgeon, critical care physician, psychiatrists, physiatrists, caregivers can expect to see more TBI patients who have pre-existing hyperlipidemia in daily practice. At present, TBI is a major cause of death and neuropsychiatric disability in humans and remains a public health challenge. Whether the treatment of hyperlipidemia prior to a TBI eventepisode helps improve post-traumatic new-onset ADs is worth exploring.

Furthermore, in a three year interventional study, the researchers found awareness of hyperlipidemia had no effect on anxiety.[3630] In contrast, the other study indicated that simvastatin, an anti-hyperlipidemia drug, caused significant anxiolytic effects in animals.[2624]In the current study, we did not investigate the impact of anti-hyperlipidemia medications in pre-existing hyperlipidemic patients before TBI, as the data were unavailable. However, in our study, we emphasize that physicians should pay more attention on the plasma hyperlipidemia level of high-risk patients to prevent the occurrence of ADs after TBI in daily practice. Well-controlled

hyperlipidemia may attenuate the risk of developing ADs if a TBI has occurred. ~~In the general population, in addition to hyperlipidemia,[20] several studies have demonstrated that Besides CAD,[14,14,15] hypertension,[16,17] DM,[16,18] and TBI[6,10,11] are risk factors for the development of ADs,. iI~~In our study, we further elucidated and provided novel findings that pre-existing hyperlipidemia is an independent risk factor for new-onset ADs after TBI, even when we controlled for DM, ~~hypertension~~ HTN and CAD. Therefore, hyperlipidemia's neuropathological effects on the development of ADs after TBI should be investigated. Vogelzangs et al. reported an elevation in the systemic inflammation biomarker C-reactive protein in individuals with a late-onset anxiety disorder.[37~~31~~] Salim et al. also demonstrated that anxiety is associated with neuroinflammation.[38~~32~~] Esmaillzadeh et al. showed a positive association between hyperlipidemia and markers of systemic inflammation and endothelial dysfunction.[39~~33~~] Furthermore, inflammatory actions of the neuroimmune system may contribute to the development of anxiety disorders following TBI.[40~~34~~] Taken together, we suppose that the inflammatory entity of hyperlipidemia could aggravate new-onset ADs developed after TBI. Despite our results, there remains insufficient evidence to conclude what the role of the neuropathological consequences of pre-existing hyperlipidemia may play in the development of new-onset ADs after TBI. However, we propose post-injury anti-inflammation therapy may be a clinically useful strategy to prevent new-onset ADs in humans. This hypothesis should be investigated in the future.

Our study found that hyperlipidemic women, specifically aged between 35 and 65 years, had an increased risk of new-onset ADs after TBI compared to men. In a two-year national general population survey of comorbidity, the researchers found that the lifetime prevalence rates for ADs were 30.5% for women and 19.2% for men; women were more likely to develop ADs in their lifetime compared with men.[41~~35~~] The

other studies reported the male to female prevalence ratios of ADs for 12-month and lifetime were 1:1.79 and 1:1.7, respectively.[42~~36~~] The possible explanations as to the greater susceptibility of women to ADs may be multifactorial. For example, genetic or environmental factors,[43~~37~~] the difference of absorption and distribution after specific anti-anxiety drug administration (psycho pharmacokinetic)~~ differences~~ during the treatment of women with anxiety disorders,[44~~38~~] and female reproductive hormones, such as estrogen, may play a protective role in the development of ADs in women.[18, 45~~1439~~] Thus, our results are consistent with previous reports which showed that TBI female patients with hyperlipidemia had a significantly higher risk for ADs than males. Using a subgroup analysis, we further found that TBI females with hyperlipidemia aged 35~50 years and 50~65 years have a significantly increased risk of new-onset ADs (HR: 2.53 and 2.97, respectively) than males. Further, when only females were considered, we found hyperlipidemia females aged 50~65 years have a significantly increased risk of new-onset ADs after TBI (HR: 2.04) than older females (age>65). ~~Because n~~ 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.[46]~~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.~~ However, as estrogen levels were unavailable in our study, there is no sufficient evidence could conclude whether estrogen has anti-anxiety effects on the development of new-onset ADs after TBI patients with pre-existing hyperlipidemia. Therefore, we consider the role of estrogen and the interaction between estrogen and hyperlipidemia in ADs development after TBI as a critical issue to evaluate in the future.

There are several limitations to our study. First, the diagnoses, including ADs and other comorbidities, all relied on the claims data and ICD-9-CM diagnosis codes;

thus, some disease misclassifications may exist. Second, we did not evaluate socioeconomic status, which may influence the development of ADs after TBI. Third, ~~Finally,~~ information regarding the severity of ~~TBI and~~ hyperlipidemia was~~ere~~ unavailable, which may also intervene the occurrence of ADs. 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.

Conclusions

Pre-existing hyperlipidemia is an independent predictor for new-onset ADs after TBI. Hyperlipidemic women, specifically aged between 35~65 years, had a significantly higher risk of new-onset ADs compared with men after TBI. Therefore, it is suggested that physicians should pay more attention to the plasma hyperlipidemia level of high-risk patients to prevent the development of ADs after TBI.

Acknowledgement

This study is based in part on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes.

Author Contributions

Conceived and designed the experiments: Chung-Han Ho, Jinn-Rung Kuo, and Kuang-Yang Hsieh. Performed the experiments: Chung-Han Ho, Kuang-Yang Hsieh, Jinn-Rung Kuo, and Chia-Jung, Li. Analyzed the data: Chung-Han Ho, Fu-Wen

Liang, Jinn-Rung Kuo, Contributed reagents/materials/analysis tools: Jhi-Joung Wang, Chung-Ching Chio, and Chin-Hung, Chang. Wrote the paper: Chung-Han Ho, Jinn-Rung Kuo, Fu-wen Liang, and Kuang-Yang Hsieh.

Funding

No current external funding sources for this study.

Competing interests

None declared.

Ethics approval

Institutional Review Board (IRB), Chi-Mei Medical Center, Tainan approved these study.

References

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. Gururaj G, Sastry Koeluri V, Chandramouli B, Subbakrishna D. Neurotrauma registry in the nimhans. *National Institute of Mental Health & Neurosciences, Bangalore, India*. 2004
5. 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
6. Consensus conference. Rehabilitation of persons with traumatic brain injury. Nih consensus development panel on rehabilitation of persons with traumatic brain injury. *JAMA*. 1999;282:974-983
7. Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the united states, 2005. *The Journal of Head Trauma Rehabilitation*. 2008;23:394-400
8. Fann JR, Burington B, Leonetti A, Jaffe K, Katon WJ, Thompson RS. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. *Archives of General Psychiatry*. 2004;61:53
9. Whelan-Goodinson R, Ponsford J, Johnston L, Grant F. Psychiatric disorders following traumatic brain injury: Their nature and frequency. *The Journal of Head Trauma Rehabilitation*. 2009;24:324-332
10. Bryant RA, O'donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. *American Journal of Psychiatry*. 2010;167:312-320
11. Rockhill CM, Jaffe K, Zhou C, Fan M-Y, Katon W, Fann JR. Health care costs associated with traumatic brain injury and psychiatric illness in adults. *Journal of Neurotrauma*. 2012;29:1038-1046
12. Rosen JB, Schulkin J. From normal fear to pathological anxiety. *Psychological review*. 1998;105:325
13. Klonoff H. Factor analysis of a neuropsychological battery for children aged 9 to 15. *Perceptual and motor skills*. 1971;32:603-616

14. Moore EL, Terryberry-Spohr L, Hope DA. Mild traumatic brain injury and anxiety sequelae: A review of the literature. *Brain Injury*. 2006;20:117-132
15. Rogers JM, Read CA. Psychiatric comorbidity following traumatic brain injury. *Brain Injury*. 2007;21:1321-1333
16. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: The national comorbidity survey replication. *Archives of General Psychiatry*. 2010;67:489
17. Bromberger JT, Kravitz HM, Chang Y, Randolph JF, Jr., Avis NE, Gold EB, et al. Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. *Menopause*. 2013;20:488-495
18. Olafiranye O, Jean-Louis G, Zizi F, Nunes J, Vincent M. Anxiety and cardiovascular risk: Review of epidemiological and clinical evidence. *Mind & brain: the journal of psychiatry*. 2011;2:32
19. Tully PJ, Cosh SM, Baune BT. A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. *Psychology, health & medicine*. 2013:1-18
20. Huang C-J, Chiu H-C, Lee M-H, Wang S-Y. Prevalence and incidence of anxiety disorders in diabetic patients: A national population-based cohort study. *General hospital psychiatry*. 2011;33:8-15
21. Schmieder RE, Grassi G, Kjeldsen SE. Patients with treatment-resistant hypertension report increased stress and anxiety: A worldwide study. *Journal of hypertension*. 2013;31:610-615
22. Smith KJ, Béland M, Clyde M, Gariépy G, Pagé V, Badawi G, et al. Association of diabetes with anxiety: A systematic review and meta-analysis. *Journal of psychosomatic research*. 2012
23. van Reedt Dortland AK, Giltay EJ, Van Veen T, Zitman FG, Penninx BW. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *Acta Psychiatrica Scandinavica*. 2010;122:30-39
24. van Reedt Dortland AK, Vreeburg SA, Giltay EJ, Licht CM, Vogelzangs N, van Veen T, et al. The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression. *Psychoneuroendocrinology*. 2013;38:209-218
25. Kawamoto R, Tabara Y, Kohara K, Miki T, Abe M, Kusunoki T. Increased high-density lipoprotein cholesterol is associated with a high prevalence of pre-hypertension and hypertension in community-dwelling persons. *Endocrine*. 2012;42:321-328
26. Can ÖD, Ulupinar E, Özkay ÜD, Yegin B, Öztürk Y. The effect of simvastatin

treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet. *Behavioural Pharmacology*. 2012;23:582-592

27. Chien I, Lin C-H, Chou Y-J, Chou P. Increased risk of hyperlipidemia in patients with major depressive disorder: A population-based study. *Journal of psychosomatic research*. 2013;75:270-274
28. Cheng T-M. Taiwan's new national health insurance program: Genesis and experience so far. *Health Affairs*. 2003;22:61-76
29. Cheng T-M. Taiwan's national health insurance system: High value for the dollar. *Six Countries, Six Reform Models: Their Healthcare Reform: Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan. Hackensack, NJ: World Scientific*. 2009:171-204
30. Havel RJ, Rapaport E. Management of primary hyperlipidemia. *The New England journal of medicine*. 1995;332:1491-1498
31. Chang H-Y, Yeh W-T, Chang Y-H, Tsai K-S, Pan W-H. Prevalence of dyslipidemia and mean blood lipid values in taiwan: Results from the nutrition and health survey in taiwan (nahsit, 1993-1996). *Chinese Journal of Physiology*. 2002;45:187-198
32. Chen Y-C, Yeh H-Y, Wu J-C, Haschler I, Chen T-J, Wetter T. Taiwan's national health insurance research database: Administrative health care database as study object in bibliometrics. *Scientometrics*. 2011;86:365-380
33. Chung SD, Lin HC. Association between chronic prostatitis/chronic pelvic pain syndrome and anxiety disorder: A population-based study. *PloS one*. 2013;8:e64630
34. Hiott DW, Labbate L. Anxiety disorders associated with traumatic brain injuries. *NeuroRehabilitation*. 2002;17:345-355
35. 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
36. Einvik G, Ekeberg O, Lavik JG, Ellingsen I, Klemsdal TO, Hjerkinn EM. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. *J Psychosom Res*. 2010;68:567-572
37. Vogelzangs N, Beekman A, de Jonge P, Penninx B. Anxiety disorders and inflammation in a large adult cohort. *Translational psychiatry*. 2013;3:e249
38. Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv Protein Chem Struct Biol*. 2012;88:1-25
39. Esmaillzadeh A, Azadbakht L. Increased levels of inflammation among

women with enlarged waist and elevated triglyceride concentrations. *Annals of Nutrition and Metabolism*. 2010;57:77-84

40. Hoge E, Brandstetter K, Moshier S, Pollack M, Wong K, Simon N. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depression and anxiety*. 2009;26:447-455
41. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of dsm-iii-r psychiatric disorders in the united states: Results from the national comorbidity survey. *Archives of General Psychiatry*. 1994;51:8
42. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of psychiatric research*. 2011;45:1027-1035
43. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Generalized anxiety disorder in women: A population-based twin study. *Archives of General Psychiatry*. 1992;49:267
44. Jensvold MF, Halbreich UE, Hamilton JA. *Psychopharmacology and women: Sex, gender, and hormones*. American Psychiatric Association; 1996.
45. Shear MK. Anxiety disorders in women: Gender-related modulation of neurobiology and behavior. *Seminars in reproductive endocrinology*. 1997;15:69
46. Dratva J, Real FG, Schindler C, Ackermann-Liebrich U, Gerbase MW, Probst-Hensch NM, et al. Is age at menopause increasing across europe? Results on age at menopause and determinants from two population-based studies. *Menopause*. 2009;16:385-394

Figure Legends

Figure 1. Overall prevalence of new-onset anxiety disorders for traumatic brain injury patients with/without pre-existing hyperlipidemia.

Figure 2. Kaplan-Meier plot for traumatic brain injury patients with anxiety disorders by hyperlipidemia.

Tables

Table 1. Demographics and clinical characteristics of traumatic brain injury patients with and without pre-existing hyperlipidemia

Table 2. Incidence of anxiety disorders in traumatic brain injury patients with and without pre-existing hyperlipidemia

Table 3. Incidence of anxiety disorders in traumatic brain injury patients stratified by age group

Table 4. Adjusted hazard ratios for anxiety disorders in traumatic brain injury patients with hyperlipidemia

Table 1. Demographics and clinical characteristics of traumatic brain injury patients with and without pre-existing hyperlipidemia

	TBIs with hyperlipidemia (N=1274)	TBIs without hyperlipidemia (N=2548)	p-value*
Age (mean±SD)	59.45±15.37	59.45±15.37	0.9991
Age Group			
<=35	82(6.44)	164(6.44)	1.0000
35~50	274(21.51)	548(21.51)	
50~65	399(31.32)	797(31.28)	
>65	519(40.74)	1039(40.78)	
Gender			
Male	860(67.50)	1720(67.50)	1.0000
Female	414(32.50)	828(32.50)	
Hypertension			
Yes	557(43.72)	425(16.68)	<.0001
No	717(56.28)	2123(83.32)	
Diabetes mellitus			
Yes	446(35.01)	217(8.52)	<.0001
No	828(64.99)	2331(91.48)	
Cardiovascular disease			
Yes	201(15.78)	135(5.30)	<.0001
No	1073(84.22)	2413(94.70)	
Anxiety disorders			
Yes	137(10.75)	177(6.95)	<.0001
No	1137(89.25)	2371(93.05)	
Time to anxiety disorders (years)			
Median(IQR)	2.40(0.93-4.42)	2.70 (0.91-4.81)	0.3968

TBI= traumatic brain injury; SD= standard deviation; IQR= interquartile range.
*the p-value was determined by Student's t-test or Wilcoxon test for continuous variables and Pearson's chi-square test for categorical variables.

Table 2. Incidence of anxiety disorders in traumatic brain injury patients with and without pre-existing hyperlipidemia

	TBI with hyperlipidemia				TBI without hyperlipidemia				IRR* (95% CI)	Crude HR (95% CI)	Adjusted** HR (95% CI)
	N	ADs	PY	IR	N	ADs	PY	IR			
Total	1274	137	7217.41	189.82	2548	177	14890.15	118.87	1.60(1.28-2.00)‡	1.58(1.27-1.98)‡	1.58(1.24-2.02)‡
Age											
<=35	82	7	651.46	107.45	164	8	1335.06	59.92	1.79(0.65-4.94)	1.00(ref.)	1.00(ref.)
35~50	274	29	1779.58	162.96	548	36	3657.26	98.43	1.66(1.02-2.70)$	1.47(0.84-2.58)	1.33(0.75-2.33)
50~65	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10(1.44-3.07)‡	1.87(1.09-3.21)$	1.52(0.88-2.64)
>65	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22(0.86-1.75)	1.82(1.07-3.11)$	1.43(0.82-2.49)
Gender											
Male	860	70	4925.39	142.12	1720	93	9997.31	93.03	1.53(1.12-2.08)$	1.00(ref.)	1.00(ref.)
Female	414	67	2292.02	292.32	828	84	4892.85	171.68	1.70(1.24-2.35)$	1.90(1.52-2.37)‡	1.84(1.47-2.30)‡
Hypertension											
No	717	78	4517.91	172.65	2123	144	12891.99	111.70	1.55(1.17-2.04)$	1.00(ref.)	1.00(ref.)
Yes	557	59	2699.50	218.56	425	33	1998.16	165.15	1.32(0.86-2.03)	1.43(1.12-1.82)$	1.16(0.88-1.54)
Diabetes Mellitus											
No	828	95	4995.69	190.16	2331	164	13814.23	118.72	1.60(1.24-2.06)‡	1.00(ref.)	1.00(ref.)
Yes	446	42	2221.72	189.04	217	13	1075.93	120.83	1.56(0.84-2.91)	1.14(0.85-1.52)	0.80(0.58-1.10)
Cardiovascular Disease											
No	1073	114	6119.97	186.28	2413	163	14189.06	114.88	1.62(1.28-2.06)‡	1.00(ref.)	1.00(ref.)
Yes	201	23	1097.44	209.58	135	14	701.10	199.69	1.05(0.54-2.04)	1.47(1.05-2.08)$	1.20(0.83-1.75)

TBI= traumatic brain injury; ADs= anxiety disorders; PY=person-year; IR= incidence rate, per 10,000 person-years; IRR= incidence rate ratio; HR= hazard ratio; CI= confidence interval; ref.= reference group.

*Estimated with Poisson regression.

**The model was adjusted by age, gender, hypertension, diabetes mellitus, and cardiovascular disease.

‡:P<.001; $: P<.05

Table 3. Incidence of anxiety disorders in traumatic brain injury patients stratified by age group

	TBI with Hyperlipidemia				TBI without Hyperlipidemia				IRR* (95% CI)	Adjusted** HR(95% CI)
	N	ADs	PY	Rate	N	ADs	PY#	Rate		
Age<35										
Total	82	7	651.46	107.45	164	8	1335.06	59.92	1.79(0.65-4.94)	2.63(0.58-4.71)
Male	72	7	591.77	118.29	144	8	1217.52	65.71	1.80(0.65-4.96)	1.00(ref.)
Female	10	0	59.69	0.00	20	0	117.53	0.00	N/A	N/A
Age: 35~50										
Total	274	29	1779.58	162.96	548	36	3657.26	98.43	1.66(1.02-2.70)$	1.42(0.82-2.47)
Male	208	16	1359.21	117.72	417	18	2751.44	65.42	1.80(0.92-3.53)	1.00(ref.)
Female	66	13	420.36	309.26	131	18	905.82	198.72	1.56(0.76-3.18)	2.81(1.73-4.58)ǂ
Age: 50~65										
Total	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10(1.44-3.07)ǂ	2.54(1.68-3.83)ǂ
Male	249	20	1344.10	148.80	495	23	2752.23	83.57	1.78(0.98-3.24)	1.00(ref.)
Female	150	33	7847.11	420.86	302	30	1718.87	174.53	2.41(1.47-3.95)ǂ	2.44(1.65-3.60)ǂ
Age: >65										
Total	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22(0.86-1.75)	1.13(0.77-1.67)
Male	331	27	1630.31	165.61	664	44	3276.11	134.31	1.23(0.76-1.99)	1.00(ref.)
Female	188	21	1027.85	204.31	375	36	2150.63	167.39	1.22(0.71-2.09)	1.30(0.92-1.85)

TBI= traumatic brain injury; ADs= anxiety disorders; PY=person-year; IR= incidence rate, per 10,000 person-years; IRR= incidence rate ratio; HR= hazard ratio; CI= confidence interval; ref.= reference group; N/A= Not available.

*Estimated with Poisson regression.

**The model was adjusted by gender, hypertension, diabetes mellitus, and cardiovascular disease.

ǂ:P<.001; $: P<.05

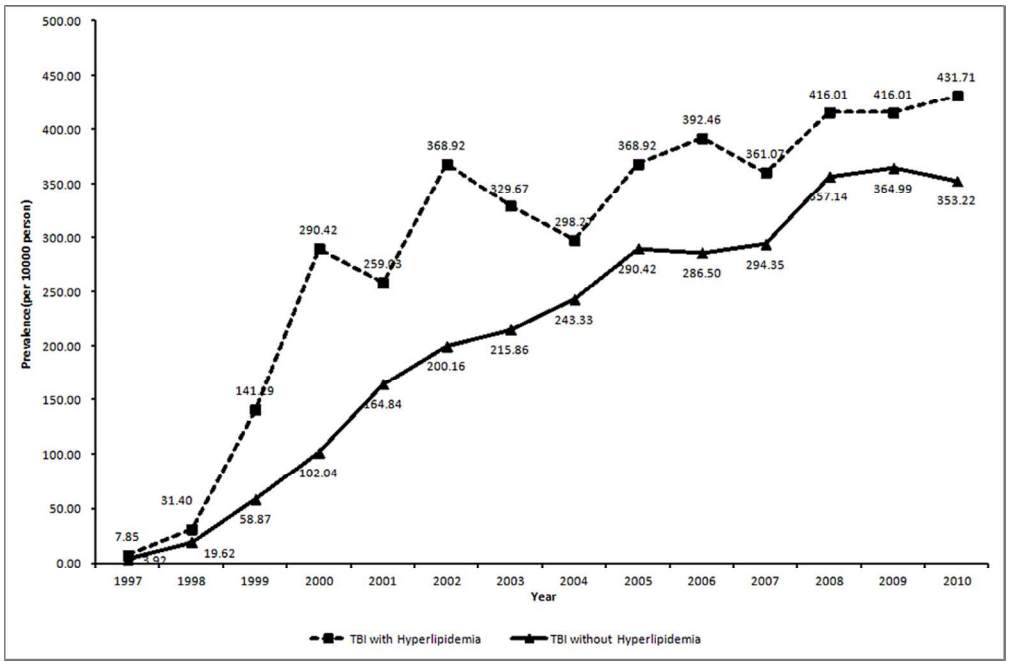
Table 4. Adjusted hazard ratios for anxiety disorders in traumatic brain injury patients with hyperlipidemia

Adjusted* HR (95% CI)	Overall	<=35 only	35~50 only	50~65 only	>65 only	Female only
Age Group						
<=35	1.00 (ref.)					--
35~50	1.27 (0.55-2.92)					1.65 (0.80-3.41)
50~65	1.62 (0.72-3.66)					2.04 (1.17-3.57)$
>65	1.12 (0.49-2.59)					1.00 (ref.)
Gender						
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
Female	1.97 (1.40-2.77)$	--	2.53 (1.21-5.27)$	2.97 (1.70-5.21)$	1.27 (0.72-2.26)	
Hypertension						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.14 (0.78-1.68)	11.73 (1.37-100.58)$	2.45 (1.08-5.55)$	0.61 (0.32-1.14)	1.39 (0.75-2.60)	1.17 (0.69-1.98)
Diabetes Mellitus						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.81 (0.55-1.19)	--	1.06 (0.47-2.42)	0.59 (0.30-1.14)	0.97 (0.54-1.76)	0.86 (0.50-1.47)
Cardiovascular disease						
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.18 (0.73-1.90)	--	1.51 (0.44-5.21)	1.86 (0.80-4.37)	0.96 (0.50-1.85)	1.05 (0.50-2.22)

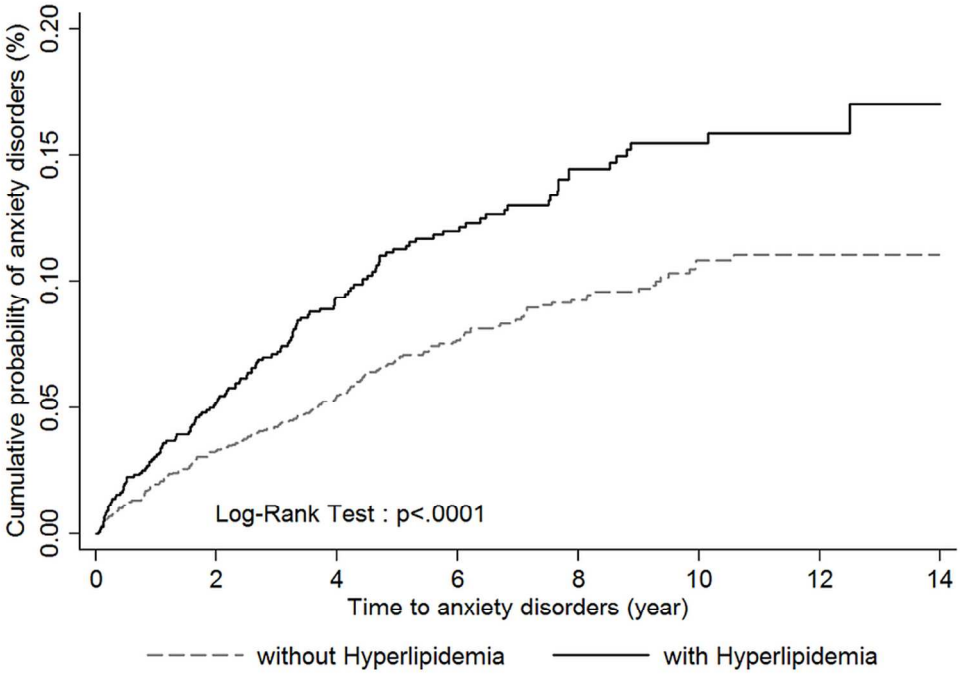
HR= hazard ratio; CI= confidence interval; ref.= reference group; N/A= Not available.

**The model was adjusted by hypertension, diabetes mellitus, and cardiovascular disease.

$p<0.05



90x58mm (300 x 300 DPI)



90x65mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract " Pre-existing hyperlipidemia increased the risk of new-onset anxiety disordersafter traumatic brain injury - A 14-year population-based study", **page1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found The abstract included objective, setting, participant, results, and conclusion in **page2-3**.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported All presented on the part of introduction, **Page4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses " the aim of this study was to evaluate the risk factors for developing ADs in TBI patients with or without previous hyperlipidemia ", **Page5**
Methods		
Study design	4	Present key elements of study design early in the paper "a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected", **page6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection All of the above criteria is in the part of "study selection", **Page5-6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up " data were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan between January 1997 and December 2010.", **page5** "The study protocol was as follows: patients with a diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010 were selected. Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis.", **Page6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed " a 1:2 age- and gender- matched ", **page6** & "A total of 3822 adult patients were enrolled in this study.", page8; "TBI with hyperlipidemia=1274 & TBI without hyperlipidemia=2548", **Table1, page21**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable "The diagnostic criteria was based on " the International Classifications of Disease-9 (ICD-9-CM)", **page5**; " diagnosis of TBI (ICD-9-CM code: 801-804 and 850-854) between 1997 and 2010; Pre-existing hyperlipidemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis; The event of ADs was defined as three times of outpatient visits or one inpatient admission with a AD diagnosis (ICD-9-CM code: 300.xx were included but 300.04 was excluded) between the date of

		TBI diagnosis and December 31, 2010. The baseline comorbidities prior to TBI, including hypertension (HTN; ICD-9-CM code: 401~405,437.2, and 362.11), diabetes mellitus (DM; ICD-9-CM code: 250, 357.2, 362.0, and 366.41), and cardiovascular disease (CAD; ICD-9-CM code: 410~414)", **page5-6**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group " To estimate the risk of ADs, demographic and clinical information, including age, sex, hyperlipidemia, DM, HTN, and CAD, were obtained directly from each subject's file in the NHI insurance database. Age was classified into four categories: ≦35, 35–50, 50-65 and ≥65 years old.", **page6**
Bias	9	Describe any efforts to address potential sources of bias " To avoid potential confounders, a 1:2 age- and gender- matched cohort without pre-existing hyperlipidemia was selected.", **page6**
Study size	10	Explain how the study size was arrived at " We accessed the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Subjects were selected from the partial sample of the 1 million individuals.", **page5-6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why " Age was classified into four categories: ≦35, 35–50, 50-65 and ≥65 years old.", **page6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding All of the above criteria is in the part of " Statistical analysis", **Page5-7**
		(*b*) Describe any methods used to examine subgroups and interactions None, there is no subgroups in this study.
		(*c*) Explain how missing data were addressed None. The missing data were excluded before selecting the enrolled subjects.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed " the subjects who died were considered censored, and the censoring date was their date of mortality.", **page7**
		(*e*) Describe any sensitivity analyses None

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed This study applied the clams dataset, so we did not have above information.
		(b) Give reasons for non-participation at each stage "The NHIRD covers 99% of inpatient and outpatient medical benefit claims for Taiwan's 23 million residents.", **page5.** In addition, this study applied the clams dataset, so we did not have above information.
		(c) Consider use of a flow diagram None.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders "Table 1 shows the distribution of demographical variables between TBI patients with and without hyperlipidemia. A total of 3822 adult patients were enrolled in this study. After matching by age and gender, group differences in comorbidity of HTN, DM, and CAD were determined. ", **page7.**
		(b) Indicate number of participants with missing data for each variable of interest None.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) " The overall follow-up median time is 5.44 years (IQR: 2.20-9.07)." , **page7**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time " TBI patients with hyperlipidemia (10.75%) had significantly more ADs than TBI patients without hyperlipidemia (6.95%).TBI patients with hyperlipidemia developed new-onset ADs (median: 2.40 years, interquartile range [IQR]: 0.93-4.42) earlier than TBI patients without hyperlipidemia (median: 2.70 years, IQR: 0.91-4.81).", **page7**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included " The overall incidence rate of new-onset ADs after TBIs is 142.03 per 10,000 person-years.", **page8; "**TBI patients with hyperlipidemia have a 1.58-fold (95% CI: 1.24-2.02) risk of ADs compared with TBI patients without hyperlipidemia, even when controlling for age, sex, HTN, DM, and CAD.", **page8**
		(*b*) Report category boundaries when continuous variables were categorized None.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period All information presented on the part of results, **page7-9.**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses None.
Discussion		
Key results	18	Summarise key results with reference to study objectives " To the best of our knowledge, this is the first study to demonstrate that pre-existing

		hyperlipidemia, especially in females aged 35-65 years, is an independent risk factor for developing new-onset ADs after TBI.", **page9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias " There are several limitations to our study. First, the diagnoses, including ADs and other comorbidities, all relied on the claims data and ICD-9-CM diagnosis codes; thus, some disease misclassifications may exist. Second, we did not evaluate socioeconomic status, which may influence the development of ADs. Finally, information regarding the severity of TBI and hyperlipidemia were unavailable, which may also intervene the occurrence of ADs.", **page12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence All information presented on the part of discussion, **Page9-12**
Generalisability	21	Discuss the generalisability (external validity) of the study results " Pre-existing hyperlipidemia is an independent predictor for new-onset ADs after TBI. Hyperlipidemic women, specifically aged between 35~65 years, had a significantly higher risk of new-onset ADs compared with men after TBI. Therefore, it is suggested that physicians should pay more attention to the plasma hyperlipidemia level of high-risk patients to prevent the development of ADs after TBI.", **page13**.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based "No current external funding sources for this study.", **page14**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.