

BMJ Open Pre-existing hyperlipidaemia increased the risk of new-onset anxiety disorders after traumatic brain injury: a 14-year population-based study

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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 hyperlipidaemia and three major comorbidities (diabetes mellitus, hypertension and cardiovascular disease), in patients with TBI.

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 participants (1274 patients with TBI with hyperlipidaemia and 2548 age-matched and gender-matched patients with TBI without hyperlipidaemia).

Outcome measures: The incidence and HRs 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 patients with TBI with hyperlipidaemia is 142.03/10 000 person-years (PYs). Patients with TBI with hyperlipidaemia have a 1.60-fold incidence rate ratio ($p<0.0001$) and increased HR of ADs (1.58, 95% CI 1.24 to 2.02) compared with those without hyperlipidaemia. The incidence rates of ADs for males and females with hyperlipidaemia, respectively, were 142.12 and 292.32/10 000 PYs, which were higher than those without hyperlipidaemia (93.03 and 171.68/10 000 PYs, respectively). Stratified by age group, hyperlipidaemia is a risk factor of ADs for patients with TBI aged 65 years or younger.

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

INTRODUCTION

Traumatic brain injury (TBI) has a high incidence rate and is a major cause of death and

Strengths and limitations of this study

- To the best of our knowledge, there are no published studies investigating the risk of new-onset anxiety in traumatic brain injury (TBI) patients with hyperlipidaemia based on the population database.
- The information that hyperlipidaemia 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 International Classifications of Disease-9 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.

disability in humans. From the global estimation, 57 million people may have been hospitalised with TBIs and about 1.5 million die.¹ The annual incidence of TBI is ~1.7 million in the USA.² The yearly incidence of TBI is estimated at 235/100 000 people in the European Union,³ and about 160–344/100 000 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 (ADs) and behavioural problems. These post-TBI neuropsychiatric impairments contribute to disability after TBI, which becomes a chronic problem for an estimated 3.17 million in the USA.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



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65%.^{8–10} Patients with TBI with psychiatric disorders were associated with significantly greater costs (approximately 3.39 times) than patients with TBI without psychiatric disorders; hence, TBI represents a major public health issue.¹¹ ADs, one of the common psychiatric disorders, is defined as worrying about the future state of arousal with the feeling of a non-specific threat¹²; 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.

Besides TBI insults, age,¹⁶ sex,¹⁷ cardiovascular disease (CAD),^{18 19} hypertension (HTN),^{20 21} diabetes mellitus (DM)^{20 22} and hyperlipidaemia are risk factors associated with ADs.^{23 24} Among these AD risk factors, hyperlipidaemia was also related to the risk of CAD, DM²⁰ and HTN.²⁵ It has been reported that taking anti-hyperlipidaemia drugs, such as Statin, could restore anxiety-like deficits after TBI in an animal model.²⁶ Furthermore, hyperlipidaemia has been considered associated with depression in general condition.²⁷ However, to the best of our knowledge, few studies have examined the association between hyperlipidaemia and the risk of new-onset ADs in patients with TBI.

So far, the incidence and risk factors of new-onset AD symptoms in patients with TBI with hyperlipidaemia remain unclear. Therefore, the aim of this study was to evaluate the risk factors for developing ADs in patients with TBI with or without previous hyperlipidaemia using data from the nationwide database of the National Health Insurance (NHI) Programme in Taiwan (1997–2010). We attempted to clarify the long-term effects of pre-existing hyperlipidaemia on new-onset ADs among patients with TBI. We propose that awareness of the incidence and risk factors for new-onset ADs in patients with TBI 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 participant, 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-based medical research purpose, the NHIRD has released a database of medical claims of 1 000 000 random participants, 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. Participants were selected from the partial sample of the one 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 hyperlipidaemia was defined as three times of outpatient visits or one inpatient admission due to hyperlipidaemia (ICD-9-CM code: 272.0, 272.1, 272.2, 272.4) before the TBI diagnosis. Since hyperlipidaemia was often in men aged older than 35 and women older than 55,³⁰ a 1:2 age-gender and gender-matched cohort without pre-existing hyperlipidaemia was selected for avoiding potential confounders.

To avoid potential confounders, a 1:2 age-gender and gender-matched cohort without pre-existing hyperlipidaemia was selected. The event of ADs was defined as three times of outpatient visits or one inpatient admission with an AD diagnosis (ICD-9-CM code: 300.xx were included but 300.4: dysthymic disorder was excluded) between the date of TBI diagnosis and 31 December 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, hyperlipidaemia, 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 χ^2 test was used to analyse distribution differences in age group, gender, AD, HTN, DM and CAD between patients with TBI with and without hyperlipidaemia. Student 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 patients with TBI with ADs divided by the total person-years as rates per 10 000 PYs of observation. The Poisson regression was applied to calculate the incidence rate ratios of ADs with 95% CIs between patients with TBI with/without hyperlipidaemia. 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) (V.9.3; SAS Institute, Inc, Cary, North Carolina, USA), was used to perform all statistical analyses. Kaplan-Meier curves were generated using STATA (V.12; Stata Corp., College Station, Texas, USA). All significance levels were set at p value <0.05 .

RESULTS

Table 1 shows the distribution of demographical variables between patients with TBI with and without hyperlipidaemia. 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. Patients with TBI with hyperlipidaemia (10.75%) had significantly more ADs than patients with TBI without hyperlipidaemia (6.95%). Patients with TBI with hyperlipidaemia developed new-onset ADs (median: 2.40 years, IQR: 0.93–4.42) earlier than patients with TBI without hyperlipidaemia (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 patients with TBI with hyperlipidaemia increased from 7.85/10 000 in 1997 to 431.71/10 000 in 2010. The estimated

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

The overall incidence rate of new-onset ADs after TBIs is 142.03/10 000 PYs. **Table 2** shows that patients with TBI with hyperlipidaemia have a 1.60-fold incidence rate ratio of ADs compared with patients with TBI without hyperlipidaemia. The patients with TBI aged 35–65 years had a significant difference in the ADs incidence ratio between patients with/without hyperlipidaemia. In addition, female patients with TBI with hyperlipidaemia had a higher incidence rate (292.32/10 000 PYs) than males (142.12/10 000 PYs). 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. Patients with TBI with hyperlipidaemia have a 1.58-fold (95% CI 1.24 to 2.02) risk of ADs compared with patients with TBI without hyperlipidaemia, even when controlling for age, sex, HTN, DM and CAD. Females have a 1.84-fold (95% CI 1.47 to 2.30) risk of ADs compared with male patients with TBI.

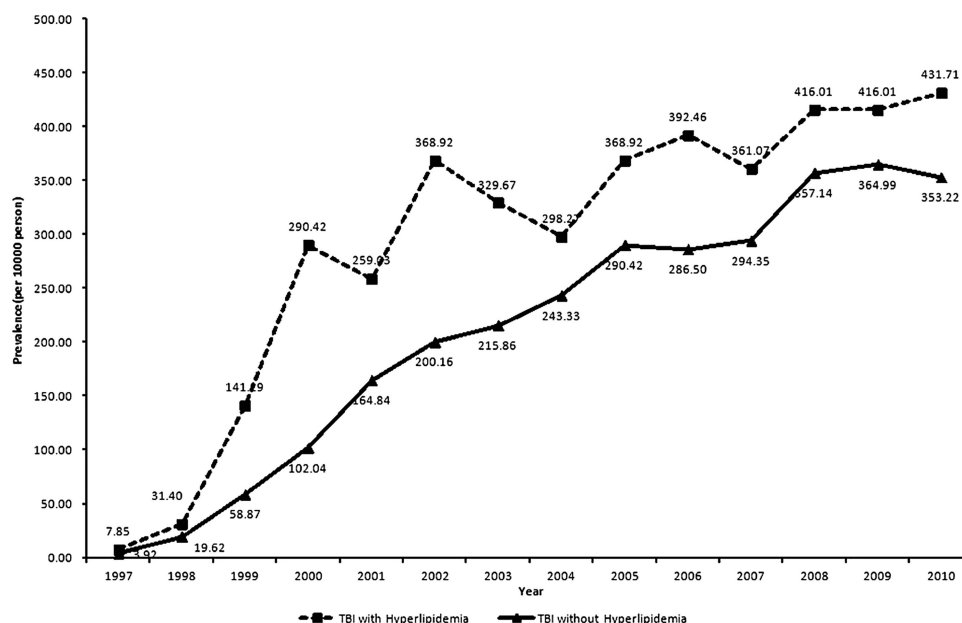
In addition, patients with TBI with hyperlipidaemia were more likely to experience ADs than those without hyperlipidaemia in any given month during the follow-up. The Kaplan-Meier plot (**figure 2**) indicated that patients with TBI with hyperlipidaemia developed ADs more quickly than those without hyperlipidaemia. The cumulative probability of ADs in hyperlipidaemia patients was 3.00% (95% CI 2.17% to 4.14%) at 1 year,

Table 1 Demographics and clinical characteristics of traumatic brain injury (TBI) patients with and without pre-existing hyperlipidaemia

	TBIs with hyperlipidaemia (N=1274)	TBIs without hyperlipidaemia (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)	<0.0001
No	717 (56.28)	2123 (83.32)	
Diabetes mellitus			
Yes	446 (35.01)	217 (8.52)	<0.0001
No	828 (64.99)	2331 (91.48)	
Cardiovascular disease			
Yes	201 (15.78)	135 (5.30)	<0.0001
No	1073 (84.22)	2413 (94.70)	
Anxiety disorders			
Yes	137 (10.75)	177 (6.95)	<0.0001
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

*The p value was determined by Student t test or Wilcoxon test for continuous variables and Pearson's χ^2 test for categorical variables.

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



7.10% (95% CI 5.72% to 8.79%) at 3 years, 11.26% (95% CI 9.43% to 13.42%) at 5 years and 15.35% (95% CI 12.98% to 18.09%) at 10 years; in patients without hyperlipidaemia, the cumulative probability of ADs was 1.92% (95% CI 1.44% to 2.26%) at 1 year, 4.17% (95% CI 3.41% to 5.10%) at 3 years, 6.83% (95% CI 5.79% to 8.05%) at 5 years and 10.83% (95% CI 9.28% to 12.62%) at 10 years.

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

Table 4 shows the adjusted HRs of ADs for patients with TBI with hyperlipidaemia. Female patients with TBI with hyperlipidaemia presented a 1.97-fold (95% CI 1.40 to 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% CI 1.21 to 5.27 and HR: 2.97, 95% CI 1.70 to 5.21, respectively). Further, the TBI females aged 50–65 years have a higher risk (2.04, 95% CI 1.17 to 3.57) than older females (age >65).

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate that pre-existing hyperlipidaemia, 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 patients with TBI with pre-existing hyperlipidaemia 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 patients with TBI with hyperlipidaemia increased from 7.85/10 000 in 1997 to 431.71/10 000 in 2010. We also found the incidence of new-onset ADs in pre-existing hyperlipidaemia after TBI is 10.75% and 189.43/10 000 PYs, the overall cumulative ADs rate is 17.62%, and approximately 43% of ADs cases occurred within 2 years after TBI, which were all significant when compared with patients with TBI without hyperlipidaemia ($p < 0.0001$). The incidence rate of ADs supports the validity of the high prevalence rate of ADs among patients with TBI with pre-existing hyperlipidaemia. These results imply these individuals are at increased risk for AD after TBI and pre-existing hyperlipidaemia may play an important role in the development of new-onset ADs after TBI.

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

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

	TBI with hyperlipidaemia				TBI without hyperlipidaemia				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 to 2.00)‡	1.58 (1.27 to 1.98)‡	1.58 (1.24 to 2.02)‡
Age											
≤35	82	7	651.46	107.45	164	8	1335.06	59.92	1.79 (0.65 to 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 to 2.70) [§]	1.47 (0.84 to 2.58)	1.33 (0.75 to 2.33)
50–65	399	53	2128.21	249.04	797	53	4471.10	118.54	2.10 (1.44 to 3.07)‡	1.87 (1.09 to 3.21) [§]	1.52 (0.88 to 2.64)
>65	519	48	2658.16	180.58	1039	80	5426.74	147.42	1.22 (0.86 to 1.75)	1.82 (1.07 to 3.11) [§]	1.43 (0.82 to 2.49)
Gender											
Male	860	70	4925.39	142.12	1720	93	9997.31	93.03	1.53 (1.12 to 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 to 2.35) [§]	1.90 (1.52 to 2.37)‡	1.84 (1.47 to 2.30)‡
Hypertension											
No	717	78	4517.91	172.65	2123	144	12891.99	111.70	1.55 (1.17 to 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 to 2.03)	1.43 (1.12 to 1.82) [§]	1.16 (0.88 to 1.54)
Diabetes mellitus											
No	828	95	4995.69	190.16	2331	164	13814.23	118.72	1.60 (1.24 to 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 to 2.91)	1.14 (0.85 to 1.52)	0.80 (0.58 to 1.10)
Cardiovascular disease											
No	1073	114	6119.97	186.28	2413	163	14189.06	114.88	1.62 (1.28 to 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 to 2.04)	1.47 (1.05 to 2.08) [§]	1.20 (0.83 to 1.75)

‡p<0.001; §p<0.05.

*Estimated with Poisson regression.

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

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

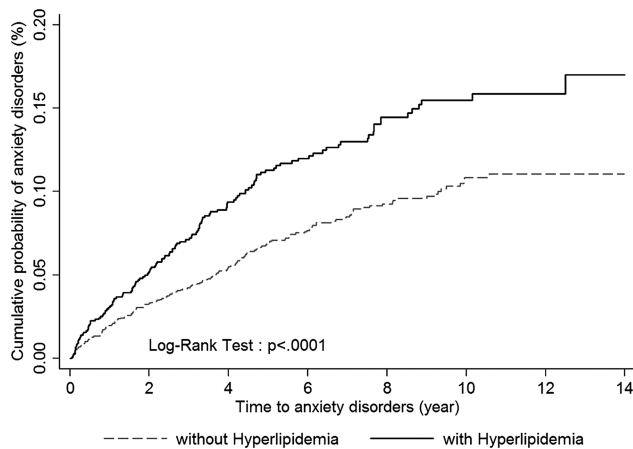


Figure 2 Kaplan-Meier plot for traumatic brain injury patients with anxiety disorders by hyperlipidaemia.

programme, the behaviours of health-seeking and cultural or social issues may affect the lower prevalence rate of ADs in patients with TBI,³⁵ our finding indicated that the situation is changing, which could be from the improvement of health insurance programme or the change of health-seeking behaviours. Importantly, the prevalence of ADs in patients with TBI with pre-existing hyperlipidaemia was always higher than that in patients without hyperlipidaemia. Therefore, the physicians including neurosurgeon, critical care physician, psychiatrists, physiatrists, caregivers can expect to see more patients with TBI who have pre-existing hyperlipidaemia 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 hyperlipidaemia prior to a TBI event helps improve post-traumatic new-onset ADs is worth exploring.

Furthermore, in a 3-year interventional study, the researchers found awareness of hyperlipidaemia had no effect on anxiety.³⁶ In contrast, the other study indicated that simvastatin, an antihyperlipidaemia drug, caused significant anxiolytic effects in animals.²⁶ In the current study, we did not investigate the impact of anti-hyperlipidaemia medications in pre-existing hyperlipidaemic patients before TBI, as the data were unavailable. However, in our study, we emphasise that physicians should pay more attention on the plasma hyperlipidaemia level of high-risk patients to prevent the occurrence of ADs after TBI in daily practice. Well-controlled hyperlipidaemia 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 hyperlipidaemia is an independent risk factor for new-onset ADs after TBI, even when we controlled for DM, HTN and CAD. Therefore, hyperlipidaemia'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 AD.³⁷ Salim *et al* also demonstrated that anxiety is associated with neuroinflammation.³⁸ Esmailzadeh *et al* showed a positive association between hyperlipidaemia and markers of systemic inflammation and endothelial dysfunction.³⁹ Furthermore, inflammatory actions of the neuroimmune system may contribute to the development of ADs following TBI.⁴⁰ Taken together, we suppose that the inflammatory entity of

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

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

*Estimated with Poisson regression.

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

‡p<0.001; \$p<0.05.

ADs, anxiety disorders; IR, incidence rate, per 10 000 person-years; IRR, incidence rate ratio; N/A, not available; PY, person-year; ref., reference group; TBI, traumatic brain injury.

Table 4 Adjusted HRs for anxiety disorders in traumatic brain injury patients with hyperlipidaemia

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 to 2.92)					1.65 (0.80 to 3.41)
50–65	1.62 (0.72 to 3.66)					2.04 (1.17 to 3.57) [§]
>65	1.12 (0.49 to 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 to 2.77) [§]	to	2.53 (1.21 to 5.27) [§]	2.97 (1.70 to 5.21) [§]	1.27 (0.72 to 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 to 1.68)	11.73 (1.37 to 100.58) [§]	2.45 (1.08 to 5.55) [§]	0.61 (0.32 to 1.14)	1.39 (0.75 to 2.60)	1.17 (0.69 to 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 to 1.19)	to	1.06 (0.47 to 2.42)	0.59 (0.30 to 1.14)	0.97 (0.54 to 1.76)	0.86 (0.50 to 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 to 1.90)	to	1.51 (0.44 to 5.21)	1.86 (0.80 to 4.37)	0.96 (0.50 to 1.85)	1.05 (0.50 to 2.22)

[§]p<0.05.

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

NA, not available; ref., reference group.

hyperlipidaemia 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 hyperlipidaemia 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 hyperlipidaemic women, specifically aged between 35 and 65 years, had an increased risk of new-onset ADs after TBI compared to men. In a 2-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 months 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 antianxiety drug administration (psycho pharmacokinetic) during the treatment of women with ADs,⁴⁴ and female reproductive hormones, such as oestrogen, 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 hyperlipidaemia had a significantly higher risk for ADs than males. Using a subgroup analysis, we further found that TBI females with hyperlipidaemia 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 hyperlipidaemic 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 occurs 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 oestrogen levels were unavailable in our study, there was no sufficient evidence to conclude whether oestrogen has anti-anxiety effects on the development of new-onset ADs after patients with TBI with pre-existing hyperlipidaemia. Therefore, we consider the role of oestrogen and the interaction between oestrogen and hyperlipidaemia 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 hyperlipidaemia 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 hyperlipidaemia is an independent predictor for new-onset ADs after TBI. Hyperlipidaemic women, specifically aged between 35 and 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 hyperlipidaemia level of high-risk patients to prevent the development of ADs after TBI.

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