

RISK OF SLEEP DISORDERS IN PATIENTS WITH DECOMPRESSION SICKNESS: A NATIONWIDE, POPULATION-BASED STUDY IN TAIWAN

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SUMMARY

Background: Decompression sickness (DCS) primarily manifests musculoskeletal pain, cutaneous manifestations, lymphatic symptoms, and neurological symptoms. DCS might affect the central nervous system and induce the stress in the patients, but few studies about the psychiatric morbidity after DCS have been conducted. This study aimed to investigate the association between DCS and the risk of developing psychiatric disorders.

Subjects and methods: This study was a population-based, matched-cohort design. A total of 738 enrolled patients, with 123 study subjects who had suffered from DCS, and 615 controls matched for sex and age, from the Longitudinal Health Insurance Databank from 2000-2010 in Taiwan, and selected from the National Health Insurance Research Database. After adjusting for the confounding factors, Cox proportional hazards analysis was used to compare the risk of developing psychiatric disorders during the 10 years of follow-up period.

Results: Of the study subjects, 10 (8.13%) developed psychiatric disorders when compared to 35 (5.69%) in the control group. The study subjects were more likely to develop psychiatric disorders (crude hazard ratio [HR]: 2.79 (95% CI=1.37-5.69, $P<0.01$). After adjusting for sex, age, monthly income, urbanization level, geographic region, and comorbidities, the adjusted HR was 3.83 (95% CI=1.60-9.16, $P<0.01$). Sleep disorders was associated with DCS with the adjusted HR as 5.74 (95% CI=1.04-31.56, $P<0.01$). Hyperbaric oxygenation therapy was not associated with a lower risk of psychiatric disorders.

Conclusions: Patients who suffered from DCS have a 3.8-fold risk of developing psychiatric disorders, and a 5.7-fold risk of sleep disorders. This finding is a reminder for the clinicians that a regular psychiatric follow-up might well be needed for these patients.

Key words: decompression sickness - psychiatric disorders - sleep disorders - National Health Insurance Research Database - Cohort study

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INTRODUCTION

Decompression sickness (DCS) is a disease caused primarily by bubbles formed from the dissolved gas in the blood and/or tissue after an acute reduction in ambient pressure (Edmonds et al. 2015). DCS had traditionally been subdivided into type I and type II categories, and the manifestations of type II DCS are neurological, vestibular, and cardiopulmonary symptoms (Jain 2016). DCS might affect the central nervous system, but few studies about the psychiatric morbidity after DCS have been completed (Hopkins & Weaver 2001, Nicolas et al. 2000). Therefore, the study for the risk of psychiatric disorders after DCS is, as yet, to be examined.

Intracerebral white matter lesions have been reported on magnetic resonance imaging (MRI) in divers, even

without a history of DCS (Connolly & Lee 2015). Nitrogen microbubbles may be responsible for these lesions and could lead to chronic neurological dysfunction (Kohshi et al. 2014). In addition to the direct influence on the central nervous system (CNS), there might well be an indirect impact on sleep quality due to the microbubbles and diving. A recent study concluded that diving, as a stress stimulant, induced higher cortisol levels (Pourhashemi et al. 2016), which could influence the diver's sleep quality (Vgontzas et al. 2003). DCS might affect the central nervous system, and the stress from diving itself and DCS could also influence the patients, but few studies about the psychiatric morbidity after DCS have been conducted (Hopkins & Weaver 2001, Morgan 1995, Nicolas et al. 2000). Therefore, the study for the risk of psychiatric disorders after DCS is important and needed to be examined.

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, included contracts with 97% of the medical providers with approximately 23 million beneficiaries, or more than 99% of the entire population in Taiwan (Ho Chan 2010). Therefore, we used the National Health Insurance Research Database (NHIRD) to study the association between the DCS and the risk of sleep disorders. Therefore, we could utilize the National Health Insurance Research Database (NHIRD) to test the hypothesis that DCS is associated with the risk of psychiatric disorders.

SUBJECTS AND METHODS

Data sources

The present study used the NHIRD to identify inpatients with a discharge diagnosis of DCS, based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code (993.3) during 2000-2010. The NHIRD, which contains all claims data of the beneficiaries, uses ICD-9-CM codes to record diagnoses, and has the advantage in providing a large-scale, longitudinal, reliable dataset, leading to extensive usages for population-based researches (Chen et al. 2010). It covers both the outpatient and inpatient services for approximately 99% of the entire 23 million population of Taiwan. In this study, we used outpatient and hospitalization data from the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD, which contains 1,000,000 original claims data which were randomly sampled from the 2005 registry of all the beneficiaries under the NHI program. Individuals with incomplete information in sex and age were excluded from the data analyses. The database would then review and remove the duplications of data from the technical or registration problems, since each insured individual is supposed to have only one entry of data in the NHI records.

Study design and sampled participants

This study was a population-based, matched-cohort design. Patients with newly diagnosed DCS were selected from the Inpatient Dataset from January 1, 2000, to December 31, 2010, according to a diagnosis of DCS (ICD-9-CM 993.3). All diagnoses of DCS were made by board-certified undersea and hyperbaric medicine physicians, according to the clinical findings. Licensed medical records technicians verified the coding before claiming the reimbursements in hospitals and clinics. The NHI Bureau appoints several senior external specialists in undersea and hyperbaric medicine for randomly reviewing the records of ambulatory care visits and in-patient claims to verify the accuracy of the diagnoses. The patients with DCS before 2000 were excluded. In addition, the patients diagnosed with psychiatric disorders before the first visit for DCS were also excluded. All patients aged <20 years were also excluded.

The DCS patients were matched by using 1:5 sex, age, and index year-matched controls. The 1:5 match was used due to the statistical power achieved being 0.901 at this ratio, while the ratio was 1:1 to 1:4, the statistical power would have been lower than 0.9 (Figure 1). Type I DCS was defined by the symptoms involved skin, musculoskeletal or lymphatic system, and Type II DCS involved central nervous system, and the type II could be divided as mild and severe form of neurological DCS (Francis et al. 2003, Howle et al. 2017).

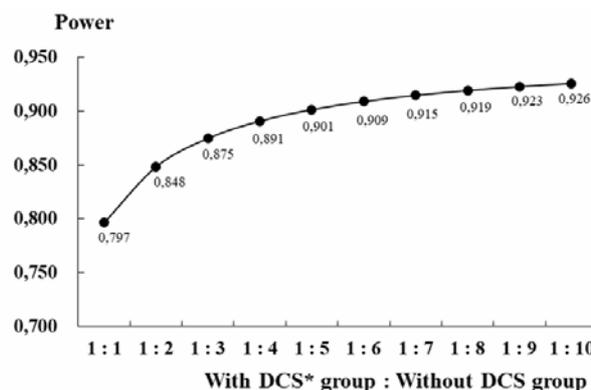


Figure 1. The statistical power of the different ratios of DCS* and the matching of non-DCS group (* DCS= decompression sickness)

Ethics

Access of the NHIRD has been approved by the National Health Research Institutes (NHRI) Ethics Review Committee. The Institutional Review Board (IRB, the ethical committee) of Tri-Service General Hospital approved the research with waiving the need for individual written informed consent in such a study (IRB No. 1-104-05-145).

Covariates

The covariates are demographic factors that included sex, age group (20-44, 45-64, ≥65 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence, seasons, levels of care, occupational injury, and monthly income (Table 1). One study in Mexico has reported that the age range was as wide as 20 to 59 years in the patients with DCS (Huchim-Lara et al. 2017), therefore, we used the age groups as above to analyze the effects of different age groups. The usage of the hyperbaric oxygen (HBO) therapy for either group was also recorded.

Comorbidity

Pre-defined comorbidities included diabetes mellitus (ICD-9-CM 250), hypertension (ICD-9-CM 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, 405.9), hyperlipidaemia (ICD-9-CM 272.x), coronary artery disease (CAD, ICD-9-CM code 410-414), and obesity (ICD-9-CM 278).

Table 1. Demographic factors enrollees in this study

Covariates	Descriptions
Sex	female vs male
Age groups	20-44, 45-64, ≥65 years
Urbanization level of residence*	
Level 1	Population: >1,250,000, with a specific designation as political, economic, cultural, and metropolitan development
Level 2	Population: 500,000-1,249,999, playing an important role in the politics, economy, and culture
Level 3	Population: 149,999-499,999
Level 4	Population: <149,999
Seasons	Spring, summer, autumn, and winter
Levels of care	Medical centers, regional hospitals, and local hospitals
Occupational injury**	Gave kind 1 and 2
Monthly incomes	≥35,000 NT\$ 18,000–34,999 NT\$ <18,000 NT\$

DCS= Decompression sickness; NT\$= New Taiwan Dollars; *Defined according to the population and various indicators of the level of development; ** In the National Health Insurance Research Database, a column named “Gave Kind” indicated different types of conditions, including: “1” for occupational injury, “2” for occupational disease, “3” for non-occupational injury, and “4” for non-occupational disease

Outcome measures

All of the study participants were followed from the index date until the onset of a depressive disorders (ICD-9-CM 296.2-296.3, 300.4, 311), anxiety disorders (ICD-9-CM 300.0, 300.2-300.3, 300.9), sleep disorders (excluding sleep apnoea, ICD-9-CM 307.4, 780.5), stress-related disorders (adjustment disorders, ICD-9-CM 309.0-309.4, 309.82-309.83, 309.89, 309.9; posttraumatic stress disorders, PTSD, ICD-9-CM 309.81; acute stress disorder, ASD, ICD-9-CM 308; acute and reactive psychosis, ICD-9-CM 298), delirium (ICD-9-CM 293), dementia and other cognitive disorders (ICD-9-CM 290, 294), withdrawal from the NHI program, or the end of 2010.

Statistical analysis

All statistical analyses were performed using the SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY). χ^2 and t tests were used to evaluate the distributions of the categorical and continuous variables, respectively, with Fisher’s exact examination. Cox proportional hazards analysis was used to determine the risk of psychiatric disorder. The results were presented as hazard ratio (HR) with a 95% confidence interval (CI). Differences in the risk of psychiatric disorders between the study and control groups were estimated using the Kaplan-Meier method with the log-rank test. A 2-tailed p value <0.05 was considered to indicate statistical significance and the uncertain possibility of type II errors.

RESULTS

In the dataset of the LHID, 182 individuals with DCS were found. Those with DCS diagnosed before 2000, psychiatric disorders before the first visit for DCS, unknown sex, or aged <20 were excluded. Therefore, a total of 738 patients were enrolled, including 123 subjects with DCS and 615 controls without DCS (Table 2). Among the 182 individuals with DCS, 59 were excluded for diagnosis with DCS before 2000, with psychiatric disorders before the tracking, with unknown, or of age <20 (Figure 2). Table 2 shows the distributions of the demographic characteristics and medical comorbidities among patients with and without DCS in Taiwan. As expected from our matching methodology, there were no significant differences in sex and age. A comparison with controls revealed that the patients with DCS were less likely to have the comorbidities of diabetes mellitus (4.1% vs 9.4%, $P=0.03$), and coronary artery disease (0.8% vs 4.9%, $P<0.01$). When compared with the control subjects, the DCS cases showed significant associations with those residing in the south (30.9% vs 29.1%), and east (7.3% vs 3.7%) ($P<0.01$), urbanization level 2 (50.4% vs 40.2%), and level 4 (39.9% vs 16.4%) ($P<0.01$), local hospitals (48.8% vs 35.5%, $P=0.009$), HBO therapy (39.8% vs 0.3%, $P<0.001$), and occupational injury (4.1% vs 1.5% $P=0.01$) (Table 2).

Within the follow-up period, 8.1% ($n=10$) of the patients were diagnosed with psychiatric disorders in the DCS group, and 35 (5.7%) were diagnosed with psychiatric disorders in the control group. The study subjects had higher frequency in those aged 45-64 years than in the controls (47.2% vs 36.8%, $P=0.01$, data not shown). Figure 3 shows the Kaplan-Meier analysis for the cumulative incidence of psychiatric disorders in the study and control groups. In addition, at the sixth year of follow-up, the difference of the cumulative incidences of psychiatric disorders between the two groups became significant (log rank test, $P<0.01$). The difference of the cumulative incidences of psychiatric disorders was shown in Table 3. Table 4 shows the results of the single and multi-variable analysis for the factors of psychiatric disorders. After adjusting for sex, comorbidities, season, urbanization level, level of care, HBO therapy, occupational injury, and insured premium, the Cox regression analysis showed that the adjusted HR for the case patients diagnosed with psychiatric disorders was 3.83 (95% CI=1.60-9.16, $P<0.01$), when compared with the control group. In addition, patients aged 45-64 have a decreased risk of developing psychiatric disorders with the reference of the age group of 20-44 (HR=0.40; 95% CI 0.19 to 0.82; $P=0.01$). Among these psychiatric disorders, only sleep disorders had a significant increased risk. (Table 5).

In the Table 6, the adjusted HRs of psychiatric and sleep disorders increased with the severity of DCS, and increased risk of psychiatric disorders, especially sleep

Table 2. Characteristics of study at the baseline

Decompression sickness Variables	With		Without		P
	n	%	n	%	
Total	123	16.7	615	83.3	
Gender					0.99
Male	113	91.9	565	91.9	
Female	10	8.1	50	8.1	
Age (years)					0.99
20-44	67	54.5	335	54.5	
45-64	49	39.8	245	39.8	
>65	7	5.7	35	5.7	
Comorbidity					
DM	5	4.0	58	9.4	0.03*
Hypertension	5	4.0	41	6.7	0.19
Hyperlipidaemia	1	0.8	15	2.4	0.22
CAD	1	0.8	30	4.9	<0.01**
Obesity	0	0	0	0	-
Season					0.03*
Spring (March-May)	36	29.3	167	27.2	
Summer (June-August)	41	33.3	137	22.3	
Autumn (September-November)	26	21.1	166	27.0	
Winter (December-February)	20	16.3	145	23.6	
Location					<0.01**
Northern Taiwan	34	27.6	223	36.3	
Middle Taiwan	7	5.7	186	30.2	
Southern Taiwan	38	30.9	179	29.1	
Eastern Taiwan	9	7.2	23	3.7	
Outlets islands	35	28.5	4	0.7	
Urbanization level					<0.01**
1 (The highest)	11	8.9	205	33.3	
2	62	50.4	247	40.2	
3	1	0.8	62	10.1	
4 (The lowest)	49	39.8	101	16.4	
Level of care					<0.01**
Hospital center	26	21.1	201	32.7	
Regional hospital	37	30.1	196	31.9	
Local hospital	60	48.8	218	35.5	
HBO therapy	49	39.8	2	0.3	<0.01**
Occupational injury	5	4.1	9	1.5	0.01*
Insured premium (NT\$)					0.24
<18,000	119	96.8	605	98.4	
18,000-34,999	4	3.3	8	1.3	
>35,000	0	0	2	0.3	

P (Chi-square/Fisher exact test): *P<0.05, **P<0.01; DM: Diabetes mellitus; CAD: Coronary artery disease; HBO: Hyperbaric oxygenation therapy

Table 3. The cases of psychiatric disorders in the years after Decompression sickness

Decompression sickness Tracking years	With Psychiatric disorders (N)	Without	P
1	3	8	0.668
2	3	13	0.795
3	6	16	0.844
4	8	18	0.097
5	10	22	0.151
6	10	26	0.008
7	10	27	0.018
8	10	30	0.003
9	10	31	0.009
10	10	33	0.015
11	10	35	0.003

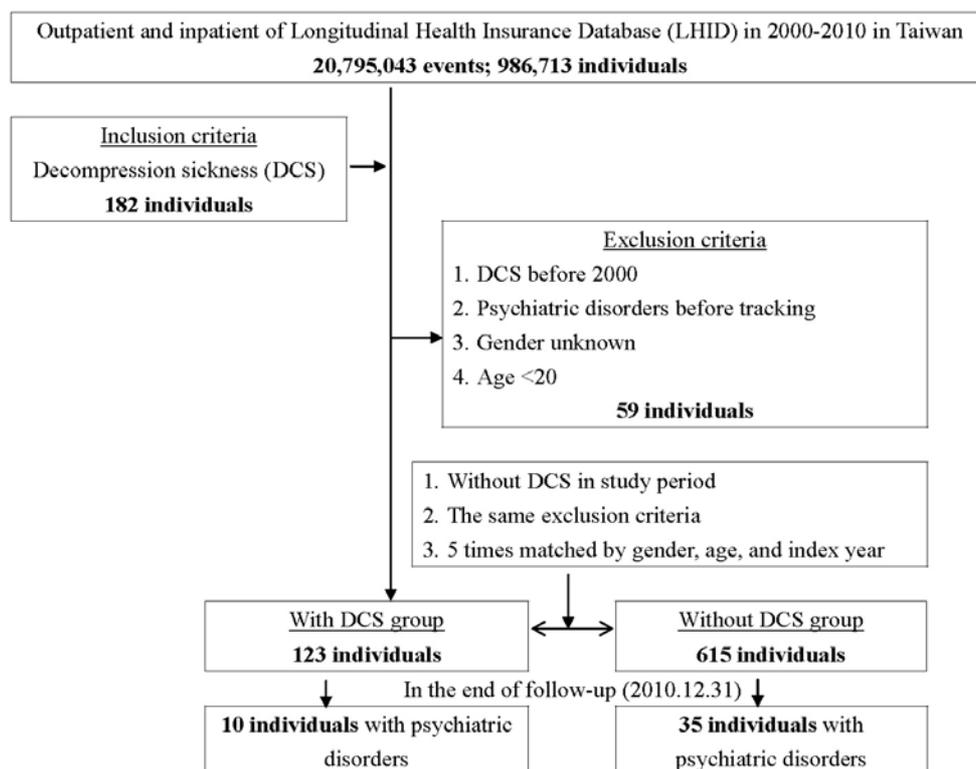


Figure 2. The flowchart of study sample selection from National Health Insurance Research Database in Taiwan

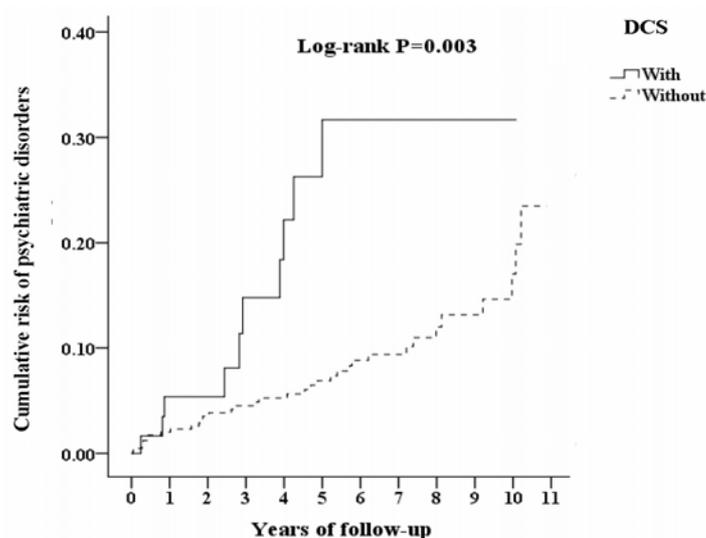


Figure 3. Cumulative risk of psychiatric disorders among aged 20 and over stratified by decompression sickness (DCS) with log-rank test

Table 4. Factors of psychiatric disorders by using Cox regression

Variables	Crude HR	95% CI	95% CI	P	Adjusted HR	95% CI	95% CI	P
Decompression sickness (Reference: without)	2.79	1.37	5.69	<0.01**	3.83	1.60	9.16	<0.01**
Gender (Reference: female)	0.58	0.25	1.38	0.22	0.87	0.34	2.20	0.77
Age (years) (Reference: 20-44)								
45-64	0.42	0.21	0.84	0.01*	0.40	0.19	0.82	0.01*
>65	0.64	0.31	1.34	0.24	0.67	0.30	1.48	0.32
HBO therapy (Reference: without)	1.98	0.61	6.42	0.26	0.76	0.17	3.31	0.71

HR = hazard ratio; CI = confidence interval; Adjusted HR: Adjusted variables listed in the Table 1; *P<0.05, **P<0.01

Table 5. Factors of subgroups of psychiatric disorders in the end of follow-up by using Cox regression

Decompression sickness Psychiatric disorders	With		Without		Adjusted HR	95% CI	95% CI	P
	Event	Rate (per 105 PYs)	Event	Rate (per 105 PYs)				
Overall	10	2,160.76	35	1,604.16	3.827	1.600	9.156	0.003
Depressive disorder	2	432.15	11	504.16	0.417	0.040	4.348	0.465
Anxiety disorder	1	216.08	3	137.50	4.452	0.057	6.238	0.498
Sleep disorder	3	648.23	14	641.66	5.738	1.043	31.557	0.045
Stress-related disorders	3	648.23	0	0.00	-	-	-	-
Adjustment disorders	0	0.00	0	0.00	-	-	-	-
PTSD	1	216.08	0	0.00	-	-	-	-
ASD	1	216.08	0	0.00	-	-	-	-
Acute and reactive psychosis	1	216.08	0	0.00	-	-	-	-
Delirium	0	0.00	0	0.00	-	-	-	-
Dementia and other cognitive disorder	1	216.08	8	366.66	1.428	0.161	12.696	0.749

PYs = Person-years; Adjusted HR = Adjusted Hazard ratio; Adjusted for the variables listed in Cox sheet; CI = confidence interval; PTSD: posttraumatic stress disorder; ASD = acute stress disorder

Table 6. Factors of risk of psychiatric disorders / sleep disorders among different type of decompression sickness by using Cox regression

Decompression sickness (With vs. without)	Adjusted HR	95% CI	95% CI
Psychiatric disorders	3.83**	1.600	9.160
Type	2.67**	1.680	13.190
Type-mild	4.71*	1.620	11.400
Type-severe	5.98**	1.750	8.710
Sleep disorders	5.74*	1.043	31.557
Type	4.13*	1.035	31.564
Type-mild	5.73*	1.001	30.298
Type-severe	5.86*	1.052	33.497

Adjusted HR = Adjusted Hazard ratio; Adjusted for variables listed in Table 1; CI = confidence interval; P: *P<0.05, **P<0.01

disorders, were associated with no matter whether type I or type II DCS. The mean time from diagnosis of DCS to the first visit for psychiatric disorders was 994.41 (SD=594.75) days, and the psychiatric treatment duration in the DCS patients in the follow up period was 17.09 (SD=16.06) months.

DISCUSSION

In this nationwide population-based retrospective study, the principal finding is that the patients with DCS had an increased risk (HR=3.83; 95% CI 1.60 to 9.16, P<0.01) for the development of psychiatric disorders within the follow-up period, as compared with an age- and sex-matched control group. In addition, patients with DCS who were male or older than 45 years, had a higher HR in comparison to the control group. Sleep disorders are associated with an adjusted HR of 5.74 (95% CI=1.04 to 31.56, P<0.05). We have also found that the mean duration from diagnosis of DCS to the first visit for psychiatric disorders was 994.41 (SD=594.75) days, and the treatment of psychiatric disorders in the follow up period was 17.09 (SD=16.06) months, respectively. In addition, the risk of psychiatric and sleep disorders increased with the severity of DCS.

Therefore, the psychiatric disorders after DCS were not just in an acute or transient course. This is the first nationwide, population-based, cohort study about the risk of psychiatric disorders in a DCS patient, to the best of our knowledge.

In this study, the treatment prevalence of psychiatric disorders in the control group was 5.7%, which is similar to the previous studies using the NHIRD to investigate the risk of psychiatric disorders in some physical diseases, which ranged from 5-8%, for examples, 5.6% of psychiatric disorders in the control group in a study for pelvic inflammatory disease (Shen et al. 2016), 4.42% in a study for primary Sjögren syndrome (Shen et al. 2015), 5.01% in a study for ankylosing spondylitis (Shen et al. 2016), 7.5% in a study for Guillain-Barre syndrome (Tzeng et al. 2017), or 8.77% in a study for patients who received weight control surgery (Chien et al. 2017), respectively. One previous study has reported that there were 19% of psychiatric difficulties in the group of diving accidents, which included DCS and other accidents in the diving, in comparison to control group of 5% of psychiatric difficulties, by scoring above the cut-off from the 28-item version of the General Health Questionnaire (GHQ) (McQueen et al. 1994). However, the present study focused on the percentage

of psychiatric disorder in the DCS group, as 8.1%. No comparable studies using the NHIRD were found, we thus tried to investigate on a similar topic, traumatic brain injury (TBI), while several studies about the association between TBI and psychiatric disorders found that there were 5.9% bipolar disorders (Huang et al. 2018), 1.78% substance-related disorders (Wu et al. 2016), or 1.41%-2.97% mood disorders (Chi et al. 2016, Tsai et al. 2014), and 28.34% insomnia (Chiu et al. 2015), in the patients of TBI. Since there were no previous studies about the prevalence of psychiatric disorders in Taiwan, a community survey for this topic is needed in the future. In addition, there were no stress-related disorders, for example, PTSD, in the control group in this study. This seem to be extraordinary low, however, in one study using NHIRD for the study of psychiatric disorders in patients after occupational injury, the incidence of PTSD in the control group of any diseases instead of occupational injury was 0.03% (Chen et al. 2014), which is lower than the prevalence rates in Western countries (Javidi & Yadollahie 2012, Lukaschek et al. 2013). This might be related to the underestimate or under-diagnosis of PTSD or other stress-related psychiatric disorders in Taiwan (Chen et al. 2017, Chien et al. 2017).

In this study, the people with DCS of age 45-64, with the reference of age 20-44, was associated with a lower risk of psychiatric disorders (adjusted HR=0.40 (95% CI: 0.19 to 0.82, $p=0.01$)). We hypothesize that diving is generally appropriate for younger individuals (Strauss et al. 2017), and older people might be more cautious in obeying both the diving and the decompression protocols. Therefore, the DCS could be less severe if it did occur, and thus be associated with a lower risk of psychiatric disorders in this age group.

Several previous reports found that DCS could make an impact on the patients' brains. Long-term neuropsychological changes in divers who had used compressed air were first described in 1966 (Rozsahegyi & Roth 1966). Furthermore, divers with a history of DCS have an increased risk of neuropsychological symptoms (Bast-Pettersen et al. 2015, Trevett et al. 2010). Several studies had reported that long term memory impairment might be related to the cumulative diving exposure (Bast-Pettersen et al. 2015, Calder 1992, Edmonds & Boughton, Hemelryck et al. 2014, Irgens et al. 2007, McQueen et al. 1994, Pourhashemi et al. 2016, Ross et al. 2007, Slosman et al. 2004, Sutherland et al. 1993, Taylor et al. 2006, Tetzlaff et al. 1999, Trevett et al. 2010, Vaernes et al. 1989, Williamson et al. 1987). However, the neurocognitive function in either the military or the highly professional divers, such as construction divers (Bast-Pettersen 1999), German Navy divers (Cordes et al. 2000), U.S. Navy saturation divers (Curley 1988), and elite apnea divers (Ridgway & McFarland 2006), does not change. Depressive response, denial, and feelings of conflicts were also noted in the psychological responses in several patients

with DCS (Hunt 1996). Neurological DCS, include visual, cognitive, motor, and sensory difficulties (Auten et al. 2010, Cianci & Slade 2006, Wirjosemito et al. 1989). Although the residual symptoms were as low as 1.5-6.9% (Wirjosemito et al. 1989), we speculate that these residual neurological difficulties, as the psychological impacts, might also contribute the risk of psychiatric disorders. The underlying mechanisms of the increased risk of psychiatric disorders in DCS patients remain unclear.

In addition, it is also worthwhile considering that some divers are different from the general population. Several studies have investigated the differences of personality traits between the divers and the general population (Bonnet et al. 2003, Harding & Gee 2008, van Wijk 2017). Among the personality traits, the risk-taking behaviors is associated with sensitivity to negative emotions, and there might be a link between the divers and the risk of psychiatric disorders, rather than simply DCS (Bonnet et al. 2003). Further research is therefore needed for examining the relationship between the divers' personality traits and the risk of DCS and psychiatric disorders, and the personality disorders in patients with DCS and psychiatric disorders by using NHIRD.

In our study, sleep disorders were significantly associated with DCS, in comparison to other psychiatric disorders. Previous studies had shown sleep disorders were one of the acute symptoms of neurological DCS and high-pressure neurological syndrome (Jain 1994). Several studies have reported the association between the TBI, white matter, and sleep (Fakhran et al. 2013). Although the microbubbles were mainly located in the cortex and subcortical white matter (Kohshi et al. 2014), which was not a major contributor to the circadian rhythm of sleep, the volume of cerebral lesions might be underestimated because of the low sensitivity of a brain MRI in divers (Gronning et al. 2005). However, this is the first study of sleep disorders as the delayed effects of DCS. Professional or career diving may involve shift work (Gamedze 2014, Hitchen 2013, Park et al. 1983), and shift work has pronounced negative effects on sleep and health (Akerstedt & Wright 2009, Cheng et al. 2017), and we would recommend more researches that focus on the work-shift patterns and occupational stress, which might be related to sleep disorders, in the professional divers.

HBO therapy is widely used in the treatment of the neurological symptoms of DCS, but no previous literatures have studied the effects on the psychiatric disorders in the patients with DCS (Boussuges et al. 1996, Germonpre et al. 2016, Rios-Tejada et al. 1997, Sheffield & Davis 1976, Wang et al. 2002). Therefore, we also investigate the previous researched on the TBI and the neuropsychiatric sequelae. Some pilot studies have tried to treat psychiatric disorders. For example, in several previous studies, HBO therapy was associated with improvements in the TBI-associated cognitive

deficits, PTSD, and post-concussive symptoms (Boussi-Gross et al. 2013, Eve et al. 2016, Hadanny et al. 2018, Harch et al. 2012). However, one randomized clinical control trials found that the observed improvements in the post-concussive symptoms were not HBO mediated but may reflect nonspecific improvements related to placebo effects (Miller et al. 2015). In the present study, HBO therapy was not associated with a decreased risk of the psychiatric disorders, and a further randomized control study is needed to evaluate whether HBO therapy would be effective in the prevention of psychiatric disorders in the DCS patients.

Limitations

Several limitations of the study must be taken into consideration. First, patients with DCS in Taiwan are mostly males, and the generalization of this finding to female patients with DCS is limited. Second, the time and depths of diving, which is crucial in microbubble exposure is not clear in such a dataset. Third, DCS can be regarded as a traumatic event, however, the records of traumatic events other than the DCS were not available in the NHIRD, either in the DCS or non-DCS group. We could not analyze the traumatic events other than the DCS in the subjects in this medical claims dataset-based study. Fourth, we have only enrolled individuals aged >20 in this study, and the results didn't include the influences of the DCS on the teenage groups. Fifth, the end time of inclusion period overlaps with the end of follow-up period. However, the difference of cumulative incidence of psychiatric disorders reached statistical significance between DCS and non-DCS groups since the sixth year of follow up (Table 3), which seems to be reasonable duration for the patients with DCS to the development of psychiatric disorders. Sixth, in this study, only ten patients with DCS developed psychiatric disorders, and this small number could limit the ability in generalizing the findings, and this could be the largest limitation in the present study. Lastly, even though we have included DM, hypertension and hyperlipidemia as the comorbidity, the body mass index (BMI) and serum cholesterol levels, which are risk factors for the development of DCS (Jain 2016), are not included in the claims dataset. A future study for the recruitment of more DCS patients with detailed descriptions is therefore warranted.

CONCLUSION

Patients who have suffered from DCS are associated with an increased risk of psychiatric disorders (adjusted HR: 3.83; 95% CI 1.60 to 9.16; P<0.01), especially sleep disorders. This finding should be considered as a reminder to the clinicians, that a regular psychiatric follow-up might well be needed for these patients.

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Contribution of individual authors:

Wei-Shih Tseng: concept and design of the article; literature searches; data collection, interpretation, and analysis, writing the manuscript; approval of the final version;

Wu-Chien Chien & Chi-Hsiang Chung: statistical analysis, data interpretation, comments on the draft paper; approval of the final version;

Yu-Ching Chou: data interpretation, comments on the draft paper; approval of the final version;

Nian-Sheng Tzeng: concept and design of the article; literature searches; data collection, interpretation, and analysis, statistical analysis, approval of the final version.

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