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Post-traumatic stress disorder and asthma risk: A nationwide longitudinal study

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ABSTRACT

Background: Increasing evidence suggests that post-traumatic stress disorder (PTSD) interferes with the immunological system and is correlated with cardiovascular disease, respiratory disease, and chronic pain conditions. However, the association between PTSD and asthma remains unknown.

Methods: A total of 5518 patients with PTSD and 22,072 age- and sex-matched healthy individuals were enrolled between 2001 and 2009 and followed until the end of 2011. Individuals who developed asthma during the follow-up period were identified.

Results: During the follow-up period, the patients with PTSD had an increased risk of asthma (hazard ratio [HR] = 2.27), particularly those belonging to the youngest age group (HR = 4.01). The findings were consistent in subsequent sensitivity analyses after the exclusion of the first year of surveillance or allergic disorders.

Discussion: This study showed a significant link between PTSD and asthma after adjusting for demographic data and related comorbidities. The risk of developing asthma in patients with PTSD was consistently higher than that in the controls during the study period. Additional studies are necessary to clarify the underlying mechanisms involved in this association between PTSD and asthma.

1. Introduction

Post-traumatic stress disorder (PTSD) is defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders as a sequelae syndrome after a traumatic event, with symptoms including re-experience, avoidance, and negative alterations in cognition and mood associated with the event. PTSD has grown in importance due to an increase in the number of soldiers returning from combat, people exposed to natural disasters or sexual traumas, and severe worldwide accidents. US studies on the prevalence of PTSD have reported that 5%–6% of men and 10%–14% of women have PTSD, making it the fourth most common psychiatric disorder (Yehuda, 2002). In Taiwan, a 10-month follow-up study after the 1999 Jiji earthquake reported that the prevalence of PTSD was 10.3% (Lai et al., 2004). This psychiatric illness causes lasting dysfunction in daily life and affects social and economic state due to not only the mental distress but also the physical diseases associated with PTSD.

Studies have reported physiological changes, physical symptoms, and disease development in humans following exposure to traumatic events. For example, people with PTSD after experiencing the World Trade Center disaster had a higher risk of heart disease (Jordan et al., 2011). Another study reported that people who underwent military combat had increased risks of developing cardiovascular disease, respiratory disease, peptic ulcer, and autoimmune diseases (Boscarino,

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1997, 2004; O'Toole and Catts, 2008a). Moreover, several studies have reported similar results for people exposed to other traumatic events, such as childhood abuse and natural disasters (Felitti et al., 1998; Goodwin and Stein, 2004; Sareen et al., 2007; Spitzer et al., 2009; Weisberg et al., 2002). Studies have discussed several hypotheses on the influence of PTSD on physical illnesses and behaviors, such as biological changes, engagement in poor health behaviors, and dysfunctional coping (Boscarino, 2004; O'Toole and Catts, 2008a). Considering the biological mechanism, PTSD is believed to be involved in alterations in the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal medullary (SAM) system, which lead to changes in the immune system (Rohleder and Karl, 2006). At the molecular level, Cohen et al. demonstrated that high levels of proinflammatory cytokines, such as interleukin (IL)-6 and IL-8, and low levels of regulatory cytokines, such as transforming growth factor-β, were predicted by more severe acute stress symptoms (Cohen et al., 2011). Growing evidence also reveals an increase in the levels of proinflammatory mediators, including cytokines (IL-1, IL-6, and tumor necrosis factor [TNF]-α) and immune cells (Th1 and Th17 cells), in patients with PTSD (Cohen et al., 2011; Gola et al., 2013; Newton et al., 2014; Sommershof et al., 2009; von Känel et al., 2007). These findings imply the potential presence of an immune imbalance in patients with PTSD. Additional studies are warranted to investigate whether patients with PTSD are more likely to develop certain allergic or autoimmune diseases.

Asthma is a chronic inflammatory disorder of the airways and causes such typical symptoms as repeated periods of shortness of breath, wheezing, chest tightness, and persistent decrements in pulmonary function that are detectable throughout childhood, adolescence, and adulthood (Strunk et al., 2006; Weiss et al., 1992). Early detection and management in individuals at risk of developing asthma may prevent recurrent exacerbations and further harmful outcomes (National and Prevention, 2007). Notably, PTSD was revealed to be associated with airflow limitation during pulmonary function testing. In a study conducted by Spitzer et al., the mean ratio of forced expiratory volume in one second to forced vital capacity was significantly lower in participants with PTSD when compared with control participants (Spitzer et al., 2011). Goodwin et al. also examined the association between PTSD symptoms and asthma among twins in the Vietnam Era Twin Registry; they reported an increased likelihood of developing asthma, even after adjustment for confounding factors, among those who exhibited higher PTSD symptoms (Goodwin et al., 2007). Shiratori et al. investigated New York residents who were exposed to the World Trade Center disaster; they found that after adjustment for sex, ethnicity, income, smoking status, dust exposure, and nonspecific psychological distress, patients with probable PTSD had a 1.65-fold risk of developing subsequent asthma when compared with those without probable PTSD (Shiratori and Samuelson, 2012). Nonetheless, in an epidemiological study, PTSD was associated with lower odds for asthma (Tsai and Shen, 2017). In addition, earlier studies have reported that a history of previous sexual assault was not associated with asthma in older adults and primary care patients (Norman et al., 2006; Stein and Barrett-Connor, 2000). The inconsistent results may be potentially biased by small sample sizes, variations in cross-sectional study designs, and short follow-up periods.

Hence, in the current study, we performed a longitudinal study using a large sample size and a longer follow-up period to investigate the association between PTSD and asthma. We hypothesized that patients with PTSD have an elevated risk of developing asthma later in life when compared with those without PTSD.

2. Methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program was implemented in 1995 and offers comprehensive medical care coverage to all residents of Taiwan. The National Health Research Institutes (NHRI) manages the insurance claims database, the National Health Insurance Research Database (NHIRD), which consists of health care data from more than 99% of the entire Taiwanese population. The NHRI audits and releases the NHIRD for use in health service studies. Patients included in the NHIRD are anonymous to ensure that their individual privacy is maintained. The database contains comprehensive information on the insured patients, including demographic data, dates of clinical visits, and disease diagnoses. But, medical records and details of medical history, such as traumatic events and symptomology, were not available. The diagnostic codes used were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in numerous epidemiologic studies in Taiwan (Chen et al., 2016, 2015; Li et al., 2012, 2013). Taipei Veterans General Hospital Institutional Review Board permitted this study.

2.2. Inclusion criteria for patients with PTSD and the control group

Patients who were diagnosed with PTSD (ICD-9-CM code: 309.81) by psychiatrists based on their clinical judgment and diagnostic interview between January 1, 2001 and December 31, 2009 and who had no history of asthma (ICD-9-CM code: 493) before enrollment were included in the PTSD cohort. Patients, who were not included in the PTSD cohort, had not been diagnosed with PTSD at any time, and had not been diagnosed with asthma before enrollment, were randomly selected to construct an age-, sex-, and date of enrollment-matched (1:4) control cohort. Cases of asthma (ICD-9-CM code: 493) diagnosed by board-certified pulmonologists, rheumatologists, pediatricians, internal medicine physicians, and emergency room physicians on the basis of clinical judgment or the pulmonary function test were identified during the follow-up period and followed until December 31, 2011 or the date of death. Furthermore, the asthma-related risk factors were assessed: depressive disorder, allergic rhinitis, and atopic dermatitis. The level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed (Liu et al., 2006).

2.3. Statistical analysis

For between-group comparisons, an independent *t*-test was used for continuous variables and Pearson's chi-squared test was used for categorical variables. The Cox Proportional Hazard regression model was used to investigate the hazard ratios (HRs) with 95% confidence intervals (CIs) for developing asthma after adjusting for demographic data as well as allergic and psychiatric comorbidities. Sensitivity tests were performed to validate the findings after we excluded observations on the first year or we excluded the allergic comorbidities. A sub-analysis stratified by different age group (i.e., age < 20 years, age $= 20$–64 years, and age $\geqq 65$ years) was performed to investigate the risk of developing asthma in both PTSD and control groups. All data processing and statistical analyses were performed using the Statistical Package for Social Science (SPSS) Version 17 software (SPSS Inc.) and Statistical Analysis Software (SAS) Version 9.1 (SAS Institute, Cary, NC).

3. Results

We enrolled 5518 patients with PTSD and 22,072 age- and sex-matched individuals as the control group. Overall, 77.3% of the study population were women, and the average age was 34.73 years (standard deviation: 14.78 years) at diagnosis of PTSD and enrollment. The patients with PTSD lived in less urbanized areas ($p < 0.001$) and had a lower level of income-related insurance ($p < 0.001$) compared with those patients in the control group. Regarding the comorbidities, patients with PTSD had a higher incidence of allergic rhinitis (18.9% vs. 11.8%, $p < 0.001$), atopic dermatitis (3.0% vs. 2.3%, $p = 0.006$),

Table 1
Demographic data and incidence of asthma of patients with PTSD and the control group.

	Patients with PTSD (n = 5518)	Controls (n = 22,072)	p-value
Age at diagnosis of PTSD/ enrollment (years, SD, n,%)	34.73 (14.78)	34.73 (14.79)	0.992
Sex (n,%)			>0.999
Male	1254 (22.7)	5016 (22.7)	
Female	4264 (77.3)	17,056 (77.3)	
Asthma (n, 1000 person-year)	146 (4.74)	199 (1.59)	<0.001
Age at diagnosis (years, SD)	41.99 (15.42)	49.12 (17.56)	<0.001
Duration between PTSD/ enrollment and diagnosis (years, SD)	2.92 (2.21)	4.77 (2.24)	<0.001
Allergic and psychiatric comorbidities (n,%)			
Allergic rhinitis	1041 (18.9)	2605 (11.8)	<0.001
Atopic dermatitis	164 (3.0)	513 (2.3)	0.006
Depressive disorder	3677 (66.6)	843 (3.8)	<0.001
Level of urbanization (n,%)			<0.001
1 (most urbanized)	1336 (24.2)	7240 (32.8)	
2	1809 (32.8)	6808 (30.8)	
3	817 (14.8)	3685 (16.7)	
4	666 (12.1)	2799 (12.7)	
5 (most rural)	890 (12.1)	1540 (7.0)	
Income-related insured amount			<0.001
≤ 15,840 NTD/month	2595 (47.0)	7799 (35.3)	
15,841–25,000 NTD/month	1792 (32.5)	7858 (35.6)	
≥ 25,001 NTD/month	1131 (20.5)	6415 (29.1)	

PTSD: post-traumatic stress disorder; SD: standard deviation; NTD: New Taiwan Dollar.

depressive disorder (66.6% vs. 3.8%, $p < 0.001$), and an earlier age of onset of asthma diagnosis (41.99 ± 15.42 vs. 49.12 ± 17.56 years, $p < 0.001$) (Table 1). During the follow-up period, 146 patients in the PTSD group were diagnosed with asthma and 199 patients in the control group, with an incidence rate of 4.74 and 1.59 (1000 person-years), respectively. A shorter duration of asthma diagnosis (2.92 ± 2.21 years vs. 4.77 ± 2.24 years, $p < 0.001$) was observed in the patients with PTSD compared with the controls, as shown in Table 1.

Patients with PTSD had an increased risk of asthma (HR = 2.27), especially for the patients aged < 20 years (HR = 4.01), compared with the controls (Table 2). Such a finding was also observed in the middle age group (20–64 years, HR = 2.30) but was not significant in the geriatric group (≥65 years) (Table 2). The risk of developing asthma associated with PTSD decreased with age. In sensitivity analyses, the main findings of elevated asthma risk in patients with PTSD were still consistent after excluding the first year of surveillance or other allergic disorders (HR = 1.62 and 2.21, respectively), indicating that PTSD may be an independent risk factor for developing asthma (Table 3). During the follow-up period, the risk of developing asthma in the PTSD group is consistently higher than the controls, as shown in Fig. 1.

Table 3
Sensitivity tests for the risk of developing asthma of patients with PTSD and the control group.

	Total*	> 1 year[a]	Excluding allergic disorders[b]
	HR (95% CI)	HR (95% CI)	HR (95% CI)
PTSD, presence vs. absence	**2.27 (1.65–3.11)**	**1.62 (1.14–2.29)**	**2.21 (1.50–3.26)**

PTSD: post-traumatic stress disorder; HR: hazard ratio; CI: confidence interval.
Bold type indicates the statistical significance.
[a] Adjusted by demographic data and allergic and psychiatric comorbidities and PTSD as a binary variable.
[b] Adjusted by demographic data and psychiatric comorbidities and PTSD as a binary variable.

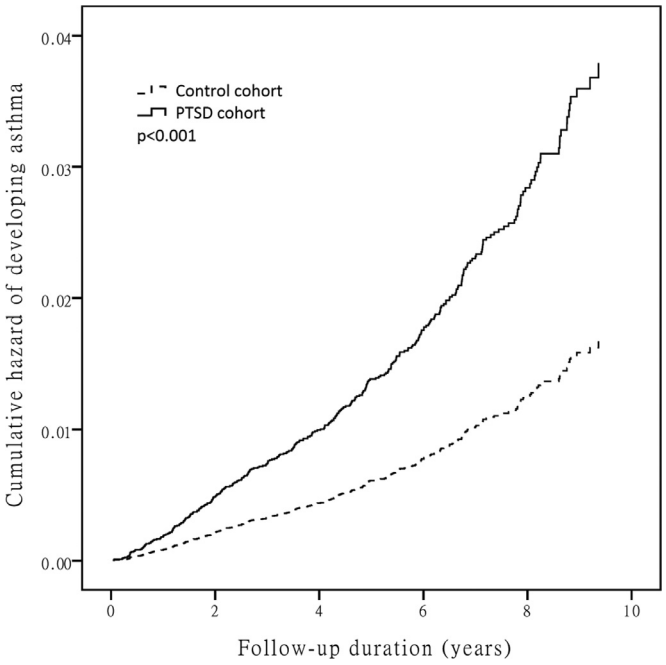

Fig. 1. Cumulative hazard of developing asthma among patients with PTSD and control group.
PTSD: post-traumatic stress disorder.

4. Discussion

Our nationwide cohort study revealed that patients diagnosed with PTSD had an increased risk of developing asthma compared with patients without PTSD. Furthermore, the period between enrollment and asthma diagnosis was shorter in the PTSD group, which suggests that PTSD symptoms affected the development of asthma. These results remained consistent after the data were adjusted for demographic

Table 2
Risk of developing asthma of patients with PTSD and the control group[a].

	< 20 years HR (95%CI)	20–64 years HR (95%CI)	≧65 years HR (95%CI)	Total HR (95%CI)
PTSD, presence vs. absence[a]	**4.01 (1.69–9.51)**	**2.30 (1.60–3.30)**	0.82 (0.26–2.61)	**2.27 (1.65–3.11)**
Comorbidities, presence vs. absence				
Allergic rhinitis	2.22 (1.00–4.97)	**2.61 (2.01–3.39)**	**2.35 (1.13–4.92)**	**2.55 (2.02–3.22)**
Atopic dermatitis	–	0.80 (0.33–1.94)	1.29 (0.17–9.79)	0.72 (0.32–1.61)
Depressive disorder	0.72 (0.25–2.10)	1.41 (0.98–2.04)	1.76 (0.54–5.73)	1.32 (0.95–1.82)

PTSD: post-traumatic stress disorder; HR: hazard ratio; CI: confidence interval.
Bold type indicates the statistical significance.
[a] Adjusted by demographic data and allergic and psychiatric comorbidities and PTSD as a binary variable.

findings and allergic and psychiatric comorbidities.

PTSD has a considerable effect on physical health, particularly with respect to cardiovascular and pulmonary disease (Spitzer et al., 2009). Our findings are consistent compatible with those of previous studies (Alonso et al., 2014; Boscarino, 1997, 2004; O'Toole and Catts, 2008a,b; Sareen et al., 2007). For example, a twin study reported that the severity of PTSD symptoms was positively correlated with the possibility of developing asthma. Patients with PTSD symptoms in the highest quartile were 2.3 times more likely to have asthma when compared with those in the lowest quartile (Goodwin et al., 2007). Brain et al. conducted a study on Australian Vietnam veterans by using a series of sensitivity analyses and reported that PTSD was associated with an elevated risk of asthma (O'Toole and Catts, 2008b). Furthermore, a study using a large dataset from the World Mental Health (WMH) survey in 19 countries revealed the association between PTSD and subsequent asthma in adulthood (Alonso et al., 2014). However, limitations in some of the methodologies used in these studies may reduce the credibility of the evidence that targets the association between PTSD and asthma. Most studies have adopted the cross-sectional study design or a short follow-up period (approximately 2 years); therefore, the possibility of developing asthma over time may not have been sufficiently observed and assessed after the onset of PTSD. In our cohort study, we assessed the risk of developing asthma following PTSD onset as well as the temporal relationship between them. We also adopted a population-based study design on a nationwide scale, which accounted for numerous trauma events and potential confounding factors. Our results showed that PTSD was associated with biological factors and environmental circumstances of asthma etiology and that the risk increased over time.

The definite pathophysiology between PTSD and asthma risk remained unknown. Increasing evidence suggested that people who were exposed to not only airway-related trauma (i.e., World Trade Center rescue and recovery workers) but also non-airway-related trauma (i.e., sexual violence survivors, hurricane survivors) were more likely to develop subsequent asthma later in life (Arcaya et al., 2014; Brackbill et al., 2009; de la Hoz et al., 2016; Santaularia et al., 2014). This phenomenon may imply that the PTSD-related compromise of local respiratory and general systemic systems may be related to asthma risk. Numerous studies have reported that PTSD plays a role in altering the HPA axis, SAM system, and immune system (Rohleder and Karl, 2006), not only in disease correlation studies but also studies that have examined changes in biomarkers, even in animal models. Previous studies have demonstrated an association between PTSD and an increased incidence of several allergic and autoimmune diseases, such as chronic idiopathic urticaria, thyroiditis, inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus (Hunkin and Chung, 2012; von Känel et al., 2007). Increased levels of proinflammatory mediators, including cytokines (IL-1, IL-6, and TNF-α) and immune cells (Th1 and Th17 cells), have been observed in patients with PTSD (Cohen et al., 2011; Gola et al., 2013; Newton et al., 2014; Sommershof et al., 2009; von Känel et al., 2007). In one study, predator-exposed rats demonstrated increased oxidative stress in the adrenal glands, brain, and blood as well as upregulation of proinflammatory cytokine mRNA and neurological inflammatory-related proteins (Wilson et al., 2013). In the current study, increased prevalence of allergic rhinitis, atopic dermatitis, and asthma was noted in patients with PTSD when compared with the controls. Taken together, these findings may affirm the presence of an immune imbalance in patients with PTSD, which may be associated with the etiology of asthma. However, the definite pathophysiology between PTSD and subsequent asthma development requires further investigation.

Various physical and mental comorbidities and adverse psychosocial factors, including cardiovascular symptoms, endocrine symptoms, neurological symptoms (Boscarino, 2004; O'Toole and Catts, 2008a), depressive disorders, substance use disorders, anxiety disorders (Brady et al., 2000), early retirement and job loss (Yu et al., 2016), and heightened family conflicts (Klarić et al., 2012; Renshaw et al., 2011), may occur sequentially during the chronic clinical course of PTSD. These factors may further interfere with the immune and inflammatory systems and intensify the likelihood of developing asthma. The chronic low-grade inflammation state in patients with PTSD is characterized by increased levels of inflammatory cytokines in the plasma and imbalances in immune cell compositions (Guo et al., 2012; Jergović et al., 2014; Passos et al., 2015; Zhou et al., 2014); this state could raise the risk of developing multiple physical diseases over time. Moreover, Gill et al. reported that inflammatory biomarker levels were similar in women who recovered from PTSD and in the nontraumatized controls (Gill et al., 2013). SSRIs, the mainstream treatment modality for PTSD, have been shown to reduce the release of proinflammatory cytokines from activated macrophages, thereby facilitating the feedback inhibition of the HPA axis (Leonard, 2001). Nevertheless, additional studies are required to determine whether the risk of asthma is reduced after recovery from PTSD; in addition, the extent of reduction after receiving psychotropic agents must be assessed.

Age is a major factor for asthma treatment. In Taiwan, Wu et al. assessed the incidence of asthma onset based on age groups and reported the highest incidence at ages 0–12 (1.9/1000 person-years) and 36–40 (2.03/1000 person-years) years (Wu et al., 2014). Furthermore, in more than 50% of cases, persistence or relapse was observed in early-onset asthma (onset age, ≤12 years) (Wu et al., 2014). In another Taiwanese national study conducted during 2000–2007, the prevalence of asthma ranged between 11.9% and 15.7% in the <20-year-old group (Hwang et al., 2010). Increased allergen sensitivity and allergic symptoms were found in patients with early-onset (<12 years old) asthma when compared with those with late-onset (>12 years old) asthma (Miranda et al., 2004), which may correspond to the aforementioned hypothesis that PTSD is involved in immune alterations and the subsequent development of asthma. Furthermore, a subanalysis revealed differences between the three age groups. In the group aged less than 20 years, the HR of developing asthma between the PTSD and control groups was 4.01, whereas in the middle-aged and geriatric groups, the HRs were 2.30 and 0.82, respectively. These discrepancies may be attributed to multiple factors, such as the atopic state, prevalence of asthma, and lung function at different ages. Nevertheless, our result may be partially in line with the nonsignificant finding between previous history of sexual assault and asthma risk in elderly people (Stein and Barrett-Connor, 2000). Thus, monitoring the risk of asthma among patients with PTSD, especially younger patients, is crucial.

This nationwide cohort study comprised 9 years of follow-up and covered more than 99% of the Taiwanese population. Therefore, the study comprised patients of various ages with PTSD who were exposed to numerous traumatic events and episodes. Nonetheless, the study still has several limitations. First, the PTSD group comprised patients who sought medical consultation and treatment; therefore, the possibility of underestimating the prevalence of PTSD cannot be excluded. Second, some factors, such as severity of disease, maternal smoking history, type of traumatic events, smoke/dust exposure, family history, and environmental factors, are unavailable in the NHIRD; consequently, their effects could not be evaluated in this study. Particularly, NHIRD does not include the information of traumatic events so that we cannot assess the relationship between specific trauma (i.e., fire, toxic air) and asthma risk although it was possible that the respiratory system may be compromised in such a condition, further increasing the subsequent asthma risk. In addition, the diagnoses of asthma and PTSD were made by board-certified physicians and psychiatrists, thereby improving the diagnostic validity. Additional studies are required to determine the effects of different traumatic exposures on the asthma risk factor scale; furthermore, the effect of PTSD treatment on lowering the risk of asthma development must be evaluated.

In conclusion, the present study showed a significant link between PTSD and asthma after adjusting for demographic data and related comorbidities. Public health officials and physicians should focus on

performing surveillance and interventions in patients with PTSD, particularly children and adolescents.

Conflict of interest

No conflict of interest.

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