#### ORIGINAL RESEARCH

# Healthcare Utilization, Physical and Psychiatric Comorbidities Before Self-Injurious Behavior in Patients with Asthma: A Nested Case-Control Study

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**Background:** Patients with asthma experience more physical, psychological, and financial burdens; a link between asthma and suicidality has been reported in research.

Purpose: This study analyzed the medical utilization and comorbidity before their self-injurious behavior in patients with asthma.

**Methods:** We enrolled 186,862 patients newly diagnosed with asthma between 1999 and 2013 from the National Health Insurance Research Database in Taiwan. A total of 500 case subjects had ever conducted self-injurious behaviors during the study period. Based on a nested case-control study, each case was matched with 10 controls derived from the asthma cohort to analyze differences between them and their medical use models.

**Results:** The results indicated that, compared to the control group, the cases presented higher frequencies of outpatient visits and hospitalizations. Regarding comorbidity, the cases had more cardiovascular diseases (adjusted odds ratio [aOR]=1.58; p<0.001), bipolar disorder (aOR=2.97; p<0.001), depression (aOR=4.44; p<0.001), and sleep disorder (aOR=1.83; p<0.001) than the controls. **Conclusion:** The evidence-based information serves as a reference for medical staff to reduce the occurrence of self-injurious behavior in patients with asthma.

Keywords: self-injurious behavior, asthma, medical utilization, psychiatric comorbidity, physical comorbidity

#### Introduction

Asthma is one of the most pervasive respiratory diseases in the world, affecting approximately 339 million people.<sup>1</sup> Asthma is closely related to multiple comorbidities, such as atopic disease, respiratory disease, sleep disturbances, and mental illness, all of which increase physical and psychological burdens<sup>2</sup> Asthma induces multiple substantial disease loads, including decreased quality of life and premature death, in people of all ages.<sup>3</sup> Moreover, poor asthma control is associated with greater direct and indirect costs.<sup>4,5</sup> Because patients with asthma experience more physical, psychological, and financial burdens, a link between asthma and suicidality has been reported in research.<sup>2,6</sup>

Suicidal behavior is related to physical disease, emotional disturbance, and risk-taking behavior, which are frequently noted in individuals with asthma.<sup>6</sup> Although the relationship between asthma and suicide mortality, ideation, and attempts is widely acknowledged, the underlying process remains unclear. Asthma has multiple adverse effects on quality of life, including sleeplessness, daytime fatigue, decreased activity level, and mental health problems. Studies have contained methodological limitations, including restrictions on limited unrepresentative samples and reliance on self-reported

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asthma diagnosis.<sup>6,7</sup> According to our previous population-based research in Taiwan, a higher risk of suicide mortality was exhibited in patients who currently have asthma and severe asthma symptoms.<sup>8</sup> Another study in Taiwan<sup>9</sup> reported that self-injurious risk factors for patients with asthma included younger age, rural residence, psychiatric disorder diagnosis, and a higher Charlson Comorbidity Index score. The association between asthma and suicide ideation and attempts has been studied in research from South Korea<sup>10</sup> and the United States.<sup>11</sup> Research from the United Kingdom, Canada, the United States, Japan, and Taiwan have suggested that asthma is associated with significantly increased healthcare use and cost, including hospitalizations, emergency department visits, and ambulatory care claims.<sup>12–17</sup> Chronic asthma is associated with higher exacerbation frequency, more comorbid diseases, and related outpatient service visits, emergency department/hospitalization readmission, and mortality.<sup>16,18,19</sup> Patients with asthma generally have more diagnostic codes and medical use for all comorbidity groups, particularly for diseases of the respiratory system, endocrine, metabolic system, mental health system, circulatory system, and musculoskeletal system, and other hypersensitivity diseases.

To the best of our knowledge, although self-injurious behavior has been associated with asthma in many studies, no research has focused on medical utilization before patients with asthma harmed themselves. Investigating the health-seeking behavior patterns of patients with asthma before their self-deliberate harm may allow the detection of suicide problems earlier and thus halt their development. The present study collected data from a large cohort with asthma and aimed to analyze patterns of medical use between patients with asthma with and without self-injurious behavior.

## Method

#### **Data Sources**

The National Health Insurance (NHI) program, which was implemented on March 1, 1995 is a single-payer insurance system offering universal medical care to nearly all Taiwanese residents (>99.5%).<sup>20</sup> The National Health Insurance Research Database (NHIRD) covers medical reimbursement claims information of the Taiwanese population. The NHIRD uses the 2001 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for disease codes. NHIRD data are officially encrypted, and anonymous data are provided for medical research after formal application and approval. This study was approved by the Institutional Review Board of the Committee on Human Subjects of Taipei City Hospital (TCHIRB-10412111-E). The requirement of informed consent was waived because of the retrospective nature of this study and the use of deidentified data in the NHIRD.

Data used in this nested case-control study were collected from the Longitudinal Health Insurance Database 2005 (LHID 2005). The LHID 2005 contains the medical reimbursement claims of one million beneficiaries randomly sampled from all registered beneficiaries of the NHIRD in 2005. The LHID 2005 and the original whole NHIRD contain no significantly different sex and age distributions between patients.

An incident of asthma in a patient from the LHID 2005 in this study was defined as a beneficiary diagnosed with asthma between January 1, 1999, and December 31, 2013. Beneficiaries diagnosed with asthma (ICD-9-CM code 493.\*\*) were excluded between January 1, 1996, and December 31, 1998. The first record date of diagnosis of asthma in the LHID 2005 was defined as the baseline date. This asthma cohort contained 187,223 patients (detailed information in Figure 1).

Suicide was likely to be under-estimated by clinical staff, and the instances with undetermined causes contributed to the most commonly misclassified category.<sup>21</sup> Therefore, this study defined self-injurious behavior based on the following ICD-9 codes: E950-E959 (self-injurious causes) and E980-E989 (undetermined causes).<sup>9</sup> Accordingly, in this asthma cohort, patients with at least one self-injurious behavior from the baseline date to December 31, 2013, were enrolled and defined as cases with self-injurious behavior.

## Nested Case-Control Study Design

A nested case–control study derived from the asthma cohort was used to analyze patterns of identification and medical utilization among patients with asthma with and without self-injurious behavior. We randomly selected 10 asthma controls from the cohort for each self-injurious case subject. All controls were matched for age and sex through risk-

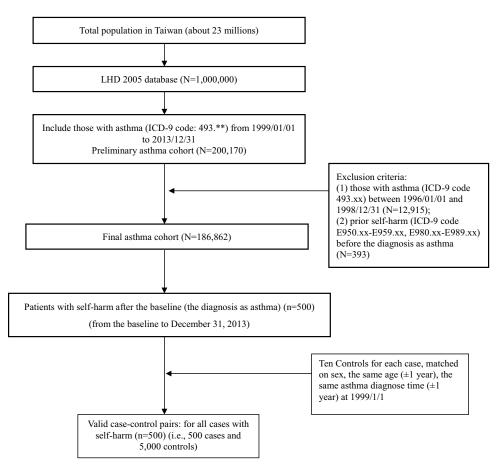


Figure I Study flow diagram.

set sampling (density sampling). The date of the new self-injurious diagnosis record was defined as the index date. Controls were assigned the same index date as that of their corresponding cases. Cases identified later during the followup were eligible to serve as controls for earlier cases. All control patients in the study had at least one medical claim record after the corresponding index date to confirm that they were alive before the corresponding index date. Therefore, 500 cases with asthma and self-injurious behavior were matched to 5,000 controls with asthma.

#### Variables

Demographic variables, including sex, age, urbanization level, employment, and Charlson Comorbidity Index score, are listed in Table 1 for each case and their corresponding controls. The urbanization level was coded as level 1 (highly urbanized area), level 2 (moderately urbanized area), level 3 (newly urbanized area), level 4 (township area), and level 5 (rural area).<sup>22</sup> The Charlson Comorbidity Index score, representing the sum of the weighted scores of 31 comorbid conditions, was used to assess general health status. Medical utilization of cases and controls within 12 months before the index date was investigated. This included the number of outpatient clinic visits, the number of hospital admissions, physical comorbidity, and concomitant use of medications. Medications were classified according to the Anatomical Therapeutic Chemical Classification System (ATC/DDD Index 2019. <u>http://www.whocc.no/atc\_ddd\_index/</u> [accessed August 1, 2019]).

#### Statistical Analysis

Based on the nested case-control study design, we employed conditional logistic regression to assess the differences between self-injurious cases and their corresponding controls, including demographic and clinical characteristics (Table 1) and medical utilization before attempted suicide (Table 2). This regression analysis was conducted using the

	Cases (N=500)	Control (N=5000)	Crude odds ratio <sup>a</sup>	95% CI	P value
	N (%)	N (%)			
Sex					
Male	246 (49.2)	2460 (49.2)	Reference		
Female	254 (50.8)	2540 (50.8)	-	-	-
Age, mean±SD (yrs)	38.8 (24.0)	38.7 (23.9)			
<18	126 (25.2)	1264 (25.3)	Reference		
18–29	76 (15.2)	770 (15.4)	-	-	-
30–39	71 (14.2)	678 (13.6)	-	-	-
40-49	59 (11.8)	609 (12.2)	-	-	-
50–59	53 (10.6)	531 (10.6)	-	-	-
60–69	51 (10.2)	494 (9.9)	-	-	-
70–79	40 (8.0)	410 (8.2)	-	-	-
≥80	24 (4.8)	244 (4.9)	-	-	-
Charlson comorbidity Index <sup>a</sup>					
0	236 (47.2)	2660 (53.2)	Reference	-	-
I	156 (31.2)	1503 (30.1)	1.30	1.02-1.66	0.038
≧2	108 (21.1)	837 (16.7)	1.76	1.31–2.36	<0.001
Urbanization <sup>b</sup>					
Level I	123 (24.6)	1648 (33.0)	Reference	-	-
Level 2	106 (21.2)	1589 (31.8)	0.90	0.69-1.19	0.469
Level 3	214 (42.8)	693 (13.9)	4.34	3.40-5.53	<0.001
Level 4	38 (7.6)	635 (12.7)	0.86	0.59-1.25	0.419
Level 5	19 (3.8)	435 (8.7)	0.68	0.42-1.09	0.108
Hospital level <sup>c</sup>					
Medical center	32 (6.40)	379 (7.58)	Reference	-	-
Regional hospital	214 (42.80)	589 (11.78)	3.92	2.63-5.85	<0.001
Local hospital	183 (36.60)	506 (10.12)	3.94	2.63–5.92	<0.001
Local clinic	70 (14.00)	3522 (70.44)	0.19	0.12-0.29	<0.001
Others	I (0.20)	4 (0.08)	4.17	0.45–38.74	0.209
Employment					
Yes	287 (57.4)	2756 (55.1)	Reference	-	-
No	213 (42.6)	2244 (44.9)	1.21	0.96-1.51	0.105

Table I Demographic and Clinical Characteristics of Patients with (Cases) and Without Self-Harm
(Control Group; Ratio: 1:10) at the Index Date

**Notes**: <sup>a</sup> Univariable conditional logistic regression.<sup>b</sup> Urbanization level was categorized as level 1 (highly urbanized area), level 2 (moderately urbanized area), level 3 (newly urbanized area), level 4 (township area), and level 5 (rural area).<sup>c</sup> Cases: at the index date (self-harm event). Controls: visit closest to the index date (within 1 year). Significance was set as p < 0.001 in this study.

Proc Phreg function of SAS v9.2 (SAS Institute Inc., Cary, NC, USA). The significance level was set as p < 0.001 for all analyses. Multivariable regression based on backward variable selection was then applied. We proposed two explanatory multivariable models for suicide attempts in the population with asthma—physical and psychiatric comorbidities (Table 3)—within 1 year before the attempted suicide and a model of the medications (Table 4) used within 1 year before the attempted suicide.

## Results

## Incidence of Self-Injurious Behavior in Asthma Cohort

There were 186,862 cases newly diagnosed with asthma between January 1, 1999, and December 31, 2013. Of this cohort, 500 cases had a diagnostic record of self-injurious attempts from the baseline date to December 31, 2013. The

	Cases (N=500)	Control (N=5000)			
Number of visits on the specialists, not including the visit at the index (corresponding) date <sup>a</sup>	Mean (SD)	Mean (SD)	Crude odds ratio <sup>a</sup>	95% CI	P value
ALL	32.6 (28.4)	22.8 (20.1)	1.02	1.02-1.02	<0.001
Family practice	4.6 (8.8)	3.13 (6.8)	1.03	1.02-1.04	<0.001
Internal medicine	6.0 (10.4)	4.44 (8.2)	1.02	1.01-1.03	<0.001
Surgery	1.1 (3.0)	0.64 (2.4)	1.05	1.03-1.08	<0.001
Pediatrics	2.1 (5.9)	2.05 (5.8)	1.00	0.98-1.02	0.844
Gynecology	1.0 (3.0)	0.87 (2.9)	1.01	0.98-1.05	0.384
Orthopedics	1.2 (3.1)	0.64 (2.5)	1.06	1.03-1.09	<0.001
ENT	2.3 (5.2)	2.05 (4.4)	1.01	0.99–1.03	0.332
Ophthalmology	1.3 (3.1)	1.10 (2.6)	1.03	1.00-1.07	0.066
Dermatology	0.9 (2.7)	0.68 (2.1)	1.04	1.00-1.07	0.046
Neurology	0.7 (2.3)	0.41 (2.0)	1.05	1.02-1.09	0.006
Psychiatrist	1.8 (5.6)	0.30 (1.9)	1.13	1.11–1.16	<0.001
Rehabilitation	0.8 (4.2)	0.47 (3.1)	1.02	1.00-1.05	0.048
Emergent department	0.8 (1.9)	0.23 (0.8)	1.44	1.33–1.56	<0.001
Dentistry	1.3 (2.3	1.39 (2.5)	0.99	0.95-1.03	0.485
Chinese herb medicine	2.5 (6.0)	1.96 (5.0)	1.02	1.00-1.03	0.027
Others	4.4 (9.8)	2.48 (6.2)	1.04	1.02-1.05	<0.001
Hospital admission number within I year before the index date	Mean (SD)	Mean (SD)			
Total	0.5 (1.4)	0.2 (0.9)	1.21	1.12-1.30	<0.001
Non-psychiatric	0.4 (1.1)	0.2 (0.9)	1.15	1.07-1.24	<0.001
Psychiatric	0.1 (0.8)	0.0 (0.2)	1.80	1.33–2.44	<0.001

 Table 2 Patterns of Medical Utilization Within 1 Year Before the Index Date Among Patients with Asthma with (Cases) and Without Self-Harm (Control Group; Ratio: 1:10)

Notes: <sup>a</sup>Including departments with a mean visit number > 0.5 of cases. Those with less than 0.5 were merged with others.

**Table 3** Multivariable Conditional Logistic Regression of Physical and Psychiatric Comorbidities Within 1 YearBefore the Index Date Between Cases with Self-Harm and the Controls Derived from the Asthma Cohort from1999 to 2013

Characteristic N (%)	Cases (N=500)	Controls (N=5000)	Adjusted odds ratio <sup>a</sup>	95% CI	P-value
	N (%)	N (%)			
Physical Illness					
Cardiovascular disease	162 (32.4)	1338 (26.8)	I.58*	1.22-2.06	<0.001
Psychiatric Comorbidity					
Depressive disorder	72 (14.4)	136 (2.7)	4.44*	3.14-6.30	<0.001
Bipolar disorder	25 (5.0)	36 (0.7)	2.97*	1.65-5.35	<0.001
Sleep disorder	112 (22.4)	550 (11.0)	I.83*	1.40-2.39	<0.001

**Notes**: p < 0.001. <sup>a</sup>Variables regarding physical and psychiatric comorbidities (<u>e-Table 1</u>) were included for multivariable conditional logistic regression. Variables with a strongly significant association (p < 0.001) remained in the final multivariable model.

incidence proportion was 500 cases per 186,862 asthma cases per 15 years. The incidence rate of self-injurious behavior was 0.18 cases per 1,000 person-years in this asthma cohort.

## Characteristics of Cases and Controls

Table 1 displays the matching characteristics of the 10 controls for each case in our study. The sex distribution between cases and controls was the same, and the two groups' age distribution and employment rate were similar.

Characteristic N (%)	Case (N=500)	Controls (N=5000)	Adjusted odds ratio <sup>a</sup>	95% CI	P-value
	N (%)	N (%)			
Antidepressants	112 (22.4)	292 (5.8)	2.75*	2.05-3.70	<0.001
Benzodiazepines					
Short-acting	117 (23.4)	424 (8.5)	1.78*	1.33-2.38	<0.001
Long-acting	236 (47.2)	1302 (26.0)	2.11*	1.64-2.71	<0.001
Anti-Parkinson drugs	47 (9.4)	171 (3.4)	l.97*	1.35–2.85	<0.001

Table 4 Multivariable Conditional Logistic Regression of Concomitant Medications Used Within I YearBefore the Index Date Between Cases with Self-Harm and the Controls Derived from the Asthma Cohortfrom 1999 to 2013

**Notes:** \*p < 0.001. <sup>a</sup>Variables regarding concomitant medications (<u>e-Table 2</u>) were included for multivariable conditional logistic regression. Variables with a strongly significant association (p < 0.001) remained in the final multivariable model.

Univariable regression revealed that asthma cases with self-injurious behavior had higher Charlson Comorbidity Index scores ( $\geq 2$ ) in the year before the index date than did controls (crude odds ratio = 1.76, p < 0.001). Patients in newly urbanized areas were more likely to have self-injurious behavior (crude odds ratio = 4.34, p < 0.001).

#### Medical Utilization Before Self-Injurious Behavior

Table 2 presents medical utilization within 12 months before the index date for self-injurious cases and controls. Compared with control patients with general asthma, self-injurious cases had a higher frequency of outpatient visits (32.4 vs 22.8, p < 0.001) and more nonpsychiatric and psychiatric hospitalizations. They were more likely to visit the family practice, internal medicine, surgery, orthopedics, psychiatry, and emergency departments. Univariable regression indicated that self-injurious cases had more psychiatric outpatient visits (odds ratio = 1.13, p < 0.001) and hospitalizations (odds ratio = 1.8, p < 0.001). They also visited surgery (odds ratio = 1.05, p < 0.001), orthopedics (odds ratio = 1.06, p < 0.001), and emergency (odds ratio = 1.44, p < 0.001) departments more frequently.

## Physical and Psychiatric Comorbidities Associated with Self-Injurious Behavior

Univariable analysis unsurprisingly showed that self-injurious cases had more comorbid physical diseases and psychiatric illnesses within the year before the index date than did control cases (Supplement, e-Table 1). These variables were then included in multivariable conditional logistic regression. Variables with a strongly significant association (p < 0.001) remained in the final multivariable model with a stepwise selection strategy. Our multivariable analysis revealed that bipolar disorder (adjusted odds ratio = 2.97, p < 0.001) and depressive disorder (adjusted odds ratio = 4.44, p < 0.001) were significantly associated with self-injurious behavior. Cardiovascular diseases (adjusted odds ratio = 1.58, p < 0.001) were the only physical comorbidity in our multivariable analysis. In our multivariable analysis, sleep disorders were moderately associated with self-injurious behavior (adjusted odds ratio = 1.83, p < 0.001).

#### Concomitant Medications Associated with Self-Injurious Behavior

Univariable analysis of concomitant medications indicated that self-injurious cases used more physical and psychiatric concomitant medications within a year before the index date (Supplement, e-Table 2). Variables with a strongly significant association (p < 0.001) remained in the final multivariable model with a stepwise selection strategy. Multivariable analysis of concomitant medications revealed that anti-Parkinson drugs, antidepressants, short-acting benzodiazepine, and long-acting benzodiazepine were significantly associated with self-injurious behavior. In addition, substantial portions (47.2%) of self-injurious cases and 26.0% of controls took long-acting benzodiazepine before the index date.

## Discussion

The strength of our study is its representative nationwide sample from the general population in the Taiwanese national health care system. Based on a nested case-control study, we investigated factors associated with self-injurious behavior

in asthma patients and analyzed differences in medical utilization between patients with asthma with and without selfinjurious behavior.

## Main Findings

Asthma patients with self-deliberate harm behavior had more comorbid diseases and medical use within 1 year before their self-injurious behavior. These patients were more likely to visit internal medicine, surgery, orthopedics, psychiatry, and emergency departments. Cardiovascular diseases, bipolar disorder, depression, and sleep disorders were more closely associated with self-injurious behavior. Medications, anti-Parkinson drugs, antidepressants, and benzodiazepines were more related to these self-injurious behaviors. Understanding the risk factors of self-injurious behavior is critical for early detection and intervention. Our study provided valuable information on the medical utilization patterns of patients with asthma before their self-injurious behavior. Identification of modifiable risk factors, such as psychiatric and physical comorbidities, may direct intervention strategies against suicide in the population with asthma.

# Association of Physical Disease and Suicide in Patients with Asthma

Asthma was reported to be highly correlated with cardiovascular diseases in a previous study.<sup>23</sup> However, there were no studies to report that cardiovascular diseases increase suicide risk in patients with asthma. The present study confirms that patients with asthma who experience cardiovascular diseases have a high risk of suicide. In the literature, studies have indicated that 5.4%–17% of patients with cardiovascular diseases have suicidal ideation.<sup>24,25</sup> The risk factor for suicide among patients with cardiovascular diseases could be depression<sup>26</sup> due to psychological distress and physical function decline.<sup>27</sup> Therefore, a patient with asthma who was comorbid with cardiovascular disease could deteriorate physical function and increase psychological stress, with a synergistic effect on increasing the risk of suicide.

## Psychiatric Comorbidity and Suicide in Patients with Asthma

Patients with asthma are more likely to report symptoms of depression and suicide.<sup>28</sup> In this study, we confirmed that depression increased suicidal risk in patients with asthma, which was consistent with previous studies. The literature has shown that patients with asthma and depression have increased suicidal risk.<sup>10</sup> The effect of depression on suicidal behavior is well known. Studies have indicated that one-half to two-thirds of suicidal deaths were patients with depression.<sup>29,30</sup> Recent studies have suggested that despite controlling the effect of economic condition, physical condition, comorbidity, and depression, patients with asthma still have an increased risk of suicidal ideation and attempts, which indicates that asthma may be an independent risk factor for suicide.<sup>8,31</sup> Accordingly, patients with asthma and comorbid depression have a higher risk of attempting suicide than those without comorbid depression. This finding alerts the medical staff to be aware of asthmatic patients with depression to prevent suicides.

Intriguingly, our study is the first to indicate that, after adjusting for comorbid mental and physical illnesses, patients with asthma with bipolar disorder exhibited a 2.97-fold risk of developing deliberate self-injurious behavior. Patients with bipolar disorder have a higher risk of suicide;<sup>32</sup> however, the association between bipolar disorder and self-injurious behavior in patients with asthma is overlooked in the literature. Previous studies have proposed the comorbid relationship between asthma and bipolar disorder.<sup>33</sup> Chen et al<sup>20</sup> proposed that asthma in early adolescence is associated with an increased risk of bipolar disorder, major depression, and any depressive disorder. In addition, a meta-analysis by Wu et al<sup>33</sup> revealed a higher prevalence rate of asthma in patients with asthma that in healthy controls.

The underlying mechanism of asthma, bipolar disorder, and self-injurious behavior has not been fully elucidated. Previous studies on somatic illness in people with bipolar disorder have indicated that patients with bipolar disorder have a higher comorbidity, premature mortality rate, and suicide rate than do people without bipolar disorder.<sup>34–36</sup> A study<sup>37</sup> showed that patients with bipolar disorder were admitted for somatic illness, had a more severe course of somatic illness, and had more comorbidities than did age- and gender-matched controls. A review article reported that patients with bipolar disorder were admitted for somatic state than those without bipolar disorder.<sup>38</sup> Therefore, these two diseases (ie, asthma and bipolar disorder) could have a synergistic effect on suicide risk in the real world. Patients with asthma have a higher risk for suicide if comorbid with bipolar disorder than those without bipolar disorder. The

findings of our research suggested an opportunity to identify the critical role of bipolar disorder in suicide prevention for patients with asthma.

Our study discovered that the risk of suicide attempts in asthmatic patients with sleep disorders was 1.83-fold that of patients with asthma but without sleep disorders. Asthma significantly compromises the quality of life of patients by affecting sleep and cognition and increasing fatigue and psychological distress.<sup>39</sup> Previous studies have noted that sleep problems are an independent risk factor for suicide attempts,<sup>40,41</sup> after adjustment for mental disorders. Sleep disorders in patients with asthma could be a precipitating factor in the risk of suicide and warrant the clinical staff members to pay attention.

Furthermore, the present study found cases with suicide significantly took more short-acting and long-acting benzodiazepines than the controls with asthma. For these findings, the use of benzodiazepines could serve as the proxy marker indicating the severity of sleep disorder. Using more benzodiazepines means a higher severity of sleep disorder, which was associated with a higher risk of subsequent suicide attempts.

#### Outpatient Service Visits of Patients with Asthma with Self-Injurious Behavior

Asthma is a chronic respiratory disease and easily causes other diseases. Patients with asthma who presented selfinjurious behavior required higher medical use than did those who did not present self-injurious behavior, which indicated that patients with asthma who presented self-injurious behavior were highly associated with other diseases.

In addition, our results showed that these patients with suicide attempts were more likely to visit internal medicine, surgery, orthopedics, psychiatry, and emergency departments before the attempts, which reminded the medical staff in such departments to recognize the potential cases with suicide risk earlier.

## Limitations

The present study has some limitations. First, we may have underestimated the rate of patients with asthma who attempted suicide but failed. Patients recruited in this study were those with asthma who attempted suicide and were sent to a hospital for crisis intervention. Therefore, those with asthma who attempted suicide but were not sent to a hospital were not included in this study. Second, we cannot determine whether patients with asthma and bipolar disorder attempted suicide during their mania or depression phase and thus cannot provide a useful method for preventing suicidal behavior. Third, as data on the severity of asthma was not available, we were unable to recognize the differences in asthma severity between the cases and controls and how these differences impact the estimation of associations. Moreover, the data we collected does not include lifestyles; therefore, we cannot understand the relationship between patients' lifestyles and suicidal behavior.

#### Implications

This study discovered that during the year before patients presented self-injurious behavior, their medical use increased, particularly for internal medicine, surgery, orthopedics, psychiatry, and emergency departments. Thus, patients with asthma are likely to have suicidal ideation or behavior because of comorbidity with other diseases. In addition, we found that comorbidities, such as cardiovascular diseases, bipolar disorder, depression, and sleep disorders, were associated with attempted suicide in patients with asthma. Regarding medication, anti-Parkinson drugs, antidepressants, and benzodiazepines were often used by patients with asthma. Therefore, in the future, we can identify patients with asthma who may present self-injurious behavior according to their rate of visiting clinics, comorbidity conditions, and psychotropic drug use. A timely intervention can reduce the risk of self-injurious or suicidal behavior by patients with asthma.

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#### **Author Contributions**

Drs. Huang and Kuo conceived of and designed the study. Dr. Kuo acquired the data. Dr. Liao and Mr. Su performed statistical analysis. Drs. Chiou and Pan provided administrative and material support. Drs. Huang, Kuo and Ms. Wang drafted the manuscript. Dr. Kuo made critical revisions to the manuscript for crucial intellectual content, and Drs. Kuo and Chen supervised the study. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

## References

- D GB. Chronic respiratory disease collaborators. global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: A systematic analysis for the global burden of disease study 2015. Lancet Respir Med. 2017;5(9):691–706.
- 2. Zhang Y, Cheng J, Li Y, et al. Suicidality among patients with asthma: a systematic review and meta-analysis. J Affect Disord. 2019;256:594–603. doi:10.1016/j.jad.2019.06.031
- 3. Global Asthma Network. The global asthma report 2018. Auckland, New Zealand Global Asthma Network; 2018.
- 4. Accordini S, Corsico AG, Braggion M, et al. The cost of persistent asthma in Europe: an international population-based study in adults. *Int Arch Allergy Immunol.* 2013;160(1):93–101. doi:10.1159/000338998
- Dean BB, Calimlim BM, Kindermann SL, Khandker RK, Tinkelman D. The impact of uncontrolled asthma on absenteeism and health-related quality of life. J Asthma. 2009;46(9):861–866. doi:10.3109/02770900903184237
- 6. Barker E, Kolves K, De Leo D. The relationship between asthma and suicidal behaviours: a systematic literature review. *Eur Respir J.* 2015;46 (1):96–106. doi:10.1183/09031936.00011415
- 7. Goodwin RD. Asthma and suicide: current knowledge and future directions. Curr Psychiatry Rep. 2012;14(1):30-35. doi:10.1007/s11920-011-0243-x
- 8. Kuo CJ, Chen VC, Lee WC, et al. Asthma and suicide mortality in young people: a 12-year follow-up study. Am j Psychiatry. 2010;167 (9):1092–1099. doi:10.1176/appi.ajp.2010.09101455
- 9. Chen VC, Wang TN, Liao YT, Lin TC, Stewart R, Lee CT. Asthma and self-harm: a population-based cohort study in Taiwan. J Psychosom Res. 2014;77(6):462–467. doi:10.1016/j.jpsychores.2014.08.017
- 10. Han CH, Chung JH. Asthma and other allergic diseases in relation to suicidal behavior among South Korean adolescents. J Psychosom Res. 2018;115:94–100. doi:10.1016/j.jpsychores.2018.10.015
- 11. Steinberg L, Aldea I, Messias ME. Asthma, depression, and suicidality. J Nerv Ment Dis. 2015;203(9):664-669. doi:10.1097/ NMD.00000000000349
- Gershon AS, Wang C, Guan J, To T. Burden of comorbidity in individuals with asthma. *Thorax*. 2010;65(7):612–618. doi:10.1136/thx.2009.131078
   Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med*. 2017;17(1):74. doi:10.1186/s12890-017-0409-3
- Inoue H, Kozawa M, Milligan KL, Funakubo M, Igarashi A, Loefroth E. A retrospective cohort study evaluating healthcare resource utilization in patients with asthma in Japan. NPJ Prim Care Respir Med. 2019;29(1):13. doi:10.1038/s41533-019-0128-8
- 15. Sun HL, Lue KH. Health care utilization and costs of adult asthma in Taiwan. Allergy Asthma Proc. 2008;29(2):177-181. doi:10.2500/aap.2008.29.3095
- 16. Tavakoli H, FitzGerald JM, Chen W, et al. Ten-year trends in direct costs of asthma: a population-based study. Allergy. 2017;72(2):291-299. doi:10.1111/all.12993
- Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol. 2012;129(5):1229–1235. doi:10.1016/j.jaci.2012.01.039
- Lisspers K, Janson C, Larsson K, et al. Comorbidity, disease burden and mortality across age groups in a Swedish primary care asthma population: An epidemiological register study (PACEHR). *Respir Med.* 2018;136:15–20. doi:10.1016/j.rmed.2018.01.020
- 19. Kauppi P, Linna M, Jantunen J, et al. Chronic comorbidities contribute to the burden and costs of persistent Asthma. *Mediators Inflamm*. 2015:819194. doi:10.1155/2015/819194
- 20. Chen MH, Su TP, Chen YS, et al. Higher risk of developing major depression and bipolar disorder in later life among adolescents with asthma: a nationwide prospective study. *J Psychiatr Res*. 2014;49:25–30. doi:10.1016/j.jpsychires.2013.10.015

- Chang SS, Sterne JA, Lu TH, Gunnell D. 'Hidden' suicides amongst deaths certified as undetermined intent, accident by pesticide poisoning and accident by suffocation in Taiwan. Soc Psychiatry Psych Epidem. 2010;45(2):143–152. doi:10.1007/s00127-009-0049-x
- 22. Liu CY, Hung YT, Chuang YL, et al. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. J Health Manage. 2006;4(1):1–22.
- Tattersall MC, Guo M, Korcarz CE, et al. Asthma predicts cardiovascular disease events: the multi-ethnic study of atherosclerosis. Arterio Thromb Vasc Biol. 2015;35(6):1520–1525. doi:10.1161/ATVBAHA.115.305452
- 24. Lossnitzer N, Muller-Tasch T, Lowe B, et al. Exploring potential associations of suicidal ideation and ideas of self-harm in patients with congestive heart failure. *Depress Anxiety*. 2009;26(8):764–768. doi:10.1002/da.20587
- 25. Moazzami K, Dolmatova EV, Feurdean M. Suicidal ideation among adults with cardiovascular disease. Gene Hosp Psych. 2018;51:5-9. doi:10.1016/j.genhosppsych.2017.12.001
- 26. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol. Psych.* 2003;54(3):227-240. doi:10.1016/S0006-3223(03)00587-0
- 27. Hawton K, van Heeringen K. Suicide. Lancet. 2009;373(9672):1372-1381. doi:10.1016/S0140-6736(09)60372-X
- 28. Kolves K, Barker E, De Leo D. Allergies and suicidal behaviors: a systematic literature review. *Allergy Asthma Proc.* 2015;36(6):433-438. doi:10.2500/aap.2015.36.3887
- 29. Rich CL, Young D, Fowler RC. San Diego suicide study. I. Young vs old subjects. Arch Gen Psych. 1986;43(6):577-582. doi:10.1001/ archpsyc.1986.01800060071009
- Harwood D, Hawton K, Hope T, Jacoby R. Psychiatric disorder and personality factors associated with suicide in older people: a descriptive and case-control study. Int j Geriatric Psych. 2001;16(2):155–165. doi:10.1002/1099-1166(200102)16:2<155::AID-GPS289>3.0.CO;2-0
- 31. Chung JH, Kim SH, Lee YW. Suicidal ideation and suicide attempts among asthma. Annals Gene Psych. 2016;15:35. doi:10.1186/s12991-016-0122-2
- 32. Tsai SY, Kuo CJ, Chen CC, Lee HC. Risk factors for completed suicide in bipolar disorder. J Clin Psychiatry. 2002;63(6):469-476. doi:10.4088/ JCP.v63n0602
- Wu MK, Wang HY, Chen YW, Lin PY, Wu CK, Tseng PT. Significantly higher prevalence rate of asthma and bipolar Disorder Co-Morbidity: A meta-analysis and review under PRISMA guidelines. *Medicine*. 2016;95(13).
- Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. Br J Psychiatry. 2017;211(3):175–181. doi:10.1192/bjp.bp.117.202606
- 35. John A, McGregor J, Jones I, et al. Premature mortality among people with severe mental illness New evidence from linked primary care data. *Schizophr Res.* 2018;199:154–162. doi:10.1016/j.schres.2018.04.009
- 36. Schaffer A, Isometsa ET, Tondo L, et al. Epidemiology, neurobiology and pharmacological interventions related to suicide deaths and suicide attempts in bipolar disorder: Part I of a report of the international society for bipolar disorders task force on suicide in bipolar disorder. Aust N Z J Psychiatry. 2015;49(9):785–802. doi:10.1177/0004867415594427
- 37. Schoepf D, Heun R. Bipolar disorder and comorbidity: increased prevalence and increased relevance of comorbidity for hospital-based mortality during a 12.5-year observation period in general hospital admissions. J Affect Disord. 2014;169:170–178. doi:10.1016/j.jad.2014.08.025
- Nielsen RE, Kugathasan P, Straszek S, Jensen SE, Licht RW. Why are somatic diseases in bipolar disorder insufficiently treated? Int J Bipolar Disord. 2019;7(1):12. doi:10.1186/s40345-019-0147-y
- 39. Vargas PA, Robles E. Asthma and allergy as risk factors for suicidal behavior among young adults. J of ACH. 2019;67(2):97–112. doi:10.1080/07448481.2018.1462822
- Wong MM, Brower KJ, Craun EA. Insomnia symptoms and suicidality in the national comorbidity survey adolescent supplement. J Psychiatr Res. 2016;81:1–8. doi:10.1016/j.jpsychires.2016.06.004
- 41. Porras-Segovia A, Perez-Rodriguez MM, Lopez-Esteban P, et al. Contribution of sleep deprivation to suicidal behaviour: a systematic review. *Sleep Med Rev.* 2019;44:37–47. doi:10.1016/j.smrv.2018.12.005

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