

Research report

Association of asthma and anxiety: A nationwide population-based study in Taiwan

Yi-Chen Lee^{a,b,1}, Charles Tzu-Chi Lee^{c,d,1}, Yung-Rung Lai^e, Vincent Chin-Hung Chen^{f,g,*,1}, Robert Stewart^h^a School of Occupational Therapy, Chung Shan Medical University, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan^b Occupational Therapy Room, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan^c Department of Public Health, Kaohsiung Medical University, No. 100, Shih-Chuan 1st Road, Kaohsiung 80708, Taiwan^d Department of Health Promotion and Health Education, National Taiwan Normal University, 162, Section 1, Heping E. Rd., Taipei City 106, Taiwan^e Department of Pharmacy, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201, Taiwan^f Chang Gung Medical Foundation, Chiayi Chang Gung Memorial Hospital, No. 6–8, West Section, Jiapu Road, Puzi City, Chiayi County 613, Taiwan, ROC^g Chang Gung University, 259 Wen-Hwa 1st Road, Kwei-Shan, Tao-Yuan 333, Taiwan^h King's College London (Institute of Psychiatry, Psychology and Neuroscience), De Crespigny Park, London SE5 8AF, United Kingdom

ARTICLE INFO

Article history:

Received 25 December 2014

Received in revised form

7 July 2015

Accepted 21 September 2015

Available online 25 September 2015

Keywords:

Anxiety

Asthma

Prednisone

Gender

Age

Residence area

ABSTRACT

Background: Few studies have investigated the bidirectional relationship between asthma and anxiety; we sought to investigate asthma and anxiety in a large national sample.**Methods:** Cases were identified from Taiwan's National Health Insurance Research Database with a new primary diagnosis of asthma (ICD-9:493) aged more than 15 years between 2000 and 2007. Case status required the presence of any inpatient diagnosis of asthma and/or at least one year diagnosis of asthma in outpatient service. These 22,797 cases were compared to 22,797 sex-, age-, residence- and insurance premium-matched controls and both groups were followed until the end of 2008 for instances of anxiety, defined as ICD-9 codes 300.0, 300.01, 300.02, 300.2, 300.21, 300.23, 300.3. Competing risk adjusted Cox regression analyses were applied, adjusting for sex, age, residence, insurance premium, prednisone use, Charlson comorbidity index, cardiovascular disease, diabetes, depression disorder, and hospital admission days for any disorder. The effect of asthma on the risk of panic disorder and the effect of anxiety disorder on the risk of later asthma were also examined as competing risk adjusted Cox regression analyses**Results:** Of the 45,594 subjects, 2792 were ascertained as having anxiety during a mean (SD) follow-up period of 5.3 (2.5) years. Asthma, females, older age, rural residence, depression disorder, and prednisone use were independent risks on anxiety in the fully adjusted model. Anxiety, older age, rural residence, and prednisone use were independent risks on asthma in the fully adjusted model.**Limitations:** The severity of asthma and anxiety disorder, the duration of prednisone treatment and adherence, stressful life events, smoking, family history and relationship were not evaluated.**Conclusions:** Bidirectional relationship between asthma and anxiety disorder was confirmed in this population, in dependent of a number of potential confounding factors.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Asthma is a common and complex disease that impacts over 300 million people worldwide (Marco et al., 2011). Asthma is associated not only with high medical co-morbidity, mortality, and health care use (Mrazek, 2003), but also has adverse personal and

social consequences (Fernandes et al., 2010; Jonas et al., 1999; Wijnhoven et al., 2003), including impaired quality of life, insomnia, school absences and difficulties, as well as physical and psychological distress (Bussing et al., 1996; Fernandes et al., 2010; Jonas et al., 1999). Childhood asthma also has parental impacts including work absences, infra-familial stress and emotional problems (Bussing et al., 1996; Jonas et al., 1999; Oraka et al., 2010).

High prevalence of comorbid anxiety disorders are found in people with asthma: up to 30% in children and adolescents and 34% in adults (Katon et al., 2004; Weiser, 2007). Recent reviews conclude that asthma is a complex multifactorial illness with

* Corresponding author at: No. 6–8, West Section, Jiapu Road, Puzi City, Chiayi County 613, Taiwan (R.O.C.). Tel.: 886 5 3623002; fax: 886 5 3621000.

E-mail address: hjccch@yahoo.com.tw (V.-H. Chen).

¹ These authors contributed equally to this study.

attacks that may result from an interaction between behavioral, psychological, functional, neural, endocrine and immune processes (Marco et al., 2011; Mrazek, 2003). Increasing evidence supports a bidirectional relationship (Hasler et al., 2005; Jonas et al., 1999; Jones et al., 1976; Katon et al., 2004; Marco et al., 2011), with asthma increasing the risk of comorbid psychiatric problems such as anxiety disorder (Hasler et al., 2005; Katon et al., 2007; Lavoie et al., 2006), and anxiety disorders leading to higher asthma incidence and/or deterioration and/or functional impact (Hasler et al., 2005; Jonas et al., 1999; Marco et al., 2011). However, the high correlation between anxiety and asthma may simply reflect a broader relationship between chronic disease and reduced psychological well-being (Marco et al., 2006). Longitudinal studies are needed to examine the sequence of onset and the role of environmental factors in the association between asthma and anxiety to further clarify causative mechanisms (Goodwin et al., 2003).

Corticosteroids are the mainstay of therapy for asthma (O'byrne and Pendersen, 1998). Though efficacious, these drugs are well known to cause somatic side effects such as disturbed growth in children and deficient bone mineral density (Agertoft and Pedersen, 2000; Bonala et al., 2000; Wong et al., 2000). However, the psychiatric complications remain poorly characterized (Dubovsky et al., 2012). Anxiety was one of the most common psychiatric symptoms after corticosteroid medication (Sirois, 2003), but received relatively little attention. One study (Bonala et al., 2003) found that higher doses of corticosteroids correlated directly with higher anxiety symptoms in patients with asthma. However, the cross-sectional design and small size are potentially important limitations for this study.

Most studies of comorbid anxiety in people with asthma are limited by small and non-representative samples, self-reported asthma status, lack of consideration of confounders such as asthma medications, and cross-sectional designs that do not examine the temporal relationship between anxiety and asthma (Dubovsky et al., 2012; Katon et al., 2007; McCauley et al., 2007; Oraka et al., 2010). The prevalence and longitudinal impact of anxiety comorbidity need to be examined within a large population-based sample with asthma and thoroughly clarify the influence of participants' characteristics and clinical variables. In the study reported here, we used a nationwide, population-based cohort in Taiwan to investigate the role of asthma in the subsequent development of anxiety disorder and explored the risk factors.

2. Methods

2.1. Sample

A retrospective cohort study was assembled using data from the Taiwan National Health Insurance Research Database (NHIRD) provided by that country's National Health Research Institute (NHRI) which includes information on outpatient, ambulatory, and hospital inpatient care, as well as dental services. The National Health Insurance (NHI) program provides compulsory universal health insurance, implemented from March 1995, covering all delivery of health care in 98% of the national population. In co-operation with the Bureau of NHI, the NHRI extracted a randomly sampled representative database of 1,000,000 people from the registry of all NHI enrollees using a systematic sampling method for research purposes, forming the Longitudinal Health Insurance Database (LHID). There are no statistically significant differences in age, sex, or health care costs between this sample and all enrollees (National Health Research Institute, 2013).

Asthma cases were identified based on a recorded International Classification of Disease, Ninth revision (ICD-9) code 493. All medical claims made under this diagnostic code between 1997

and 2007 were collected from NHIRD for further analysis. The definition of asthma for this analysis required an inpatient diagnosis and/or at least one year's worth of diagnosed asthma from outpatient services, a definition consistent with other research using this database (Cazzola et al., 2012). To define new cases, people who had received any asthma diagnosis in medical claim data from 1997 to 1999 were excluded from the analysis. Therefore, asthma patients were required not to have any asthma diagnosis for at least three years prior to their first diagnosis date in our database. In this way, 22,797 new asthma cases aged 16 or above were defined between 2000 and 2007. For assessing the association between asthma and risk of anxiety disorder, one control per case was randomly sampled from the remaining sample, matching for sex, age within 1 year, residence (urban/rural) and insurance premium category (see below). Both cases and controls were followed for anxiety disorder as an outcome. Anxiety disorders were defined in this study on the basis of ICD-9 codes 300.0, 300.01, 300.02, 300.2, 300.21, 300.23, 300.3 (WHO, 1975). To define incident anxiety disorder, people who had received any anxiety diagnosis in medical claim data from 1997 to 1999 were excluded from the analysis. Anxiety disorder required the presence of any inpatient diagnosis of anxiety disorder and/or at least one year diagnosis of anxiety disorder in an outpatient service. We also excluded an anxiety disorder first diagnosis before asthma. The sampling process is summarized in Fig. 1.

Covariates considered in this analysis comprised age, sex, area of residence (urban/rural), insurance premium, cardiovascular disease, diabetes, depression disorder, prednisone use, Charlson comorbidity index and hospital admission days for any disorder. The insurance premium served as an indicator of economic status and was classified into one of four categories: (i) fixed premium and dependent, (ii) monthly income less than New Taiwan Dollars (NTD) 20,000, (iii) NTD 20,000–40,000, and (iv) NTD 40,000 or more (1US \$=32.1 NTD in 2008). The fixed premium group was the group that required social welfare support, which included low-income citizens and veterans, and the 'dependent' insurance group referred to family members that did not have a fixed salary income. The annual average cumulative defined daily dose (DDD) of prednisone was calculated and divided into 3 groups (0–30, 31–60, 60+). The defined daily dose recommended by the WHO is a unit for assessing the standard dose of drug, and cumulative DDD, which indicates the exposed duration of drug use for a period, was estimated as the sum of dispensed DDD of drug within a time period. The annual average cumulative DDD was used to measure the dose usage of prednisone in the follow-up time period. General physical health was quantified using the Charlson comorbidity index (D'hoore et al., 1993). Hospital admission days for any disorder served as an indicator of asthma severity.

The NHIRD consists of robustly de-identified secondary data released to the public for research purposes. This study was thus exempt from Institutional Review Board review.

2.2. Statistical analysis

Death prior to anxiety disorder onset was considered as a competing risk event. The death-adjusted cumulative incidences of anxiety disorder were calculated using the Fine and Gray method (Fine and Gray, 1999). Each person's first presentation of anxiety disorder within the study period was used in the calculation of outcome risk over given time intervals. The risks of anxiety disorder during the follow-up period were calculated using survival analysis, with the time function represented as the number of years from the index date of asthma diagnosis to December 31, 2008 (end of follow-up) or until the date of death or migration if earlier. The index date was the first diagnosis date of asthma and we also assigned this date to their matched controls.

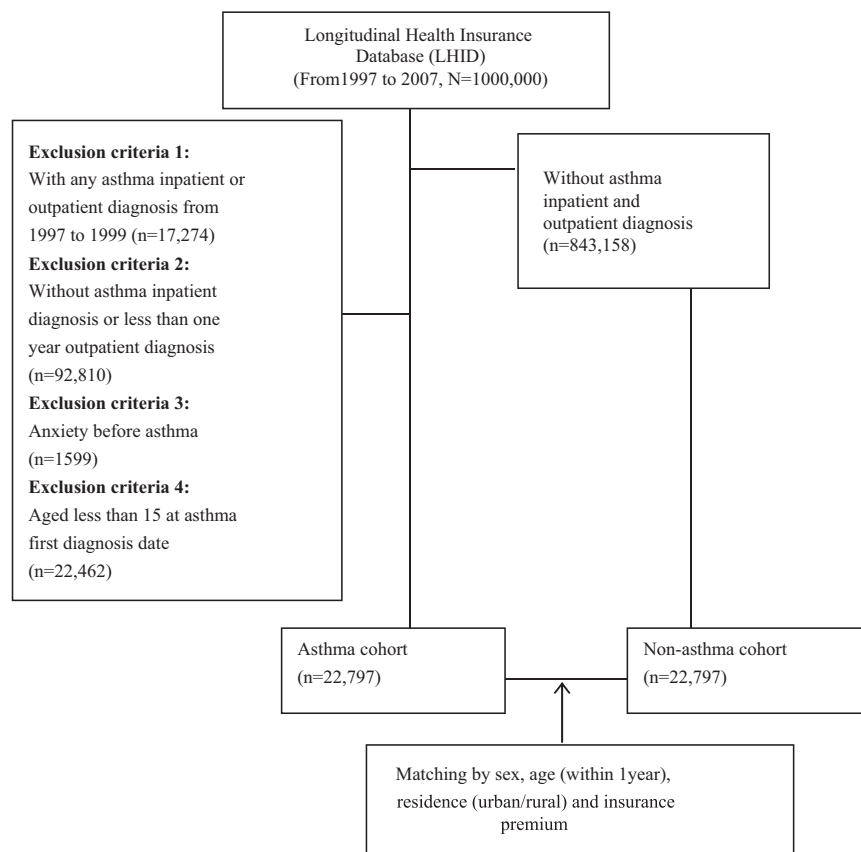


Fig. 1. Flow chart of data collection in this study.

Competing risk adjusted Cox regression models (Fine and Gray, 1999) were fitted to estimate the associations between asthma and anxiety disorder incidence, adjusting for sex, age, residence, insurance premium, cardiovascular disease, diabetes, depression disorder, prednisone use, Charlson comorbidity index and hospital admission days for any disorder. Competing risk adjusted hazard ratios with 95% confidence intervals were calculated. The model was tested first with all the sample cases included. The subgroups were then divided according to sex, and age group tested next. All data management was performed using SAS9.3 software (SAS Institute Inc., Cary, NC, USA). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the R package “cmprsk” (Gray, 2010).

The main study explored the longitudinal association between asthma and later anxiety disorder. However, the reverse association between anxiety and later asthma development had also been investigated in previous research (Alati et al., 2005; Hasler et al., 2005). We therefore also tested the hypothesis that anxiety increases risk of further asthma from competing risk adjusted Cox regression models (Fine and Gray, 1999). Furthermore, because previous research had suggested that panic was associated with asthma specifically (Goodwin and Eaton, 2003; Goodwin and Pine, 2002; Hasler et al., 2005), we also explored the association between asthma and risk of panic disorder with/without agoraphobia (ICD-9: 300.02 and 300.21) as a sensitivity analysis.

3. Results

3.1. Sample characteristics

The two cohorts comprised 22,797 people with new-diagnosis asthma and 22,797 matched controls ascertained from the

database covering 2000–2007. The mean (SD) follow-up interval for the total sample was 5.3 (2.5) years. Cohort characteristics are described and compared in MPSTable 1. Good matching was evident for sex, age, residence and insurance premium. Of the total sample of 45,549 subjects, 2792 were recorded as having anxiety disorder during the surveillance period: 1835 (8.1%) in the asthma cohort and 957 (4.2%) in the control cohort. Both the mean Charlson comorbidity indices and hospital admission days were higher in the asthma cohort.

3.2. Association between asthma and risk of anxiety disorder

Analyses of associations of interest are summarized in Table 2 and Fig. 2. In the fully adjusted Cox regression model for competing risk analysis which included adjustment for sex, age group, residence, insurance premium, cardiovascular disease, diabetes, depression disorder, prednisone, Charlson comorbidity index and hospital admission days for any disorder, asthma was positively associated with anxiety disorder incidence. Additional factors associated with the incidence of anxiety disorder were female sex, older age, rural residence, cardiovascular disease, diabetes, depression disorder, and prednisone use. Fig. 2 also showed that asthma was positively associated with anxiety disorder incidence in univariate analysis or so-called unadjusted analysis exception for the controlling of mortality ($P < 0.001$). Furthermore, Fig. 3 showed the mortality of asthma group to be higher than non-asthma group ($P < 0.001$).

In secondary analyses within the asthma cohort, factors associated with the incidence of anxiety were female sex, older age, rural residence, cardiovascular disease, diabetes, depression disorder, and prednisone use which were similar to findings in the combined cohorts (Table 3).

In the stratified analysis (Table 4), associations of interest were

Table 1
Characteristics of asthma cases and their matched^a controls in Taiwan, 2000–2007.

Characteristic	Asthma		Non-asthma ^a		Chi-square test <i>p</i> value
	<i>N</i>	%	<i>N</i>	%	
Gender					
Female	11,761	51.59	11,761	51.59	1.000
Male	11,036	48.41	11,036	48.41	
Age group					
15–24	2377	10.43	2377	10.43	0.996
25–44	6097	26.74	6096	26.74	
45–64	7459	32.72	7480	32.81	
65+	6864	30.11	6844	30.02	
Residence					
Rural	6292	27.6	6292	27.6	1.000
Urban	16,505	72.4	16,505	72.4	
Insurance premium					
Fixed premium and dependent	6559	28.77	6559	28.77	1.000
Less than NTD ^b 20,000	5369	23.55	5369	23.55	
NTD 20,000–40,000	8591	37.68	8591	37.68	
NTD 40,000 or more	2278	9.99	2278	9.99	
Prednisone (DDD)^c					
0–30	20,192	88.57	22,434	98.41	< 0.001
31–60	1247	5.47	185	0.81	
60+	1358	5.96	178	0.78	
Cardiovascular disease^d					
No	20,288	88.99	20,916	91.75	< 0.001
Yes	2509	11.01	1881	8.25	
Diabetes^e					
No	18,298	80.26	19,320	84.75	< 0.001
Yes	4499	19.74	3477	15.25	
Depression disorder^f					
No	21,730	95.32	22,233	97.53	< 0.001
Yes	1067	4.68	564	2.47	
Anxiety disorder^g					
No	20,962	91.95	21,840	95.8	0.004
Yes	1835	8.05	957	4.2	
Panic^h					
No	22,740	99.75	22,771	99.89	0.001
Yes	57	0.25	26	0.11	
Charlson indexⁱ	3.96 ± 2.94		2.41 ± 2.78		< 0.001
Hospital days (day)^j	37.96 ± 142.70		18.96 ± 96.73		< 0.001

^a Matched by sex, age (± 1 years old), residence and insurance premium.^b 1US \$ = 32.1 NTD in 2008.^c DDD: Define daily dose.^d ICD-9: 430–436.^e ICD-9: 250.^f ICD-9: 296.2X, 296.3X, 300.4, and 311.^g ICD-9: 300.0, 300.01, 300.02, 300.2, 300.21, 300.23, 300.3.^h ICD-9: 300.01, 300.21.ⁱ Mean ± SD.**Table 2**
Competing risk adjusted Cox regression analysis of incident anxiety disorder in the combined cohorts with/without asthma.

Variable	Unadjusted hazard ratio		Adjusted hazard ratio	
	Estimate (95% CI ^a)	<i>P</i> value	Estimate (95% CI ^a)	<i>P</i> value
Asthma				
No	1.00		1.00	
Yes	1.89 (1.75–2.05)	< 0.001	1.80 (1.66–1.95)	< 0.001
Gender				
Male	1.00		1.00	
Female	1.68 (1.56–1.82)	< 0.001	1.75 (1.62–1.90)	< 0.001
Age (10 years)				
	1.14 (1.12–1.16)	< 0.001	1.14 (1.12–1.16)	< 0.001
Residence				
Rural	1.00		1.00	
Urban	0.78 (0.72–0.85)	< 0.001	0.87 (0.80–0.95)	0.002
Insurance premium				
Fixed premium and dependent	1.00		1.00	
Less than NTD ^b 20,000	0.99 (0.90–1.08)	0.780	1.06 (0.95–1.17)	0.301
NTD 20,000–40,000	1.06 (0.98–1.14)	0.158	1.08 (0.98–1.18)	0.131
NTD 40,000 or more	0.64 (0.55–0.74)	< 0.001	0.93 (0.79–1.10)	0.391
Cardiovascular disease^c				
No	1.00			
Yes	0.94 (0.83–1.07)	0.365		
Diabetes^d				
No	1.00			
Yes	1.00 (0.91–1.11)	0.938		
Depression disorder^e				
No	1.00		1.00	
Yes	3.56 (3.17–4.00)	< 0.001	3.03 (2.68–3.43)	< 0.001
Prednisone (DDD)^f				
0–30	1.00		1.00	
31–60	1.52 (1.28–1.81)	< 0.001	1.15 (0.96–1.38)	0.132
60+	1.73 (1.47–2.03)	< 0.001	1.28 (1.08–1.52)	0.005
Charlson comorbidity index	1.07 (1.05–1.08)	< 0.001	0.98 (0.96–1.00)	0.046
Hospital admission days for any disorder (100 days)	0.96 (0.87–1.06)	0.426		

^a CI: Confidence interval.^b 1US \$ = 32.1 NTD in 2008.^c ICD-9: 430–436.^d ICD-9: 250.^e ICD-9: 296.2X, 296.3X, 300.4, and 311.^f DDD: Define daily dose.

significant for both sex and different ages in the fully adjusted Cox regression models for anxiety.

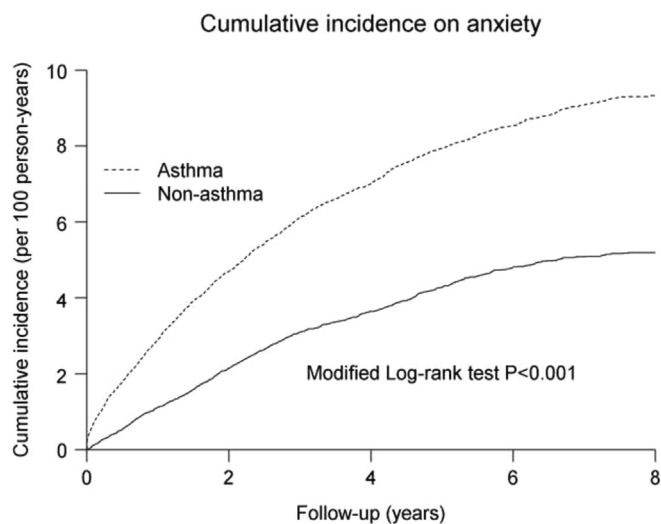


Fig. 2. Cumulative incidence on anxiety disorder by study groups (asthma vs. non-asthma).

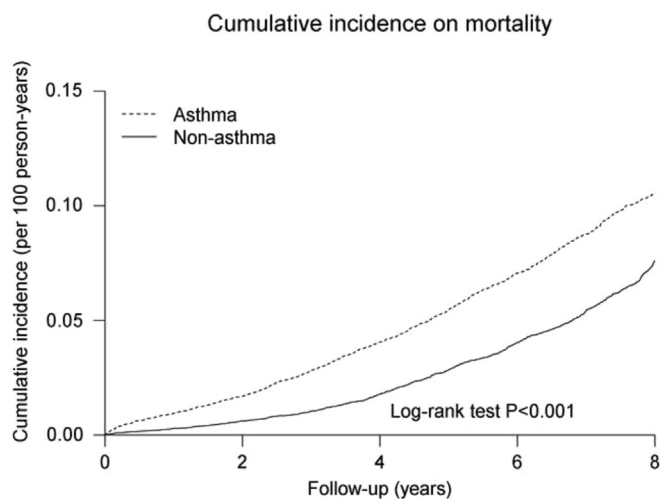


Fig. 3. Cumulative incidence on mortality by study groups (asthma vs. non-asthma).

3.3. Association between anxiety disorder and risk of asthma

The results from competing risk adjusted Cox regression models revealed that asthma and anxiety have a bidirectional association. Anxiety was also positively associated with further asthma (HR=1.80, 95% CI: 1.65–1.96, $P < 0.001$) after controlling for potential confounding factors. Additional factors associated with the incidence of asthma were older age, rural residence and prednisone use. In addition, asthma was positively associated with panic disorder with/without agoraphobia (HR=1.73, 95% CI: 1.06–2.83, $P=0.028$).

4. Discussion

This study used a population-based sample to examine the bi-directional relationship between clinically diagnosed asthma and anxiety disorder. Longitudinally, after adjusting for potential confounding variables (i.e., sex, age, residence, insurance premium, cardiovascular disease, diabetes, depression disorder, prednisone use, Charlson comorbidity index, and hospital admission days), newly-diagnosed asthma was associated with an approximately two-fold increased risk of developing anxiety disorder compared

Table 3

Competing risk adjusted Cox regression analysis of incident anxiety disorder within the asthma cohort.

Variable	Unadjusted hazard ratio		Adjusted hazard ratio	
	Estimate (95% CI ^a)	P value	Estimate (95% CI ^a)	P value
Gender				
Male	1.00		1.00	
Female	1.55 (1.41–1.7)	< 0.001	1.60 (1.45–1.76)	< 0.001
Age (10 years)				
	1.10 (1.08–1.13)	< 0.001	1.13 (1.10–1.16)	< 0.001
Residence				
Rural	1.00		1.00	
Urban	0.79 (0.72–0.87)	< 0.001	0.87 (0.78–0.96)	0.007
Insurance premium				
Fixed premium and dependent	1.00		1.00	
Less than NTD ^b 20,000	1.02 (0.92–1.14)	0.657	1.07 (0.94–1.22)	0.279
NTD 20,000– 40,000	1.08 (0.98–1.19)	0.107	1.08 (0.96–1.21)	0.224
NTD 40,000 or more	0.65 (0.54–0.78)	< 0.001	0.87 (0.71–1.06)	0.171
Cardiovascular disease^c				
No	1.00		1.00	
Yes	0.84 (0.72–0.99)	0.033	0.64 (0.54–0.76)	< 0.001
Diabetes^d				
No	1.00		1.00	
Yes	0.84 (0.75–0.95)	0.006	0.69 (0.61–0.79)	< 0.001
Depression disorder^e				
No	1.00		1.00	
Yes	2.91 (2.53–3.35)	< 0.001	2.87 (2.48–3.31)	< 0.001
Prednisone (DDD)^f				
0–30	1.00		1.00	
31–60	1.17 (0.97–1.41)	0.096	1.12 (0.92–1.35)	0.266
60+	1.33 (1.12–1.58)	0.001	1.25 (1.04–1.50)	0.015
Charlson comorbidity index				
	1.03 (1.01–1.05)	0.001	1.02 (0.99–1.04)	0.168
Hospital admission days for any disorder (100 days)				
	0.94 (0.80–1.11)	0.485		

^a CI: Confidence interval.

^b 1US \$ = 32.1 NTD in 2008.

^c ICD-9: 430–436.

^d ICD-9: 250.

^e ICD-9: 296.2X, 296.3X, 300.4, and 311.

^f DDD: Define daily dose.

with a non-asthma matched comparison group (Fig. 1). We found asthma, female sex, older age, rural residence, depression disorder, and prednisone use to be independent risk factors for anxiety disorder (Table 2). In the asthma cohort, cardiovascular disease and

Table 4Effect^a of asthma on anxiety disorder by gender and age group.

Subgroup	Adjusted hazard ratio on anxiety disorder	
	Estimate (95% CI ^b)	P value
Total	1.80 (1.66–1.95)	< 0.001
Gender		
Male	2.13 (1.85–2.44)	< 0.001
Female	1.66 (1.50–1.83)	< 0.001
Age group		
15–24	2.82 (1.76–4.51)	< 0.001
25–44	1.95 (1.62–2.33)	< 0.001
45–64	1.69 (1.49–1.92)	< 0.001
65+	1.71 (1.48–1.96)	< 0.001

^a Competing risk adjusted Cox regression analysis controlling by gender (when not stratified for this), age (when not stratified for this), residence, insurance premium, cardiovascular disease, diabetes, depression disorder, prednisone, Charlson comorbidity index and hospital admission days for any disorder.

^b CI: Confidence interval.

diabetes were associated with decreased risk for anxiety disorder (Table 3), whereas previous studies found cardiovascular disease (Roy-Byrne et al., 2008) and diabetes (Grigsby et al., 2002) were associated with increased risk. However, the effect of the interaction of cardiovascular disease and diabetes with asthma on anxiety disorder is unclear. Future studies may need to explore the mechanism of decreasing comorbidity of anxiety disorder in people with asthma and cardiovascular disease or diabetes. In addition, anxiety was associated with later asthma. We found older age, rural residence, and prednisone use to be independent risk factors for asthma (Table 5). To our best knowledge, this is the first large-scale and longitudinally-designed study of asthma and anxiety disorder in the Asian area.

The risk of panic disorder in asthma in this study (HR=1.73, 95% CI: 1.06–2.83) was higher than that in other cross-national studies which included samples from Asia (OR=1.4; 95% CI: 1.0–2.0) (Alonso et al., 2014). However, asthma patients in our study were recruited from the health care system and might have more severe symptoms and higher risk of anxiety disorder than patients recruited from community with self-reported asthma in the previous study (Alonso et al., 2014).

The risk of developing anxiety disorder among people with newly diagnosed asthma was higher than that in matched controls. This finding is consistent with previous studies (Adams et al., 2004; Goodwin and Eaton, 2003; Goodwin et al., 2003; Goodwin and Pine, 2002; Hasler et al., 2005; Moussas et al., 2008), although most previous studies have been limited methodologically, including cross-sectional design (Adams et al., 2004; Goodwin et al., 2003; Moussas et al., 2008), small sample sizes (Adams et al., 2004; Moussas et al., 2008), use of self-reported asthma (Adams et al., 2004; Moussas et al., 2008) or anxiety symptoms (Adams et al., 2004; Moussas et al., 2008), and without a matched control group (Moussas et al., 2008), and there has been limited longitudinal research (Goodwin and Eaton, 2003; Hasler et al., 2005). One study (Goodwin and Eaton, 2003) followed a community sample for only one year. The other longitudinal study (Hasler et al., 2005) followed a community sample for 20 years and found higher risks of anxiety disorder (panic disorder) after asthma (OR=4.5, 95% CI, 1.1, 20.1) than findings in this study (OR=1.85, 95% CI, 1.70–2.00). The present study included only people with newly-diagnosed asthma and later anxiety disorder by excluding any diagnosis of anxiety disorder before asthma, while the sequence of onset of asthma and anxiety disorder was not examined in the previous study (Hasler et al., 2005). In addition, several

Table 5

Competing risk adjusted Cox regression analysis of incident asthma in the combined cohorts with/without anxiety.

Variable	Unadjusted hazard ratio		Adjusted hazard ratio	
	Estimate (95% CI ^a)	P value	Estimate (95% CI ^a)	P value
Anxiety				
No	1.00		1.00	
Yes	1.83 (1.68–2.00)	< 0.001	1.80 (1.65–1.96)	< 0.001
Gender				
Male	1.00			
Female	1.08 (0.99–1.18)	0.079		
Age (10 years)				
	1.33 (1.30–1.37)	< 0.001	1.28 (1.24–1.32)	< 0.001
Residence				
Rural	1.00		1.00	
Urban	0.74 (0.68–0.81)	< 0.001	0.84 (0.77–0.92)	< 0.001
Insurance premium				
Fixed premium and dependent	1.00		1.00	
Less than NTD ^b 20,000	0.82 (0.73–0.91)	< 0.001	0.95 (0.85–1.06)	0.337
NTD 20,000– 40,000	0.77 (0.70–0.85)	< 0.001	0.93 (0.84–1.03)	0.145
NTD 40,000 or more	0.44 (0.37–0.53)	< 0.001	0.67 (0.55–0.80)	< 0.001
Cardiovascular disease^c				
No	1.00		1.00	
Yes	1.60 (1.41–1.81)	< 0.001	0.88 (0.77–1.01)	0.067
Diabetes^d				
No	1.00		1.00	
Yes	1.42 (1.28–1.57)	< 0.001	0.95 (0.85–1.06)	0.342
Depression disorder^e				
No	1.00			
Yes	1.02 (0.90–1.15)	0.792		
Prednisone (DDD^f)				
0–30	1.00		1.00	
31–60	5.34 (4.45–6.41)	< 0.001	3.75 (3.11–4.51)	< 0.001
60+	3.90 (3.21–4.74)	< 0.001	2.82 (2.31–3.45)	< 0.001
Charlson comorbidity index	1.14 (1.12–1.16)	< 0.001	1.01 (0.99–1.04)	0.308
Hospital admission days for any disorder (100 days)	1.18 (1.10–1.26)	< 0.001	1.06 (0.96–1.18)	0.255

^a CI: Confidence interval.

^b 1US \$=32.1 NTD in 2008.

^c ICD-9: 430–436.

^d ICD-9: 250.

^e ICD-9: 296.2X, 296.3X, 300.4, and 311.

^f DDD: Define daily dose.

major clinical variables were controlled on the estimation of risk of asthma on later anxiety disorder in this study including general health conditions (i.e., hospital admission days and Charlson comorbidity index) or asthma medication (i.e., prednisone) but not in the previous study (Hasler et al., 2005). The present study showed a narrower 95% confidence interval with larger sample size.

Conversely, a relatively strong association between anxiety disorder and later asthma was found in this study. Previous longitudinal studies found mixed findings between anxiety and later asthma (Alati et al., 2005; Hasler et al., 2005). The inconsistent findings may be resulted from the severity of anxiety. Clinical diagnosis of anxiety disorder (Hasler et al., 2005) significantly predict later asthma, while minor psychological distress such as internalizing symptoms (Alati et al., 2005) did not.

Examining the risk of newly diagnosed anxiety disorder after first onset of asthma may provide insights on possible mechanisms underlying co-morbidity of asthma and anxiety disorder. Asthma attacks, which can possibly be life-threatening including suffocation, may increase the level of anxiety. With episodic, sudden and repeat experiences, potentially through suffocation-induced fear conditioning and carbon dioxide hypersensitivity, anxiety disorder develops in people with asthma and certain risk factors (Wong et al., 2000). In addition, asthma medication may induce anxiety (Sirois, 2003), and anxiety may associate with increased requests for as-needed medications (Fernandes et al., 2010), more emergency room visits (O'byrne and Pendersen, 1998) and longer length of asthma-related hospitalization (Goodwin and Pine, 2002).

On the other hand, hyperventilation has been seen as one of the potential mechanism linking anxiety to later asthma (Ritz, 2012). Rapid respiration is associated with anxiety disorder. Dehydration of the airway occurs as a result of passing large volumes of air in a short period of time. Drying of the airway and increase of airway fluid osmolality may contribute to the airway narrowing and induce asthma (Anderson, 2010). A bi-directional vicious interaction of asthma and anxiety disorder further strengthens the importance of asthma–anxiety link in clinical practice.

This study found that people with a higher level of prednisone use had increased incidence of anxiety disorder both in the combined cohorts and in those with asthma. Previous findings have been inconsistent concerning the relationship of prednisone use with anxiety disorder in asthma. Some studies found anxiety to be associated with increased use of corticosteroid (Bonala et al., 2003; Fernandes et al., 2010; Kinsman et al., 1974; Romero-Frais et al., 2005) or with prednisone dependence (Amelink et al., 2014), while two studies found no significant relationship (Katon et al., 2007; Lavoie et al., 2006). Magnitude of prednisone use may account for the different findings. Patient's anxiety is associated with prescription of higher doses of oral corticosteroids by physicians (Amelink et al., 2014; Bonala et al., 2003; Fernandes et al., 2010; Kinsman et al., 1974; Romero-Frais et al., 2005), instead of use of prednisone use or not (Katon et al., 2007; Lavoie et al., 2006). Findings in this study replicated this association within the Asian context and in a relatively large sample.

Consistent with previous studies, we found female sex (Alonso et al., 2014; Fernandes et al., 2010; Oraka et al., 2010), and rural residence (Cohen et al., 2007) to be independent risk factors.

4.1. Strengths and limitations

The strengths of this study include a longitudinal design with a large nationally representative dataset, and the capacity to examine the bidirectional relationship between asthma and anxiety disorder. As mentioned, previous studies have been limited with a cross-sectional design and small sample sizes. A further strength

of the study was the use of physician diagnosed asthma to define cohorts, in contrast to the reliance of other longitudinal studies based on self-report and without delineation of the temporal relationship (Hasler et al., 2005; Jonas et al., 1999). Thirdly, considering strengths, matching was possible with controls by sex, age, urban/rural residence and insurance premium, and several demographic and clinical measures were controlled in regression models.

There are several limitations in this study. First, the level of prednisone use in this study was determined by average cumulative DDD, whereas previous studies have suggested that medication patterns such as duration (Amelink et al., 2014) or frequency (Fernandes et al., 2010) also play an important role. Second, this study did not directly assess the severity of asthma and anxiety disorder. However, hospital admission days, an indirect indicator of asthma severity, was assessed and found not to be associated with risk of anxiety disorder. Thirdly, the routine data from medical services used in these analyses did not contain information on potential risk factors such as stressful life events, smoking status, family history and relationship issues, or treatment adherence. This may have limited the findings: for example, the mental health status of family members has been found to be an important factor in the association of anxiety and asthma (Feldman et al., 2011; Ortega et al., 2004). Fourthly, this study included only participants above the age of 15 years, and the results cannot be generalized to younger age groups. Fifthly, the finding of this study confirmed that asthma itself linked to the risk of anxiety disorder. However, it is also possible that asthma and anxiety are linked by a common underlying mechanism (Marcoa et al., 2011). Further studies may be needed to confirm the mechanism underlying the association between anxiety disorder and asthma. Finally, since asthma is increasingly considered as a heterogeneous disorder, this study did not distinguish allergic asthma from non-allergic asthma. Further studies are warranted to compare the effect of allergy asthma and non-allergy asthma on the anxiety disorders.

Significant risk factors of anxiety disorders including asthma, female, older age, rural residence, depression disorder, and prednisone use were identified. Clinicians need to consider screening, evaluation and treatment of anxiety disorder particularly in patients with the above risk factors. Asthma and anxiety disorder are each leading causes of functional impairments, utilization of health-care services, morbidity and mortality across all age-ranges and ethnicity (Katon et al., 2004; Marcoa et al., 2011; Weiser, 2007). Further research is needed to explore underlying mechanisms linking asthma to anxiety and vice versa, and determining if treatment of one can prevent and improve outcomes of the other.

Conflict of interest

None.

Role of funding source

RS is part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

Acknowledgments

This study was based on the data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, Taiwan, and was managed by the National Health Research Institutes. The interpretations and conclusions contained herein did not represent those of the Bureau of National Health Insurance, Department of Health, or of the National Health Research Institutes.

References

- Adams, R.J., Wilson, D.H., Taylor, A.W., Daly, A., D'espaignet, E.T., Grande, E.D., Ruffin, R.E., 2004. Psychological factors and asthma quality of life: a population based study. *Thorax* 59, 930–935.
- Agertoft, L., Pedersen, S., 2000. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N. Eng. J. Med.* 343, 1064–1069.
- Alati, R., O'callaghan, M., Najman, J.M., Williams, G.M., Bor, W., Lawlor, D.A., 2005. Asthma and internalizing behavior problems in adolescence: a longitudinal study. *Psychosom. Med.* 67, 462–470.
- Alonso, J., Jonge, P., Lim, C.C.W., Aguilar-Gaxiola, S., Bruffaerts, R., Caldas-De-Almeida, J.M., Liu, Z., O'Neill, S., Stein, D.J., Viana, M.C., Al-Hamzawi, A.O., Angermeyer, M.C., Borges, G., Ciutan, M., Girolamo, G., Fiestas, F., Haro, J.M., Hu, C., Kessler, R.C., Lepine, J.P., Levinson, D., Nakamura, Y., Posada-Villa, J., Wojtyniak, B.J., Scott, K.M., 2014. Association between mental disorders and subsequent adult onset asthma. *J. Psychiatr. Res.* 59, 179–188.
- Amelink, M., Hashimoto, S., Spinhoven, P., Pasma, H.R., Sterk, P.J., Bel, E.H., Brinke, A.T., 2014. Anxiety, depression and personality traits in severe prednisone dependent asthma. *Respir. Med.* 108, 438–444.
- Anderson, S.D., 2010. Indirect challenge tests. *Chest* 138, 25S–30S.
- Bonala, S.B., Pina, D., Silverman, A., Amara, S., Bassett, C.W., Schnaider, A.T., 2003. Asthma severity, psychiatric morbidity, and quality of life: correlation with inhaled corticosteroid dose. *J. Asthma* 40, 691–699.
- Bonala, S.B., Reddy, B.M., Silverman, B.A., Bassett, C.W., Rao, Y.A., Amara, S., Schneider, A.T., 2000. Bone mineral density in women with asthma on long-term inhaled corticosteroid therapy. *Ann. Allergy Asthma Immunol.* 85, 495–500.
- Bussing, R., Burket, R.C., Kelleher, E.T., 1996. Prevalence of anxiety disorders in a clinic-based sample of pediatric asthma patients. *Psychosomatics* 37, 108–115.
- Cazzola, M., Calzetta, L., Bettoncelli, G., Cricelli, C., Romeo, F., Matera, M.G., Rogliani, P., 2012. Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. *Respir. Med.* 106, 249–256.
- Cohen, R.T., Canino, G.J., Bird, H.R., Shen, S., Rosner, B.A., Celedon, J.C., 2007. Area of residence, birthplace, and asthma in Puerto Rican children. *Chest* 131, 1331–1338.
- D'hoore, W., Sicotte, C., Tilquin, C., 1993. Risk adjustment in outcome assessment: the Charlson comorbidity index. *Methods Inf. Med.* 32, 382–387.
- Dubovsky, A.N., Arvikar, S., Stern, T.A., Axelrod, L., 2012. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics* 53, 103–115.
- Feldman, J.M., Pérez, E.A., Canino, G., McQuaid, E.L., Goodwin, R.D., Ortega, A.N., 2011. The role of caregiver major depression in the relationship between anxiety disorders and asthma attacks in island Puerto Rican youth and young adults. *J. Nerv. Ment. Dis.* 199, 313–318.
- Fernandes, L., Fonseca, J., Martins, S., Delgado, L., Pereira, A.C., Vaz, M., Branco, G., 2010. Association of anxiety with asthma: subjective and objective outcome measures. *Psychosomatics* 51, 39–46.
- Fine, J.P., Gray, R.J., 1999. A proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* 94, 496–509.
- Goodwin, R.D., Eaton, W.W., 2003. Asthma and the risk of panic attacks among adults in the community. *Psychol. Med.* 33, 879–885.
- Goodwin, R.D., Jacobi, F., Thefeld, W., 2003. Mental disorders and asthma in the community. *Arch. Gen. Psychiatry* 60, 1125–1130.
- Goodwin, R.D., Pine, D.S., 2002. Respiratory disease and panic attacks among adults in the United States. *Chest* 122, 645–650.
- Gray, R., 2010. *cmprsk: Subdistribution analysis of competing risks. R package version 2.2-1.* from <http://CRAN.R-project.org/package=cmprsk>.
- Grigsby, A.B., Anderson, R.J., Freedland, K.E., Clouse, R.E., Lustman, P.J., 2002. Prevalence of anxiety in adults with diabetes: a systematic review. *J. Psychosom. Res.* 53, 1053–1060.
- Hasler, G., Gergen, P.J., Kleinbaum, D.G., Ajdacic, V., Gamma, A., Eich, D., Rössler, W., Angst, J., 2005. Asthma and panic in young adults: a 20-year prospective community study. *Am. J. Respir. Crit. Care Med.* 171, 1224–1230.
- Jonas, B.S., Wagener, D.K., Lando, J.F., Feldman, J.J., 1999. Symptoms of anxiety and depression as risk factors for development of asthma. *J. Appl. Biobehav. Res.* 4, 91–110.
- Jones, N.F., Kinsman, R.A., Schum, R., Resnikoff, P., 1976. Personality profiles in asthma. *J. Clin. Psychol.* 32, 285–291.
- Katon, W., Lozano, P., Russo, J., Mccauley, E., Richardson, L., Bush, T., 2007. The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls. *J. Adolesc. Health* 41, 455–463.
- Katon, W.J., Richardson, L., Lozano, P., Mccauley, E., 2004. The relationship of asthma and anxiety disorders. *Psychosom. Med.* 66, 349–355.
- Kinsman, R.A., Spector, S., Shucard, D.W., Luparello, T.J., 1974. Observations on patterns of subjective symptomatology of acute asthma. *Psychosom. Med.* 36, 129–143.
- Lavoie, K.L., Bacon, S.L., Barone, S., Cartier, A., Ditto, B., Labrecque, M., 2006. What is worse for asthma control and quality of life depressive disorders, anxiety disorders, or both? *Chest* 130, 1039–1047.
- Marco, F.D., Santusb, P., Centanni, S., 2011. Anxiety and depression in asthma. *Curr. Opin. Pulm. Med.* 17, 39–44.
- Marco, F.D., Verga, M., Reggente, M., Casanova, F.M., Santus, P., Blasi, F., Allegra, L., Centanni, S., 2006. Anxiety and depression in COPD patients: the roles of gender and disease severity. *Respir. Med.* 100, 1767–1774.
- Marco, F.D., Santusb, P., Centanni, S., 2011. Anxiety and depression in asthma. *Curr. Opin. Pulm. Med.* 17, 39–44.
- Mccauley, E., Katon, W., Russo, J., Richardson, L., Lozano, P., 2007. Impact of anxiety and depression on functional impairment in adolescents with asthma. *Gen. Hosp. Psychiatry* 29, 214–222.
- Moussas, G., Tselebis, A., Karkanas, A., Stamouli, D., Ilias, I., Bratis, D., Vassila-Demi, K., 2008. A comparative study of anxiety and depression in patients with bronchial asthma, chronic obstructive pulmonary disease and tuberculosis in a general hospital of chest diseases. *Ann. Gen. Psychiatry* 7 (7), 1–4.
- Mrazek, D.A., 2003. Psychiatric symptoms in patients with asthma causality, comorbidity, or shared genetic etiology. *Child Adolesc. Psychiatry Clin. N. Am.* 12, 459–471.
- O'byrne, P.M., Pendersen, S., 1998. Measuring efficacy and safety of different inhaled corticosteroid preparations. *J. Allergy Clin. Immunol.* 102, 879–886.
- Oraka, E., King, M.E., Callahan, D.B., 2010. Asthma and serious psychological distress prevalence and risk factors among US adults, 2001–2007. *Chest* 137, 609–616.
- Ortega, A.N., McQuaid, E.L., Canino, G., Goodwin, R.D., Fritz, G.K., 2004. Comorbidity of asthma and anxiety and depression in Puerto Rican children. *Psychosomatics* 45, 93–99.
- Ritz, T., 2012. Airway responsiveness to psychological processes in asthma and health. *Front. Physiol.* 3, 343.
- Romero-Frais, E., Vázquez, M.I., Sández, E., Blanco-Aparicio, M., Otero, I., Vereja, H., 2005. Prescription of oral corticosteroids in near-fatal asthma patients: relationship with panic-fear, anxiety and depression. *Scand. J. Psychol.* 46, 459–465.
- Roy-Byrne, P.P., Davidson, K.W., Kessler, R.C., Asmundson, G.J., Goodwin, R.D., Kubzansky, L., Lydiard, R.B., Massie, M.J., Katon, W., Laden, S.K., Stein, M.B., 2008. Anxiety disorders and comorbid medical illness. *Gen. Hosp. Psychiatry* 30, 208–225.
- Sirois, F., 2003. Steroid psychosis: a review. *Gen. Hosp. Psychiatry* 25, 27–33.
- Weiser, E.B., 2007. The prevalence of anxiety disorders among adults with asthma: a meta-analytic review. *J. Clin. Psychol. Med. Settings* 14, 297–307.
- Wijnhoven, H.A.H., Kriegsman, D.M.W., Snoek, F.J., Hesselink, A.E., Haan, M.D., 2003. Gender differences in health-related quality of life among asthma patients. *J. Asthma* 40, 189–199.
- Wong, C.A., Walsh, L.J., Smith, C.J., Wisniewski, A.F., Lewis, S.A., Hubbard, R., Cawte, S., Green, D.J., Pringle, M., Tattersfield, A.E., 2000. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 355, 1399–1403.