

PSYCHOLOGY

Relationship between Current Psychological Symptoms and Future Risk of Asthma Outcomes: A 12-Month Prospective Cohort Study

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Background. Subjects with asthma are more susceptible to psychological symptoms, but it is uncertain whether psychological symptoms are linked to future risk of asthma outcomes. **Objective.** To investigate the relationship between current psychological symptoms and future risk of asthma outcomes. **Methods.** We conducted a prospective cohort study with a 12-month follow-up period of 297 patients with asthma. Psychological symptoms, lung function, asthma control test, and Asthma Quality of Life Questionnaire at baseline were assessed. Asthma outcomes including exacerbations, unplanned visits, emergency visits, hospital admissions, intensive care unit admissions, and length of hospital stays were monitored monthly. The time to the first asthma outcomes was analyzed. Furthermore, the association between psychological symptoms and future risk of asthma outcomes was calculated as adjusted relative risk (RR) using logistic regression models. **Results.** The asthma patients were assigned to one of three groups: neither anxiety nor depression symptoms (NAD, $n = 102$), either anxiety or depression symptoms (A/D, $n = 68$), or anxiety and depression symptoms (AD, $n = 120$). Logistic regression models indicated that asthma patients in the AD group, but not the A/D group, had an increased adjusted RR for unplanned visits and emergency visits (RR = 2.33, 95% confidence interval (CI) = [1.50, 3.61]; and RR = 3.13, 95% CI = [1.90, 5.17], respectively). The time to the first asthma outcomes including exacerbations, unplanned visits, and emergency visits was shorter in patients with psychological symptoms than those without (all $p < .001$). **Conclusion.** Current psychological symptoms, especially anxiety combined with depression, independently predict the future risk of asthma outcomes.

Keywords anxiety, asthma outcomes, depression, future risk, psychological symptoms

INTRODUCTION

Asthma is a serious global health problem and is characterized by reversible airways obstruction, airway inflammation, and airway hyperresponsiveness (AHR), varying in severity from very mild to disabling and life-threatening. The prevalence of asthma is increasing in most countries, and it is a significant burden, not only in terms of healthcare costs, but also in terms of lost productivity and reduced participation in family life (1). The high costs associated with asthma appear to be largely related to loss of asthma control rather than to management of controlled asthma. Although laudable efforts have been taken to improve asthma care over the past decade, current evidence indicates that asthma remains poorly controlled in the vast majority of patients (2, 3).

Recently published asthma guidelines (1) and the Task Force report by the American Thoracic Society/European

Respiratory Society (4) have recognized that control of asthma involves current control and long-term components referred to as “risk” or “future risk” (5). Achieving optimal asthma control relies on several behavioral factors such as self-monitoring, treatment adherence, and managing exposure to environmental triggers. The ability of an asthma patient to adopt these behavioral precautions may be influenced by psychological and emotional factors (6–8), particularly anxiety and depression. Population-based studies indicate that asthma sufferers are significantly more likely than those without asthma to have symptoms of anxiety and depression (9–12). These psychological symptoms or psychiatric disorders are significantly associated with poor asthma control, impaired quality of life, and increased healthcare utilization such as increased length of hospital stays, frequent visits to healthcare providers, and increased use of steroid medication, which could further impair their health (2, 6, 13–21). However, these evaluations of poor asthma outcomes are mainly based on cross-sectional or retrospective studies, and potential interactions between anxiety and depression were not taken into account. Therefore, we undertook a prospective cohort study with a 12-month follow-up period, to test the hypothesis that current psychological symptoms independently predict future risk of asthma outcomes and

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that different types of psychological symptoms (anxiety, depression, or both) interact to influence the future risk of asthma outcomes. Our study highlights the need to carefully consider the future risk in asthma patients with additional psychological symptoms and can be helpful to exemplify novel phenotypes of asthma, even as a complex, heterogeneous disease, in psychological issues, which may improve the treatment of asthma.

SUBJECTS AND METHODS

Design

This is a prospective cohort study with a 12-month follow-up period, conducted in the outpatient asthma clinic of West China Hospital from September 2007 to October 2009. The Medical Ethics Committee of Chinese Clinical Trial Registry at West China Hospital, Sichuan University, reviewed and approved this study, and all participants gave informed consent.

Subjects

Adult patients suspected of having asthma were recruited and asthma was diagnosed according to the criteria determined by the Global Initiative for Asthma (GINA) (1). To be eligible, patients had to meet the following criteria: (1) age between 15 and 60 years; (2) AHR with inhaled methacholine (Mch) (provocative concentration causing a 20% fall in forced expiratory volume in first second (FEV₁) [PC₂₀] <8 mg/mL) or a documented bronchodilator reversibility in FEV₁ of more than 12% predicted and 200 mL; and (3) diagnosed with chronic persistent asthma. The following exclusion criteria were also used: (1) currently experiencing acute exacerbations; (2) current alcoholism or drug addiction; (3) family history of any mental health disorder or dementia; (4) current pregnancy or currently breast-feeding; (5) history of cancer or other severe chronic diseases such as chronic obstructive pulmonary disease, ischemic heart disease, hypertension, diabetes mellitus, or renal insufficiency; and (6) inability to fully understand, comply with, and/or complete the present study. Patients could take any medications for treatment of psychological symptoms during the follow-up period.

Asthma Severity, Control, and Quality of Life Assessment

Asthma severity was defined according to GINA (1). To assess asthma control, participants completed the Asthma Control Test (ACT) (22). The ACT questionnaire is a validated self-administered questionnaire, which comprises five multiple-choice questions pertaining to the control of asthma during the previous 4 weeks. The five questions related to episodes of breathlessness, nocturnal awakenings, limitations in daily activities, need for rescue medication, and patient self-rating of asthma control. Each of the five possible answers to each question is assigned a score from 1 to 5 and the total ACT score is the sum of the scores (5–25) for all five questions. The

internal consistency reliability of the five-item ACT in Chinese patients is more than 0.85 (23, 24).

To assess asthma quality of life, subjects completed the revised Asthma Quality of Life Questionnaire (AQLQ) (25, 26) on four life domains that may be negatively impacted by asthma (activity limitations, emotional distress, environmental stimuli, and symptoms). The AQLQ contains 32 items rated on a 7-point scale (1 = maximal impairment, 7 = no impairment) to yield a mean score out of 7. The AQLQ has demonstrated very good measurement properties, including high intraclass correlation coefficients (between 0.90 and 0.95) and good construct, cross-sectional, and longitudinal validity, including in Chinese patients (25, 27).

Identification of AHR and Measurements of Lung Function

FEV₁ and forced vital capacity (FVC) were measured with body plethysmography (SensorMedics 6200, Yorba Linda, CA, USA). Airway responsiveness was measured by Mch challenge, using a standardized dosimeter method. As a safety precaution, Mch challenge test was undertaken in subjects with FEV₁ of $\geq 70\%$ predicted. Based on the standardized operating procedure (28), asthma was diagnosed if PC₂₀ FEV₁ was less than 8 mg/mL or if the bronchodilator reversibility test identified reversibility in FEV₁ that indicates asthma is accepted as both $\geq 12\%$ and ≥ 200 mL from the pre-bronchodilator value (1).

Assessment of Psychological Symptoms at Baseline

Anxiety and depression symptoms were assessed at baseline using the Hospital Anxiety and Depression Scale (HADS) (29). HADS is a validated screening tool for symptom severity although it is not a diagnostic tool for psychiatric disorders per se in both hospitalized and primary care patients with chronic diseases including asthma (30–32). HADS consists of seven questions relating to anxiety and seven questions relating to depression. The scores were totaled to give an anxiety score and a depression score (range 0–21), and a score ≥ 9 was used as a cut-off point for diagnosing anxiety and depression symptoms in Chinese patients (33, 34). This protocol has 100% sensitivity and 90% specificity for anxiety and 100% sensitivity and 100% specificity for depression in Chinese (33, 34).

Asthma Outcomes

Six kinds of end-point events in asthma outcomes were identified, including exacerbations, unplanned visits, emergency visits, hospital admissions, intensive care unit (ICU) admissions, and length of hospital stays. Exacerbations were defined as the occurrence of any of the following: unplanned or emergency visits, hospitalization for asthma by patient or physician, 3-day use of systemic corticosteroids for asthma, a decrease in the morning peak expiratory flow rate to more than 35% below the baseline value on 2 consecutive days, or use of 10 puffs or more per day of rescue β -agonist for 2 consecutive days

(35). Only one occurrence was recorded if emergency visits, hospital admissions, or ICU admissions from a primary care setting took place within 1 week of each other. The short, structured questionnaire, answerable by “yes” or “no” for the six types of events, was used during monthly telephone interviews over a 12-month period to collect the data on asthma outcomes. Clinical information on asthma outcomes was self-reported by the patients. To promote accuracy of the questionnaire responses, prior to the study, participants received a detailed description of the study aims and were told that their responses would not influence subsequent treatment. All interviewers were trained to administer the questionnaire in the same manner and were also blinded to the patients’ levels of psychological symptoms at baseline and during follow-up.

Statistical Analysis

Patients who received medications for psychological symptoms during follow-up were excluded from the analysis. All continuous variables were expressed as mean $\pm$ standard deviation, and differences were analyzed with ANOVA or with nonparametric statistics if continuous variables were not normally distributed. Categorical data were compared using the chi-squared test or Fisher’s test. The effects of anxiety and depression symptoms and their interaction at baseline on the future risk of asthma outcomes were examined using general linear models adjusted for covariates such as age, sex, body mass index (BMI), anaphylactic history, smoke index, education, household income, work status, health insurance, asthma duration, asthma severity, FEV₁% predicted, and ACT according to published papers and our results (19, 36), which were statistically significant differences among the groups at baseline. Asthma outcomes were presented as the number of patients with asthma outcomes (yes or no), the number of asthma outcomes (frequencies, n), and the time to first asthma outcomes (time, months) (19, 31). The time to first asthma outcomes was described with Kaplan–Meier curves and was compared between groups with differing psychological symptoms using a log-rank test. In addition, we used logistic regression models to evaluate the prospective impact of psychological symptoms on future risk of asthma outcomes during longitudinal follow-up. Multivariate proportional hazards analysis was used to adjust for sex, age, smoking index, anaphylactic history, BMI, household income, education levels, health insurance, work status, asthma duration, asthma severity, FEV₁% predicted, and ACT, followed by calculation of adjusted relative risk (RR) with 95% confidence intervals (CIs).

To achieve adequate statistical power, we determined the minimum sample size using the formula $\geq 50 + 8n$, where n represents the number of predictor variables (37). Statistical analysis was performed using SPSS software for Windows (version 12.5, SPSS, Inc., Chicago, IL, USA). A double-sided p -value of less than .05 was considered statistically significant.

RESULTS

Study Profile

A total of 574 consecutive patients with suspected asthma were admitted to the Asthma Clinic in our hospital, and diagnosis of asthma was confirmed in 501 subjects. After lung function testing, 297 eligible patients with asthma were included in this study. Twenty-one subjects (7.07%) were withdrawn from the study during the 12-month follow-up. Fourteen of these were lost to contact, three refused, and four violated the study protocol. The data for the 17 withdrawals, except for the four subjects who violated the study protocol and the three refusals without any follow-up data, were entered into our analysis. Based on the 9 cut-off point of the HADS scores, the study subjects were classified into three groups: (1) neither anxiety nor depression symptoms (NAD, $n = 102$); (2) either anxiety or depression symptoms (A/D, $n = 68$); (3) anxiety and depression symptoms (AD, $n = 120$). The study flow chart is shown in Figure 1.

Sociodemographic and General Medical Characteristics at Baseline

Sociodemographic and general medical characteristics of subjects are presented in Table 1. There were statistically significant differences in sex, age, education levels, anaphylactic history, household income, work status, and health insurance among the NAD, A/D, and AD groups at baseline (all $p < .05$). The A/D and AD groups had a greater proportion of females, older age, low education levels and household income, unemployed, anaphylaxis, and absence of health insurance than the NAD group.

Clinical Asthma Characteristics and Asthma Medications at Baseline

The clinical asthma characteristics and asthma medications for subjects are shown in Table 2. There were statistically significant differences in asthma duration, asthma severity, ACT scores, AQLQ scores, and lung functions in the different psychological groups (all $p < .01$). The AD group had a higher proportion of patients with moderate and severe asthma and a longer duration of asthma compared with the NAD and A/D groups. Patients with psychological symptoms had poor asthma control (decreased ACT scores) and low quality of life compared with subjects without anxiety or depression symptoms (the NAD group). In addition, FEV₁, FEV₁% predicted, and FEV₁/FVC% predicted were significantly lower in the AD group. However, there were no significant differences between the groups in the proportion of patients receiving various asthma medications including aminophylline, β_2 -agonists, or corticosteroids.

Effect of Current Psychological Symptoms on Asthma Outcomes

There were statistically significant statistical differences in asthma exacerbations, unplanned visits, emergency

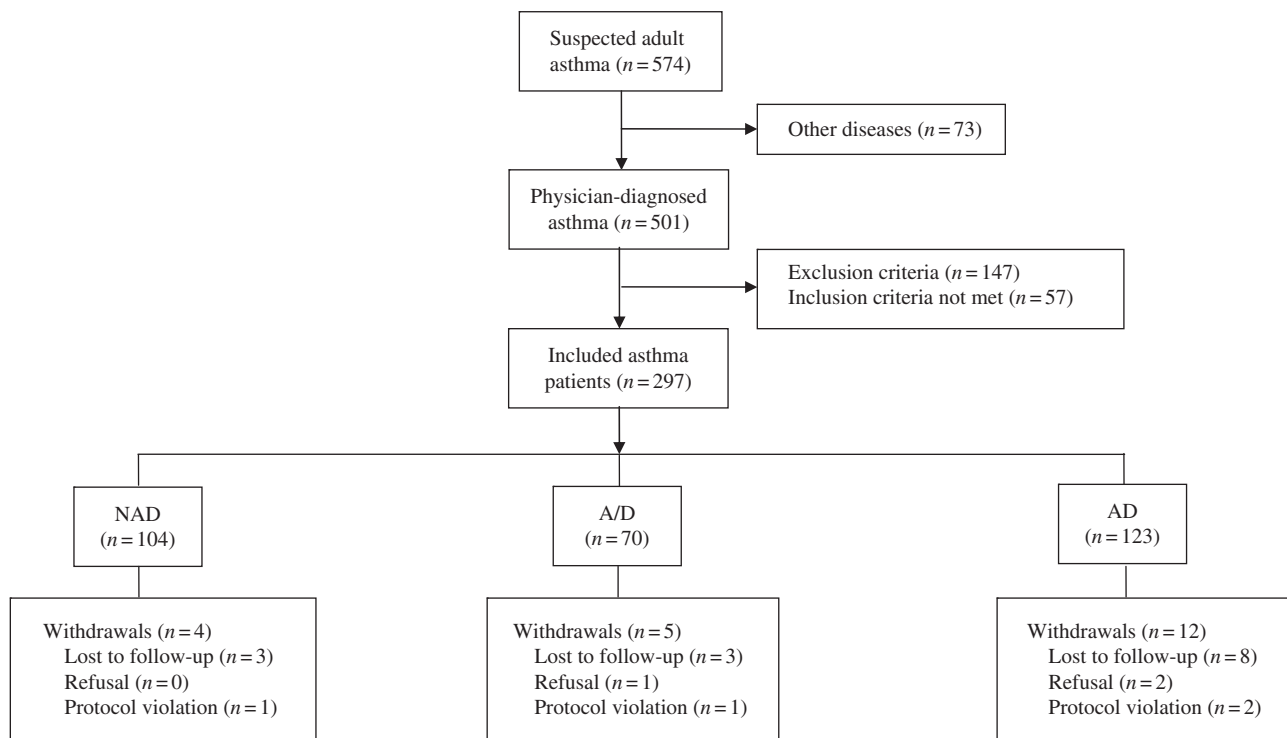


FIGURE 1.—Study flow chart. NAD, neither anxiety nor depression symptoms; A/D, either anxiety or depression symptoms; AD, both anxiety and depression symptoms.

TABLE 1.—Sociodemographic and general medical characteristics in asthma patients grouped by psychologic symptoms.

Characteristic	NAD	A/D	AD	χ^2/F	<i>p</i>
<i>n</i>	102	68	120		
Sex (F/M)	34/68	34/34*	60/60**	7.45	.024
Age (years)	35.9 ± 11.7	37.0 ± 11.7*	43.1 ± 11.8**	11.73	<.001
BMI (kg/m ²)	22.5 ± 4.3	22.1 ± 3.0	22.3 ± 3.4	0.27	.766
Education				34.26	<.001
Primary school or less	5	11**	29**		
High school	49	38**	73**		
University degree	48	19**	18**		
Smoking index				2.76	.471
$\bar{x} \pm SD$	54.6 ± 161.6	78.1 ± 221.4	53.8 ± 131.3		
Median (minimum, maximum)	0 (0, 800)	0 (0, 800)	0 (0, 600)		
Anaphylactic history (Y/N)	40/62	41/27**	78/42**	15.87	<.001
Household income				18.73	.005
Low	40	40*	78**		
Medium	50	22*	36**		
High	12	6*	6**		
Work status				38.91	<.001
Unemployed	15	27**†	54**		
Retired/student/home duties	12	6**†	24**		
Part-time	15	8**†	4**		
Full time	60	27**†	38**		
Health insurance (Y/N)	60/42	25/43**	38/82**	17.81	<.001

Note: Compared with NAD, **p* < .05, ***p* < .01; compared with AD, †*p* < .05, ‡*p* < .01.

NAD, neither anxiety nor depression symptoms; A/D, either anxiety or depression symptoms; AD, both anxiety and depression symptoms.

visits, hospital admissions, hospitalized days, and the proportion of patients with poor asthma outcomes in the different study groups (all *p* < .05) (Table 3).

A multiple linear regression model was established containing sex, age, BMI, smoking index, anaphylactic history, household income, work status, education level,

health insurance, asthma duration, asthma severity, FEV₁% predicted, ACT, anxiety or depression symptoms, and interaction of anxiety and depression symptoms for future risk of asthma outcomes excluding ICU admissions (Table 4). The model showed that there were independent effects of either anxiety or depression symptoms, and interaction between anxiety and depression symptoms,

TABLE 2.—Asthma characteristics, asthma medications, and lung function grouped according to psychological symptoms.

Characteristic	NAD	A/D	AD	χ^2/F^a	p^a
<i>n</i>	102	68	120		
Asthma duration (months)				6.327	.002
$\bar{x} \pm SD$	58.8 $\pm$ 90.7	53.5 $\pm$ 93.6 $\ddagger$	102.4 $\pm$ 127.7**		
Median (minimum, maximum)	24 (0.5, 396)	24 (0.5, 480)	48 (0.5, 660)		
Asthma severity				35.97	<.001
Intermittent	43	16*	15**		
Mild	46	35*	57**		
Moderate	9	12*	28**		
Severe	4	5*	20**		
Asthma medications					
Aminophylline (Y/N)	19/83	13/55	29/91	1.22	.545
β_2 -agonists (Y/N)	9/93	8/60	13/107	0.43	.805
Corticosteroids (Y/N)	8/94	1/67	7/113	3.22	.070
ACT	19.0 $\pm$ 3.1	17.9 $\pm$ 2.6* $\ddagger$	16.1 $\pm$ 3.3**	24.52	<.001
AQLQ	4.5 $\pm$ 1.2	3.7 $\pm$ 1.0** $\ddagger$	3.1 $\pm$ 1.1**	41.21	<.001
FEV ₁ (L)	2.87 $\pm$ 0.77	2.70 $\pm$ 0.96 $\ddagger$	2.31 $\pm$ 0.74**	13.43	<.001
FEV ₁ (% predicted)	90.14 $\pm$ 16.12	89.43 $\pm$ 22.33 $\ddagger$	79.30 $\pm$ 24.20**	8.41	<.001
FEV ₁ /FVC (% predicted)	84.50 $\pm$ 12.07	84.04 $\pm$ 14.20 $\ddagger$	78.61 $\pm$ 14.13**	5.28	.006

Notes: NAD, neither anxiety nor depression symptoms; A/D, either anxiety or depression symptoms; AD, both anxiety and depression symptoms.

Compared with NAD, * p < .05, ** p < .01; compared with AD, $\ddagger p$ < .05, $\ddagger p$ < .01.

^aAdjusted for sex, age, education levels, anaphylactic history, household income, work status, and health insurance.

TABLE 3.—Asthma outcomes after 12-month follow-up grouped according to psychological symptoms.

Characteristic	NAD	A/D	AD	χ^2/F	p
<i>n</i>	102	68	120		
Exacerbations				4.61	.011
Y/N	51/51	46/22* $\ddagger$	97/23**		
$\bar{x} \pm SD$	2.8 $\pm$ 6.8	4.3 $\pm$ 13.2* $\ddagger$	9.0 $\pm$ 21.7**		
Median (minimum, maximum)	0.5 (0, 50)	2 (0, 105)* $\ddagger$	6 (0, 230)**		
Non-planned visits				44.73	<.001
Y/N	13/89	25/43** $\ddagger$	77/43**		
$\bar{x} \pm SD$	0.2 $\pm$ 0.5	0.6 $\pm$ 0.9** $\ddagger$	2.2 $\pm$ 2.4**		
Median (minimum, maximum)	0 (0, 3)	0 (0, 4)** $\ddagger$	2 (0, 13)**		
Emergency visits				35.93	<.001
Y/N	3/99	10/58** $\ddagger$	59/61**		
$\bar{x} \pm SD$	0.03 $\pm$ 0.17	0.15 $\pm$ 0.36** $\ddagger$	0.86 $\pm$ 1.17**		
Median (minimum, maximum)	0 (0, 1)	0 (0, 1)** $\ddagger$	0 (0, 5)**		
Hospital admissions				13.93	<.001
Y/N	0/102	0/68 $\ddagger$	20/100**		
$\bar{x} \pm SD$	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0 $\ddagger$	0.30 $\pm$ 0.74**		
Median (minimum, maximum)	0 (0, 0)	0 (0, 0) $\ddagger$	0 (0, 3)**		
ICU admissions				1.43	.242
Y/N	0/102	0/68	2/118		
$\bar{x} \pm SD$	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.02 $\pm$ 0.13		
Median (minimum, maximum)	0 (0, 0)	0 (0, 0)	0 (0, 1)		
Hospitalized days				13.33	<.001
$\bar{x} \pm SD$	0.0 $\pm$ 0.1	0.0 $\pm$ 0.0 $\ddagger$	3.7 $\pm$ 9.3**		
Median (minimum, maximum)	0 (0, 1)	0 (0, 0) $\ddagger$	0 (0, 48)**		

Notes: NAD, neither anxiety nor depression symptoms; A/D, either anxiety or depression symptoms; AD, both anxiety and depression symptoms.

Compared with NAD, * p < .05, ** p < .01; compared with AD, $\ddagger p$ < .05, $\ddagger p$ < .01.

that accounted for the variance in unplanned visits, emergency visits, and hospital admissions (all p < .05). Independent effects of the interaction between anxiety and depression symptoms accounted for the variance in asthma exacerbations (p < .001) and hospitalized days (p = .007). The time to first asthma outcomes was also assessed in the three groups (Figure 2). According to the Kaplan–Meier survival analysis, patients with psychological symptoms experienced a reduced time to the first asthma outcomes such as asthma exacerbations,

unplanned visits, and emergency visits after adjustment for sex, anaphylactic history, BMI, household income, education levels, health insurance, work status, asthma duration, asthma severity, FEV₁ % predicted, and ACT (all p < .0001).

Patients with anxiety and depression symptoms had an increased RR for unplanned visits and emergency visits compared to those without psychological symptoms, after adjustment for sex, age, smoking index, anaphylactic history, BMI, household income, education levels, health

TABLE 4.—Linear regression models for future risk of asthma outcomes after 12-month follow-up.

Variables	Asthma exacerbations					Unplanned visits					Emergency visits					Hospital admissions					Hospitalized days				
	R ²	F	B	t	p	R ²	F	B	t	p	R ²	F	B	t	p	R ²	F	B	t	p	R ²	F	B	t	p
Sex	0.00	1.01	0.54	1.06	.316	0.00	1.80	0.40	1.39	.181	0.01	4.14	0.27	2.03	.043	0.03	5.95	0.22	2.44	.016	0.03	5.37	2.61	2.32	.022
Age	0.00	0.12	0.01	0.33	.731	0.01	2.14	0.02	1.44	.145	0.01	6.31	0.01	2.51	.013	0.00	0.68	0.00	0.82	.410	0.00	0.36	0.03	0.60	.549
BMI	0.00	0.50	-0.05	-0.78	.482	0.00	0.18	-0.02	-0.48	.672	0.00	0.04	0.00	0.20	.834	0.00	0.44	-0.01	0.66	.506	0.00	0.19	-0.07	0.44	.663
Smoking index	0.00	0.37	0.00	-0.66	.545	0.00	0.07	0.00	-0.30	.793	0.00	0.01	0.00	0.10	.935	0.00	0.00	0.00	0.00	.946	0.00	0.00	0.00	0.00	.936
Anaphylactic history	0.00	0.58	0.51	1.12	.450	0.00	0.03	0.02	0.09	.867	0.00	0.40	-0.06	0.63	.526	0.00	0.07	0.01	0.26	.789	0.00	0.57	-0.37	0.75	.453
Household income	0.00	0.18	-0.12	-0.21	.668	0.00	0.14	-0.07	-0.22	.704	0.00	0.00	0.03	0.00	.996	0.00	0.76	-0.07	0.87	.385	0.00	0.96	-0.93	0.98	.328
Work status	0.02	3.36	-0.65	-2.25	.069	0.02	3.63	-0.35	-2.18	.058	0.02	6.83	-0.22	2.61	.009	0.03	5.77	-0.14	2.40	.017	0.03	4.87	-1.67	2.21	.029
Education	0.00	0.02	-0.03	-0.07	.876	0.00	0.12	0.10	0.41	.726	0.00	0.45	0.03	0.67	.833	0.00	1.10	0.08	1.05	.296	0.00	0.80	0.93	0.89	.374
Health insurance	0.00	0.30	0.34	0.58	.581	0.00	0.04	0.08	0.24	.824	0.00	0.51	0.10	0.71	.474	0.01	2.11	0.15	1.45	.148	0.01	2.72	2.14	1.65	.101
Asthma duration	0.00	0.11	0.00	0.11	.736	0.00	0.80	0.00	-0.58	.373	0.00	0.25	0.00	0.50	.617	0.00	1.31	0.00	1.14	.254	0.00	0.27	0.00	0.52	.602
Asthma severity	0.03	3.20	0.93	2.00	.075	0.02	4.58	0.41	2.14	.033	0.048	5.24	0.31	2.29	.023	0.07	6.53	0.22	2.55	.011	0.05	4.82	2.49	2.19	.029
FEV ₁ (% predicted)	0.00	0.46	0.01	0.74	.499	0.00	0.53	-0.00	-0.34	.466	0.014	1.88	0.01	1.37	.172	0.00	0.42	-0.00	0.65	.517	0.00	0.37	-0.02	0.61	.544
ACT	0.01	2.13	0.11	0.86	.146	0.04	7.87	0.06	2.81	.005	0.05	10.69	0.16	3.27	.001	0.02	3.64	0.02	1.91	.058	0.01	2.13	0.22	1.46	.146
A/D	0.02	3.03	1.34	1.75	.083	0.03	3.94	0.84	1.95	.049	0.04	4.92	0.45	2.22	.028	0.04	4.35	0.27	2.09	.038	0.03	3.51	3.14	1.87	.063
AD	0.49	11.09	2.10	7.53	<.001	0.42	9.57	1.02	3.09	<.001	0.43	8.53	0.45	2.92	<.001	0.31	5.18	0.18	2.28	<.001	0.291	4.70	2.10	2.17	<.001
Model	0.48	11.44			<.001	0.42	8.67			<.001	0.42	8.85			<.001	0.30	5.19			<.001	0.28	4.65			<.001

Note: A/D, either anxiety or depression symptoms; AD, both anxiety and depression symptoms.

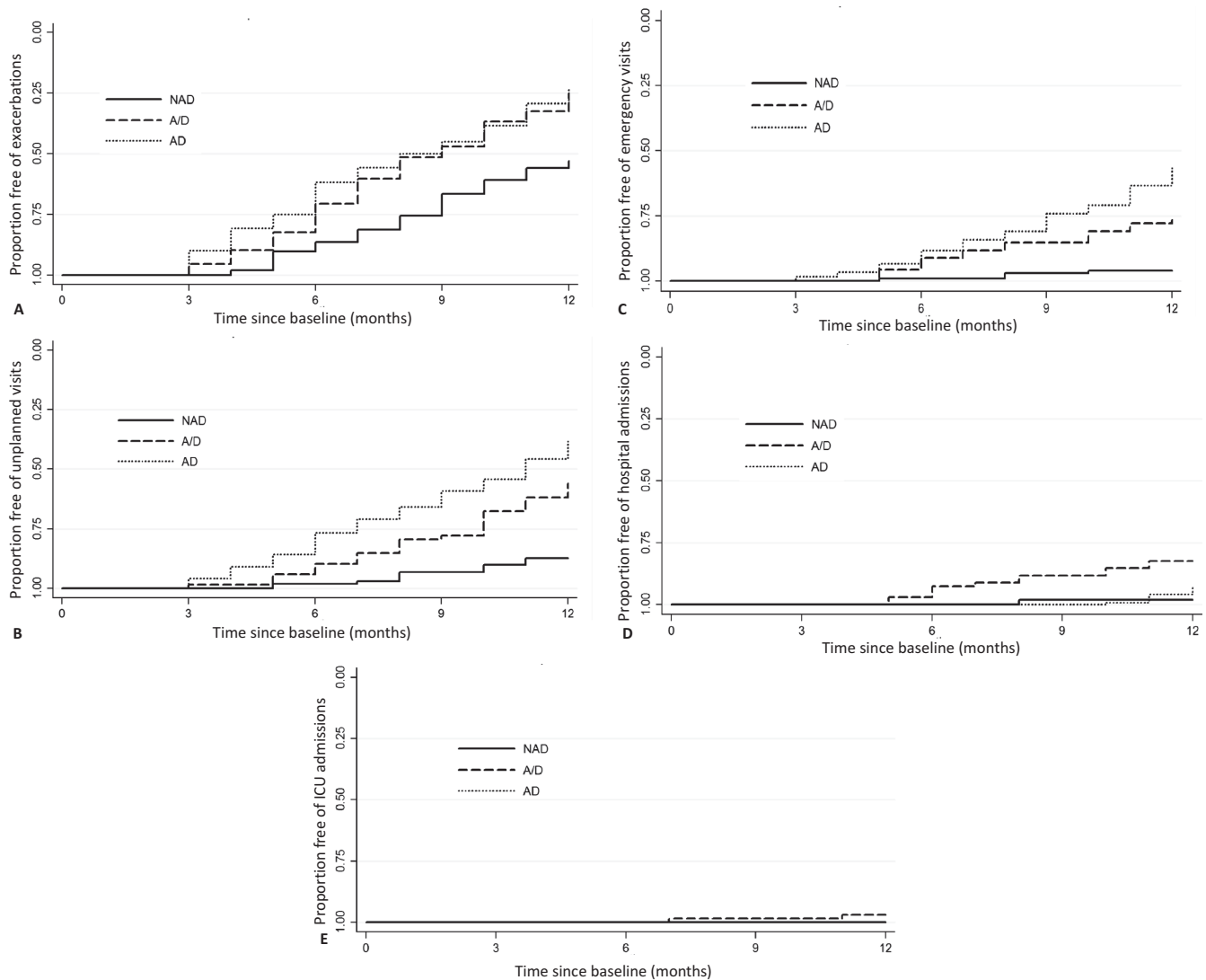


FIGURE 2.—Kaplan–Meier plot of time to first asthma outcomes in groups by psychological symptoms adjusted for sex, anaphylactic history, BMI, household income, education levels, health insurance, work status, asthma duration, asthma severity, FEV₁ % predicted, and ACT. (A) Asthma exacerbations ($p < .0002$); (B) unplanned visits ($p < .0001$); (C) emergency visits ($p < .0001$); (D) hospital admissions ($p = .9639$); (E) ICU admissions ($p = .780$). NAD, neither anxiety nor depression symptoms; A/D, either anxiety or depression symptoms; AD, both anxiety and depression symptoms.

insurance, work status, asthma duration, asthma severity, FEV₁ % predicted, and ACT (RR = 2.33, 95% CI = [1.50, 3.61], and RR = 3.13, 95% CI = [1.90, 5.17], respectively) (Table 5).

TABLE 5.—Relative future risk of asthma outcomes in patients with psychological symptoms after 12-month follow-up.

Variables	Exacerbations		Unplanned visits		Emergency visits	
	RR ^a	95% CI	RR ^a	95% CI	RR ^a	95% CI
NAD	1	Reference	1	Reference	1	Reference
A/D	1.89	0.63–5.71	1.15	0.36–3.65	2.76	0.26–29.2
AD	1.54	0.96–2.45	2.33	1.50–3.61	3.13	1.90–5.17

Notes: RR, relative risk; CI, confidence interval.

^aAdjusted for sex, age, smoking index, anaphylactic history, BMI, household income, education levels, health insurance, work status, asthma duration, asthma severity, FEV₁ % predicted, and ACT.

DISCUSSION

Our findings indicate that there is an independent association between psychological symptoms at baseline and future risk of asthma outcomes. The patients with psychological symptoms had considerably more asthma exacerbations, unplanned visits, emergency visits and hospital admissions, and the time to those outcomes was reduced in comparison with patients without psychological symptoms, regardless of sex, age, smoking index, anaphylactic history, BMI, household income, education levels, health insurance, work status, asthma duration, asthma severity, lung function, and level of asthma control. The present findings also suggest that there are significantly different outcomes within the groups of patients with psychological symptoms. Asthmatics with both anxiety and depression symptoms had the worst asthma outcomes and the shortest time to the first asthma outcomes. These findings highlighted the relationship

between psychological disturbances and future risk of asthma outcomes.

To our knowledge, a small number of prospective studies based on an *a priori* hypothesis have been undertaken to search for a possible temporal association between psychological issues and future risk of asthma outcomes. Most previous studies (9, 13, 18, 20) were cross-sectional or retrospective and may have suffered from recall bias. Although four studies were prospective or longitudinal (15, 17, 19, 38), there were concerns that limited their validity. For instance, odds of the presence and/or the severity of psychological symptoms such as anxiety and/or depression were likely influenced by the failure to exclude subjects with respiratory diseases other than asthma or other co-morbidities such as chronic obstructive pulmonary disease, hypertension, and diabetes. Unlike our study, many of the previous studies neglected possible effects of different follow-up times and seasonal variations, which may have confounding effects. Additionally, many other studies did not attempt to differentiate between specific types of psychological symptoms, and the interaction between anxiety and depression symptoms was not considered in any of the long-term longitudinal studies published to date. Finally, asthma outcomes such as exacerbations, unplanned visits, emergency visits, hospital admissions, ICU admissions, length of hospital stays, and time to these outcomes were not exactly defined and reported in previous studies.

Most of our results were consistent with previous investigations (9, 13, 17–20, 38, 39). In our study, 188 of 290 patients (64.83%) had anxiety or depression symptoms, which was high compared with other studies that reported 30–35% of symptoms. There are two possible explanations for this difference. First, the specific psychological scales used in the studies varied considerably and included HADS (39), the standardized and validated Patient Health Questionnaire 8 (9), the Center for Epidemiologic Studies Depression Scale (19), the Zung Self-Rating Anxiety and Depression Scale (2), the Geriatric Mental State schedule (40), the Health and Life Experiences Questionnaire (41), the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (6), and the Kessler Psychological Distress Scale (42). Second, the subjects in the different studies had differing asthma control levels. For example, we compared our study with a cross-sectional study by DiMarco et al. (39), which also used the HAD scale. The asthma control levels were considerably worse in our study, with only 17.2% of our subjects having well-controlled asthma compared to 71.0% reported by DiMarco et al. (39). In ten Brinke's study (20), asthma patients with psychological symptoms had increased odds ratio (OR) for ICU admission and mechanical ventilation (adjusted OR = 1.6 and OR = 16.0, respectively). We did not find that psychological symptoms at baseline were associated with ICU admissions, which may reflect the lower proportion of patients with severe asthma in our population. We previously found that interactions between anxiety and depression symptoms were associated

with lower asthma-related quality of life, suggesting that physicians should consider the impact of negative mood states, especially the interaction between anxiety and depression symptoms, when establishing treatment strategies for patients with asthma (2). Therefore, we conducted the present study to explore, for the first time, the relationship between different types of current psychological symptoms and future risk of asthma outcomes. Of the patients with psychological symptoms, those with both anxiety and depression symptoms had the worst asthma outcomes and the shortest time to the first outcomes. This may indicate that there is a synergistic interaction between anxiety and depression symptoms that influences asthma outcomes.

In asthma patients, an interaction between anxiety and depression symptoms may decrease self-esteem, decrease internal feelings of control, and ultimately undermine self-efficacy of asthma control. Thus, patients with both anxiety and depression symptoms have reduced asthma-related emotional functioning and response to environment stimuli and have more difficulty coping with their disease (2). This could lead to further activity limitations and/or negatively affect medication compliance. In this situation, avoidance, as a coping mechanism, may detrimentally affect asthma quality of life, with the possibility of fueling even greater anxiety and depression symptoms in an ongoing negative cycle. Such a feedback loop could generate additional feelings of fear and/or imminent catastrophe, which could provoke asthma exacerbations and other adverse asthma outcomes (2). One recent study indicated that breathing training could improve the psychological symptoms in patients with asthma, which would result in better asthma outcomes (43).

Our study has several limitations. First, the sample size is small. There were only 29 patients with GINA-diagnosed severe asthma and 10 subjects with anxiety symptoms only. Hence, we combined the anxiety-only group with the depression-only group to equalize the sample size across groups. Second, although medications that affect psychological symptoms, such as anxiolytic agents, antidepressive drugs, and leukotriene receptor antagonist, were recorded during the follow-up period, our data did not include medications for the treatment of asthma. Third, although asthma outcomes were defined in considerable detail, they were self-reported and were not verified by chart review. Similarly, there was no actual psychiatric interview to assess the psychological symptoms of the patients.

CONCLUSIONS

In conclusion, we have prospectively shown that current psychological symptoms predict future risk of asthma outcomes, independent of sex, age, smoking index, anaphylactic history, BMI, household income, education levels, health insurance, work status, asthma duration, asthma severity, lung function, and level of asthma control. Furthermore, we identified an interaction between anxiety

and depression symptoms that significantly contribute to those outcomes. Further randomized controlled trials to investigate the role of screening and the effects of treatment of psychological symptoms in asthmatics are needed.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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