

REVIEW ARTICLE

Prevalence of anxiety and depressive symptoms in adolescents with asthma: A meta-analysis and meta-regression

Yanxia Lu¹, Kwok-Kei Mak², Hugo P. S. van Bever³, Tze Pin Ng¹, Anselm Mak⁴ & Roger Chun-Man Ho¹

¹Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; ²Department of Community Medicine and School of Public Health, Faculty of Medicine, University of Hong Kong, Hong Kong; ³Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; ⁴Division of Rheumatology, Department of Medicine, National University of Singapore, Singapore

To cite this article: Lu Y, Mak K-K, van Bever HPS, Ng TP, Mak A, Ho RC-M. Prevalence of anxiety and depressive symptoms in adolescents with asthma: A meta-analysis and meta-regression. *Pediatr Allergy Immunol* 2012; **00**.

Keywords

adolescent; anxiety symptoms; asthma; depressive symptoms; meta-analysis; prevalence; psychiatric comorbidity.

Correspondence

Roger Chun-Man Ho, Department of Psychological Medicine, National University of Singapore, National University Hospital, 5 Lower Kent Ridge Road, 119074, Singapore.
Tel.: 65 6772 4511
Fax: 65 67722191
E-mail: roger_ho@nuhs.edu.sg

Accepted for publication 15 July 2012

DOI:10.1111/pai.12000

Abstract

It remains unclear whether anxiety and depressive symptoms are more prevalent in adolescents with asthma when compared with healthy individuals. This meta-analysis aimed to evaluate the difference in the aggregate prevalence of depressive and anxiety symptoms between adolescents with asthma and healthy controls and to explore the underlying moderators that potentially explain the heterogeneity of the effect size. A meta-analysis of published work was performed using the random effects model. The differences in aggregate prevalence of depressive and anxiety symptoms between adolescents with asthma and healthy controls were determined. Meta-regression and subgroup analysis were performed to identify factors that may contribute to heterogeneity. A total of eight studies were eligible for analysis. The aggregate prevalence of depressive and anxiety symptoms was significantly higher among 3546 adolescents with asthma than that of 24,884 controls (depression, 0.27; 95% CI, 0.18–0.39 vs. 0.13; 95% CI, 0.09–0.19; anxiety, 0.33; 95% CI, 0.19–0.52 vs. 0.21; 95% CI, 0.12–0.33). The risk of developing depression and anxiety is significantly higher among adolescents with asthma when compared with controls (depression: pooled odds ratio, 2.09; 95% CI, 1.65–2.64; $p < 0.001$; anxiety: pooled odds ratio, 1.83; 95% CI, 1.63–2.07; $p < 0.001$). Meta-regression revealed that the proportions of Caucasian ($p = 0.008$) and smokers ($p < 0.001$) were significant moderators which explained the significant heterogeneity when comparing the risk of developing depressive symptoms among adolescent asthma patients vs. controls while age, gender, and severity of asthma were not significant. Family doctors, pediatricians, and healthcare providers should formulate strategies to detect depressive and anxiety symptoms in adolescents with asthma and offer psychological interventions to reduce the burden of psychiatric comorbidity.

Asthma is a global public health problem because of its increasing prevalence especially in children (1) and its substantial morbidity and mortality (2, 3). As a leading cause of disease burden, the World Health Organization has estimated that 15 million disability-adjusted life years are lost annually because of asthma, representing 1% of the total global disease burden (4). The increased prevalence and severity of asthma amidst the background of increasing mental health problems in adolescents call for research into

the relationship between psychological distress and asthma (5).

Clinical and population-based studies reported that young people with asthma are at increased risk of comorbid anxiety and depressive symptoms (6–9). The comorbidity of an anxiety or depressive symptoms is associated with adverse outcomes including poor control of asthma symptoms, poorer quality of life, and increased healthcare utilization even after controlling for the severity of asthma (10, 11). However, a

recent qualitative review concluded that the correlation between asthma and psychological comorbidity is yet to be well understood (12). In addition, it remains unclear whether anxiety and depressive symptoms are more prevalent in patients with asthma when compared with healthy individuals. McQuaid et al. (13) conducted a meta-analytic review of the behavioral adjustment of children with asthma using the data of nearly 5000 children from 26 studies. They demonstrated a modest but consistent association between behavioral difficulties and asthma, with the effect of internalizing behaviors (e.g. anxious and depressive symptoms) being greater than that of externalizing behaviors (e.g. oppositional or hyperactive symptoms). Increased asthma severity was shown to be associated with higher risk of behavioral difficulties. However, this review was mainly based on the analysis of data on young children with the mean age of 8.4 yr, and only two studies (14, 15) included in this meta-analysis specifically addressed behavioral problems in adolescents. As more studies (6, 16–20) have recently been published, an updated meta-analysis is required to establish the aggravate prevalence of anxiety and depressive symptoms in adolescents with asthma and to determine whether there is a significant risk of depressive and anxiety symptoms in adolescents with asthma when compared with healthy controls.

Before planning treatment provision targeting at these two conditions, it is necessary to estimate the aggregate prevalence of depressive and anxiety symptoms in adolescents with asthma accurately. This study systematically combines studies on the comorbidities of depressive and anxiety symptoms in adolescents with asthma vs. healthy controls using random effects meta-analysis following the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) guidelines (21) to generate an effect size for an aim to identify (i) the aggregate prevalence of and its difference in depressive and anxiety symptoms between adolescent asthma patients and healthy adolescents and (ii), the moderators accounting for the potential heterogeneity when comparing the risk of developing depressive and anxiety symptoms among adolescents with asthma vs. controls.

Materials and methods

Search strategy

We performed an extensive literature search using the keywords 'psych*', 'depress*', 'anxiety', 'behaviour', 'asthma', 'pediatric', 'children', 'adolescent', and 'youth' in various combinations to identify case-control studies published in English from different computerized databases: PubMed (from 1966 to November 2011), Embase (from 1980 to November 2011), PsychINFO (from 1806 to November 2011), BIOSIS (from 1926 to November 2011), Science Direct (from 2006 to November 2011), and Cochrane CENTRAL (from 1993 to November 2011). We also searched articles from the bibliographies of the retrieved studies and review articles. The corresponding authors were contacted for information that was lacking in their published articles.

Criteria for selecting articles

All observational case-control studies addressing the difference in depressive or anxiety symptoms between adolescent asthma patients and healthy controls were included. Studies were included if they met the following criteria: (i) conduction of human studies involving adolescents (i.e. those persons between 13 and 18 yr of age) with asthma and healthy controls; (ii) identification of clinically relevant depressive or anxiety symptoms; (iii) having a sample size of at least 50 subjects. We included both cross-sectional and the first round data collection of prospective studies. Two investigators (YL and RCMH) independently assessed the manuscripts generated for relevancy and manuscripts with the following criteria were excluded: (i) comparisons were not made between asthma patients and healthy controls; (ii) a standardized effect size could not be calculated. As this meta-analysis mainly involved data from published studies, an institutional review board approval was not required.

Data abstraction

All articles were first de-identified (blinded title, author(s), journal name, and year of publication) before selection. The abstracts of the studies were independently reviewed by two of the authors (YL and RCMH). Data were independently extracted into a standard electronic form. Any discrepancies were resolved by consensus. If consensus could not be reached, the only principal investigator (RCMH) would make the final decision for study eligibility and data extraction.

Statistical analyses

All statistical analyses in this meta-analysis were performed using the Comprehensive Meta-analysis Programme, version 2 (Biostat, Englewood, NJ, USA). The figures were prepared using R (22). To normalize the distribution of the effect sizes, the prevalence was transformed by taking the logit of the event rates. After the meta-analysis, the effect sizes were converted back into aggregate prevalence for the ease of interpretation. Because prevalence of depressive and anxiety symptoms of adolescents with asthma and the healthy control groups was available for all studies, the log odds ratio between the asthma and the control groups were calculated in comparing the prevalence between the asthma and the control groups. Random effects meta-analysis was conducted to test whether the aggregate prevalence of depressive and anxiety symptoms was the same in these two groups.

Heterogeneity was evaluated by the Cochran Q -test. As the number of studies of this meta-analysis may be limited, the Cochran Q -test for heterogeneity may yield a low statistical power (23). A value of significance at 10% ($p \leq 0.1$) was therefore considered statistically significant for heterogeneity (24). Meanwhile, we assessed heterogeneity with I^2 , which can be defined as the percentage of total variation of all studies caused by heterogeneity rather than change. High values of I^2 suggest increased heterogeneity. For models with considerable heterogeneity and statistically significant effect size,

meta-regression was performed to identify demographic and disease-related factors (age, gender, ethnicity, smoking status, and severity of asthma) that might contribute to the heterogeneity (25). Because the covariates chosen were not expected to explain all the heterogeneity of the studies, mixed-model meta-regression was used in considering the presence of 'residual heterogeneity' (25). The regression coefficients and the associated standard error (s.e.), the *z*-score, degree of freedom (df), and *p*-values were reported for the meta-regression analysis. Publication bias was evaluated with Egger's test in our analysis.

Results

Seven hundred and sixty-six abstracts were initially identified through database searches. We excluded 741 articles because they did not meet the inclusion criteria. In the remaining 25 articles, nine studies failed to have a healthy control group with a sample size of at least 50; four studies lacked standardized assessment of depressive or anxiety symptoms; two studies had the same data with other studies, which were already included; two studies did not provide sufficient information to calculate an effect size. The selection process was summarized in Fig. 1. Finally, we included eight articles (6, 16–20, 26, 27) in our analysis, and the studies were mainly conducted in Western countries (Table 1). In these eight studies, 3546 patients and 24,884 controls were involved.

Aggregate prevalence and pooled odds ratio of depressive symptoms in adolescents with asthma vs. healthy controls

The aggregate prevalence of depressive symptoms among adolescents with and without asthma using the random effects model was 0.27 (95% CI, 0.18–0.39) and 0.13 (95% CI, 0.09–0.19), respectively (Fig. 2a,b). The risk of developing depressive symptoms was significantly higher in patients with asthma than that of the controls (OR = 2.09; 95% CI, 1.65–2.64; $Z = 6.154$; $p < 0.001$). Fig. 3a shows the forest plot generated for the asthma and the control groups from the studies. Statistically significant heterogeneity ($\tau^2 = 0.068$, Q -value = 30.0, $df = 7$, $p < 0.001$, $I^2 = 76.7$) was present when calculating the OR. Mixed-model meta-regression was conducted to explore the impact of our a priori sources of heterogeneity (demographic and disease-related factors including age, gender, ethnicity, smoking status, and severity of asthma) in all studies. Results showed that the mean age ($B = -1.444$, $z = -0.826$, $p = 0.409$) and the proportion of female ($B = -3.850$, $z = -1.815$, $p = 0.069$) of all subjects and the severity of asthma ($B = -0.030$, $z = -0.053$, $p = 0.958$) of asthma patients were nonsignificant moderators (Table 2). However, proportions of Caucasian ($B = 0.746$, $z = 2.665$, $p = 0.008$) and smokers ($B = 0.875$, $z = 4.383$, $p < 0.001$) in the sample were significant moderators for heterogeneity (Table 2).

We also tested for the presence of publication biases using funnel plots and Egger's regression test (28). No significant publication bias was detected (intercept = 1.29; s.e. = 1.38; 95% CI, -2.08 to 4.66; $t = 0.94$; $df = 6$, $p = 0.384$) of all studies.

Aggregate prevalence and pooled odds ratio of anxiety symptoms in adolescents with asthma vs. healthy controls

The aggregate prevalence of anxiety symptoms among the asthma patients and normal controls was 0.33 (95% CI, 0.19–0.52) and 0.21 (95% CI, 0.12–0.33), respectively (Fig. 2c,d). Three studies were not used in synthesizing the effect size of the aggregate prevalence of anxiety symptoms as they did not report data on anxiety symptoms (16, 20, 27) (Table 1). The risk of developing anxiety symptoms was significantly higher in asthma patients compared with the healthy controls (OR = 1.83; 95% CI, 1.63–2.07; $Z = 9.876$; $p < 0.001$; Fig. 3b). No significant heterogeneity ($\tau^2 = 0.000$, Q -value = 3.3, $df = 7$, $p = 0.517$, $I^2 = 0.0$) and no publication bias (intercept = -11.25; s.e. = 10.26; 95% CI, -43.89 to 21.39; $t = 1.10$; $df = 3$; $p = 0.353$) were detected in all studies.

Discussion

Higher prevalence of depressive symptoms among adolescents with asthma

This study to our knowledge is the first meta-analysis aiming to estimate the aggregate prevalence of depressive and anxiety symptoms in adolescents with asthma compared with healthy controls. The aggregate prevalence of depressive symptoms in adolescents with asthma was 27.0%, suggesting that at least one in four adolescents with asthma may experience depressive symptoms. The aggregate prevalence of depressive symptoms was twice as high in adolescents with asthma as those without asthma. These findings suggest that asthma is a risk factor for depressive symptoms in adolescents and this is hardly surprising, as asthma affects daily functions that would require physical activity such as ambulation, mobility and school activities and psychosocial functioning (10). Previous studies have clearly demonstrated the impact of asthma on quality of life; thus, the increased prevalence of depressive symptoms in people with asthma is expected.

Our meta-regression demonstrated that proportions of Caucasian and smokers significantly increased the heterogeneity, whereas age, gender, and severity of asthma did not. Smoking has long been considered a risk factor for anxiety and depressive symptoms (29–31). Higher likelihood of frequent nocturnal coughing and breathing problems in smokers was reported in adolescent studies (32, 33). In Korean (34) and Hong Kong (32) adolescents, higher odds of having exercise-induced bronchospasm were reported. In a 2-yr longitudinal study, respiratory problems such as bronchitis and pneumonia in adolescents were found to be associated with higher smoking prevalence and average daily cigarette consumption (35). These findings were supported by demonstrating poorer lung functions as indicated by reduced forced expiratory volume in 1 s (FEV₁) and forced inspiratory flow 25–75% (FEF_{25–75%}) (36) and exhaled nitric oxide levels (37) in adolescent smokers. In addition, nocturnal asthma symptoms, which are prevalent among smokers, are associated with poor sleep quality and impaired quality of life, as well as higher prevalence of anxiety and depressive symptoms (32, 38, 39). Moore et al. (40) found that night-time awakenings in children can significantly affect

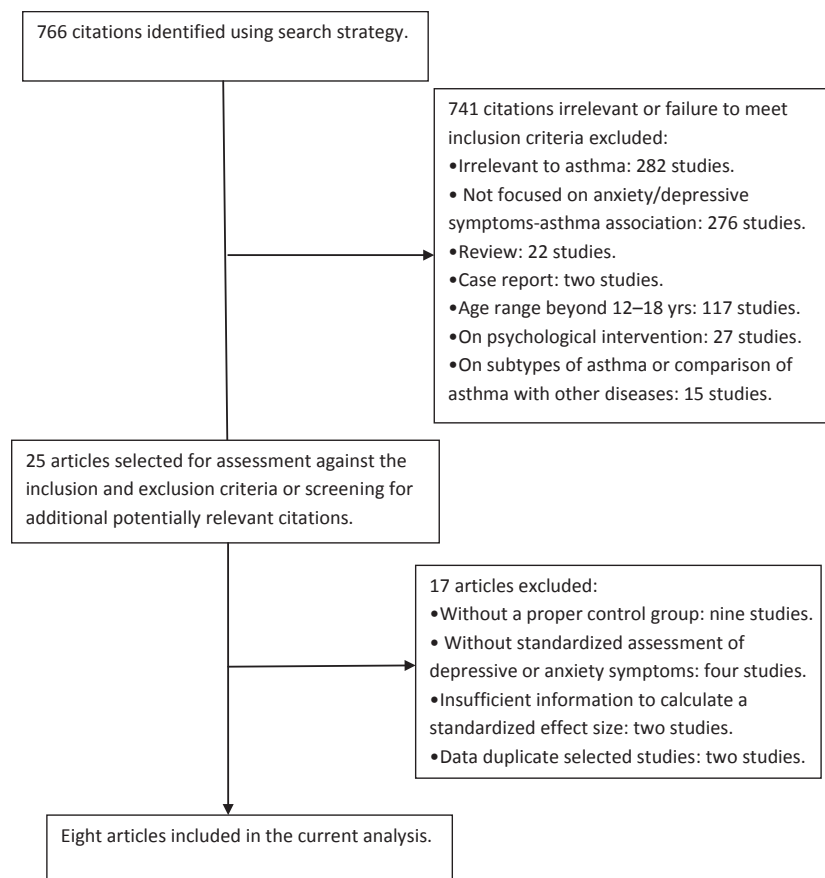


Figure 1 Flowchart describing the process of study selection.

daytime functioning among children and their parents, including daytime sleepiness, increased behavior problems, decreased neurocognitive functioning, and family stress. An exploratory study indicated that sleep disturbances in children with nocturnal asthma may affect cognitive functioning as well as mood and behavior (39). Although the National Heart Lung and Blood Institute (NHLBI) recommends that persons with asthma should not smoke or be exposed to tobacco smoke in their environment, studies have found that the prevalence of smoking among those with asthma is the same as of those without asthma (41–43) or in some instances higher (26, 44, 45). The higher prevalence of smoking can be explained by the self-medication hypothesis (46), which describes the use of tobacco, drugs, or other self-soothing forms of behavior to treat untreated and often undiagnosed mental distress, stress, and anxiety (47–49). This is often seen as a struggle to gain personal independence from conventional medical treatment (50). Specifically, smoking may function as a compensatory means to modulate effects and treat distressful psychological states, whereby individuals with asthma may choose it to manage their depressive and anxiety symptoms and help them achieve emotional stability (51, 52). As a potential confounder, stressful life events encountered by adolescents can independently affect the course of asthma while adolescents with asthma tend to cope with stressful life events by smoking (53).

Consistent with other multi-ethnicity reports (54–56), our analysis revealed the variability of prevalence of depressive symptoms in different ethnicities. Higher rates of depressive symptoms among Caucasians may reflect a tendency of them to express psychological distress compared with other ethnicities (56). Furthermore, Caucasians generally tend to have higher socioeconomic status and more knowledge on psychological status and availability and accessibility of mental health services utilization such as insurance, time, and transportation compared with the ethnic minorities (57–59).

From our meta-regression analysis, severity of asthma was not a significant moderator in explaining the heterogeneity of calculating the OR of depressive symptoms among adolescents with asthma vs. controls. This is consistent with studies indicating that anxiety and depressive symptoms in asthma patients may be independent of the severity of asthma (48, 60). It may be the presence of asthma, but not the severity of the disease, which is associated with the comorbidities of psychological distress.

Higher prevalence of anxiety symptoms among adolescents with asthma

In this meta-analysis, it is noticeable that the adolescents with asthma have higher risk (OR = 1.83) to develop anxiety

Table 1 Study design and baseline characteristics of studies included

Study name and location	Study design	Description of asthma patients	Description of controls	Number of subjects (n) asthma	Proportion of female subjects in all subjects (%)	Mean age in years (all subjects)	Proportion of Caucasian subjects in all subjects (%)	Depressive /anxiety symptoms method	Prevalence of depressive symptoms (%) asthma /controls	Prevalence of anxiety symptoms (%) asthma /controls	Proportion of smokers in asthma patients (%)	Proportion of severe asthma patients (%)
Otten et al. (20)	Across Netherlands	Observational cohort study	Population-based screen for asthma using ISAAC	Population-based sample without asthma	600/4553	52.2	12.97	NA	21.3/10.7	NA	38.5	17.6
Bender (16)	YRBS of US	Observational cohort study	Self-report of asthma diagnosis	All others considered no asthma	718/13,148	51.9	NA	44.0	45.3/29.3	NA	20.6	NA
Katon et al. (6)	100 clinics in Washington State	Cross-sectional	Parent confirmation of asthma diagnosis and medication use	No asthma diagnoses or medication use	781/598	48.3	14.04	6.9	7.3/4.0	18.7/9.1	4.5	30.3
Goodwin et al. (18)	CHDS in New Zealand	Observational cohort study	Self-report of asthma diagnosis	Those without experience of asthma	386/1650	49.8	NA	NA	32.4/20.6	21.0/13.6	NA	NA
Gillaspay et al. (17)	A Jobs Corps (Midwestern US)	Case-controlled	25 adolescents with asthma	25 matched controls	25/25	52.0	18.5	36.0	32.0/8.0	32.0/24.0	NA	NA
Ortega et al. (19)	MECAMDS in Atlanta, New Haven, New York, and Puerto Rico	Cross-sectional	Parental reports of asthma	Youths from selected communities	199/1059	47.0	NA	51.7	13.4/11.7	49.2/37.7	NA	NA
Forero et al. (26)	South Western Sydney population study	Case-controlled	Survey of asthma diagnosis	Community sample without asthma	797/3751	51.0	13.52	82.0	42.4/30.4	50.1/35.0	NA	NA
Seigel et al. (27)	New York	Case-controlled	Outpatients	Matched for socioeconomic status	40/100	NA	NA	NA	62.5/13.0	NA	NA	100.0

YRBS, Youth Risk Behavior Survey; CHDS, Christchurch Health and Development Study; MECAMDS, Methods for the Epidemiology of Child and Adolescent Mental Disorders study; ISAAC, Standardized methodology of the International Study of Asthma and Allergy in Childhood; YRBS, Youth Risk Behavior Survey; ASI, Childhood Anxiety Sensitivity Index; CIDI, Composite International Diagnostic Interview; DISC, Diagnostic Interview Schedule for Children; HBSC, Health Behaviour Among School Children; BDI, Beck Depression Inventory.

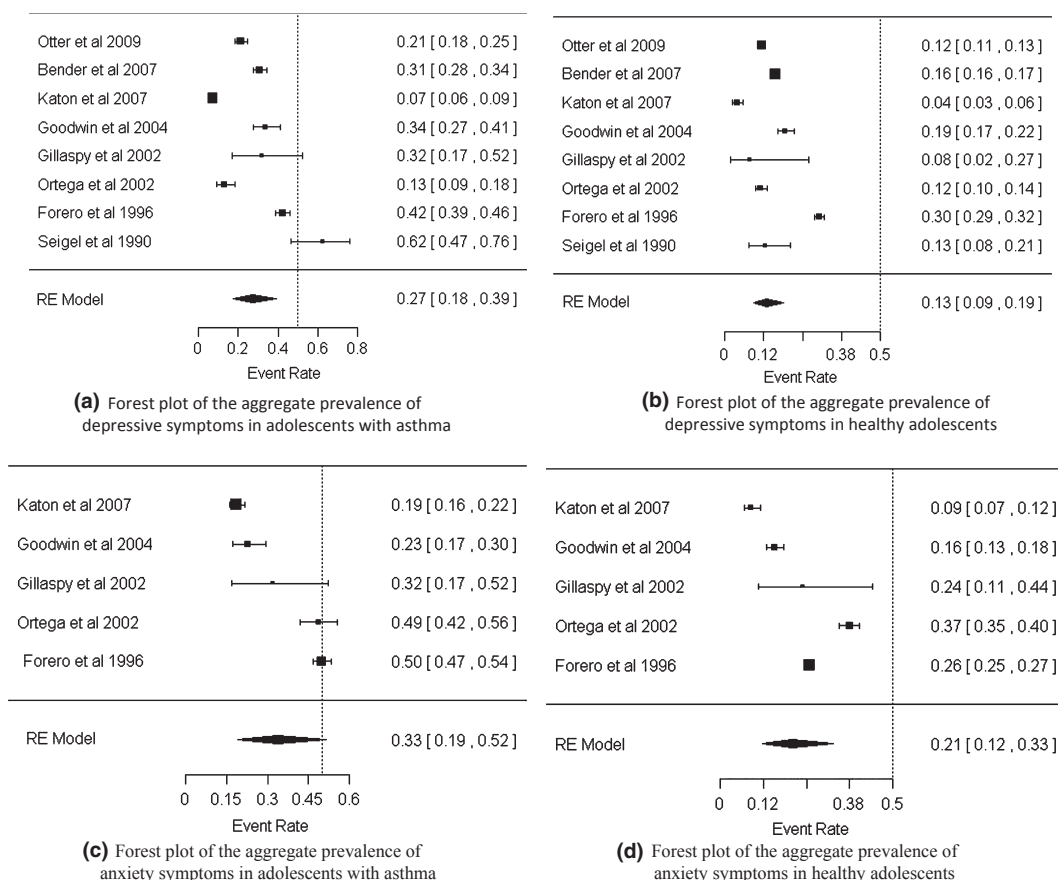


Figure 2 Forest plots of the aggregate prevalence of depressive and anxiety symptoms in adolescents with asthma and healthy controls. Forest plot of the aggregate prevalence of (a) depressive symptoms in adolescents with asthma, (b) depressive symptoms in healthy adolescents, (c) anxiety symptoms in adolescents with asthma and (d) anxiety symptoms in healthy adolescents.

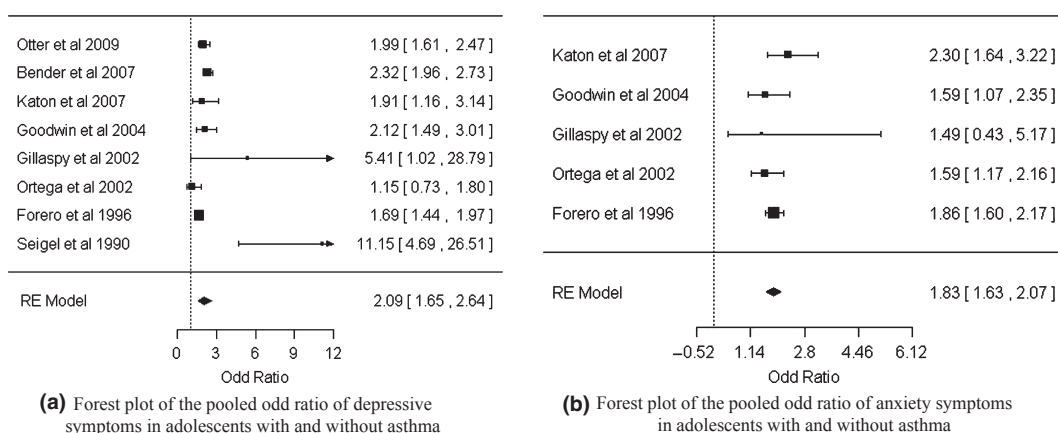


Figure 3 Forest plot of the pooled odd ratio of depressive and anxiety symptoms in adolescents with asthma vs. healthy controls. Forest plot of the pooled odd ratio of (a) depressive symptoms and (b) anxiety symptoms in adolescents with and without asthma.

symptoms and this finding is congruent with previous studies (61–63).

Several theories have been proposed to explain the elevated risk of anxiety symptoms especially panic disorder among asthma patients. The cognitive theory suggests that

the unpredictable and longitudinal experience with asthma attacks may generate fearful or catastrophic beliefs which provoke panic attacks and anticipatory anxiety (50, 64). The biologic and behavioral theories suggest that repetitive experience with hypoxia and hypercapnia in asthma attack may

Table 2 Meta-regression analysis of potential moderators to explain heterogeneity of prevalence of depressive symptoms

Factor	Regression coefficient (s.e.)	Z-score	τ^2	df	p
Mean age, yrs	-1.444 (1.748)	-0.826	0.000	2	0.409
Female, %	-3.850 (2.121)	-0.053	0.005	5	0.958
Caucasian, %	0.746 (0.280)	2.665	0.026	3	0.008
Severe asthma, %	-0.030 (0.563)	-0.053	0.124	1	0.958
Smokers, %	0.875 (0.200)	4.383	0.000	1	<0.001

sensitize the amygdala and locus coeruleus and leads to over-reaction to subsequent episodes of asthma attacks as a result of classical conditioning by pairing conditioned stimuli (i.e. sensation of breathlessness) and conditioned response (i.e. fear and anxiety) (50, 51). Children with anxiety disorders were found to report more somatic symptom during inhalation of CO₂-enriched air compared with children without anxiety disorder (4, 52). Furthermore, anxiety and fear also cause changes in airway tone and precipitate an asthma attack (65).

The impact of depressive and anxiety symptoms in patients with asthma is an important research area as it may be related to disease control and prognosis (66). Alexander et al. and Weingarten et al. measured the effect of relaxation therapy on peak expiratory flow of asthmatic children and found effects favoring the treatment group compared with the control group (67, 68). Brown et al. (69) performed a randomized controlled trial by comparing the effects of citalopram, a selective serotonin reuptake inhibitor and placebo in asthma patients with depressive symptoms, and found that antidepressant-treated patients required fewer oral corticosteroids than the placebo group. Furthermore, there is a lack of studies to draw conclusions regarding the utility of psychological approaches for improving asthma-related outcome. There is still a considerable need for good quality prospective studies to continue investigation into the causality and temporal relationship between asthma and depressive and anxiety symptoms and response to treatment.

The strength of this meta-analysis includes meta-regression and subgroup effect size analyses. Majority of the studies (seven of eight) involved asthma patients from communities with relatively large sample size or population-based study design, and this reflected the true prevalence in primary care

that is largely free of clinical selection bias. Hence, our findings are more relevant to family physicians and public health policy makers in formulating strategies to reduce the burden of depressive and anxiety symptoms among adolescents with asthma in the community (70, 71).

There are a few limitations in the current meta-analysis. The major limitation is that depressive and anxiety symptoms were assessed by various questionnaires and interviews but not clinical diagnosis by doctors. Hence, the results of this study refer to the aggregate prevalence of depressive symptoms rather than depressive disorder. This study examined the cross-sectional data or the baseline data of cohort studies which cannot determine the causation or temporality of the association between psychological symptoms and adolescent asthma. Another limitation of the current study is the small number of studies involved, although the number of participants was reasonable (3546 adolescent asthma patients and 24,884 healthy adolescent controls). Despite the abundance of literature reporting data on depressive and anxiety symptoms, only eight studies met the inclusion criteria. This reflects the paucity of high-quality studies examining the prevalence of depressive symptoms in adolescent asthma. We have considered only a small number of demographic and disease-related moderators in the meta-regression analysis because of the limited number of studies.

In conclusion, adolescents with asthma are at higher risk to develop depression and anxiety.

Family doctors, pediatricians, and healthcare providers should formulate strategies to detect depressive and anxiety symptoms in adolescents with asthma and offer psychological interventions to reduce the burden of psychiatric comorbidity.

References

- Pearce N, Douwes J, Beasley R. The rise and rise of asthma: a new paradigm for the new millennium? *J Epidemiol Biostat* 2000; **5**: 5–16.
- Goldney RD, Ruffin R, Fisher LJ, Wilson DH. Asthma symptoms associated with depression and lower quality of life: a population survey. *Med J Aust* 2003; **178**: 437–41.
- Douwes J, Brooks C, Pearce N. Asthma nervosa: old concept, new insights. *Eur Respir J* 2011; **37**: 986–90.
- Perna G, Ieva A, Caldirola D, Bertani A, Bellodi L. Respiration in children at risk for panic disorder. *Arch Gen Psychiatry* 2002; **59**: 185–6.
- Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; **31**: 143–78.
- Katon W, Lozano P, Russo J, McCauley E, Richardson L, Bush T. The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls. *J Adolesc Health* 2007; **41**: 455–63.
- Goodwin RD, Messineo K, Bregante A, Hoven CW, Kairam R. Prevalence of probable mental disorders among pediatric asthma patients in an inner-city clinic. *J Asthma* 2005; **42**: 643–7.
- Feldman JM, Ortega AN, McQuaid EL, Canino G. Comorbidity between asthma attacks and internalizing disorders among Puerto Rican children at one-year follow-up. *Psychosomatics* 2006; **47**: 333–9.
- Ortega AN, McQuaid EL, Canino G, Goodwin RD, Fritz GK. Comorbidity of asthma and anxiety and depression in Puerto Rican children. *Psychosomatics* 2004; **45**: 93–9.
- Richardson LP, Lozano P, Russo J, McCauley E, Bush T, Katon W. Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. *Pediatrics* 2006; **118**: 1042–51.

11. McCauley E, Katon W, Russo J, Richardson L, Lozano P. Impact of anxiety and depression on functional impairment in adolescents with asthma. *Gen Hosp Psychiatry* 2007; **29**: 214–22.
12. Di Marco F, Santus P, Centanni S. Anxiety and depression in asthma. *Curr Opin Pulm Med* 2011; **17**: 39–44.
13. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. *J Dev Behav Pediatr* 2001; **22**: 430–9.
14. Silverglade L, Tosi DJ, Wise PS, Dcosta A. Irrational beliefs and emotionality in adolescents with and without bronchial-asthma. *J Gen Psychol* 1994; **121**: 199–207.
15. Stawski M, Auerbach JG, Barasch M, Lerner Y, Zimin R, Miller MS. Behavioral problems of adolescents with chronic physical illness: a comparison of parent-report and self-report measures. *Eur Child Adolesc Psychiatry* 1995; **4**: 14–20.
16. Bender BG. Depression symptoms and substance abuse in adolescents with asthma. *Ann Allergy Asthma Immunol* 2007; **99**: 319–24.
17. Gillaspay SR, Hoff AL, Mullins LL, Van Pelt JC, Chaney JM. Psychological distress in high-risk youth with asthma. *J Pediatr Psychol* 2002; **27**: 363–71.
18. Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med* 2004; **34**: 1465–74.
19. Ortega AN, Huertas SE, Canino G, Ramirez R, Rubio-Stipec M. Childhood asthma, chronic illness, and psychiatric disorders. *J Nerv Ment Dis* 2002; **190**: 275–81.
20. Otten R, Van de Ven MOM, Engels RCME, Van den Eijnden RJJM. Depressive mood and smoking onset: a comparison of adolescents with and without asthma. *Psychol Health* 2009; **24**: 287–300.
21. Pine DS. Respiration in children at risk for panic disorder – in reply. *Arch Gen Psychiatry* 2002; **59**: 185–6.
22. Team RDC. R: A Language and Environment for Statistical Computing. Vienna, Austria: Team RDC, 2010.
23. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Stat Med* 1998; **17**: 841–56.
24. Fletcher J. What is heterogeneity and is it important? *BMJ* 2007; **334**: 94–6.
25. Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; **21**: 1559–73.
26. Forero R, Bauman A, Young L, Booth M, Nutbeam D. Asthma, health behaviors, social adjustment, and psychosomatic symptoms in adolescence. *J Asthma* 1996; **33**: 157–64.
27. Seigel WM, Golden NH, Gough JW, Lashley MS, Sacker IM. Depression, self-esteem, and life events in adolescents with chronic diseases. *J Adolesc Health* 1990; **11**: 501–4.
28. Jennings JH, Digiiovine B, Obeid D, Frank C. The association between depressive symptoms and acute exacerbations of COPD. *Lung* 2009; **187**: 128–35.
29. Kandel DB, Davies M. Adult sequelae of adolescent depressive symptoms. *Arch Gen Psychiatry* 1986; **43**: 255–62.
30. Tercyak KP. Psychosocial risk factors for tobacco use among adolescents with asthma. *J Pediatr Psychol* 2003; **28**: 495–504.
31. Cheron-Launay M, Le Faou AL, Sevilla-De-dieu C, Gilbert F, Kovess-Masfety V. Smoking and the consumption of antidepressants, anxiolytics and hypnotic drugs: results of a large, French epidemiological study in 2005. *Addict Behav* 2011; **36**: 743–8.
32. Mak KK, Ho RC, Day JR. The associations of asthma symptoms with active and passive smoking in Hong Kong adolescents. *Respir Care* 2012; Feb 17 [Epub ahead of print].
33. Mallol J, Castro-Rodriguez JA, Cortez E. Effects of active tobacco smoking on the prevalence of asthma-like symptoms in adolescents. *Int J Chron Obstruct Pulmon Dis* 2007; **2**: 65–9.
34. Yoo S, Kim HB, Lee SY, et al. Effect of active smoking on asthma symptoms, pulmonary function, and BHR in adolescents. *Pediatr Pulmonol* 2009; **44**: 954–61.
35. Myers MG, Brown SA. Smoking and health in substance-abusing adolescents: a two-year follow-up. *Pediatrics* 1994; **93**: 561–6.
36. Tager IB, Munoz A, Rosner B, Weiss ST, Carey V, Speizer FE. Effect of cigarette smoking on the pulmonary function of children and adolescents. *Am Rev Respir Dis* 1985; **131**: 752–9.
37. Van Miert E, Sardella A, Bernard A. Biomarkers of early respiratory effects in smoking adolescents. *Eur Respir J* 2011; **38**: 1287–93.
38. Gregory AM, Van der Ende J, Willis TA, Verhulst FC. Parent-reported sleep problems during development and self-reported anxiety/depression, attention problems, and aggressive behavior later in life. *Arch Pediatr Adolesc Med* 2008; **162**: 330–5.
39. Stores G, Ellis AJ, Wiggs L, Crawford C, Thomson A. Sleep and psychological disturbance in nocturnal asthma. *Arch Dis Child* 1998; **78**: 413–9.
40. Moore M, Meltzer LJ, Mindell JA. Bedtime problems and night wakings in children. *Prim Care* 2008; **35**: 569–81, viii.
41. Backer V, Nepper-Christensen S, Ulrik CS, von Linstow ML, Porsbjerg C. Factors associated with asthma in young Danish adults. *Ann Allergy Asthma Immunol* 2002; **89**: 148–54.
42. Brook U, Shiloh S. Attitudes of asthmatic and nonasthmatic adolescents toward cigarettes and smoking. *Clin Pediatr* 1993; **32**: 642–6.
43. Forero R, Bauman A, Young L, Larkin P. Asthma prevalence and management in Australian adolescents: results from three community surveys. *J Adolesc Health* 1992; **13**: 707–12.
44. Kaplan BA, MascieTaylor CGN. Smoking and asthma among 23-year-olds. *J Asthma* 1997; **34**: 219–26.
45. Ringlever L, Otten R, Van Schayck OC, Engels RC. Early smoking in school-aged children with and without a diagnosis of asthma. *Eur J Public Health* 2011; **22**: 394–8.
46. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res* 2008; **10**: 1691–715.
47. Feldman JM, Acosta Perez E, Canino G, McQuaid EL, Goodwin RD, Ortega AN. 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* 2011; **199**: 313–8.
48. Valenca AM, Falcao R, Freire RC, et al. The relationship between the severity of asthma and comorbidities with anxiety and depressive disorders. *Rev Bras Psiquiatr* 2006; **28**: 206–8.
49. Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. *Psychosom Med* 2004; **66**: 349–55.
50. Roy-Byrne P, Stein MB. Inspiring panic. *Arch Gen Psychiatry* 2001; **58**: 123–4.
51. Gorman JM, Kent J, Martinez J, Browne S, Coplan J, Papp LA. Physiological changes during carbon dioxide inhalation in patients with panic disorder, major depression, and premenstrual dysphoric disorder: evidence for a central fear mechanism. *Arch Gen Psychiatry* 2001; **58**: 125–31.
52. Pine DS, Klein RG, Coplan JD, et al. Differential carbon dioxide sensitivity in childhood anxiety disorders and nonill comparison group. *Arch Gen Psychiatry* 2000; **57**: 960–7.
53. Turyk ME, Hernandez E, Wright RJ, et al. Stressful life events and asthma in adolescents. *Pediatr Allergy Immunol* 2008; **19**: 255–63.
54. Doerfler LA, Felner RD, Rowleson RT, Raley PA, Evans E. Depression in children and adolescents: a comparative analysis of the utility and construct validity of two assessment measures. *J Consult Clin Psychol* 1988; **56**: 769–72.
55. Roberts RE. Manifestation of depressive symptoms among adolescents. A comparison of Mexican Americans with the majority

- and other minority populations. *J Nerv Ment Dis* 1992; **180**: 627–33.
56. Parker G, Gladstone G, Chee KT. Depression in the planet's largest ethnic group: the Chinese. *Am J Psychiatry* 2001; **158**: 857–64.
 57. Leaf PJ, Bruce ML, Tischler GL, Holzer CE III. The relationship between demographic factors and attitudes toward mental health services. *J Community Psychol* 1987; **15**: 275–84.
 58. Norquist G, Wells K. Mental health needs of the uninsured. *Arch Gen Psychiatry* 1991; **48**: 475–8.
 59. Padgett DK, Patrick C, Burns BJ, Schlesinger HJ. Ethnic differences in use of inpatient mental health services by blacks, whites, and Hispanics in a national insured population. *Health Serv Res* 1994; **29**: 135–53.
 60. ten Brinke A, Ouwerkerk ME, Bel EH, Spinhoven P. Similar psychological characteristics in mild and severe asthma. *J Psychosom Res* 2001; **50**: 7–10.
 61. Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med* 1994; **149**: 930–4.
 62. Bonala SB, Pina D, Silverman BA, Amara S, Bassett CW, Schneider AT. Asthma severity, psychiatric morbidity, and quality of life: correlation with inhaled corticosteroid dose. *J Asthma* 2003; **40**: 691–9.
 63. Bender BG. Risk taking, depression, adherence, and symptom control in adolescents and young adults with asthma. *Am J Respir Crit Care Med* 2006; **173**: 953–7.
 64. Carr RE, Lehrer PM, Rausch LL, Hochron SM. Anxiety sensitivity and panic attacks in an asthmatic population. *Behav Res Ther* 1994; **32**: 411–8.
 65. Greenberg M, Wise MG, Rundell JR. Textbook of Consultation-Liaison Psychiatry, 2nd edn. Washington, DC: American Psychiatric Press, 2002.
 66. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; **160**: 2101–7.
 67. Alexander AB, Miklich DR, Hershkoff H. The immediate effects of systematic relaxation training on peak expiratory flow rates in asthmatic children. *Psychosom Med* 1972; **34**: 388–94.
 68. Weingarten MA, Goldberg J, Teperberg Y, Harrison N, Oded A. A pilot study of the multidisciplinary management of childhood asthma in a family practice. *J Asthma* 1985; **22**: 261–5.
 69. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biol Psychiatry* 2005; **58**: 865–70.
 70. Rojas-Martinez R, Perez-Padilla R, Olaiz-Fernandez G, et al. Lung function growth in children with long-term exposure to air pollutants in Mexico city. *Am J Respir Crit Care Med* 2007; **176**: 377–84.
 71. Martinez FJ, Curtis JL, Sciurba F, et al. Sex differences in severe pulmonary emphysema. *Am J Respir Crit Care Med* 2007; **176**: 243–52.