

Depression symptoms and Risk of Incident Asthma in Adults

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ABSTRACT

Background: Earlier studies have recommended that asthmatic patients regularly have comorbid depression; nonetheless, temporal associations remain uncertain.

Objectives: To determine whether depression predicts asthma and, on the other hand, whether asthma predicts depression.

Methods: A literature search was conducted without language restrictions using Pubmed, Embase, Cochrane and PsycINFO for studies published before April, 2017. Papers referenced by the obtained articles were correspondingly reviewed. Only comparative prospective studies with reported risk estimates of the association between depression and asthma were included. In order to examine whether one of these conditions was predictive of the other, studies were excluded if enrolled participants had pre-existing depression or asthma. A random effects model was used to calculate the pooled risk estimates for two outcomes: depression predicting asthma and asthma predicting depression.

Results: Seven citations, derived from 8 cohort studies, met our inclusion criteria. Of these, six studies reported that depression predicted incident adult-onset asthma, including 83,684 participants and 2,334 incident cases followed for 8 to 20 years. Conversely, two studies reported that asthma predicted incident depression. These studies involved 25,566 participants and 2,655 incident cases followed for 10 and 20 years, respectively. The pooled adjusted relative risks (RRs) of acquiring asthma associated with baseline depression were 1.43 (95% CI, 1.28–1.61) ($P < 0.001$). The adjusted RRs for acquiring depression associated with baseline asthma was 1.23 (95% CI, 0.72–2.10) ($P = 0.45$).

Conclusions: Depression was associated with a 43% increased risk of developing adult-onset asthma. However, asthma did not increase the risk of depression based on limited studies. Further prospective studies confirming the true association between asthma and subsequent risk of depression are warranted.

Keywords: Depression, Asthma, Depression predicting asthma, Asthma predicting depression.

INTRODUCTION

Depression and asthma are two highly widespread chronic diseases worldwide, imposing intolerable social and economic burdens on the public healthcare system^[1,2]. Equally detrimental, asthma affects 300 million individuals worldwide^[3], with increasing commonness in many countries^[4]. As both depression and asthma carry out substantial public health burdens, the association between these two conditions has attracted attention over the past numerous decades.

A number of prospective studies have evaluated the temporal relationship between asthma and depression; nonetheless, the outcomes were indecisive. An earlier meta-analysis of prospective studies^[5] described a bidirectional relationship amid psychosocial factors and atopic disorders. Nonetheless, this meta-analysis only involved studies published before 2007, and was lacking studies which definitely address the relationship

between depression and asthma (there were only two investigating depression predicting asthma and none examined asthma predicting depression). Since then, many well-designed prospective studies have been published^[6-8], allowing for a more detailed analysis of the temporal relationship between these two disease.

Consequently, the purpose of this study was to systematically examine whether depression predicts asthma and, on the other hand, whether asthma predicts depression by conducting a meta-analysis of prospective studies.

MATERIALS AND METHODS

A literature search was conducted without language restrictions using Pubmed, Embase, Cochrane and PsycINFO for studies published before January, 2015. Papers referenced by the obtained articles were also reviewed. Only

comparative prospective studies with reported risk estimates of the association between depression and asthma were included.

Abstracts published in scientific conferences or website materials were excluded, because these studies have not been peer-reviewed and their inclusion may bias the results of a meta-analysis.

The study was done after approval of ethical board of Imam Muhammad ibn Saud Islamic university.

- **Data extraction**

We extracted data from selected articles, with certain regards to: the last name of the first author, publication year, country of region, study population, follow-up time, number of cases and size of the cohort, measurements of depression and asthma, the most fully adjusted risk estimate and corresponding 95% CI, and statistical adjustment for the main confounding or mediating factors.

We assessed the quality of each included study using the Newcastle-Ottawa Quality Assessment Scale for cohort studies^[9] to determine the quality of selection, comparability, exposure, and outcome of study participants, giving a maximum of 9 points. Two authors independently extracted the data and evaluated the study quality, with disagreements resolved through mutual discussion.

- **Statistical Analysis**

The RRs were utilized as the common measure of association between depression and asthma across studies. The hazard ratios (HRs) and odds ratios (ORs) were directly considered equivalent to RRs. Two separate analyses were conducted: depression predicting asthma, and asthma predicting depression. If a study only presented stratified risk estimates (i.e. smoking status)^[10], we combined the estimates using a random-effects model and then the pooled estimate was used for the meta-analyses. For studies presenting with graded relationships (i.e. low, medium, high depression symptoms)^[10,11], we only used the estimate for the highest category.

Heterogeneity across the studies were tested by using the I^2 statistic^[12], which is a quantitative measure of inconsistency across studies, with recommended thresholds for low (25%-50%), moderate (50%-70%) and high (>75%) heterogeneity, respectively. A random-effects model, which considered both within-study and between-study variation, was used to obtain the combined risk estimates regardless of heterogeneity. Given that the studies differed in sample characteristics (i.e. gender, age and race), depression measure, asthma diagnosis, degree of

adjustment, follow-up periods, we further conducted sensitivity analyses to explore possible explanations and to examine the robustness of the pooled risk estimates based on various exclusion criteria. We also investigated the impact of a single study on the overall pooled estimate by omitting one single study at a time and recalculating the pooled effect estimate of other remaining studies.

The sensitivity analyses and publication bias were performed only for depression predicting asthma but not asthma predicting depression due to the small numbers of studies available. P value < 0.005 considered statistically significant. Statistical analysis was performed using Stata 12.0 and Cochrane Collaboration Review Manager 5.1.2 software.

RESULTS

A total of 1221 citations were retrieved from electronic databases. After initial screening of titles and abstracts using the above-mentioned criteria, 21 articles were identified for full-text review. Of these, 15 were further excluded, leaving 7 eligible articles. Seven articles were included in the final meta-analysis^[6-8,10,11,13,14]. Between the included articles, five studies precisely described results on depression predicting asthma^[6,7,10,11,13]. One study examined asthma predicting depression^[14], and another study looked at both depression predicting asthma and asthma predicting depression^[8]. A flow diagram of the literature search and exclusion of the other 14 studies are shown in Fig 1 and Table 1, respectively.

Table 1 presents the characteristics of 7 studies investigating whether depression predicts beginning of asthma. Follow up period ranged from 8 to 20 years across studies, with a median of 11.5 years. Five studies were showed in both genders^[6,8,10,11,13], and one only in women^[7]. The sample sizes ranged from 3,614 to 31,848, resulting in a total of 83,684 participants and 2,334 incident cases across studies. In defining depression, 5 studies used a self-reported symptoms scale^[6-8,10,11], and one other used a structured clinical diagnostic interview^[13]. Two cohort studies investigating whether baseline asthma predicted future risk of incident depression were included^[8,14], with study characteristics and adjusted confounding factors shown in Table 1 and Table 2, respectively. The first study^[8] was a prospective cohort study carried out in the United States with a follow up period of 20 years and 3016 participants aged 23 to 35 years. Asthma was diagnosed by self-report, and depression was defined by a self-reported symptom scale.

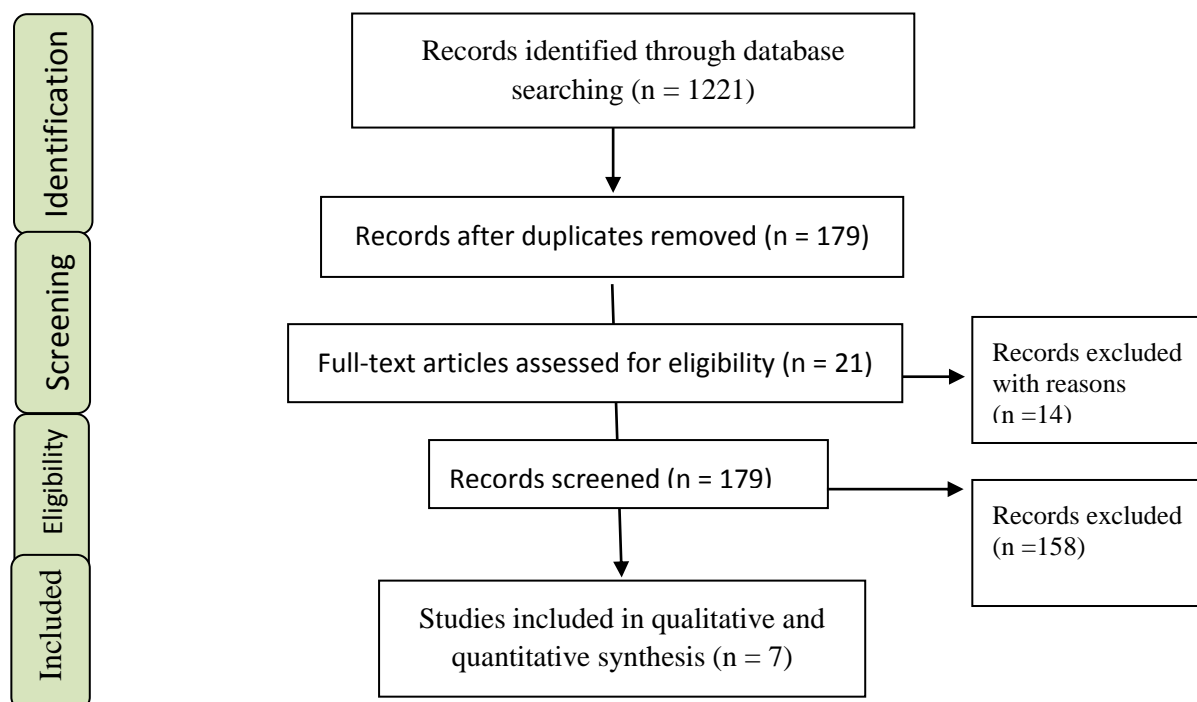


Figure 1: Flow diagram showing the selection criteria of assessed studies.

Table 1. Characteristics of included prospective studies

Sources	Study participants	No. Of cases	Duration, y	Depression assessment	Asthma Ascertainment
Studies for depression predicting incident asthma					
Brumpton BM et al, 2013 [6]	23,599 men and women aged 19–55 y	890	11	14-Item HADS-D \geq 8	Self-report
Brunner WM et al, 2014 [8]	3,614 men and women aged 23–35 y	429	Mean 20	20-Item CES-D \geq 6	Self-reported provider-diagnosed asthma (asthma was defined by a new report of asthma medication use and/or self-reported provider diagnosis of asthma)
Coogan PF et al, 2014 [7]	31,848 African American women aged 21–69 y	771	12	20-Item CES-D \geq 6	Self-report physician-diagnosed asthma (asthma was defined as a firstdiagnosis of asthma with concurrent use of asthma medication)
Patten SB et al, 2008 [13]	14,278 women and men aged over 12 y	NA	8	Composite International Diagnostic Interview Short Form (CIDI-SF)	Self-report
Jonas BS et al, 1999 [10]	5,231 women and men aged 25–74 y	181	Mean 9.4	GWB-D, score 0–12	Self-report
Loerbroks A et al, 2010 [11]	5,114 women and men aged 40–65 y	63	Median 8.5	Paranoid DepressivenessScale	Self-report
Studies for asthma predicting risk of depression					
Walters P 2011 [14]	22,550 men and women aged over 16 y	1752	10	medical diagnosis (defined by Read/OXMIS codes)	medicaldiagnosis
Brunner WM et al, 2014 [8]	3,016 men and women aged 23–35 y	903	20	20-Item CES-D \geq 6	Self-reported provider-diagnosed asthma (asthma was defined by a new report of asthma medication use and/or self-reported provider diagnosis of asthma)

Asthma was recognized by self-report in all selected studies [6–8,10,11,13]. Participants with asthma at baseline were excluded in all six studies. To control for confounding factors, all of the encompassed studies were adjusted for age, sex, and half of them were also adjusted for smoking and body mass index (Table 2).

Table 2. Adjustment for potential confounding factors

Author, year	Adjustment
Studies for depression predicting incident asthma	
Brumpton BM et al, 2013 [6]	Age, sex, smoking, physical activity, family history of asthma, education, social benefit and economic difficulties, BMI
Brunner WM et al, 2014 [8]	Age, sex, race, education, physical activity, study center, smoking status, BMI
Coogan PF et al, 2014 [7]	Age, calendar time, BMI, female hormone use, presence of sleep apnea, income, pack-years of smoking
Patten SB et al, 2008 [13]	Age, sex, health care use
Jonas BS et al, 1999 [10]	Age, sex, race, education, poverty index, urban versus rural residence, respiratory symptoms, and predicted to observed Forced expiratory volume in one second ratio
Loerbroks A et al, 2010 [11]	Age, sex, education, smoking status, alcohol consumption, BMI, physical exercise, family history of asthma
Studies for asthma predicting risk of depression	
Walters P 2011 [14]	Diabetes, cardiovascular disease, cerebrovascular disease, smoking status, age and sex
Brunner WM et al, 2014 [8]	Age, sex, race, education, physical activity, study center, smoking status, BMI

For the sensitivity analyses (Table 3), the final results did not substantially change for numerous exclusion criteria. The exclusion of any single study likewise did not alter the total combined RR, with a range of 1.39 (95% CI, 1.22–1.59) to 1.51 (95% CI, 1.32–1.73).

Table 3. Sensitivity Analyses Based on Various Exclusion Criteria for depression predicting incident adult-onset asthma.

Outcome	No. Studies	No. Participants	No. Cases	RR (95% CI)	P Value	I ² , %	P value for heterogeneity
Studies adjusted for family history of asthma	2	28713	953	1.38 (1.13–1.69)	<0.001	0	0.59
Studies adjusted for smoking status and BMI	4	64175	2153	1.39 (1.23–1.57)	<0.001	0	0.53
Large-scale studies (number >5000)	5	80070	1905	1.49 (1.30–1.71)	<0.001	0	0.77
All included studies	6	83684	2334	1.43 (1.28–1.61)	<0.001	0	0.48
Long-term follow-up durations (>10 y)	3	59061	2090	1.38 (1.22–1.57)	<0.001	0	0.38

DISCUSSION

The results indicated a strong and strong relation between depression and frequency of adult-onset asthma after adjustment for potential confounding factors. Conversely, no relation was found between asthma and subsequent risk of depression, but this may have resulted from the few available studies. Our current meta-analysis, based on stringent inclusion criteria, revealed strong evidence that depression is associated with

increased risk of asthma without heterogeneity among studies (I² = 0, P = 0.48). This conclusion is in agreement with that of a recent meta-analysis of four cross-sectional studies (OR, 3.17; 95% CI, 2.82–3.56) [15]. In an attempt to extract more precise pooled estimates, we only included prospective studies that clearly specified the enrollment of patients without comorbid asthma at baseline. In addition, exclusion of any single study

and sensitivity analyses based on various exclusion criteria did not materially alter the final results, which increased the robustness of our findings. All of these adjustments increased the strength and reliability of our final conclusion. Consequently, the association between depressive symptoms and incident asthma was clear. Further studies are required to be done to clarify whether prevention or effective treatment of depression can have implications for asthma prevention as well as psychological functioning and health.

In contrast to depression predicting incident asthma, this meta-analysis investigated the effect of asthma on incident depression presented a trend toward increased RRs but did not reach a significant statistical difference with high heterogeneity. This might be mostly as a result of the limited number of high-quality studies encompassed. Though we recognized 2 further prospective studies that could be pooled, they did not exclude participants who reported depressive symptoms at baseline^[16, 17].

Consequently, we preferred to stumble on the side of having inaccurate but unbiased estimates rather than having precise but possibly deceptive estimates. Of the two added studies, one reported that asthma in early adolescence was allied with an elevated risk of developing major depression (HR, 1.81; 95% CI, 1.14–2.89) over 12 years^[16], and the other presented that asthmatic adolescents with comorbid attention-deficit hyperactivity disorder (ADHD) but not asthma-alone had an increased risk of developing major depression (HR: 10.25, 95% CI: 3.86–27.19; HR: 2.11, 95% CI: 0.71–6.23, with 7 years of follow-up)^[17]. These inconsistent findings might be explained by differences in asthma control, medicine use, comorbid conditions, and quality of life across studies. However, additional studies considering the above factors are required to better understand the influence of asthma on subsequent elevated depressive symptoms.

Depression can subsidize to asthma over a variability of mechanisms. First, depression has been positively associated with high systemic levels of inflammatory mediators (especially IL-4, IL-6 and TNF- α)^[15], which have essential pathogenic roles in asthma. Second, depression has known neuroendocrine effects (i.e. deregulation of the hypothalamic-pituitary-adrenocortical axis and autonomic nervous system), which can utilize a connection between depression and asthma^[18]. Third, depressed individuals incline to be obese and smokers, and these conditions have been verified to independently increase the risk of asthma^[19, 20].

Nonetheless, our sensitivity analyses for only containing studies adjusted RR with smoking and/or BMI as covariates did not affect the final conclusions, which attenuates the feasibility of this explanation. Fourth, depression has been associated with increased oxidative stress levels and decreased antioxidant functions, and oxidative stress contributes to the pathogenesis of asthma^[21]. Generally, numerous mechanisms in patients with genetic susceptibility, either alone or combined, could be implicated in the development of asthma.

CONCLUSION

The current meta-analysis of the prospective studies specified that depression increases the risk of subsequent adult-onset asthma. Nonetheless, there is no evidence for a positive relation between asthma and incident depression symptoms due to the limited available data. Additional largescale epidemiologic studies establishing the true association between asthma and subsequent risk of depression, and experimental studies examining the underlying mechanisms linking depression and asthma are warranted.

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