

Research paper

Suicidality among patients with asthma: A systematic review and meta-analysis



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ABSTRACT

Background: Asthma is associated with multiple psychiatric comorbidities. However, the relationship between asthma and suicidality has not been well established.

Methods: According to the PRISMA guidelines, protocol of the study was registered in the PROSPERO database (CRD42019123150). A systematic search of the PubMed, Embase and PsycINFO databases was performed for relevant studies published from its inception to January 25, 2019. Studies that reported the risk of suicidal ideation, attempts and mortality in asthmatics compared with non-asthmatics were included. A random-effects model was used to synthesize the estimates and the quality of the included studies was assessed under the Newcastle-Ottawa Scale.

Results: Twenty-eight studies including 2,759,841 asthmatic patients and 16,290,362 non-asthmatic controls were pooled and analyzed in the current study. The pooled data showed that asthmatic patients had increased risk of exhibiting suicidal ideation (OR, 1.52; 95%CI, 1.37–1.70), suicide attempts (OR, 1.60; 95%CI, 1.33–1.92) and suicide mortality (OR, 1.31; 95%CI, 1.11–1.55) compared to non-asthmatic controls. Noticeably, adolescent asthmatic patients had a more than 2-fold risk of suicide mortality compared to non-asthmatic controls (OR, 2.14; 95%CI, 1.61–2.83).

Limitations: The limitations of the present study were variability in study designs and various measures of asthma and suicidality, which possibly contribute to notable heterogeneity.

Conclusions: Patients with asthma have a significantly increased risk of suicidal ideation, suicide attempts and suicide mortality. Clinical physicians should pay more attention to the increased risk of suicidality in asthmatics, screen for these suicidal thoughts and behaviors, and make appropriate mental health referrals when necessary.

1. Introduction

Asthma is a commonly occurring chronic inflammatory airway disease affecting approximately 300 million adults and children around the world (World Health Organization 2007). It is closely related with multiple physical comorbidities, such as atopic dermatitis (AD), allergic rhinitis (AR), chronic pulmonary disease, sleep disturbances and metabolic syndrome, all of which may contribute to the increased physical burden of the disease (Kauppi et al., 2015). Numerous asthmatic patients also experience a huge and profound psychosocial and psychiatric burden, like asthma impaired school performance in adolescents (Nilsson et al., 2018; Kim et al., 2017), and adults with asthma

performed significantly worse at work compared with healthy adults (Karvala et al., 2014). Asthma can significantly affect the quality of life including sleeplessness, daytime fatigue, reduced activity levels and mental health problems (Van Herck et al., 2018; Katon et al., 2007).

There is a gap in the literature determining the relationship between asthma and risk of suicidality. Population-based studies suggest that asthmatic patients may experience an increased prevalence of suicidality. Suicidality can be defined as 3 components as follows: suicidal ideation, suicide attempts and suicide mortality (suicide death or completed suicide) (Meyer et al., 2010). Suicidal ideation means to have thoughts to commit suicide. Suicide attempt means to have acts for attempting suicide while the individual survives. Suicide mortality

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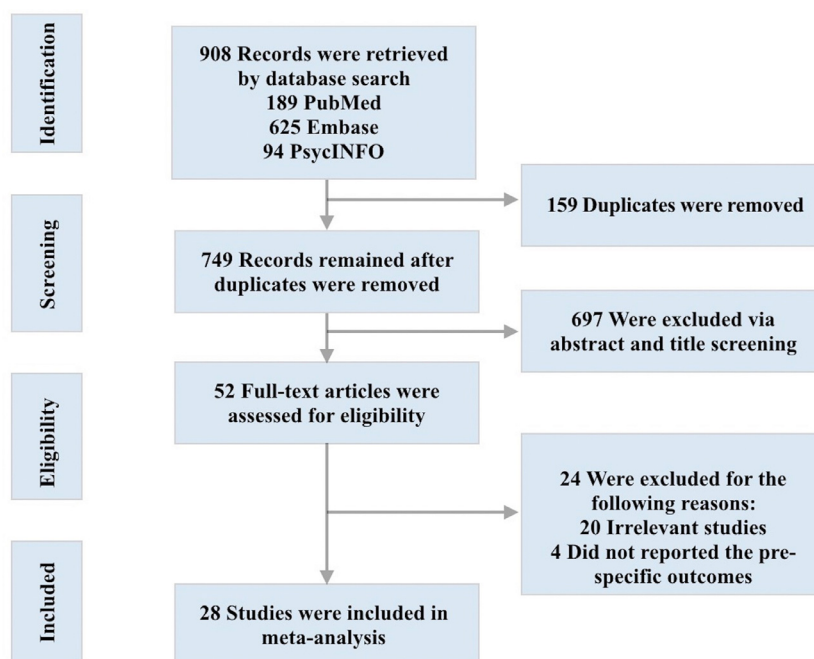


Fig. 1. PRISMA style flow chart of study selection.

means to complete successful suicide attempts that lead to death. Psychosocial factors, such as depression and anxiety from disability and discomfort associated with asthma (Adewuya and Adeyeye, 2017), may all contribute to the increased risk of suicidality. However, the risk of suicidality among asthmatics has not been well established. The current study was performed to synthesize the available studies and elucidate the epidemiologic association between asthma and suicidality.

2. Methods

2.1. Protocol and registration

This study was performed referring to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010), and it was registered on PROSPERO databases (CRD42019123150).

2.2. Data sources and search strategy

A comprehensive and systematic search was performed in PubMed, Embase, PsycINFO databases for eligible studies published from its inception to January 25, 2019. The keywords included: (asthma AND (suicide OR suicidality OR suicidal ideation OR suicide, attempted OR suicide attempt OR suicidal behavior OR suicide death OR suicide mortality)). Studies that reported the risk of suicidal ideation, suicide attempt, and/or suicide mortality in asthmatic patients compared to non-asthmatic controls were included.

2.3. Eligibility criteria

Two authors (Y.Z., J.C.) independently reviewed all the titles and abstracts after removing the duplicates, and the full text of the articles was further assessed in case the content was not very clear from the title and abstract. Disagreement on the study selection would be resolved by discussing with a third author (Y.L.). Inclusion criteria were as follows: 1) Studies that reported the risk of suicidality (including suicidal ideation, attempts, and/or mortality) in asthmatic patients compared to non-asthmatic controls; 2) study population with any age, gender, race and ethnicity; 3) studies reported pre-specific outcomes for risk of

suicidality with odds ratio (OR), risk ratio (RR), rate ratio (RR), hazard ratio (HR), or data that could be used to calculate those; 5) English-language articles. Case reports and case series, review article, meta-analysis, conference abstracts were excluded.

2.4. Study selection and data extraction

Two independent reviewers (Y.Z. and J.C.) performed the literature search. Studies were selected and data were extracted separately, and any disagreement would be discussed with a third reviewer (Y.L.) and resolved by consensus. Senior reviewers (X.S., P.P., C.H.) were consulted when necessary. The following data were extracted from the included studies: name of the first author, publication year of the article, country where the study performed, type of study design, characteristics of participants including baseline age, number, measurement of asthma and suicidality and adjusted factors for outcomes of suicidality. Estimates of suicidality were extracted from the included studies respectively. When only crude count data was provided, unadjusted estimate would be calculated by established methods.

When unadjusted and adjusted risks of suicidality were available, adjusted estimates were extracted to conduct meta synthesis. When adjusted estimates were conducted for several models in one study, the adjusted estimate with the most confounding factors was extracted.

2.5. Synthesis of results

We extracted estimates of OR, RR, or HR, and the respective 95% CI for suicidal ideation, suicide attempts, and suicide mortality. Different ratio measures of association including OR, RR and HR were reported in the included studies. Since the incidence of suicide was rare, these different measures would be fairly similar. Therefore, the pooled OR was used.

In the current meta-analysis, the pooled ORs and 95% CIs for suicidal ideation, suicide attempts and suicide mortality were calculated by using STATA (version 15.0) software package. Random-effects model was performed to pool the data in this meta-analyses, which enables the generalizability of results by assuming that the analyzed studies are a random sample of effect sizes and take into account both within-study and between study variability. Statistical significance was

Table 1
Characteristics of the included studies.

First author, year	Country	Study design	No. asthma/ non-asthma participants	Baseline age(yrs)	Measurement of asthma
Goodwin et al. (Goodwin et al., 2003), 2003	USA	Cross-sectional	176/822	18–70	Asthma diagnosis from primary-care physicians
Goodwin et al. (Goodwin and Marusic, 2004), 2004	USA	Cross-sectional	75/1089	9–17	Parental reports of past hospitalization for asthma
Goodwin et al. (Goodwin and Eaton, 2005), 2005	USA	Cohort study	251/3102	≥ 18	Self-reported asthma
Bender et al. (Bender, 2007), 2007	USA	Cross-sectional	718/13,148	Grades 9–12 students	Self-reported lifetime diagnosis of asthma and asthma symptoms in past 12 months
Nomura et al. (Nomura et al., 2007), 2007	USA	Cohort study	111/1414	29 ± 2.5	Self-reported current or past asthma
Clarke et al. (Clarke et al., 2008), 2008	USA	Cross-sectional	683/5009	≥ 18	Self-reported diagnosed asthma
Kuo et al. (Kuo et al., 2010), 2010	China	Cohort study	30,132/132,634	11–16	Self-reported current and previous asthma symptoms
Bae et al. (Bae et al., 2011), 2011	Korea	Cross-sectional	5879/69,359	Middle or high school students	Self-reported diagnosis and treatment of asthma
Chan et al. (Chan et al., 2011), 2011	China	Cross-sectional	218/3378	≥ 65	Self-reported diagnosis of asthma
Christiansen et al. (Christiansen and Stenager, 2012), 2012	Denmark	Nested case-control	2522/70,243	16–22	Hospital records of asthma treated in a somatic hospital
Goodwin et al. (Goodwin et al., 2012), 2012	USA	Cross-sectional	323/5182	20–39	Self-reported diagnosed asthma
Rai et al. (Rai et al., 2012), 2012	UK	Cross-sectional	886/6517	≥ 16	Doctor-diagnosed asthma
Webb et al. (Webb et al., 2012), 2012	UK	Nested case-control	1708/16,625	Adults	Asthma diagnosis from primary-care records
Crump et al. (Crump et al., 2014), 2014	Sweden	Cohort study	136,367/7,004,222	≥ 18	Diagnosed asthma recorded in outpatient and hospital registries
Singhal et al. (Singhal et al., 2014), 2014	UK	Cohort study	2,500,814/7,976,297	10–> 65	Hospital admissions for asthma
Bolton et al. (Bolton et al., 2015), 2015	Canada	Nested case-control	6092/28,472	No age restriction	Recorded physician-diagnosed asthma
Crawford et al. (Crawford et al., 2015), 2015	UK	Cohort study	387/10,476	University students	Self-reported asthma
Lee et al. (Chen et al., 2015), 2015	Korea	Cross-sectional	6586/66,652	Middle or high schools students	Self-reported asthma
Chen et al. (Lee et al., 2015), 2015	China	Cohort study	30,131/132,635	11–16 junior high school students	Self-reported asthma
Chung et al. (Chung et al., 2016), 2016	Korea	Cross-sectional	6372/222,372	≥ 19	Physician-diagnosed asthma
Chang et al. (Chang et al., 2017), 2017	Korea	Cross-sectional	266/2010	High school students	Self-reported questionnaires of allergic symptoms, video questionnaires, and the methacholine challenge test.
Ahmedani et al. (Ahmedani et al., 2017), 2017	USA	Case-control	15,187/254,887	39.5 ± 21.9	Via diagnostic codes within the healthcare systems
Kye et al. (Kye and Park, 2017), 2017	Korea	Cross-sectional	317/19,282	56 ± 0.12	Self-reported physician-diagnosed asthma
Han et al. (Han and Chung, 2018), 2018	Korea	Cross-sectional	7177/215,154	12–18	Self-reported asthma
Bedolla-Barajas et al. (Bedolla-Barajas et al., 2018), 2018	Mexico	Cross-sectional	115/96	20–50	Physician-diagnosed asthma
Muhammad et al. (Han et al., 2018), 2018	USA	Cross-sectional	2814/10,340	9th- to 12th-grade students	Self-reported asthma
Han and Forno et al. (Muhammad et al., 2018), 2018	USA	Cross-sectional	312/2737	18–64	Self-reported asthma
Han et al. (Han et al., 2019), 2019	USA	Cross-sectional	3222/21,390	9th- to 12th- grade high school students	Self-reported physician-diagnosed asthma

Table 2
Outcomes of the included studies.

First author, year	Suicidality Suicidal ideation	Suicide attempts	Suicide mortality	Adjusted factors
Goodwin et al. (Goodwin et al., 2003), 2003	AOR 1.9(1.03, 3.4)	NR	NR	Adjusted for age, gender, race, marital status, education, comorbid mental disorders and suicidal ideation.
Goodwin et al. (Goodwin and Marusic, 2004), 2004	AOR 3.25(1.04, 10.1)	NR	NR	Adjusted for socio-demographic factors and mental disorders.
Goodwin et al. (Goodwin and Eaton, 2005), 2005	AOR 2.33(1.03, 5.25)	AOR 3.54(1.4, 8.99)	NR	Adjusted for gender, age, race, treatment for asthma, and major depression (lifetime).
Bender et al. (Bender et al., 2007), 2007	OR 2.33(1.98, 2.75)	OR 2.36(1.93, 2.88)	NR	NR
Nomura et al. (Nomura et al., 2007), 2007	AOR 2.8(1.4, 5.8)	NR	NR	Adjusted for mother's age, education, parity, marital status and poverty level at delivery and child's sex, age at last interview, race at poverty level at age 7.
Clarke et al. (Clarke et al., 2008), 2008	AOR 0.90 (0.68–1.25)	AOR 1.53 (1.06, 2.21)	NR	Adjusted for adjusted for age, sex, and race/ethnicity, smoking and nicotine dependence, depression, panic disorder, and alcohol dependence or abuse, sociodemographic, smoking, and mental health factors.
Kuo et al. (Kuo et al., 2010), 2010	NR	NR	Current asthma: AHR 2.26(1.43, 3.58) Previous asthma: AHR 1.76(0.90, 3.43)	Adjusted for gender, age, cigarette smoking by at least one member of the family, cigarette smoking, and allergic rhinitis.
Bae et al. (Bae et al., 2011), 2011	Current asthma: AOR 1.36(1.19, 1.55) Former asthma: AOR 1.40(1.27, 1.54)	Current asthma: AOR 1.55(1.25, 1.92) Former asthma: AOR 1.54(1.29, 1.84)	NR	Adjusting for gender, grade, self-rated school records, perceived socioeconomic status, current alcohol use, and/or current cigarette use, and/or suicidal ideation.
Chan et al. (Chan et al., 2011), 2011	OR 2.84(1.76, 4.58)	NR	NR	NR
Christiansen et al. (Christiansen and Stenager, 2012), 2012	NR	Male: AHR 1.11(0.78, 1.59) Female: AHR 1.02(0.83, 1.24)	NR	Adjusted for all other variables and child's psychiatric history, parents' psychiatric history, use of psychopharmacological drugs, level of income, level of education, death and cohabitation.
Goodwin et al. (Goodwin et al., 2012), 2012	Current asthma: AOR 1.77(1.11, 2.84) Former asthma: AOR 1.28(0.74, 2.22)	Current asthma: AOR 3.26(1.97, 5.39) Former asthma: AOR 2.10(0.92, 4.80)	NR	Adjusted for age, gender, race/ethnicity and poverty index, smoking status, self-report allergies to animals, dust, pollen or occupational exposures
Rai et al. (Rai et al., 2012), 2012	AOR 1.5(1.2, 1.8);	AOR 1.5(1.1, 2.1)	NR	Adjusted for age, gender, marital status, highest educational qualification, employed or economically inactive, and number of comorbid physical illnesses.
Webb et al. (Webb et al., 2012), 2012	NR	NR	AOR 0.84(0.66, 1.08)	Controlling for depression
Crump et al. (Crump et al., 2014), 2014	NR	NR	Male: AHR 1.44(1.16, 1.80) Female: AHR 1.71(1.35, 2.17); RR 1.2(1.1, 1.3)	Adjusted for age, marital status, country of birth, education, employment status, income, urban/rural status and psychiatric and somatic disorders.
Singhal et al. (Singhal et al., 2014), 2014	NR	NR	NR	NR
Bolton et al. (Bolton et al., 2015), 2015	NR	AOR 0.84(0.75, 0.93)	AOR 1.03(0.88, 1.22)	Aggregated Diagnosis Group (ADG) count, depression, anxiety disorders, substance abuse or dependence, schizophrenia, dementia, other psychosocial disorders,
Crawford et al. (Crawford et al., 2015), 2015	NR	NR	AHR 0.92(0.13, 6.73)	and all physical disorders simultaneously.
Lee et al. (Chen et al., 2015), 2015	AOR 1.23(1.15, 1.32)	NR	NR	Adjusted for sex, height, number of siblings, birth order, fathers social class, body mass index and current smoking.
Chen et al. (Lee et al., 2015), 2015	NR	NR	AHR 2.20(1.45, 3.34)	Adjusted for school and family factors
Chung et al. (Chung et al., 2016), 2016	AOR 1.53 (1.42, 1.65)	AOR 1.32 (1.01, 1.73)	NR	Adjusted for gender, age, the highest education of parents, SHS exposure, cigarette smoking, the lifetime asthma, allergic rhinitis, and alcoholic drinking.
Chang et al. (Chang et al., 2017), 2017	Definite asthma: AOR 5.23 (1.37, 19.94) Self-reported asthma: AOR 2.45(1.10, 4.77)	NR	NR	Adjusted for age, sex, income, education, job, marital status, smoking, alcohol,
Ahmedani et al. (Ahmedani et al., 2017), 2017	NR	NR	AOR 0.99(0.84, 1.16)	exercise, physician diagnosed diseases, depression. Adjusted for sex, age, income, maternal education, active smoking, and passive smoking, depression status and forced expiratory volume in 1 s.

(continued on next page)

Table 2 (continued)

First author, year	Suicidality Suicidal ideation	Suicide attempts	Suicide mortality	Adjusted factors
Kye et al. (Kye and Park, 2017), 2017	AOR 1.27(0.92, 1.76)	AOR 2.14(0.90, 5.10)	NR	Adjusted for age, sex, marital status, household income, education, depression, depressive mood, physical discomfort, stress perception, high-risk drinking, and other diseases.
Han et al. (Han and Chung, 2018), 2018	AOR 1.08(1.01, 1.17)	AOR 1.23(1.10, 1.38)	NR	Adjusted for age, sex, school type, residence area, family structure, family affluence scale, smoking, alcohol, regular exercise, sleep duration and satisfaction, substance use, sexual experience, perceived stress and health status, depressive mood.
Bedolla-Barajas et al. (Bedolla-Barajas et al., 2018), 2018	OR 1.98(0.78, 4.64)	NR	NR	NR
Muhammad et al. (Han et al., 2018), 2018	OR 1.47(1.32, 1.63)	OR 1.75(1.53, 2.01)	NR	NR
Han and Forno et al. (Muhammad et al., 2018), 2018	NR	AOR 3.01(1.80, 5.01)	NR	Adjusted for monthly family income and employment.
Han et al. (Han et al., 2019), 2019	OR 1.58(1.43, 1.73)	OR 1.82(1.60, 2.07)	NR	NR

Note: OR: Crude odd ratio; AOR: Adjusted odd ratio; RR: Crude risk ratio; ARR: Adjusted risk ratio; HR: Crude hazard ratio; AHR: Adjusted hazard ratio; NR: Not reported.

assumed at $P < 0.05$. Heterogeneity was assessed by the I^2 statistic. Funnel plot analysis and the Egger test would be performed to determine publication bias when there were more than 10 included studies (Sterne et al., 2011).

2.6. Quality assessment

Two independent authors (Y.Z. and J.C.) assessed the quality of the included studies referring to the Newcastle-Ottawa Scale (NOS) (Wells et al., 2019). NOS criteria judge cohort studies and case-control studies with 0–9 stars based on the categories of selection (1–4 points), comparability (1–2 points), and ascertainment of the interested outcomes (suicidality) or exposure (asthma) (1–3 points). A modified NOS was referred to assess the quality of cross-sectional studies. Disagreements in quality assessment were discussed with a third author (R.H) and resolved by consensus.

3. Results

3.1. Study selection and characteristics

According to our search strategies, we initially identified 908 citations in three electronic databases (PubMed, Embase, PsycINFO), and the search strategy and results are summarized in the **Table S1 in the supplementary**. We excluded 856 articles based on the removing duplicates and screening the titles and abstracts, and further excluded 24 articles after reading the full texts. Finally, we identified a total of 28 studies (involving 2,759,841 asthmatic participants and 16,290,362 non-asthmatic controls) that met the selection criteria (Goodwin et al., 2003; Han et al., 2019). The PRISMA style flow chart of study selection was show in **Fig. 1**. The included studies consisted of 7 cohort studies, 4 case-control studies and 17 cross-sectional studies. Eleven studies were performed in the United States, 6 studies in Korea, and 4 studies in the UK, 3 studies in China, and 1 study was from Canada, 1 study from Mexico, 1 study from Sweden and 1 study from Denmark. Eighteen studies included suicidal ideation as an outcome, 14 studies reported suicide attempts as an outcome and 8 studies investigated suicide mortality as an outcome. Ten studies reported the risk of suicidality in adolescent asthmatic patients. The characteristics and pre-specific outcomes of the included studies were summarized in the **Table 1 and Table 2** respectively. We evaluated the quality of individual study using the Newcastle-Ottawa Scale criteria (12) (**Table S2 in the supplementary**).

3.2. Meta-analytical results

3.2.1. Suicidal ideation

In the current study, 18 studies investigated suicidal ideation and the pooled data showed that asthmatic patients had significantly increased risk of having suicidal ideation (OR 1.52, 95%CI 1.37, 2.10, $I^2=96.2\%$, **Fig. 2**). Subgroup analysis based on age showed at asthmatic patients across the whole age spectrum had comparable increased risk of suicidal ideation (adult: OR 1.60, 95%CI 1.30, 1.98, $I^2=63.6\%$; adolescents: OR 1.50, 95%CI 1.30, 1.74, $I^2=91.6\%$; mixed age: OR 1.50, 95%CI 1.22, 1.84, **Fig. 2**). There were more than 10 extracted estimates in the category of suicidal ideation, so funnel plot were conducted to detect possible publication bias. Minimal asymmetry was shown from the visual inspection of the funnel plots (**Figure S1 in the supplementary**), and insignificant Egger test was found in suicidal ideation (Egger test; SE, 0.82; 95% CI, -0.05 to 3.40 ; $P = 0.056$), which suggested possible publication bias among these studies but without statistical significance.

3.2.2. Suicide attempts

In the current study, 14 studies investigated suicide attempts and the pooled data showed that patients with asthma had greater risk of

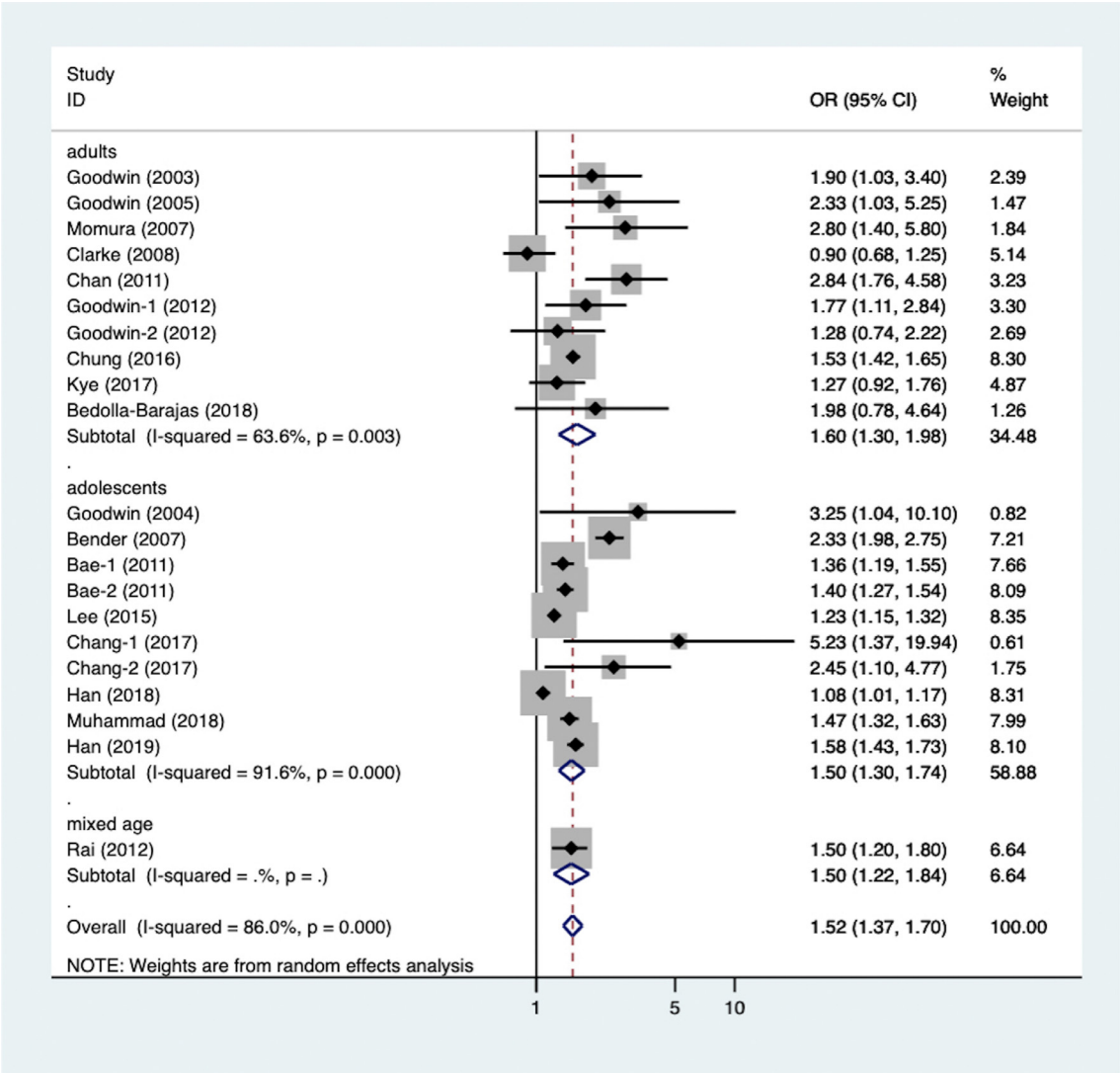


Fig. 2. Forest plots for the risk of suicidal ideation among asthmatic patients.

experiencing suicide attempts (OR1.60, 95%CI 1.33, 1.92, $I^2=91.2\%$, Fig. 3). Subgroup analysis based on age showed increased risk of suicide attempts was found in adult and adolescent asthmatic patients compared to their non-asthmatic controls (adults: OR 2.13, 95%CI 1.52, 2.99, $I^2=65.5\%$; adolescents: OR 1.67, 95%CI 1.39, 1.99, $I^2=87.8\%$, Fig. 3) but not in asthmatic patients with mixed-age group (OR 1.06, 95%CI 0.83, 1.34, Fig. 3). No obvious asymmetrical funnel plot was exhibited from visual inspection (Figure S1 in the supplementary) and insignificant Egger test was detected for suicide attempts (Egger test; SE, 1.48; 95% CI, -0.57 to 5.75 ; $P=0.102$), which suggested no obvious evidence of publication bias among these studies.

3.2.3. Suicide mortality

In the current study, 8 studies investigated suicide mortality and the pooled data showed that asthmatic patients had increased risk of suicide mortality (OR 1.31, 95%CI 1.11, 1.55, $I^2=79.9\%$, Fig. 4). Noticeably, subgroup analysis based on age showed adolescent asthmatic patients, but not adult asthmatic patients, had a more than 2-fold risk of suicide mortality compared to non-asthmatic controls (OR 2.14; 95%CI, 1.61, 2.83, Fig. 4). No obvious asymmetrical funnel plot was shown from visual inspection (Figure S1 in the supplementary) and insignificant Egger test was detected for suicide attempts (Egger test; SE, 1.20; 95% CI, -1.45 to 4.10 ; $P=0.303$), which suggested no evidence of publication bias among these studies.

3.2.4. Sensitivity analysis

A sensitivity analysis was performed by removing any individual study successively and analyzing the pooled OR and 95% CI with the remaining studies using the random-effects model, which determined the effect of each single study on the combined effect estimate. Sensitivity analysis were performed and showed that the pooled OR were not considerably altered, which indicated the results were relatively stable and reliable for our meta-analysis (Table S3 in supplementary).

4. Discussion

This is the first extensive and comprehensive meta-analysis to determine the risk of suicidality in asthmatic patients. Overall, the pooled results exhibited that asthmatic patients experienced an increased risk of suicidal ideation, suicide attempts and suicide death.

Asthmatic patients experience more physical and psychosocial burden, which could potentially result in the increased risk of suicidality. Severe asthmatic patients experience more debilitating respiratory symptoms of wheezing, cough and shortness of breath, which may contribute to more frequent thoughts of suicide with increasing severity. Psychosocial factors, such as depression and anxiety from discomfort and disability associated with asthma (Adewuya and Adeyeye, 2017), the shame and inferiority (Bender and Bender, 2005;

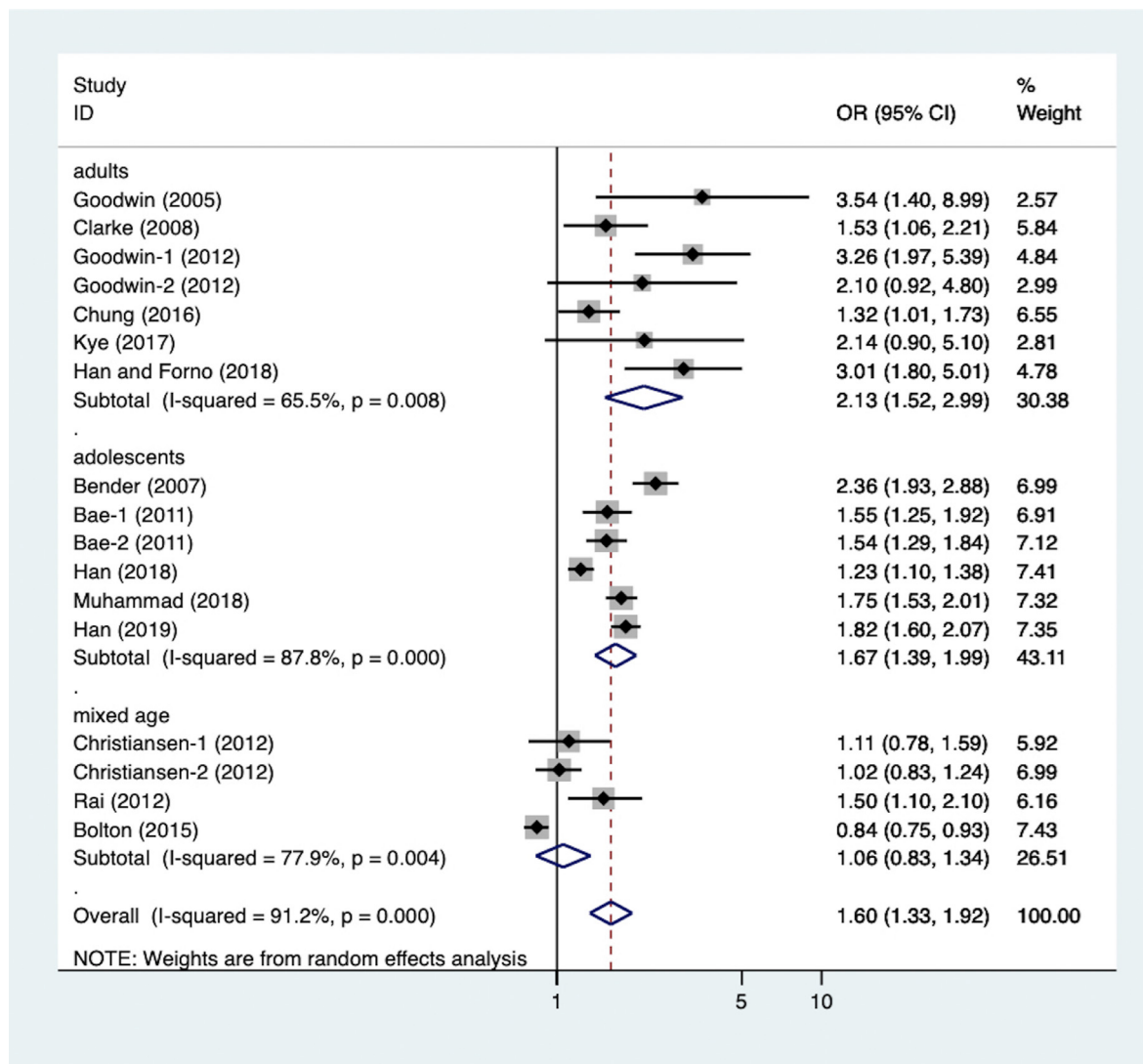


Fig. 3. Forest plots for the risk of suicide attempts among asthmatic patients.

Ahmad et al., 2014), poor school or workplace performance, and impairment of quality of life experienced from the disease, all may contribute to the observed increased likelihood of suicidal thoughts and behaviors in asthmatic patients (Karvala et al., 2014; Nilsson et al., 2018). Furthermore, asthmatic patients experience more insomnia and sleep loss, which may also result in higher levels of depression and anxiety symptoms, and poor quality of life (Luyster et al., 2016), thus contributing to the increased likelihood of suicidality.

In addition, asthma is closely associated with higher levels of pro-inflammatory cytokines, which may participate in the pathogenesis of suicidality in asthmatics. Activation of inflammatory signaling pathway may alter serotonin metabolism in the central nervous system (CNS), thus resulting the disorders of neurotransmitter system (Koo et al., 2017; Davami et al., 2016). Persistent exposure to increased inflammatory cytokines and alterations in neurotransmitter systems can further cause neuropsychiatric disorders and depression (Felger and Lotrich, 2013). Elevated pro-inflammatory cytokines in cerebrospinal fluid were detected in those people who attempted suicide than in their controls who did not attempt suicide, further indicating the potential role of cytokines in the pathogenesis of suicidal behaviors (Lindqvist et al., 2009).

There are some suggestions that particular medications for controlling the symptoms of asthma, such as corticosteroids and montelukast sodium, have been reported the link with mood disorders

similar to major symptoms of depression (Patten and Neutel, 2000; Philip et al., 2009), which may help to explain the observed increased likelihood of suicidality in asthmatic patients. However, the researches aiming to determine the association between the use of asthma medications and risk of suicidality provided very mixed and controversial findings, and numerous studies failed to find robust evidence of increased suicidality in asthma individuals using these medications (Jick et al., 2009; Philip et al., 2009; Schumock et al., 2012).

The current study conducted subgroup analysis based on age spectrum. It's noteworthy that adolescent asthmatics had a greater risk of suicide mortality than other age-stage patients compared to their non-asthmatic controls. Adolescent asthmatics may potentially experience more psychological burden from the disease than adult patients with lower self-esteem, less social participation, parental over protection, and/or more comorbidity with clinical levels of depression and anxiety (Katon, 2010). Therefore, interventions aimed at helping mental comorbidities in adolescents with asthma are paramount. Moreover, Han's study showed adolescent asthmatic girls experienced more higher risks of suicidal ideation and attempts than those boys after gender stratification (Han and Chung, 2018). A higher risk of suicide mortality was also shown in female asthmatic patients than male asthmatic patients in Bolton's study (Bolton et al., 2015). However, there were not sufficient studies to further determine the association between asthma and the risk of suicidality in asthmatic patients stratified by gender. Further

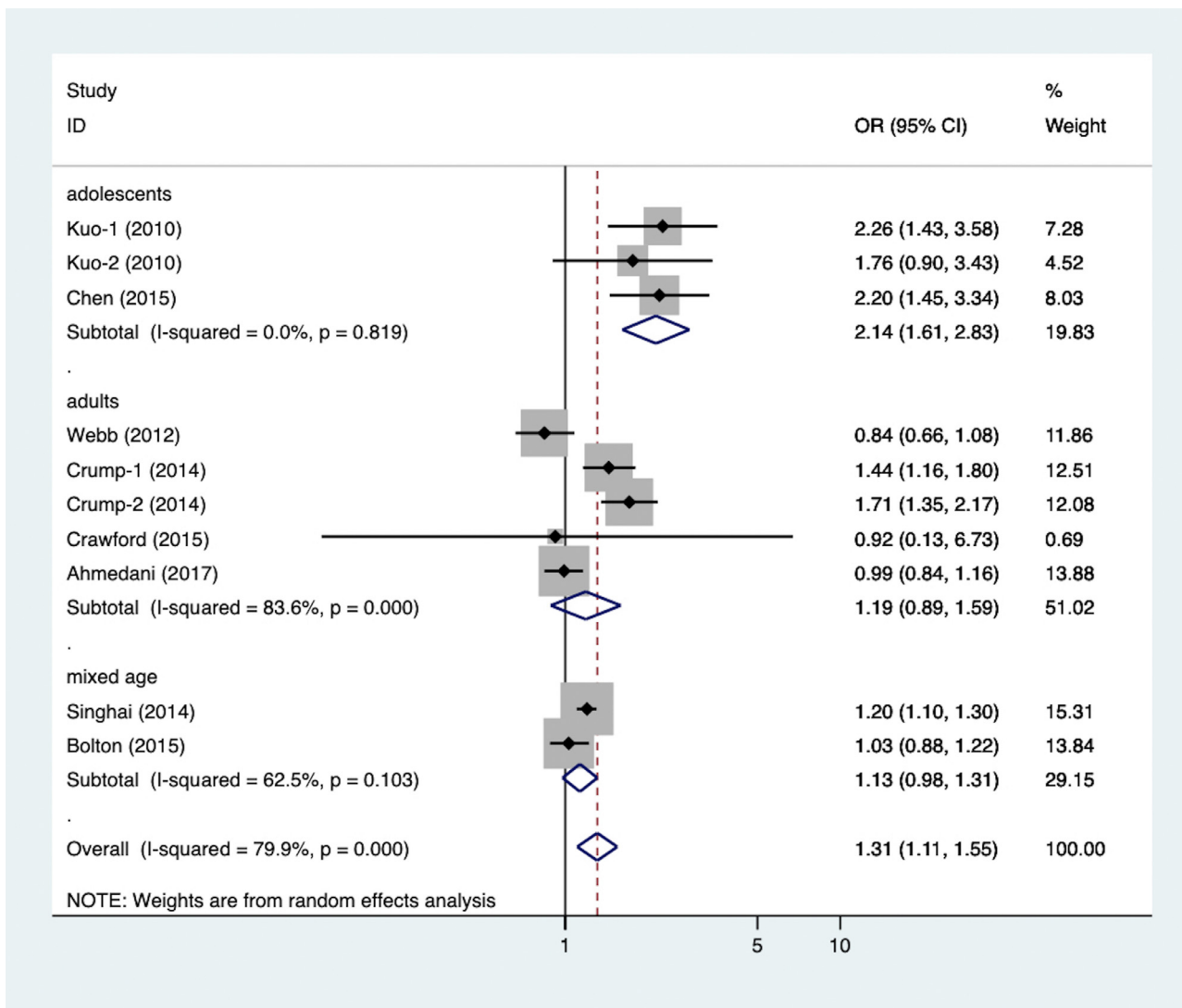


Fig. 4. Forest plots for the risk of suicide mortality among asthmatic patients.

powerful studies should explore in more detailed association of suicidality among asthma stratified by gender and age.

5. Strengths and limitations

This study has some limitations. First, variability in study designs (including case-control studies, cohort studies and cross-sectional studies) of the included studies were likely to introduce heterogeneity. Second, various measures of asthma and suicidality can also attribute to the possible heterogeneity, which would be larger in those studies which use less validated self-reported questionnaires compared to the studies using more well-validated and psychometrical sound instruments or medical records. We were unlikely to determine the amount of heterogeneity caused by variability of study measurement and actual differences in individual study. There are some other physical and psychological comorbidities involved in the included populations, which may also confound these results. Therefore, the random-effects model was conducted in the current meta-analyses to account for the heterogeneity caused by variability both within-study and between study.

6. Clinical implications

Our comprehensive meta-analysis revealed an increased risks of

suicidal ideation, suicide attempts and suicidal mortality in asthmatic patients. Monitoring for suicidality in asthmatic patients is crucial to improve patients outcomes. Clinical physician may use several tools, such as asking patients about suicidal ideation with a question (Have you ever thought of killing yourself?) or using validated questionnaires to screen for depression, dysphoria and anhedonia, to screen patients with asthma for suicidality. If a patient screens positive for suicidality, the physician should make appropriate referrals to mental health professionals and provide close follow-up care.

7. Conclusions

In summary, this study suggests that asthmatic patients experience significantly higher risks of suicidal ideation, attempts and mortality. It is important for clinical physicians to be aware of this increased risk of suicidal thoughts and behaviors, and make appropriate referrals to mental health professionals when necessary.

Declarations of interest

none.

CRediT authorship contribution statement

Zhang Yan: Conceptualization, Methodology, Data curation, Writing - original draft, Validation. **Cheng Jun:** Methodology, Data curation, Validation. **Li Yuanyuan:** Data curation, Writing - review & editing, Validation. **He Ruoxi:** Data curation, Writing - review & editing, Validation. **Abira A Choudhry:** Data curation, Writing - review & editing, Validation. **Jiang Juan:** Data curation, Formal analysis, Writing - review & editing, Validation. **Pan Pinhua:** Data curation, Formal analysis, Writing - review & editing, Validation. **Su Xiaoli:** Data curation, Formal analysis, Writing - review & editing, Validation. **Hu Chengping:** Conceptualization, Supervision, Funding acquisition, Writing - review & editing, Validation.

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None

Conflict of interest

All other authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jad.2019.06.031](https://doi.org/10.1016/j.jad.2019.06.031).

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Table S1. Search strategy.

Embase	Number of identified paper
#1 asthma	309407
#2 suicide	105341
#3 suicidality	7266
#4 suicidal ideation	20476
#5 suicide attempted	8270
#6 suicide attempts	32154
#7 suicidal behavior	22993
#8 suicide death	21713
#9 suicide mortality	11011
#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	120972
#11 #1 AND #10	625

PubMed	No.
#1 asthma	177643
#2 suicide	80008
#3 suicidality	5400
#4 suicidal ideation	11074
#5 suicide attempted	20666
#6 suicide attempts	23274
#7 suicidal behavior	21184
#8 suicide death	17435
#9 suicide mortality	9807
#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	84685
#11 #1 AND #10	189

PsyINFO	No.
#1 asthma	7691
#2 suicide	55278
#3 suicidality	6454
#4 suicidal ideation	13575
#5 suicide attempted	15143
#6 suicide attempts	12419
#7 suicidal behavior	11812
#8 suicide death	4025
#9 suicide mortality	1307
#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	61207
#11 #1 AND #10	94

Table S2. Quality assessment of the included studies under the the Newcastle-Ottawa Scale.

First author, year of publication	Study design	Selection		Comparability						Total Score
		Exposure								
		Case Definition Adequate ?	Case Representative?	Selection of Controls	Definition of Controls	Based on Design or Analysis	Ascertainment of Exposure	Same Method for Cases and controls	Non-Response Rate	
Christiansen 2012[22]	Nested case-control	—	+	—	+	++	—	+	—	5
Webb 2012[25]	Nested case-control	—	+	—	+	++	—	+	—	5
Bolton 2015[28]	Nested case-control	—	+	—	+	—	—	+	—	3
Ahmedani 2017[34]	Case-control	—	+	—	+	—	+	+	—	3

First author, year of publication	Study design	Selection		Comparability				Exposure		Total Score
		Exposed Cohort Representative?	Selection of Non-Exposed Cohort	Ascertainment of Exposure	Outcome not present at study start?	Based on Design or Analysis	Assessment of outcome	Time of Follow-up	Adequate Follow-up	
Goodwin 2005[15]	Cohort study	+	+	+	—	++	—	—	—	5
Nomura 2007[17]	Cohort study	+	+	+	+	—	—	+	+	6
Kuo 2010[19]	Cohort study	+	+	+	+	—	+	+	+	7
Crump 2014[26]	Cohort study	+	+	+	+	—	+	+	+	7
Singhal 2014[27]	Cohort study	+	+	+	—	—	+	—	—	4
Crawford 2015[29]	Cohort study	+	+	—	+	—	+	+	+	6
Chen 2015[30]	Cohort study	+	+	+	+	—	+	+	+	7

First author, year of	Study design	Selection Exposure	Comparability	Total Score
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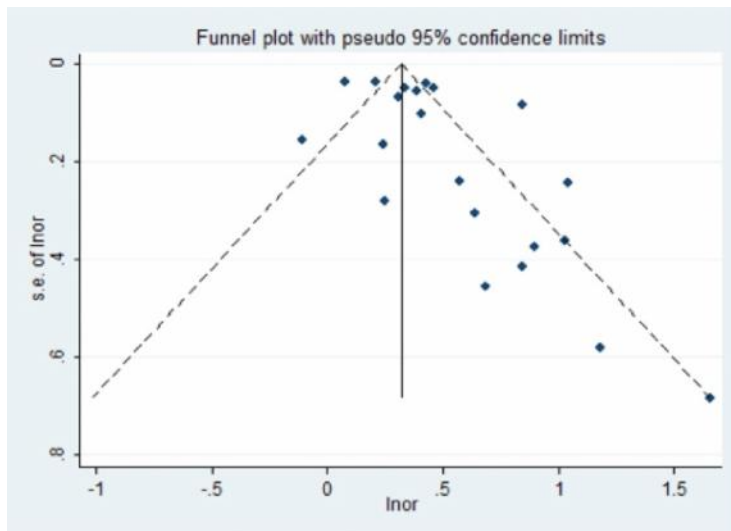
publication		Representative sample?	Sample Size Adequate	Non-Respondents	Ascertainment of Exposure	Based on Design or Analysis	Ascertainment of outcome	Statistical Tests	
Goodwin 2003[13]	Cross-sectional	+	+	+	+	—	+	+	6
Goodwin 2004[14]	Cross-sectional	+	+	—	+	++	+	+	7
Bender 2007[16]	Cross-sectional	+	+	—	+	—	+	+	5
Clarke 2008[18]	Cross-sectional	+	+	—	+	—	++	+	6
Bae 2011[20]	Cross-sectional	+	+	+	+	—	+	+	6
Chan 2011[21]	Cross-sectional	+	+	+	+	—	+	+	6
Goodwin 2012[23]	Cross-sectional	+	+	—	+	—	+	+	5
Rai 2012[24]	Cross-sectional	+	+	+	+	—	+	+	6
Lee 2015[31]	Cross-sectional	+	+	+	+	—	+	+	6
Chung 2016[32]	Cross-sectional	+	+	—	+	—	+	+	5
Chang 2017[33]	Cross-sectional	+	+	—	+	—	++	+	6
Kye 2017[35]	Cross-sectional	+	+	+	+	—	+	+	6
Han 2018[36]	Cross-sectional	+	+	—	+	—	+	+	5
Bedolla-Barajas 2018[37]	Cross-sectional	+	+	—	+	+	++	+	7
Muhammad 2018[39]	Cross-sectional	+	+	+	+	—	+	+	6
Han and Forno 2018[38]	Cross-sectional	+	+	+	+	—	++	+	7
Han 2019[40]	Cross-sectional	+	+	+	+	—	+	+	6

Table S3. Sensitivity analysis of relationship between asthma and suicidality under the random-effects model.

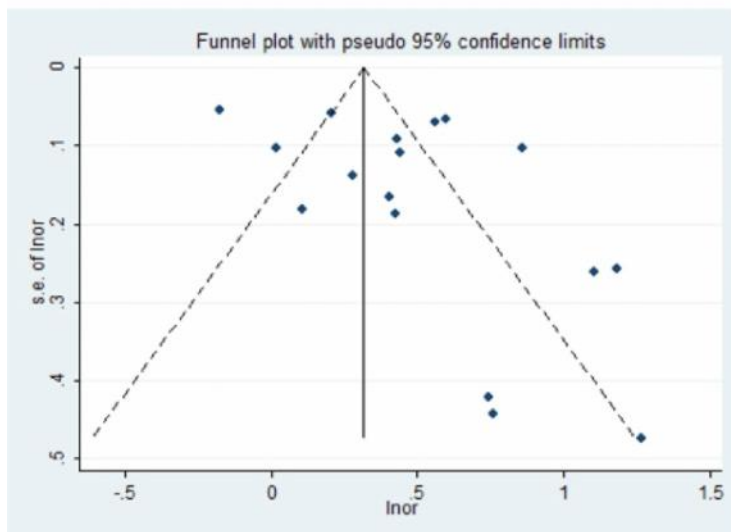
Study omitted	OR(95% CI)	I²
suicidal ideation		
-	1.53(1.37, 1.71)	87%
Goodwin, 2003	1.52(1.36, 1.70)	87%
Goodwin, 2004	1.52(1.36, 1.70)	87%
Goodwin, 2005	1.52(1.36, 1.70)	87%
Bender, 2007	1.46(1.32, 1.61)	83%
Nomura, 2007	1.51(1.35, 1.69)	87%
Clarke, 2008	1.57(1.41, 1.76)	87%
Chan, 2011	1.49(1.34, 1.67)	87%
Bae-1, 2011	1.55(1.38, 1.74)	88%
Bae-2, 2011	1.55(1.37, 1.75)	88%
Goodwin-1, 2012	1.52(1.36, 1.70)	87%
Goodwin-2, 2012	1.54(1.37, 1.72)	88%
Rai, 2012	1.53(1.37, 1.72)	88%
Lee, 2015	1.57(1.39, 1.77)	87%
Chung, 2016	1.54(1.36, 1.73)	87%
Chang-1, 2017	1.51(1.35, 1.68)	87%
Chang-2, 2017	1.52(1.36, 1.69)	87%
Kye, 2017	1.54(1.38, 1.73)	88%
Bedolla-Barajas, 2018	1.53(1.37, 1.70)	88%
Han, 2018	1.56(1.41, 1.73)	80%
Muhammad, 2018	1.54(1.37, 1.74)	87%
Han, 2019	1.53(1.36, 1.72)	87%
suicide attempt		
-	1.60(1.33, 1.92)	91.2%

Goodwin, 2005	1.56(1.31, 1.88)	91%
Bender, 2007	1.54(1.29, 1.84)	90%
Clarke, 2008	1.60(1.33, 1.94)	91%
Bae, 2011-1	1.61(1.33, 1.95)	91%
Bae, 2011-2	1.61(1.32, 1.95)	91%
Christiansen, 2012-1	1.64(1.36, 1.97)	91%
Christiansen, 2012-2	1.65(1.37, 2.00)	91%
Goodwin, 2012-1	1.54(1.28, 1.84)	91%
Goodwin, 2012-2	1.59(1.32, 1.90)	91%
Rai, 2012	1.61(1.33, 1.94)	91%
Bolton, 2015	1.65(1.43, 1.91)	82%
Chung, 2016	1.62(1.34, 1.96)	91%
Kye, 2017	1.59(1.32, 1.90)	91%
Han, 2018	1.64(1.34, 2.01)	91%
Muhammad, 2018	1.59(1.31, 1.93)	91%
Han and Forno, 2018	1.55(1.29, 1.85)	91%
Han, 2019	1.58(1.31, 1.92)	90%
Adjusted suicide mortality		
-	1.31(1.11 1.55)	80%
Kuo, 2010-1	1.25(1.06, 1.47)	81%
Kuo, 2010-2	1.29(1.08, 1.53)	82%
Webb, 2012	1.38(1.16, 1.64)	78%
Crump-1, 2014	1.29(1.07, 1.56)	83%
Crump-2, 2014	1.25(1.06, 1.48)	78%
Singhal, 2014	1.36(1.08, 1.70)	82%
Bolton, 2015	1.37(1.13, 1.66)	81%
Crawford, 2015	1.31(1.11, 1.56)	82%
Chen, 2015	1.24(1.06, 1.46)	78%
Ahmedani, 2017	1.37(1.14, 1.66)	80%

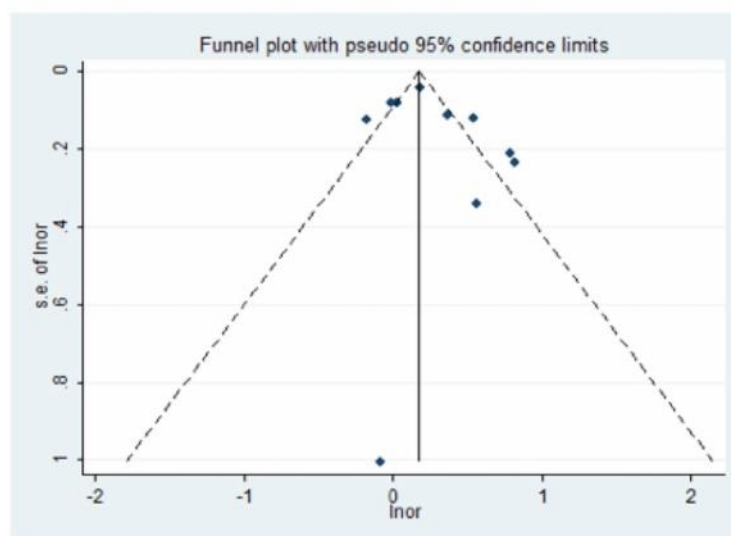
Figure S1. Funnel plots for the risk of publication bias of suicidality among asthmatic patients.



Suicidal ideation



Suicide attempts



Suicide mortality