Depression and asthma across the lifespan

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INTRODUCTION

Asthma affects approximately 300 million people and is the most common chronic respiratory disease among children worldwide (1). Despite advances in treatment, a recent multinational study reported that asthma was poorly controlled in 30% to 50% of adults with moderate to severe disease (2). In the United States (U.S.), asthma affects approximately 26.8 million people, including ~4.5 million children and ~22.3 million adults (3). Asthma causes nearly 1 million emergency department (ED) visits and 95,000 hospitalizations in the U.S., posing enormous costs to healthcare systems (3).

Depression is a major public health problem worldwide, affecting approximately 280 million people (including 23 million children and adolescents) in 2019 (4). In the U.S., more than 14% of persons 12 years and older reported symptoms of depression in the past two weeks, and more than 8.3% of adults had at least one major depressive episode in the previous year, with higher disease burden in females and in younger adults (5). Depression frequently coexists with other chronic medical conditions such as asthma, often complicating their management and worsening patient outcomes (6, 7).

Current evidence supports a bidirectional association between depression and asthma (8, 9). Although the link between these two conditions is not fully understood, there are likely shared biological and psychological pathways (10). Depression has been linked to poor asthma control and severe asthma exacerbations, diminished quality of life, and increased healthcare utilization (11). Conversely, other studies have shown that asthma is a risk factor for depression (12).

Understanding the depression-asthma link is critical for improving patient care, especially in at-risk and vulnerable populations including children and socioeconomically disadvantaged persons, as psychosocial stressors such as poverty and exposure to violence can worsen both depression and asthma (13). We conducted a PubMed review of epidemiologic studies and clinical trials on depression and asthma that were published between January 2016 and December of 2025. In brief, search terms included depression ("depression", "depressive disorder", "depressive symptoms", "major depressive disorder", "MDD") AND asthma ("asthma", "exacerbations", "asthma outcomes", "asthma controls", "ED visit", "hospitalization", or "lung function"). The results of these studies were then summarized by study design and timing of exposure (see **Tables 1 to 3)**. In this review, we critically assess published literature over the last 10 years, focusing on whether depression causes or worsens asthma; consider potential mechanisms underlying this link; and discuss the clinical implications of the available evidence and future directions for research in this field.

Maternal depression and childhood asthma

Multiple epidemiologic studies have reported an association between maternal depression or anxiety and increased risk of wheeze and asthma during childhood (**Table 1**). However, findings in infants and preschool children must be cautiously interpreted because asthma can be more accurately diagnosed after age 6 years.

Three large birth registry or birth cohort studies in Denmark, Sweden and the Netherlands reported that prenatal maternal depression was associated with 30% to 44% increased

odds of asthma (14), 25% increased risk of asthma (15), and 36% increased risk of wheeze (16) in children aged 2 to 5 years. Although two studies conducted in France and Mexico did not find an association between prenatal depression and wheeze or asthma, they had relatively small sample sizes and thus limited statistical power to detect weak to moderate associations (17, 18).

Three analyses of large birth cohort studies (one from Canada (19) and two from Norway and the Netherlands (20, 21)) reported that prenatal maternal depression was associated with 22% to 84% increased odds of asthma (19, 21) and 5%-19% increased risk of asthma (20) in school-aged children, while two analyses of a smaller birth cohort study from the U.S. reported that prenatal maternal depression was associated with asthma at age 7 years but not at age 10 years (22, 23). Interestingly, the Dutch study found significant associations between maternal depression during pregnancy and current asthma and reduced FEV_1 and FVC at age 10 years, even after adjustment for postnatal maternal psychological distress (21). Two separate birth cohort studies used prenatal use of any antidepressants as a surrogate for more severe depression. While one of these studies found no association between prenatal use of antidepressants and asthma in Norwegian children at age 7 years, another larger study of Danish children found that use of older types of antidepressants was associated with asthma at age 3 years (15, 20). However, depression may be well controlled in adults treated with antidepressants, and thus these findings must be cautiously interpreted.

Postpartum or postnatal maternal depression has also been associated with childhood wheeze or asthma in longitudinal studies. Two birth cohort studies conducted in Sweden and Taiwan reported that postpartum or postnatal depression increased the odds of asthma at age 5 years by 24% to 35% (14, 24). In another study from the U.S., prenatal and postnatal depression was associated with 24% to 54% increased odds of wheeze from ages 1 to 3 years (25), while a Canadian study reported that postpartum maternal depression was strongly associated with wheeze by age 3 years in girls, but not in boys (26). Interestingly, a study of 601 mother-child pairs from Mexico reported that postnatal, but not prenatal, maternal depression was associated with wheeze or asthma by age 2 years, with stronger estimated effects for recurrent maternal depression (18).

Two studies conducted in Australia and Canada found that maternal postpartum or postnatal depressive symptoms were associated with 1.5 to 2 times increased odds of asthma at ages 6-7 years (27, 28), while a smaller U.S. cohort reported that postpartum or postnatal depression was significantly associated with increased odds of current wheeze with low atopy at ages 7 and 10 years (22, 23). In another study in Puerto Rico, persistent maternal depressive symptoms reported at two visits by school-aged children (the first at ages 6-14 years and the second at ages 9-20 years, approximately 5 years apart) were associated with reduced lung function growth over time and 3.5 times increased odds of severe asthma exacerbations (SAEs) at the second visit (29). Although another cross-sectional study including 87 Chilean children reported no association between depression in the child's caregiver and asthma control, this could be explained by limited statistical power (30).

A few studies have examined interactions between maternal depression and the child's sex or maternal asthma on childhood asthma. Some studies have reported no sex-specific associations (24, 27), while others found that maternal depression was more significantly or strongly associated with childhood asthma in girls than in boys (18, 26). In a single cross-sectional study including Puerto Rican and Swedish children, maternal depression was significantly associated with 4 to 6.5 times increased odds of asthma in school-aged children whose mothers had asthma, but that maternal depression was not associated with childhood asthma in the absence of co-existing maternal asthma (31).

Published studies on maternal depression and asthma have been variably limited by: 1) insufficient assessment of the presence and severity of maternal depression or asthma, with diagnoses derived from registries, symptoms, treatment with antidepressants, or self-report and/or lack of data on asthma-related phenotypes such as lung function, allergic sensitization or airway responsiveness; 2) timing of assessment of maternal depression or asthma, with some studies lacking data on pre- and post-maternal depression and others focusing on asthma before age 6 years; and 3) residual confounding by anxiety- or stress-related disorders and factors including air pollution, medication use and healthcare access. Despite such limitations, the aggregate evidence suggests weak to moderate effects of prenatal and postnatal maternal depression on childhood asthma, with limited or inconsistent evidence of interactions between maternal depression and the child's sex or maternal asthma on the risk of childhood asthma.

Depression and asthma in children and adolescents

Several studies, mostly cross-sectional, have found that children and adolescents with depression or depressive symptoms (often co-existing with anxiety) are more likely to have worse asthma outcomes (**Table 2**).

A small prospective study of 43 children and adolescents who completed one to six visits to a severe asthma clinic in Boston (MA) showed that 58.3% of participants had at least one symptom of anxiety or depression, and that 18.4% had a clinically significant threshold score (>2) on a standardized questionnaire (the Patient Health Questionnaire-4 or PHQ-4) (32). In an analysis adjusting for age, sex, race and asthma medication step, a PHQ-4 >2 was significantly associated with worse asthma control in girls but not in boys. Further, there was no association between anxiety or depression and FEV_1/FVC (32).

Four cross-sectional studies of children and adolescents (n=87 to n=250) in the U.S., Italy, and India found significant associations between depression and at least one measure of worse asthma control or worse asthma-related quality of life, with one study reporting no sex-specific associations (33-36). Consistent with detrimental effects of depression on asthma, two analyses of large public databases for patients ages 6 to 21 years found that depression was associated with increased healthcare utilization and mortality due to asthma (37, 38). Similarly, two U.S.-based cross-sectional studies including 205 to 277 participants reported that depression was associated with worse asthma-related quality of life, limited activity level, and less sleep among youths with asthma (33, 39).

Depression was not associated with lung function in two studies (one longitudinal and another cross-sectional) in the U.S. and India, though both had relatively small sample sizes (32, 36). In another cross-sectional study, 250 children and adolescents were stratified according to the presence of overweight or obesity (40). In 140 youths with asthma who were overweight or obese, depressive symptoms (assessed with the Children's Depression Inventory or CDI) were associated with lower FEV_1 and vagal bias under emotion/stress, and vagal bias was in turn associated with increased airway resistance. In contrast, there were no significant association between CDI score and FEV_1 or vagal bias in 110 youths with asthma of normal weight. These findings suggest that depression may worsen lung function and increase airway resistance through parasympathetic/vagal autonomic nervous system (ANS) dysregulation in overweight or obese youths or, alternatively, that reduced lung function due to overweight/obesity lead to dysregulation of the parasympathetic/ANS, which increases depression risk (40).

In sum, lack of well-powered longitudinal studies precludes any conclusions as to whether depression precedes or follows the development or worsening of asthma in children and adolescents. Further studies are needed to evaluate whether sex and/or gender and overweight or obesity modifies any potential effects of depression on asthma outcomes in youths.

Depression and asthma in adults.

Several observational studies have examined whether depression is associated with asthma or worse asthma outcomes, and a few clinical trials have assessed whether pharmacologic treatment of depression improves asthma control (**Table 3**).

Recent cross-sectional studies have examined depression and asthma or asthma outcomes in adults (10, 41-45). Four separate analyses of data from the National Health and Nutrition Examination Survey (NHANES, a representative survey of the U.S. population) showed that depression significantly increased the odds of asthma by 1.3 to 3.4-fold and increased the odds of asthma exacerbations, healthcare use, sleep disturbance, activity limitation, and reduced bronchodilator responsiveness (BDR) in adults with asthma (10, 42, 45, 46). While these cross-sectional studies reported consistent results, they could not determine temporal relationships and were susceptible to potential misclassification and recall biases. In a separate cohort from England, there was a genetically predicted causal effect of depression on asthma while the reverse causal pathway (asthma leading to depression) was not found (10). Similar results for asthma or asthma outcomes were reported in another large U.S. population-based cross-sectional study (43) and one twin study from Sweden (44). Of interest, findings from two cross-sectional studies suggest a dose-response relationship between depression severity and asthma (42, 46) and reduced BDR (46).

An analysis of 2000-2010 data from a large longitudinal national health insurance database in Taiwan reported that physician-diagnosed major depressive disorder (MDD) was significantly associated with 1.66 times higher risk of incident asthma, with such risk

228 further increased in adults with each of the following comorbid conditions: allergic rhinitis,
229 obesity, and chronic obstructive pulmonary disease (COPD) (47). While this analysis was
230 adjusted for age, sex, comorbidities, and use of aspirin or beta-blockers, there was no
231 adjustment for tobacco use. In another prospective analysis of 2017-2019 primary care
232 health records for British adults with asthma, depression was significantly associated with
233 1.34 times increased risk of acute asthma exacerbations, even after adjusting for anxiety,
234 smoking status, and comorbidities (48).
235
236 Clinical trials have tested whether selective serotonin reuptake inhibitors (SSRIs) improve
237 asthma outcomes in adults with co-existing depression. In a 12-week randomized
238 placebo-controlled trial including 139 adults with asthma and MDD who were stratified *a*
239 *priori* according to higher (n=42) vs. lower (n=97) severity of depressive symptoms and
240 asthma, escitalopram improved asthma control and reduced oral corticosteroid use in 21
241 participants with greater severity of depression and asthma who completed the trial,
242 compared with the placebo group (49). There were no significant effects of escitalopram
243 on asthma control or oral corticosteroid use in a *post-hoc* analysis of all participants. In a
244 separate pooled analysis of data from 255 participants in three randomized clinical trials
245 of citalopram or escitalopram in adults with asthma and depression, participants who
246 received an SSRI had decreased depression severity scores and were less likely to use
247 corticosteroids for asthma (50). In an analysis restricted to a subgroup of 96 participants
248 prone to asthma exacerbations, SSRI use was additionally associated with improved
249 asthma control (50). A retrospective U.S.-based study using electronic health records
250 further reported that use of antidepressants is associated with reduced risks of SAEs and

corticosteroid use in adults with asthma (51). In a separate cross-sectional study of a convenience sample of Brazilian adults with asthma, depression was significantly associated with twofold increased odds of post-bronchodilator airflow obstruction (an $FEV_1/FVC < 0.70$) in participants not taking antidepressants, but this association was not present in those taking antidepressants (41). Antidepressant use was not significantly associated with improved asthma control in participants with uncontrolled asthma (41).

Current evidence suggests weak to moderate effects of depression, particularly severe depression, on asthma onset in adults, though the potential separate or synergistic effects of concurrent anxiety and residual confounding by environmental risk factors such as outdoor air pollution have not been adequately assessed. Findings from both observational studies and a few clinical trials suggest beneficial effects of SSRIs on asthma-related outcomes, particularly asthma exacerbations requiring oral corticosteroids. These results justify large RCTs to determine whether newer antidepressants in adults with MDD or severe depressive symptoms improve asthma control and reduce the frequency of severe exacerbations in adults with moderate to severe asthma. Such trials should carefully assess the presence of anxiety and stress-related disorders such as post-traumatic stress disorder, as they have also been implicated in asthma (52).

Potential pathways linking depression to asthma

While a comprehensive discussion of the presumptive pathways linking depression and asthma is beyond the scope of this review, a brief overview of potential mechanisms is shown in **Figure 1**.

A growing body of evidence suggests direct effects of depression on asthma, including dysregulation of neuroendocrine signaling, alteration of immune responses, and abnormal gene expression due to epigenetic dysregulation. Depression and depressive symptoms, with or without concurrent anxiety, could cause or worsen asthma through dysfunction of the hypothalamic pituitary axis (HPA) and sympathetic–adrenal–medullary (SAM) system, which can alter secretion of catecholamines and cortisol, leading to airway hyperresponsiveness and airflow obstruction while reducing response to bronchodilators and corticosteroids (46, 53-55). Depression can affect immune responses and increase airway inflammation by elevating pro-inflammatory cytokines (including IL-1, IL-4, IL-6, and TNF-α)(10, 56, 57), Moreover, adversity-related DNA methylation changes have been associated with increased risk of both depression and asthma (58), and depression-associated DNA methylation markers have been linked to immune pathways including IL-6 and tumor necrosis factor beta (TNF-β) (59), which are also implicated in asthma. The top-ranked depression-associated differentially methylated region in *LTB4R2*, a leukotriene receptor gene, further highlights this potential overlap, as leukotriene pathways are central to asthma pathophysiology (60).

Maternal immune activation (MIA, due to conditions such as obesity, asthma, psychosocial stress, and depression) has been associated with increased susceptibility

to neuroinflammation, allergic airway inflammation, wheeze, and asthma in the offspring through epigenetic regulation or imprinting (61, 62). Further, dysregulation of neuroendocrine and neurotransmitter receptors such as the glucocorticoid receptor (NR3C1) and the neuromedin U receptor 1 (NMUR1) has been reported in stressed mothers and their children (63).

Depression may also influence asthma outcomes through indirect mechanisms, including impaired adherence to treatment or reduced efficacy in caring for a child with asthma (64, 65), reduced physical activity and poor dietary habits leading to overweight or obesity and altered metabolic pathways (all risk factors for asthma) (66), tobacco or substance use, chronic stress and stress-related disorders (67-70), and misperception of symptoms such as dyspnea (66, 71, 72). Further, social determinants of health (i.e. ethnicity, education, access to health care, social support) and environmental risk factors such as air pollution could modify potential effects of depression on asthma (73-76).

While not the focus of this review, asthma can contribute to depressive symptoms and the depression-asthma link can thus operate in both directions simultaneously. Provocation of airway inflammation in persons with asthma increases neural sensitivity to emotionally-salient cues (77-80). These effects are likely mediated by multiple mechanisms that alter neurotransmission and brain immunity: 1) increased levels of circulating cytokines important in asthma pathophysiology (e.g. IL-1, IL-17, TNF-$\propto$) can provoke depression-like symptoms, via interaction with the blood-brain barrier (81), 2)

direct neural transmission from airway afferents (82, 83), and 3) recruitment of primed innate immune cells to the CNS (84).

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Over the last decade, findings from epidemiologic studies and a few clinical trials implicate depression in the pathogenesis of asthma morbidity. Large longitudinal studies with careful assessment of both depression and asthma are needed to elucidate whether maternal depression causes childhood asthma or whether depression during childhood or adolescence leads to incident asthma. Depression should be carefully assessed via standardized questionnaires, while also paying attention to co-existing conditions such as stress-related disorders. The latter is important, as depression with and without chronic stress may have differential effects on asthma. Because both depression and asthma are more common in vulnerable and economically disadvantaged populations, future studies should account for known or potential risk factors for asthma, including indoor and outdoor pollutants, active smoking and second-hand smoke, and co-morbidities such as obesity. Given that asthma is a heterogeneous syndrome, objective assessment of both phenotypes and endotypes is key to gaining novel insights on depression-related asthma. For example, is depression more strongly linked to T2-low asthma endotypes?

Large clinical trials of newer generation antidepressants to evaluate their efficacy in preventing SAEs and improving asthma control in adults are justified by results from observational studies and RCTs. Such trials should be well powered to detect moderate effects and be initially focused on patients with more severe depression and asthma. In

parallel, non-pharmacologic approaches (e.g., meditation training or psychotherapy) should be tested as adjuvant to treatment in patients with depression and more severe asthma (85, 86).Preliminary support for the efficacy of such approaches has already emerged (87).

Ongoing research should not preclude vigorous efforts to improve clinical care and implement sound policies designed to diagnose and treat older children and adults with co-existing depression and asthma, as this is a common occurrence. To this effect, adolescents and adults with asthma should be screened for depression using standardized brief questionnaires such as the Patient Health Questionnaire-9 (PHQ-9) and referred for pharmacologic or non-pharmacologic treatment, as appropriate, as such intervention should positively impact both mental health and asthma management (88, 89).

FIGURE LEGEND

Figure 1. Potential causal effects of depression on asthma.

Footnote: HPA=Hypothalamic Pituitary Adrenal, SAM=sympathetic adrenal medullary, TNF-β=tumor necrosis factor beta. While not the focus of this review, some of the depression-asthma links illustrated in the figure can be bi-directional. This figure was created with BioRender.

REFERENCES

1. Asthma GBD, Allergic Diseases C. Global, regional, and national burden of asthma and atopic dermatitis, 1990-2021, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Respir Med* 2025; 13: 425–446.
2. Czira A, Turner M, Martin A, et al. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. *Respir Med* 2022; 191: 106670.
3. US Center for Disease Control and Prevention. Most Recent Asthma Data. [serial online] 2024. Available from: https://www.cdc.gov/asthma-data/about/most-recent-asthma-data.html. Accessed on May 2, 2026.
4. World Health Organization. Fact Sheets-Depressive disorder (depression). [serial online] 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/depression. Accessed on May 2, 2026.
5. National Instiute of Mental Health. Major Depression. [serial online] 2023. Available from: https://www.nimh.nih.gov/health/statistics/major-depression. Accessed on May 2, 2026.
6. Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med* 2011; 9: 90.
7. Delmas MC, Guignon N, Chee CC, Fuhrman C, Herbet JB, Gonzalez L. Asthma and major depressive episode in adolescents in France. *J Asthma* 2011; 48: 640–646.
8. Liu X, Plana-Ripoll O, McGrath JJ, Petersen LV, Dharmage SC, Momen NC. Bidirectional Associations Between Asthma and Types of Mental Disorders. *J Allergy Clin Immunol Pract* 2023; 11: 799–808 e714.
9. Wamboldt MZ, Hewitt JK, Schmitz S, et al. Familial association between allergic disorders and depression in adult Finnish twins. *Am J Med Genet* 2000; 96: 146–153.
10. Ji T, Lv Y, Yang J, Diao X, Gu J. Association between depression and asthma: insight from observational and genetic evidence. *BMC Psychiatry* 2025; 25: 786.

11. Ogbu CE, Ravilla J, Okoli ML, et al. Association of Depression, Poor Mental Health Status and Asthma Control Patterns in US Adults Using a Data-Reductive Latent Class Method. *Cureus* 2023; 15: e33966.
12. 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: 437–441.
13. Weil CM, Wade SL, Bauman LJ, Lynn H, Mitchell H, Lavigne J. The relationship between psychosocial factors and asthma morbidity in inner-city children with asthma. *Pediatrics* 1999; 104: 1274–1280.
14. Brew BK, Lundholm C, Viktorin A, Lichtenstein P, Larsson H, Almqvist C. Longitudinal depression or anxiety in mothers and offspring asthma: a Swedish population-based study. *Int J Epidemiol* 2018; 47: 166–174.
15. Liu X, Olsen J, Pedersen LH, Agerbo E, Yuan W, Li J. Antidepressant use during pregnancy and asthma in the offspring. *Pediatrics* 2015; 135: e911–917.
16. van Gelder M, van Wijk EJC, Roukema J, Roeleveld N, Verhaak CM, Merkus P. Maternal depressive symptoms during pregnancy and infant wheezing up to 2 years of age. *Ann Epidemiol* 2023; 88: 43–50.
17. Zhou C, Ibanez G, Miramont V, et al. Prenatal maternal depression related to allergic rhinoconjunctivitis in the first 5 years of life in children of the EDEN mother-child cohort study. *Allergy Rhinol (Providence)* 2017; 8: 132–138.
18. Alcala CS, Orozco Scott P, Tamayo-Ortiz M, et al. Longitudinal assessment of maternal depression and early childhood asthma and wheeze: Effect modification by child sex. *Pediatr Pulmonol* 2023; 58: 98–106.
19. van der Leek AP, Bahreinian S, Chartier M, et al. Maternal Distress During Pregnancy and Recurrence in Early Childhood Predicts Atopic Dermatitis and Asthma in Childhood. *Chest* 2020; 158: 57–67.
20. Magnus MC, Wright RJ, Roysamb E, et al. Association of Maternal Psychosocial Stress With Increased Risk of Asthma Development in Offspring. *Am J Epidemiol* 2018; 187: 1199–1209.

21. van Meel ER, Saharan G, Jaddoe VW, et al. Parental psychological distress during pregnancy and the risk of childhood lower lung function and asthma: a population-based prospective cohort study. *Thorax* 2020; 75: 1074–1081.
22. Bacharier LB, Beigelman A, Calatroni A, et al, Consortium NsI-CA. Longitudinal Phenotypes of Respiratory Health in a High-Risk Urban Birth Cohort. *Am J Respir Crit Care Med* 2019; 199: 71–82.
23. Ramratnam SK, Lockhart A, Visness CM, et al, Inner-City Asthma C. Maternal stress and depression are associated with respiratory phenotypes in urban children. *J Allergy Clin Immunol* 2021; 148: 120–127.
24. Wen HJ, Chiang TL, Lin SJ, Guo YL. Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors. *Pediatr Allergy Immunol* 2015; 26: 272–279.
25. Ramratnam SK, Visness CM, Jaffee KF, et al. Relationships among Maternal Stress and Depression, Type 2 Responses, and Recurrent Wheezing at Age 3 Years in Low-Income Urban Families. *Am J Respir Crit Care Med* 2017; 195: 674–681.
26. Alton ME, Zeng Y, Tough SC, Mandhane PJ, Kozyrskyj AL. Postpartum depression, a direct and mediating risk factor for preschool wheeze in girls. *Pediatr Pulmonol* 2016; 51: 349–357.
27. Giallo R, Bahreinian S, Brown S, Cooklin A, Kingston D, Kozyrskyj A. Maternal depressive symptoms across early childhood and asthma in school children: findings from a Longitudinal Australian Population Based Study. *PLoS One* 2015; 10: e0121459.
28. Kozyrskyj AL, Letourneau NL, Kang LJ, Salmani M. Associations between postpartum depressive symptoms and childhood asthma diminish with child age. *Clin Exp Allergy* 2017; 47: 324–330.
29. Stevens EL, Han YY, Rosser F, et al. Maternal Depressive Symptoms, Lung Function, and Severe Asthma Exacerbations in Puerto Rican Children. *J Allergy Clin Immunol Pract* 2021; 9: 1319–1326 e1313.
30. Rioseco A, Serrano C, Celedon JC, Padilla O, Puschel K, Castro-Rodriguez JA. Caregiver's depressive symptoms and asthma control in children from an underserved community. *J Asthma* 2017; 54: 1059–1064.

31. Medsker BH, Brew BK, Forno E, et al. Maternal depressive symptoms, maternal asthma, and asthma in school-aged children. *Ann Allergy Asthma Immunol* 2017; 118: 55–60 e51.
32. Griffiths D, Giancola LM, Welsh K, et al. Asthma control and psychological health in pediatric severe asthma. *Pediatr Pulmonol* 2021; 56: 42–48.
33. Kulikova A, Lopez J, Antony A, et al. Multivariate Association of Child Depression and Anxiety with Asthma Outcomes. *J Allergy Clin Immunol Pract* 2021; 9: 2399–2405.
34. Patel NB, Cespedes A, Liu J, Bruzzese JM. Depressive symptoms are related to asthma control but not self-management among rural adolescents. *Front Allergy* 2023; 4: 1271791.
35. Licari A, Castagnoli R, Ciprandi R, et al. Anxiety and depression in adolescents with asthma: a study in clinical practice. *Acta Biomed* 2022; 93: e2022021.
36. Saragondlu Lakshminarasappa D, Chandrasekaran V, Kandasamy P. Co-morbid anxiety and depression in childhood asthma and its effect on symptom control: A cross sectional study. *Pediatr Pulmonol* 2021; 56: 378–383.
37. Bardach NS, Neel C, Kleinman LC, et al. Depression, Anxiety, and Emergency Department Use for Asthma. *Pediatrics* 2019; 144.
38. Munoz FA, Benton LD, Kops SA, Kowalek KA, Seckeler MD. Greater length of stay and hospital charges for severe asthma in children with depression or anxiety. *Pediatr Pulmonol* 2020; 55: 2908–2912.
39. Shankar M, Fagnano M, Blaakman SW, Rhee H, Halterman JS. Depressive Symptoms Among Urban Adolescents with Asthma: A Focus for Providers. *Acad Pediatr* 2019; 19: 608–614.
40. Hsu CY, Lehman HK, Wood BL, Benipal J, Humayun Q, Miller BD. Comorbid Obesity and Depressive Symptoms in Childhood Asthma: A Harmful Synergy. *J Allergy Clin Immunol Pract* 2020; 8: 2689–2697.
41. Theodoro EE, Rocha DGD, Bertolino JR, et al. Evaluating the effect of antidepressants on the relationship between depression and asthma. *Respir Med* 2023; 207: 107099.

42. Ran M, Zhang Y, Zhang W, Wang M, Luo S. Depression increases the risk of asthma: Evidence from a cross-sectional study and two-sample Mendelian randomization analysis. *Medicine (Baltimore)* 2025; 104: e44972.
43. Chen Y, Cai H, Ye X, et al. Association of depression, anxiety with asthma outcomes and allergic comorbidities: results from the National Health Interview Survey. *J Affect Disord* 2025; 389: 119677.
44. Tedner SG, Lundholm C, Olsson H, Almqvist C. Depression or anxiety in adult twins is associated with asthma diagnosis but not with offspring asthma. *Clin Exp Allergy* 2016; 46: 803–812.
45. Patel PO, Patel MR, Baptist AP. Depression and Asthma Outcomes in Older Adults: Results from the National Health and Nutrition Examination Survey. *J Allergy Clin Immunol Pract* 2017; 5: 1691–1697 e1691.
46. Han YY, Forno E, Marsland AL, Miller GE, Celedon JC. Depression, Asthma, and Bronchodilator Response in a Nationwide Study of US Adults. *J Allergy Clin Immunol Pract* 2016; 4: 68–73 e61.
47. Shen TC, Lin CL, Liao CH, Wei CC, Sung FC, Kao CH. Major depressive disorder is associated with subsequent adult-onset asthma: a population-based cohort study. *Epidemiol Psychiatr Sci* 2017; 26: 664–671.
48. Pickard-Michels T, Adderley NJ, Nagakumar P, et al. Association between mental health disorders and asthma exacerbations in adults: a retrospective cohort study in UK primary care. *BMJ Open Respir Res* 2025; 12.
49. Brown ES, Sayed N, Van Enkevort E, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Escitalopram in Patients with Asthma and Major Depressive Disorder. *J Allergy Clin Immunol Pract* 2018; 6: 1604–1612.
50. Agarwal CD, Palka JM, Gajewski AJ, Khan DA, Brown ES. The efficacy of citalopram or escitalopram in patients with asthma and major depressive disorder. *Ann Allergy Asthma Immunol* 2024; 132: 374–382.
51. Shoair OA, Cook EA, Shipman D, Dunn RL. Antidepressant Target Dose Optimization and Control of Severe Asthma Exacerbations in Uninsured and Underinsured Patients with Anxiety and/or Depression. *Pharmacotherapy* 2020; 40: 320–330.

533 52. de la Hoz RE, Jeon Y, Miller GE, Wisnivesky JP, Celedon JC. Post-traumatic Stress
534 Disorder, Bronchodilator Response, and Incident Asthma in World Trade Center
535 Rescue and Recovery Workers. *Am J Respir Crit Care Med* 2016; 194: 1383–
536 1391.
537 53. Taylor-Clark TE, Undem BJ. Neural control of the lower airways: Role in cough and
538 airway inflammatory disease. *Handb Clin Neurol* 2022; 188: 373–391.
539 54. Ritz T, Kroll JL, Patel SV, et al. Central nervous system signatures of affect in
540 asthma: associations with emotion-induced bronchoconstriction, airway
541 inflammation, and asthma control. *J Appl Physiol (1985)* 2019; 126: 1725–1736.
542 55. Amasi-Hartoonian N, Sforzini L, Cattaneo A, Pariante CM. Cause or consequence?
543 Understanding the role of cortisol in the increased inflammation observed in
544 depression. *Curr Opin Endocr Metab Res* 2022; 24: 100356.
545 56. Guo S, Lin Y, Li J, et al. Relationship of depression and asthma: a observational
546 and Mendelian randomization study. *J Asthma* 2025; 62: 1156–1165.
547 57. Zhu Z, Zhu X, Liu CL, et al. Shared genetics of asthma and mental health disorders:
548 a large-scale genome-wide cross-trait analysis. *Eur Respir J* 2019; 54.
549 58. Schuurmans IK, Dunn EC, Lussier AA. DNA methylation as a possible mechanism
550 linking childhood adversity and health: results from a 2-sample mendelian
551 randomization study. *Am J Epidemiol* 2024; 193: 1541–1552.
552 59. Shen X, Barbu M, Caramaschi D, et al. A methylome-wide association study of
553 major depression with out-of-sample case-control classification and trans-
554 ancestry comparison. *Nat Ment Health* 2025; 3: 1152–1167.
555 60. Crawford B, Craig Z, Mansell G, et al, Yaghootkar H, Ji Y, Major Depressive
556 Disorder Working Group of the Psychiatric Genomics C, Mullins N, Lewis CM,
557 Mill J, Murphy TM. DNA methylation and inflammation marker profiles associated
558 with a history of depression. *Hum Mol Genet* 2018; 27: 2840–2850.
559 61. Takao T, Matsui A, Kikutake C, et al. Maternal asthma imprints fetal lung ILC2s via
560 glucocorticoid signaling leading to worsened allergic airway inflammation in
561 murine adult offspring. *Nat Commun* 2025; 16: 631.

562 62. Han VX, Patel S, Jones HF, Dale RC. Maternal immune activation and
563 neuroinflammation in human neurodevelopmental disorders. *Nat Rev Neurol*
564 2021; 17: 564–579.
565 63. Trump S, Bieg M, Gu Z, et al. Prenatal maternal stress and wheeze in children:
566 novel insights into epigenetic regulation. *Sci Rep* 2016; 6: 28616.
567 64. Pape K, Cowell W, Sejbaek CS,et al. Adverse childhood experiences and asthma:
568 trajectories in a national cohort. *Thorax* 2021; 76: 547–553.
569 65. Brown ES, Palka JM, Lehman HK,et al. The Impact of Caregiver Depression on
570 Child Asthma Outcomes: Pathways and Mechanisms. *J Allergy Clin Immunol*
571 *Pract* 2023; 11: 200–209.
572 66. Stubbs MA, Clark VL, Gibson PG, Yorke J, McDonald VM. Associations of
573 symptoms of anxiety and depression with health-status, asthma control,
574 dyspnoea, dysfunction breathing and obesity in people with severe asthma.
575 *Respir Res* 2022; 23: 341.
576 67. Lewkowich I, Ahlbrand R, Johnson E,et al. Modulation of fear behavior and
577 neuroimmune alterations in house dust mite exposed A/J mice, a model of
578 severe asthma. *Brain Behav Immun* 2020; 88: 688–698.
579 68. Han YY, Celedon JC. The effects of violence and related stress on asthma. *Ann*
580 *Allergy Asthma Immunol* 2024; 133: 630–640.
581 69. Landeo-Gutierrez J, Celedon JC. Chronic stress and asthma in adolescents. *Ann*
582 *Allergy Asthma Immunol* 2020; 125: 393–398.
583 70. Landeo-Gutierrez J, Forno E, Miller GE, Celedon JC. Exposure to violence,
584 psychosocial stress and asthma. *Am J Respir Crit Care Med* 2020; 201:917-922.
585 71. Boulding R, Stacey R, Niven R, Fowler SJ. Dysfunctional breathing: a review of the
586 literature and proposal for classification. *Eur Respir Rev* 2016; 25: 287–294.
587 72. Denton E, Bondarenko J, Tay T, et al Factors Associated with Dysfunctional
588 Breathing in Patients with Difficult to Treat Asthma. *J Allergy Clin Immunol Pract*
589 2019; 7: 1471–1476.
590 73. Clausing ES, Tomlinson CJ, Non AL. Epigenetics and social inequalities in asthma
591 and allergy. *J Allergy Clin Immunol* 2023; 151: 1468–1470.

74. Grant T, Croce E, Matsui EC. Asthma and the social determinants of health. *Ann Allergy Asthma Immunol* 2022; 128: 5–11.
75. Burbank AJ, Hernandez ML, Jefferson A, et al. Environmental justice and allergic disease: A Work Group Report of the AAAAI Environmental Exposure and Respiratory Health Committee and the Diversity, Equity and Inclusion Committee. *J Allergy Clin Immunol* 2023; 151: 656–670.
76. Sun Q, Liu J, Yang Y, et al. Mediating role of depressive symptoms in the association between adverse childhood experiences and asthma. *Child Abuse Negl* 2024; 149: 106662.
77. Dill-McFarland KA, Altman MC, Esnault S, Jarjour NN, Busse WW, Rosenkranz MA. Molecular pathways underlying lung-brain axis signaling in asthma: Relevance for psychopathology and neuroinflammation. *J Allergy Clin Immunol* 2024; 153: 111–121.
78. Laubacher C, Imhoff-Smith TP, Klaus DR, et al. Salience network resting state functional connectivity during airway inflammation in asthma: A feature of mental health resilience? *Brain Behav Immun* 2024; 122: 9–17.
79. Rosenkranz MA, Busse WW, Johnstone T, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Sci U S A* 2005; 102: 13319–13324.
80. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. *PLoS One* 2012; 7: e40921.
81. Gryka-Marton M, Grabowska AD, Szukiewicz D. Breaking the Barrier: The Role of Proinflammatory Cytokines in BBB Dysfunction. *Int J Mol Sci* 2025; 26.
82. Trevizan-Bau P, Mazzone SB. Neuroimmune pathways regulating airway inflammation. *Ann Allergy Asthma Immunol* 2023; 131: 550–560.
83. Undem BJ, Carr MJ. The role of nerves in asthma. *Curr Allergy Asthma Rep* 2002; 2: 159–165.
84. Wohleb ES, Powell ND, Godbout JP, Sheridan JF. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. *J Neurosci* 2013; 33: 13820–13833.

623 85. Higgins ET, Davidson RJ, Busse WW, et al. Clinically relevant effects of
624 Mindfulness-Based Stress Reduction in individuals with asthma. *Brain Behav*
625 *Immun Health* 2022; 25: 100509.
626 86. Laubacher C, Kral TRA, Imhoff-Smith T,et al. Resting state functional connectivity
627 changes following mindfulness-based stress reduction predict improvements in
628 disease control for patients with asthma. *Brain Behav Immun* 2024; 115: 480–
629 493.
630 87. Sharrad KJ, Sanwo O, Cuevas-Asturias S, Kew KM, Carson-Chahhoud KV, Pike
631 KC. Psychological interventions for asthma in children and adolescents.
632 *Cochrane Database Syst Rev* 2024; 1: CD013420.
633 88. Guo Y, Yan J. Association between asthma and depression: results from the
634 NHANES 2005-2018 and Mendelian randomization analysis. *Postgrad Med J*
635 2025; 101: 291–301.
636 89. Kew KM, Nashed M, Dulay V, Yorke J. Cognitive behavioural therapy (CBT) for
637 adults and adolescents with asthma. *Cochrane Database Syst Rev* 2016; 9:
638 CD011818.

Table 1. Summary of epidemiologic studies on maternal depression and childhood asthma

Reference	Study population	Depression measures	Primary outcomes	Main findings and study limitations
Longitudinal studies				
Brew et al, 2018(14)	360,526 children born between July 2006 and December 2009 in the Swedish Medical Birth Register, Sweden	Depressive disorder: ICD-10 codes of F30-F34, F38 and F39 recorded in the National Patient Register (NPR). As: pre-conception, during pregnancy, postnatal, or current.	Asthma at age 5 years: an ICD-10 code J45 in the NPR *or* an asthma medication prescription in the previous 12 months AND either: a second asthma medication prescription between ages 1 and 5 years *or* an asthma diagnosis between ages 1 and 5 years in the NPR.	Adjusting for maternal education, maternal asthma, number of siblings, and the child's gender: • Maternal depression at any period was associated with childhood asthma at age 5 years (aOR=1.30, 95 % CI= 1.26-1.35) • Cumulative exposure to maternal depression during two periods was associated with childhood asthma at age 5 years (aOR= 1.44, 95% CI= 1.38-1.52). • **Limitations:** - Underestimation of depression during pregnancy may have biased the results towards the null hypothesis. - Potential selection bias due to missingness for a large proportion of diagnoses from the primary healthcare records
Liu et al, 2015 (15)	733,685 children born between January1996 and December 2007 from the Danish Medical Birth Registry, Denmark	Depressive disorder: ICD-10 codes F32.00 through F33.99, or by antidepressant use 1 year before or during pregnancy. Prenatal: 1 year before or during pregnancy.	Using data from Danish National registries, asthma was defined as: ≥2 prescriptions for asthma medications *or* ≥1 asthma hospital contact (ICD 10 codes J45 and J46) after age 3 years.	Adjusting for maternal country of origin, parity, maternal age, SES, maternal asthma, maternal smoking during pregnancy, and the child's gender: • Prenatal maternal depression (HR= 1.25 [1.20-1.30]) and prenatal use of any antidepressant (HR=1.25 [1.18-1.33]) was associated with childhood asthma after age 3 years. HRs for childhood asthma by type of prenatal antidepressant use: - Selective serotonin reuptake inhibitors (SSRIs) only: HR=0.95 (0.88-1.03) - Newer antidepressants only: HR=1.11 (0.89-1.39) - Older antidepressants only: HR=1.26 (1.02-1.55) - ≥ 1 type of antidepressants: HR=1.29 (1.04-1.60) • **Limitations**: - Potential misclassification of depression due to lack of data on antidepressant adherence and/or unrecorded treatment

				- A hospitalization registry may capture more severe asthma, thus limiting generalizability to non-severe asthma. - Potential confounding by depression severity.
Van Gelder et al, 2023 (16)	5,294 deliveries in the PRIDE Study from the Netherlands, 2013-2019	Depressive symptoms: HADS-D ≥ 8 or EDPS ≥ 11.Perinatal (gestational weeks of 5-16, 15-22, and 32-35).	Wheeze: At age 24 months, maternal report of wheeze/whistling in the prior two years (primary outcome). At ages 6, 12, and 18 months, maternal report of wheeze or whistling in the prior six months (secondary outcomes)	Adjusting for maternal: age, ethnicity, income, parity, depression, asthma, pre-pregnancy BMI, and time-varying confounders (smoking, antidepressant use, and depressive symptoms): • Maternal depressive symptoms in gestational weeks 15–22 was associated with: - Any wheeze in the first 2 years (aRR=1.36, 95% CI= 1.04-1.78) - Wheeze at 12 months (aRR= 1.29, 95% CI= 1.03-1.61) - Wheeze at 18 months (aRR= 1.33, 95% CI= 1.04-1.69). • Depressive symptoms at gestational weeks 32–35 were associated with wheeze at 12 months (aRR=1.28 [1.02-1.60]) and at 2 years (aRR= 1.27 [0.96-1.69]). • **Limitations**: - Participants in PRIDE had higher SES than the general population, limiting generalizability. - Continuous scores of HADS-D and EDPS could not be used in the trajectory models due to different scale ranges - Potential misclassification of wheeze due to recall bias.
Zhou et al, 2018 (17)	1,139 mother-child pairs recruited in 2003 and followed to age 5 years in France	Depression: CES-D ≥ 16. Prenatal (between 24 and 28 weeks of amenorrhea).	Asthma: Parental report of physician-diagnosed asthma (ever) and wheeze or whistling in the chest, from birth to age 5 years	Adjusting for the child's gender and maternal: age, BMI, education, smoking during pregnancy, and family history of atopy: • Prenatal maternal depression was not associated with wheeze (aOR=1.12, 95% CI=0.91-1.39) or physician-diagnosed asthma (aOR=1.23, 95% CI=0.81-1.85) at age 5 years. • **Limitations**: - Potential misclassification of wheeze due to recall bias.

				- Maternal depression during pregnancy may have been underestimated - Potential selection bias due to loss of follow up
Alcala et al., 2023 (18)	601 mother-child pairs recruited in the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study in 2007-2011 in Mexico	Depression: EPDS > 12 (clinically relevant cutoff).Perinatal (3rd trimester) and postpartum (1-, 6-, 12-,18-, 24-, and 48-months.	Asthma: Parental report of asthma (ever) and wheeze or whistling in the chest in the previous year, at ages 48 and 72 months.	Adjusting for the child's sex and maternal: age and education at enrollment, parity, second-hand smoke in the home during the second or third trimesters, and average $PM_{2.5}$ exposure during pregnancy and at first year postpartum: • Prenatal depression was not associated with wheeze or asthma at any time • Postpartum depression was associated with any current wheeze (RR=1.68, 95% CI=1.09-2.59), current wheeze at 48 months (RR=1.87, 95% CI= 1.21-2.90]), and asthma at 48 months (RR=2.42, 95% CI=1.01-5.81]) • Recurrent depression was associated with any current wheeze (RR=2.22, 95% CI=1.42-3.49]), current wheeze at 48 months (RR=2.41, 95% CI=1.53-3.79]), and asthma at 48 months (RR=2.45, 95% CI=1.02-5.84) • The effect estimates for current wheeze at 48 months were higher in girls (RR=4.34) than in boys (RR=1.89, P<0.1 for interaction) • **Limitations**: - Potential misclassification of wheeze due to recall bias. - Cutoff for depressive symptoms may differ across time - Residual confounding due to unmeasured factors

van der Leek et al, 2020 (19)	12,587 Canadian children born and recorded in the Manitoba Population Research Data Repository of the Manitoba Centre for Health Policy in 2004	Maternal distress: ≥ 1 health care contact or prescription of medications for depression or anxiety), and Newborn Screen Inventory. Prenatal and postnatal evaluations (on a yearly basis in the first to the fifth year postpartum).	Asthma at age 7 years: ≥ 1 asthma hospitalization, ≥ 2 physician visits for asthma, *or* ≥ 2 prescriptions of asthma medications between 9 months prior to and 3 months following the child's seventh birthday in a Manitoba (Canada) database.	Adjusting for the child's: sex, birthweight, antibiotic use in the first year, newborn respiratory distress, maternal age, asthma/atopy, parity, and urban residence: • Maternal distress (depression or anxiety) at different periods was associated with 1.2-1.7 times increased odds of childhood asthma at age 7 years: - Prenatal: aOR=1.57 (95% CI=1.29-1.91). - Postnatal (first postpartum year): aOR=0.76 (95% CI=0.52-1.11) - Recurrent postnatal (1-5 years): aOR for all=1.23 (95% CI=0.99-1.54). - Late-onset postnatal (2-5 years after birth): aOR=1.22 (95% CI=1.01, 1.46) • Prenatal depression was associated with asthma in boys and girls; recurrent and late-onset postnatal depression was associated with asthma in boys but not in girls • **Limitations**: - Potential misclassification of maternal postnatal distress - Residual confounding by treatment status and severity of depression and/or SES.
Magnus et al, 2018 (20)	63,626 mother-child pairs in the Norwegian Mother and Child Cohort Study, children born in 2000-2007, Norway	Major depressive symptoms: ≥ 3 affirmative answers to the 5-item symptom checklist (SCL-5).Prenatal (during pregnancy) and lifetime.	Asthma at age 7 years: dispensed asthma medication in the prior year AND a second dispensed prescription within one year after the first, as registered in the Norwegian Prescription Database. Secondary outcome: Maternal report of physician-diagnosed	Adjusting for maternal: age, parity, education, pre-pregnancy BMI, smoking during pregnancy, and history of asthma: • At 18 weeks of gestation, maternal lifetime depressive symptoms (aRR=1.05, 95% CI=1.02-1.07]) and lifetime history of major depressive symptoms (aRR=1.19, 95% CI=1.09-1.30]) were associated with childhood asthma at age 7 years • At 30 weeks of gestation, use of antidepressants, anxiolytics, and/or hypnotics during pregnancy was not associated with childhood asthma at age 7 years • **Limitations**: - Potential misclassification of asthma

			asthma AND either current symptoms *or* use of asthma medications in the prior year.	- Non-adjustment for multiple testing - Small sample size for sibling analysis
Van Meel et al, 2020 (21)	4,231 children in the Generation R Study, with delivery date from April 2002 to January 2006 in the Netherlands	Depression symptoms: 53-item Brief Symptom Inventory. Prenatal (2nd trimester) and postnatal (3 years after pregnancy).	Asthma at age 10 years: parental report of physician-diagnosed asthma (ever) AND wheeze or use of asthma medication in the previous 12 months. Lung function measures.	Adjusting for the child's sex, gestational age, birthweight, and daycare attendance; and maternal: age, parity, education, smoking during pregnancy, baseline BMI, history of asthma/atopy and pet keeping, ethnicity, and breastfeeding: • At age 10 years, clinically relevant maternal depressive symptoms during pregnancy were associated with: - Current asthma (aOR=1.84, 95% CI= 1.21-2.80) - Lower FEV_1 z-score= −0.13, 95% CI= −0.24 to –0.01 - Lower FVC z-score= −0.13, 95% CI= −0.24 to –0.02]) • **Limitations**: - Potential for selection bias (due to loss to follow up) and misclassification of asthma - Intensity or persistence of maternal depression was not determined - Potential residual confounding by stress disorders or air pollution

Bacharier et al, 2019 (22)	442 children from the URECA cohort recruited from 2005 to 2007 in inner-city urban areas in the U.S.	Depression: EPDS ≥ 10. Prenatal and postnatal (ascertained annually until age 3 years).	Asthma at age 7 years: parental report of physician-diagnosed asthma between ages 4 and 7 years plus asthma symptoms *or* use of asthma medications in ≥6 of the prior 12 months; OR airway hyper-responsiveness to methacholine *or* bronchodilator responsiveness plus asthma symptoms or use of asthma medications in ≥6 of the prior 12 months; OR ≥ 2 wheezing episodes *or* ≥ 2 doctor visits for asthma/wheeze *or* ≥ 1 hospitalization for asthma/wheeze in the prior 12 months, and/or use of controller medications in ≥6 of the prior 12 months.	• At age 7 years, maternal depression score was highest among children with frequent wheeze and low degree of atopy. • **Limitations:** - Limited generalizability to children of higher SES or those with milder asthma - Potential confounding by early-life environmental exposures. - Sample size may be too small to identify interactions between depression and other factors

Ramratnam et al, 2021 (23)	442 children from the URECA cohort recruited from 2005 to 2007 in inner-city urban areas, U.S.	Depression: EPDS ≥ 10. Prenatal and postnatal (ascertained annually to the first 3 years).	Asthma at age 10 years: defined as in reference 22 above (Bacharier et al, 2019).	Adjusting for maternal: race/ethnicity, smoking during pregnancy and in the first year of the child's life, birth season, number of previous live births, and asthma; and the child's sex and birth weight: • At age 10 years, postnatal maternal depression was associated with the moderate wheeze–low atopy phenotype (aOR=1.13; 95% CI= 1.05-1.20). • Prenatal maternal depression was inversely associated with the low wheeze-low atopy phenotype (aOR=0.94, 95% CI =0.89- 0.99). • No association with atopic wheeze or lung function measures. • **Limitations:** - Limited generalizability - Potential residual confounding by environmental exposures in early life and during childhood.
Wen et al, 2015 (24)	19,192 mother newborn-pairs from the 2005 Taiwan birth registry in Taiwan	Method used to assess depression was not reported. Postnatal (6 months to 5 years).	Caretaker report of physician-diagnosed asthma (ever) at age 5 years	Adjusting for SES, parental atopy, urban residency, and the child's history of atopic dermatitis: • Postpartum depression was associated with asthma at age 5 years: - In boys: aOR=1.24 (95% CI=1.02-1.48) - In girls: aOR=1.28 (95% CI= 1.02-1.59) • **Limitations:** - Potential selection bias at study entry and/or due to loss of follow up. - Possible misclassification of depression and asthma. - Likely residual confounding by environmental exposures.

Ramratnam et al, 2017 (25)	560 mother-child pars in the URECA cohort from Baltimore, Boston, New York City and St Louis, U.S., 2005-2007	EDPS was standardized for depression. Prenatal and postnatal (ascertained annually to age 3 years).	Recurrent wheeze: ≥ 2 episodes of wheezing during the first 3 years of life, with ≥ 1 episode during the third year of life.	Adjusting for maternal: race/ethnicity, smoking during pregnancy and in the first year of the child's life, asthma, previous live births; and the child's: sex, birthweight and birth season: • Maternal depression was associated with recurrent wheeze between ages 1 and 3 years (aOR= 1.30 to 1.54, P<0.02 in all instances) • Maternal depression was not associated with allergic sensitization • **Limitations:** - Limited generalizability - Potential misclassification of wheeze due to recall bias. - Residual confounding by environmental exposures.
Alton et al, 2016 (26)	791 Canadian women and their children recruited for the Community Perinatal Care Trial (CPC), Calgary, 2001-2004	Depression: EPDS ≥ 10. Postpartum (8-week after childbirth to 3 years).	Maternal report of wheeze at age 3 years: a health care worker diagnosis of "chronic breathing problems such as asthma, chronic obstructive pulmonary disease or bronchopulmonary dysplasia".	Adjusted gender-specific logistic regression was conducted: • In girls, postpartum depression was associated with the development of wheeze at age of 3, adjusting for prenatal severe maternal distress (aOR=4.50, 95% CI=1.12, 18.1). • In boys, postpartum depression was not associated with wheeze at age of 3 (aOR=0.44, 0.10, 1.94) • **Limitations:** - Lack of validation, as the same data was used for model-building and subsequent hypothesis testing - Potential misclassification of asthma and residual confounding by environmental exposures and preterm birth - High rate of missing data on EPDS

Giallo et al, 2015 (27)	4,164 mother-child pairs from the Longitudinal Study of Australian Children recruited in 2004	Depressive symptoms: Kessler-6 items (K6) ≥ 8, based on DSM-IV criteria. Postnatal (ages 3-12 months to 6-7 years).	Asthma at age 6-7 years: caregiver's report of physician-diagnosed asthma; AND presence of wheeze and/or whistling, *or* an illness accompanied by wheezing in the previous 12 months; AND prescription of an asthma medication in the previous 12 months.	Adjusting for maternal: age, smoking and antidepressant use during pregnancy, single parenthood, and low SES: • Persistent and increasing maternal depressive symptoms were associated with childhood asthma at ages 6–7 years (aOR= 2.36, 95% CI= 1.61-3.45), • No significant interaction between maternal depressive trajectories and the child's gender on childhood asthma • **Limitations:** - Results may not be generalizable to families from non-English speaking, Aboriginals or Torres Strait Islanders, and those of lower SES. - Lack information on maternal mental health during pregnancy, maternal use of antibiotics and infections during pregnancy, and early life environmental exposures
Kozyskyj et al, 2017 (28)	1,696 children born in 1994-2004 from the Canadian National Longitudinal Survey of Children and Youth	Depressive symptoms: 12-items depression scale that was shortened from CES-D ≥ 12. Postpartum.	Asthma: health professional-diagnosed asthma AND at least one of the following: an asthma attack in the past 12 months *or* wheezing/whistling in the chest in the past 12 months *or* taking asthma medications on a regular basis.	Adjusting for the child's: sex, being firstborn, birthweight; prenatal smoking and family functioning; and maternal: asthma, immigration status, and SES: • Postpartum depressive symptoms were associated with childhood asthma at ages 6 (aOR=1.48, 95% CI= 1.01-2.95), 7 (aOR=1.47, 95% CI=1.02-2.11), and 8 (aOR=1.43, 95% CI=1.04-1.97) years. • **Limitations:** - No data on asthma onset - Lack of information on the chronicity of depression before or after maternal report - Potential residual confounding by environmental exposures and stress-related disorders.

Stevens et al, 2021 (29)	386 youth aged 6–14 years recruited in 2009-2010 in Puerto Rico, with a second visit ~5 years later	Significant depressive symptoms: CES-D ≥ 21. Postnatal, current and persistent.	Asthma: parental report of physician-diagnosed asthma AND ≥ 1 episode of wheeze in the previous year. Change in FEV_1 and FEV_1/FVC. Severe asthma exacerbations: ≥ 1 hospitalization for asthma *or* ≥ 1 visit to the emergency department or urgent care for asthma requiring treatment with systemic corticosteroids in the previous year *or* ≥ 1 course of systemic steroids for asthma in the previous year	• Adjusting for asthma status and type of health insurance, 1 unit increased in maternal CESD was associated with decreased change in %predicted FEV_1 (ß=-0.15, P=0.03) and %predicted FEV_1/FVC (ß=-0.10, P=0.05). • Adjusting type of health insurance and use of ICS in the prior 6 months, persistent maternal depressive symptoms were associated with 3.52 increased odds of severe asthma exacerbations (95% CI=1.10-11.32). • **Limitations:** - Limited statistical power to detect modest associations between maternal depressive symptoms and lung function - Potential selection bias - Lack of data on maternal depressive symptoms or asthma in prenatal or early postnatal life - Residual confounding due to unmeasured variables such as paternal depression, maternal diet, or adherence to ICS.
Cross-sectional studies				

Rioseco et al., 2017 (30)	87 Chilean children with asthma aged 4–11 years who attended a primary care clinic in an underserved area of Santiago, from 2013 to 2014	Depression in the child's primary caregiver was defined as: Beck Depression Inventory vision II (BDI-II) score > 13.	Controlled asthma (case group, n=41): doctor-diagnosed asthma with cACT score ≥ 20 points Uncontrolled asthma (control group, n=47): doctor-diagnosed asthma with cACT score ≤ 19 points.	• Depressive symptoms in primary caregivers (70%-80% of whom were mothers) were higher in children with uncontrolled asthma than in those with controlled asthma (39.1% vs. 19.5%, P= 0.04) • Inverse correlation was reported between BDI-II score and cACT score (r= −0.254, P= 0.02) • Adjusting for age, gender, ICS use, and family health vulnerability, caregiver's depression was not associated with asthma control in children • Serum biomarkers (IFN-γ, IL-4, IL-13, TGF-β, cortisol, and total IgE) were not significantly different between groups. • **Limitations**: - Temporal relationships cannot be determined - Small sample size with limited statistical power - Convenience sample from a single center

Medsker et al., 2017 (31)	Children aged 6–14 years recruited from 2009 to 2010 in Puerto Rico (*n* = 655), and from 2005 to 2006 in Sweden (*n* = 6,887)	Significant depressive symptoms: CES-D ≥ 21. Postnatal and current.	Puerto Rican cohort: parental report of physician-diagnosed asthma AND ≥ 1 episode of wheeze in the previous year. Swedish cohort: An asthma diagnosis (ICD: J45 or J46) and/or: 1) any asthma medication (except β2-agonists) dispensed at least twice from July 2005 or 2) any asthma medication dispensed ≥ thrice during 1 calendar year from 2006 to 2010	Adjusting for age, sex, income, and second-hand smoke in early life: • Puerto Rican cohort: Maternal depressive symptoms with maternal asthma were associated with childhood asthma (aOR=6.5, 95% CI= 3.3-12.9). • Swedish cohort: Maternal depressive symptoms with maternal asthma were associated with childhood asthma (aOR= 4.0, 95% CI= 1.7-9.6) • In both cohorts, maternal depressive symptoms alone (without maternal asthma) were not associated with childhood asthma • **Limitations/Potential bias:** - Non-assessment of exposure to prenatal or perinatal maternal depression - Lack of data on early-life environmental exposures - Physician-diagnosed maternal depression not available in the Puerto Rican cohort

aOR= adjusted Odds Ratio; aRR= adjusted Relative Risk; BMI=body mass index, cACT= childhood asthma control test; CES-D= Center for Epidemiologic Studies Depression Scale; CI= Confidence Interval; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EPDS= Edinburgh Postnatal Depression Scale; FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; GLI= Global Lung Function Initiative**;** HADS-D= Hospital Anxiety and Depression; HR= Hazard Ratio; ICD= International Classification of Diseases; OR= Odds Ratio; ICS= inhaled corticosteroids; RR=relative risks; SES=socioeconomic status; URECA= Urban Environment and Childhood Asthma

Table 2. Summary of epidemiologic studies on depression and asthma outcomes in children and adolescents

Reference	Study population	Depression measures	Primary outcomes	Main findings and study limitations
Longitudinal studies				
Griffiths et al., 2021 (32)	43 children aged 4-18 years with severe asthma (attending severe asthma program) from Boston (MA), U.S., 2017-2019	PHQ-4> 2 indicates at least mild depression and/or anxiety	ACT or c-ACT and lung function measures	Adjusting for age, sex, race and medication step: • Inverse correlation between PHQ-4 and ACT (r= -0.41, P< 0.01) • Girls with PHQ-4> 2 had worse asthma control (7 points lower ACT/cACT) than those with PHQ-4≤ 2 (95% CI= -10.88 to -3.12, P= 0.01). • PHQ-4 score was not associated with asthma control in boys. • No association between PHQ-4> 2 and FEV_1/FVC. • **Limitations**: - PHQ-4 is not the gold standard for diagnosing anxiety or depression in clinical practice. - Some patients were younger than the PHQ-4 validated ages - Prior treatment of anxiety or depression is unknown - Small sample size and limited generalizability
Cross-sectional studies				
Kulikova et al., 2021 (33)	205 U.S. children aged 7-17 years with moderate to severe asthma	CDI, total score (0-57) was transformed into a T-score	Moderate to severe asthma: EPR3 criteria or requiring at least Step 3 therapy ACT or c-ACT, PAQOL, CASI (a five-domain measure of asthma severity) and FEV_1	Adjusting for age, sex, and race: • 42.2% (P< 0.01) of the variance was shared between depression and anxiety symptoms and 4 asthma outcomes (ACT, PAQOL, CASI, and % predicted FEV_1) • Similar findings in girls and boys • CDI was associated with worse asthma outcomes, with PAQOL and ACT being the primary drivers of the relationship between depression and anxiety and asthma outcomes • **Limitations:**

				- The canonical correlation analysis (CCA) model did not control for use of ICS. - Limited generalizability to children with severe or uncontrolled asthma - Potential residual confounding by environmental exposures - Unable to determine temporal relationships
Patel et al., 2023 (34)	197 rural adolescents ≥ 13 years old diagnosed with asthma in S. Carolina, U.S., Fall 2019 and 2020	Clinical depression: CES-D ≥ 16	Asthma: a diagnosis AND signs and symptoms of asthma in the past month *or* asthma-related ED visit, hospitalization, or use of systemic steroids in the prior 12 months Asthma self-management (asthma prevention index, asthma management index, and asthma management self-efficacy index) Asthma control: ACT	Adjusting for gender and race/ethnicity: • Depressive symptoms were associated with worse asthma control (ACT, β = -0.085, 95% CI= -0.14 to -0.03]) • Depressive symptoms were not associated with asthma self-management. • **Limitations:** - Potential residual confounding by exposure to cigarette smoke, obesity, and environmental factors - Limited generalizability (most participants had poorly controlled asthma, were female or Black, and lived in rural areas) - Lack of objective measures (e.g. lung function) - Unable to examine temporality
Licari et al., 2022 (35)	87 Italian adolescents with asthma aged 12-18 years, 2017	Depression: CDI > 20	Asthma and asthma symptoms were based on GINA guidelines. Asthma control: ACT and GINA-guidelines	• High CDI scores were associated with uncontrolled asthma (P= 0.01) • Mild inverse correlation between CDI and ACT score (r= -0.27) • **Limitations:** - Cannot determine temporal relationships - Relatively small sample size and lack of control group - Potential residual confounding by SES and environmental exposures

Lakshminarasappa et al., 2021 (36)	176 children aged 6-14 years with asthma from Puducherry, India, 2017-2019	Depression: CES-DC ≥ 15	GINA guidelines for asthma: clinical symptoms, response to medications, evidence of obstructive lung disease, use of asthma controllers for ≥ 3 consecutive months Asthma control: ACT or cACT	• In the multivariable analysis, depression alone was associated with uncontrolled asthma symptoms (aOR=36, 95% CI= 7.5- 173.77). • Depression was not associated with lung function measures. • **Limitations:** - Lack of a control group - A full psychiatric diagnostic assessment was not considered - Residual confounding by environmental exposures - Inability to determine temporal relationships
Bardach et al., 2019 (37)	65,342 U.S. children aged 6 -21 years with asthma from the MA 2015 Claims database	1 diagnosis-related ICD 9 or 10 code in inpatient, outpatient, or ED claims by DSM-V	Identifiable asthma: Prior hospitalization due to asthma (1st or 2nd diagnosis with ICD-10); OR qualified events after age 5 years (≥ 1 ambulatory visit with asthma as primary diagnosis, or ≥ 2 ambulatory visit with asthma as a diagnosis, or 1 ambulatory visit with asthma as a diagnosis and ≥1 asthma-related prescription); OR other qualifying events at any age (≥ 3 ambulatory visits with a diagnosis of asthma, or ≥ 3 ambulatory visits with a diagnosis of asthma and ≥ 1 asthma-related prescription).	Adjusting for age, sex, insurance type, and other chronic illnesses: • Patients with depression had a higher rate of ED visits for asthma per 100 child-years (21.7, 95% CI: 18.3- 25.0) than those without depression or anxiety (15.5, 95% CI= 14.5-16.4) • **Limitations/Potential bias:** - Limited generalizability (single database) - ICD codes could underestimate mental health diagnoses - ICD codes from administrative claims databases often do not accurately represent asthma severity - Residual confounding by race and ethnicity and environmental exposures - Inability to determine temporal relationships

Munos et al., 2020 (38)	52,485 admissions in patients aged 10–21 years with severe asthma, U.S. 2000–2012 Healthcare Cost and Utilization Project's Kids' Inpatient Databases	Major depressive affective disorder and bipolar depression, ICD-9 codes 296-296.99, 311; Depression)	Severe asthma: ICD-9 codes with either status asthmaticus (493.01, 493.11, 493.21, 493.91) OR any asthma (493, 493.0, 493.00, 493.02, 493.1, 493.10, 493.12, 493.2, 493.20, 493.22, 493.8, 493.9, 493.90, 493.92) associated with a procedure code for endotracheal intubation (96.02 or 96.04)	• Patients with depression were more likely to have longer hospitalizations (P< 0.001), higher in-patient mortality (P= 0.004), and higher total charges (P< 0.001), compared with patients without depression • **Limitations:** - Inability to determine temporal relationships - Potential misdiagnosis of severe asthma - Inability to track individual patients over time - Residual confounding by environmental exposures and stress disorders
Shankar et al., 2019 (39)	277 adolescents with asthma aged 12-17 years in New York, U.S., 2014- 2017	Clinical depression: CES-D ≥ 16	Asthma case: caregiver report of physician-diagnosed asthma and persistent or poorly controlled asthma according to national guidelines (EPR-3). PAQLQ score, school absenteeism due to asthma, sleep (enough or not), and activity limitations assessed by the Children's Health Survey for Asthma	Adjusting for race, ethnicity, gender, and caregiver education level: • Depressive symptoms were associated with lower PAQOL and less sleep (P< 0.001 for both). • Depressive symptoms were associated with limited activity due to asthma in the previous 14 days - In gym (aOR=2.33, 95% CI= 1.30-4.17) - Mild activity (aOR= 2.60, 95% CI= 1.34-5.02) - Moderate activity (aOR=2.56, 95% CI= 1.41-4.61) • **Limitations:** - Inability to determine temporal relationships - Potential recall bias - Likely residual confounding by anxiety, obesity and environmental exposures

Hsu et al., 2020 (40)	250 children with asthma aged 7-17 years in Buffalo (NY), U.S., 2002-2011	Clinical depression: CDI ≥ 12	Asthma was confirmed by allergists based on national guidelines (EPR-3), and baseline FEV_1 was measured	Adjusting for age, gender, ethnicity, maternal education, and medication adherence: • In overweight/obese children with asthma (but in children of normal weight), depressive symptoms were associated with decreased FEV_1 (β= -0.67, P< 0.008) and parasympathetic/vagal autonomic nervous system dysregulation • **<u>Limitations:</u>** - Limited generalizability to children of other ethnic backgrounds - Inability to determine temporal relationships - Residual confounding by environmental exposures

aOR=adjusted odds ratio; ACT=asthma control test; cACT=childhood asthma control test; CASI=Composite Asthma Severity Index; CDI= Children's Depression Inventory; CES-D= Center for Epidemiologic Studies Depression Scale; CES-DC= Center for epidemiological studies–depression scale for children; CI=confidence interval; DMS-V=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ED=emergency department; EPR-3= National Asthma Education and Prevention Program Expert Panel Report 3 criteria; FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; GINA= Global Initiative for Asthma; GLI= Global Lung Function Initiative; OR=odds ratio; PAQOL=Pediatric Asthma Quality of Life; PHQ-4= Patient Health Questionnaire-4; U.S.=United States

Table 3. Summary of epidemiologic studies on depression and asthma and asthma outcomes in adults

Reference	Study population	Depression measures	Primary outcomes	Main findings and study limitations
Longitudinal studies				
Shen et al., 2017 (47)	150,845 adults ≥ 20 years with newly diagnosed MDD from the Longitudinal Health Insurance Database, Taiwan, 2000-2010	Physician's diagnosis of MDD based on ICD-9-CM (clinical modification) codes 296.2–296.3.	New asthma cases: Patients with a discharge code of asthma in the admission dataset or patients with ≥ 2 visits for asthma in a year in the outpatient dataset	Adjusting for age, sex, comorbidities, and medications: • MDD was associated with incident asthma (aHR=1.66, 95% CI=1.55-1.78) • Patients with both MDD and COPD had a 3.4-fold higher incidence of asthma compared with patients who had MDD without COPD (Asthma incidence: 21.3 vs. 6.31 per 1,000 person-years). • **Limitations:** - Potential misclassification and under-diagnosis of asthma - Likely residual confounding by SES, BMI, environmental exposures, and family history - Non-assessment of severity of MDD or asthma
Pickard-Michels et al., 2025 (48)	873,482 adults ≥ 18 years with asthma from the United Kingdom, 2017-2019.	Depression was identified with diagnostic codes in primary care (SNOMED-CT)	Incidence of asthma exacerbations were identified in primary care based on the SNOMED-CT codes.	Adjusting for age, sex, ethnicity, BMI, smoking, comorbidities and other mental health disorders: • Depression was associated with asthma exacerbations (IRR= 1.34, 95% CI= 1.32-1.37). • **Limitations:** - High missing rates for confounders (ethnicity and BMI) - Lack of SES data in the pre-collected dataset - Potential misclassification or under-diagnosis of depression - Non-assessment of severity of depression or asthma
Cross-sectional studies				

Ji et al., 2025 (10)	31,434 adults ≥18 years old from the U.S. (NHANES, 2007-2018) 17,021 adults ≥50 years old from England (ELSA, 2004-2019) GWAS data obtained from the FinnGen R12 release (59,100 cases and 259,839 controls)	Depression: PHQ-9 ≥ 10 in NHANES and 8-item CES-D ≥ 4 in ELSA	NHANES and ELSA: Self-reported asthma (ever) diagnosed by a health professional.	Adjusting for age, gender, race/ethnicity, smoking status, drinking status, education, BMI, family history of asthma (in NHANES only) and comorbidities: • Depression was associated with asthma - NHANES: aOR=1.29 (95% CI= 1.15-1.46) - ELSA: aOR=1.44 (95% CI= 1.25-1.66) • Linkage disequilibrium score regression (LDSC) revealed a significant positive genetic correlation between depression and asthma (rg = 0.35, P< 0.001). • MR analyses demonstrated that depression genetically predicted 33%-43% increased asthma risk after adjusting for smoking, drinking, or education (P< 0.001 in all models). • Reverse MR analyses found no evidence that genetic liability to asthma causally increases depression risk. • **Limitations/Potential bias:** - Inability to determine temporal relationships - Potential recall bias and misclassification of asthma - Residual confounding by environmental exposures
Theodoro et al., 2023 (41)	309 patients with asthma ≥ 18 years old in Brazil.	Depression: Physician-diagnosed depression with regular antidepressant use two months before the study visit or Montgomery & Åsberg Depression Rating Scale (MADRS) >19	Asthma: medical record review by a physician, BDR >12%, and clinical evidence of asthma (wheezing, cough, dyspnea lasting longer than 1 year). Airway obstruction: FEV_1/FVC below the lower limit of normal	Adjusting for age, sex, and BMI: • Compared with those without depression (controls), adults with depression who did not use antidepressants were more likely to have uncontrolled asthma symptoms (aOR=3.10, 95% CI=1.56-6.15) and post-bronchodilator airway obstruction (aOR=2.41, 95% CI=1.24, 4.69) • Compared with controls, adults with depression who used antidepressants were more likely to have uncontrolled asthma symptoms (aOR=3.02, 95% CI=1,50-6.07]), but not pre-bronchodilator airway obstruction (aOR=1.24, 95% CI=0.87-1.77) • **Limitations/Potential bias:** - Inability to determine temporal relationships

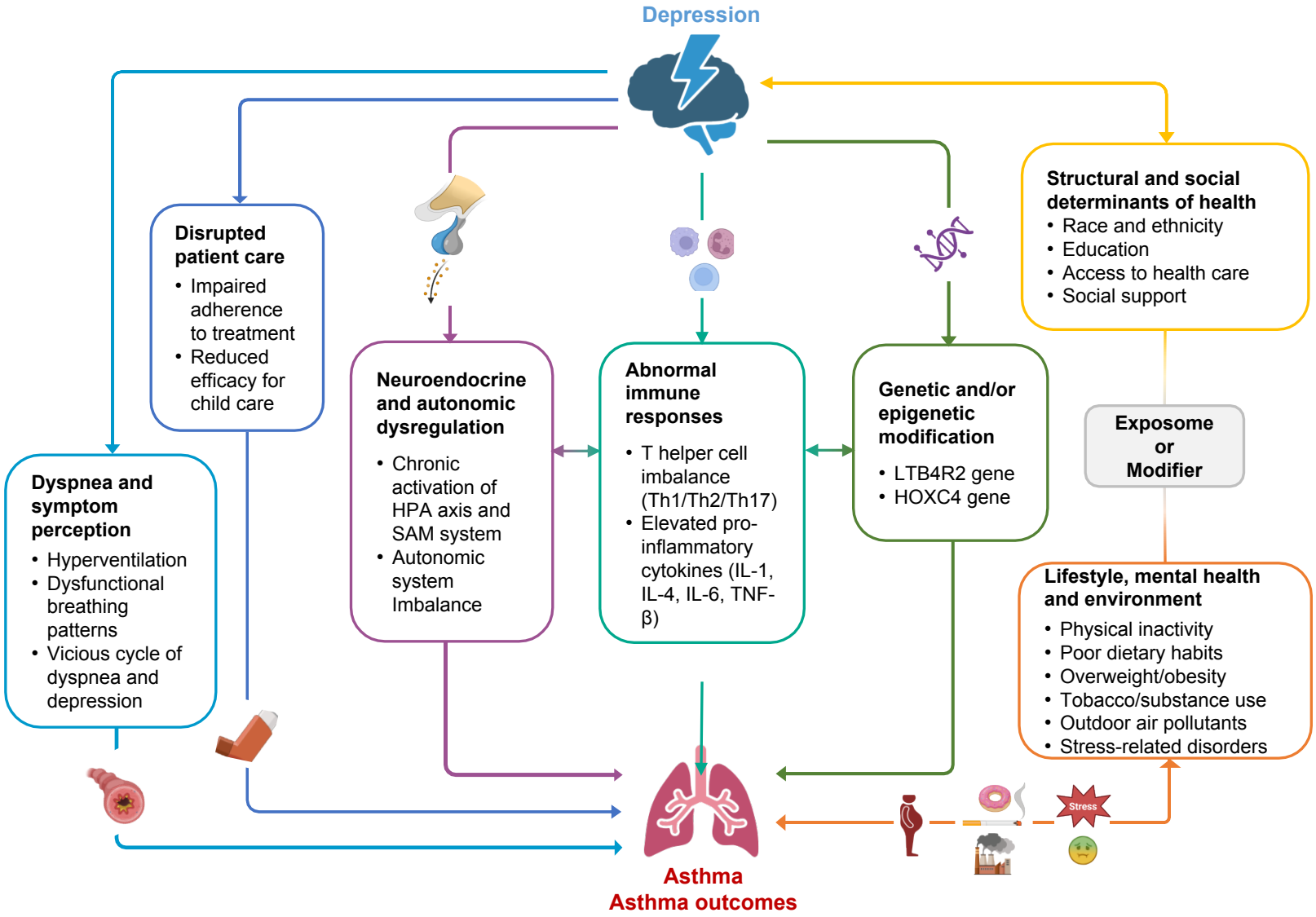
			Uncontrolled asthma symptoms: ACT score ≤19 points	- Potential misclassification of asthma - Likely residual confounding by stress disorders and environmental exposures
Ran et al, 2025 (42)	38,127 U.S. participants in NHANES 2005-2023	Depression: PHQ-9: ≥10= clinically significant 10-14= moderate 15-19= moderately severe 20-27= severe	Asthma (self-reported): asthma diagnosed by a health professional *or* ≥1 asthma attack in the prior year	Adjusting for age, gender, race/ethnicity, PIR, education, BMI, and smoking: each 1-point increment in PHQ-9 was associated with 5% increased odds of asthma (95% CI=1.05-1.06). • Compared to participants without depressive symptoms, depression severity was associated with asthma (P for trend <0.01): - Moderate depression: aOR=1.56, 95% CI=1.35-1.80 - Moderately severe asthma: aOR=1.97, 95% CI=1.59-2.44 - Severe asthma: aOR=2.02, 95% CI=1.48-2.76) • The MR analysis showed a potential causal effect of depression on asthma (aOR=1.29, 95% CI=1.19,1.40). • **Limitations:** - Possible misclassification of asthma - Inability to determine temporal relationships - Potential residual confounding by environmental exposures
Chen et al., 2025 (43)	231,460 U.S. adults in the NHIS 2010-2022	Depression: PHQ-8: 0-4: none/minimal 5-9: mild 10-14: moderate 15-24: severe Kessler-6 scale: 0-4: none/minimal 5-12: moderate 13-24: severe	Current asthma (self-reported): asthma diagnosed by a healthcare professional and still has asthma. Asthma remission (if ever asthma): has been told that currently does not have asthma	Adjusting for age, gender, region, race and ethnicity, PIR, education, marital status, insurance, BMI, smoking and alcohol status, health insurance coverage, and self-report health status: • Depression was associated with: - Asthma (aOR= 1.34, 95% CI=1.25-1.44) - Decreased asthma remission (aOR=1.19, 95% CI=1.04- 1.35) - More frequent asthma exacerbations (aOR=1.31, 95% CI=1.15- 1.50) • No significant association between depression and ED visits for asthma. • **Limitations/Potential bias:** - Cannot determine temporal relationships - Possible misclassification of asthma

				- Potential recall bias - Possible residual confounding by environmental exposures
Tedner et al., 2016 (44)	25,381 adult twins aged 20-47 years in Sweden, 2005-2006.	Possible major depression: CES-D ≥ 12 or DSM-IV criteria	Register-based asthma: ICD code J45 or J46 as a primary or secondary diagnosis and/or prescription of asthma drugs Self-reported asthma: has asthma with current symptoms	Adjusting for age, sex, BMI, education, and smoking: • Major depression (by CES-D) was associated with registry-based asthma (aOR=1.42, 95% CI= 1.23-1.64) and self-report asthma (aOR=1.42, 95% CI=1.27-2.58) • Major depression (by DSM-IV criteria) was associated with registry-based asthma (aOR=1.56, 95% CI=1.36-1.79) and self-report asthma (aOR= 1.44, 95% CI=1.29-1.61) • Similar associations were found after in addition adjusted for general and familial environmental factors. • **Limitations:** - Possible misclassification of depression and asthma - Potential selection bias - Inability to determine temporal relationships - Likely residual confounding by stress disorders and environmental exposures
Patel et al., 2017 (45)	7,256 U.S. adults aged 55 years and older, NHANES 2007-2012	Mild depression: PHQ9= 5-9 Moderate to severe depression: PHQ9 ≥ 10	Self-reported current asthma: asthma diagnosed by a health professional AND still has asthma Self-reported asthma outcomes: symptom episodes, ED visits, sleep disturbance, activity limitations,	Adjusting for age, gender, marital status, education, SES, race/ethnicity, BMI, comorbidity burden, and years living with asthma: • In older adults with asthma, depression was associated with asthma episodes, ED/urgent care visits for asthma, sleep disturbance due to asthma, and activity limitation • Depression was not associated with lung function • **Limitations:** - Lack of information on use of antidepressants or asthma medications, medication adherence, hospitalizations, and physician-diagnosed depression

			health-related quality of life Lung function measures	- Misclassification of asthma due to recall or reporting bias - Inability to determine temporal relationships
Han et al., 2016 (46)	20,272 U.S. participants aged 20 to 79 years, NHANES 2007-2012	Major depression: PHQ-9 ≥ 15	Self-reported current asthma: asthma diagnosed by a health professional AND ≥ 1 asthma attack in the previous year BDR	Adjusting for age, sex, education, smoking status, BMI, and anxiety: • Major depression was associated with 3.4 times increased odds of asthma (aOR=3.4, 95% CI=2.6-4.5) • In a model with additional adjustment for pre-FEV_1, major depression was associated with a 4.2% reduction in BDR (95% CI= -7.5%, -0.8%) in adults with asthma • **Limitations:** - Temporality cannot be established - Misclassification of asthma due to report bias or selection bias - Lack of detailed information on use of medications for asthma or antidepressants - BDR was measured only in adults with reduced FEV_1/FVC and/or FEV_1
Shoair et al., 2020 (51)	61 U.S. patients with asthma aged 18-65 years who were initiated on a single antidepressant and maintained on a stable dose for 8 weeks (index date), 2014-2018	MDD without psychotic symptoms: ICD-10 codes F33.0–F33.9 and F32.0–F32.9	Asthma: ICD-10 codes J45.2-J45.998 Severe asthma exacerbation (primary outcome): use of systemic corticosteroids or an increased dose from a stable ICS maintenance dose for at least 3 days; OR a hospitalization or ED visit due to asthma that required systemic corticosteroids	Adjusting for severe exacerbations in the year pre-index date, BMI, tobacco use, and allergic rhinitis: • Patients on antidepressants had lower risk of severe exacerbations than the control group: - At 1-year: adjusted risk reduction (aRR)= 0.46, 95% CI= 0.26-0.82 - At 2-years: aRR= 0.50, 95% CI= 0.30-0.82 • Antidepressant use was associated with a reduced number of steroid bursts (but not with asthma hospitalizations) at both 1 and 2-years • **Limitations:** - Retrospective assessment of antidepressant use - Different distribution of antidepressant therapeutic classes used between target and control groups

				- Decreased sample size due to missing data on antidepressant dose or duration of use - Limited generalizability: cohort derived from uninsured and underinsured patients - Lack of information on medication adherence
Clinical trials				
Brown et al., 2018 (49)	A 12-week, randomized, double-blind, parallel-group, placebo-controlled trial of escitalopram (10 mg/d) in 139 U.S. patients with asthma and MDD aged 18-70 years, 2010-2015.	MDD: $HRSD_{17} \geq 20$, Structured Clinical Interview for DSM 4 (SCID-IV), and inventory pf depressive symptomatology (IDS-SR)	Asthma: a diagnosis of asthma AND currently receiving asthma treatment AND ≥ 1 asthma - related physician visit in the prior 6 months; AND an ACQ total score ≥ 1 point.	• In 21 of 42 participants with higher severity depression who completed the trial, those taking escitalopram had significantly improved asthma control (P= 0.04) and lower corticosteroid use (P= 0.04) • No significant differences in asthma outcomes were observed in a post-hoc analysis of all participants • **Limitations:** - Modest sample size and high attrition rate - Unable to evaluate whether a specific asthma phenotype may be more responsive to SSRI therapy - Observation period may be too short to fully evaluate the impact of the SSRI treatment on asthma

Agarwal et al., 2024 (50) Efficacy study of 3 selected serotonin reuptake inhibitors (SSIRs) trials	255 U.S. adults with asthma and MDD but no other psychiatric illness aged ≥ 18 years who participated in three 12-week, randomized, double-blind, placebo-controlled, parallel-group trials: 20mg/day of citalopram, 10mg/day of escitalopram, or placebo	Mild depression: $HRSD_{17}$ = 8-16 Moderate depression: $HRSD_{17}$ =17-23 Severe depression: $HRSD_{17}$ ≥ 24	Asthma: physician-diagnosed asthma and current use of asthma medications Asthma control: ACQ score.	Adjusting for baseline $HRSD_{17}$and ACQ score, number of study visits, study (trial), age, sex, race, and marital status: • Pooled sample (n=255): - Citalopram/escitalopram treatment was associated with lower corticosteroid use than placebo (aOR=0.59, P< 0.001). - Antidepressant treatment was not associated with asthma control. • High-exacerbation subgroup (subset of the pooled sample who reported ≥3 prednisone bursts in the previous 12 months) - Treatment group had slightly lower ACQ (~0.25 points) than placebo group (P= 0.004) - Treatment group had lower corticosteroid use than placebo group (aOR=0.59, P= 0.003) • **Limitations:** - All three studies were conducted by the same research group - Limited generalizability, as all participants were recruited from the same geographic regions - Divergency in interval of study visits and inclusion/exclusion criteria across the three studies
ACQ= asthma control questionnaire; aHR= adjusted hazard ratios; aOR=adjusted odds ratio; ARR= Absolute Relative Risk; aRR= Adjusted Relative Risk; BMI=body mass index; BDR=bronchodilator response; CES-D= Center for Epidemiologic Studies Depression Scale; CI=confidence interval; COPD= chronic obstructive pulmonary disease; DMS-V=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ED= emergency department; ELSA= and English Longitudinal Study of Ageing; FEV_1= forced expiratory volume in one second; GWAS= genome-wide association study; HADS-D= Hospital Anxiety and Depression; $HRSD_{17}$= 17-item Hamilton Rating Scale for Depression; ICD-9-CM= International Classification of Diseases, 9th Revision, Clinical Modification; IRR=incidence rate ratio; MDD=major depressive disorder; MR= Mendelian randomization; NHANES= National Health and Nutrition Examination Survey; NHIS=National Health Interview Survey; OR= Odds Ratio; PHQ=patient health questionnaire; PR= prevalence ration; PIR=poverty income ratio; RR= Relative Risk; SES=socioeconomic status; SNOMED-CT= Systematized Nomenclature of Medicine Clinical Terms; U.S.=United States				


Depression
Disrupted patient care
• Impaired adherence to treatment
• Reduced efficacy for child care
Neuroendocrine and autonomic dysregulation
• Chronic activation of HPA axis and SAM system
• Autonomic system Imbalance
Abnormal immune responses
• T helper cell imbalance (Th1/Th2/Th17)
• Elevated pro-inflammatory cytokines (IL-1, IL-4, IL-6, TNF-β)
Genetic and/or epigenetic modification
• LTB4R2 gene
• HOXC4 gene
Structural and social determinants of health
• Race and ethnicity
• Education
• Access to health care
• Social support
Exposome or Modifier
Lifestyle, mental health and environment
• Physical inactivity
• Poor dietary habits
• Overweight/obesity
• Tobacco/substance use
• Outdoor air pollutants
• Stress-related disorders
Dyspnea and symptom perception
• Hyperventilation
• Dysfunctional breathing patterns
• Vicious cycle of dyspnea and depression
Stress
Asthma
Asthma outcomes