Asthma, Anxiety, and Depression

E. Sherwood Brown, MD, PhD, MBA

Professor and Vice Chair for Clinical Research
Lou and Ellen McGinley Distinguished Chair in Psychiatric Research
Aradine S. Ard Chair in Brain Science
Distinguished Teaching Professor
Department of Psychiatry
Immediate Past President, Academy of Consultation-Liaison Psychiatry (ACLP)

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Depression

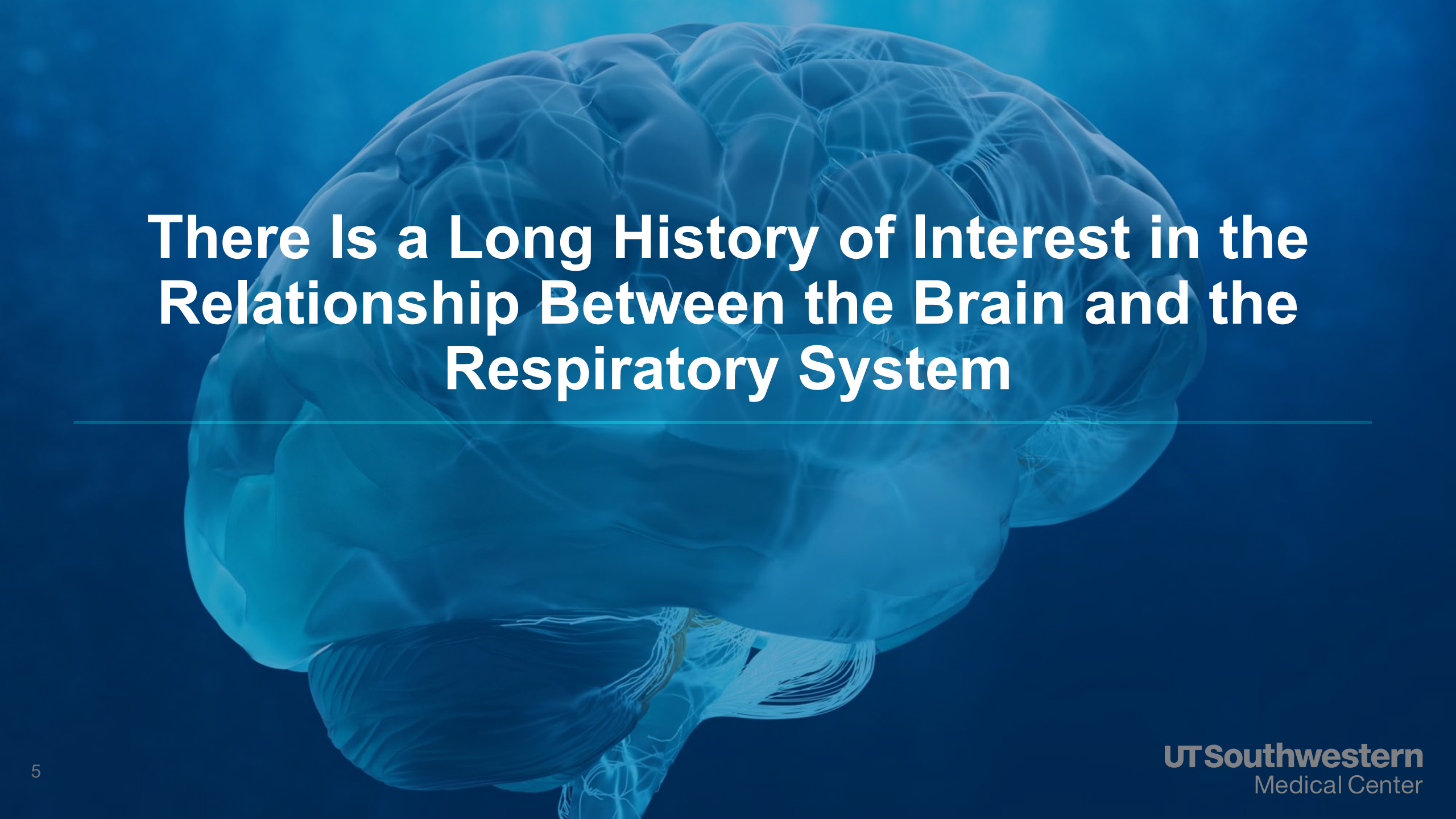
- Leading cause of ill health and disability worldwide
- Globally affects 300 million people
- Associated with losses in productivity
- The prevalence of depression and anxiety is increasing

World Health Organization (WHO, 2017)

Anxiety

- Approximately 19% of US adults had an anxiety disorder in the past year
- Approximately 23% of women and 14% of men had an anxiety disorder
- 31% lifetime prevalence

(National Institute of Mental Health [NIMH], 2017)



There Is a Long History of Interest in the Relationship Between the Brain and the Respiratory System

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Early Conceptualization of Relationship Between the Respiratory System and the Brain

- The Greek and Roman physician Galen of Pergamon (129–216 AD) suggested that intermittent breathing obstruction was due to secretions dripping from the brain into the lungs

(Miller, 2002)

Historical Perspective on the Connection Between Emotions and Asthma

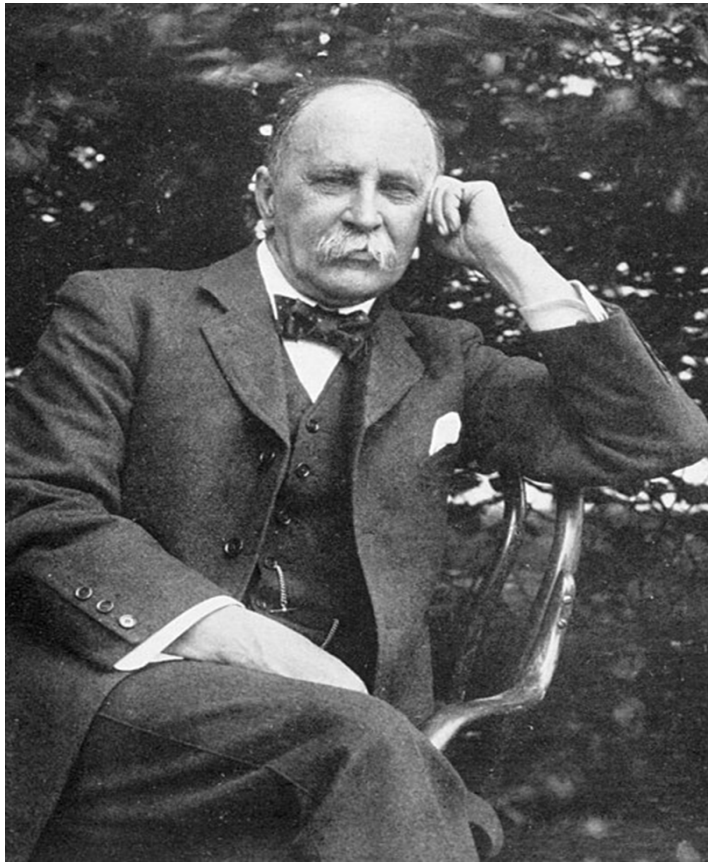
(Rosner, 1981)

- In *Treatise on Asthma* Maimonides (1138-1204) devoted a chapter to emotional factors, suggesting that being emotionally upset causes physical well-being to suffer, eventually leading to physical illness.

Late 19th or Early 20th Century Perspective

- Sir William Osler, a founder of Johns Hopkins Hospital and often called the Father of Modern Medicine wrote, “All writers agree that there is, in a majority of cases of bronchial asthma, a strong neurotic element. Many regard it as a neurosis.”

(Harrison, 1998)



Asthma Connection to Mood and Emotions?

- Franz Alexander included asthma among the original “holy seven” psychosomatic illnesses
- This does not mean asthma is “all in the head”

(Hange et al., 2007)

How I Became Interested in Asthma

- I was a research track resident, but I was not sure what I wanted to do
- A faculty member saw an allergist (David Khan, MD) and they discussed the psychiatric effects of prescription corticosteroids

My Early Research in this Area

- I studied the effects of corticosteroids on mood and later the hippocampus
- I assessed asthma patients receiving prescription corticosteroids as a model for the effects of cortisol on the brain
- I noted the high rates of psychiatric diagnoses on structured clinical interviews

(Brown et al., 2000)

Our Initial Findings in Asthma Patients

- We conducted structured diagnostic interviews in people with asthma
- In a sample of 32 patients with moderate to severe asthma, 25% had a current major depressive disorder, but only 25% of these were receiving treatment for it
- 47% lifetime prevalence of a mood disorder and 59% for anxiety disorder
- In another sample (n = 44), we observed a 41% lifetime prevalence of a mood disorder

(Brown et al., 2000); (Nejtek et al., 2001)

Risk of Depression and Anxiety in People with Asthma

Study	*Odds Ratio (95% CI)*
Scott KM et al., (2007)	
• World Mental Health Survey (17 countries)	
• Depression	1.6 (1.4, 1.8)
• Anxiety	1.5 (1.4, 1.7)
• Alcohol	1.7 (1.4, 2.1)
Loerbroks A et al., (2012)	
• World Health Survey (57 countries)	
• Depression	2.4 (2.1, 2.7)
• Highest was S. America	2.9 (2.3, 3.6)
• Lowest was Australia	1.7 (1.1, 2.4)

Greater OR in men than women on every continent except Africa

Additional Risk Studies

Study	*Odds Ratio (95% CI)*
Lev-Tzion R et al., (2007)	
• Male Israeli Army Recruits	
• Any Psychiatric Disorder	1.2 (1.1-1.3)
• Mood and Anxiety Disorders	1.3 (1.2-1.5)
Trojan TD et al., (2014)	
• Cooper Center Longitudinal Study	
• Depression	1.4 (1.2, 1.7)
• Anxiety	1.4 (1.2, 1.7)
Akula M et al., (2018)	
• Dallas Heart Study	
• Any Psychiatric Disorder	1.8 (1.3, 2.6)
• Depression	1.6 (1.1, 2.3)

The Risk of Depression is Also Increased in Older People with Asthma

- N = 3,232 Wisconsin high school graduates from 1957 assessed in 1992, 2004, 2011 (ages approximately 53, 65, and 72 years)
- Depressive symptoms scores (CES-D) significantly higher in 2004 and 2011 in those with asthma

Frequency of Likely Depression (CES-D ≥16)

Year	Men (controls)	Men (asthma)	Women (controls)	Women (asthma)
2004	7.0%	11.7%	10.8%	16.4%
2011	9.2%	13.0%	12.6%	16.8%

(Palka et al., 2024)

Asthma and Seasonal Allergies May Increase Suicide Risk

Study		*Odds Ratio (95% CI)*
Chung JH et al., (2016)		
• Suicidal Ideation	(asthma)	1.5 (1.4, 1.7)
• Suicidal attempts	(asthma)	1.3 (1.0,1.7)
Messias E et al., (2010)		
• Suicidal ideation	(allergies)	1.3 (1.0,1.6)
• Suicide attempts	(allergies)	1.2 (0.9, 1.5)

When Present, Depression and Anxiety are Associated with Adverse Consequences in People with Asthma

- Poorer functioning and lower quality of life with depression
- Greater urgent care service utilization with depression
  - ER visits OR 2.1 (1.0, 4.1); Hospitalization OR 3.7 (1.6, 8.4)
- Poor medication adherence with depression
  - OR 11.4 (2.2, 58.2)
- Exaggerated perception of asthma symptoms with anxiety
- Asthma-related death with depression
  - HR 2.7 (95% CI 1.3, 5.8)

(Bellia et al., 2007); (Pilipenko et al., 2016); (Eisner et al., 2005); (Smith et al., 2006); (Steele et al., 2012); (Miller, 1987)

Caregivers of Depressed Children Also Have Elevated Rates of Psychiatric Illness

- Meta-analysis of 25 studies concluded both depression and anxiety were more common in caregivers of children with asthma than caregivers of healthy children
  - (Easter et al., 2015)
- Psychiatric symptoms are associated with increased asthma service utilization (depression 50% increase in unscheduled visits; anxiety 43% increase in asthma-related hospitalizations)
  - (Brown et al., 2006)

Caregiver Mental Health is Associated with Asthma Symptoms

- 129 female caregivers of preschool children (12-59 months) with recurrent wheezing followed for 6 months
- Three caregiver clusters identified: low-risk, moderate-risk, and high-risk based on mental and social health measures
- High-risk caregivers (27% of sample) experienced persistent depression, anxiety, social isolation, and perceived stress over 6 months
- Children of high-risk caregivers had more frequent respiratory symptoms and higher occurrence of wheezing episodes, but paradoxically lower outpatient physician utilization

(Fitzpatrick et al., 2023)

Mechanisms Linking Asthma and Depression

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Which Came First?

Does asthma cause depression or does depression cause asthma?

- Meta-analysis of eight prospective studies.
  - Six studies found depression predicts asthma onset RR 1.4 (95% CI [1.3, 1.6], $p < 0.001$).
  - Two found asthma predicts depression onset RR 1.2 (95% CI [0.7, 2.1], p = NS)

(Gao et al., 2015)

Genetics

- Polygenic risk score for depression is a modest predictor of childhood asthma risk
  - (Liu et al., 2020)
- Shared genetic influences between asthma and depression and neuroticism but not anxiety
  - (Lehto et al., 2019)
- Mixed findings in twins
  - (Brew et al., 2018); (Wamboldt et al., 2000)
- Flinders line rats proposed as models of both depression and asthma
  - (Overstreet et al., 2005)

Further Genetic Links Between Depression, Anxiety, and Asthma

- Test whether depression or anxiety cause asthma (or vice versa)
- Used large genetic datasets (GWAS) in European populations
- Genetic correlation analysis (LDSC)
- Bidirectional Mendelian Randomization (MR)
- Genetic risk for depression increases risk of asthma OR ≈ 1.5–1.7
- Genetic liability to asthma is associated with higher risk of depression
- No clear causal link with anxiety (in either direction)

(Yan et al., 2024)

More Genetic Analyses

- Utilized data from the National Health and Nutrition Examination Survey (NHANES) 2009–2014
- Employed logistic regression to assess the correlation between depression and asthma
- Subsequent Mendelian randomization (MR) analysis, selected single nucleotide polymorphisms (SNPs) closely linked to both depression and asthma as instrumental variables, based on summary data from genome-wide association studies (GWAS).
- Depression was a better predictor of asthma than asthma of depression
- Findings suggested a causal relationship between depression and asthma

(Guo et al., 2025)

Immune and Endocrine

- Immune/inflammation
  - Meta-analysis found elevated IL-1, IL-4,IL-6, TNF-α in depression
    - (Jiang et al., 2014)
- Endocrine
  - Glucocorticoid resistance
    - (Rodriguez et al., 2016)
  - Allergen exposure to induce airway inflammation in young mice altered brain gene expression related to stress regulation (corticotropin releasing hormone receptor 1, glucocorticoid receptor, serotonin function)
    - (Caulfield et al., 2018)
  - Mood symptoms related to corticosteroid medications
    - (Brown, 2009)

Hippocampal Volume was Lower in People with Asthma

- 1,287 participants in Dallas Heart Study
- After controlling for demographic characteristics those with asthma (n = 139) had smaller left, right and total hippocampal volumes
- Subgroup analysis found difference in men (mean difference 3%) but not women (0.6%) with asthma

(Carlson et al., 2017)

Subcortical Grey Matter Reduction and Asthma

- Asthma control, asthma catastrophizing negatively associated with putamen volume
- Asthma duration, catastrophizing with palladium volume
- Putamen is part of the dorsal striatum within the basal ganglia and is involved in reward processing, motivation, and reinforcement learning
- These are functions tied to depressive symptoms such as anhedonia

(Ritz et al., 2020)

Task-Based fMRI Study

- 15 men and women with asthma (mean age 26 years)
- Viewed distressing film clips, neutral ones and crosshair image (baseline)
- BOLD signal and airway response to film clips assessed
- Airway resistance increased viewing distressing film clips
- Increased activation superior frontal gyrus, precentral gyrus, thalamus, lateral geniculum body, fusiform gyrus, lingual gyrus, cuneus, and occipital gyrus
- Airway resistance correlated with activation anterior and middle cingulate

(Ritz et al., 2019)

Treatment

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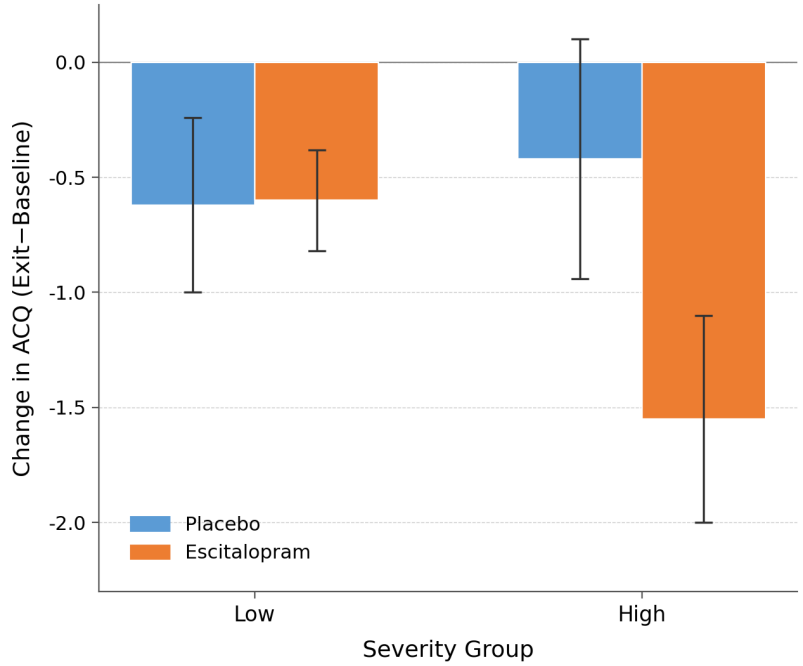
Antidepressant Treatment Appears to be Associated with Improvement in Asthma Control in Depressed Asthma Patients

- 90 outpatient adults with asthma and depression were randomized to the SSRI citalopram or placebo for 12 weeks
- Group receiving citalopram required less prednisone for asthma exacerbations than those on placebo

(Brown et al., 2005)

Larger Study in Depressed Asthma Patients

- 139 outpatients with asthma and depression were randomized to escitalopram or placebo for 12 weeks
- Randomization stratified to high severity group (high levels of depression and frequent asthma exacerbations) and others.
- In high severity group improvement in Asthma Control Questionnaire (ACQ) and fewer exacerbations with escitalopram than placebo.
- No significant effect on depression.
- No between-group differences in less severe group.



(Brown et al., 2018)

Pooled Analysis of Three Studies of Citalopram or Escitalopram in People with Asthma and Depression

- Pooled data from three placebo-controlled trials (n = 255)
- Improvement in depressive symptoms severity and 41% fewer exacerbations with citalopram or escitalopram than placebo
- Improvement in asthma control (ACQ) was also significant in the high-severity subgroup

(Agarwal et al., 2024)

Treatment of Depressed Asthma Caregivers May Improve the Child's Asthma Control

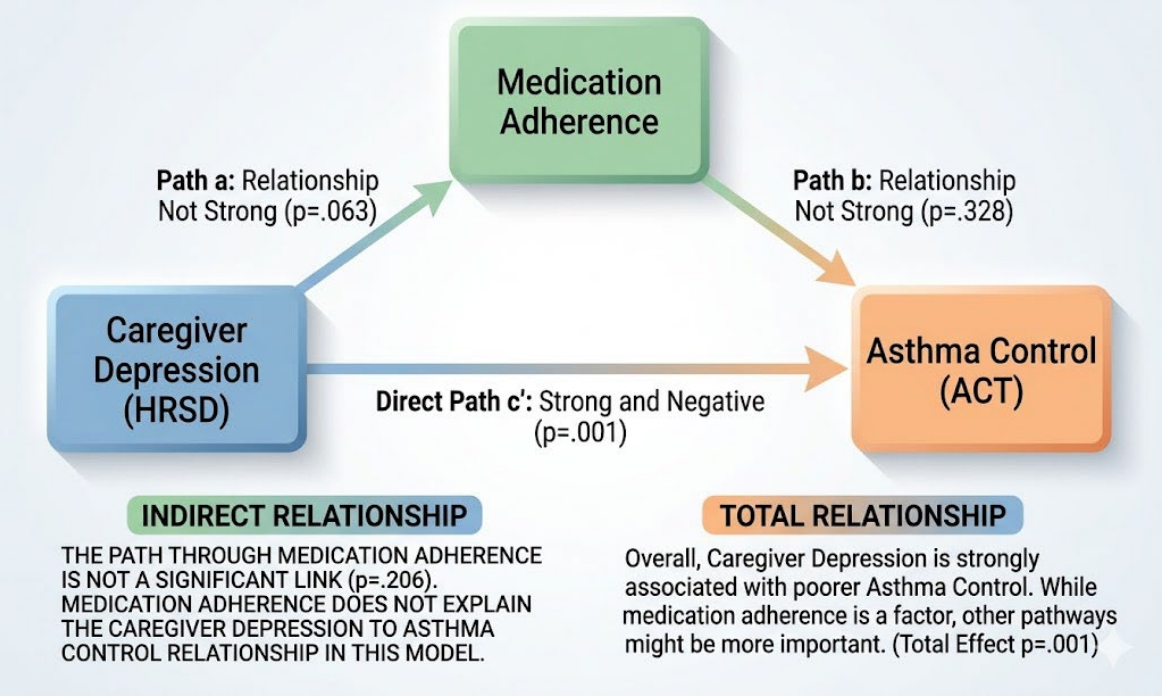
- Two site study with SUNY Buffalo
- 205 depressed caregivers (mostly mothers) and child with persistent asthma were observed for 12 months
- Most but not all caregivers received depression treatment
- We followed the caregiver's depressive symptom severity and the child's asthma control
- **We hypothesized that improvement in caregiver depression would be associated with improvement in the child's asthma control mediated through improved medication adherence and/or improvement in the child's mood**

(Brown et al. 2023)

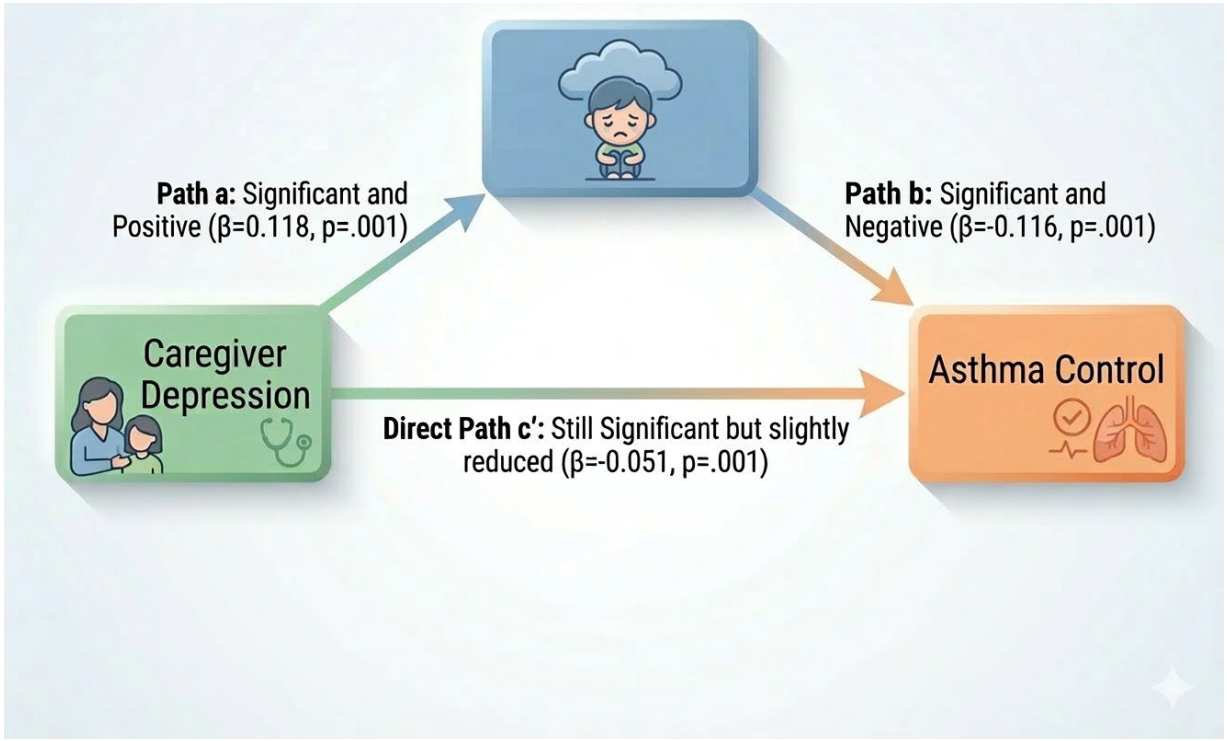
Main Findings from the Caregiver Study

- Proportion of caregiver visits with depression remission (virtual absence of depressive symptoms) significantly predicted baseline to exit change in both the child's asthma control and FEV_1% predicted (proportion of a person's vital capacity that they can expire in the first second of forced expiration)

Relationship was Not Mediated Through Medication Adherence



Relationship Between Caregiver Depression and Child's Asthma Control was Partially Mediated Through Improvement in the Child's Depressive Symptoms



Current Research

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A Selective Serotonin Reuptake Inhibitor for Asthma Patients with Frequent Exacerbations

- 24-week, randomized, double-blind, placebo-controlled trial of escitalopram in 105 people with moderate to severe persistent asthma with ≥ 3 asthma exacerbations in the past 12 months
- Asthma exacerbations and asthma control are assessed
- Subclinical depressive symptoms are assessed
- IL-6 and FeNO levels, psychological triggers of asthma exacerbations, sex and T2-low asthma status are used as response predictors.

Specific Aims

- **Primary Aim:** Determine if escitalopram treatment is associated with fewer asthma exacerbations requiring oral corticosteroid use than placebo in outpatients with moderate to severe asthma with frequent exacerbations.
- **Secondary Aim:** Determine if escitalopram treatment is associated with greater improvement in the Asthma Control Questionnaire (ACQ) than placebo in outpatients with asthma.

Conclusions

- Asthma has long been appreciated as an illness with potential connections to the brain
- However, it is only in recent years that this topic has received substantial research attention
- Mood disorders are very common in asthma patients and treatment may have a positive effect on asthma
- Similar findings are observed in caregivers of children with asthma

Collaborators

- David A. Khan, MD
- Thomas Ritz, PhD
- Bruce D. Miller, MD
- Beatrice L. Wood, PhD
- Heather Lehman, MD

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