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Anxiety, depression, and asthma: New perspectives and approaches for psychoneuroimmunology research

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ABSTRACT

The field of psychoneuroimmunology has advanced the understanding of the relationship between immunology and mental health. More work can be done to advance the field by investigating the connection between internalizing disorders and persistent airway inflammation from asthma and air pollution exposure. Asthma is a prominent airway condition that affects about 10% of developing youth and 7.7% of adults in the United States. People who develop with asthma are at three times increased risk to develop internalizing disorders, namely anxiety and depression, compared to people who do not have asthma while developing. Interestingly, sex differences also exist in asthma prevalence and internalizing disorder development that differ based on age. Exposure to air pollution also is associated with increased asthma and internalizing disorder diagnoses. New perspectives of how chronic inflammation affects the brain could provide more understanding into internalizing disorder development. This review on how asthma and air pollution cause chronic airway inflammation details recent preclinical and clinical research that begins to highlight potential mechanisms that drive comorbidity with internalizing disorder symptoms. These findings provide a foundation for future studies to identify therapies that can simultaneously treat asthma and internalizing disorders, thus potentially decreasing mental health diagnoses in asthma patients.

1. Introduction

Internalizing conditions are characterized by inward-focused symptoms, including sadness, fear, and social withdrawal, and understanding of mechanisms underlying internalizing disorders, namely anxiety and mood disorders, has increased dramatically in recent years (Wilner et al., 2016). Overall in the United States, mental health conditions affect 20.6% of the adult population, and anxiety disorders and major depression affect 19.1% and 7.1% of adults, respectively (NIH Mental Health Information: Statistics, 2021). Lifetime risk was reported as 31% for developing any anxiety disorder and 21.4% for any mood disorder by age 75 years, and this was greater in females compared to males (Altemus, 2006; Costello et al., 2003; Jalnapurkar et al., 2018; Katon et al., 2007; Kessler et al., 2007; Strine et al., 2008). Brain regions (e.g. amygdala, hippocampus, prefrontal cortex) and neurotransmitters/proteins (e.g. serotonin, brain derived neurotrophic factor (BDNF), gamma-Amniobutyric acid, glutamate) implicated in these types of disorders are becoming better understood, and their activation pathways are harnessed for treatment of mental health conditions (McEwen et al., 2012; Rieder et al., 2017; Spear, 2000). An important predictor of depression, anxiety, and other mental health conditions is respiratory function/problems (i.e. asthma, exposure to air pollution), and mental health research may well be served by understanding mechanisms specific to these precursors. (see Fig. 1)

Psychoneuroimmunology research broadly focuses on understanding the interaction of mental health and immunology. Specifically related to mental health, elevated cytokine levels have been associated with anxiety and depression disorders. For example, elevated interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and C reactive protein are more frequently observed in patients with anxiety compared to controls (Costello et al., 2019). Elevated circulating IFN-γ and interleukin (IL)-6 were observed in major depression disorder (MDD) compared to control subjects (Gabbay et al., 2009; Mitchell and Goldstein, 2014). Increased peripheral cytokine levels activate brain cells, including microglia and astrocytes, to promote cytokine production in the brain, leading to manifestation of mood disorder symptoms (Brites and Fernandes, 2015; Capuron and Miller, 2011). Gene and protein IL-1β, TNF-α, and IL-6 levels were elevated in prefrontal cortex samples from people with DSM-IV-diagnosed depression-related conditions who committed suicide compared to non-depressed patient samples (Pandey et al., 2012). Enlarged, hyperactive microglia in this and other emotion-related brain regions are associated with increased depression- and anxiety-like behavior in rodents, and sex differences exist in glial and mental

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Fig. 1. Jasmine Caulfield. Jasmine's neuroimmunology research journey began at the University of Delaware in 2013 as an undergraduate research assistant in Dr. Jaclyn Schwarz's laboratory. She earned her bachelor's degree in May 2015 with a double major in Neuroscience and Cognitive Science. She completed her Neuroscience undergraduate thesis with Dr. Schwarz's guidance using a rodent model to investigate neuroimmune function, microglia, and the impact of a neonatal immune challenge on juvenile cognition and anxiety-related behavior. Jasmine began her doctoral training with Dr. Sonia Cavigelli in August 2015 at Pennsylvania State University. Her research under Dr. Cavigelli utilized a mouse model for adolescent asthma to investigate long-term anxiety- and depression-related ramifications in adulthood using metrics including behavior, HPA function, and cytokine gene expression. During her time at Penn State, Jasmine earned numerous dissertation awards, including the Alumni Association Dissertation Award, a prestigious university-wide dissertation award only granted to a select few graduate students to recognize outstanding achievements in scholarship and other professional accomplishments. Jasmine earned her PhD in Neuroscience in June 2020, and in August 2020 she began a postdoctoral associate position at Yale University in the department of Medical Oncology with Dr. Harriet Kluger to develop novel therapies for treatment of kidney cancer, melanoma, and brain metastases. Jasmine has a strong passion for mentorship in neuroscience and served as a peer mentor to help new neuroscience graduate students transition to the program each year while at Penn State. Additionally, she trained over 30 undergraduate research assistants (including 5 thesis students) in the Cavigelli lab in all aspects of research, from reading and dissecting scientific literature, to collecting, analyzing, interpreting, and presenting data in a poster format for scientific conferences. Jasmine looks forward to continued opportunities for research progress and mentorship in neuroimmunology research in the years to come.

disorder development (Schwarz and Bilbo, 2012; Stein et al., 2017). There is still much work needed to optimize treatments for patients with mental health conditions, however recent mechanistic studies highlight an important role of the immune system in the brain and mental health.

Psychoneuroimmunology research focuses on immune-brain interactions and how immune function relates to mental health. Significant work details how short-term/transient immune and stress challenges that briefly activate the immune system also alter behavior (Arad et al., 2017; Cavigelli et al., 2018; Gibb et al., 2011; Gibney et al., 2013; Henry et al., 2008; Wohleb et al., 2012). A broader scope in this work will help understand how immune activation affects mental health, particularly in the case of chronic immune activation. This will require a better integration of studies in the psychoneuroimmunology literature that use different kinds of long-term immune system activation and outcome measures that are highly specific to mental health symptoms. The purpose of this review is to highlight how chronic challenges to the immune system, specifically those associated with asthma and air pollution, cause lasting inflammation that can have specific mental health implications. Preclinical models and clinical research are only beginning to identify important connections between immune system and brain areas/pathways associated with mental health conditions. This work serves as the foundation to improve treatment for patients affected by chronic immune and comorbid mental health conditions.

2. Asthma and air pollution: lung immunology and mental health relationship

Asthma affects ~10% of youth in the United States and ~36% of youth worldwide, making it the most common chronic health challenge that children and adolescents experience (Akinbami et al., 2012, 2016; Mattiuzzi and Lippi, 2020). Asthma can persist throughout life, and overall asthma prevalence as of 2018 in the United States was 8.9% (Zhou and Liu, 2020). Sex differences exist in asthma that differ by age, where asthma is more prevalent and experienced as worse disease in boys under 10 years of age but in girls at/after puberty and in adulthood (Flores et al., 2019; McCallister and Mastronarde, 2008; Skobeloff et al., 1992). Lung inflammation is a hallmark characteristic of asthma. Dendritic cells in the airway stimulated by antigens promote a T_H2 immune response featuring critical cytokines, including IL-4, IL-5, and IL-13, that promote recruitment of eosinophils, proliferation of mast cells, mucus buildup, and B cell class switching to immunoglobulin E (Burrows et al., 1989; Busse and Lemanske, 2001; Fujita et al., 2012; Gour and Wills-Karp, 2015; Holgate, 2008; Kips, 2001). Asthma has a distinct immunology that can lead to many outward symptoms, including bronchoconstriction, wheezing, and mucus production (Gordon, 2008). Such chronic immune activation and inflammatory symptoms experienced early in development can lead to perpetuating later-life health consequences.

Air pollution serves as a significant stressor for healthy living, can affect respiratory health, and is associated with elevations in cytokines and immune molecules. Individuals with greater exposure to air pollution demonstrated higher breath levels of TNF-α, leukotriene B_4, and nitrous oxide derivatives compared to those with lower exposure (Dauchet et al., 2018; Vossoughi et al., 2014). Air pollution exposure during early life was also associated with higher circulating IL-6 and IL-10 (Dauchet et al., 2018). Urban environments are detrimental for human health due to high exposure to air pollution among other health stressors, and as such, urbanization is a significant risk factor for asthma onset (e.g. odds ratio: 1.2, 95% CI: 1.04 to 1.5, $p = 0.01$) and worse asthma disease (Aligne et al., 2000; Beasley et al., 2015; Kurt et al., 2016; Theoharides et al., 2012; To et al., 2012). Interestingly, people living in urban environments are at greater odds to develop anxiety (21%) and mood disorders (39%) compared to people in rural environments (Peen et al., 2010). Thus, it is important to consider how external environmental factors like air pollution affect a person's asthma, immunology, and mental health.

One important downstream co-morbidity observed after having childhood asthma is later-life anxiety and/or depression, with onset as early as adolescence. A recent meta-analysis indicated anxiety disorders were prevalent in almost 23% of adolescents with asthma, as compared to 7–8% prevalence in the general youth population (Dudeney et al., 2017; Ghandour et al., 2019). Adolescents with asthma also had higher incidence and likelihood to develop major depression compared to controls (Chen et al., 2014). Other survey studies have indicated between 16.3 and 35% of participants met criteria for anxiety or depressive disorder diagnoses, and these conditions were more common in people with worse asthma symptoms (Katon et al., 2007; Richardson et al., 2006; Vila et al., 2000). Similar findings are indicated in rodent models of asthma, where mice or rats exposed to allergens later exhibited increased anxiety-like and depression-like behaviors (Caulfield et al., 2017, 2018;

Lewkowich et al., 2020; Tonelli et al., 2009). While research clearly shows a link between having asthma in early life and subsequent development of internalizing disorder symptoms, work has just begun to uncover potential driving mechanisms. A focus on this connection between asthma-related immunology and mental health would help fill this gap in the literature and help broaden the scope and depth of psychoneuroimmunology research.

3. Preclinical models of asthma

Recent preclinical studies have begun to investigate broad mechanisms underlying the connection between asthma and anxiety. In one model, inflammation and bronchoconstriction were independently induced with chronic house dust mite (HDM) and methacholine (MCH) exposure, respectively, during development (Caulfield et al., 2017, 2018, 2021b). HDM exposure stimulated increased expression of genes associated with an acute inflammatory response (e.g. increases in IL-5, IL-1β mRNA). Increased airway inflammation, mucus, and T_H2 cytokine gene expression were also observed in adulthood three months after the end of HDM exposure, indicating a long-term inflammatory effect. Mice exposed to HDM demonstrated depressive-like behaviors three months after exposures ceased, demonstrating a lasting effect on mental health paired with the persistent airway inflammation (Caulfield et al., 2017, 2018, 2021b). After chronic exposure to MCH throughout development, mice demonstrated increased anxiety-like behaviors and increased corticosteroid production in adulthood, along with decreased brainstem serotonin transporter expression, increased hippocampal corticotropin releasing hormone (CRH) receptor 1 (Crhr1), and elevated hippocampal serotonin receptor 1a expression (Caulfield et al., 2017). Further, marginal increases in hippocampal microglial activation were observed in early adulthood following chronic MCH exposure (Caulfield et al., 2021b). Together, these results reveal that central nervous system changes, specifically related to serotonin- and CRH-signaling pathways, are implicated in the relationship between different asthma and internalizing disorder symptoms.

In another rodent study on broad immune effects related to post-traumatic stress disorder and panic disorder, adult male mice exposed to HDM did not show anxiety-like or depression-like behavior (elevated zero maze and forced swim test, respectively). However, exposure to HDM did produce increased freezing behavior in a contextual fear paradigm, global brain increases in IL-17 A-secreting cells, and elevated neuronal activation in emotion-associated brain regions (prefrontal cortex and basolateral amygdala) (Lewkowich et al., 2020). Another rodent study indicated that re-exposure to ovalbumin (OVA) caused increased anxiety-like behaviors in mice as well as increased activity in and greater activation of microglia and astrocytes in the amygdala and medial prefrontal cortex (Dehdar et al., 2019). Together, these findings indicate that peripheral immune challenges to stimulate allergic asthma symptoms also alter prefrontal cortex, hippocampus, and amygdala activity and immune cell activity in the brain. These are all potential pathways that may influence symptoms associated with anxiety and depression and set the stage for further investigation into underlying mechanisms.

Other preclinical research has been conducted to identify behavioral and brain changes associated with asthma therapy. Inhaled corticosteroids, a common class of medications for asthma, are used to control lung inflammation by reducing immune cells in the airway and preventing cytokine production and other factors that enhance inflammation (Barnes, 2010, 2017; Crim et al., 2001; Hossny et al., 2016). The two most common corticosteroids used are fluticasone propionate (FLU) and budesonide. In one study, mice were chronically exposed to HDM and FLU during development – a period that is analogous to when asthma is most prevalent in humans. FLU exposure led to reduced weight gain during development, elevated basal glucocorticoid concentrations in circulation, and reduced anxiety-like behavior in adulthood. Additionally, HPA function-associated gene expression in the hippocampus (CRH, Crhr1, and CRH receptor 2), circulating corticosterone, and anxiety-like behavior were associated with one another (Caulfield et al., 2021a). Another study, which utilized OVA and budesonide in adolescent female mice, demonstrated that OVA exposure increased anxiety-like behavior, decreased dendritic length and number of spines on hippocampal pyramidal cells, and increased hippocampal BDNF expression. Budesonide reversed some anxiety-like behaviors and the number of dendritic spines, but it did not affect dendrite length in hippocampal neurons or BDNF expression (Zhuang et al., 2018). Overall, animal studies suggest that corticosteroid treatment during development may alleviate anxiety-related behavioral symptoms associated with allergic asthma but not associated hippocampal function. In humans, worse anxiety and depression symptoms have been reported in clinical asthma patients who are corticosteroid dependent, and asthma patients with depression suffer from worse asthma symptoms and increased emergency room visits (Ahmedani et al., 2013; Amelink et al., 2014). A better understanding of how inhaled corticosteroids affect mental health pathways in asthma could inform novel clinical therapies for patients that exhibit asthma and develop comorbid internalizing disorders.

4. Preclinical models of air pollution

Some rodent studies have investigated airway inflammation in the context of air pollution and its relation to anxiety and depression-like behaviors, and the results are informative and represent real-world human experiences. One study investigated the effects of exposure to traffic-related particulate matter in utero and during early development in male rat pups. Rats exposed to pollution particulates had decreased circulating IL-18 and vascular endothelial growth factor, increased anxiety-like behavior, and less developed neurons in the anterior cingulate and hippocampus (Nephew et al., 2020). Another study chronically exposed male mice to particulate matter for nine months beginning in adolescence, which resulted in increased depressive-like behaviors in the forced swim test and increased anxiety-like behavior on the open field test. Mice exposed to this particulate matter also demonstrated increased pro-inflammatory cytokine expression (TNF-α, IL-1β) and decreased neuronal spine density in the hippocampus (Fonken et al., 2011). Thus, these results provide further evidence toward the importance of understanding long-term effects of chronic immune activation on mental health measures. Research on young male and female mice aimed to determine how maternal stress and prenatal exposure to diesel exhaust pollution would affect mental health-related outcomes in the offspring. Male and female offspring differentially regulated IL-10 expression in the brain in utero (embryonic day 18), and only males exposed to pollution exhibited increased IL-1β in the brain in adulthood. Stress and pollution exposure together resulted in a synergistic increase in Tlr4 gene expression in the brain at postnatal day 30 and increased anxiety-like behavior in adulthood (Bolton et al., 2013). Thus, exposure to air pollution as an immune stressor can affect the brain and mental health-related outcomes, suggesting possible mechanisms to further explore to better understand how such immune challenges are driving behavior.

5. Clinical asthma and mental health connections

Clinical research on asthma patients has established a significant comorbidity with mental health conditions, especially in younger populations (Dudeney et al., 2017; Peters and Fritz, 2011). In recent years, studies have investigated brain areas that may play a mechanistic role in asthma and internalizing disorder comorbidity in humans using magnetic resonance imaging (MRI). For example, patients with asthma demonstrated abnormal structural connectivity in the bilateral frontal gyri, right-side temporal and parietal cortices, and limbic regions compared to healthy controls, suggesting altered emotion-related brain area function in patients with asthma (Gao et al., 2019). Activity in emotion-processing brain circuits (e.g. anterior insula) has also been associated with increased inflammation in asthma (Rosenkranz et al., 2012). In one

study, patients with asthma were assessed to have high or low chronic life stress. Following the Trier Social Stress Test, those with low stress had increased glucose metabolism in the anterior insula and decreased glucose metabolism in the mid-cingulate cortex and higher levels of airway inflammation as measured by fraction of exhaled nitric oxide (FeNO) compared to high-stress patients. Additionally, worse asthma control was associated with worse internalizing disorder symptoms (anxiety and depression). Expression of IL-17 pathway cytokines in sputum may serve as markers for the relationship between psychological stress and asthma-related inflammation (Rosenkranz et al., 2016). In patients with asthma, smaller volume of pallidum was associated with increased anxiety in response to a stressor, whereas in controls the anxiety responses were associated with hippocampus and amygdala volume, suggesting that different regions are involved in anxiety pathology in asthma (Ritz et al., 2020). Further, among participants with asthma, those with depression demonstrated decreased homogeneity in the pallidum compared to that of participants without depression, and this was associated with worse and unusual asthma symptoms (Xiong et al., 2016). Together, these findings implicate critical limbic and emotion-related brain areas in the pathology of asthma that may serve as links to internalizing disorders. These studies suggest that these brain regions should be an area of focus for further research on asthma and mental health comorbidity. In addition, these areas could be targeted for improved treatment to prevent internalizing disorder development in people with asthma.

6. Conclusions and future directions

To better understand how different aspects of immunology are associated with mental health outcomes, utilizing preclinical models is vital and can allow for a more controlled setting to understand disease processes and highlight translational relevance to real-world conditions. These studies can inform clinical research by pointing to specific brain regions and pathways that may be the most important biological mechanisms underlying asthma-mental health comorbidity. Knowledge of underlying mechanisms will help optimize development of targeted therapies. Preclinical and clinical evidence suggests that asthma is associated with development of internalizing disorder symptoms, and broad pathways have been described that should be further investigated to elucidate specific mechanisms driving these connections. The future of psychoneuroimmunology can benefit from embracing these lines of study, highlighting relationships and uncovering mechanisms connecting mental health and chronic immune activation. Preclinical models are translationally relevant to the clinical world. Treatments can be designed that target specific immunological challenges and dysregulation. Further, once neural pathways are identified, specific treatments can be developed that may alleviate both asthma and internalizing disorder symptoms, potentially allowing for decreased rates of internalizing disorders and symptom development in these asthma patients. Finally, we must recognize that many health conditions do not present the same way in both males and females, and with this understanding, we can approach future research where both sexes are accounted for and that studies are designed with the power to examine sex differences in all analyses for the best clinical success.

Conflict of interest statement

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References

Ahmedani, B.K., Peterson, E.L., Wells, K.E., Williams, L.K., 2013. Examining the relationship between depression and asthma exacerbations in a prospective follow-up study. Psychosom. Med. 75, 305–310. https://doi.org/10.1097/PSY.0b013e3182864ee3. Examining.

Akinbami, L.J., Moorman, J.E., Bailey, C., Zahran, H.S., King, M., Johnson, C.A., Liu, X., 2012. Trends in asthm a prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 94, 1–8.

Akinbami, L.J., Simon, A.E., Rossen, L.M., 2016. Changing trends in asthma prevalence among children. Pediatrics 137, e20152354. https://doi.org/10.1542/peds.2015-2354.

Aligne, A.C., Auinger, P., Byrd, R.S., Weitzman, M., 2000. Risk factors for pediatric asthma. Am. J. Respir. Crit. Care Med. 162, 873–877. https://doi.org/10.1164/ajrccm.162.3.9908085.

Altemus, M., 2006. Sex differences in depression and anxiety disorders: potential biological determinants. Horm. Behav. 50, 534–538. https://doi.org/10.1016/j.yhbeh.2006.06.031.

Amelink, M., Hashimoto, S., Spinhoven, P., Pasma, H.R., Sterk, P.J., Bel, E.H., Ten Brinke, A., 2014. Anxiety, depression and personality traits in severe, prednisone-dependent asthma. Respir. Med. 108, 438–444. https://doi.org/10.1016/j.rmed.2013.12.012.

Arad, M., Piontkewitz, Y., Albelda, N., Shaashua, L., Weiner, I., 2017. Immune activation in lactating dams alters sucklings' brain cytokines and produces non-overlapping behavioral deficits in adult female and male offspring: a novel neurodevelopmental model of sex-specific psychopathology. Brain Behav. Immun. 63, 35–49. https://doi.org/10.1016/j.bbi.2017.01.015.

Barnes, P.J., 2017. Cellular and molecular mechanisms of asthma and COPD. Clin. Sci. 131, 1541–1558. https://doi.org/10.1042/CS20160487.

Barnes, P.J., 2010. Inhaled corticosteroids. Pharmaceuticals 3, 514–540. https://doi.org/10.3390/ph3030514.

Beasley, R., Semprini, A., Mitchell, E.A., 2015. Risk factors for asthma: is prevention possible? Lancet 386, 1075–1085. https://doi.org/10.1016/S0140-6736(15)00156-7.

Bolton, J.L., Huff, N.C., Smith, S.H., Mason, S.N., Foster, W.M., Auten, R.L., Bilbo, S.D., 2013. Maternal stress and effects of prenatal air pollution on offspring mental health outcomes in mice. Environ. Health Perspect. 121, 1075–1082. https://doi.org/10.1289/ehp.1306560.

Brites, D., Fernandes, A., 2015. Neuroinflammation and depression: microglia activation, extracellular microvesicles and microRNA dysregulation. Front. Cell. Neurosci. 9, 476. https://doi.org/10.3389/fncel.2015.00476.

Burrows, B., Martinez, F.D., Halonen, M., Barbee, R.A., Cline, M.G., 1989. Association of asthma with serum IgE levels and skin-test reactivity to allergens N 320, 271–277.

Busse, W.W., Lemanske, R.F., 2001. Asthma. N. Engl. J. Med. 344, 350–362.

Capuron, L., Miller, A.H., 2011. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol. Ther. 130, 226–238. https://doi.org/10.1016/j.pharmthera.2011.01.014.

Caulfield, J.I., Caruso, M.J., Bourne, R.A., Chirichella, N.R., Klein, L.C., Craig, T., Bonneau, R.H., August, A., Cavigelli, S.A., 2018. Asthma induction during development and adult lung function, behavior and brain gene expression. Front. Behav. Neurosci. 12, 188. https://doi.org/10.3389/fnbeh.2018.00188.

Caulfield, J.I., Caruso, M.J., Michael, K.C., Bourne, R.A., Chirichella, N.R., Klein, L.C., Craig, T., Bonneau, R.H., August, A., Cavigelli, S.A., 2017. Peri-adolescent asthma symptoms cause adult anxiety-related behavior and neurobiological processes in mice. Behav. Brain Res. 326, 244–255. https://doi.org/10.1016/j.bbr.2017.02.046.

Caulfield, J.I., Ching, A.M., Cover, E.M., August, A., Craig, T., Kamens, H.M., Cavigelli, S.A., 2021a. Inhaled corticosteroids as treatment for adolescent asthma: effects on adult anxiety-related outcomes in a murine model. Psychopharmacology (Berlin) 238, 165–179. https://doi.org/10.1007/s00213-020-05666-x.

Caulfield, J.I., Schopf, K.J., Cavigelli, S.A., 2021b. Peri-adolescent asthma: acute impacts on innate immune response, corticosterone, and microglia in mice. J. Neuroimmunol. 350, 577450. https://doi.org/10.1016/j.jneuroim.2020.577450.

Cavigelli, S.A., Bao, A.D., Bourne, R.A., Caruso, M.J., Caulfield, J.I., Chen, M., Smyth, J.M., 2018. Timing matters: the interval between acute stressors withing chronic mild stress modifies behavioral and physiologic stress responses in male rats. Stress 21, 453–463. https://doi.org/10.1080/10253890.2018.1459557.Timing.

Chen, M.H., Su, T.P., Chen, Y.S., Hsu, J.W., Huang, K.L., Chang, W.H., Chen, T.J., Bai, Y.M., 2014. Higher risk of developing major depression and bipolar disorder in later life among adolescents with asthma: a nationwide prospective study. J. Psychiatr. Res. 49, 25–30. https://doi.org/10.1016/j.jpsychires.2013.10.015.

Costello, E.J., Mustillo, S., Erkanli, A., Keeler, G., Angold, A., 2003. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch. Gen. Psychiatr. 60, 837–844. https://doi.org/10.1001/archpsyc.60.8.837.

Costello, H., Gould, R.L., Abrol, E., Howard, R., 2019. Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and

generalised anxiety disorder. BMJ Open 9, e027925. https://doi.org/10.1136/bmjopen-2018-027925.
Crim, C., Pierre, L.N., Daley-Yates, P.T., 2001. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. Clin. Therapeut. 23, 1339–1354. https://doi.org/10.1016/S0149-2918(01)80113-2.
Dauchet, L., Hulo, S., Cherot-Kornobis, N., Matran, R., Amouyel, P., Edmé, J.L., Giovannelli, J., 2018. Short-term exposure to air pollution: associations with lung function and inflammatory markers in non-smoking, healthy adults. Environ. Int. 121, 610–619. https://doi.org/10.1016/j.envint.2018.09.036.
Dehdar, K., Mahdidoust, S., Salimi, M., Gholami-Mahtaj, L., Nazari, M., Mohammadi, S., Dehghan, S., Jamaati, H., Khosrowabadi, R., Nasiraei-Moghaddam, A., Barkley, V., Javan, M., Mirnajafi-Zadeh, J., Sumiyoshi, A., Raoufy, M.R., 2019. Allergen-induced anxiety-like behavior is associated with disruption of medial prefrontal cortex - amygdala circuit. Sci. Rep. 9, 1–13. https://doi.org/10.1038/s41598-019-55539-3.
Dudeney, J., Sharpe, L., Jaffe, A., Jones, E.B., Hunt, C., 2017. Anxiety in youth with asthma: a meta-analysis. Pediatr. Pulmonol. 9999, 1–9. https://doi.org/10.1002/ppul.23689.
Flores, K.F., Bandoli, G., Chambers, C.D., Schatz, M., Palmsten, K., 2019. Asthma prevalence among women aged 18 to 44 in the United States: national health and nutrition examination survey 2001–2016. J. Asthma 1–10. https://doi.org/10.1080/02770903.2019.1602874, 0.
Fonken, L.K., Xu, X., Weil, Z.M., Chen, G., Sun, Q., Rajagopalan, S., Nelson, R.J., 2011. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol. Psychiatr. 16, 987–995. https://doi.org/10.1038/mp.2011.76.
Fujita, H., Soyka, M.B., Akdis, M., Akdis, C.A., 2012. Mechanisms of allergen-specific immunotherapy. Clin. Transl. Allergy 2, 1–8.
Gabbay, V., Klein, R.G., Alonso, C.M., Babb, J.S., Nishawala, M., De Jesus, G., Hirsch, G.S., Hottinger-Blanc, P.M.Z., Gonzalez, C.J., 2009. Immune system dysregulation in adolescent major depressive disorder. J. Affect. Disord. 115, 177–182. https://doi.org/10.1016/j.jad.2008.07.022.
Gao, X., Xiao, Y., Lv, P., Zhang, W., Gong, Y., Wang, T., Gong, Q., Ji, Y., Lui, S., 2019. Altered brain network integrity in patients with asthma: a structural connectomic diffusion tensor imaging study. Respir. Physiol. Neurobiol. 266, 89–94. https://doi.org/10.1016/j.resp.2019.05.004.
Ghandour, R.M., Sherman, L.J., Vladutiu, C.J., Ali, M.M., Lynch, S.E., Bitsko, R.H., Blumberg, S.J., 2019. Prevalence and treatment of depression, anxiety, and conduct problems in US children. J. Pediatr. 206, 256–267. https://doi.org/10.1016/j.jpeds.2018.09.021.
Gibb, J., Hayley, S., Poulter, M.O., Anisman, H., 2011. Effects of stressors and immune activating agents on peripheral and central cytokines in mouse strains that differ in stressor responsivity. Brain Behav. Immun. 25, 468–482. https://doi.org/10.1016/j.bbi.2010.11.008.
Gibney, S.M., McGuinness, B., Prendergast, C., Harkin, A., Connor, T.J., 2013. Poly I: C-induced activation of the immune response is accompanied by depression and anxiety-like behaviours, kynurenine pathway activation and reduced BDNF expression. Brain Behav. Immun. 28, 170–181. https://doi.org/10.1016/j.bbi.2012.11.010.
Gordon, B.R., 2008. Asthma history and presentation. Otolaryngol. Clin. 41, 375–385. https://doi.org/10.1016/j.otc.2007.11.007.
Gour, N., Wills-Karp, M., 2015. IL-4 and IL-13 signaling in allergic airway disease. Cytokine 75, 68–78. https://doi.org/10.1016/j.cyto.2015.05.014.
Henry, C.J., Huang, Y., Wynne, A., Hanke, M., Himler, J., Bailey, M.T., Sheridan, J.F., Godbout, J.P., 2008. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. J. Neuroinflammation 5, 15. https://doi.org/10.1186/1742-2094-5-15.
Holgate, S.T., 2008. Pathogenesis of asthma. Clin. Exp. Allergy 38, 872–897. https://doi.org/10.1111/j.1365-2222.2008.02971.x.
Hossny, E., Rosario, N., Lee, B.W., Singh, M., El-ghoneimy, D., Soh, J.Y., Souef, P. Le, 2016. The use of inhaled corticosteroids in pediatric asthma : update. World Allergy Organ. J. 9, 26. https://doi.org/10.1186/s40413-016-0117-0.
Jalnapurkar, I., Allen, M., Pigott, T., 2018. Sex differences in anxiety disorders: a review. J Psychiatr Depress Anxiety 4. https://doi.org/10.24966/pda-0150/100012, 012.
Katon, W., Lozano, P., Russo, J., McCauley, E., Richardson, L., Bush, T., 2007. The Prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls. J. Adolesc. Health 41, 455–463. https://doi.org/10.1016/j.jadohealth.2007.05.023.
Kessler, R.C., Angermeyer, M., Anthony, J.C., de Graff, R., Demyttenaere, K., Gasquet, I., De Girolamo, G., Gluzman, S., Gureje, O., Haro, J.M., Kawakami, N., Karam, A., Levinson, D., Mora, M.E.Medina, Oakley Browne, M.A., Posada-Villa, J., Stein, D.J., Adley Tsang, C.H., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Heeringa, S., Pennell, B.-E., Berglund, P., Gruber, M.J., Petukhova, M., Chatterji, S., Ustun, T.B., 2007. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's world mental health survey initiative. World Psychiatr. 6, 168–176.
Kips, J.C., 2001. Cytokines in asthma. Eur. Respir. J. 18, 24s–33s. https://doi.org/10.1183/09031936.01.00229601.
Kurt, O.K., Zhang, J., Pinkerton, K.E., 2016. Pulmonary health effects of air pollution. Curr. Opin. Pulm. Med. 22, 138–143. https://doi.org/10.1097/MCP.0000000000000248. Pulmonary.
Lewkowich, I., Ahlbrand, R., Johnson, E., McAlees, J., Nawreen, N., Raman, R., Lingel, I., Hargis, J., Hoover, C., Sah, R., 2020. Modulation of fear behavior and neuroimmune alterations in house dust mite exposed A/J mice, a model of severe asthma. Brain Behav. Immun. 88, 688–698. https://doi.org/10.1016/j.bbi.2020.04.084.
Mattiuzzi, C., Lippi, G., 2020. Worldwide asthma epidemiology: insights from the global health data exchange database. Int. Forum Allergy Rhinol. 10, 75–80. https://doi.org/10.1002/alr.22464.
McCallister, J.W., Mastronarde, J.G., 2008. Sex differences in asthma. J. Asthma 45, 853–861. https://doi.org/10.1080/02770900802444187.
McEwen, B.S., Eiland, L., Hunter, R.G., Miller, M.M., 2012. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology 62, 3–12. https://doi.org/10.1016/j.neuropharm.2011.07.014.
Mitchell, R.H.B., Goldstein, B.I., 2014. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. J. Am. Acad. Child Adolesc. Psychiatry 53, 274–296. https://doi.org/10.1016/j.jaac.2013.11.013.
Nephew, B.C., Nemeth, A., Hudda, N., Beamer, G., Mann, P., Petitto, J., Cali, R., Febo, M., Kulkarni, P., Poirier, G., King, J., Durant, J.L., Brugge, D., 2020. Traffic-related particulate matter affects behavior, inflammation, and neural integrity in a developmental rodent model. Environ. Res. 183. https://doi.org/10.1016/j.envres.2020.109242.
NIH Mental Health Information: Statistics, 2021. National Institutes of Mental Health.
Pandey, G.N., Rizavi, H.S., Ren, X., Fareed, J., Hoppensteadt, D.A., Roberts, R.C., Conley, R.R., Dwivedi, Y., 2012. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. J. Psychiatr. Res. 46, 57–63. https://doi.org/10.1016/j.jpsychires.2011.08.006.
Peen, J., Schoevers, R.A., Beekman, A.T., Dekker, J., 2010. The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr. Scand. 121, 84–93. https://doi.org/10.1111/j.1600-0447.2009.01438.x.
Peters, T.E., Fritz, G.K., 2011. Psychological considerations of the child with asthma. Pediatr. Clin. 58, 921–935. https://doi.org/10.1016/j.pcl.2011.06.006.
Richardson, L.P., Lozano, P., Russo, J., McCauley, E., Bush, T., Katon, W., 2006. Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. Pediatrics 118, 1042–1051. https://doi.org/10.1542/peds.2006-0249.
Rieder, R., Wisniewski, P.J., Alderman, B.L., Campbell, S.C., 2017. Microbes and mental health: a review. Brain Behav. Immun. 66, 9–17. https://doi.org/10.1016/j.bbi.2017.01.016.
Ritz, T., Kroll, J.L., Aslan, S., Janssens, T., Khan, D.A., Pinkham, A.E., Brown, E.S., 2020. Subcortical gray matter volumes in asthma: associations with asthma duration, control, and anxiety. Brain Imaging Behav 14, 2341–2350. https://doi.org/10.1007/s11682-019-00188-3.
Rosenkranz, M.A., Busse, W.W., Sheridan, J.F., Crisafi, G.M., Davidson, R.J., 2012. Are there neurophenotypes for asthma? functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS One 7, e40921. https://doi.org/10.1371/journal.pone.0040921.
Rosenkranz, M.A., Esnault, S., Christian, B.T., Crisafi, G., Gresham, L.K., Higgins, A.T., Moore, M.N., Moore, S.M., Weng, H.Y., Salk, R.H., Busse, W.W., Davidson, R.J., 2016. Mind-body interactions in the regulation of airway inflammation in asthma: a PET study of acute and chronic stress. Brain Behav. Immun. 58, 18–30. https://doi.org/10.1016/j.bbi.2016.03.024.
Schwarz, J.M., Bilbo, S.D., 2012. Sex, glia, and development: interactions in health and disease. Horm. Behav. 62, 243–253. https://doi.org/10.1016/j.yhbeh.2012.02.018.
Skobeloff, E.M., Spivey, W.H., Clair S S, St, Schoffstall, J.M., 1992. The influence of age and sex on asthma admissions. J. Am. Med. Assoc. 268, 3437–3440.
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24, 417–463. https://doi.org/10.1016/S0149-7634(00)00014-2.
Stein, D.J., Vasconcelos, M.F., Albrechet-Souza, L., Ceresér, K.M.M., De Almeida, R.M.M., 2017. Microglial over-activation by social defeat stress contributes to anxiety-and depressive-like behaviors. Front. Behav. Neurosci. 11, 207. https://doi.org/10.3389/fnbeh.2017.00207.
Strine, T.W., Mokdad, A.H., Balluz, L.S., Gonzalez, O., Crider, R., Berry, J.T., Kroenke, K., 2008. Depression and anxiety in the United States: findings from the 2006 behavioral risk factor surveillance system. Psychiatr. Serv. 59, 1383–1390.
Theoharides, T.C., Enakuaa, S., Sismanopoulos, N., Asadi, S., Papadimas, E.C., Angelidou, A., Alysandratos, K.D., 2012. Contribution of stress to asthma worsening through mast cell activation. Ann. Allergy Asthma Immunol. 109, 14–19. https://doi.org/10.1016/j.anai.2012.03.003.
To, T., Sanja, S., Moores, G., Gershon, A.S., Bateman, E.D., Cruz, A.A., Boulet, L.-P., 2012. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Publ. Health 12, 204.
Tonelli, L.H., Katz, M., Kovacsics, C.E., Gould, T.D., Joppy, B., Hoshino, A., Hoffman, G., Komarow, H., Postolache, T.T., 2009. Allergic rhinitis induces anxiety-like behavior and altered social interaction in rodents. Brain Behav. Immun. 23, 784–793.
Vila, G., Nollet-Clemençon, C., De Blic, J., Mouren-Simeoni, M.C., Scheinmann, P., 2000. Prevalence of DSM IV anxiety and affective disorders in a pediatric population of asthmatic children and adolescents. J. Affect. Disord. 58, 223–231. https://doi.org/10.1016/S0165-0327(99)00110-X.
Vossoughi, M., Schikowski, T., Vierkötter, A., Sugiri, D., Hoffmann, B., Teichert, T., Herder, C., Schulte, T., Luckhaus, C., Raulf-Heimsoth, M., Casjens, S., Brüning, T., Krämer, U., 2014. Air pollution and subclinical airway inflammation in the SALIA cohort study. Immun. Ageing 11, 5. https://doi.org/10.1186/1742-4933-11-5.
Wilner, C.J., Gatzke-Kopp, L.M., Bray, B.C., 2016. The dynamics of internalizing and externalizing comorbidity across the early school years. Dev. Psychopathol. 28, 1033–1052. https://doi.org/10.1017/S0954579416000687.
Wohleb, E.S., Fenn, A.M., Pacenta, A.M., Powell, N.D., Sheridan, J.F., Godbout, J.P., 2012. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social

withdrawal in socially defeated mice. Psychoneuroendocrinology 37, 1491–1505. https://doi.org/10.1016/j.psyneuen.2012.02.003.

Xiong, X., Zhu, H., Wang, T., Ji, Y., 2016. Altered intrinsic regional brain activity in female asthmatics with or without depressive symptoms: a resting-state functional magnetic resonance imaging study. J. Asthma 53, 922–929. https://doi.org/10.3109/02770903.2016.1161050.

Zhou, Y., Liu, Y., 2020. Recent trends in current asthma prevalence among US adults, 2009-2018. J. Allergy Clin. Immunol. Pract. 8, 2814–2816. https://doi.org/10.1016/j.jaip.2020.04.041.

Zhuang, T.T., Pan, C., Chen, J.J., Han, F., Zhu, X.L., Xu, H., Lu, Y.P., 2018. Chronic asthma-induced behavioral and hippocampal neuronal morphological changes are concurrent with BDNF, cofilin1 and Cdc42/RhoA alterations in immature mice. Brain Res. Bull. 143, 194–206. https://doi.org/10.1016/j.brainresbull.2018.09.006.