Title Page

**Exposure to Violence, Psychosocial Stress, and Asthma**

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**Abstract**

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University of Pittsburgh, 2020

**Abstract**

Over the last two decades, a growing body of evidence has linked chronic psychosocial stress to asthma. Exposure to violence can lead to chronic stress and has received recent attention in the asthma literature, as is a common exposure for people living in urban settings, particularly in the U.S. Improving our understanding of whether and how exposure to chronic stressors causes or worsens asthma could help us gain insights into disease pathogenesis, design public health policies, and develop new interventions. In this essay, the evidence linking violence or stress to asthma is explored, including recent insights on potential mechanisms, and a discussion on current challenges and future directions. To date, experimental and observational studies support a causal association between chronic stress and worse asthma control, and increasing evidence suggests that pre- or post-natal chronic stress may lead to new-onset asthma. Such evidence supports conducting randomized controlled trials of stress-reduction interventions to improve asthma control in subjects with high chronic stress. On the other hand, more experimental and longitudinal studies are needed to better understand if violence exposure leads to asthma or worse asthma outcomes. Longitudinal studies with assessment of co-exposures and coping mechanisms are key to not only better understand the independent effects of violence or stress on asthma but also to identify factors that could ameliorate or worsen such effects.

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Preface

I would like to express my most sincere gratitude to all the faculty members of the Pediatric Pulmonology Department at UPMC Children’s Hospital of Pittsburgh, for sharing their unique talents with me an shaping me during my fellowship training.

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# Introduction

Asthma is a major public health problem, affecting approximately 235 million people worldwide (1). In the United States (U.S.), the 2016 National Health Interview Survey (NHIS) estimated the overall prevalence of current asthma as 8.3% in adults and 8.3% in children (2).

In the U.S., certain ethnic minority groups -such as Puerto Ricans and African Americans- are both heavily affected by asthma and frequently exposed to chronic psychosocial stressors such as violence, poverty, and discrimination (3–5). Moreover, stress-related disorders such as post-traumatic stress disorder (PTSD) are common in certain minority groups at risk for asthma (6,7). For example, Puerto Rican veterans of the Vietnam War were shown to be at greater risk of PTSD and to have more severe PTSD symptoms than non-Hispanic white Vietnam veterans (7).

Over the last two decades, an expanding body of evidence has linked chronic psychosocial stress to asthma or morbidity from asthma in children and adults (**Figure 1**) (3–5,8–16). Much of this research has focused on exposure to violence and related stressors such as poverty, though of late studies are considering a broader array of adversities such as racial or ethnic discrimination (4). Alongside these advances, experimental and population-based studies have yielded novel insights into the potential pathways underlying these connections, such as stress-related changes in epigenetic processes, gene expression, and immune responses (17). Such studies have also begun to examine complex interactions between stressors and other risk factors for asthma, including outdoor air pollution (14,15,18–21), diet and obesity (22–24).

Improving our understanding of whether and how exposure to chronic stressors causes or worsens asthma could help us gain novel insights into disease pathogenesis, design and support public health policies, and develop new interventions. In this review, we assess the evidence linking stress and asthma, describe recent insights on potential mechanisms, and discuss challenges and future directions in this field. We begin by considering the evidence for violence, because it has been the subject of much recent attention in the asthma literature (25,26), and is a common exposure of significant public health concern.

# Violence and Asthma

Children and adults can be exposed to violence in their households, workplaces, and neighborhoods. In some of the most common exposures to violence, a family member is the perpetrator, e.g., child maltreatment, intra-partner violence, but physical and sexual assaults can also be committed by friends, colleagues, acquaintances, and strangers. Besides these direct exposures to victimization, it is also important to consider instances where people are indirectly exposed to violence, e.g., an individual hears about the victimization of someone close to them, or a victimization that has occurred in their neighborhood. For example, studies indicate that living in a neighborhood with high murder rates is associated with worse cardiometabolic health, even after accounting for personal victimization and potential confounders such as race or ethnicity, financial security or availability of nutritious food (27). Recent observational studies have shown that exposure to different types of violence may lead to new onset asthma or worsen asthma in affected individuals (3,14–16,28–42). We summarize this evidence below, according to lifespan stage and type of exposure.

Preliminary evidence supports an association between maternal exposure to violence during pregnancy and childhood asthma. In a study of 787 mother-child pairs of predominantly Hispanic or African American ethnicity, prenatal exposure to community violence was associated with nearly twofold increased odds of current wheeze at age 2 years, even after accounting for outdoor pollutants, cockroach allergen levels, and other potential confounders (14). In this cohort, a separate analysis (unadjusted for pollutants) showed that chronic maternal interpersonal trauma (IPT), defined as exposure to IPT during childhood or adolescence and adulthood was significantly associated with childhood asthma at age 6 years. After stratification by sex, this association was significant in boys but not in girls (28). In that study, a path analysis further showed that chronic maternal IPT was significantly associated with maternal active asthma during pregnancy, and that ~12% of the estimated effect of chronic maternal IPT on childhood asthma was mediated or explained by maternal active asthma during pregnancy.

Post-natal exposure to violence or traumatic experiences has been linked to asthma at various life stages. At the individual level, a large cross-sectional study of adults in the Americas and Asia found that childhood adversities were associated with adult-onset asthma in a dose-response fashion (29). In that study, early-onset depressive or anxiety disorders were also associated with asthma. Consistent with these findings, childhood abuse -a severe type of adversity- has been associated with asthma in children and young adults. For example, a case-control study of Puerto Rican children reported that a history of physical or sexual abuse in the previous year was associated with asthma, healthcare utilization for asthma, and use of asthma medications, even after accounting for household income, health insurance, and other confounders (30). Physical abuse during childhood was subsequently linked to asthma in a prospective study of African American women (31). Similar results for childhood abuse and asthma were reported in a cross-sectional study of young adults in New Zealand (32), in a large prospective study of Australian children followed from birth until age 21 years (33), and in Puerto Rican children exposed to violence (34). Consistent with findings for childhood abuse, a cross-sectional study of U.S. women with current asthma showed that women who were victims of sexual violence (unwanted touching, attempted unwanted intercourse or forced unwanted intercourse) were twice as likely to report an asthma attack in the previous year as those not victimized (35).

Exposure to violence in the household has been linked to asthma (36). Among 2,013 children who participated in the Fragile Families and Child Wellbeing Study, maternal report of chronic exposure to intimate partner violence (IPV) and having experienced house disarray were each associated with childhood asthma (15). In that study, children whose mothers had a history of IPV and had experienced house disarray were at highest risk of asthma. In another study that collected data on maternal exposure to IPV and salivary cortisol in children from ages 7 to 48 months, children whose mothers experienced IPV and who had increased cortisol levels at ages 7 and 15 months had increased odds of report of physician-diagnosed asthma at age 4 years (37), suggesting that children who are physiologically reactive are particularly vulnerable to the detrimental effects of household violence on asthma.

Community violence has been implicated in asthma. In a longitudinal study of 2,071 children in Chicago, medium and high levels of community violence were associated with 1.6 times increased odds of report of physician diagnosed-asthma, even after accounting for potential confounders at the individual or neighborhood level (3). However, there was no adjustment for indoor or outdoor pollutants, which often co-localize with neighborhood violence, and thus could be the agent driving these associations. Similar results were obtained in a cross-sectional study of 1,232 parents (or guardians) in Salvador (Brazil) where wheezing in the prior year was more common in children exposed to violence in the community than in those unexposed (38). In that study, children exposed to high levels of violence were also nearly twice as likely to have asthma symptoms as those who were unexposed. In another cross sectional study of 92,486 Indian households, women who experienced domestic violence had increased odds of self-reported asthma, and all individuals living in those women’s households were also at increased risk of reported asthma (39).

Other studies have used neighborhood crime rates, instead of participant reports of exposure, to characterize levels of community violence. These crimes rates capture both personal victimization and indirect exposures to violence. In a retrospective study of 4,638 asthma-related emergency department (ED) visits and hospitalizations in Cincinnati, both census-level violent crime rates (VCR, r=0.61) and census-level all-crime rates (ACR, r=0.54) were correlated with asthma utilization rates (16). After adjustment for census-tract poverty, unemployment, and substandard housing, VCR -but not ACR- remained associated with higher asthma utilization rates. Moreover, VCR explained ~35% of the population-level variability in asthma utilization rates. Similar findings were obtained in a cross-sectional study in Chicago, where living in a neighborhood with high violent criminal activity was significantly associated with higher prevalence of caregiver reported childhood asthma compared to neighborhoods with lower criminal activity, even after adjusting for individual and sociodemographic characteristics (40).

In a related study that addressed direct exposure, lifetime gun violence (defined as having heard a gunshot more than once) was associated with 1.8 times increased odds of report of physician-diagnosed asthma in 466 Puerto Rican children, (41). Of interest, the estimated effect of gun violence on asthma was even stronger among children who were both exposed to gun violence and afraid to leave their home due to violence. A subsequent analysis of the same cohort of Puerto Rican children reported that global African ancestry (measured using genetic markers) interacted with gun violence to further increase asthma risk (42).

# Stress and Asthma

A growing body of evidence supports a link between other chronic stressors and asthma risks at both the pre- and post-natal stages (17). Prenatal stress may increase the risk of childhood wheeze or asthma, through mechanisms including altered Th1/Th2 cytokine balance with persistent Th2 immune responses in early life (43), changes in DNA methylation and/or gene expression, abnormal regulation of neuroendocrine or neurotransmitter receptor interactions (44), altered glucocorticoid receptors in the fetus with postnatal abnormalities in the hypothalamic-pituitary-adrenal axis (45), and abnormal lung organogenesis due to altered information trafficking between the feto-placental and maternal compartments (46).

In two separate meta-analyses, children born to mothers exposed to any stressor during pregnancy had increased risks of early-onset wheeze, persistent wheeze, and asthma (8,47). However, preliminary evidence suggests that ethnicity, sex, and outdoor air pollutants may modify potential effects of prenatal stress on asthma. In a birth cohort study, the risk of lifetime wheeze in the offspring of mothers who experienced anxiety during pregnancy, two or more negative life events, and low paternal support was modestly higher in the offspring of Latinas than in those of non-Hispanic white women, independent of income level (48). This finding may be explained by an increased perception of stress among Latinas and inadequate access to mental health resources or practices that would help develop coping mechanisms. In a separate birth cohort study of predominantly minority women-child pairs, prenatal stress was more significantly and strongly associated with asthma in boys, while postnatal stress was more significantly and strongly associated with asthma in girls (49). Similar results were obtained in a separate prospective study of Mexican children (50). With regard to air pollution, prenatal exposure to particulate matter with a diameter less than 2.5 um or nitrate has been associated with current wheeze or asthma in children whose mothers were highly stressed during pregnancy, with one study reporting an association in boys but not in girls (19,20). Pre- and early post-natal stress may affect lung function growth, as one prospective study showed that high levels of stress (≥5 negative life events) during pregnancy and within the first 2 years of life were associated with decrements in FEV1 and FVC by age 7 years, even after adjustment for confounders (51).

Preliminary evidence supports an association between post-natal stress and new-onset asthma. In a prospective study, children without an asthma diagnosis by age 16 years but who had a high life events score had fourfold significantly increased odds of developing asthma by age 29 years (9). Moreover, adolescents who lose a close relative have been shown to have a modestly increased risk of hospitalization due to asthma and are less likely to use asthma medications (52). This could be partly explained by a transient increase in the production of cytokines (IL-4, IL-5, IFN-Y) associated with acute stressful events, particularly in children with high chronic stress (53).

There is also a growing literature asking whether chronic stress affects the course of asthma. Preliminary evidence suggests that distinct stressful situations may have a different impact on asthma outcomes. In a two-year study of young subjects with asthma, a history of targeted rejections (intentional rejections of a person by another person or by a group of people) were associated with decreased expression of mRNA for the glucocorticoid receptor and β2-adrenergic receptor genes in white blood cells (10). Racial or ethnic discrimination can be considered a type of targeted rejection, and perception of such discrimination has been associated with asthma and worse asthma control in African American children (4). In that study, Mexican Americans who perceived racial or ethnic discrimination had increased odds of asthma only if they were of low socioeconomic status (SES). In a small randomized two-period crossover study among college students with mild asthma, perceived stress during final exams was associated with eosinophilia and eosinophil-derived neurotoxin in sputum after inhaled antigen challenge, as well as with a decline in FEV1 (54).

In adults with asthma, stress at home or at work can lead to worse asthma control and decreased medication adherence (55). Although a cross-sectional study showed that over-commitment at work was associated with worse asthma control (56), a meta-analysis of prospective data from 102,175 adults in 11 European studies found no significant association between job strain and severe asthma exacerbations (57). Thus, personal characteristics such as resiliency and available coping mechanisms may be more influential than actual work conditions in subject with asthma. Consistent with this hypothesis, asthmatic children of low SES who reinterpret stressors in a more positive light and remain optimistic about the future (shift and persist) have been shown to have less airway inflammation at baseline, and lower use of rescue inhaler and fewer missed school days after six months of follow up (58).

Stress may worsen asthma control and asthma outcomes by reducing response to short-acting beta2-agonists and corticosteroids (59). As noted above, targeted rejection has been associated with down-regulation of mRNA for the receptors through which these agents signal (43). Consistent with this possibility, a cross-sectional study of Puerto Rican children with asthma showed that children with high levels of chronic stress had lower bronchodilator response (BDR) than those with lower levels of chronic stress (11). In that study, anxiety or anxiety disorders were associated with reduced BDR in two independent cohorts of racially or ethnically diverse children with or at risk for asthma (11). Of interest, the estimated effect of chronic stress on reduced BDR in Puerto Rican children was enhanced when both children and their mothers had high chronic stress. Moreover, a single nucleotide polymorphism (SNP) in the gene for adenylate cyclase activating polypeptide 1 receptor type 1 (*ADCYAP1R1*) was shown to be associated with reduced BDR in a meta-analysis of data from seven cohorts of children with asthma, with reduced expression of the gene for the beta2-adrenergic receptor (*ADRB2*) in CD4+ lymphocytes from children and adults with asthma, and with reduced functional connectivity of the amygdala and the insula (a marker of anxiety) in functional magnetic resonance imaging (MRI) studies of the brain of inner-city women with asthma (11). Taken together, these findings suggest that high chronic stress leads to down-regulation of the beta2-adrenergic receptor in genetically susceptible children, perhaps due to persistent secretion of catecholamines.

Specific neuronal pathways may mediate the effects of stress on airway inflammation in subjects with asthma. In a study of 30 subjects with mild allergic asthma, those with chronic stress had a larger HPA-axis response to an acute social stressor than subjects without chronic stress (60). Moreover, positron emission tomography (PET) scans showed that increased metabolism in the anterior insula correlated with increased fractional exhaled nitric oxide and that greater activity in the mid-cingulate cortex during acute stress was associated with increased IL-23A mRNA expression in subjects with chronic stress. In another study of six subjects with mild allergic asthma, activity in the anterior cingulate complex and the insula was associated with inflammatory markers and airflow obstruction after antigen inhalation challenge (61).

# PTSD and Asthma

PTSD and PTSD symptoms have been linked to asthma. In a study conducted using the Vietnam Era Twin Registry, twins with PTSD symptoms in the upper quartile had twice the odds of having asthma when compared to twins with PTSD symptoms in the lower quartile. This association persisted even after a within-pair analysis was conducted (62). Following the terrorist attack on New York’s World Trade Center (WTC) on September 11 of 2001, a large 9-year study of rescue and recovery workers reported that the cumulative incidences of asthma and PTSD were 27.6% and 31.9%, respectively (12). In a separate cross-sectional study of 71,473 participants in the WTC Health Registry (including lower Manhattan residents, office workers, and passersby), probable PTSD (a score ≥ 44 points in the PTSD Checklist questionnaire) at a baseline visit in 2003-2004 was associated with 1.65 times increased odds of newly diagnosed asthma, even after accounting for SES, dust exposure, and smoking (63). A follow-up study of the WTC Health Registry was conducted in 2006-2007, when 46,322 (68%) of participants agreed to participate (64). In that follow-up study, intense cloud exposure around the WTC attack was a significant contributor to a new asthma diagnosis within 5 to 6 years, with the highest rate of PTSD symptoms in passersby.

In a study of 11,481 WTC rescue and recovery workers, probable PTSD at the baseline visit (post-9/11) was associated with 1.43 times increased odds of BDR (defined as an increment of ≥12% and ≥200 ml in FEV1 after bronchodilator administration) at the same visit, even after accounting for SES, smoking status, pack-years of smoking, body mass index (BMI), and WTC occupational exposure (65). Similar results were obtained when the analysis was restricted to 6,133 never smokers without asthma. In that study, probable PTSD at the baseline visit was associated with 2.4 times increased odds of incident asthma (3.7 to 5.9 years later) among 3,757 never smokers who had not been diagnosed with asthma at or prior to the baseline visit, even after accounting for baseline BDR, WTC occupational exposure, BMI, and other confounders (65). In a separate cross-sectional study of 1,772 German adults, PTSD was associated with reduced FEV1 and FEV1/FVC, and airflow limitation (66). Little is known about PTSD and asthma or lung function in children, with one cross-sectional study linking PTSD to asthma in adolescents (67).

PTSD is present in in 5% to 24% of subjects exposed to a natural disaster (68). Studying PTSD and asthma after natural disasters is challenging, as such events can also increase exposure to allergens such as mold and pollen, and limit access to healthcare. In a study of victims of Hurricane Katrina (13), post-traumatic stress symptoms were not associated with asthma, but each 1- point increment in the IES-R (Impact of Event Scale-Revised) avoidance score (which correlates with behaviors and avoidant coping mechanisms) was associated with twofold increased odds of an asthma attack or episode since the hurricane. Although that study did not account for confounders, it highlights the importance of preparing to care for mental illness and asthma after natural disasters. For example, the population of Puerto Rico is commonly affected by both PTSD and asthma, and local healthcare providers have been alarmed by an increased occurrence of asthma attacks after Hurricane Maria (69).

# Conclusions, Challenges, and Future Directions

Available evidence from experimental and observational studies supports a causal association between chronic stress and worse asthma control, and a growing body of literature suggests that pre- or post-natal chronic stress may lead to new-onset asthma. Such evidence supports conducting randomized controlled trials of stress-reduction interventions to improve asthma control in subjects with high chronic stress. On the other hand, the evidence of a causal link between exposure to violence and asthma is weaker than that for chronic stress and asthma, due to the paucity of experimental or longitudinal studies.

Subjects exposed to violence or experiencing chronic stress are often co-exposed to risk factors for asthma or worse asthma control, including poverty, smoking, second-hand smoke, indoor and outdoor pollutants, limited access to healthcare or medications, reduced adherence to controller medications, an unhealthy diet, and obesity. Thus, longitudinal studies with assessment of co-exposures are key to not only better understand the independent effects of violence or stress on asthma but also to identify factors that could ameliorate or worsen such effects. In particular, we need to improve our understanding of whether and how gender, pollutants, diet, and obesity affect asthma risk in individuals exposed to violence or experiencing chronic stress, while also characterizing the complex interactions between violence exposure and chronic stress on asthma. Moreover, future studies should address the role of coping mechanisms in mitigating the detrimental effects of stress on asthma. In this context, the unfortunate recent increase in natural disasters should motivate both observational and interventional studies to improve our preparation and response to such events.

Identification and improved understanding of the mechanisms underlying the link between stress and asthma are needed to move this field forward. Preliminary evidence suggests that chronic stress affects expression of genes conferring susceptibility to asthma, either directly or through epigenetic regulation. As is the case with epidemiologic studies, future studies should pay attention to co-exposures that may affect DNA methylation or gene expression (e.g., pollutants and smoking) and carefully choose the cells to be studied, as epigenetics is cell-specific.

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Figure 1 Exposure to violence, chronic stress, and asthma

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