## **Child Maltreatment and Asthma**

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#### Abstract

A growing body of evidence suggests a link between child maltreatment and asthma. Determining whether and how child maltreatment causes or worsens asthma would have major implications for disease prevention, treatment, and public health policy. This article examines epidemiologic studies of child maltreatment and asthma and asthma-related outcomes, reviews the available evidence for potential mechanisms underlying the child maltreatment-asthma association, and discusses future directions in this area. To date, child maltreatment has been associated with asthma in most but not all observational studies of children and adults, with discrepant findings likely explained by differences in study design. All studies have been limited by potential under-reporting of child maltreatment, selection bias, and limited assessment of asthma. Despite these limitations, the aggregate evidence from epidemiologic studies suggests a causal link between child maltreatment and asthma, though the relative contributions of various types of maltreatment (physical, sexual, emotional, or neglect) are unclear. To date, there is weak and insufficient evidence of an association between child maltreatment and lung function or severe asthma exacerbations in children or adults. Limited evidence further suggests that child maltreatment could influence the development or severity of asthma through direct effects on regulation of stress responses, immunity, and airway inflammation, as well as indirect effects such as increased risk of obesity. Future prospective studies should aim to adequately characterize both child maltreatment and asthma, while also obtaining high-quality data on relevant covariates and biomarkers of stress, immune, and therapeutic responses.

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### Preface

I would like to thank the faculty members of the Pediatric Pulmonology Department at UPMC Children's Hospital of Pittsburgh for imparting their knowledge and wisdom upon me over the past three years during my fellowship.

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#### **1.0 Introduction**

Asthma is the most common chronic lung disease among children worldwide (1), affecting  $\sim$ 7% of children in the United States (U.S.) (2). In this country, Puerto Rican and African American children share a disproportionate burden of asthma and are often exposed to violence at the individual, family, and community levels (3). Over the last two decades, both exposure to violence (4–9) and chronic stress (10–13) have been implicated in causing and worsening childhood asthma.

Adverse Childhood Experiences (ACEs) (14) can have a long lasting negative impact on physical and psychological health (15–21). Child maltreatment, a stressful ACE that may involve direct exposure to violence, is unfortunately a common problem: at least 1 in 7 children in the U.S. have experienced child abuse or neglect in the past year, and this is likely an underestimate (22). Child maltreatment has been associated with chronic conditions and diseases such as asthma (15,23).

Determining whether and how child maltreatment causes or worsens asthma could have major implications for the prevention and treatment of asthma across life stages, while also impacting public health policy. In this article, we examine findings from epidemiologic studies of child maltreatment and asthma and asthma-related outcomes, review the available evidence for potential mechanisms underlying the link between child maltreatment and asthma, and discuss future directions in this area. While it could be argued that adverse experiences like racism and gun violence are forms of child maltreatment that occur outside the home, this review is focused on child maltreatment in the traditional sense, encompassing physical abuse, sexual abuse, emotional abuse, and neglect (22).

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#### 2.0 Child Maltreatment, Asthma, and Asthma-Related Outcomes

### 2.1 Asthma in Children

Child maltreatment was first reported to be associated with pediatric asthma in a crosssectional study of 1,213 Puerto Ricans aged 6 to 16 years living in the metropolitan area of San Juan and Caguas (Puerto Rico) (24). In the year prior to that study, 14% of participating children had witnessed an act of violence, 7% had been victims of violence, and 6% had been victims of physical or sexual abuse. Compared with children without a history of physical or sex abuse, those with a history of physical or sexual abuse had a higher prevalence of current asthma (50% vs. 39%). In a multivariable analysis adjusting for age, parental history of asthma, and annual household income, physical or sexual abuse was associated with significantly increased odds of current asthma (adjusted odds ratio [aOR]=2.5, 95% confidence interval [CI]=1.3-5.0]) and medication use for asthma (aOR=2.4, 95% CI=1.1-5.3) (24). Similar findings were reported in a subsequent cross-sectional study of 1,413 subjects aged 16 to 27 years in New Zealand, in which child maltreatment was defined as a history of involvement by a child protection agency (extracted from a national database) (25). In that study, child maltreatment was significantly associated with a lifetime diagnosis of asthma, even after adjusting for socioeconomic status (SES), lifetime mental disorders, body mass index (BMI) and lifetime smoking (aOR=2.3, 95% CI=1.3-3.8) (25). In a secondary analysis, self-reported child maltreatment was not significantly associated with lifetime asthma, a negative finding that could be explained by recall bias in a study of adolescents and young adults.

Asthma is a syndrome comprising various phenotypes such as atopic asthma and nonatopic asthma. A cross-sectional study of 1,370 Brazilian children aged 4 to 12 years examined the relation between intrafamilial violence and asthma symptoms according to atopy (defined as an IgE  $\geq$ 0.70 IU/ml to  $\geq$ 1 common allergen) (26). In a multivariable analysis adjusting for secondhand smoke, maternal education, living conditions, and other covariates, maltreatment through non-violent discipline (aOR=2.0, 95% CI=1.2–3.2) and maltreatment through violent discipline (aOR= 1.5, 95% CI= 1.0–2.2) were associated with non-atopic asthma symptoms. Although child maltreatment was not associated with atopic asthma symptoms, there was a limited assessment of asthma and atopy may have been misclassified due to the small number of allergens tested and the threshold used to define a positive IgE (i.e.,  $\geq$ 0.70 IU/ml instead of  $\geq$ 0.35 IU/ml).

Children born to mothers who experienced traumatic events during adulthood, including intimate partner violence (27,28), domestic violence (29), or interpersonal trauma (30) may be at increased risk of incident asthma. With regard to maternal history of child maltreatment, a Canadian prospective cohort study followed 1,551 (45.8%) of 3,388 mother-child pairs for two years after birth (31). In that study, children born to mothers who self-reported a history of childhood abuse were significantly more likely to be diagnosed with asthma by age 2 years than children born to mothers without a history of childhood abuse, even after accounting for maternal education, maternal race, household income, parity, and the child's sex (aOR=1.9, 95% CI=1.0-3.4) (31). Of note, maternal symptoms of depression assessed in late pregnancy and maternal symptoms of depression and anxiety at 24 months postpartum were both significant mediators of the association between maternal child maltreatment and childhood asthma, but such mediation effects were not quantified(31). In a separate prospective cohort study conducted in Brisbane (Australia), 3,762 (52.1%) of 7,223 mother-child dyads enrolled at a baseline visit were followed

up to 21 years after birth. Of the 3,762 participating youth, 130 (3.5%) had experienced any child maltreatment (substantiated by a child protection agency) up to age 14 years and 1,274 (33.9%) had ever been diagnosed with asthma by a physician (32). Of the various types of child maltreatment, only emotional abuse was significantly associated with lifetime physician-diagnosed asthma after adjustment for maternal age, *in utero* smoking, current smoking, BMI and other potential confounders (aOR=1.6, 95% CI=1.0-2.5). Although there was a trend for a dose-response relationship between the number of child maltreatment events and lifetime asthma, this was not statistically significant in a multivariable analysis (P=0.06).

#### 2.2 Asthma in Adults

Child maltreatment has also been associated with asthma in adults. A cross-sectional study of 18,303 adults from 10 different countries in the Americas, Europe, and Japan showed that self-reported physical abuse before age 18 years was significantly associated with self-reported physician-diagnosed asthma after age 20 years, even after accounting for age, sex, study site, and current smoking (adjusted hazard ratio [aHR]=1.9, 95%CI 1.3-2.8)(33). In that study, there was a dose-response relationship between ACEs (including but not limited to physical or sexual abuse) and asthma after age 20 years (33). Similar findings for physical abuse were reported in a cross-sectional study of 400 adults ages 40 to 60 years in Saudi Arabia, in which a self-reported history of being beaten at home during childhood was associated with a diagnosis of asthma (34). In contrast, a cross-sectional study of 3,000 women in New Zealand found that self-reported sexual (but not physical) abuse before age 16 years was significantly associated with asthma in the previous year, though the analysis was not adjusted for potential confounders (unadjusted OR=

2.3, 95% CI=1.1–4.8) (35). In a separate cross-sectional study of 3,081 pregnant women in Peru, neither self-reported physical abuse nor self-reported sexual abuse during childhood was significantly associated with self-reported asthma at or after age 18 years (36). However, women who reported 3 or more abuse events (physical or sexual) during childhood had 1.9 times significantly increased odds of asthma (95% CI for aOR=1.1-3.3), even after accounting for BMI, difficulty paying for basics, education, smoking history, and alcohol consumption history (36).

Potential mediators of the observed association between child maltreatment and asthma in adults include cigarette smoking and mental illnesses such as depression and anxiety. In a recent cross-sectional study of British adults older than 40 years, 157,366 (46%) of 339,092 participants who were invited to complete an online mental health questionnaire emailed their responses (37). Of those 157,366, 120,732 were eligible for inclusion in the study; 81,105 (67.2%) of the 120,732 eligible subjects had complete data on all relevant covariates and were included in the primary multivariable analysis. In that analysis, self-report of any child maltreatment was associated with self-report of current physician-diagnosed asthma (aOR=1.2, 95% CI=1.1-1.3). In a mediation analysis adjusted for household income, educational attainment, smoking status, pack-years of smoking, and other covariates, lifetime generalized anxiety disorder (GAD) and lifetime major depressive disorder (MDD) explained 21.8% and 32.5%, respectively, of the child maltreatmentcurrent asthma association in participating adults. Similar results were obtained after excluding current smokers and former smokers with  $\geq 10$  pack-years of smoking from the mediation analysis, suggesting that GAD and MDD partly mediate an association between child maltreatment and asthma in adults, independently of smoking. Those findings were essentially unchanged in a sensitivity analysis including all 120,732 eligible subjects after imputation of missing data.

A prospective cohort study of African American women aged 21 to 59 years examined the relation between self-reported child maltreatment and incident (new-onset asthma) during 14 years of follow up (38). Of the 59,009 participants, 54,886 subjects did not report asthma of childhood onset and had no asthma diagnosed before the baseline visit. Of those 54,886 eligible subjects, 28,456 (52%) were included in the primary analysis. During 417,931 person-years of follow-up, 1,160 participants reported incident asthma (defined as physician-diagnosed asthma and concurrent use of asthma medication). Compared with women who experienced no abuse during childhood or adolescence, the adjusted incidence rate ratio (aIRR) for any childhood abuse was 1.2 (95% CI=1.1-1.5), and 1.1 for any adolescent abuse (95% CI=0.9-1.4). This association was stronger for childhood physical abuse (aIRR=1.3 95% CI= 1.1-1.5) than for childhood sexual abuse (aIRR=1.2, 95% CI=0.9-1.5). Of interest, the observed associations were stronger in women who were older than 40 years than in younger women (38).

A separate one-year prospective study of 668 predominantly non-Hispanic white (81%) and African American (19%) adolescents aged 12 to 18 years living in western Pennsylvania examined the relation between traumatic events (including child abuse) and health-related symptoms in 15 areas, including "heart and lung" (39). Although there was no association between traumatic events and self-reported asthma, that study was limited by loss of follow up for 113 (17%) of the 668 participants, limited statistical power, unclear assessment or definition of asthma, and non-inclusion of neglect as a form of child abuse (39).

#### **2.3 Lung Function**

In a recent 48-week longitudinal study of data from 98 diverse youth aged 6 to 16 years who were treated with low-dose inhaled corticosteroids for mild persistent asthma (40), increased distress related to exposure to violence (including but not limited to child abuse) was associated with significant decrements in percent predicted (%pred)FEV<sub>1</sub> (-3.27% for each 1-point increment in a validated scale, with 95% CI= -6.44% to -0.22%) and %pred FVC, as well as with reduced asthma-related quality of life. In that report, increased violence-related distress was also significantly associated with reduced FEV<sub>1</sub> and FVC in an ~5-year prospective study of 232 Puerto Rican youth aged 6 to 14 years (40). Taken together, those results suggest that increased violence-related distress between childhood and adolescence leads to reduced FEV<sub>1</sub> and FVC in subjects with asthma, and that this may be partly explained by reduced sensitivity to inhaled steroids (40).

In contrast to findings for violence-related distress in youth with asthma, there has been no or inconsistent association between child maltreatment and reduced lung function in studies of children (32) and adults (41,42) in the general population. In an Australian prospective cohort study of children followed from birth until age 21 years, child maltreatment was not associated with decrements in FVC, FEV<sub>1</sub>, or forced expiratory flow mid expiratory phase (FEF<sub>25%-75%</sub>) (32). However, that study was limited by plausible selection bias due to substantial loss of follow up (~48%) and potential under-reporting of child maltreatment (as only 3.5% of subjects had an event captured by a child protection agency) (32). In a cross-sectional study of German adults older than 20 years, child maltreatment was significantly associated with asthma attacks and asthma symptoms (e.g., wheeze without a cold) but not with FVC, FEV<sub>1</sub>, or FEV<sub>1</sub>/FVC(41). However, only 1,386 (32.2%) of the original 4,308 study participants were included in the analysis, which

was not adjusted for medication use or disease status (e.g., asthma or chronic obstructive pulmonary disease [COPD]) (41).

In a case-control study nested within a prospective study, child maltreatment was defined as cases of physical abuse, sexual abuse, or neglect captured by the judicial system of a U.S. mid-Western metropolitan area by age 11 years (42). After mean follow up of ~30 years, neglect -but not physical or sexual abuse- was significantly associated with a reduced peak air flow, even after accounting for SES indicators, mental illness, smoking, and other covariates (aOR=4.0, 95% CI=1.1-15.3) (42).

#### 2.4 Asthma Hospitalizations

In a study of administrative data for 6,262 predominantly Black children of low SES who lived in a mid-Western metropolitan area in the U.S and were followed for an average of 16 years, any report of child maltreatment (abuse or neglect) was significantly associated with increased risk of a hospitalization for asthma during follow up, even after accounting for parental education, census-level indicators of SES, parental mental illness, and other covariates (aHR=1.7, 95% CI=1.5-2.0) (43). Given a database-driven design, that study was limited by non-adjustment for potential confounders at the individual level (e.g., smoking, household income).

#### 2.5 Summary

Child maltreatment has been associated with asthma in most but not all published observational studies of children and adults, with discrepant findings likely explained by differences in study design and quality. Unlike prospective studies, cross-sectional studies cannot assess temporal relationships and exclude "reverse causation" (i.e., if children with asthma were more likely to be abused). All studies have been limited by potential under-reporting of child abuse, as self-report is subject to recall bias and information extracted from databases (e.g., child protection agencies) may miss non-reported and less severe events. Similarly, selection bias cannot be excluded as an alternative explanation in most studies, whether cross-sectional or prospective (the latter resulting from differential loss of follow up related to child maltreatment and asthma). Moreover, asthma may have been misclassified in studies of young children (who may have had transient wheeze) and smoking adults (who may have COPD), as most studies have relied on self-report from questionnaires. In addition, most studies have classified childhood- vs. adult-onset asthma based on retrospective assessments.

Despite all limitations listed above, the aggregate evidence from epidemiologic studies conducted in different populations and various geographic regions does suggest a causal link between child maltreatment and asthma, but the relative contributions of various types of maltreatment (physical, sexual, emotional, or neglect) are unclear. To date, there is weak and insufficient evidence of an association between child maltreatment and lung function measures or severe asthma exacerbations in children or adults.

#### **3.0 Potential Mechanisms**

Psychosocial stressors such as child maltreatment could influence the development or severity of asthma through direct and indirect effects (3,13) (Figure 1). Child maltreatment leads to chronic distress, which may affect methylation and expression of genes that regulate physiologic responses to stress (44), including those mediated by the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic-adrenal-medullary (SAM) axis, and the autonomic nervous system (45). Chronic alteration of stress responses, including increased circulating levels of cortisol, epinephrine, and norepinephrine can in turn lead to downregulation of receptors and decreased HPA axis responsiveness, abnormal immune responses, and a reduced response to asthma therapies such as short-acting bronchodilators and corticosteroids (45-50). Moreover, child maltreatment has been linked to the development of depressive and anxiety disorders(51), which have been shown to increase the risk of incident asthma in adults (33,52,53). Indeed, GAD and MDD were recently shown to be significant mediators of the association between child maltreatment and asthma in adults (see above) (37). Chronic stress from child maltreatment could also impact asthma through indirect mechanisms such as reduced adherence with controller medications, poor diet and decreased physical activity, overweight or obesity, and substance use (13). Further, children who experience maltreatment could be co-exposed to other risk factors such as outdoor air pollution, which may have synergistic detrimental effects on asthma.



Figure 1. Potential mechanisms for the association between child maltreatment and asthma. HPA = hypothalamic-pituitary-adrenocortical, SAM = sympathetic-adrenal-medullary

To our knowledge, there have been no experimental studies of the effects of child maltreatment on physiologic responses to stress or immune responses. However, indirect evidence for such effects is provided by two studies of other types of intrafamilial conflict or violence. The first study examined parent-child conflict and expression of the genes for the glucocorticoid receptor (*NR3C1*) and the  $\beta_2$ -adrenergic receptor (*ADRB2*) in white blood cells (WBCs) from 57 Canadian children with asthma (54). Parent-child pairs participated in a conflict task, and coders rated interactions for evidence of harsh and supportive behaviors. In that study, harsh conflict behaviors were associated with lower expression levels of *NR3C1* and *ADRB2* in WBCs, as well as more asthma symptoms in participating children. Of note, most participants were atopic (54), limiting the generalizability of those findings to children with non-atopic asthma. The second study

examined exposure to maternal intimate partner violence (IPV) and HPA axis reactivity and asthma during early childhood in 1,292 low-income, predominantly non-Hispanic white (59%) children from the U.S. Northeast (55). Salivary cortisol samples were collected from participating children with validated stress reactivity paradigms at ages 7, 15, 24, 35, and 48 months old, when maternal reports of IPV were also obtained. Maternal exposure to IPV when the child was 7 months old was associated with subsequent reports of childhood asthma, but this association differed according to the child's HPA reactivity status: IPV-exposed children who were "cortisol reactors" (~43% of participants) were at significantly increased risk of asthma at ages 7 months ( $\beta$ =0.17, P=0.02) and 15 months ( $\beta$ =0.17, P=0.02). Although asthma cannot be accurately diagnosed in early childhood, those findings suggest that young children who are physiologically reactive may have increased risk of asthma- or wheeze-related outcomes when exposed to stressors such as IPV (55).

#### **4.0 Future Directions**

Child maltreatment is a highly sensitive but potentially important risk factor for asthma. To overcome the limitations of previous work, large studies with a prospective design should examine both the number and types of child maltreatment from early life to adolescence. Accurate detection of all cases is unlikely, and thus assessing child maltreatment using high-quality databases from child protection agencies could capture most moderate to severe events while ensuring that affected children are provided with compassionate care and appropriate follow up. An alternative approach would be to use self-reported maltreatment by the child's parents, but this is suboptimal and would likely lead to reporting and selection biases, as the child's parent would have to be informed of the potential need for referral to child protective services during the informed consent process. Indeed, findings from studies of exposure to violence in older children suggest substantial under-reporting by their parents (56,57).

In parallel with assessment of child maltreatment, future studies should adequately characterize asthma phenotypes (e.g., "obese asthma", childhood- vs. adult-onset) and endotypes (e.g., Th2-high vs. non-Th2 high asthma). Because asthma cannot be appropriately diagnosed before age 6 years, a high retention of study participants into adolescence and adulthood will require appropriate strategies to avoid loss of follow-up. Moreover, future studies should obtain data on covariates that may confound or modify the relationship between child maltreatment and asthma (e.g., outdoor air pollution, second-hand smoke, obesity) while also examining "omics" and biomarkers of HPA reactivity, immunity, and inflammatory and treatment responses in order to yield novel insights into the mechanisms underlying the child maltreatment-asthma link.

The need for further research does not preclude much needed public health policies to prevent child maltreatment and its negative consequences for children with and without asthma. Moreover, current evidence supports screening for child maltreatment and associated mental illnesses (e.g., GAD, MDD, and post-traumatic stress disorder) in adolescents and adults with or at risk for asthma.

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