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Evidence establishing a link between prenatal and early life stress and asthma development

Maria José Rosa, DrPH[1], **Alison Lee, MD, MS**[2], and **Rosalind J. Wright, MD, MPH**[1,3,4]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[3]Institute for Exposomic Research, Icahn School of Medicine at Mount Sinai, New York, NY, United States

[4]Department of Pediatrics, Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Abstract

Purpose of Review—The objectives of this review is to provide an update on our evolving understanding of the effects of stress in pregnancy and during earlier development on the onset of asthma-related phenotypes across childhood, adolescence and into early adulthood.

Recent Insights—Accumulating evidence over the past two decades has established that prenatal and early life psychological stress and stress correlates (e.g., maternal anxiety or depression) increase the risk for childhood respiratory disorders. Recent systematic reviews and meta-analyses including numerous prospective epidemiological and case-control studies substantiate a significant effect of prenatal stress and stress in early childhood on the development of wheeze, asthma and other atopic-related disorders (eczema and allergic rhinitis), with many studies showing an exposure-response relationship. Offspring of both sexes are susceptible to perinatal stress, but effects differ. The impact of stress on child wheeze/asthma can also be modified by exposure timing. Co-exposure to prenatal stress can enhance the effect of chemical stressors, such as prenatal traffic-related air pollution, on childhood respiratory disease risk. Understanding complex interactions among exposure dose, timing, child sex, and concurrent environmental exposures promises to more fully characterize stress effects and identify susceptible subgroups. While the link between perinatal stress and childhood asthma related phenotypes is now well established, pathways by which stress predisposes children to chronic respiratory disorders are not as well delineated. Mechanisms central to the pathophysiology of wheeze/asthma and lung growth and development overlap and involve a cascade of events that include disrupted immune, neuroendocrine and autonomic function as well as oxidative stress. Altered homeostatic functioning of these integrated systems during development can enhance vulnerability to asthma and altered lung development.

Corresponding Author: Rosalind J. Wright, MD, MPH, One Gustave L. Levy Place, Box 1198, New York, NY 10029, USA. Telephone: +1 (212) 241-5287; Fax: +1 (212) 289-8569; rosalind.wright@mssm.edu.

Future Directions—Mechanistic studies that more comprehensively assess biomarkers reflecting alterations across these interrelated stress response systems and associated regulatory processes, in both pregnant women and young children, could be highly informative. Leveraging high-throughput systems-wide technologies to include epigenomics (e.g., DNA methylation, microRNAs), transcriptomics, and microbiomics as well as integrated multi-omics are needed to advance this field of science. Understanding stress-induced physiological changes occurring during vulnerable life periods that contribute to chronic respiratory disease risk could lead to the development of preventative strategies and possible therapeutic interventions.

Introduction

Clinicians and scientists have long been challenged by the complexity of 'what is asthma' and whether it is of the mind or the body. The concept that emotion plays a role in asthma dates back at least to the 12th century[1]. As recently as the first half of the twentieth century, Western medicine categorized asthma as a psychogenic phenomenon and treatment recommendations primarily consisted of psychoanalysis and other "talking cures"[2]. As our understanding of the pathophysiology of airway inflammation and bronchial hyperresponsiveness started to evolve in the 1960's, the psychiatric theory of asthma was largely set aside by the biomedical community which increasingly recognized asthma as a physical condition related to genetics and disrupted immunity. Advances in psychoneuroimmunology swung the pendulum once again and led scientists to reconsider the role of psychological stress in asthma pathogenesis, including the onset of disease[3]. Initiatives led by the US National Institutes of Health (NIH) in the 1990's [4] highlighted the need for more research and led to increased funding opportunities and a significant increase in published research on stress and asthma expression.

Asthma risk begins *in utero* during rapid lung morphogenesis when the developing fetus is particularly vulnerable to toxic insults due to immature immune, neuroendocrine and antioxidant defenses. In addition, infants continue to be vulnerable as these systems are still developing and remain highly reactive and labile in response to environmental stressors in early life, particularly in the first two years. Exposure to psychological stress in vulnerable developmental periods can result in alterations in homeostatic functioning of these interrelated stress response systems (e.g., immune, autonomic, neuroendocrine, oxidation) and associated regulatory processes in both pregnant women and young children that play a role in the development and progression of respiratory disorders [5–8]

Accumulating evidence, particularly over the last two decades, has established that prenatal and early life psychological stress and stress correlates (e.g., maternal anxiety or depression) increase the risk for new onset respiratory disorders including wheeze and asthma. Underlying mechanisms linking stress to respiratory disease programming are not as well elucidated, particularly in human studies. This overview briefly summarizes the collective evidence from a growing number of prospective epidemiological studies linking prenatal maternal stress and asthma development in children synthesized in a recent systematic review [9•] and two independent meta-analyses [10,11••] of published observational studies. We expand upon more recent research further substantiating these associations as well as studies demonstrating complex interactions between stress, child sex, and chemical

environmental exposures to more fully elucidate those at greatest risk. Future promising research directions that have potential to better delineate pathways by which prenatal and early life stress predispose children to respiratory disorders are also discussed.

General Mechanistic Paradigm

Potential mechanisms linking prenatal stress and childhood respiratory outcomes have been the topic of numerous reviews including a recent overview highlighting the import role of the placenta [12]. Stressors are largely thought to affect pathogenesis by initiating dysregulated biobehavioral states resulting in lasting effects on key physiological processes that influence disease risk [13–15]. As a response to stress, normal homeostatic functions of the body's key physiological systems are disrupted; the disturbed balance of these systems is most relevant to disease risk. For instance, a defensive biological response by the neural, immune, and endocrine systems is important for the short-term stress response; however, this type of response may produce long-term adverse health consequences if not checked and terminated [16]. Although the disturbance of the hypothalamic-pituitary-adrenal (HPA) axis is most widely studied, research suggests that autonomic imbalance or dysfunction, independent of hormonal or neuroendocrine abnormalities, may be just as important[17••, 18•]. Both animal and human data suggest that the disruption of these key stress systems in the mother resulting from her own stress history [19] can influence immune functioning and other mechanisms in the developing fetus that in turn have been linked to asthma development [6,20]. For example, biomarker correlates of disrupted stress-response systems in pregnant women, such as cortisol, have been linked to early respiratory outcomes in children [21,22•]. Increased prenatal stress and cortisol have also been associated with immune profiles (e.g., T-helper [T_H] 2 response, T_H17 pathway promotion) at birth related to increased childhood asthma risk [23].

Synthesis of evidence from observational studies

Andersson et al. performed a systematic review of existing epidemiological studies examining prenatal maternal stress (operationalized as stressors including negative life events or stressful conditions and negative emotions including distress, anxiety or depressive symptoms) and risk of atopy-related outcomes in children (asthma, wheeze, atopic dermatitis, allergic rhinitis, and immunoglobulin E (IgE) expression) with the majority of studies documenting a significant exposure-response relationship [9•]. The magnitude of the association varied across studies, likely due to differences in populations, study design, the stress measure used, characterization of the outcome, timing of exposure, and adjusted confounders.

Shortly thereafter, van de Loo and colleagues presented a well-designed meta-analysis including 10 studies (8 prospective cohort studies, 1 case-control study, and 1 cross-sectional study) substantiating a significant association between increased prenatal maternal stress and childhood wheeze and asthma[10••]. The included studies used varied measures of stress including report of negative life events, difficult life circumstances, perceived stress assessed in terms of general stress symptoms, anxiety or depression and pregnancy-specific anxiety. The overall pooled OR of respiratory disease, including wheeze and asthma, among children

born to mothers reporting higher stress [both stress exposure (i.e., experiencing a stressful event) and perceived stress (i.e., experiencing psychological symptoms or distress)] was 1.6, with a 95% confidence interval (CI) of 1.3 to 2.0. The included studies considered a range of important confounders including maternal age, education, and race/ethnicity, parental asthma or allergy, smoking during pregnancy, preterm birth, birth weight, child gender, and breastfeeding. Findings were similar in sensitivity analyses stratifying by study quality, approach to assessing stress, and the outcome being considered (wheeze, asthma, overall respiratory morbidity). Notably, replication of findings in this meta-analysis including populations that vary in age, geographic region, and how the outcome was defined increases the generalizability of these findings. Moreover, the pooled ORs may underestimate the true effect size given that some included studies adjusted for variables that may actually be in the pathway operating between maternal prenatal stress and children's asthma risk. Mothers exposed to increased stress may be more likely to smoke prenatally and consequently are at greater risk for preterm delivery and having a lower birth weight infant, factors also linked to asthma development in early childhood. Including these pathway variables can result in over-adjustment and an underestimation of true effects [24]. Future research in this area should consider mediation analyses to formally test such indirect effects in order to more fully characterize the impact of stress on early asthma risk.

A more recently published meta-analysis by Flanigan *et al* [11••] added additional studies and considered a broader range of outcomes including asthma, atopic dermatitis, atopic sensitization, allergic rhinitis, urticaria and anaphylaxis and added studies published after the work by van de Loo and colleagues. Stress indicators in the included studies ranged from negative life events (NLEs), work-related stress, and bereavement as well as and stress correlates (e.g., anxiety, depression). These authors also examined the impact of the type of stressor and exposure timing within pregnancy. The analysis found an association between any prenatal stress (composite of stress indicators) in pregnancy and increased ORs for both current or ever wheeze (OR 1.3, 95% CI 1.2–1.5) and current or ever asthma (OR 1.2, 95% CI 1.04–1.3) in children. Maternal stress was associated with increased risk of early-onset [pooled OR 1.3, (1.1, 1.6)], late-onset [pooled OR 1.4 (0.8, 2.4), and persistent wheeze [pooled OR 1.9, (1.5, 2.4), although the association with late-onset wheeze did not quite reach statistical significance. When examining associations by specific type of stress indicator, only anxiety in pregnancy was significantly associated with asthma in children (1.3, 95% CI 1.2–1.5). When considering the timing of exposure to any stress, only stress assessed in the third trimester was significantly associated with ever or current asthma, whereas assessment of stress indicators in either the second or third trimester was significantly associated with wheeze outcomes. As cautioned by the authors, the finding of more significant associations when stress indicators were measured later in pregnancy may reflect cumulative effects of ongoing negative events, stress appraisals, or altered mood states over the pregnancy rather than revealing specific timing effects.

New insights from evolving epidemiological evidence

Evidence linking perinatal stress to asthma expression continues to grow [25–28]. A number of studies published in the past year add particular new insights which will be highlighted here [29–37].

The strength of observational studies can be enhanced by more comprehensive adjustment for confounding factors. Use of negative controls is one method more recently implemented to minimize unmeasured confounding in birth cohort studies [38]. Two recent studies conceptualized paternal stress during pregnancy as a negative control to minimize residual confounding when examining links between maternal prenatal stress and child asthma risk. Brew and colleagues used Swedish register data to examine the association between maternal and paternal distress, defined as having a diagnosis of or receiving medication for an anxiety or depressive disorder during the mother's pregnancy, and the development of asthma by age 5–6 years among all children born in Sweden (n=254,150) between 2006 and 2008 [29••]. These authors provide a detailed discussion of how paternal distress can be conceptualized as s negative control to further minimize residual confounding. Notably, only maternal distress was significantly associated with higher odds (OR: 1.3, 95% CI [1.2, 1.4]) of asthma diagnosis in children, even after adjustment for paternal distress and other important confounders. More recently, Magnus and colleagues[37••] examined child asthma development by age 7 years in the Norwegian Mother and Child Cohort Study in relation to maternal psychosocial stress during pregnancy and at 6 months after delivery (n=63,626) and in a subset with data on fathers, paternal and maternal psychosocial stress during pregnancy was also considered (n=47,619). In this large-scale birth cohort in Norway, a country with universal access to health care and relatively low social inequality, maternal symptoms of anxiety/depression and negative life events both during pregnancy and the first 6 months after delivery were positively associated with asthma in children followed to 7 years. Paternal psychosocial stress was not associated with offspring asthma indicating that the associations observed with maternal anxiety/depression and negative life events was not explained by unmeasured lifestyle characteristics linked to higher psychosocial stress shared by parents. Findings from these studies again underscore the particular importance of stress-related adaptations of the maternal-fetal environment that operating *in utero* to enhance asthma risk in offspring.

In analyses of data from the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) birth cohort in Boston, our group attempted to further disentangle the temporal effects of pre- and postnatal stress exposure on asthma while additionally considering sex differences [30••]. Stress was assessed by maternal-report of NLEs in the past 6 months collected during pregnancy and in the early perinatal period (12–18 months postnatal) and the outcome was caregiver report of physician diagnosed asthma in children followed to approximately age 6 years (n=765). When considered in separate models, there was a clear exposure response relationship between both increasing prenatal stress and increasing postnatal stress and higher odds of child asthma. When stratifying by sex, there was a significant trend for both increasing pre- and postnatal stress predicting higher odds of asthma in the boys, while only the trend in postnatal stress was significantly associated with asthma in girls. These data highlight the importance of the interplay between timing of exposure and child sex. Moreover, dose mattered. Children born to mothers experiencing difficulties over five or more life domains were 2 to 3 times more likely to develop asthma by the time they started school compared to children of women reporting the lowest levels of stress. Also, children born to women experiencing the greatest number of adverse events in both pregnancy and early infancy were at greatest risk for asthma. Rosa et al. [31•]

demonstrated similar temporal- and sex-specific effects of perinatal NLEs on wheeze outcomes in children followed to age 4 years in a Mexico pregnancy cohort study with a clear exposure response association. Taken together, this line of research suggests that while boys seem more vulnerable to stress during the prenatal period, girls were more impacted by postnatal stress and cumulative stress across both periods in relation to asthma risk. Understanding sex and temporal differences in response to early life stress may provide unique insight into asthma etiology and natural history. Notably, these findings also indicate that children are at increased risk of developing asthma when their mothers experience 'toxic levels' of stress in the perinatal period. This suggests that it will not be necessary to eliminate stress altogether but rather, interventions focused on reducing stress levels to more normative levels in pregnant women and in families with young children could reduce asthma risk in children. Clinical trials examining stress reduction modalities are needed to understand if we can indeed prevent asthma onset.

Other research provides different insights into timing effects. For example, researchers used data from the Canadian National Longitudinal Survey of Children and Youth (NLSCY) (n=1696), a nationally representative sample of children, to link reports of postpartum depression and asthma diagnosis at every age between 5 and 10 years in children [32•]. Report of postpartum depression was associated with higher odds of asthma diagnosis at ages 6–8 but the association was no longer present past age 9 with the authors positing that the effect of maternal stress diminishes as children encounter other home and school stressors although this will need to be more explicitly examined in future studies.

A few recent studies have focused on adolescents and young adults which remain understudied with respect to stress effects on asthma development. Investigators using data from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A), a population-based national survey of mental disorders in US adolescents, looked at exposure to violence (physical abuse, intimate partner violence, victimization by someone other than caregiver/partner, mugging with a weapon, sexual assault/rape, stalking, witnessing family violence) in relation to self-report of several chronic health conditions, including asthma [35•]. Exposure to any violence, direct or indirect, was associated with higher odds of asthma in adolescents. This corroborates earlier prospective data linking direct and indirect experiencing of family or community violence to subsequent asthma onset in childhood [39,40]. In a combined analysis of SAGE (n=954) and Genes-Environments and Admixture in Latino Americans study (GALA II, n=1,121) data, experiences of discrimination was examined as a stressor in relation to asthma diagnosis and asthma control [36•]. When stratifying by race/ethnicity, report of any discrimination was associated with higher odds of asthma diagnosis amongst African Americans but not Mexican American, other Latino/a or Puerto Rican islanders. The Tucson Children's Respiratory Study also examined stress in adolescence ascertained through a life events questionnaire in relation to concurrent and new onset asthma [41••]. While there was no association between higher stress and concurrent asthma, the authors reported greater risk of new onset asthma in late adolescence and early adulthood during follow-up between 16–29 years in relationship to stress exposure.

As summarized thus far, existing studies examining links between prenatal maternal stress and child asthma risk have considered stress occurring proximate to the index pregnancy

[e.g., current negative life events or prenatal psychological functioning (e.g., anxiety)]. However, evolving research underscores the need for a broader view that considers stress experienced over the mother's lifecourse when characterizing risk to the next generation. In this paradigm, researchers have focused in particular on traumatic experiences which are especially likely to lead to persistent psychophysiological alterations in women carried into pregnancy, and have documented intergenerational effects[42]. For example, a large body of literature links interpersonal trauma (IPT), including child abuse and/or interpersonal violence experienced across the lifecourse, to physiologic correlates of stress in pregnant women long after the exposure, including altered cortisol levels [43,44], autonomic imbalance [45], immune disruption and chronic inflammation [46,47]. For example, women experiencing traumatic events such as abuse and neglect in childhood/adolescence [46] or intimate partner violence [47] have been found to have elevated levels of C-reactive protein (CRP), a marker of systemic inflammation, relative to women who do not have these experiences. Overlapping research has linked elevated CRP in pregnancy to increased asthma risk in children by age 3 years [48•]. Thus, overlapping lines of evidence indicate that IPT over a woman's lifecourse can have lasting effects on key stress-response systems and related biomakres during pregnancy which can influence child development. The timing of trauma exposure in the mother may also be important. Exposures during sensitive developmental periods in the mothers, with both early childhood and adolescence identified as periods susceptible to traumatic stress effects[49], or cumulative stress due to ongoing IPT over the lifetime may be particularly likely to affect psychophysiological functioning at childbearing age [50]. Thus, maternal IPT may be linked to fetal and infant health through more latent effects (i.e., lasting effects from childhood), proximate effects (i.e., trauma experienced in or around the pregnancy), or cumulative effects (i.e., traumas occurring over multiple periods in the mother's lifecourse).

A woman's exposure to trauma generating lasting biological changes in her immune and neuroendocrine systems that continue to exert their effects into adulthood and pregnancy may be directly operating to influence asthma programming in offspring. In addition to direct programming effects, maternal traumatic stress may operate through intermediary pathways to indirectly influence asthma development in children. For example, lifetime trauma can lead to adverse behavioral and physical health consequences in women that in turn are known antecedents of adverse fetal development and asthma risk. For instance, our group and others have linked IPT in earlier life with current asthma in adult women [51,52]; thus, trauma exposure may make it more likely for women to have persistent and active asthma at the time of pregnancy. Maternal active asthma during pregnancy, in turn, has been associated with increased asthma incidence in children [53–55]. Other studies link trauma histories to adverse psychological functioning in mothers, pre-pregnancy obesity [56] and smoking during pregnancy [57], factors that are also linked to childhood asthma [58].

Studies specifically examining associations between lifetime maternal trauma and child asthma are starting to emerge. The All Our Babies (AOB) prospective birth cohort in Calgary examined intergenerational effects of stress by focusing on mother's report of abuse in childhood and parental report of doctor diagnosed asthma in their children at age 2 years [33••]. These authors also examined whether this effect was mediated by perinatal maternal psychological functioning. Maternal report of child abuse was associated with higher odds

of asthma in their children and in mediation analysis, symptoms of depression in pregnancy and depression and anxiety in the postpartum period were significant indirect pathways in these relationships. Leveraging a lower-income, ethnically diverse prospective birth cohort, Brunst and colleagues examined associations between lifetime IPT in women and asthma in their children [34••]. Cumulative IPT over the mothers' lifetime was significantly associated with asthma in children followed to age 6 years when adjusting for maternal age, education, race/ethnicity, and child's sex (OR = 1.82, 95% CI 1.06–3.13). In sex stratified analyses, the association between chronic maternal IPT and offspring asthma risk was seen in boys (OR = 2.87, 95% CI = 1.48–5.57) but not girls (OR = 0.69, 95% CI = 0.23–2.12) ($p_{interaction}$ = .04). Structural equation modeling was used to examine indirect pathways that may be operating between maternal IPT and children's asthma development. The study found that women experiencing chronic lifetime IPT were more likely to have active asthma during pregnancy which, in turn, mediated the association with asthma in the next generation. There was a suggestion that chronic IPT may operate indirectly through greater likelihood of experiencing other negative life events during pregnancy but path analyses did not support a role for maternal pre-pregnancy obesity, maternal smoking during pregnancy, and/or increased prenatal exposure to adverse environmental factors (air pollution) in mediating the relationship between maternal IPT and childhood asthma.

Considering stress mixtures

It has likely become clear to the reader that maternal prenatal stress is a complex phenomenon encompassing many correlated, yet distinct, domains. As reviewed above, these can include the environmental stressors (both remote and current) that women experience as well as her psychological response, which, in turn, influence fetal development through a network of different pathways. Each stress construct is typically considered individually in relationship to outcomes. However, there may be significant advantages to considering these factors as integrated constructs conceptualized as a "stress mixture" in order to more comprehensively characterize stress in pregnant women or children. Moreover, stress measures are often moderately correlated; thus, it is important to statistically adjust for co-stressor collinearity using appropriate methods when trying to identify which components within the "stress mixture" are most pertinent to outcomes. It may be possible to gain greater insights into the programming effects of stress by taking lessons from other areas of environmental research. For example, conceptualizing stress as a complex mixture, our group implemented weighted quantile sum (WQS) regression, a variable selection technique that has been used successfully for studying the health effects of chemical mixtures[59] to characterize prenatal stress exposure[60•]. This approach reduces the multiple comparisons inherent in testing multiple domains in separate regressions by integrating information on multiple stressors, and serves as an integrated index of overall stress. Furthermore, the weights allow investigators to gauge the relative contribution of each component of the stress index to the outcome of interest.

Considering chemical interactions

Environmental exposures do not occur in isolation and growing evidence indicates that the co-occurrence of psychological stress and chemical stressors further magnifies risk,

especially in susceptible sub-populations. Specifically, recent studies in North America and Europe add to the literature showing that prenatal psychological stress enhances the effects of concurrent ambient air pollutant exposures, on respiratory outcomes in children. In our Boston ACCESS cohort, higher prenatal stress indexed through negative life events modified the association between prenatal nitrate (NO_3^-) exposure during pregnancy and asthma development by age 6 years [61••]. Moreover, effects were sex-specific. Increasing nitrate exposure during pregnancy was associated with greater odds of asthma at age 6 only among boys born to mothers who reported high stress prenatally. In this same sample, boys born to mothers exposed to both increased particulate matter less than or equal 2.5 microns in diameter ($PM_{2.5}$) and a higher number of NLEs in pregnancy were at elevated risk for asthma by early school age, with a significant 3-way interaction (PM x stress x child sex) [62••]. In this study, highly temporally resolved $PM_{2.5}$estimates (daily) were derived based on residence over pregnancy using a novel spatiotemporal model incorporating moderate resolution imaging spectroadiometer satellite-derived aerosol optical depth (AOD) combined with tradition land use regression predictors. Analyses coupled highly temporally resolved air pollution exposure estimates with advanced statistical methods (distributed lag models) to more objectively define vulnerable periods for effects and to enhance power to detect complex interactions. As discussed in this publication, more definitive characterization of vulnerable windows can provide greater insights into underlying mechanism when coupled with the understanding of lung growth, airway structural and functional development, and asthma pathophysiology. Similarly analyses in a prospective birth cohort in Mexico City [63•] also demonstrated a significant interaction between prenatal $PM_{2.5}$ and higher maternal stress (increased NLEs) in association with greater odds of wheeze in the past 12 months in 4 year olds. In a subset of the Paris prospective birth cohort (n=2,015), investigators examined effect modification by parental report of stressful life events during the first 2 years of life on the association between exposure to traffic related air pollution estimated by nitrogen oxides (NO_x) air dispersion modeling taking into account both home and day care locations over the first year of the child's life and asthma and respiratory symptoms in preschoolers [64•]. Stressful life events were defined as parental separation/divorce, loss of job, serious health problem or death in the family. Increased exposure to NO_x in the first year of life was associated with ever asthma, asthma with current symptoms, and persistent wheeze at age 4 years only in children whose parents also reported experiencing stressful life events. Stratified analyses found that boys exposed to higher NO_x in early life were at greatest risk for adverse respiratory outcomes but they did not test a 3-way interaction between NO_x x stress x child sex. These studies highlight the importance of considering complex interactions to more fully characterize the impact of stress as well as identify susceptible subgroups.

Emerging evidence for molecular programming mechanisms

While the effect of prenatal and early life stress on the development of childhood asthma related phenotypes is now well established, pathways by which stress predisposes individuals to chronic respiratory disorders remain poorly elucidated. Mechanisms central to the pathophysiology of wheeze/asthma and lung growth and development involve a complex cascade of events that include disrupted immune, neuroendocrine and autonomic function as

well as oxidative stress. Mechanistic studies that more comprehensively characterize effects across these interrelated stress-response systems and associated regulatory processes, in both pregnant women and young children, could be particularly informative. Figure 1 provides a schematic specifically highlighting promising systems biology approaches that have potential to better delineate pathways by which prenatal and early life stress predispose to subsequent respiratory disease risk, which will be the focus of the remainder of this overview.

Environmental epigenetics can help us understand how social factors, including psychological stress, impact disease risk [65•] although this has not been widely studied in relationship to early life stress and asthma development in children. One recent study used whole genome bisulfite sequencing to examine changes in DNA methylation and transcriptional analyses in mothers and their children in relation to prenatal stress and assessed whether this played a role in the development of wheeze in children [66••]. These authors found that high prenatal stress was associated with increased risk of repeated wheeze. They also identifiey potentially involved signaling pathways which were subsequently validated using targeted approaches. Specifically, epigenetically deregulated neuroendocrine and neurotransmitter receptor pathways were evident in both mothers and children, while in children, calcium- and Wnt-signaling involved in lung maturation were epigenetically deregulated.

Another pathway of interest is the mediation of stress effects through the maternal and fetal microbiome which may also inform observed sex-specific effects in the observational studies summarized earlier. The microbiome is a regulator of host immunity and is increasingly implicated in asthma pathogenesis[67]. During early life, bacterial communities in the maternal gut and/or vagina can influence these processes in the developing child. For example, recent animal studies show that prenatal stress alters the temporal and spatial dynamics of maternal microbiome in both the gut and vagina and influences offspring bacterial community assembly in a temporal- and sex-specific manner [68,69••]. Studies examining the role of stress-related disruption of maternal and child microbiome dynamics in critical prenatal and early life windows on childhood asthma risk may identify novel interventions[70].

The role of the placenta also warrants particular attention in future stress-asthma research efforts. Trafficking of information between the feto-placental and maternal compartments is necessary for normal fetal development. Environmentally induced alterations in these signaling networks can negatively influence development, impacting lung organogenesis and programming future respiratory disease. While mechanisms are complex and not fully understood, placental oxidative stress (OS) and maternal and fetal HPA axis functioning and cortisol production play key roles. Maternal stress impairs the placenta’s tight regulation of fetal cortisol exposure. For example, chronic stress has been shown to down-regulate placental 11-β-hydroxysteroid dehydrogenase-type 2 (11β-HSD2), increasing fetal cortisol exposure[71]. Maternal stress also stimulates secretion of placental corticotrophin-releasing hormone (pCRH), which plays a fundamental role in fetal HPA axis development and acts to increase fetal cortisol[72]. Our group and others have shown that women with higher childhood trauma or higher cumulative lifetime stress have elevated pCRH, specifically in

the second half of gestation, and their offspring have elevated cortisol[73•,74]. Increased fetal cortisol activates fetal stress responses (i.e., HPA axis, catecholamines and neurotrophins), induces a T helper type 2 cell predominance (i.e., an immune phenotype predisposing to asthma) and alters ANS systems. Our group recently linked cumulative lifetime trauma with decreased placental mitochondrial DNA copy number, an index of increased OS over gestation [60]. Enhanced placental OS, in turn, has been shown to alter fetal development, including immunological development which is relevant to asthma risk[75].

Prenatal exposures, including maternal stress, can induce signature changes in other placental biomarkers, including microRNAs (miRNAs), small non-coding RNA molecules that are critical regulators of numerous pathways and biological processes. Placental trophoblasts sort miRNAs into extracellular vesicles (EVs) that are then released into the extracellular environment and trafficked to distant maternal and fetal tissues where they repress gene expression via messenger RNA (mRNA) silencing[76]. MiRNAs play key roles in organogenesis, including respiratory outcomes[77••]. EV-encapsulated placental miRNAs circulate at high levels during pregnancy, are easily identified in maternal and fetal plasma, and have unique properties contributing to their potential as biomarkers to detect maternal prenatal stress effects on respiratory development. Placental miRNAs also traffic bi-directionally between maternal and fetal compartments. Animal models establish that these EV-encapsulated miRNAs traffic across the placenta, infiltrate developing fetal organs, including the lung, and alter fetal gene expression[78]. EV-encapsulated placental miRNAs also regulate interrelated systems important in stress programming, including immune and HPA axis function and OS. Thus, circulating EV-encapsulated placental miRNAs may orchestrate complex stress-related signaling networks to influence fetal respiratory development and should be examined in future studies elucidating mechanisms linking prenatal stress to asthma risk in children.

Conclusions and Future Directions

The evidence establishing that there is an increased risk of asthma with exposure to psychosocial stress, particularly during the prenatal and early postnatal period, continues to mount. Understanding sex and temporal differences in response to early life stress may provide unique insights into asthma etiology and natural history. Additional mechanistic studies are needed to elucidate the biological mechanisms linking these exposures to asthma development. Mechanisms central to the pathophysiology of wheeze/asthma and lung growth and development overlap and involve a cascade of events that include disrupted immune, neuroendocrine and autonomic function as well as oxidative stress. Homeostatic functions of these integrated systems are disrupted in response to chronic stress (i.e., stress-response systems). Altered stress-response functioning carried into pregnancy as a result of the mother’s own stress history can disrupt optimal programming of these integrated systems in the fetus leading to enhanced vulnerability to asthma and altered lung development. Because these exposures do not happen in a vacuum, further exploration into the interactions between psychological (nonchemical) and chemical stressors are also needed. Understanding stress-induced physiological changes that occur during vulnerable life periods that contribute to respiratory disease risk could lead to the development of

preventative strategies and possible therapeutic interventions. Mechanistic studies that more comprehensively assess biomarkers across interrelated stress response systems implicated in asthma pathophysiology and associated regulatory processes, could be highly informative. Leveraging high-throughput systems-wide technologies to include epigenomics (e.g., DNA methylation, microRNAs), transcriptomics, and microbiomics as well as integrated multi-omics are needed to advance this field of science. Research designed to assess the impact of stress reduction techniques on asthma development and exacerbation are also needed.

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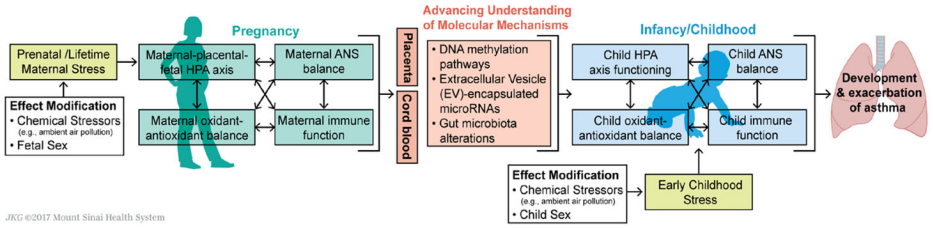

Figure 1. Stress and Asthma: State of the Science and Potential Mechanisms

This conceptual diagram summarizes the state of the science reviewed herein and highlights promising mechanistic pathways that warrant future investigation.