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Moving towards making social toxins mainstream in children's environmental health

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Abstract

Purpose of Review—While traditional disciplinary research theory and methods have focused separately on how social and physical environmental factors affect children's health, evolving research underscores important integrated effects.

Recent findings—This review outlines the specific reasons why social determinants should be considered mainstream in children's environmental health research with particular focus on interactive effects between social and physical hazards. These include (a) sensitivity of overlapping physiological systems, via epigenesis, programming, and plasticity to social and physical environmental moderation that may impact health across the life span; (b) ways in which social environmental vulnerabilities moderate the effects of physical environmental factors providing specific examples related to respiratory health and neurodevelopment; (c) overlapping exposure distribution profiles; and (d) relevance to pediatric health disparities.

Summary—Because of the covariance across exposures and evidence that social stress and other environmental toxins (e.g., pollutants, tobacco smoke) may influence common physiological pathways (e.g., oxidative stress, pro-inflammatory immune pathways, autonomic disruption), understanding the potential synergistic effects promises to more completely inform children's environmental health risk. While this discussion focuses around the respiratory and neurological systems, these concepts extend more broadly to children's psychological and physical development.

Keywords

children; social toxins; physical hazards; health disparities

Introduction

An area of particular interest in children's environmental health is the search for mechanisms responsible for health disparities across economic and ethnic groups. Recent consensus statements by both the National Academy of Science[1] and the National Institutes of Environmental Health Sciences[2] support the position that examining disparities in environmental health requires attention to both physical environmental hazards and social conditions. Yet, while contemporary accounts acknowledge this, traditional disciplinary research has focused separately, by in large, on the influence of social and physical factors. Indeed, far more attention has been given to physical toxins including tobacco smoke, air pollutants, allergens, and metals (e.g., lead, mercury)[3-5].

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This review outlines specific reasons why social determinants should be considered mainstream in children's environmental health research with particular focus on interactive effects between social and physical hazards. This is discussed in light of recent studies focused on leading pediatric public health outcomes (i.e., respiratory disorders, neurodevelopment) which illustrate situations in which social stressors influence susceptibility to future environmental exposures and when contemporaneously exposed, how social x physical environmental interactions may account for more variance in explaining risk than main effects. Conversely, socially enriched environments may protect children from the toxic effects of other environmental hazards which may have implications for prevention and intervention.

Social Toxins

Increasingly, it has been recognized that children are being raised in social contexts that may be as detrimental to their development as these physical factors. References to "socially toxic environments" have existed in the psychology literature for some time. James Garbarino, an American psychologist, coined the term in the 1970s to describe rearing conditions such as violence, poverty and other economic pressures on parents and their children[6]. Others including Urie Bronfenbrenner have been issuing increasingly serious "social smog alerts" since first sounding the alarm in *Two Worlds of Childhood*[7]. While a number of theoretical models explaining how social conditions "get into the body" to impact health more broadly, the psychosocial stress model has been increasingly adopted in this regard[8-12]. In this framework, psychological stress can be conceptualized as a social toxin/pollutant that can be 'breathed' into the body resulting in the disruption of a number of key integrated physiological systems similar to how air pollutants and other physical toxicants lead to adverse health risks.

Developmental Plasticity and Life Course Epidemiology

The conceptualization of a life course approach to epidemiology is only briefly introduced here albeit is central to our discussion (for more details see [13, 14]). These authors provide a concise overview of the life course epidemiological approach bridging biological, psychological and social models of disease causation relevant to health disparities. They use chronic respiratory disease and/or impaired respiratory function as a specific example. Plasticity is a consequence of environmental exposures during critical life periods affecting key physiological systems that operate in orchestrating underlying developmental processes[15]. Children are particularly vulnerable to disruption of developmental processes during relatively narrow time windows. Exposure to environmental toxicants during prenatal and/or early postnatal development may alter the normal course of morphogenesis and maturation, resulting in changes that affect both structure and function of multiple organ systems including the respiratory and neurological systems[15]. Moreover, when normal development is altered, the early effects may persist into adult life, magnifying the public health impact [16, 17].

Respiratory and cognitive function may operate under common regulatory processes and thus have shared vulnerabilities to a host of environmental factors during development[18]. While the mechanisms of early life environmental influences are not completely understood, evidence suggests that the developmental origins of the structural and functional organization of the respiratory and neurological systems involve, in part, the coordinated maturation of the immune, neural, and endocrine systems[19, 20]. Mechanisms underlying perinatal programming related to physical factors have been previously described in the environmental health literature and will not be reiterated here[4, 21, 22]. Instead, the evidence for stress effects on such programming is described in order to make the case that because stress and physical hazards (e.g., pollutants, tobacco smoke) may disrupt common physiological pathways (e.g., oxidative stress, pro-inflammatory immune pathways, autonomic disruption), we need to understand their integrated effects to more fully understand children's environmental health risk.

Environmental Programming of Key Physiological Systems

Figure 1 depicts a conceptual model for pathways linking stress experienced during critical periods of development (i.e., perinatal programming) and enhanced vulnerability to concomitant and subsequent environmental toxicant exposures. The following discussion provides a background for the model. Stressors influence pathogenesis by causing dysregulated biobehavioral states [e.g., depression, anxiety, posttraumatic stress disorder] which, in turn, exert lasting effects on physiological processes that influence disease risk[23]. In response to stress, physiological systems may operate at higher or lower levels than in normal homeostasis. It is the disturbed balance of these systems that is relevant to disease. Immune and neuroendocrine defensive biological responses important for the short-term response to stress, may produce long-term damage if not checked and eventually terminated[20].

The hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system [sympathetic-adrenal-medullary (SAM) system] seem particularly susceptible to early-life programming in relation to stress and other environmental toxins. Disturbed regulation of these systems due to maternal stress may, in turn, modulate immune and autonomic function in the offspring beginning *in utero*[24, 25]. That is, offspring may inherit a biological vulnerability to disrupted stress regulatory systems altering the child's reactivity to subsequent challenges [26] (i.e., both subsequent stressors as well as other environmental toxins).

Both early and long-term developmental effects related to prenatal stress result, in part, from altered maternal and/or fetal glucocorticoid exposure[25]. Animal models as well as human studies support the connection between an adverse intrauterine environment and experiences in early postnatal life and alterations of autonomic nervous system balance (e.g., sympathovagal balance) as well [27-29]. While these *in utero* responses may be adaptive in the short term, geared toward coping with anticipated environmental challenges, ultimately they may exact a toll in contributing to increased risk of diseases in later life.

In addition, the acquisition of the ability to regulate one's response to stress ("self regulation") progresses through several stages in the early years of development[30]. The HPA system starts to become organized between 2 and 6 months of age through transactions between the child and caregiver [31]. The infants' autonomic responses show developmental changes with relative stability between 6 to 12 months of age [32]. Studies have consistently demonstrated that the quality of caregiving that the child receives during early development predicts the emergence of later self-regulation abilities, with sensitive caregiving associated with more adaptive self-regulatory abilities and more optimal functioning of the child's HPA system[33]. Increased maternal stress, in turn has been associated with lower levels of parenting sensitivity and higher levels of negative parenting behaviors [34, 35]. A number of correlates of perinatal maternal stress have also been associated with poor stress regulation and other negative outcomes in both animal and human offspring[36-39]. Essex and colleagues demonstrate prospectively how how early life stress may alter vulnerability to subsequent experiences of stress as indexed by cortisol and behavioral stress responses.

Such neurohormonal alterations have been subsequently linked to fetal and early life immunomodulation[8]. Aberrant or excessive pro-inflammatory immune responses as well as oxidant-induced changes, both locally and systemically, are a central determinant of structure-function changes in both the respiratory [40-42] and neurological systems[43-46].

Shared Vulnerability Pathways

The notion that stress and other environmental toxins operate through overlapping mechanisms has been previously reviewed[47]. For example, tobacco smoke exposure in early development influences immune function as indexed by alterations in cytokine production by the

fetoplacental unit and in cord blood, patterns of fetal mononuclear cell responses in vitro, and altered signaling through Toll-like receptors[48, 49]. Air pollution exposures have been linked to disruption of neuroimmune responses[45, 50] and autonomic reactivity (particularly increasesd parasympathetic tone) even in young healthy subjects[51]. Moreover, both tobacco smoke and air pollutants may generate reactive oxidative species to influence health through oxidative stress pathways similar to psychological stressors[47]. It is thus plausible that the biologically compromised system(s) related to early life stress may be more vulnerable to subsequent environmental toxins and vice versa (life course perspective).

Examples from Leading Pediatric Developmental Disorders

The subsequent discussion focuses on specific examples demonstrating the independent and interactive effects of correlates of social environmental stress on trajectories of disease expression in the respiratory and neurological systems.

Respiratory System

While the origins of chronic lung diseases are multi-factorial, the central underlying mechanisms leading to reduced lung function and exaggerated responsiveness to bronchoconstirctor stimuli involve chronic airway inflammation associated with a cycle of injury, repair and remodeling[40, 52]. The fundamental cause of the underlying airway inflammation is aberrant and/or excessive immune responses to various environmental agents [40] and oxidant-induced inflammation[42]. Airway inflammation and early remodeling occur and progress even in the presymptomatic and/or subclinical state[53], i.e. lung function may be ‘set’ in the first years of life[54].

Research continues to delineate the relationships among early environmental influences, immunodeviations, and developmental outcomes in the lungs [41, 42, 55]. The most common cause of chronic airway inflammation in early childhood is asthma. Although diverse pathogenic mechanisms are likely involved in different forms of asthma and the consequential airway changes [i.e., airway hyperreactivity (AHR), which is thought to be present in all patients with asthma [56]], there has been a major focus on the influence of the systemic propensity for type 2 T-helper (Th2) allergic responses and eosinophils [57]. These mechanisms have their roots in early life with an immunological bias towards a Th2 phenotype *in utero*[41, 58]. Perinatal stress may influence the evolving systemic propensity for type Th2 responses (i.e., enhanced adaptive immunity)[8]. Antigen-independent responses including innate immune cells (e.g., bronchial epithelial cells, alveolar macrophages, and dendritic cells) may also be important in modifying airway inflammation [59]. Factors, including stress, that slow maturation of local immune networks (e.g., dendritic cells [DCs], epithelial cells [ECs], regulatory T cells) may predispose to a Th2 phenotype [60].

The balance between functional parasympathetic and sympathetic activity in relation to stress, emotional stimuli, and immune function may also be important for the expression of atopic disorders as well as early airway inflammation and reactivity [47]. A bidirectional network of interactions between the central nervous system, the endocrine system and the immune system is well documented[61]. The immune and nervous system are closely related in both physiological and pathological reactions in the lung. Communications between neurons and immune cells resulting in airway inflammation and the development of airway hyperreactivity are a consequence of neuronal dysregulation[62, 63]. Finally, animal studies suggest that neural control of airway smooth muscle and the irritant receptor systems are established during early life and sensitive to environmental programming [27]. Lung and airway reflexes through the central nervous system (CNS) are crucial in maintaining airway and respiratory function as well as defensive mechanisms. These central pathways (e.g., nucleus tractus solitarius (NTS)]

have been shown to undergo neuroplasticity under a variety of conditions (e.g., exposures to environmental tobacco smoke, pollutants, stress)[64].

Perinatal stress and emotional arousal may influence airway narrowing through inflammatory pathways and imbalance in sympathovagal activity. Nogueira and colleagues[65] were first to demonstrate that prenatal stress increased allergen-induced airway inflammation in adult mice offspring. Similarly, allergen aerosol challenge has been associated with increased airway hyperresponsiveness in mice exposed to prenatal stress[66]. Mice exposed to prenatal stress were also more likely to express a Th2 adaptive immune response.

More recent evidence suggests that stress modifies the response to other environmental toxins to influence the expression of respiratory phenotypes. We recently demonstrated an association between traffic-related air pollution (NO2) and risk for childhood asthma in an urban sample only among children who were also exposed to elevated social stress[67]. No main effects were evident for either NO2 or the stressor in this study. Similarly, Chen and colleagues[68] showed that chronic traffic-related pollution exposure and stress interacted in predicting both increased asthma symptoms and heightened inflammatory profiles in adolescents with asthma.

Neurodevelopment/Behavior/Cognition

Social stress and physical environmental toxins impact overlapping biological processes which determine adaptive plasticity in early neurodevelopment as well. Developmental CNS organization into functional neuronal and synaptic networks is determined by environmental signals which modify neuronalgenesis, synaptic formation and synaptic pruning[69]. Environmental factors can promote or disrupt this process depending on whether they are positive (social supports, good nutrition, etc.) or negative (psychosocial stress, chemical toxicants, malnutrition, trauma, etc.). While plasticity allows recovery from short term toxic exposures, the neural mechanisms underlying the plasticity of the developing brain exposed to chronic stress could induce permanent structural or organizational changes via altered neuronal growth and/or synaptogenesis/pruning. As the hippocampus is the brain region with the highest density of glucocorticoid receptors which modulate the process of neuron and synaptogenesis, it is not surprising that with regard to the neurological effects of chronic stress, the primary functional endpoint appears to be changes in the development and formation of memory. While acutely, stress may enhance memory formation[70], chronic stress inhibits it. In animals, chronic stress induces atrophy of apical dendrites in the hippocampus[71, 72] and a reduction in dendritic length and branching density[73]. Animal behavioral studies have confirmed the adverse effects of pre- and post-natal chronic stress on memory and learning[74, 75].

More recent evidence suggests that stress modifies the response to environmental toxins to influence the expression neurobehavioral phenotypes[76, 77]. Studies in animals have demonstrated that combined exposure to maternal lead and stress in the prenatal environment may act synergistically to enhance behavioral and neurochemical toxicity in the offspring[78] with evidence of mediation through HPA disregulation[79, 80]. In addition, recent epidemiologic evidence supports the role of stress as a modifier of physical toxins (e.g., lead, ETS exposure). Rauh et al[81] measured pre-and post-natal exposure to ETS and Bayley Scales of infant development in urban children enrolled during pregnancy and followed longitudinally. Prenatal ETS exposure predicted a 5 point decrement in the Bayley MDI scores (p=0.02). Material hardship predicted a 3 point decrement in MDI (p=0.07). The children with both prenatal hardship and ETS performed an average of 10 points lower on the Bayley MDI than children with neither exposure.

Converse Protective Effects

Animal studies have also shown that environmental enrichment can reverse the effects of early stress experiences on stress reactivity[82]. For example, Schneider[83] and Guilarte et al,[84] demonstrated that animals raised in social isolation were more sensitive to the neurotoxic effects of lead than animals raised in an enriched environment. Laviola et al and Morley-Fletcher et al have shown that environmental enrichment eliminates the outcomes of prenatal stress on corticosterone response and reactivity to an immune-suppressive agent in offspring later in life [85, 86]. Similarly, Francis et al has shown that environmental enrichment can reverse the effects of early stress (maternal separation) on HPA activation and behavioral response to stress in rat offspring[87].

There is also evidence from a range of studies in humans to suggest that maternal psychosocial functioning (e.g., stress, anxiety, depression, self-esteem) has a significant effect on the mother-infant relationship and parenting, and that this in turn can have consequences for both the short and long-term health and functioning of the child[33]. A recent prospective study in humans demonstrates that postnatally, maternal sensitivity can modify the effects of prenatal stress experiences and maternal psychological functioning on infant stress reactivity [88]. We have previously linked intimate partner violence (IPV) in the home during early development (a particular social stressor) to adverse respiratory outcomes in children including increased risk for asthma[89] and reduced lung function in early childhood[90]. More recent analysis show that, while maternal IPV is associated with increased childhood asthma risk, factors contributing to a supportive caregiving environment appear to buffer the maternal IPV-asthma association[91]. Also, parental social support which may buffer stress experiences, has been shown to be inversely associated with asthma prevalence among children [92]. Another recent study demonstrates the direct positive effect of higher levels of maternal self-esteem on children's cognitive functioning as assessed using the Bayley's Scale of Infant Development at age 24 months[93]. Moreover, there was evidence that enhanced maternal self-esteem attenuated the negative effects of lead exposure on cognitive functioning in these children. And finally, Thahn and colleagues[94] investigated the relationships among neonatal stress, cognitive indices and basal cortisol levels in very low gestational age infants and found that maternal factors (parenting stress, interactive behaviors) ameliorated adverse effects of stress on cortisol and focused attention in these infants. These studies have important implications for prevention and intervention studies.

It is worth mentioning in this context that the potential programming effects of stress on childhood health outcomes may occur at an even more fundamental level, i.e., through epigenetic programming[95, 96]. A variety of environmental factors have been identified which influence DNA methylation including stress[97]. Epigenetic mechanisms may even explain why maternal behavior toward young offspring affects the size of the offspring's hippocampus in adulthood, depending on the offspring's genotypes[98].

Implications for Health Disparities

The environmental hazards discussed herein co-occur. Marginalized populations of lower-socioeconomic position that are disproportionately exposed to irritants (e.g., tobacco smoke), pollutants (e.g., diesel-related particles) and indoor allergens (e.g., cockroach, mouse allergen) may also live in communities that are increasingly socially toxic which, in turn, may be related to increased experience of psychosocial stress[67, 99, 100]. Thus, those living in disadvantaged social circumstances may be most at risk for synergistic effects.

Summary

Taken together, these lines of evidence point toward the need to consider social environmental factors as mainstream in children's environmental epidemiology. The likelihood of multiple mechanistic pathways with complex interdependencies must be considered when examining the integrative influence of social and physical environmental toxins on children's environmental health. Because these factors tend to cluster in the most socially disadvantaged, this line of research may better inform the etiology of growing health disparities. While the focus of this discussion has been around the respiratory and neurological systems, these concepts extend more broadly to children's psychological and physical development. Design of future epidemiologic studies and effective intervention programs will need to address environmental toxicants and social stress jointly to impact public health most effectively[101, 102].

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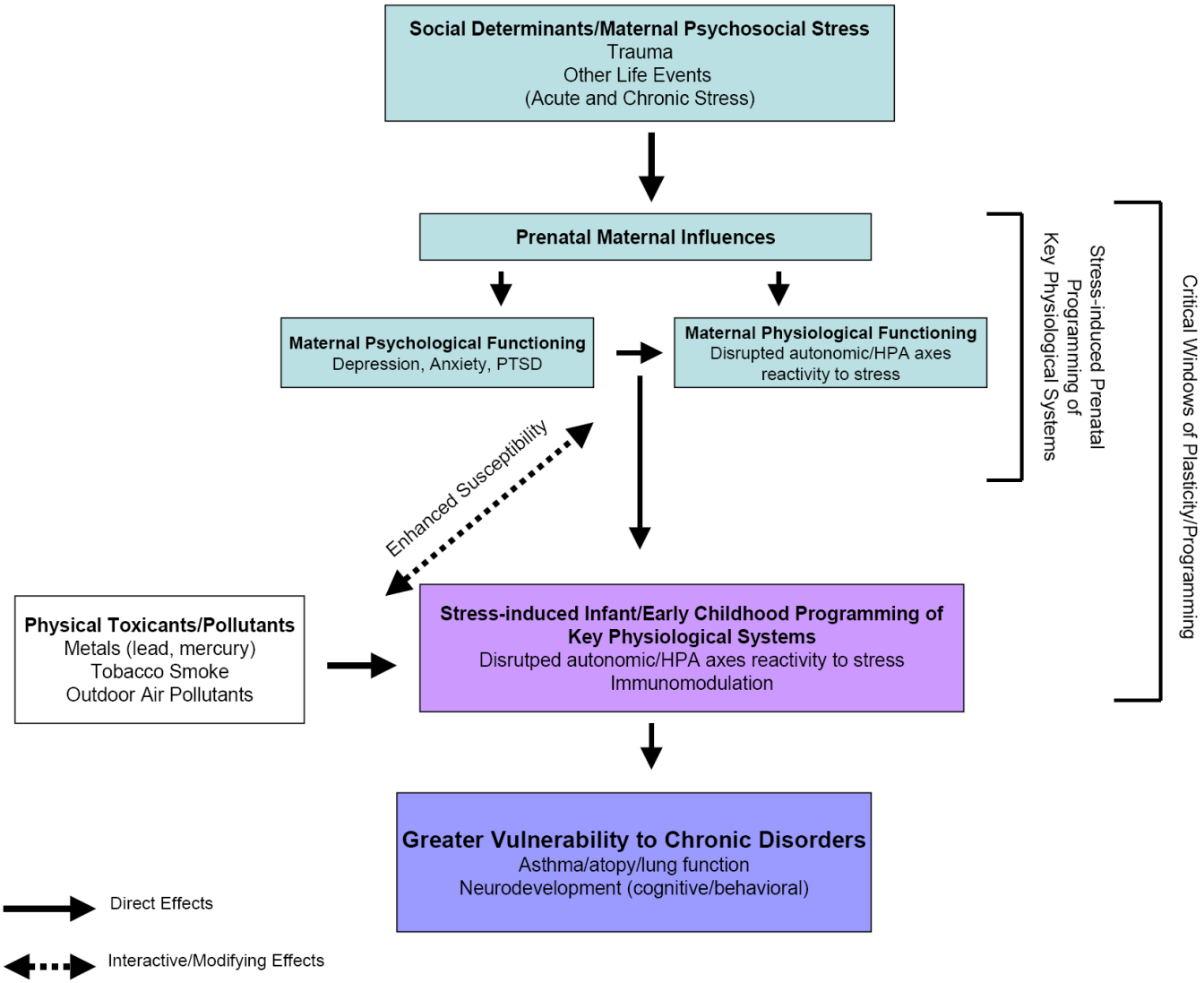

Figure 1.
Conceptual Model for Pathways Linking Perinatal Stress to Altered Vulnerability to Physical Environmental Toxins and Health Risk