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Maternal Early Life Adversity and Next Generation Wheeze and Allergy

by

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Abstract

Chronic trauma in childhood can program an abnormal stress reaction, resulting in lifelong difficulties with stress management and poor health outcomes linked to changes in the immune system. At the same time, maternal stress during pregnancy has been linked to childhood asthma. Given the potential for a mother's early life maltreatment to shape her later response to stress during pregnancy, we hypothesized that preschoolers would be more likely to have a wheeze or allergic disorder if their mother has a history of adversity. We found a significant positive association between a mother's early experience of household dysfunction and childhood wheeze. Maternal childhood psychological abuse was associated with children's allergies. In summary, stressful maternal childhood experiences are associated with the development of wheeze and allergy in children. These findings emphasize the necessity of services aimed at lowering the stress of new mothers and the value of inquiring about early life experiences.

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Introduction

Researchers have known for decades that psychological stress takes a toll on the body (1). It is generally believed that stress does this by modifying the physiological reactions of the brain, which in turn generates inappropriate immune responses in the body.

Chronic stress activates brain pathways normally used only for emergency situations. It sensitizes these neural pathways and over develops regions of the brain involved with emotional responses, giving rise to abnormal stress reactions to everyday hassles (2). New evidence reveals that traumatic events in childhood may result in lifelong difficulties with stress management and poor health outcomes linked to changes in the immune system. It is thought that while the effects of chronic stress are usually not permanent, trauma early in life comes at a sensitive period, making reprogramming of the brain's stress reaction difficult (3-6).

Maternal stress and depression during pregnancy and the postpartum period has been linked to a number of diseases in childhood, including wheeze and asthma (7;8). It is thought that the mother's distress acts much like a traumatic event for the infant, encoding the infant's stress reaction in the brain and in turn causing immune related illnesses (9). Mothers with a history of childhood trauma may have an especially hard time dealing with the stress of pregnancy and looking after a newborn (10). Given the potential for her own maltreatment in childhood to shape a mother's later response to stress during pregnancy, it seems plausible that children may demonstrate inheritance of their mother's childhood trauma through their own health

issues. Research on the intergenerational transmission of stress and its effects on physical health has only just begun but early findings are promising and are bolstered by a decade of consistent results in mental health (11;12).

This investigation tests the hypothesis that preschool children are more likely to have a wheeze or allergic disorder if their mother has a history of childhood trauma, independent of her distress during pregnancy. Specifically, we investigate the effects of: neglect; physical, sexual, and psychological abuse; parental separation or divorce, and substance abuse and interpersonal violence in the home. We also explore the possibility of a dose-response relationship between the number of co-occurring types of abuse and wheeze and allergic outcomes in offspring.

Definition and prevalence of childhood maltreatment

Following asthma and allergies, childhood abuse is the third most common public health concern for children (13). Maltreatment is perhaps the most conspicuous cause of stress in early life and it can have lifelong psychobiosocial consequences. Though different forms of maltreatment are highly interrelated, it has nevertheless become apparent that different kinds of abuse are associated with different health and behavioural outcomes (14-17). It is also clear that a dose response relationship is likely, as “the greater the number of childhood abuses, the poorer one's adult health” (18-20). Borrowing from the posttraumatic stress disorder literature, which uses the term ‘traumatic load’ for the number of event types experienced, the label

‘maltreatment load’ has been suggested to describe the number of abuses suffered(21).

Most international prevalence studies on child abuse have chosen to focus on either sexual or physical abuse or both. These report estimated rates of physical abuse between 10-31% in men and 6-40% in women and rates of childhood sexual abuse of 3-29% in men and 7-36% in women(22). Aggregate data on the experience of any form of maltreatment is rarer. The National Society for the Prevention of Cruelty to Children (NSPCC)’s report on child maltreatment in the United Kingdom notes that 5 per cent of children under age 11, 13.4 percent of 11–17s and 14.5 percent of 18-24s experienced severe maltreatment of any type during their childhood (23). A recent Quebec study found that one in three adults reported having experienced at least one form of childhood abuse (24). The great variability in estimated rates across reports and countries (even among industrial nations) is likely due to methodological differences and definitional issues.

Official estimates of the prevalence of childhood maltreatment instead generally come from studies of children reported to welfare authorities. The 2008 Canadian Incidence Study of Reported Child Abuse and Neglect (CIS-2008) discloses a rate of 14.19 cases of substantiated child maltreatment per 1 000 children, a considerable decrease over the 2003 report, likely due to changes in measurement methods. At approximately 1-2%, this rate is comparable to most studies of a similar design in the United States, Australia and the United Kingdom.

"The CIS-2008 definition of child maltreatment consists of 32 forms of maltreatment subsumed under five categories: physical abuse, sexual abuse, neglect, emotional maltreatment, and exposure to intimate partner violence. Physical abuse was comprised of six forms: shake, push, grab or throw, hit with hand, punch kick or bite, hit with object, choking or poisoning or stabbing, and 'other physical abuse'. Sexual abuse contained nine forms: penetration, attempted penetration, oral sex, fondling, sex talk or images, voyeurism, exhibitionism, exploitation, and 'other sexual abuse'. Neglect was comprised of eight forms: failure to supervise: physical harm, failure to supervise: sexual abuse, permitting criminal behaviour, physical neglect, medical neglect (including dental), failure to provide psychiatric or psychological treatment, abandonment, and educational neglect. Emotional maltreatment included six forms: terrorizing or threat of violence, verbal abuse or belittling, isolation or confinement, inadequate nurturing or affection, and exploiting or corrupting behavior. Exposure to intimate partner violence was comprised of three forms: direct witness to physical violence, indirect exposure to physical violence, and exposure to emotional violence"

The CIS is a good descriptor here, as it covers most of the adverse childhood experiences described in the literature. This Canada-wide study revealed that neglect and exposure to interpersonal violence were the most common primary forms of maltreatment (each represent 34% of all substantiated cases), followed by physical abuse (20%), emotional abuse (9%), and sexual abuse (3%) (25). While emotional abuse appears low on the list, it is important to note that emotional harm is the most likely form of abuse to co-occur with others. In fact, emotional abuse was noted in 29% of all substantiated maltreatment investigations. Though no longer calculated in 2008, in 2003 an additional 24% of cases had suspected (but unsubstantiated) emotional abuse (26). This means well over half of all maltreatment cases have suspected or substantiated emotional abuse. The low primary rates but high co-occurrence numbers are to be expected, both because most forms of child maltreatment can lead to emotional harm and because without adjoining physical symptoms, emotional abuse is easily

overlooked. That is to say, it is highly unlikely that emotional abuse in isolation will prompt an investigation unless it is extremely severe. As a result, other forms of abuse are more likely to win the ‘primary’ abuse spot. Moreover, since prevalence rates of childhood maltreatment generally come from studies of children reported to welfare authorities (like CIS), the numbers we have on psychological abuse are almost certainly an underestimation of reality.

Emotional maltreatment, however, may be more harmful in its long term effects than other forms of mistreatment. This is because emotional neglect and abuse, when compared to sexual and physical abuse, is a better predictor of mental illness, as well as interpersonal difficulties, somatic complaints, poor emotional regulation, self-esteem, violent relationships, substance abuse, and criminality (27-29) . Furthermore, it was recently shown in a large sample of healthy adults without current psychopathology that a self-reported history of childhood emotional abuse, regardless of subthreshold depressive/anxiety symptoms, predicted a significantly diminished cortisol response, independent of other forms of child abuse (30). In this particular study, emotional neglect and abuse were the only forms of maltreatment to show an association with cortisol levels.

Summary

Abuse and other adverse events are common childhood experiences. The emotionally stressful nature of these events may be the critical characteristic which leads to poor mental and physical health. Indeed, when

compared to other forms of maltreatment, psychological abuse—arguably a series of purely emotionally stressing experiences, is associated with the worst mental and behavioural outcomes. The maltreatment load—the experience of multiple types of adversity, is also associated with poorer health. Since psychological abuse co-occurs with so many different types of abuse but is rarely studied, it seems plausible that some of the adult outcomes formerly attributed to other kinds of abuse may in fact hinge on their co-occurrence with psychological abuse.

Childhood Maltreatment and Adult Health

The connection between childhood maltreatment and poor mental health in adulthood is well documented (31-35). Supporting the concept of maltreatment load, studies looking into the psychopathology of victims of child abuse find that frequency and duration of abuse are key in explaining greater psychological difficulties (36). The new wave in child abuse research focuses instead on physical health outcomes and has so far seen an excess of results recording greater illness in both clinical and non-clinical populations (16;37;38). The bulk of this new research has focused on the health effects of sexual abuse. Child sexual abuse has been associated with numerous chronic diseases, medical and reproductive health problems and medically unexplained syndromes (37;39-43).

The impression should not be made, however, that this research is limited to sexual abuse. For instance, in the late 1990s, Walker *et al.* investigated the effects of all types of child abuse on adult health status within

a large health maintenance organization. They found that any history of child abuse was associated with perceived poorer overall health, greater physical and emotional functional disability, increased numbers of distressing physical symptoms and a greater number of health risk behaviours (38). Like other studies investigating a dose-response relationship, they found that women who experienced multiple categories of early life maltreatment had a greater number of symptoms and physician diagnoses. Around the same time, Felitti *et al.* discovered that emotional, physical and sexual abuse, along with household dysfunction, had a positive linear relation with adulthood disease status (44).

These studies are only a few examples of many which have uncovered relationships between traumatic early life experiences and adult outcomes. Associations have been found between all types of childhood trauma with risk factors like obesity, substance abuse and risky sexual behavior, and with diseases including cancer, heart disease, chronic lung disease, skeletal fractures, and liver disease, just to name a few (44). Along with medical diagnoses, women with histories of child abuse report more health concerns, poorer perceptions of their health, higher health care costs and greater impairment in their everyday lives due to physical health problems (39;45-47).

Summary

Previous studies have concentrated on the mental illness outcomes of childhood maltreatment. More recently, the literature has shifted its gaze

towards physical health consequences. While many of the studies looking at physical outcomes have focused on sexual abuse as the antecedent, connections have been established between all types of adversity with the many facets of health including diagnoses, risk factors for disease, general well-being, and economic costs.

Toxic Stress and the Brain

Though rare, it is true that extreme child abuse involving bodily harm may directly cause poor adult health. Abuse may also indirectly cause adult health issues by increasing the likelihood of a range of social, behavioral, and emotional problems which are more proximate causes of physical health troubles (48). But, as mentioned earlier, most forms of abuse carry emotional maltreatment with them, so it is plausible that the psychological stress of trauma is the ultimate cause of these poor mental and physical health outcomes.

Although stress can be adaptive, for instance, by motivating a fight-or-flight response in an appropriate situation, it can also be harmful to one's health when exposure to the stressor is frequent or prolonged. To appreciate traumas' power over health, we need to better understand how the brain responds to cumulative stress.

The brain is the chief regulatory organ for stress responses. Stressors set off physiological and behavioural responses aimed at reinstating homeostasis. This is known as allostasis, the ability to achieve stability in a system through change (49). McEwen and Stellar coined the term allostatic

load to describe the price of this accommodation to stress, which is the 'wear and tear' that results from chronic overactivity or underactivity of stress systems (50).

The hypothalamus-pituitary-adrenal (HPA) axis is the neuroendocrine system involved in the production of the stress hormone cortisol by the adrenal glands. There is a complex and finely tuned mix of direct influences and feedback interactions between all the components of the HPA axis, which regulates many body processes including emotion, digestion and immune function. It comes as no surprise then, that how our bodies respond to stress plays a huge part in determining our overall health.

When the HPA axis is activated, corticotropin releasing factor (CRF) is secreted from the hypothalamus, which in turn, induces the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH then stimulates the release of glucocorticoids from the adrenal cortex. Cortisol is a glucocorticoid, named so because of its ability to alter the function of tissue in order to mobilize or store energy when dealing with a stressor (51).

Evidence points to the neurotoxic effects of cortisol and inflammation on brain structure and function as the pathophysiology in question. Cortisol's' capacity to negatively impact the brain was first described by the Sapolsky *et al.* in their 1986 Glucocorticoid Cascade Hypothesis, which has since become the classic theory of the field (52). It describes a vicious cycle of excess glucocorticoid and downregulation of glucocorticoid receptors in the hippocampus, triggering a feed-forward cascade with serious

pathophysiological consequences (53). The glucocorticoid cascade hypothesis was written at a time when glucocorticoid receptors (GR) were thought to be the only mediators of cortisol and corticosterone in the brain. Mineralocorticoid (MR), another corticosteroid has since been discovered, resulting in a number of new theories. These new hypotheses build on the cascade hypothesis by incorporating the need for MR and GR balance and recognizing the role of epigenetic modulations and environmental exposures (53).

Corticosteroids alter brain function by binding to two nuclear receptors that also serve as transcriptional factors: GR in the hippocampus and MR throughout the brain (54). The two receptor types “mediate a finely balanced mechanism that governs the often opposing molecular and cellular changes”(51). As a result, glucocorticoids can do much more than simply inhibit the HPA axis. As just mentioned, GR is abundant within the hippocampus. The “enhanced susceptibility of hippocampal neurons to atrophy or necrosis in response to metabolic challenges” is well known (55). The hippocampus is central to learning and memory, and as the ‘seat’ of the HPA axis, mediates cortisol feedback inhibition (55). It is also well known that stress impedes memory function. It is thought that abnormal basal cortisol levels take advantage of hippocampal neuroplasticity (part of the enhanced susceptibility mentioned above), damaging the hippocampus and thus impairing hippocampus-dependent learning and memory (56). There are also a number of animal models to support the theory that excessive

glucocorticoid exposure results in hippocampal damage, and so too, cognitive functioning (56;57).

We also have a wealth of findings from the depression literature which highlight lower hippocampal volumes in depressed individuals (58). Smaller hippocampal volumes are associated with increased cortisol secretion during the day. Deficits in tasks associated with the hippocampus, like learning and memory, are likewise known to accompany depression. At this point the pre-eminent role of childhood trauma in the development of depression and other mood and anxiety disorders should again be noted (28;44;59-61). In classic chicken or egg form, we know that depression is associated with elevated glucocorticoid levels and at the same time, that chronically altered levels of cortisol increase the risk of later psychopathology, like depression (62;63). And, as mentioned earlier, abnormal cortisol levels have a suppressing effect on the immune system, which can cause excessive inflammation. It follows that depressed persons have compromised immunity (64). This association between impaired stress systems, mood disorders and health is to be expected. Activation of glucocorticoid receptors in the hippocampus inhibits the HPA axis by reducing the release of corticotropin releasing factor (CRF). Corticotropin-releasing factor neurons are found not only in the hypothalamus, but also in the neocortex and the central nucleus of the amygdala. Structural neuroimaging studies have highlighted deficits in brain volume and gray and white matter in these areas in children and adults with abuse histories (65). The amygdala is central to emotional processing in the brain and plays an important role in the pathophysiology of mood disorders. It

should come as no surprise then, that CRF may also affect the stress reaction via other brain structures, like the amygdala, which ultimately activate the HPA axis (66). From all of these intimate associations, one can reason that childhood maltreatment creates changes in the HPA axis and other regions of the brain, impairing stress reactivity and mental and physical health.

Summary

Chronic stress produces an overflow of cortisol and inflammation, forcing the brain to reorganize itself in order to achieve homeostasis. This reorganization can affect many bodily processes including immune function. The neurophysiology of these changes, as well as the related immune suppression and inflammation, are common to mood and anxiety disorders. These structural changes and deficits are also seen in persons' who experienced childhood adversity. Since a history of childhood maltreatment is a significant risk factor for these mental disorders, this is further support for the role of HPA dysregulation in the pathway between childhood adversity and poor adult health.

Early Life Maltreatment, Cortisol Responses and the HPA axis

Child abuse is associated with persistent changes in HPA axis activity (67;68). This programming leads to sensitization or hyperactivity of stress systems in reaction to even mild stressors in adulthood (69-71). Cortisol responses are a relatively noninvasive way of testing for potential HPA axis dysregulation programming (72). Animal studies have supported this by providing direct evidence linking early life experiences with structural and

neuroendocrine changes, including altered cortisol profiles (73;74). Human studies have followed suit, demonstrating the association between childhood adversity and cortisol. One of the earliest and easily the most famous of these is the Romanian orphan study, in which toddlers who experienced severe social deprivation demonstrated blunted cortisol patterns (75). A follow up study at 6.5 years post adoption found that infants who were institutionalized for at least 8 months in their first years of life now exhibited increased cortisol levels throughout the day (76).

In their landmark 2000 study, Heim et al. demonstrated persistent changes in stress reactivity in adult survivors of early trauma, specifically, increased pituitary-adrenal and autonomic responses to stress when compared to controls (69). The decade following was filled with a number of studies looking at the relationship between chronic abuse and cortisol. A recent systematic review found 27 of 30 studies reporting significant effects of both physical and psychological adversity on the cortisol stress response in children (67). Both increases and decreases in cortisol were considered to be an effect. Hypocortisolism, in theory, may be a defensive response with some protective and advantageous effects—for instance, some have argued it may lower allostatic load, and consequently reduce wear and tear on the stress system (77). However, it also presents with an increased vulnerability for the development of stress-related bodily disorders. Appropriately, McEwen and Stellar's definition of allostatic load includes both underactivity and hyperactivity of the stress system (50). This is because insufficient glucocorticoid signaling may have just as devastating effects on bodily

function as too much; it is well known that stress-related neuropsychiatric disorders are associated with both hypocortisolism (underproduction) and hypercortisolism (overproduction) (78). For instance, post-traumatic stress disorder (PTSD) is associated with hypocortisolism, and incidentally, PTSD presents with many of the same cognitive deficits as depression, a disorder marked by hypercortisolism (79-81). Not all investigations have confirmed the apparent opposite pattern of hypercortisolism for major depressive disorder (MDD) and hypocortisolism for PTSD (82;83). The same can be said of child maltreatment, as one recent study found healthy adults reporting significant early life abuse had decreased cortisol levels in response to stress, at odds with the general finding of hypercortisolism in the literature (70). Another study found children with PTSD and a history of abuse had high urinary cortisol levels—at odds with the common belief that PTSD presents with hypocortisolism (84). It has been suggested that the contrasting results in hypo/hyper cortisolism between studies might be accounted for by current life stress or psychopathology, with an underlying disordered stress system being the constant factor. It seems then, that it is the abnormal, inappropriate nature of the stress reaction in victims of adversity that is key and less so its direction.

Though the majority of studies demonstrate dysregulation of the HPA axis after childhood abuse, there are some which have found null results. Schury & Kolassa argue that this is likely due to methodological issues, specifically, how cortisol has been measured in these studies (21). In a follow–up to her landmark 1991 study, in which Kaufman found an increase in

cortisol secretion in maltreated children, Kaufman et al. initially uncovered no differences in cortisol secretion (85;86). Upon further exploration, Kaufman and her research team discovered a bi-modal response in post CRF ACTH release (86). Some were 'ACTH' responders— others weren't. ACTH responses were seen only in those children living in environments that continued to subject them to psychological abuse (marital violence, emotional abuse, lack of social supports) (86). This demonstrates the need to control for chronic or current life stressors, as well as the power of emotional maltreatment.

It is also interesting to consider the effect of subject age within these studies. While studies of adults with abuse histories consistently demonstrate a pattern of hypercortisolism, early life adversity appears to result in high cortisol levels in infants (87-89), but low cortisol levels in children(90). Looking to studies that focus on depression in children, there is often no significant difference in cortisol levels between depressed children and adolescents and their non-depressed counterparts (85). It is suspected that these differences in direction of cortisol abnormalities might have something do with the severity of the disorder, as melancholic children still display a decrease in post-CRF ACTH levels, and suicidal and severely depressed children do exhibit high baseline cortisol levels (85). Severity can be thought of as a function of chronic stress—with those presenting greater symptomatology suffering greater, chronic present day stresses. It is also interesting to consider the switch in cortisol direction seen in the Romanian orphans as they aged. This suggests that while dysregulation of the stress systems might be

consistent, how markers like cortisol present that dysregulation may evolve with age. This makes sense as we know that the effects of stress and immunotoxicants vary across the life span, no doubt a result of physiological changes in the body.

It seems important then, that factors like age, chronicity and severity be considered when comparing studies. It is also clear that despite sometimes conflicting results, there is an overall pattern of abnormality visible in most studies, even in the face of a host of potential methodological issues and confounders. Overall, this suggest that childhood abuse leads to dysregulation of the HPA axis.

Summary

Cortisol levels are often used to measure HPA dysregulation in humans. Persistent changes in cortisol reactivity have been seen in children and adults with a history of child abuse. Both increases and decreases in normal cortisol levels have been revealed, mimicking the abnormal profiles seen in persons with depression and PTSD. Both directions represent an increased vulnerability for poor health. These underlying atypical responses appear to be further altered by current life factors, like stress and age.

Intergenerational Transmission of HPA Dysregulation

We know from both human and animal studies that the nature of early maternal care influences the development of the neural systems responsible for behavioral and endocrine responses to stress (91). An insecure bond with a primary caregiver devotes an infant's resources to activating the stress

system, putting other growth processes ‘on hold’, negatively affecting the development of other brain regions (2;92). Children exposed to inadequate or inappropriate nurturance are at risk for a host of difficulties, including cognitive delays, physical health problems, and other psychosocial impairments; issues accompanied by altered neuroendocrine function (93;94).

While only a few studies address the problem, the potential for abnormal HPA axis behavior to be transmitted from mother to child has been highlighted. Women with a history of early life adversity have greater HPA sensitivity to stress during adulthood and pregnancy is an undeniably stressful period for many women (95;96). The post-partum period too is associated with a number of transitions, hormonal and otherwise, as well as an increased vulnerability to depression and anxiety (97). Indeed, women who have had a previous depressive episode (as those who have been maltreated are likely to have had) are especially vulnerable to perinatal depression (98).As mentioned earlier, mood disorders have been associated with HPA axis alteration; it is thus not surprising that newborns of depressed mothers have biochemical/physiological profiles that mimic their mothers’ own prenatal profiles, including elevated cortisol (99). Though much more limited in number, research looking at maternal PTSD and infant profiles reveals the same duplication of profiles between mother and child but with decreased cortisol, as can be expected in the case of PTSD (100). A recent longitudinal study examining the intergeneration transmission of depression found that youth exposed to maternal depression before age 5 had a higher risk not only for depression but also for continued experiences of acute and chronic stress

from childhood to age 20 (11). This is an excellent example of the long term effects of early altered neuroendocrine profiles and it also demonstrates the capacity for such a condition to compound and advance within a community over time.

In a study aimed at examining intergenerational predictors of cortisol in early childhood, Fisher et al. (2007) found that along with other maternal characteristics and behaviours, mothers' histories of social withdrawal in childhood were associated with their young children's lowered cortisol responses (93). This is particularly interesting, given that many stress-linked human conditions like depression and PTSD are characterized by social withdrawal. It also emphasizes how childhood characteristics can predict next generation cortisol profiles. Knowing that child abuse predicts later life stress outcomes and that stress during pregnancy can be transmitted to an infant, there was a natural interest to see if those abnormal stress outcomes were visible in the pregnancy period. Bulbitz and Stroud recently found that childhood sexual abuse predicted an increased cortisol awakening response during pregnancy, independent of anxiety symptomology (101). Their study found this result to be exclusive to childhood sexual abuse over other forms of abuse and neglect. However, they failed to address how multiple abuse experiences might affect cortisol. Gonzalez *et al.* were, conversely, able to demonstrate an association between all forms of childhood maltreatment, including psychological abuse, with a higher awakening cortisol response and sustained high levels throughout the morning in the postpartum period (97). These effects were independent of depression or anxiety symptomology.

They also showed that this response was even higher in women who experienced more than one form of abuse (97). Knowing that childhood abuse predicts maternal HPA dysregulation during pregnancy and the postpartum period, which in turn is associated with infants' abnormal neuroendocrine profiles throughout infancy and beyond, Brand *et al.* attempted to place all the pieces together. They were able to show that maternal child abuse was associated with lowered HPA axis function for both mother and infant in the postpartum period. They were also successful in demonstrating a moderating effect of depressive state, stressful life events and co-morbid PTSD on infant and maternal cortisol: mothers who suffered from both child abuse and current symptomology or stressors had higher cortisol levels. This gives some credence to the suggestion that current life experiences modulate childhood adversity's effect on the HPA axis, determining the direction of cortisol responses at any given point in time. All three of these studies examining maternal child abuse and cortisol in the pregnancy period controlled for maternal smoking. This strengthens the argument that while maternal stress might influence wheeze and allergy through stress-induced behaviours, like smoking, it is also likely that biologic processes are responsible for changes in the infants' development.

Summary

Adverse experiences in childhood are known to increase a woman's risk for mood and anxiety disorders during pregnancy and the postpartum. Mothers who are depressed or anxious have difficulty bonding with their children and practice abnormal attachment styles. Women who do not suffer

from mental illness, but have a history of childhood maltreatment also demonstrate poor attachment behaviours. Depression, anxiety and a history of childhood adversity have also been shown to independently effect women's cortisol profiles during pregnancy and in the postpartum. Nonetheless, there is obviously a complex interplay of these factors at work in the stress regulation of many new and expecting mothers. The resultant effects can be seen postnatally in infants' own cortisol levels, confirming the suspicion of earlier studies that intergenerational transmission of stress dysfunction is possible.

Infant HPA dysregulation, the immune system and asthma and allergies

The HPA axis is the core system for stress regulation, and as such, has a powerful effect on the immune system. Reports indicate that infants' immune systems are particularly sensitive to prenatal stress (102). This is not unexpected, given that the effects of maternal childhood maltreatment on an infants' HPA axis have been established, and that we know these changes increase the risk for stress-related illnesses (103).

Both genetic and environmental factors, like stress, impact the development of wheeze or allergy. Asthma is one of the most important diseases of childhood, causing substantial morbidity. Food allergy affects up to 6% to 8% of children less than 3 years of age and is also associated with significant morbidity and mortality (104). There is widespread concern that the prevalence of asthma and allergic disease is increasing in both western and developing countries. This has been met with a paradigm shift that

reconsiders the influence of psychosocial factors on both behavioral and biologic processes that may, in turn, cause wheeze and allergic disorder (8). Indeed, stressful life events, like abuse and exposure to violence and conflict have been identified as key toxic social contributors to asthma and allergies (105;106). Psychological stress has been shown to influence the onset, progression, and severity of these diseases (107).

Here, we wish to reiterate that the immune-related diseases of asthma and allergy are among the many physical health problems linked to child abuse mentioned earlier (108;109). And while data is limited on the effects of prenatal stress on the developing immune system, it has been implicated in the development of asthma and atopy (110). For instance, maternal stress, anxiety, and depression during pregnancy and the postpartum period is associated with asthma and allergy, along with a handful of other childhood diseases (7;8;111). We also know that mood disorders are common during the perinatal period and that there are extremely high rates of childhood abuse histories among women seeking treatment for perinatal depression (112-114).

While the etiology of wheeze and allergic disease is not yet understood, stress-induced neuroendocrine or immunologic changes may affect airway inflammation and reactivity through immunologic and neural pathways (e.g. the HPA axis), ultimately leading to wheeze and atopy (8;115). For instance, disruption of the HPA axis could exacerbate oxidative stress, which in turn might alter the delicate prooxidant–antioxidant balance of the placenta and thus disrupt the strict regulation of cortisol transfer to the

fetus (116;117). Maternal stress might also increase the risk of wheeze by enhancing children's vulnerability to respiratory infections (118). Maternal stress is thought to affect the infant, either by pre/postnatal programming of moms' abnormal neural profiles, or later, through maternal behaviours influenced by childhood trauma, like attachment style. Either way, they can both be considered to function via the same biological pathway to atopy and wheeze—inheritance of an abnormal stress reaction.

We know that stress reactivity in adulthood is determined by a combination of genetics and early experience. Genetic background can also play a role in determining stress reactivity right from birth. Epigenetics describe the genomic markings which are inherited between cell generations but make no changes in the primary DNA sequence. Essentially, they are the means to connect environmental exposures with gene expression and cell/tissue function (119). The suggestion that epigenetic mechanisms are involved in the intergenerational transmission of childhood trauma makes sense (21). Fetal programming via stress during pregnancy, and postnatal mother–infant interactions might directly alter a child's epigenome and thus the gene expression of the HPA axis. In animal models, poor early maternal care is associated with changes in offsprings' HPA stress response as a result of changes in the epigenetic regulation of glucocorticoid receptor gene NR3C1 (120). We also know that adults with a history of child abuse show increased methylation of glucocorticoid receptor gene NR3C1 (121). Finally, prenatal stress and depressed maternal mood, even at non clinical levels, is

associated with increased infant HPA stress responsiveness and predicted NR3C1 methylation status (122;123).

Given that maternal stress and depression during pregnancy and the postpartum period are thought to affect infants through the same neuroendocrine mechanisms—potentially through the epigenome, it seems plausible that children might demonstrate inheritance of their mother's childhood trauma through their own asthma and allergies.

Summary

Psychosocial stressors play an important role in the development of wheeze and allergies. Prenatal distress has also been implicated in the development of asthma and atopy. Women with a history of child abuse are both at an increased risk for distress and more likely to present with underlying dysfunction in their stress systems. There is evidence that this dysfunction can be transmitted from mother to child, possibly through epigenetic mechanisms or a modified fetal environment. It is suspected that when stress and immune dysregulation is inherited, fetal immune and lung development are affected, leading to the development of wheeze and allergic conditions.

Overall Summary

There is accumulating support for the relationship between the various forms of childhood maltreatment and several physical health concerns. It is thought the biological mechanism responsible is an impaired stress system. A considerable amount of research suggests that stress in early childhood

has a programming effect, resulting in lifelong abnormal stress reactions, which women may transmit to the next generation—whether through their biochemical/physiological profiles or their atypical parenting behaviours. Because of the relationship between an impaired stress system and dysregulated immunity in early childhood, health problems such as wheeze and allergy might be expected in the next generation.

It is a novel idea that maternal experiences which predate pregnancy by years and even decades can contribute to a child's health. It is thus not surprising that very few studies have empirically tested this hypothesis. To date, intergenerational transmission has mostly been limited to the context of low socioeconomic status (SES). Examples from these studies show that a parent's childhood SES, regardless of current income, predicts outcomes like an offspring's cardiovascular and atopic risk (124;125). The primary investigators of the latter study on atopy have also studied maternal interpersonal trauma over the life course. They found early life and chronic abuse was independently associated with cord blood IgE (a predictor of atopic risk) in their unadjusted models; after adjustment, an association remained for early life abuse, though it was no longer significant at a 95% confidence level (125) . Chronic abuse remained significant with an OR of 2.18 (125). One reason why early life abuse may not have maintained its significance may be the authors choice of measurement for interpersonal trauma—the revised conflict tactics scale (R-CTS) short form which tends to focus on physical abuse and specific forms of behavioural abuse only (126). The scale has consequently been criticized for failing to properly address

emotional abuse—a potentially critical factor in the link between maternal early life trauma and offspring health.

Present Study

The present study uses data from the Community Perinatal Care (CPC) Study to investigate how past maternal trauma, including emotional maltreatment, neglect, household dysfunction, physical and sexual abuse, might be associated with preschool wheeze and allergy outcomes in children through the intergenerational transmission and continuity of psychosocial stress (127). The conceptual framework (figure 1) presented below illustrates the suggested process.

Conflict within close relationships, in particular emotional abuse and neglect within the childhood family dynamic has been linked to poor emotional regulation, immunoincompetence and an increase in infection and illness behaviour (128-134). Any study on maternal child abuse and offspring health outcomes which assumes immune dysregulation to be the mechanism of action will be significantly lacking if it fails to address emotional maltreatment. The majority of CM research investigates only the impact of sexual abuse or the cumulative effect of all experienced abuse, without differentiating among the various forms of maltreatment. Consequently, an advantage of this study is its examination of each form of abuse on its own, including psychological abuse.

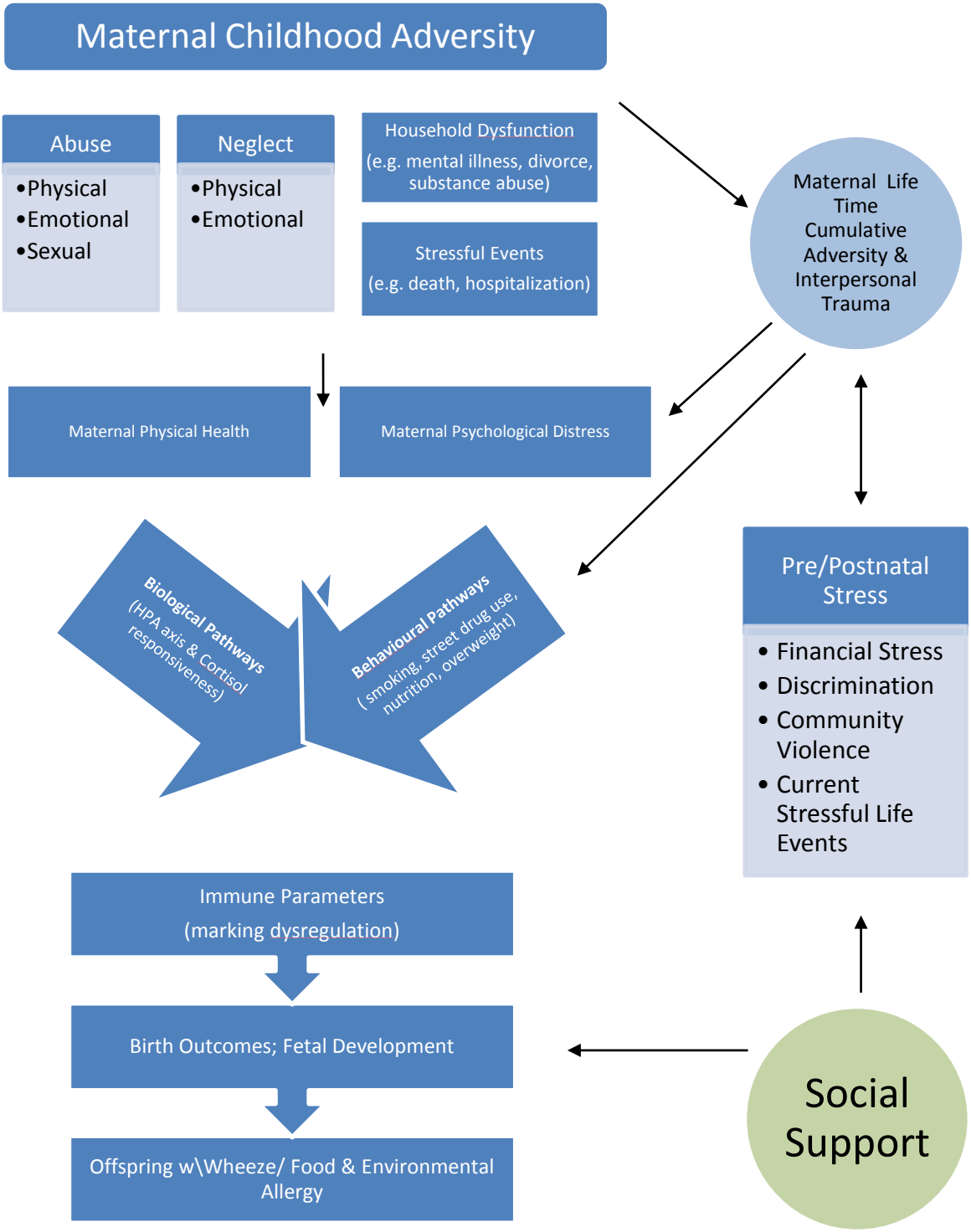

Figure 1. Conceptual framework of hypothesized pathway linking maternal childhood adversity, maternal stress and infant wheeze and allergy outcomes.

Research Questions

1. Is maternal early life trauma associated with wheeze and allergy in young children?

a) Does a dose-response relationship exist between the numbers of co-occurring types of abuse and wheeze outcomes in offspring?

2. Are child maltreatment types differentially associated with wheeze and allergy in children?

a) Is psychological abuse, including both emotional neglect and abuse, predictive of wheeze or allergy in young children?

b) Is physical abuse predictive of wheeze or allergy in young children?

c) Is sexual abuse predictive of wheeze or allergy in young children?

d) Is household dysfunction, defined as the presence of domestic violence and substance abuse, predictive of wheeze or allergy in young children?

e) Is neglect predictive of wheeze or allergy in young children?

Research Hypothesis

Preschool children are more likely to have a wheeze/allergic disorder if their mother has a history of maltreatment in her childhood, independent of the mother's distress during pregnancy and postnatally. This risk increases with the number of co-occurring traumatic experience types.

Methods

Participants

The longitudinal Community Perinatal Care (CPC) Study of Calgary provides extensive data on medically low risk mothers who sought services at one of three participating maternity clinics. Low medical risk refers to women who did not require an obstetrician for prenatal care and had an uncomplicated pregnancy requiring no specialists during delivery (135). Mothers completed two questionnaires during pregnancy which collected data on demographics, life events, pregnancy related issues and resource utilization. 791 women completed a follow-up questionnaire when their children were 3 years of age. This particular questionnaire provides our outcome variables of interest and so this group of women still participating in the CPC study at year 3 makes up our particular sample. Figure 2 in the appendix A demonstrates the recruitment and consent process.

Participants had a mean age of 29.2 years (SD= 5.0). 84 percent of women in the study were of Caucasian ethnicity and 84 percent of women had some college or university level education. 94 percent of women were married or common law. 91 percent had a combined family income of over $40,000 and 55% had incomes above $80,000. Additional demographic details for this sample can be found elsewhere (135).

Procedures

Moms who gave renewed consent participated in follow up phone surveys which focused on the health of their children and themselves. Before

completing the questionnaire, women were reminded that their participation was voluntary, that their responses would be linked to the original trial data, and that all information would be kept confidential (135). The study received ethical approval from the Conjoint Medical Bioethics Committee of the University of Calgary and Calgary Health Region.

Measures & Measurement Validity

When their children were 3 years of age, 61 mothers (7.7%) answered yes to the question: "Has a health care worker ever told you that your child has chronic breathing problems such as asthma, chronic obstructive pulmonary disease, or BPD which stand for bronchopulmonary dysplasia?" 77 mothers (9.7%) responded yes to the same question about allergies. Yes and no responses to these questions composed our dependent outcome variables of early childhood wheeze and allergies. Parental report of wheeze and allergy has been validated in a number of studies(136).

Our explanatory variables focus on different forms of early life maltreatment and conflict. Rates of reported child abuse vary by type, but overall child abuse rates in international non-clinical samples report between 6% and 40%, with the majority reporting rates in the low to mid-teens (137-140). Much of the variability in reported prevalence rates of child abuse is explained by the usual methodological factors—like the samples assessed, but perhaps especially in the case of maltreatment, by the definitions used (141). We began with the very comprehensive categorical definitions of abuse as laid out in the World Health Organization's 2012 report on preventing child maltreatment. At the same time, we scanned the literature

and made comparisons to popular, gold standard questionnaires like the Adverse Childhood Experiences and the Childhood Maltreatment Schedule. At this point we had a general idea of which questions tested what type of abuse. In the case of some types of abuse, like physical or sexual, we had only one measure, a direct generic question. For others, like emotional abuse and neglect, we had a number of questions to draw from. So at this point, to back up our categorizations whilst reducing our number of variables, a principal component analysis was also done. It was thought that the sample size should be sufficient and the ratio of cases to variables (questions) entered was also adequate. We predicted that the variables would be highly related, as abuse forms rarely occur in isolation. Our actual correlation values were, however, quite low, with very few above 0.3. Knowing that if the relationship is weak between variables, PCA does not work well to reduce data, it was felt that the literature should be our primary source of information regarding categorization. Interestingly, with the exception of the first component, which as usual contained the majority of our loadings and items we wanted to test individually, PCA supported our groupings for our composite variables of emotional abuse and household dysfunction.

There is one more thing to note with regards to the construction of our variables and to the rates observed. Childhood abuse stats are often presented for all cases under the age of 18 or 16. Because we chose to limit ourselves to early childhood years whenever possible, our presented rates and variables intentionally represent a subset of the abused population.

Studies which focus on the relationship between early life maltreatment and neurobiological change often fail to report on the age of the

children, simply referring to the stage of particular vulnerability as early childhood, or prepubertal. So while there has been some argument in the literature that the first 1, 3 or 5 years should be period of interest for the field, this seems somewhat arbitrary given how little research has been done on the neurobiological effects of trauma in developing children (90). Many experts in developmental traumatology, the new field which seeks to "systematically investigate the psychiatric and psychobiological impact of overwhelming and chronic interpersonal stress on the developing child," recognize that different brain regions have unique windows of vulnerability to the effects of traumatic stress. Thus, they argue that from a neurobiological stance, placing endpoints on sensitive or critical periods for trauma and stress in childhood is not reasonable at this time (68;142).

Our choice to go with age 8 and under was one of practicality—the period is still prepubescent and is the same age bracket for early childhood used by policy makers and researchers in the educational psychology context (143). It also allows us to capture a greater number of abused subjects. Indeed, many abuse prevalence studies that collect data on age have shown that a large proportion of abuse occurs after age 5 but before puberty. For instance, in the USA, it is estimated that more than 20% of children who are sexually molested, are abused before age 8, while the six year bracket of ages 0-5 captures around 12.5% (144).

There is a great deal of measurement error involved in retrospective reports of adverse experiences in childhood (145). But even after taking account of issues like false or repressed memories, reports are generally considered adequately reliable (146). Indeed, much of the measurement error

has to do with issues of dating memories, which is not surprising given issues of childhood amnesia in the first three years. Childhood amnesia is the well documented phenomenon in which adults are unable to remember events from the first 2-3 years of life; it is also well known that there is a "second phase of [childhood] amnesia in which adults recall very few memories from ages 3–7" (147). In addition to being few and far between, these autobiographical memories from pre-school and early school aged years "tend to be relatively rudimentary and loosely organized" (148). It is also known that the earlier the onset of childhood abuse, the more overgeneral a persons' memories are overall (149). Overgeneral memory is a phenomenon first recognized in depressed patients and those suffering from PTSD. Their memory recall is less specific in nature and more categoric. Categorical memories lump all experiences of a similar type into one, general summary of all occasions (150). Thus for these two reasons, or memory issues, it would be particularly difficult for victims of early abuse to accurately recall the onset of their maltreatment. By opening up our age bracket and allowing for some measurement error in dating the onset of their trauma, we not only allow ourselves to capture a higher number of subjects, but perhaps also account for some of this potential dating error.

Sexual and Physical Abuse

There is general agreement that a history of child abuse is most likely to be discovered when queried with multiple, specific questions which avoid the term "abuse" (151). Despite this, many researchers have yielded surprisingly sufficient numbers from generic questions which lack the *clear*

behavioral descriptions of experiences used by most gold standard measures. For example, McCauley et al. detected a history of child physical or sexual abuse in 22% of women in general medical clinics with 2 questions: “Were you ever physically abused before age 18?” and “Were you ever sexually abused before age 18?” (59). These rates fall within current North American estimates of 17-27% for physical and sexual childhood abuse in women (152). This relative success with generic questioning seems to be principally seen in women—so, it may be that probing, behavioural questions are especially needed with men. These questions are nearly synonymous with ours—“were you ever physically (sexually) abused and when did it start?” These questions were derived from the domestic violence committee of the former Calgary Health region and the Canadian Perinatal Nutrition Program (CPNP), who tested and reviewed the questions thoroughly. It is our hope, then, that despite the generic nature of the questions used by the CPC, their ability to capture physical and sexual abuse was augmented by the all-female subject pool. We also predict that a tendency to underreport to generic questions would bias these variables towards the null. This means that any relationship found would still be valid despite this self-report bias, though the association may appear weaker than it is in reality.

Neglect

Like our measures of child sexual and physical abuse, neglect was also asked in a generic manner (e.g. “were you neglected and when did it start”). Unfortunately, in the literature, generic questioning about neglect usually comes with a preamble that explains neglect as a failure to care and

provide for. While our measure does fail to do this, these introductions are usually included in questionnaires geared towards massive national samples and also used with children (153). Our sample is made up of adult women, of which 84.3% had some university or college training. So while the measure might be overly responsive, it is hoped that these women had a relatively reliable concept of what neglect is.

Psychological Maltreatment

Unlike physical and sexual abuse, which are considered relatively easy to identify, childhood emotional abuse has an "intangible quality", which has resulted in both medical and legal confusion (154). Psychological abuse is also the most recent form of abuse to be investigated. This may partially explain the large variation in operational definitions used, which is far greater than that of any other form of maltreatment.

The WHO provides a definition which covers the full scope of the literature; they state it is the "failure of a parent or caregiver to provide a developmentally appropriate and supportive environment…abuse of this type includes the restriction of movement; patterns of belittling, blaming, threatening, frightening, discriminating against, or ridiculing; and other nonphysical forms of rejection or hostile treatment." A slightly leaner characterization is Garbarino, Guttmann and Seeley seminal definition of emotional abuse as rejecting, isolating, terrorizing, ignoring, and corrupting behaviours (155). Many major organizations, like American Professional Society on the Abuse of Children (APSAC), use Garabrino *et al'*s definition, or a modification of it. All of these descriptives, including those of the broad

WHO definition, can be thought of as forming two main types of abuse; the first is an active harassment, the second, a passive rejection (156). And there is empirical support for this breakdown. Factor analysis of the psychological maltreatment rating scale (based on the APSAC 5 category definition) produces two factors: psychological abuse and psychological neglect (157). So we have at the heart of psychological maltreatment, two main components, emotional abuse and emotional neglect, which have "considerable but not complete overlap" (158). That is, both forms of maltreatment have been found to be consistently conceptually similar in both the behaviours of the aggressors and in the consequences for negatively affected children.

There are some that may argue that since the terms are not synonymous, emotional neglect and psychological abuse should not be lumped together into a measure of psychological maltreatment (159). The reasoning behind this is the belief that psychological abuse changes a child's cognition and/or morality, while emotional neglect creates a disturbed emotional life (159). This distinction is probably not useful, though, since "cognition and emotion are not independent of each other; that is, cognitive appraisal of experiences contribute to the affective experience and vice versa" (160). Acts of omission and commission are at the core of nearly all definitions of emotional maltreatment, and both are known to disrupt the cognitive and emotional lives of children. It's no surprise then, that emotional neglect and abuse have the same behavioural consequences in children (161).

Another argument for keeping them separate might be that, historically, most scales have failed to test for neglect within psychological maltreatment. In her review, Baker concluded that since so few commonly used measures collect on emotional neglect at all, that from a measurement perspective, psychological abuse might be treated as a unidimensional construct (162). But the failure of some popular scales to collect on psychological neglect, or, if they do (like ACE), to combine it with emotional abuse, doesn't mean that never the twain should meet. Arguably, then, there exists a real disconnect between concept and measurement in some of these questionnaires, and there have been calls for over two decades to resolve this (163). It would also be fair to say that more recent questionnaires, like the Childhood Trauma Questionnaire (CTQ) of 2003 and the Psychological Maltreatment Measure (PMM) of 2009, collect on them both, and in the case of the latter, do combine them. So there is a movement towards using both, and as a result, progress in bridging concept and measurement.

One final argument for combination might be that while emotional abuse and neglect are most often carried with other forms of abuse and neglect, they also present independently. There are numerous factors which distinguish emotional abuse and neglect from other forms of child abuse and neglect (160). That is to say, that in their non-physical nature, as well as their epidemiologic characteristics (for instance, who is the abuser), emotional abuse and neglect are so similar, and together, so different from other kinds of abuse.

We used the questions "did you feel your mother/father loved and cared about you" as our measure of emotional neglect. These questions are

taken from the well validated Childhood Maltreatment Schedule and were asked for each parent or step parent present before the age of 17 (164). We did consider whether this measure should be included in the neglect component rather than within emotional abuse, but we ultimately decided to group them under psychological maltreatment for the reasons discussed above. Principal component analysis also showed that questions of parental love loaded strongly with emotional abuse and bullying rather than with neglect. Our decision gains extra credence from the fact that Briere, the author of the Childhood Maltreatment Schedule, considers this question a measure of general psychological maltreatment (164;165).

The other half of our measure collected on the question of emotional abuse using the same generic form used by our physical and sexual abuse measures—e.g. “were you ever emotionally abused and when did it start (age)”. The only difference here was that the question was preceded by a preamble that described emotional abuse as including psychological or verbal abuse.

We classified severe emotional abuse in those respondents that felt they had at least one maternal and one paternal figure who did not love or care for them and that they were emotionally abused before age 8. Knowing that the love of a father can be as important as that of a mother to a child’s development, but that each partner can have a protective effect on a rejecting or absent parent, we chose to capture those who felt rejected by both parents (166). Children in such a situation would have no buffer, and as a result, would definitely qualify for the label of strong emotional neglect. Indeed, severity is an important factor in the case of psychological abuse, as many

participants will likely endorse at least one of the three psychological maltreatment components. Parental actions are generally considered psychologically abusive only if they are quite pervasive in a child's life (160).

Household Dysfunction

Our severe household dysfunction measure included exposure to both interpersonal violence ("Did your parents have violent arguments?") and substance abuse ("Did one of your parents drink or use drugs so much that it caused problems for the family"). The IPV question was new and was piloted by the CPC, while the question of substance abuse had been used for four cycles of Statistics Canada's National Population Health Survey (NPHS).

The Adverse Childhood Experiences (ACE) scale categorizes a battered mother and substance abuse as experiences of household dysfunction. In fact, ACE breaks up household dysfunction into five categories: substance abuse, mother treated violently, separation or divorce, mental illness and criminal behavior in the household (167). No measure for criminality in the household was available in the CPC. Measures of family history of depression and suicide were collected, but they lacked detail—age of participant when this occurred, the degree of familiarity of these relatives and whether they were in fact part of the household. Parental separation or divorced was investigated but we considered it as its own category, more on that later.

The choice to focus our measure of household dysfunction on IPV and substance abuse was not shaped only be their availability. The two are a highly correlated pair, and there is convincing evidence for a "global and

proximal association between men's use of substances and perpetration of IPV" (168). Strong debate continues over whether the link between substance abuse and marital violence is in fact casual, since they share so many risk factors in common(169). Questions of causality however, do not affect us. We recognize that a 'substance use and violence' relationship is not universal for all people, but that there exists a considerable group of families who experience both, and the children of these families are known to have at least as bad, and usually worse outcomes than those with only one exposure (170;171). Thus it makes sense from a severity point of view, to focus on those women who endured both of these environmental stressors, as a known dose-response relationship exists between the two. Also, because they are such a commonly occurring pair, observing each in isolation might be difficult.

There are some experts who consider exposure to intimate partner violence (IPV) to be a form of psychological abuse for children (i.e., witnessing violence against a parent), though most view it as a separate category of adverse childhood experiences. The argument for inclusion under the umbrella of psychological maltreatment draws upon the 'terrorizing' feature included in definitions of emotional abuse. However, much of this belief that exposure to IPV be classified as emotional maltreatment stems from and is propped up by the fact that household's with IPV often also emotionally and otherwise abuse their children (172). For instance, the 2008 Canadian Incidence Study documented found that of 34% of substantiated cases of exposure to IPV, nearly a third of these were also exposed to emotional abuse (25). But we also know that children who are exposed to

both emotional abuse and IPV often have worse outcomes than children who witness domestic violence but are not themselves abused, suggesting there might be some degree of difference between being an abused child and witnessing abuse (173-175).

Exposure to parental substance abuse has also been suggested as a form of psychological maltreatment, again due to the fact that emotional abuse or neglect is almost always part of the experience (176). From a review of the literature it appears that IPV and substance abuse are normally collected and reported under their respective labels and are not included in measures of emotional maltreatment. So while they may be a type of mental abuse, it seems important to note that children, though psychologically vulnerable to the stresses of these situations, are not the prime targets of these events, though they may sometimes participate by trying to intervene with their parents' behaviour. This makes these events somewhat more like environmental exposures than directed abuse. Because of this, it seems important to collect on household dysfunction as its own experience. It is also important to note that there exists varying degrees by which a child can witness marital conflict or substance abuse; a child may not always be present in the way he or she would need to be in order to be traditionally emotionally abused as well. In the case of IPV, over 10 different types of exposure have been identified, like seeing and hearing violent acts, seeing injuries resulting from the violence, and being told about the violence (177). Each of these might produce varying degrees in their effect on children's development. That is to say, certain kinds of witnessing might be more like emotional abuse, in that they might be more terrorizing than others.

The label of household dysfunction given to interpersonal violence and addiction by the Adverse Childhood Experiences study is quite apt. Substance abuse and marital violence are similar in kind and in that similarity, quite different from psychological abuse. It is the environmental nature of substance abuse and domestic violence that is key in their classification. It seems important to maintain categorizations based on type of abuse, for once we remove these dividers, we must recognize that all adverse care-giving experiences will almost certainly impact a child's psychological and emotional maltreatment. Divisions and nomenclature should be based on kind, lest we wish to combine all abuse together, and as a result, lose all distinctions.

One last thing that I would like to address is the fact that our question asked about violence between parents and not specifically about violence directed at mothers, as is the case in the ACE study and some others. We know that the overwhelming global burden of IPV is borne by women, and that as a result, a gender-informed perspective on IPV is the norm. We also know that in the minority of cases in which a female partner is the instigator of violence, family outcomes are equally poor. And, as in the case with men who batter, women's substance abuse is just as likely (178). As a result, we did not feel that there was any real difference between our question and one directed at battered mothers. If anything, ours may capture the experience of interpersonal violence in childhood more accurately.

Parental separation or divorce

In the ACE study, parental separation or divorce is considered its own category, and is asked in almost the very same way as ours, with a yes or no response.

Children of divorce have been found to experience substantial distress and divorce is associated with an increased risk for a number of adjustment, achievement and relationship difficulties (179). Indeed children of early life separation and divorce, especially those exposed to conflict, are at an increased risk for depression (180). Divorce has also been linked to children's atopic eczema (181). This finding demonstrates that the link between stress and the immune system that we are so interested in is visible within the context of family breakup. Resilience, however, is the norm for children and most children who experience parental separation adjust well and do not exhibit severe or enduring behaviour problems (182;183). We also know that separation and divorce can protect children from prolonged exposure to household violence. For this reason we felt it was appropriate to test as its own in category, rather than lumping it in with household dysfunction and risking that the very common experience of parental separation dilute the effects of household dysfunction, which captures a specific type of childhood experience which is associated with particularly poor outcomes.

Of course we still felt it important to investigate the effects of family breakup, given that children of separated and divorced parents "are still at twice the risk of problems as the non-separated community" (184).

Results

Prevalence Rates for Childhood Adversity

The research questions guiding this study involved identifying the prevalence of childhood adversity within Calgary mothers. Participants were classified as having experienced childhood physical abuse if they replied yes to the question 'were you physically abused?' According to this definition 10.37% of women were physically abused before age 18. 4.17% gave an age of 8 or less to the question 'when did it begin?' which is the group of interest in our study. Sexual abuse used the same line of questioning. 11.88% of women report being sexually abused before age 18, with 5.82% reporting abuse by age 8. Both of these are well within average prevalence rates estimated both internationally and within Canada. Neglect was asked in the same way as sexual and physical abuse. 5.7% report neglect before age 18, with 3.2% before age 9. This figure is a bit low, though not unheard of in the literature.

Psychological abuse was made up of 3 components. The first asked 'were you emotionally abused and when did it begin'. 33% of women responded that they felt they had been emotionally abused as minors, with 7.1% reporting it began by age 8. 24.1% of women responded that as a child they had a father figure who they felt did not love or care for them a great deal, while 12.0% responded they had a mother figure who they felt did not love or care for them. As we were looking for severity, we focused on persons reporting yes to all 3 questions to make up our psychological maltreatment

variable. 6.1% of women reported being psychologically maltreated before age 18, with 2.3% reporting before age 9.

Household dysfunction was also regarded for its severity, with women being considered if they reported both substance abuse and interpersonal violence within the home. 16.8% of women reported yes to the question 'did one of your parents drink or use drugs so much that it caused problems for the family?' 10.2% of these reported the substance abuse began before their ninth year. 9.4% of women answered yes to the question "did your parents have violent arguments?" with 6.7% reporting it started by age 8. Combined experience of these was reported in 4.8% of women under 18 and 3.2% under age 9.

23.8% of women answered yes to either the statement "your parents were divorced' or "your parents were separated" before age 18. 8.2% report separation or divorce by age 5.

Table 1 provides an overview of the number of women reporting each form of maltreatment and their co-occurrence with the outcomes of allergy and wheeze at age 3. In appendix A, table 1a provides the same information for the variables which had a significant sex interaction.

Table 1. *Child wheeze and allergy outcomes by maternal childhood experiences*

% of Women	Total Number	Wheeze at Age 3	Allergies at Age 3
Psychological Maltreatment by age 8			
Severe	18	5.6%	27.8%**
Moderate/None	762	7.7%	9.2%
Household Dysfunction by age 8			
Severe	25	28.0%**	4.0%
Moderate/None	757	7.1%	10.0%
Sexual Abuse by age 8			
Yes	46	10.9%	17.4%*
No	742	7.4%	9.3%
Physical Abuse by 8			
Yes	33	15.2%*	12.1%
No	756	7.4%	9.7%
Neglect by age 8			
Yes	25	20.0%**	20.0%*
No	766	7.3%	9.4%
Separation or Divorce by age 5			
Yes	65	10.8%	10.8%
No	721	7.4%	9.7%

* P<0.1
** P< 0.05

Relations among Measures

All intercorrelations among variables are presented in Table 2. Relationships among measures of childhood maltreatment were analyzed using Pearson correlations. Analyses revealed that many measures were associated with each other and that all measures were associated with neglect, physical abuse and in particular, psychological abuse. Recall that the presence of psychological abuse is sometimes considered a measure of severity for other forms. Also bear in mind that while most forms of abuse are highly interrelated and co-occur frequently, it is those individuals who were the victim of multiple forms of adversity that are at the highest risk for poor adult outcomes. Despite this, correlations values were in general quite small, supporting our decision to test different types of childhood experiences individually rather than child abuse in general.

***Table 2**.Correlations between different maternal childhood experiences*

	Psychological Abuse	Household Dysfunction	Separation or Divorce	Sexual Abuse	Physical Abuse	Neglect
Psychological Abuse		.118**	.078*	.071*	.485**	.418**
Household Dysfunction	.118**		.025	.079*	.073*	.094**
Separation or Divorce	.078*	.025		-.015	.079*	.108**
Sexual Abuse	.071*	.079*	-.015		.196**	.145**
Physical Abuse	.485**	.073*	.079*	.196**		.413**
Neglect	.418**	.094**	.108**	.145**	.413**	

**. Correlation is significant at the 0.01 level (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed)

Associations between demographic variables, like household income and maternal education, with outcomes of childhood wheeze and allergy were also analyzed. None of these proved to have significant associations within the models. Seven maternal and infant characteristics were identified as having a potential relationship with child wheeze and allergy. Psychological maltreatment and household dysfunction were our independent variables of the most interest, so they are included in the header of table 3. An extension of this table, including all variables of adversity can be found in appendix A, table 3.a.

Table 3. *Maternal childhood experiences and child wheeze and allergy outcomes by maternal characteristics*

% of Women	Total Number	Psychological Maltreatment before Age 8	Household Dysfunction before Age 8	Wheeze at Age 3	Allergies at Age 3
Prenatal Maternal Smoking					
Moderate/Heavy	84	4.8%	6.0%	10.7%	15.5%*
Light/None	668	2.1%	3.0%	7.2%	8.7%
Postnatal Maternal Smoking					
Moderate/Heavy	62	1.6%	3.3%	12.9%*	14.5%
Light/None	684	2.5%	3.3%	7.2%	9.2%
Preterm Birth					
Yes	51	3.9%	-	15.7%**	7.8%
No	694	2.3%	3.5%	7.1%	9.8%
Prenatal Maternal Vitamin Use					
Yes	727	2.4%	3.2%	7.3%**	9.5%
No	19	5.3%	5.3%	21.1%	15.8%
Breastfeeding					
< 8 Weeks	146	2.8%	5.7%*	7.5%	10.3%
> 8 Weeks	600	2.4%	2.7%	7.7%	9.5%
Prenatal Maternal Distress					
Severe	33	3.1%	9.1%	15.2%*	24.2%*
Moderate	91	4.4%	4.8%	11.0%	12.1%
None	667	1.1%	3.0%	6.9%	8.7%
Potential Postpartum Depression					
Yes	54	1.9%	9.3%**	9.3%	9.3%
No	607	2.3%	2.3%	7.4%	8.9%

*P<0.1
**P< 0.05

Postpartum depression and distress during pregnancy are the covariates most expected to be related to our dependent variables of interest (childhood maltreatment). So, it is interesting and perhaps somewhat expected that 7.5% of women with a history of at least one adverse childhood

reported severe pregnancy distress, compared to only 3.4% of women who reported no maltreatment. In those women experiencing 2 or more childhood adverse experiences that rate jumps to 18.2% versus 3.6% in those experiencing one or no abuse types. Similarly, 12.5% of women reporting at least one kind of childhood adversity experienced likely postpartum depression (as measured by the EPDS), compared to 7.2% of women reporting none. In those women reporting 2 or more adverse childhood experiences, the number likely suffering from postpartum depression jumps to 23.3%, compared to 7.4% in those experiencing none or one kind of adversity.

Model Testing

Logistic regression analysis was utilized to predict the likelihood of childhood wheeze or allergy if a mother has a history of childhood trauma. As discussed earlier, the presence of wheeze or asthma outcomes were coded 0 for a no response and 1 for a yes response to the question 'has a health care professional told you your child has chronic breathing problems/allergies'. These made up our dependent variables. Maternal and child characteristics were considered as potential confounders to the effects of maternal childhood trauma. The variables included in the logistic regression analyses were chosen based on the level of significance achieved in bivariate analyses and/or their theoretical relevance. These were as follows: prenatal maternal smoking, prenatal maternal vitamin use, preterm birth, postnatal smoking, breastfeeding, sex of child, and prenatal distress.

Based on an alpha value of 0.05 and 80% power we would have required 1702 participants (851 in each outcome group of wheeze/no wheeze). This is based on the prevalence of preschool wheeze in our sample of 0.07 and an adjusted odds ratio of 1.48, based on the findings of Sternthal *et al*. for early life maternal interpersonal trauma and upper quartile cord blood IgE levels (185). A similar number is required for allergies, using a prevalence of 0.097. Thus, due to the relatively small number of cases for some types of abuse and our outcomes of interest, it is arguable that our logistic regression analyses may have had insufficient power to include all theoretically valid variables. In two cases, this was true to the extent that we were unable to test adjusted models. Models were also run a second time with the inclusion of a variable for possible postpartum depression, a variable strongly related to prenatal distress. While postpartum depression was not significant in bivariate analyses, it is potentially theoretically relevant. Due to the small number of cases, we present both models for consideration. Cases with missing data were not included in the analyses. We choose to focus our analysis here on the effects of psychological abuse and household dysfunction. Models for other forms of abuse can be found in appendix A (tables 9-10).

The first logistic regression model presented focuses on the effects of psychological abuse by age 8 with the outcomes of wheeze and allergy at 3 years. As can be seen in table 4, maternal psychological abuse was significantly associated with allergies in toddlerhood (OR: 3.36; 95% CI: 1.12-10.10). With the inclusion of a measure of postpartum depression in table 4a,

this variable is no longer significant (OR: 2.41; 95% CI: 0.63-9.30). At the same time, we see that even the effects of child's sex on allergic outcomes, which are relatively well established, are no longer visible in a model including postpartum depression.

Table 4. *Maternal experience of psychological maltreatment and risk of wheeze and allergies in all children*

		Wheeze at age 3 Years		Allergies at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Psychological Abuse before age 8 (reference: moderate or none)		0.70 (0.10-5.34)	0.55 (0.07-4.46)	**3.75 (1.30-10.80)**	**3.36 (1.12-10.10)**
Prenatal Maternal Smoking (reference: light or none)		1.54 (0.73-3.25)	0.75 (0.19-3.01)	**1.92 (1.00-3.66)**	1.45 (0.52-4.06)
Postnatal Maternal Smoking (reference: light or none)		1.92 (0.86-4.26)	2.31 (0.54-9.78)	1.67 (0.79-3.55)	1.24 (0.38-4.03)
Preterm Birth (reference: term)		**2.45 (1.09-5.50)**	**2.46 (1.07-5.68)**	0.78 (0.27-2.24)	0.74 (0.25-2.16)
Prenatal Maternal Vitamin Use (reference: none)		**0.30 (0.10-0.92)**	**0.23 (0.07-0.76)**	0.56 (0.16-1.97)	0.58 (0.16-2.19)
Breastfeeding (reference: less than 8 weeks or none)		1.02 (0.52-2.02)	1.41 (0.67-3.00)	0.92 (0.50-1.67)	1.24 (0.64-2.42)
Prenatal Maternal Distress (reference: none)	Moderate	1.67 (0.81-3.43)	1.51 (0.69-3.31)	1.44 (0.73-2.87)	1.53 (0.75-3.12)
	Severe	2.41 (0.89-6.54)	**2.91 (1.01-8.35)**	**3.36 (1.45-7.79)**	**3.53 (1.44-8.67)**
Sex of the baby (reference: girl)		**1.99 (1.16-3.42)**	**2.21 (1.24-3.94)**	**1.66 (1.03-2.68)**	**1.77 (1.06-2.95)**

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child and duration exclusive breastfeeding.

Table 4a. *Maternal experience of psychological maltreatment and risk of wheeze and allergies in all children*

	Wheeze at age 3 Years		Allergies at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Psychological Abuse before age 8 (reference: moderate or none)	0.70 (0.10-5.34)	0.55 (0.07-4.46)	**3.75 (1.30-10.80)**	2.41 (0.63-9.30)
Prenatal Maternal Smoking (reference: light or none)	1.54 (0.73-3.25)	0.75 (0.19-3.01)	**1.92 (1.00-3.66)**	1.67 (0.58-4.80)
Postnatal Maternal Smoking (reference: light or none)	1.92 (0.86-4.26)	2.31 (0.54-9.78)	1.67 (0.79-3.55)	1.27 (0.38-4.25)
Preterm Birth (reference: term)	**2.45 (1.09-5.50)**	**2.46 (1.07-5.68)**	0.78 (0.27-2.24)	0.67 (0.20-2.29)
Prenatal Maternal Vitamin Use (reference: none)	0.30 (0.10-0.92)	**0.23 (0.07-0.76)**	0.56 (0.16-1.97)	0.56 (0.12-2.36)
Breastfeeding (reference: less than 8 weeks or none)	1.02 (0.52-2.02)	1.41 (0.67-3.00)	0.92 (0.50-1.67)	1.16 (0.57-2.36)
Prenatal Maternal Distress (reference: none) Moderate	1.67 (0.81-3.43)	1.51 (0.69-3.31)	1.44 (0.73-2.87)	1.88 (0.91-3.91)
Severe	2.41 (0.89-6.54)	**2.91 (1.01-8.35)**	**3.36 (1.45-7.79)**	**3.76 (1.32-10.74)**
Sex of the baby (reference: girl)	**1.99 (1.16-3.42)**	**2.21 (1.24-3.94)**	**1.66 (1.03-2.68)**	1.71 (0.97-3.00)
Possible Postpartum Depression (EPDS score) (reference: no depression)	1.27 (0.48-3.36)	-	1.05 (0.40-2.73)	0.76 (0.28-2.13)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child, duration exclusive breastfeeding and **potential postpartum depression**.

Table 5 and 5a test the hypothesis that a mother's experience of household dysfunction before age 9 is related to their children's wheeze and allergy outcomes. We were unable to adjust the model for any covariates in the case of allergies due to the small number reporting both allergies and household dysfunction. Household dysfunction significantly predicts wheeze in 3 year olds (OR: 4.01; 95% CI: 1.36-11.81). The effect size is lower, but still significant with the inclusion of postpartum depression (OR: 3.38; 95% CI: 1.02-11.24). This comparative resilience may be explained by the fact that we had 25 cases of childhood household dysfunction but only 18 cases of psychological abuse (the lowest of all of our adversity measures). The effects of preterm birth and prenatal vitamin use also did not fare well in the presence of postpartum depression.

Table 5. *Maternal experience of household dysfunction and risk of wheeze and allergies in all children*

		Wheeze at age 3 Years		Allergies at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Household Dysfunction before age 8 (reference: moderate or none)		**5.06 (2.03-12.65)**	**4.01 (1.36-11.81)**	0.37 (0.05-2.80)	0.37 (0.05-2.80)
Prenatal Maternal Smoking (reference: light or none)		1.54 (0.73-3.25)	0.69 (0.17-2.72)	1.92 (1.00-3.66)	-
Postnatal Maternal Smoking (reference: light or none)		1.92 (0.86-4.26)	2.55 (0.60-10.78)	1.67 (0.79-3.55)	-
Preterm Birth (reference: term)		**2.45 (1.09-5.50)**	**2.64 (1.14-6.12)**	0.78 (0.27-2.24)	-
Prenatal Maternal Vitamin Use (reference: none)		**0.30 (0.10-0.92)**	**0.24 (0.07-0.80)**	0.56 (0.16-1.97)	-
Breastfeeding (reference: less than 8 weeks or none)		1.02 (0.52-2.02)	1.45 (0.69-3.08)	0.92 (0.50-1.67)	-
Prenatal Maternal Distress (reference: none)	Moderate	1.67 (0.81-3.43)	1.46 (0.67-3.22)	1.44 (0.73-2.87)	-
	Severe	2.41 (0.89-6.54)	2.51 (0.87-7.23)	**3.36 (1.45-7.79)**	-
Sex of the baby (reference: girl)		**1.99 (1.16-3.42)**	**2.20 (1.23-3.94)**	**1.66 (1.03-2.68)**	-

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child and duration exclusive breastfeeding.

Table 5a. *Maternal experience of household dysfunction and risk of wheeze and allergies in all children*

		Wheeze at age 3 Years		Allergies at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Household Dysfunction before age 8 (reference: moderate or none)		**5.06 (2.03-12.65)**	**3.38 (1.02-11.24)**	0.37 (0.05-2.80)	0.37 (0.05-2.80)
Prenatal Maternal Smoking (reference: light or none)		1.54 (0.73-3.25)	0.73 (0.18-2.90)	1.92 (1.00-3.66)	-
Postnatal Maternal Smoking (reference: light or none)		1.92 (0.86-4.26)	2.61 (0.61-11.24)	1.67 (0.79-3.55)	-
Preterm Birth (reference: term)		**2.45 (1.09-5.50)**	1.95 (0.75-5.06)	0.78 (0.27-2.24)	-
Prenatal Maternal Vitamin Use (reference: none)		**0.30 (0.10-0.92)**	0.49 (0.10-2.38)	0.56 (0.16-1.97)	-
Breastfeeding (reference: less than 8 weeks or none)		1.02 (0.52-2.02)	1.12 (0.52-2.39)	0.92 (0.50-1.67)	-
Prenatal Maternal Distress (reference: none)	Moderate	1.67 (0.81-3.43)	1.59 (0.71-3.55)	1.44 (0.73-2.87)	-
	Severe	2.41 (0.89-6.54)	1.65 (0.44-6.22)	**3.36 (1.45-7.79)**	-
Sex of the baby (reference: girl)		**1.99 (1.16-3.42)**	**2.96 (1.54-5.66)**	1.66 (1.03-2.68)	-
Possible Postpartum Depression (EPDS score) (reference: no depression)		1.27 (0.48-3.36)	0.86 (0.31-2.43)	1.05 (0.40-2.73)	-

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child duration exclusive breastfeeding and potential postpartum depression.

Finally, we'd like to present our sex specific findings. Given sex interactions of a moderate strength with the variables of separation or divorce with wheeze (p=0.12) and sexual abuse with allergies (p=0.14), we decided to proceed with a sex centered analysis. Separation or divorce presents a borderline significant association with wheeze in daughters at age 3; a p-value of 0.059 in the adjusted model with all covariates but PPD, and a p-value of 0.052 in the adjusted model with the addition of PPD. These models can be found in table 6 and 6a respectively. The sons of mothers who were sexually abused had an increased risk of allergies in toddlerhood. This was seen both in a model containing all co-variates except PPD (OR: 2.83 95%CI: 1.03-7.72) and in a model containing PPD (OR: 3.26 95% CI: 1.16-9.18). These models can be found in table 7 and 7a. Postpartum depression had no observable relationship with allergies in girls and so we were unable to adjust for it in the larger model. However, like in the case of separation or divorce, there is arguably a small improvement seen in the sexual abuse variable when postpartum depression is added to the model, with a shift from a p-value of 0.043, down to 0.025.

Table 6. *Sex specific risk of preschool wheeze in relation to maternal childhood experience of separation or divorce*

	Girls at age 3 Years		Boys at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Separation or Divorce before age 5 (reference: none)	**3.13 (0.98-9.95)**	**3.23 (0.96-10.94)**	0.83 (0.24-2.85)	0.77 (0.21-2.81)
Prenatal Maternal Smoking (reference: light or none)	0.40 (0.05-3.08)	0.18 (0.02-1.99)	**2.41 (1.02-5.69)**	1.07 (0.26-4.37)
Postnatal Maternal Smoking (reference: light or none)	0.53 (0.07-4.08)	0.70 (0.07-7.45)	**3.38 (1.32-8.57)**	5.00 (0.91-27.49)
Preterm Birth (reference: term)	3.04 (0.82-11.25)	3.59 (0.94-13.73)	2.04 (0.73-5.73)	1.89 (0.64-5.53)
Prenatal Maternal Vitamin Use (reference: none)	**0.14 (0.04-0.58)**	0.21 (0.04-1.09)	0.68 (0.08-5.80)	0.69 (0.08-5.98)
Breastfeeding (reference: less than 8 weeks or none)	2.06 (0.47-9.09)	2.87 (0.61-13.55)	0.81 (0.37-1.80)	1.01 (0.43-2.39)
Prenatal Maternal Distress (reference: none) Moderate	1.44 (0.40-5.13)	1.68 (0.45-6.33)	1.79 (0.74-4.36)	1.40 (0.53-3.72)
Severe	**4.41 (1.15-16.90)**	**4.62 (1.15-18.51)**	1.39 (0.30-6.41)	1.62 (0.33-7.98)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth and duration exclusive breastfeeding.

Table 6a. *Sex specific risk of preschool wheeze in relation to maternal childhood experience of separation or divorce*

	Girls at age 3 Years		Boys at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Separation or Divorce before age 5 (reference: none)	**3.13 (0.98-9.95)**	**3.89 (0.99-15.31)**	0.83 (0.24-2.85)	0.79 (0.21-2.91)
Prenatal Maternal Smoking (reference: light or none)	0.40 (0.05-3.08)	0.29 (0.03-3.17)	**2.41 (1.02-5.69)**	0.91 (0.22-3.82)
Postnatal Maternal Smoking (reference: light or none)	0.53 (0.07-4.08)	1.05 (0.10-10.76)	**3.38 (1.32-8.57)**	4.17 (0.76-22.95)
Preterm Birth (reference: term)	3.04 (0.82-11.25)	3.27 (0.66-16.09)	2.04 (0.73-5.73)	1.34 (0.41-4.41)
Prenatal Maternal Vitamin Use (reference: none)	**0.14 (0.04-0.58)**	0.25 (0.03-2.29)	0.68 (0.08-5.80)	0.81 (0.10-7.29)
Breastfeeding (reference: less than 8 weeks or none)	2.06 (0.47-9.09)	1.67 (0.35-7.89)	0.81 (0.37-1.80)	0.90 (0.38-2.12)
Prenatal Maternal Distress (reference: none) Moderate	1.44 (0.40-5.13)	2.46 (0.64-9.50)	1.79 (0.74-4.36)	1.32 (0.49-3.53)
Severe	**4.41 (1.15-16.90)**	2.17 (0.25-18.77)	1.39 (0.30-6.41)	1.51 (0.29-7.77)
Possible Postpartum Depression (EPDS score) (reference: no depression)	**4.68 (1.20-18.28)**	**4.68 (1.15-19.04)**	0.48 (0.11-2.10)	0.38 (0.08-1.75)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, duration exclusive breastfeeding and possible postpartum depression.

Table 7. *Sex specific risk of preschool allergy in relation to maternal childhood sexual abuse.*

		Girls at age 3 Years		Boys at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Sexual Abuse before age 8 (reference: none)		0.63 (0.08-4.84)	0.54 (0.07-4.26)	**2.99 (1.18-7.55)**	**2.83 (1.03-7.72)**
Prenatal Maternal Smoking (reference: light or none)		1.84 (0.66-5.10)	1.32 (0.35-5.03)	1.96 (0.84-4.56)	1.45 (0.45-4.71)
Postnatal Maternal Smoking (reference: light or none)		1.35 (0.47-3.85)	0.82 (0.17-3.81)	2.43 (0.98-6.01)	1.67 (0.42-6.64)
Preterm Birth (reference: term)		1.18 (0.26-5.31)	1.29 (0.28-5.94)	0.55 (0.13-2.39)	0.52 (0.11-2.33)
Prenatal Maternal Vitamin Use (reference: none)		0.39 (0.08-1.87)	0.44 (0.09-2.21)	0.81 (0.10-6.87)	0.83 (0.09-7.42)
Breastfeeding (reference: less than 8 weeks or none)		0.84 (0.33-2.15)	1.06 (0.39-2.86)	1.01 (0.46-2.21)	1.36 (0.59-3.17)
Prenatal Maternal Distress (reference: none)	Moderate	2.20 (0.84-5.76)	2.39 (0.89-6.43)	0.99 (0.37-2.68)	0.96 (0.34-2.68)
	Severe	3.15 (0.84-11.77)	2.87 (0.74-11.09)	**3.61 (1.19-10.99)**	**3.63 (1.08-12.22)**

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth and duration exclusive breastfeeding.

Table 7a. *Sex specific risk of preschool allergy in relation to maternal childhood sexual abuse*

	Girls at age 3 Years		Boys at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Sexual Abuse before age 8 (reference: none)	0.63 (0.08-4.84)	0.54 (0.07-4.26)	**2.99 (1.18-7.55)**	**3.26 (1.16-9.18)**
Prenatal Maternal Smoking (reference: light or none)	1.84 (0.66-5.10)	1.32 (0.35-5.03)	1.96 (0.84-4.56)	1.82 (0.55-6.02)
Postnatal Maternal Smoking (reference: light or none)	1.35 (0.47-3.85)	0.82 (0.17-3.81)	2.43 (0.98-6.01)	2.23 (0.54-9.20)
Preterm Birth (reference: term)	1.18 (0.26-5.31)	1.29 (0.28-5.94)	0.55 (0.13-2.39)	0.65 (0.14-3.04)
Prenatal Maternal Vitamin Use (reference: none)	0.39 (0.08-1.87)	0.44 (0.09-2.21)	0.81 (0.10-6.87)	0.73 (0.08-6.51)
Breastfeeding (reference: less than 8 weeks or none)	0.84 (0.33-2.15)	1.06 (0.39-2.86)	1.01 (0.46-2.21)	1.17 (0.47-2.89)
Prenatal Maternal Distress (reference: none) Moderate	2.20 (0.84-5.76)	2.39 (0.89-6.43)	0.99 (0.37-2.68)	1.18 (0.41-3.37)
Severe	3.15 (0.84-11.77)	2.87 (0.74-11.09)	**3.61 (1.19-10.99)**	**5.62 (1.50-20.97)**
Possible Postpartum Depression (EPDS score) (reference: no depression)	-	-	1.53 (0.55-4.26)	1.17 (0.38-3.57)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, duration exclusive breastfeeding and possible postpartum depression.

Finally, given the literature linking the experience of two or more types of adversity in childhood with worse adult health outcomes, we wished to examine whether this measure of severity was relevant to the next generation as well. That is, theoretically speaking, if experiencing more than one type of abuse is a measure of severity associated with an increased likelihood of having an abnormal stress reaction (as made evident by the increased risk of adult related illnesses), the likelihood of transmission could theoretically increase as well. In all children, there was increased likelihood of wheeze in a model containing all covariates but PPD (OR: 3.18; 95% CI: 1.24-8.19). In a model containing PPD, this becomes borderline (OR: 2.71; 95% CI: 0.94-2.43, p-value= 0.06). These models can be seen in their entirety in table 8 and 8a. There was a significant sex interaction with the experience of 2 or more abuse experiences and wheeze outcomes (p=0.04). Thus, once again, we proceeded with a sex centered analysis. We found that maternal experience of more than two or more types of adversity increased the likelihood of daughters having a wheeze disorder in both a model containing all covariates but PPD (OR: 10.06; 95% CI: 2.77-36.52) and in a model including PPD (OR: 8.068; 95% CI: 1.82-35.80) . These models can be seen in appendix A tables 11 and 11 a. Figure 3 in appendix A provides a general overview of the findings for all types of adversity with the outcomes of wheeze and allergy.

Table 8. *Maternal experience of multiple forms of childhood adversity and risk of wheeze and allergies in children*

		Wheeze at age 3 Years		Allergies at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
2 or More Early Life Adversity Experiences (reference: one or none)		**4.26 (1.83-9.90)**	**3.18 (1.24-8.19)**	1.70 (0.64-4.54)	1.10 (0.38-3.21)
Prenatal Maternal Smoking (reference: light or none)		1.54 (0.73-3.25)	0.62 (0.16-2.44)	1.92 (1.00-3.66)	1.60 (0.57-4.48)
Postnatal Maternal Smoking (reference: light or none)		1.92 (0.86-4.26)	2.77 (0.67-11.51)	1.67 (0.79-3.55)	1.10 (0.34-3.58)
Preterm Birth (reference: term)		**2.45 (1.09-5.50)**	2.29 (0.98-5.36)	0.78 (0.27-2.24)	0.75 (0.26-2.19)
Prenatal Maternal Vitamin Use (reference: none)		**0.30 (0.10-0.92)**	0.32 (0.09-1.10)	0.56 (0.16-1.97)	0.56 (0.15-2.07)
Breastfeeding (reference: less than 8 weeks or none)		1.02 (0.52-2.02)	1.35 (0.64-2.86)	0.92 (0.50-1.67)	1.24 (0.64-2.39)
Prenatal Maternal Distress (reference: none)	Moderate	1.67 (0.81-3.43)	1.34 (0.60-2.99)	1.44 (0.73-2.87)	1.54 (0.76-3.13)
	Severe	2.41 (0.89-6.54)	2.20 (0.74-6.52)	**3.36 (1.45-7.79)**	**3.25 (1.32-7.98)**
Sex of the baby (reference: girl)		**1.99 (1.16-3.42)**	**2.16 (1.21-3.85)**	**1.66 (1.03-2.68)**	**1.71 (1.04-2.83)**

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth and duration exclusive breastfeeding.

Table 8a. *Maternal experience of multiple forms of childhood adversity and risk of wheeze and allergies in children*

		Wheeze at age 3 Years		Allergies at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
2 or More Early Life Adversity Experiences (reference: one or none)		**4.26 (1.83-9.90)**	2.71 (0.94-7.80)	1.70 (0.64-4.54)	1.00 (0.31-3.29)
Prenatal Maternal Smoking (reference: light or none)		1.54 (0.73-3.25)	0.63 (0.16-2.56)	1.92 (1.00-3.66)	1.85 (0.65-5.28)
Postnatal Maternal Smoking (reference: light or none)		1.92 (0.86-4.26)	2.82 (0.66-12.11)	1.67 (0.79-3.55)	1.14 (0.34-3.79)
Preterm Birth (reference: term)		**2.45 (1.09-5.50)**	1.70 (0.65-4.47)	0.78 (0.27-2.24)	0.68 (0.20-2.32)
Prenatal Maternal Vitamin Use (reference: none)		**0.30 (0.10-0.92)**	0.61 (0.12-3.10)	0.56 (0.16-1.97)	0.60 (0.13-2.83)
Breastfeeding (reference: less than 8 weeks or none)		1.02 (0.52-2.02)	1.04 (0.49-2.21)	0.92 (0.50-1.67)	1.14 (0.57-2.31)
Prenatal Maternal Distress (reference: none)	Moderate	1.67 (0.81-3.43)	1.51 (0.67-3.40)	1.44 (0.73-2.87)	1.91 (0.92-3.96)
	Severe	2.41 (0.89-6.54)	1.49 (0.39-5.77)	**3.36 (1.45-7.79)**	**3.31 (1.16-9.40)**
Sex of the baby (reference: girl)		**1.99 (1.16-3.42)**	**2.97 (1.55-5.69)**	**1.66 (1.03-2.68)**	1.63 (0.94-2.83)
Possible Postpartum Depression (EPDS score) (reference: no depression)		1.27 (0.48-3.36)	0.85 (0.30-2.43)	1.05 (0.40-2.73)	0.78 (0.28-2.17)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, duration exclusive breastfeeding and possible postpartum depression.

Discussion

The purpose of this research was to explore relationships between different types of maternal childhood adversity and wheeze and allergic outcomes in the next generation. The independent variables included 6 different forms of childhood adversity, which were as follows: sexual abuse, physical abuse, neglect, psychological abuse, household dysfunction and separation or divorce. Because of developmental implications, we limited our variables to those events experienced by mothers before age 8. All were considered as risk factors for the outcomes of wheeze and allergy at age 3.

The primary goal here was to examine the relationship between each kind of adversity with our dependent variables. We also hoped to examine whether the experience of more than one type of abuse by mothers was related with increased risk for poor health in children, as it has been for the victims of child abuse themselves.

It was hypothesized that abuse of a non-physical nature would have particularly strong results. It was felt that while psychological stress has taken a back seat to other, more visible forms of maltreatment in the literature, psychological abuse has been associated with worse psychopathological outcomes in adults, which are a good indicator of an abnormal stress reaction. Variables like household dysfunction and psychological abuse were thus expected to explain a significant portion of the

variance of both wheeze and allergy in toddlers, even after controlling for maternal distress during pregnancy.

Overview of Results

The sample for this study was composed of 791 mothers and their children. The prevalence rates of the abuse experienced before age 18 by this sample were consistent with those reported in other community samples.

Women with a history of severe childhood psychological abuse were more than 3 times more likely to report their toddler had allergies (adjusted OR: 3.36; 95% CI: 1.12-10.10). Similarly, maternal experience of household dysfunction increased a child's risk of wheeze 4 fold (adjusted OR: 4.01 95% CI: 1.36-11.81).

These results support the hypothesis that maternal childhood adversity is associated with both wheeze and allergy in the next generation. Moreover, despite small numbers of women reporting certain types of maltreatment, we were still able to test these distinct forms of abuse in our models. The 4 types of adversity that had significant or borderline significant associations with allergies or wheeze were psychological abuse, household dysfunction, separation or divorce, and sexual abuse. The first three are of a nonphysical nature and considered to be primarily psychologically stressing, while the latter, sexual abuse, is also known to be very closely tied with psychological abuse. Our results emphasize the importance of examining specific types of maltreatment rather than trauma in general, and that psychological stress during childhood may be particularly important in explaining abnormal stress

transmission between generations. Clinically, it highlights the importance of identifying early life trauma in the medical histories of pregnant women, especially in those already identified as at a risk for pre or postnatal depression or anxiety.

Since the intergenerational premise of our study is quite novel it comes as no surprise that only a handful of articles have been published translating this concept. For the purpose of comparisons, we are quite fortunate that 2 of these articles, coming from Sternthal *et al.*'s research group, focus on predictors of atopic disease (cord blood IgE) and wheeze outcomes (125;185).

The first study looked at early life and chronic interpersonal trauma, as well as maternal childhood SES, as the independent variables of interest. The initial association found between early life trauma and cord blood IgE levels did not hold up to adjustment (185). They did however demonstrate consistent findings for the effects of chronic interpersonal trauma and childhood SES (185). It seems possible that the second article on this cohort may have been informed by the previous study, as it focuses only on the effects of chronic trauma and childhood SES. Both demonstrated independent associations on wheeze outcomes, in addition to the previously stated effects on cord blood IgE levels. It is not clear from the article whether they assessed the relationship between early life trauma and wheeze outcomes. Should they have left out early trauma from their structural equation models based on their failure to find an adjusted association with IgE levels, this could have been unfortunate, given that the predictive

capacity of cord blood IgE is quite low (186). Arguably, using actual wheeze outcomes, as we do in our study, would have been much more ideal.

Nonetheless, their finding that childhood SES was independently predictive of wheeze is in line with our findings. It shows that psychosocial stressors in early life might program psychobiosocial changes which consequently affect the health of the next generation. At odds is their failure to find an effect of early life interpersonal trauma with cord blood IgE. As mentioned earlier, it may be that due to the lack of association with cord blood IgE levels, the authors felt it inappropriate to include early life trauma in their second study which looked at actual wheeze outcomes using structural equation models. It is also important to note that Sternthal et al. used the revised conflicts scale to establish their measure of early and lifetime adversity in both studies. The revised conflict tactics scale (R-CTS) short form tends to focus on physical abuse and specific forms of behavioural abuse only. For instance, the R-CTS does collect on psychological aggression between romantic partners, but fails to collect on most aspects of psychological abuse and has no equivalent questions appropriate for children. As highlighted in our literature review, psychological abuse in childhood, though not often studied, appears to have some of the strongest effects on adult health outcomes. Given that their variable of childhood adversity did not really capture psychological abuse, it may explain why it did not predict cord blood IgE outcomes in their earlier study, while chronic adversity and low SES did.

Nonetheless, we know that adverse childhood experiences are known to fuel chronic trauma. Since these early experiences are the historical precursors to chronic interpersonal trauma, it may be that our findings are in fact not due to events from any specific period of development. However, it is of note that Sternthal *et al.* used both childhood and teenage years to define their early life trauma category. One might argue that, temporally speaking, this is not a measure of 'early' adversity. Based on the literature describing sensitive periods of development in early childhood, we chose to look at the subset of women reporting adverse experiences by age 8. By this same reasoning, it seems likely that their inclusion of teenage experiences within this category may have diluted the effects of early childhood life events. This may be why we were able to find significant associations between early life trauma and wheeze, while they were not.

Admittedly, though, they really did not test early adversity's effects on wheeze. Barring issues with age, there is in fact a second reason why one could argue they did not truly test early life adversity in their newer study. This time around, their measure of early adversity was further categorized into a measure of one period of adversity versus none or chronic. One period meant that the experience occurred either in the childhood /teenage years or during adulthood/pregnancy. This meant that 'early' further lost its temporal meaning, replacing it instead with a measure of chronicity. It is thus arguable that the study which focused on actual wheezing outcomes did not in fact test the relationship between early adversity and wheeze.

As mentioned, their measure for chronic adversity included women who experienced their measure of early trauma and who were distressed during pregnancy and/or reported adult trauma. While we did not adjust for adult traumas, we did adjust for the effects of distress during pregnancy. Thus, we were able to capture and adjust for part of their chronic measure—arguably the most important part, as distress during pregnancy is the measure within the literature most related to children's wheeze and allergy outcomes. For these reasons, it seems plausible that the effects of early life trauma on wheeze and allergic outcomes may be demonstrable independent of chronic trauma.

Interpretation of Results: Childhood Adversity

Psychological Abuse

Childhood adversity has been linked to both abnormal HPA axis reactions and psychopathology in adulthood. Indeed, the psychobiological changes created by maltreatment in childhood are themselves highly related to psychopathology. Of all the adverse childhood experiences, the connection to stress dysregulation is arguably most observable in psychological abuse: it is a better predictor of mental illness than other forms and has been found in some studies to be the only childhood adverse experience that predicts abnormal cortisol responses in adults (30). The fact that psychological abuse is followed by more severe adult mental health and debatably more measurable HPA axis abnormality suggests that an abnormal stress reaction should be common in women with emotional neglect and abuse histories.

Studies looking at the HPA axis reactions of women who experienced childhood emotional abuse confirm this, even when taking into account current symptoms of psychopathology. The presence of this reaction is obviously necessary for transmission to the next generation. For these reasons, we expected severe psychological abuse to have a particularly strong association with our dependent outcomes.

In line with this expectation, an association was found between psychological abuse and allergies in toddlers, supporting our hypothesis. In fact the children of women who were psychologically abused were more than 3 times more likely to experience allergies in our initial model. The addition of postpartum depression to our model did remove this effect, but there are a few reasons why this may have happened. To start with, of all our adversity categories, our variable of severe psychological abuse had the fewest number of positive respondents (n=18). So it is quite possible that the model was insufficiently powered for the inclusion of postpartum depression. Indeed, even the effects of sex on allergic outcomes and those of severe prenatal distress and preterm birth on wheeze were not sustained in the presence of postpartum depression. Secondly, postpartum depression did not appear to be a good fit within our model, having no pattern of association with either of our outcomes. Moreover, as mentioned earlier, postnatal distress extending only into the postpartum period or on a short term basis has yet to be linked with wheeze or allergy. For those reasons it may not be an appropriate covariate for our regressions at age 3. Regardless, our early model containing prenatal distress and other relevant covariates is still significant support for

our hypothesis that emotional neglect and abuse in childhood is associated with next generation health outcomes.

Household Dysfunction

We anticipated that household dysfunction would have effects similar to psychological abuse since parental addiction and interpersonal violence are known to produce severe psychological distress in children. Household dysfunction has even been called a form of psychological abuse by many leading experts. In line with this reasoning, we saw a strong association between our variable of maternal household dysfunction and wheeze in toddlers. This was true of both the models containing postpartum depression and those without.

We recognize that family violence and substance abuse usually coexist with other adverse experiences, including poverty. In fact, Rodriguez *et al.* found an increased risk of domestic violence exists in the unemployed only when substance abuse is accounted for (187). This suggests that some of the effects of low SES might be quite intimately tied with our very own measure of household dysfunction (substance abuse and violent arguments). For those reasons, it might be hard to determine the individual effects of each member of this trio.

Remember, however, that Sternthal *et al.* found that low maternal childhood socioeconomic status (SES), regardless of current SES was associated with increased cord blood IgE levels and repeated wheeze in children (125). Also remember that this effect was independent of maternal

early life or cumulative lifetime adversity; the latter of which had its own independent effects on wheeze. Finally, low maternal childhood SES was not associated with maternal experience of early or lifetime interpersonal trauma. Indeed, childhood adversity, including interpersonal violence and substance abuse occurs in families at all socioeconomic levels so this independence should not be entirely surprising. It suggests that childhood adversity can be measured separately from low childhood SES. Regardless, it would have been preferable to have a measure of maternal childhood SES to include in our models.

Research also shows that within groups of abused children, a low socioeconomic background confers some additional risk for depression in adulthood above and beyond that generated by a history of adversity (188;189). This is further support that adversity and socioeconomic status might produce independent and compounding effects on the developing brain. Indeed, there are multiple studies reporting that the effects of early interpersonal violence and low SES on depression and other adult psychiatric disorders are independent and additive (180;190;191). If this is truly the case, this supports our decision to use household dysfunction as its own variable. Indeed in studies looking at the effects of interpersonal violence and socioeconomic status, it is interpersonal violence that produces the brunt of the likelihood for adults to experience depression, anxiety and high level stress (189;192). Taken together, all of this suggests that while household dysfunction and socioeconomic status may occur together in a minority of people, each experience has the potential to independently contribute to

regulatory system abnormalities. In our study, it seems those abnormalities created by household dysfunction in early life have the capacity to be transferred to the next generation.

Sexual Abuse

As mentioned before, child sexual abuse and its adverse outcomes are without a doubt the best studied of all childhood adverse experiences. It is no surprise then, that sexual abuse has extremely well documented associations with a myriad of health issues. Additionally, childhood sexual abuse is known to be associated with significant psychological distress and psychopathology; this is true both when the abuse takes place, and later, in adulthood (193;194). Finally, childhood sexual abuse has been linked to mothers' pre and postnatal cortisol reactions, as well as their infants own abnormal stress reactions. So, in the case of our intergenerational transmission hypothesis, sexual abuse is arguably the most well investigated of all adverse experiences. Accordingly, we found that the sons of women who were sexually abused by age 8 were at an increased risk for allergies.

While the role of sex in the pathogenesis of allergy is not well understood, a recent systematic review found a sex disparity in food allergy that mirrors that found in wheeze: boys experience rates of allergy at nearly 2 times the rate of girls in childhood, with the pattern reversing in adulthood (195). This might partially explain our finding that sons whose mothers were sexually abused before age 8 were at an increased risk for allergies.

Indeed, the finding that boys experience allergies at nearly twice the rate of girls fits within the well-established relationship between male sex and

worse pregnancy outcomes. Stark et al. hypothesized that antenatal glucocorticoid exposure should play a significant role in altering the placental pro-oxidant-anti-oxidant balance. They further reasoned that the effects of such an exposure might occur in a sex-specific manner because of the long recorded history of poor pregnancy outcomes for boys. And indeed, they did find that fetal sex was associated with a disturbance in the delicate balance, with male children being more affected. So, if glucocorticoid exposure affects the sexes differently, this might feasibly translates into an increased risk for translation of a mother's abnormal HPA axis functioning for boys. Our results for the effects of sexual abuse support this possibility.

Parental separation or divorce

Family disruption in early childhood has been associated with adult depression (180). It has been suggested that the developmental pathway is likely the same as that relating other childhood adverse experiences with poor adult mental and physical health outcomes. For our study, this means family separation is a probable marker of developmental disturbances in the HPA axis due to stress. In line with this premise, we found that the female children of women from disrupted homes (parents that separated or divorced before their fifth birthday) were at an increased risk for wheeze. Our models were borderline significant at a 95% confidence level, with p-values ranging between 0.052 and 0.06 in relevant models.

Once again, we need to address an association between our adverse variable of interest, family separation in childhood and socioeconomic status.

This has much to do with the number of single income female headed households which arise from family breakup, as well as the economic stresses which often precipitate marital strain and dissolution (180;196). Gilman *et al.* found that both low SES and parental separation independently predicted adult depression, but the effect of parental separation was intensified by parental conflict. This again supports the notion that our adverse experience variables should have effects independent of low childhood SES.

The susceptibility of girls seen in this model does not immediately fit within our current general knowledge of early childhood diseases, in which boys typically have poorer health outcomes than girls. There is, however, a growing body of evidence that suggests that female fetuses are especially susceptible to maternal asthma in pregnancy. Specifically, the placental vascular structure and function appears to be particularly effected in girls. Given the placenta's role in regulating fetal exposure to cortisol, one can understand how dysfunction of the placenta might lead to increased cortisol exposure in utero. Human and animal models have also highlighted female susceptibility to increased cortisol exposure and the resultant increase in female children's risk for metabolic diseases. Since we did not account for a mother's asthma or allergy status, it seems possible that an interaction between a mother's disease status during pregnancy and her experience of separation and divorce may have played a central role in these results. Given that childhood adversity is itself associated with asthma and allergy, it seems important to recognize that the incidence of maternal asthma and allergies

might be particularly high in our subjects of interest. Unfortunately, the CPC did not collect on maternal asthma and allergies and so we were unable to adjust for them.

Physical Abuse

Our measure of physical abuse had no apparent relationship with our variables of wheeze or allergy. It may be that our measure was too general, unable to capture the wide range of severity experienced by persons who believe they've were physically abused as children. It may also be that a significant portion of physical abuse experiences lack a chronic, psychologically stressing feature, which we hypothesize is the critical characteristic by which maltreatment may program functioning. As children born on average in the late 1960s, women in our study were (arguably) from the last generation in which corporal punishment was normative in Canada. While corporal punishment, especially that of a harsh nature, has been associated with many poor developmental outcomes for children, we know that when punishment use is normative in a society the effects are less negative (197). For instance, a child from earlier in the 21st century may have felt well emotionally supported and loved, but at the same time been relatively severely disciplined by today's standards. If persons in our study, because of the generic nature of our question and a modern perspective are defining their childhood punishments as physical abuse, this could dilute the potential of our variable to determine experiences that elicited severe and chronic psychological stress in childhood.

Indeed, most studies looking at physiological measures of HPA axis abnormality have only been reported for sexual or psychological abuse. While Brand *et al.* found an effect for childhood abuse, composed of either physical or sexual abuse, on HPA axis function in the postpartum period, it is of note that only 9 of the 38 female subjects had experienced physical abuse only, making the overall group make up over 75% sexual abuse victims (100). Thus it could be that physical abuse on its own does not usually elicit the significant chronic psychological stress required to make permanent changes in the brain functioning of children. Carpenter *et al.* found a strong effect for childhood physical abuse on adult cortisol reaction independent of current psychopathology, however this result did not hold when other maltreatment experiences were considered (198). Additionally, over half of the subjects had experienced more than 2 types of adversity. It's plausible that in the small sample used by Carpenter *et al.,* women who identified as having experienced physical abuse had indeed experienced a second type of adversity which was particularly psychologically stressful.

Neglect

Chi square correlations for neglect illustrated a strong connection with wheeze and a moderate connection with allergies. Further, an unadjusted regression model initially showed an association with wheeze, but it was eliminated after adjustment. The question then, is why this variable didn't elicit a significant association in our final models. While a relationship with the other covariates is possible, a few other glaring issues come to mind. The first dubious piece of evidence is that the number of women presenting with

neglect was quite low, when, in general, most studies report neglect as the most prevalent of all abuse experiences (at least it is based on studies using welfare reports). This suggests an issue with the way neglect was inquired about in the CPC study. As we mentioned earlier, unlike sexual and physical abuse, neglect possesses a vague quality. The generic way neglect was asked about provided very little context or definition for subjects, leaving the line of questioning open to personal interpretation. As a result, it is quite possible that our hope that our women would have a relatively reliable concept of what neglect is, was unfounded. This might explain the failure of our neglect variable to significantly predict wheeze or even allergy in the next generation.

'*Double Whammy'*

Double whammy or dual exposure effect is a common theme in child abuse research; it is the consistent finding that children who experience more than one type of adversity have more severe mental and physical health outcomes. When looking at all children, we saw an increased risk of wheeze with the experience of 2 or more adverse experiences, as opposed to one or none. In girls, the effect was much higher, with an 8 times increase in the likelihood to experience wheeze.

Mothers who report more than one form of abuse are hypothetically at an increased vulnerability for HPA axis dysregulation. Thus, our finding that children of mothers who experienced more than one type are at an increased risk for immune related health issues is promising in its consistency. Keeping

in mind that maternal asthma has been known to increase female offsprings' risk of wheeze, the fact that such an effect was most visible in female children suggests that maternal asthma may have played a role in this association.

Interpretation of Results: Role of Covariates

Maternal Distress during Pregnancy

This was probably the most important covariate included in our models with regards to the theoretical reasons behind our study. As discussed earlier, a number of pathways have been identified by which maternal stress during pregnancy could alter infant neuroendocrine systems in utero, and consequently, the immune system too. Maternal stress is associated with sustained excessive cortisol secretion, which could affect the developing immune system of the fetus. Indeed, increased levels of cord blood IgE have been found in infants whose mothers experienced significant stress during pregnancy (199). Since IgE levels are thought to be predictive of development of asthma and other allergic disorders, it is unsurprising that maternal prenatal cortisol disruption and distress have both been linked to childhood wheeze (200;201). Studies by Guxens *et al.* and Cookson *et al.* have shown that the association between prenatal psychological distress and children's wheeze and asthma outcomes is independent of postnatal psychological distress (202;203). They also found no association between postnatal depression or anxiety and wheeze. It can be quite difficult to separate pregnancy and postnatal psychological effects given their intimate association. However, like our study, these two projects took advantage of

their longitudinal design in order to determine psychological symptoms in real time during gestation and after delivery.

Our findings are consistent with these studies, as severe distress during pregnancy was associated with wheeze and/or allergy in nearly all of our models. We also found that in the majority of our models, the effects of prenatal distress on toddler outcomes were visible even with the addition of postpartum depression. Finally, we found no initial association between PPD and wheeze in any of our models. However, in models centered on sex, we did find a significant association between postpartum depression and wheeze in female children. While both the Guxens *et al.* and Cookson *et al.* studies adjusted for sex, it is not clear if they assessed interactions between child's sex and mother's distress.

It is important that we address the fact that, in our study, women who experienced childhood adversity reported much higher rates of distress in pregnancy than those who did not. While early childhood trauma might partly determine a woman's likelihood to experience distress during pregnancy, our hypothesis hinges on the notion that it is the abnormal biochemical/physiological profile of a mother which is the mechanism by which the next generation is ultimately programmed. We argue that this profile during pregnancy isn't exclusive to women experiencing prenatal distress. One would expect that this abnormal profile should be common in many victims of childhood adversity and thus still be present in pregnancy in these women, no matter whether they were experiencing concurrent distress or not. Thus, for our theory to prove its worth, the intergenerational effect

must be present even after taking pregnancy distress into account. And this was true in many of the models we ran. This shows that even though pregnancy distress might be highly related to earlier abuse and thus, might mask some of the effect of early life trauma, the background neuroendocrine profile produced by maltreatment in early life can produce evaluable effects above and beyond those produced by maternal distress.

Possible Postpartum Depression

Postpartum depression (PPD) is an important covariate in the same vein as prenatal distress. This is because maternal PPD may act as a traumatic event during the child's first year of life, altering the neuroendocrine systems postnatally and thus the immune system as well. There is some support in the literature that these changes may end in wheeze. For instance, Kozyrskyj *et al*. found that children exposed to continued, long term maternal distress (defined as multiple episodes in the first 7 years of life) were at increased risk for wheeze (7). This did not apply to distress in the postpartum period only or short term distress over the first five years. Similarly, using a case-control design Lefevre *et al.* found that concurrent maternal depression (extending beyond the postpartum period) had a significant impact on the severity of wheeze experienced by toddlers (204). These studies suggest that in addition to the established effects of prenatal maternal anxiety and depression, sustained, long term distress into early childhood may also have an association with wheeze. These effects were independent of postnatal distress, suggesting that the duration of symptoms experienced by many

mothers with PPD may not be sufficiently long to predispose children to wheeze or asthma.

In line with these findings, our measure of postpartum depression had no pattern of association whatsoever in the majority of models, while lowering the associations of other significant measures. We chose to present two sets of models, with and without our PPD variable, because, while theoretically relevant, PPD did not contribute in most models. Since there are few results to support the effects of postpartum or short term depression with wheeze or allergy, this was somewhat anticipated. However, as mentioned above, an effect for PPD was visible for girls' wheezing after models were centered on sex, rather than adjusted for it. *Lefevre et al.* and Kozyrskyj *et al.* adjusted for sex, but it is not clear if they also assessed sex interactions. In the case of Lefevre et al. it is clear that there was a difference in sex make up between cases (65.2% male) and controls (50.5%). This composition may have affected their ability to detect interactions with sex.

Additionally, as was also expected and seen with prenatal distress, there was an association between the experience of any kind of childhood adversity and later postpartum depression. It seems plausible that the inclusion of PPD takes away from the effect of our adversity measures in our models because of this association.

Sex

In our regression analysis, child's sex was a significant predictor of allergies in one model and of wheeze in nearly all regression models. This

was expected given the relationship between sex and wheeze outcomes in childhood. Namely, boys are more affected by wheeze and asthma than girls until puberty, at which point the opposite becomes true (205). It is thought that hormonal changes occurring in early puberty might have a role in this reversal. This is evidence that our wheeze and allergic population of three year olds had normal patterns of prevalence based on sex. It also supports our decision to investigate the possibility of sex differences in our models.

Pre and Postnatal Smoking

Passive exposure to cigarette smoke in infancy has been associated with increased risk of wheeze, while epidemiological evidence of the effect of prenatal maternal smoking with allergic diseases has been more inconsistent (206). Preliminary associations showed these associations in our data, with chi-square p-values of less than 0.05 (table 3). In logistic regression models, prenatal maternal smoking had an association with allergies in toddlers in our unadjusted models. This was not true of postnatal smoking and wheeze, contrary to expectations. Adjusted models did not show an association with wheeze or allergy for either pre or postnatal smoking.

Preterm Birth

Premature infants experience more wheezing respiratory illnesses than their full term counterparts (207-209). As anticipated, preterm birth was associated with wheeze at age 3 in unadjusted models and in some adjusted models.

Prenatal Vitamin Use

Maternal vitamin D intake during pregnancy has been associated with a decreased risk of early childhood wheeze (210). Since prenatal vitamins do raise Vitamin D levels during pregnancy, it seems feasible that this may explain the association between prenatal vitamin use and decreased wheeze found in our study, and in an earlier published paper of this cohort from our lab (211).

Breastfeeding

Though often touted, the literature on the protective effects of breastfeeding in relation to development of asthma and allergies has been conflicting. Duncan and Sears point out that “most recent studies do not confirm the 'conventional wisdom' that breastfeeding is protective against allergy and asthma”(212). For this reason, it is perhaps not surprising that breastfeeding was not associated with either wheeze or allergies in our unadjusted or adjusted models.

Study Strengths and Limitations

A major strength of this project was the large sample size of our study, as well as its longitudinal nature. The large sample size allowed us to use an age defined subset and to look at specific types of abuse.

All participants were recruited from one of three maternity clinics in Calgary. The location from which participants were chosen may mean that these medically low risk mothers may differ from mothers not receiving

prenatal care at one of these centers, high risk mothers, or those living outside of Calgary. Thus a geographic or hospital selection based bias may limit our generalizability to some degree.

While the initial rate of volunteerism for the project was high, volunteer bias in this cohort is still at play. Mothers who did not participate tended to be younger, less educated, have lower incomes, smoke, have low social support, a history of depression and separated or divorced parents (127). Those who dropped out of the study at a later date were also more likely to be non-Caucasian, single and report distress and adverse life events (127). This non respondent and volunteer bias may have played a significant role in our results, as many of the variables which predicted non participation and attrition are central or related to our adversity variables and important covariates. However, given the direction of our findings, it seems probable that this attrition only reduced the effect size of our findings, rather than impacting their validity.

Measures of adversity in childhood were self-reported and retrospective. In order to answer these questions, participants would have had to access their autobiographical memories—their personal life stories. It is important to acknowledge the inherent subjectivity of these responses: although individual autobiographical memories are generally accurate, they are still unreliable (213). The literature is filled with reports of abuse victims having large gaps in their memories of childhood and failing to remember documented early life abuse. Indeed, many studies have reported that persons with abuse histories suffer from overgeneral memory, meaning that

all memories and not just those limited to abuse events are affected. Lastly, false and altered autobiographical memories are also common, especially in the case of abuse and in particular in the case of abuse memories remembered in therapy (214). In summary, autobiographical memories are frequently incorrect and, in the case of abuse, they are often repressed and at other times falsely remembered (215). It is believed by some that these two reporting strategies (of under and over reporting) cancel each other out and tend to provide approximately accurate estimates of the prevalence of child abuse (216). Unfortunately, accurate prevalence rates do not help us—we need accuracy in our maltreatment variables. Thus, issues in misremembering may have been a real problem our study, contributing to inaccurate reports of abuse. However, having true adversity victims in our control group and pseudo victims included in our adversity variables should have lowered our chances of seeing an association. Thus, the validity of our results, though perhaps not their size, should not be compromised.

Additionally, child abuse is a sensitive issue and self-reports are consequently subject to an unacceptability bias—that is, the questions may be probing about an exposure that subjects may not feel comfortable discussing or remembering. In this case, measurement bias from self-report would create a tendency to underreport, thus biasing this variable towards the null. Again, this means that our findings should still be valid in the face of this bias, but it is quite possible that the associations that what we report are weaker than reality.

Though not nearly to the same extent, similar issues with self-report and memory may exist with our outcome variables of childhood wheeze and allergies. It is expected that a mother would remember a health care professional telling her that her child has a chronic breathing problem or allergic disorder; however, it is *always* possible for memories to fail or for respondents to knowingly withhold information. It is expected that any recall bias which may affect self-report of the wheeze outcome will be slight, due to the collection of explanatory and dependent variables at different dates—indeed, they are separated by years.

We may also have misclassified children with wheeze, causing a measurement bias. This is because the question itself may not be a sensitive enough measure and as a result, we may have failed to include some children with wheeze. It is also important to remember that wheeze is a symptom common to many pediatric diagnoses—nearly half of all children do it in infancy. Thus some of this wheeze may not be the result of or related to, our expected immune mechanism of interest. Indeed, early wheezing is most often infectious, with later wheezing and asthma showing a stronger relationship to allergy. It is possible, then, that we may include cases of wheeze which are unrelated to our suspected exposure.

As mentioned, there may be issues of measurement bias due to poor definitions and tools in our independent variables. This is especially true for those variables that were inquired about with an extremely generic form of questioning. We did our best to let the literature guide our variable construction, pushing for the most valid measures possible in our models, but

unfortunately, we were limited to the questions already collected by the CPC study. Again, since generic questioning tends to produce underreporting, we'd expect that our findings are valid, if diluted.

As Carpenter *et al.* point out, the manner in which people appraise their past is not just shaped by personality traits, but social supports, resources and coping skills all play a major role (30). All of these aspects contribute to how a person appraises and deals with stress, which may ultimately affect a person's stress reactivity. Carpenter *et al.* believe that persons who report their childhood as being psychological abusive (including emotional neglect and abuse) may be more sensitive to interpersonal rejection or have high levels of attachment anxiety (30). It follows that they would also have poor social supports as adults. Thus, they argue that it is possible that subjective individual differences such as sensitivity to interpersonal stressors and not the actual experience of psychological abuse are at the root of the HPA axis dysregulation seen in subjects who report emotional abuse and neglect (30). While plausible, a reasonable counterargument is that attachment issues and interpersonal and psychological problems are intermediates, born from the experience of psychological abuse and the result of neuroendocrine dysregulation that follows. Additionally, our finding that adverse experiences which are rooted in psychological stress, but not directly labeled as emotional abuse by participants, have similar associations with wheeze and allergies is at odds with this hypothesis. This supports the notion that effects are not due simply

to persons with stress management issues being more likely to report that they were emotionally abused.

Clinical Implications

This study emphasizes the value of including childhood adverse experiences in patient histories. Indeed, current research recommends integrating a discussion of past abuse into medical history taking. But, only the minority of providers report screening for childhood trauma, often only inquiring when symptoms of psychiatric conditions present themselves (217). Many physicians do not believe that general practitioners should routinely screen for child abuse histories, citing time limitations as a primary barrier (217;218). Research that delves deeper into physician attitudes finds that physicians with this opinion often lack confidence and usually feel uncomfortable asking about child maltreatment (123). Conversely, studies looking into the opinions of patients with a history of adversity find that they are both willing and wanting to be screened (219).

Some physicians question the utility of asking patients about childhood adversity. A general response is that it can help identify risk for the enduring consequences of abuse. In our case, this extends to health risks in the next generation, and as such, it presents the opportunity to take preventative measures against their transmission. For instance, it might help identify both new and pregnant mothers who are especially in need of services aimed at lowering their stress levels. Examples of these might include stress reduction instructions or cognitive behavioural therapy, as each have been found to

successfully decrease cortisol levels as well as perceived levels of stress and mood in pregnant women (220;221). Fetal physiological responses to maternal relaxation include lowered heart rate—an encouraging sign (222). Massage therapy and group interpersonal psychotherapy have also been shown to be effective for reducing depression and cortisol levels while also increasing serotonin and dopamine (223;224). Perhaps even more promising are studies showing prenatal maternal antidepressant use appears to normalize infant cortisol levels at and after birth (225;226). Finally, since childhood abuse is predictive of poor attachment and parenting styles, it is encouraging that early parenting supports aimed at bolstering positive interactions seem to help infants with regulatory issues (227-230). All in all, these studies demonstrate a convincing opportunity to reduce the likelihood of transmission by breaking the cycle at both the biological and behavioural level.

Future Directions

Studies looking at the potential intergenerational health effects of early life stress are only in their naissance. Within the current CPC study, next moves should include following child wheezers to see which children develop asthma, and of course, future allergy should also be monitored. It would be best to establish maternal asthma and allergy status, as well as maternal childhood SES, as these have been identified as important covariates. Better measures of maternal early life trauma, such as the adverse childhood experiences questionnaire should also be collected. A positive is that these should be relatively easy to ascertain retrospectively in future follow up

studies. The chronicity of a mother's stress over her lifetime would also be a great addition, though may be more difficult to accurately measure. This would allow us to ensure that our findings are more specifically related to the period of maternal early child development.

Although also difficult to determine, the ideal longitudinal study would collect on a child's own experience of adversity. This is especially important given that we know that adversity begets adversity; thus, it might be possible that these wheeze and allergic outcomes are actually a result of the children's own maltreatment and not their mother's. Similarly, maternal depression during an infant's first months is known to have long lasting effects on that child's psychological adjustment (231). The ideal study would collect on maternal behaviours and ascertain styles of attachment and levels of bonding and interaction between mother-infant dyads. Additionally, in a model study one might also collect genetic information from infants and their mothers', especially looking at candidate genes related to the immune system. Traffic-related pollution may have an effect on an infant's wheezing as well as on mothers and children's stress. Stress in turn may increase vulnerability to environmental exposures like pollution and tobacco (232). Thus, including measures of the physical environment, like urban pollution exposure, would provide the most complete information.

Summary

Early child adversity has been linked to a number of chronic diseases in adulthood, with changes in stress responsitivity thought to be the causal

pathway between the two. While work has begun to establish the possibility of transmission of HPA axis dysregulation in humans, little has been done to investigate the physical health effects of such an inheritance. It has been posited that due to the nature of these changes, the earliest effects of such a transmission might be related to immune dysfunction. Our finding, that different forms of maternal childhood adversity were related to the immune mediated disorders of wheeze and allergies, supports this hypothesis.

In the literature, the experience of more than one type of abuse is associated with poorer health outcomes. This is known as maltreatment load and is associated with an increased risk of stress dysregulation. The effects of maltreatment load appear to hold true for intergenerational transmission, as the children of women who experienced 2 or more types of adversity were at an increased risk for wheeze.

To our knowledge, these analyses are the first to demonstrate an association between the different types of maternal childhood adversity with children's health outcomes. It contributes to the very small but growing body of evidence showing that psychosocial factors like stress might exert their effects on a child's health decades before conception. Given the long-reaching effects of adversity, the findings from this study have important implications for health professionals; namely, that childhood adversity has an important place in medical histories. It also provides a foundation for future research into intergenerational effects of child abuse. Finally, it emphasizes the need for social policies which promote secure environments for children.

Bibliography

(1) Rabkin JG, Struening EL. Life events, stress, and illness. Science 1976;194(4268):1013-20.

(2) Shore R. Rethinking the brain: new insights into early development. Families and Work Institute; 1997.

(3) Teicher MH, Tomada A, Andersen SL. Neurobiological Consequences of Early Stress and Childhood Maltreatment: Are Results from Human and Animal Studies Comparable? Annals of the New York Academy of Sciences 2006 Jul 1;1071(1):313-23.

(4) Bosch NM, Riese Ht, Reijneveld SA, Bakker MP, Verhulst FC, Ormel J, et al. Timing matters: Long term effects of adversities from prenatal period up to adolescence on adolescentsə cortisol stress response. The TRAILS study. Psychoneuroendocrinology 2012 Sep;37(9):1439-47.

(5) Kaplow JB, Widom CS. Age of onset of child maltreatment predicts long-term mental health outcomes. Journal of Abnormal Psychology 2007;116(1):176-87.

(6) Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature Reviews Neuroscience 2009;10(6):434-45.

(7) Kozyrskyj AL, Mai XM, McGrath P, HayGlass KT, Becker AB, MacNeil B. Continued exposure to maternal distress in early life is associated with an increased risk of childhood asthma. American journal of respiratory and critical care medicine 2008;177(2):142-7.

(8) Wright RJ. Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk. Paediatric and Perinatal Epidemiology 2007 Nov 1;21:8-14.

(9) Essex MJ, Klein MH, Cho E, Kalin NH. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. Biological Psychiatry 2002 Oct 15;52(8):776-84.

(10) Bernazzani O, Bifulco A. Motherhood as a vulnerability factor in major depression: the role of negative pregnancy experiences. Social Science & Medicine 2003 Mar;56(6):1249-60.

(11) Hammen C, Hazel NA, Brennan PA, Najman J. Intergenerational transmission and continuity of stress and depression: depressed women and their offspring in 20 years of follow-up. Psychol Med 2012 May;42(5):931-42.

(12) Chen E. Life-course models of how the social environment affects childhood respiratory risk. J Allergy Clin Immunol 2011 Aug 1;128(2):346-7.

(13) Palusci VJ. Recent Trends in Response to Child Victimization: The Role of Health Care Professionals in the Response to Child Victimization. Journal of Aggression, Maltreatment & Trauma 2004;8(1-2):133-71.

(14) Briere J. Methodological issues in the study of sexual abuse effects. Journal of Consulting and Clinical Psychology 1992;60(2):196-203.

(15) Kendall-Tackett K. The health effects of childhood abuse: four pathways by which abuse can influence health. Child Abuse & Neglect 2002;26(6):715-29.

(16) Leserman J, Drossman DA, Li Z, Toomey TC, Nachman G, Glogau L. Sexual and physical abuse history in gastroenterology practice: how types of abuse impact health status. Psychosomatic Medicine 1996 Jan 1;58(1):4-15.

(17) Clemmons JC, Walsh K, DiLillo D, Messman-Moore TL. Unique and Combined Contributions of Multiple Child Abuse Types and Abuse Severity to Adult Trauma Symptomatology. Child Maltreatment 2007 May 1;12(2):172-81.

(18) Briere J. Treating Adult Survivors of Severe Childhood. The APSAC handbook on child maltreatment 2002;175.

(19) Moeller TP, Bachmann GA, Moeller JR. The combined effects of physical, sexual, and emotional abuse during childhood: Long-term health consequences for women. Child Abuse & Neglect 1993 Sep;17(5):623-40.

(20) Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield CL, Perry BD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Child: Care, Health and Development 2006 Mar 1;32(2):253-6.

(21) Schury K, Kolassa I. Biological memory of childhood maltreatment: current knowledge and recommendations for future research. Annals of the New York Academy of Sciences 2012;1262(1):93-100.

(22) Springer KW, Sheridan J, Kuo D, Carnes M. The Longterm Health Outcomes of Childhood Abuse. Journal of General Internal Medicine 2003;18(10):864-70.

(23) Cawson P, Wattam L, Brooker S, Kelly G. A study of the prevalence of child abuse and neglect. NSPCC, UK 2000.

(24) Tourigny M, Hebert M, Joly J, Cyr M, Baril K. Prevalence and co–occurrence of violence against children in the Quebec population. Australian and New Zealand journal of public health 2008;32(4):331-5.

(25) Trocmé N, Fallon B, MacLaurin B, Sinha V, Black T, Fast E, et al. Canadian Incidence Study of Reported Child Abuse and Neglect 2008 (CIS-2008): *Major Findings*. 2010.

(26) Trocmé N, Tourigny M, MacLaurin B, Fallon B. Major findings from the Canadian incidence study of reported child abuse and neglect. Child Abuse & Neglect 2003;27(12):1427-39.

(27) Chamberland C, Fallon B, Black T, Trocmé N. Emotional maltreatment in Canada: Prevalence, reporting and child welfare responses (CIS2). Child Abuse & Neglect 2011 Oct;35(10):841-54.

(28) Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. The long-term impact of the physical, emotional, and sexual abuse of children: A community study. Child Abuse & Neglect 1996 Jan;20(1):7-21.

(29) Allen B. An Analysis of the Impact of Diverse Forms of Childhood Psychological Maltreatment on Emotional Adjustment in Early Adulthood. Child Maltreatment 2008 Aug 1;13(3):307-12.

(30) Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, Price LH. Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. Biological Psychiatry 2009;66(1):69-75.

(31) Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship Between Multiple Forms of Childhood Maltreatment and Adult Mental Health in Community Respondents: Results From the Adverse Childhood Experiences Study. American Journal of Psychiatry 2003 Aug 1;160(8):1453-60.

(32) Horwitz AV, Widom CS, McLaughlin J, White HR. The Impact of Childhood Abuse and Neglect on Adult Mental Health: A Prospective Study. Journal of Health and Social Behavior 2001 Jun 1;42(2):184-201.

(33) Arnow BA. Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. J Clin Psychiatry 2004;65 Suppl 12:10-5.

(34) Arata CM, Langhinrichsen-Rohling J, Bowers D, O'Farrill-Swails L. Single versus multi-type maltreatment: An examination of the long-term effects of child abuse. Journal of Aggression, Maltreatment & Trauma 2005;11(4):29-52.

(35) Shea A, Walsh C, MacMillan H, Steiner M. Child maltreatment and HPA axis dysregulation: relationship to major depressive disorder and post traumatic stress disorder in females. Psychoneuroendocrinology 2005;30(2):162-78.

(36) Steel J, Sanna L, Hammond B, Whipple J, Cross H. Psychological sequelae of childhood sexual abuse: Abuse-related characteristics, coping strategies, and attributional style. Child Abuse & Neglect 2004;28(7):785-801.

(37) Drossman DA, Leserman J, Nachman G, Li Z, Gluck H, Toomey TC, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Annals of Internal Medicine 1990;113(11):828-33.

(38) Walker EA, Gelfand A, Katon WJ, Koss MP, Von Korff M, Bernstein D, et al. Adult health status of women with histories of childhood abuse and neglect. The American Journal of Medicine 1999 Oct;107(4):332-9.

(39) Runtz MG. Health concerns of university women with a history of child physical and sexual maltreatment. Child Maltreatment 2002;7(3):241-53.

(40) Linton SJ. A population-based study of the relationship between sexual abuse and back pain: establishing a link. Pain 1997;73(1):47-53.

(41) Wurlel SK, Kaplan GM, Keairnes M. Childhood sexual abuse among chronic pain patients. The Clinical journal of pain 1990;6(2):110-3.

(42) Walling MK, Reiter RC, Milburn AK, Gilbert LE, Vincent SD. Abuse history and chronic pain in women: I. Prevalences of sexual abuse and physical abuse. Obstetrics & Gynecology 1994;84(2):193-9.

(43) Nash MR, Hulsey TL, Sexton MC, Harralson TL, Lambert W. Long-term sequelae of childhood sexual abuse: Perceived family environment, psychopathology, and dissociation. Journal of Consulting and Clinical Psychology 1993;61(2):276.

(44) Felitti V, Anda R, Nordenberg D, Williamson D, Spitz A, Edwards V, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine 1998 May;14(4):245-58.

(45) Cloitre M, Cohen LR, Edelman RE, Han H. Posttraumatic stress disorder and extent of trauma exposure as correlates of medical problems and perceived health among women with childhood abuse. Women & Health 2001;34(3):1-17.

(46) Walker EA, Unutzer J, Rutter C, Gelfand A, Saunders K, VonKorff M, et al. Costs of health care use by women HMO members with a history of childhood abuse and neglect. Archives of General Psychiatry 1999;56(7):609.

(47) McCauley J, Kern DE, Kolodner K. Clinical characteristics of women with a history of childhood abuse: Unhealed wounds. JAMA 1997 May 7;277(17):1362-8.

(48) Springer KW. Childhood physical abuse and midlife physical health: Testing a multi-pathway life course model. Social Science & Medicine 2009 Jul;69(1):138-46.

(49) Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. 1988.

(50) McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. European journal of pharmacology 2008;583(2):174-85.

(51) De Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nature Reviews Neuroscience 2005;6(6):463-75.

(52) Sapolsky RM, Krey LC, McEwen BS. The Neuroendocrinology of Stress and Aging: The Glucocorticoid Cascade Hypothesis. Endocrine Reviews 1986 Aug 1;7(3):284-301.

(53) Oitzl MS, Champagne DL, van der Veen R, De Kloet ER. Brain development under stress: hypotheses of glucocorticoid actions revisited. Neuroscience & Biobehavioral Reviews 2010;34(6):853-66.

(54) Frodl T, O'Keane V. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiology of disease 2013;52:24-37.

(55) Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories. Nature Reviews Neuroscience 2002;3(6):453-62.

(56) Lupien SJ, de Leon M, De Santi S, Convit A, Tarshish C, Nair NP, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nature neuroscience 1998;1(1):69-73.

(57) Goosens KA, Sapolsky RM. Stress and Glucocorticoid Contributions to Normal and Pathological Aging. CRC Press; 2007.

(58) Checkley S. The neuroendocrinology of depression. Int Rev Psychiatry 1996 Jan 1;8(4):373-8.

(59) McCauley J, Kern DE, Kolodner K. Clinical characteristics of women with a history of childhood abuse: Unhealed wounds. JAMA 1997 May 7;277(17):1362-8.

(60) Stein MB, Walker JR, Anderson G, Hazen AL, Ross CA, Eldridge G, et al. Childhood physical and sexual abuse in patients with anxiety disorders and in a community sample. The American Journal of Psychiatry 1996;153(2):275-7.

(61) Kendler KS, Kuhn JW, Prescott CA. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychol Med 2004;34(8):1475-82.

(62) Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implicatons for therapy. Journal of Affective Disorders 2001;62(1):77-91.

(63) Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008 Jan;9(1):46-56.

(64) Stein M, Miller AH, Trestman RL. Depression and the immune system. In: Ader R, Felten DL, Cohen N, editors. Psychoneuroimmunology (2nd ed.).San Diego, CA, US: Academic Press; 1991. p. 897-930.

(65) Hart H, Rubia K. Neuroimaging of child abuse: a critical review. Frontiers in human neuroscience 2012;6.

(66) Graham YP, Heim C, Goodman SH, Miller AH, Nemeroff CB. The effects of neonatal stress on brain development: implications for psychopathology. Development and Psychopathology 1999;11(3):545-65.

(67) Hunter AL, Minnis H, Wilson P. Altered stress responses in children exposed to early adversity: A systematic review of salivary cortisol studies. Stress 2011;14(6):614-26.

(68) De Bellis MD. Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. Development and Psychopathology 2001;13(3):539-64.

(69) Heim C, Newport D, Heit S. PItuitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000 Aug 2;284(5):592-7.

(70) Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, et al. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. Biological Psychiatry 2007;62(10):1080-7.

(71) Seckl JR. Prenatal glucocorticoids and long-term programming. European Journal of Endocrinology 2004;151(Suppl 3):U49-U62.

(72) Clow A, Thorn L, Evans P, Hucklebridge F. The awakening cortisol response: methodological issues and significance. Stress: The International Journal on the Biology of Stress 2004;7(1):29-37.

(73) Sanchez MM, Noble PM, Lyon CK, Plotsky PM, Davis M, Nemeroff CB, et al. Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. Biological Psychiatry 2005;57(4):373-81.

(74) Kalinichev M, Easterling KW, Plotsky PM, Holtzman SG. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long–Evans rats. Pharmacology Biochemistry and Behavior 2002 Aug;73(1):131-40.

(75) Carlson M, Earls F. Psychological and Neuroendocrinological Sequelae of Early Social Deprivation in Institutionalized Children in Romania. Annals of the New York Academy of Sciences 1997 Jan 1;807(1):419-28.

(76) Gunnar MR, Morison SJ, Chisholm KIM, Schuder M. Salivary cortisol levels in children adopted from Romanian orphanages. Development and Psychopathology 2001;13(03):611-28.

(77) Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology 2005 Nov;30(10):1010-6.

(78) Raison CL, Miller AH. When Not Enough Is Too Much: The Role of Insufficient Glucocorticoid Signaling in the Pathophysiology of Stress-Related Disorders. American Journal of Psychiatry 2003 Sep 1;160(9):1554-65.

(79) Rohleder N, Joksimovic L, Wolf JM, Kirschbaum C. Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. Biological Psychiatry 2004 Apr 1;55(7):745-51.

(80) Thaller V, Vrkljan M, Hotujac L, Thakore J. The Potential Role of Hypocortisolism in the Pathophysiology of PTSD and. Coll Antropol 1999;23(2):611-9.

(81) Meewisse ML, Reitsma JB, De Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults Systematic review and meta-analysis. The British Journal of Psychiatry 2007;191(5):387-92.

(82) Inslicht SS, Marmar CR, Neylan TC, Metzler TJ, Hart SL, Otte C, et al. Increased cortisol in women with intimate partner violence-related posttraumatic stress disorder. Psychoneuroendocrinology 2006;31(7):825-38.

(83) Peeters F, Nicolson NA, Berkhof J. Levels and variability of daily life cortisol secretion in major depression. Psychiatry Research 2004;126(1):1-13.

(84) De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, et al. Developmental traumatology part I: Biological stress systems. Biological Psychiatry 1999;45(10):1259-70.

(85) Van VE, Scarpa A. The effects of child maltreatment on the hypothalamic-pituitary-adrenal axis. Trauma, violence & abuse 2004;5(4):Oct-352.

(86) Kaufman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, et al. The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. Biological Psychiatry 1997;42(8):15-679.

(87) Gutteling BM, de Weerth C, Buitelaar JK. Short Communication Maternal Prenatal Stress and 4-6 Year Old Children's Salivary Cortisol Concentrations

Pre-and Post-vaccination. Stress: The International Journal on the Biology of Stress 2004;7(4):257-60.

(88) Leung E, Tasker SL, Atkinson L, Vaillancourt T, Schulkin J, Schmidt LA. Perceived maternal stress during pregnancy and its relation to infant stress reactivity at 2 days and 10 months of postnatal life. Clinical pediatrics 2010;49(2):158-65.

(89) Saridjan NS, Huizink AC, Koetsier JA, Jaddoe VW, Mackenbach JP, Hofman A, et al. Do social disadvantage and early family adversity affect the diurnal cortisol rhythm in infants? The Generation R Study. Hormones and Behavior 2010;57(2):247-54.

(90) Cicchetti D, Rogosch FA, Gunnar MR, Toth SL. The Differential Impacts of Early Physical and Sexual Abuse and Internalizing Problems on Daytime Cortisol Rhythm in School-Aged Children. Child Development 2010 Jan 1;81(1):252-69.

(91) Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ. The role of corticotropin-releasing factorΓÇônorepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biological Psychiatry 1999 Nov 1;46(9):1153-66.

(92) Shonkoff JP, Phillips DA. From Neurons to Neighborhoods: The Science of Early Childhood Development. The National Academies Press; 2000.

(93) Ben-Dat Fisher D, Serbin LA, Stack DM, Ruttle PL, Ledingham JE, Schwartzman AE. Intergenerational predictors of diurnal cortisol secretion in early childhood. Inf Child Develop 2007 Mar 1;16(2):151-70.

(94) Dettling AC, Parker SW, Lane S, Sebanc A, Gunnar MR. Quality of care and temperament determine changes in cortisol concentrations over the day for young children in childcare. Psychoneuroendocrinology 2000 Nov;25(8):819-36.

(95) Yamamoto K, Kinney D. Pregnant women's ratings of different factors influencing psychological stress during pregnancy. Psychological Reports 1976 Aug 1;39(1):203-14.

(96) Crandon AJ. Maternal anxiety and obstetric complications. Journal of Psychosomatic Research 1979;23(2):109-11.

(97) Gonzalez A, Jenkins JM, Steiner M, Fleming AS. The relation between early life adversity, cortisol awakening response and diurnal salivary cortisol levels in postpartum women. Psychoneuroendocrinology 2009;34(1):76-86.

(98) Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. Journal of Women's Health 2003;12(4):373-80.

(99) Field T, Diego M, Hernandez-Reif M. Prenatal depression effects on the fetus and newborn: a review. Infant Behavior and Development 2006;29(3):445-55.

(100) Brand SR, Brennan PA, Newport DJ, Smith AK, Weiss T, Stowe ZN. The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. Psychoneuroendocrinology 2010;35(5):686-93.

(101) Bublitz MH, Stroud LR. Childhood sexual abuse is associated with cortisol awakening response over pregnancy: Preliminary findings. Psychoneuroendocrinology 2012 Sep;37(9):1425-30.

(102) Bellinger DL, Lubahn C, Lorton D. Maternal and early life stress effects on immune function: relevance to immunotoxicology. Journal of immunotoxicology 2008;5(4):419-44.

(103) Padgett DA, Glaser R. How stress influences the immune response. Trends in immunology 2003;24(8):444-8.

(104) Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. Journal of Allergy and Clinical Immunology 2010 Jun;125(6):1327-35.

(105) Chen E, Hanson MD, Paterson LQ, Griffin MJ, Walker HA, Miller GE. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. Journal of Allergy and Clinical Immunology 2006;117(5):1014-20.

(106) Wright RJ, Mitchell H, Visness CM, Cohen S, Stout J, Evans R, et al. Community violence and asthma morbidity: the Inner-City Asthma Study. American journal of public health 2004;94(4):625-32.

(107) Kelsay K, Leung DYM, Mrazek DA, Klinnert MD. Prospectively assessed early life experiences in relation to cortisol reactivity in adolescents at risk for asthma. Dev Psychobiol 2013 Mar 1;55(2):133-44.

(108) Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: Results from a large population-based sample of men and women. Child Abuse & Neglect 2007 May;31(5):517-30.

(109) Scott KM, Von Korff M, Alonso J, Angermeyer MC, Benjet C, Bruffaerts R, et al. Childhood adversity, early-onset depressive/anxiety disorders, and adult-onset asthma. Psychosomatic Medicine 2008;70(9):1035-43.

(110) von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. Journal of Allergy and Clinical Immunology 2002;109(6):923-8.

(111) Mathilda Chiu YH, Coull BA, Cohen S, Wooley A, Wright RJ. Prenatal and Postnatal Maternal Stress and Wheeze in Urban Children. American journal of respiratory and critical care medicine 2012 Jul 15;186(2):147-54.

(112) Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. Journal of Women's Health 2003;12(4):373-80.

(113) Benedict MI, Paine LL, Paine LA, Brandt D, Stallings R. The association of childhood sexual abuse with depressive symptoms during pregnancy, and selected pregnancy outcomes. Child Abuse & Neglect 1999;23(7):659-70.

(114) Buist A. Childhood abuse, parenting and postpartum depression. Australian and New Zealand Journal of Psychiatry 1998;32(4):479-87.

(115) Wright RJ. Perinatal stress and early life programming of lung structure and function. Biological psychology 2010;84(1):46-56.

(116) Stark MJ, Hodyl NA, Wright IMR, Clifton VL. Influence of sex and glucocorticoid exposure on preterm placental pro-oxidant-antioxidant balance. Placenta 2011 Nov;32(11):865-70.

(117) Kozyrskyj AL, Pawlowski AN. Maternal Distress and Childhood Wheeze: Mechanisms and Context. American journal of respiratory and critical care medicine 2013 Jun 1;187(11):1160-2.

(118) Boyce WT, Chesney M, Alkon A, Tschann JM, Adams S, Chesterman B, et al. Psychobiologic reactivity to stress and childhood respiratory illnesses: results of two prospective studies. Psychosomatic Medicine 1995;57(5):411-22.

(119) Mathers JC, McKay J. Epigenetics-Potential Contribution to Fetal Programming. In: Koletzko B, Decsi T, Moln+ír D+, Hunty A, editors. Early Nutrition Programming and Health Outcomes in Later Life. 646 ed. Springer Netherlands; 2009. p. 119-23.

(120) Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nature neuroscience 2004;7(8):847-54.

(121) Perroud N, Paoloni-Giacobino A, Prada P, Olie E, Salzmann A, Nicastro R, et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Transl Psychiatry 2011 Dec 13;1:e59.

(122) Mulligan CJ, D'Errico NC, Stees J, Hughes DA. Methylation changes at NR3C1 in newborns associate with maternal prenatal stress exposure and newborn birth weight. Epigenetics 2012;7(8):853-7.

(123) Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008 Mar 1;3(2):97-106.

(124) Schreier H, Chen E. Socioeconomic status in one's childhood predicts offspring cardiovascular risk. Brain, Behavior, and Immunity 2010;24(8):1324-31.

(125) Sternthal MJ, Coull BA, Chiu YHM, Cohen S, Wright RJ. Associations among maternal childhood socioeconomic status, cord blood IgE levels, and repeated wheeze in urban children. Journal of Allergy and Clinical Immunology 2011;128(2):337-45.

(126) Vega EM, O'Leary KD. Test–retest reliability of the revised conflict tactics scales (CTS2). Journal of Family Violence 2007;22(8):703-8.

(127) Tough SC, Siever JE, Johnston DW. Retaining women in a prenatal care randomized controlled trial in Canada: implications for program planning. BMC public health 2007;7(1):148.

(128) Kiecolt-Glaser JK, Glaser R, Cacioppo JT, MacCallum RC, Snydersmith M, Kim C, et al. Marital conflict in older adults: endocrinological and immunological correlates. Psychosomatic Medicine 1997;59(4):339-49.

(129) Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney Jr JM. Social ties and susceptibility to the common cold. JAMA: the journal of the American Medical Association 1997;277(24):1940-4.

(130) Sachser N, Durschlag M, Hirzel D. Social relationships and the management of stress. Psychoneuroendocrinology 1998;23(8):891-904.

(131) Taylor SE, Eisenberger NI, Saxbe D, Lehman BJ, Lieberman MD. Neural responses to emotional stimuli are associated with childhood family stress. Biological Psychiatry 2006;60(3):296-301.

(132) Yates TM, Wekerle C. The long-term consequences of childhood emotional maltreatment on development:(Mal) adaptation in adolescence and young adulthood. Child Abuse & Neglect 2009;33(1):19-21.

(133) Graham JE, Christian LM, Kiecolt-Glaser JK. Stress, age, and immune function: toward a lifespan approach. Journal of behavioral medicine 2006;29(4):389-400.

(134) Egeland B. Taking stock: Childhood emotional maltreatment and developmental psychopathology. Child Abuse & Neglect 2009;33(1):22-6.

(135) Tough S, Siever J, Leew S, Johnston D, Benzies K, Clark D. Maternal mental health predicts risk of developmental problems at 3 years of age: follow up of a community based trial. BMC Pregnancy and Childbirth 2008;8(1):16.

(136) Pearce N, Beasley R, Burgess C, Crane J. Asthma epidemiology: principles and methods. Chronic Diseases in Canada 1999;19(4):183.

(137) May-Chahal C, Cawson P. Measuring child maltreatment in the United Kingdom: A study of the prevalence of child abuse and neglect. Child Abuse & Neglect 2005 Sep;29(9):969-84.

(138) Trocmé N, Tourigny M, MacLaurin B, Fallon B. Major findings from the Canadian incidence study of reported child abuse and neglect. Child Abuse & Neglect 2003;27(12):1427-39.

(139) Scher CD, Forde DR, McQuaid JR, Stein MB. Prevalence and demographic correlates of childhood maltreatment in an adult community sample. Child Abuse & Neglect 2004 Feb;28(2):167-80.

(140) Finkelhor D, Turner H, Ormrod R, Hamby SL. Violence, Abuse, and Crime Exposure in a National Sample of Children and Youth. Pediatrics 2009 Nov 1;124(5):1411-23.

(141) Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The Long-Term Health Consequences of Child Physical Abuse, Emotional Abuse, and Neglect: A Systematic Review and Meta-Analysis. PLoS Med 2012 Nov 27;9(11):e1001349.

(142) Andersen P, Tomada MD, Vincow E, Valente MA, Polcari RN, Teicher MD. Preliminary Evidence for Sensitive Periods in the Effect of Childhood Sexual Abuse on Regional Brain Development. The Journal of Neuropsychiatry and Clinical Neurosciences 2008 Jun 1;20(3):292-301.

(143) Lee Y, Styne D. Influences on the onset and tempo of puberty in human beings and implications for adolescent psychological development. Hormones and Behavior 2013 Jul;64(2):250-61.

(144) Snyder HN. Sexual Assault of Young Children as Reported to Law Enforcement: Victim, Incident, and Offender Characteristics. A NIBRS Statistical Report. 2000.

(145) Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. Journal of Child Psychology and Psychiatry 2004 Feb 1;45(2):260-73.

(146) Maughan B, Rutter M. Retrospective Reporting of Childhood Adversity: Issues in Assessing Long-Term Recall. Journal of Personality Disorders 1997 Mar 1;11(1):19-33.

(147) Josselyn SA, Frankland PW. Infantile amnesia: A neurogenic hypothesis. Learning & Memory 2012 Sep 1;19(9):423-33.

(148) Allen JG. The Spectrum of Accuracy in Memories of Childhood Trauma. Harvard Review of Psychiatry 1995;3(2).

(149) Crane C, Duggan DS. Overgeneral autobiographical memory and age of onset of childhood sexual abuse in patients with recurrent suicidal behaviour. British Journal of Clinical Psychology 2009 Mar;48(1):93-100.

(150) Watkins E, Teasdale JD. Rumination and Overgeneral Memory in Depression: Effects of Self-Focus and Analytic Thinking. Journal of Abnormal Psychology May 2001;110(2):353-357 2001;(2):353-7.

(151) Briere J. Methodological Issues in the Study of Sexual Abuse Effects. Journal of Consulting & Clinical Psychology April 1992;60(2):196-203 1992;(2):196-203.

(152) Chiu GR, Lutfey KE, Litman HJ, Link CL, Hall SA, Mckinlay JB. Prevalence and Overlap of Childhood and Adult Physical, Sexual, and Emotional Abuse: A Descriptive Analysis of Results From the Boston Area Community Health (BACH) Survey. Violence and Victims 2013;28(3):381-402.

(153) Finkelhor D, Turner H, Ormrod R, Hamby SL. Violence, Abuse, and Crime Exposure in a National Sample of Children and Youth. Pediatrics 2009 Nov 1;124(5):1411-23.

(154) Hamarman S, Pope KH, Czaja SJ. Emotional Abuse in Children: Variations in Legal Definitions and Rates Across the United States. Child Maltreatment 2002 Nov 1;7(4):303-11.

(155) Garbarino J, Guttmann E, Seeley JW. The psychologically battered child. Jossey-Bass; 1986.

(156) Brown GW, Craig TKJ, Harris TO, Handley RV, Harvey AL. Development of a retrospective interview measure of parental maltreatment using the Childhood Experience of Care and Abuse (CECA) instrument: A life-course study of adult chronic depression. Journal of Affective Disorders 2007 Nov;103(1–3):205-15.

(157) Brassard MR, Hart SN, Hardy DB. The psychological maltreatment rating scales. Child Abuse & Neglect 1993;17(6):715-29.

(158) Baker AJL, Festinger T. Emotional abuse and emotional neglect subscales of the CTQ: Associations with each other, other measures of psychological maltreatment, and demographic variables. Children and Youth Services Review 2011 Nov;33(11):2297-302.

(159) O'Hagan KP. Emotional and psychological abuse: Problems of definition. Child Abuse & Neglect 1995 Apr;19(4):449-61.

(160) Glaser D. Emotional abuse and neglect (psychological maltreatment): a conceptual framework. Child Abuse & Neglect 2002 Jun;26(6–7):697-714.

(161) Glaser DP, Lych V. Emotional abuse and emotional neglect: antecedents, operational definitions and consequences. 2001.

(162) Baker AJL. Adult recall of childhood psychological maltreatment: Definitional strategies and challenges. Children and Youth Services Review 2009 Jul;31(7):703-14.

(163) McGee RA, Wolfe DA. Psychological maltreatment: Toward an operational definition. Development and Psychopathology 1991;3(01):3-18.

(164) Briere J, Runtz M. Differential adult symptomatology associated with three types of child abuse histories. Child Abuse & Neglect 1990;14(3):357-64.

(165) Briere J, Runtz M. Multivariate correlates of childhood psychological and physical maltreatment among university women. Child Abuse & Neglect 1988;12(3):331-41.

(166) Rohner RP. Father Love and Child Development: History and Current Evidence. Current Directions in Psychological Science 1998 Oct 1;7(5):157-61.

(167) Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Childhood Abuse, Neglect, and Household Dysfunction and the Risk of Illicit Drug Use: The Adverse Childhood Experiences Study. Pediatrics 2003 Mar 1;111(3):564-72.

(168) Testa M. The Role of Substance Use in Male-to-Female Physical and Sexual Violence: A Brief Review and Recommendations for Future Research. Journal of Interpersonal Violence 2004 Dec 1;19(12):1494-505.

(169) Boles SM, Miotto K. Substance abuse and violence: A review of the literature. Aggression and Violent Behavior 2003 Mar;8(2):155-74.

(170) Conners-Burrow NA, Johnson B, Whiteside-Mansell L. Maternal Substance Abuse and Children's Exposure to Violence. Journal of Pediatric Nursing 2009 Oct;24(5):360-8.

(171) Herrenkohl TI, Sousa C, Tajima EA, Herrenkohl RC, Moylan CA. Intersection of Child Abuse and Children's Exposure to Domestic Violence. Trauma, Violence, & Abuse 2008 Apr 1;9(2):84-99.

(172) Holt S, Buckley H, Whelan S. The impact of exposure to domestic violence on children and young people: A review of the literature. Child Abuse & Neglect 2008 Aug;32(8):797-810.

(173) Davies PT, Harold GT, Goeke-Morey MC, Cummings EM, Shelton K, Rasi JA, et al. Child emotional security and interparental conflict. Monographs of the Society for Research in Child Development 2002;i-127.

(174) Crockenberg S, Langrock A. The role of emotion and emotional regulation in children's responses to interparental conflict. In: Grych JH, editor. Interparental conflict and child development: Theory, research, and applications.New York, NY, US: Cambridge University Press; 2001. p. 129-56.

(175) Kernic MA, Wolf ME, Holt VL, McKnight B, Huebner CE, Rivara FP. Behavioral problems among children whose mothers are abused by an intimate partner. Child Abuse & Neglect 2003 Nov;27(11):1231-46.

(176) Briere J. Child abuse trauma: Theory and treatment of the lasting effects. 2 ed. Sage; 1992.

(177) Holden GW. Children exposed to domestic violence and child abuse: Terminology and taxonomy. Clinical child and family psychology review 2003;6(3):151-60.

(178) Stuart GL, Meehan JC, Moore TM, Morean M, Hellmuth J, Follansbee K. Examining a conceptual framework of intimate partner violence in men and women arrested for domestic violence. Journal of Studies on Alcohol and Drugs 2006;67(1):102.

(179) Laumann-Billings L, Emery RE. Distress among young adults from divorced families. Journal of Family Psychology 2000;14(4):671-87.

(180) Gilman SE, Kawachi I, Fitzmaurice GM, Buka SL. Family Disruption in Childhood and Risk of Adult Depression. American Journal of Psychiatry 2003 May 1;160(5):939-46.

(181) Bockelbrink A, Heinrich J, Sch+ñfer I, Zutavern A, Borte M, Herbarth O, et al. Atopic eczema in children: another harmful sequel of divorce. Allergy 2006;61(12):1397-402.

(182) Haggerty RJ, Sherrod LR, Garmezy N, Rutter M. Stress, risk, and resilience in children and adolescents: Processes, mechanisms, and interventions. Wiley Online Library; 1994.

(183) Amato PR. Children of divorce in the 1990s: An update of the Amato and Keith (1991) meta-analysis. Journal of Family Psychology 2001;15(3):355-70.

(184) McIntosh JE. Enduring conflict in parental separation: Pathways of impact on child development. Journal of Family Studies 2003;9(1):63-80.

(185) Sternthal MJ, Enlow MB, Cohen S, Canner MJ, Staudenmayer J, Tsang K, et al. Maternal interpersonal trauma and cord blood IgE levels in an inner-city cohort: a life-course perspective. Journal of Allergy and Clinical Immunology 2009;124(5):954-60.

(186) Bergmann RL, Edenharter G, Bergmann KE, Guggenmoos-Holzmann I, Forster J, Bauer CP, et al. Predictability of early atopy by cord blood IgE and parental history. Clinical & Experimental Allergy 1997;27(7):752-60.

(187) Rodriguez E, Lasch KE, Chandra P, Lee J. Family violence, employment status, welfare benefits, and alcohol drinking in the United States: what is the relation? Journal of epidemiology and community health 2001;55(3):172-8.

(188) Kessler RC, Magee WJ. Childhood family violence and adult recurrent depression. Journal of Health and Social Behavior 1994;13-27.

(189) Gilman SE, Kawachi I, Fitzmaurice GM, Buka SL. Socio-economic status, family disruption and residential stability in childhood: relation to onset, recurrence and remission of major depression. Psychol Med 2003;33(8):1341-55.

(190) Russell D, Springer KW, Greenfield EA. Witnessing domestic abuse in childhood as an independent risk factor for depressive symptoms in young adulthood. Child Abuse & Neglect 2010;34(6):448-53.

(191) Repetti RL, Taylor SE, Seeman TE. Risky Families: Family Social Environments and the Mental and Physical Health of Offspring. Psychological Bulletin March 2002;128(2):330-366 2002;(2):330-66.

(192) Malta LA, McDonald SW, Hegadoren KM, Weller CA, Tough SC. Influence of interpersonal violence on maternal anxiety, depression, stress and parenting morale in the early postpartum: a community based pregnancy cohort study. BMC Pregnancy & Childbirth 2012 Jan;12(1):153-61.

(193) Figueroa EF, Silk KR, Huth A, Lohr NE. History of childhood sexual abuse and general psychopathology. Comprehensive psychiatry 1997;38(1):23-30.

(194) Arnow BA, Hart S, Scott C, Dea R, O'Connell L, Taylor CB. Childhood Sexual Abuse, Psychological Distress, and Medical Use Among Women. Psychosomatic Medicine 1999 Nov 1;61(6):762-70.

(195) Kelly C, Gangur V. Sex disparity in food allergy: evidence from the pubmed database. Journal of allergy 2009;2009.

(196) Eggebeen DJ, Lichter DT. Race, family structure, and changing poverty among American children. American Sociological Review 1991;801-17.

(197) Durrant JE, Rose-Krasnor L, Broberg AG. Physical Punishment and Maternal Beliefs in Sweden and Canada. Journal of Comparative Family Studies 2003 Sep;34(4):585-604.

(198) Carpenter L, Shattuck T, Tyrka A, Geracioti T, Price L. Effect of childhood physical abuse on cortisol stress response. Psychopharmacology 2011;214(1):367-75.

(199) Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. American journal of respiratory and critical care medicine 2010;182(1):25.

(200) Wright RJ, Fisher K, Chiu YHM, Wright RO, Fein R, Cohen S, et al. Disrupted Prenatal Maternal Cortisol, Maternal Obesity, and Childhood Wheeze. Insights into Prenatal Programming. American journal of respiratory and critical care medicine 2013 Apr 3;187(11):1186-93.

(201) Reyes M, Perzanowski MS, Whyatt RM, Kelvin EA, Rundle AG, Diaz DM, et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. Annals of Allergy, Asthma & Immunology 2011 Jul;107(1):42-9.

(202) Guxens M, Sonnenschein-van der Voort AMM, Tiemeier H, Hofman A, Sunyer J, de Jongste JC, et al. Parental psychological distress during pregnancy and wheezing in preschool children: The Generation R Study. Journal of Allergy and Clinical Immunology 2013;(0).

(203) Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. Journal of Allergy and Clinical Immunology 2009 Apr;123(4):847-53.

(204) Lefevre F, Moreau D, Simon E, Kalaboka S, Annesi-Maesano I, Just J. Maternal depression related to infant's wheezing. Pediatric Allergy and Immunology 2011 Sep 1;22(6):608-13.

(205) Mandhane PJ, Greene JM, Cowan JO, Taylor DR, Sears MR. Sex Differences in Factors Associated with Childhood- and Adolescent-Onset Wheeze. American journal of respiratory and critical care medicine 2005 Jul 1;172(1):45-54.

(206) Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. European Respiratory Journal 1995 Mar 1;8(3):349-56.

(207) Elder DE, Hagan R, Evans SF, Benninger HR, French NP. Recurrent wheezing in very preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition 1996;74(3):F165-F171.

(208) Kelly YJ, Brabin BJ, Milligan P, Heaf DP, Reid J, Pearson MG. Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside. Thorax 1995;50(5):525-30.

(209) Jaakkola JJ, Ahmed P, Ieromnimon A, Goepfert P, Laiou E, Quansah R, et al. Preterm delivery and asthma: a systematic review and meta-analysis. Journal of Allergy and Clinical Immunology 2006;118(4):823-30.

(210) Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. The American journal of clinical nutrition 2007;85(3):853-9.

(211) Alton ME, Tough SC, Mandhane PJ, Kozyrskyj AL. Street drug use during pregnancy: potential programming effects on preschool wheeze. Journal of Developmental Origins of Health and Disease 2013;4(02):191-9.

(212) Duncan JM, Sears MR. Breastfeeding and allergies: time for a change in paradigm? Current opinion in allergy and clinical immunology 2008;8(5):398-405.

(213) Rubin D. Autobiographical Memory. Encyclopedia of Cognitive Science. John Wiley & Sons, Ltd; 2006.

(214) Geraerts E, Schooler JW, Merckelbach H, Jelicic M, Hauer JA, Ambadar Z. The Reality of Recovered Memories: Corroborating Continuous and Discontinuous Memories of Childhood Sexual Abuse. Psychological Science 2007 Jul 1;18(7):564-8.

(215) Edwards VJ, Fivush R, Anda RF, Felitti VJ, Nordenberg DF. Autobiographical memory disturbances in childhood abuse survivors. Journal of Aggression, Maltreatment & Trauma 2001;4(2):247-63.

(216) Geraerts E, Lindsay DS, Merckelbach H, Jelicic M, Raymaekers L, Arnold MM, et al. Cognitive mechanisms underlying recovered-memory experiences of childhood sexual abuse. Psychological Science 2009;20(1):92-8.

(217) Weinreb L, Savageau JA, Candib LM, Reed GW, Fletcher KE, Hargraves JL. Screening for childhood trauma in adult primary care patients: a cross-sectional survey. Primary care companion to the Journal of clinical psychiatry 2010;12(6).

(218) Richardson J, Feder G, Eldridge S, Chung WS, Coid J, Moorey S. Women who experience domestic violence and women survivors of childhood sexual abuse: a survey of health professionals' attitudes and clinical practice. The British Journal of General Practice 2001;51(467):468.

(219) Friedman LS, Samet JH, Roberts MS, Hudlin M, Hans P. Inquiry about victimization experiences: A survey of patient preferences and physician practices. Archives of internal medicine 1992 Jun 1;152(6):1186-90.

(220) Urizar J, Milazzo M, Le HN, Delucchi K, Sotelo R, Muoz RF. Impact of stress reduction instructions on stress and cortisol levels during pregnancy. Biological psychology 2004 Nov;67(3):275-82.

(221) Urizar Jr GG, Mu+¦oz RF. Impact of a prenatal cognitive-behavioral stress management intervention on salivary cortisol levels in low-income mothers and their infants. Psychoneuroendocrinology 2011;36(10):1480-94.

(222) DiPietro JA, Costigan KA, Nelson P, Gurewitsch ED, Laudenslager ML. Fetal responses to induced maternal relaxation during pregnancy. Biological psychology 2008;77(1):11-9.

(223) Field T, Diego MA, Hernandez-Reif M, Schanberg S, Kuhn C. Massage therapy effects on depressed pregnant women. Journal of Psychosomatic Obstetrics & Gynecology 2004;25(2):115-22.

(224) Field T, Diego M, Hernandez-Reif M. Prenatal depression effects and interventions: a review. Infant Behavior and Development 2010;33(4):409-18.

(225) Oberlander TF, Grunau R, Mayes L, Riggs W, Rurak D, Papsdorf M, et al. Hypothalamic–pituitary–adrenal (HPA) axis function in 3-month old infants with prenatal selective serotonin reuptake inhibitor (SSRI) antidepressant exposure. Early Human Development 2008 Oct;84(10):689-97.

(226) Brennan PA, Pargas R, Walker EF, Green P, Jeffrey Newport D, Stowe Z. Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. Journal of Child Psychology and Psychiatry 2008;49(10):1099-107.

(227) Kwako LE, Noll JG, Putnam FW, Trickett PK. Childhood sexual abuse and attachment: An intergenerational perspective. Clinical child psychology and psychiatry 2010;15(3):407-22.

(228) Lyons-Ruth K, Block D. The disturbed caregiving system: Relations among childhood trauma, maternal caregiving, and infant affect and attachment. Infant Mental Health Journal 1996;17(3):257-75.

(229) Richter N, Reck C. Positive maternal interaction behavior moderates the relation between maternal anxiety and infant regulatory problems. Infant Behavior and Development 2013 Dec;36(4):498-506.

(230) Suglia S, Enlow M, Kullowatz A, Wright RJ. Maternal intimate partner violence and increased asthma incidence in children: Buffering effects of supportive caregiving. Archives of Pediatrics & Adolescent Medicine 2009 Mar 2;163(3):244-50.

(231) Murray L, Sinclair D, Cooper P, Ducournau P, Turner P, Stein A. The Socioemotional Development of 5-year-old Children of Postnatally Depressed Mothers. The Journal of Child Psychology and Psychiatry and Allied Disciplines 1999;40(08):1259-71.

(232) Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. Proceedings of the National Academy of Sciences 2009 Jul 20.

Appendix A

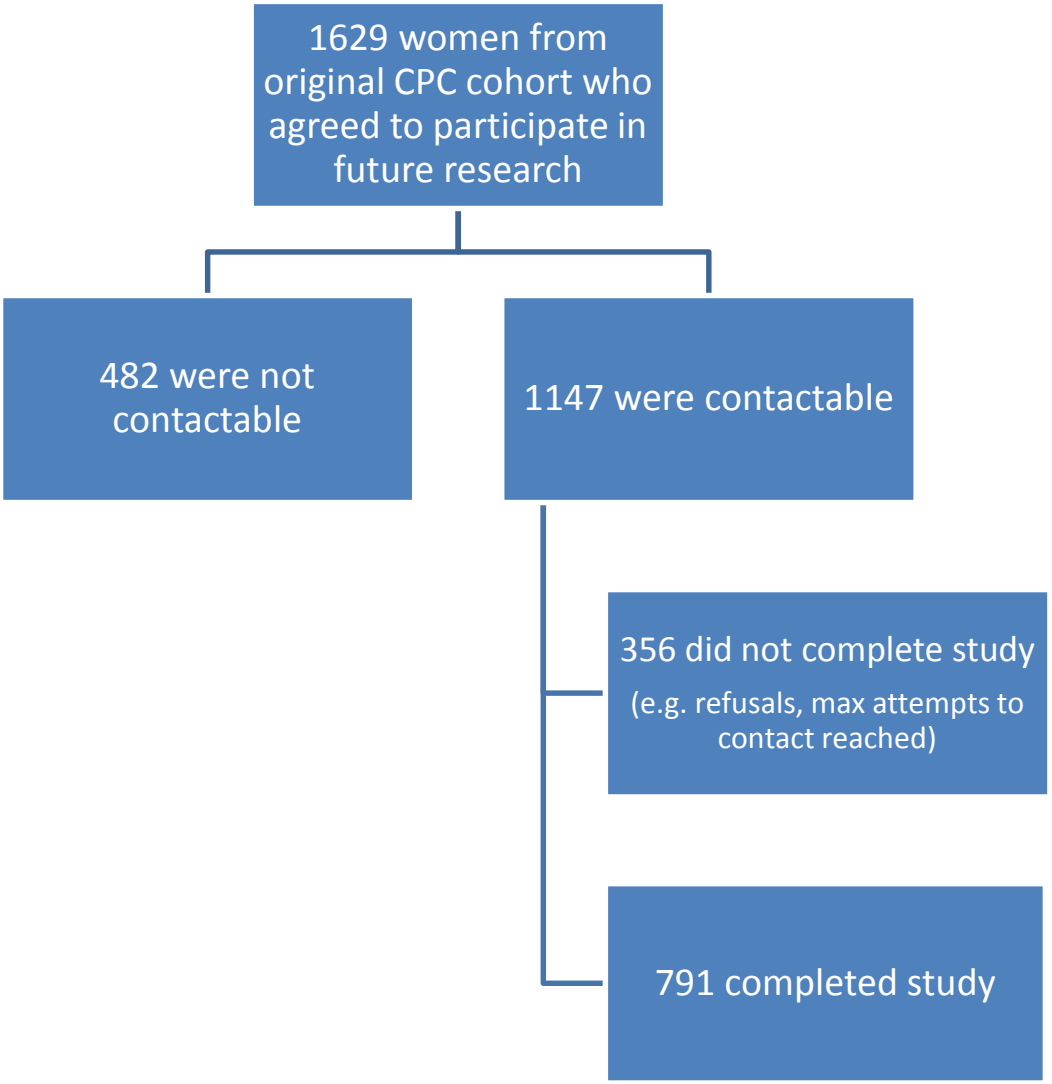

Figure 2. Study flowchart of eligibility and recruitment process. Adapted from Tough *et al.* (2008).

Table 1a. *Sex specific child wheeze and allergy outcomes by maternal childhood experience*

% with outcome		Girls at age 3 years			Boys at age 3 years		
		Total number	Wheeze (*n=22*)	Allergies (*n=31*)	Total number	Wheeze (*n=39*)	Allergies (*n=46*)
Separation or Divorce before age 5							
	Yes	31	12.9%**	9.7%	34	8.8%	12.5%
	No	376	4.5%	7.4%	345	10.4%	12.2%
Sexual Abuse before age 8							
	Yes	20	10.0%	5.0%	26	11.5%	26.9%**
	No	387	4.9%	7.8%	355	10.1%	11.0%

* P<0.1
** P< 0.05

Table 3a. *Maternal childhood experiences and child wheeze and allergy outcomes by maternal characteristics*

% of Women	Total Number	Sexual Abuse before Age 8	Physical Abuse before Age 8	Neglect before Age 8	Separation or Divorce before Age 5
Prenatal Maternal Smoking					
Moderate/Heavy	84	14.3%**	7.1%	7.1%**	17.9%**
Light/None	676	4.6%	4.0%	2.8%	6.9%
Postnatal Maternal Smoking					
Moderate/Heavy	62	8.1%	3.3%	4.8%	14.5%**
Light/None	684	5.3%	4.5%	3.2%	7.5%
Preterm Birth					
Yes	51	3.9%	3.9%	9.8%**	11.8%
No	694	5.6%	4.3%	2.9%	7.8%
Prenatal Maternal Vitamin Use					
Yes	727	5.4%	4.3%	3.2%	7.9%
No	19	10.5%	10.5%	10.5%*	16.7%
Breastfeeding					
< 8 Weeks	146	9.0%**	5.5%	2.1%	9.6%
> 8 Weeks	600	4.7%	4.2%	3.7%	7.7%
Prenatal Maternal Distress					
None	667	4.5%	3.0%	2.4%	7.9%
Moderate	91	12.1%	8.8%	6.6%	11.0%
Severe	33	15.6%**	12.1%**	9.1%**	9.1%
EPDS post-natal depression score					
Possible Depression	54	13.0%**	9.3%*	7.4%*	5.7%
No Depression	602	5.1%	4.0%	3.1%	8.1%

* P<0.1
** P< 0.05

Table 9. *Maternal experience of childhood neglect and risk of wheeze and allergies in all children*

	Wheeze at age 3 Years		Allergies at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Neglect before age 8 (reference: none)	**3.17 (1.15-8.76)**	2.19 (0.72-6.60)	2.41 (0.88-6.61)	1.94 (0.67-5.62)
Prenatal Maternal Smoking (reference: light or none)	1.54 (0.73-3.25)	0.72 (0.18-2.84)	**1.92 (1.00-3.66)**	1.56 (0.56-4.30)
Postnatal Maternal Smoking (reference: light or none)	1.92 (0.86-4.26)	2.44 (0.58-10.26)	1.67 (0.79-3.55)	1.12 (0.35-3.61)
Preterm Birth (reference: term)	**2.45 (1.09-5.50)**	2.28 (0.98-5.33)	0.78 (0.27-2.24)	0.70 (0.24-2.07)
Prenatal Maternal Vitamin Use (reference: none)	**0.30 (0.10-0.92)**	**0.26 (0.08-0.87)**	0.56 (0.16-1.97)	0.60 (0.16-2.19)
Breastfeeding (reference: less than 8 weeks or none)	1.02 (0.52-2.02)	1.32 (0.62-2.80)	0.92 (0.50-1.67)	1.20 (0.62-2.32)
Prenatal Maternal Distress (reference: none) Moderate	1.67 (0.81-3.43)	1.43 (0.65-3.15)	1.44 (0.73-2.87)	1.50 (0.74-3.05)
Severe	2.41 (0.89-6.54)	2.49 (0.86-7.20)	**3.36 (1.45-7.79)**	**3.13 (1.29-7.61)**
Sex of the baby (reference: girl)	**1.99 (1.16-3.42)**	**2.19 (1.23-3.90)**	**1.66 (1.03-2.68)**	**1.71 (1.03-2.83)**

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child and duration exclusive breastfeeding.

Table 9a. *Maternal experience of childhood neglect and risk of wheeze and allergies in all children*

	Wheeze at age 3 Years		Allergies at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Neglect before age 8 (reference: moderate or none)	3.17 (1.15-8.76)	2.16 (0.64-7.21)	2.54 (0.92-7.01)	1.85 (0.57-5.96)
Prenatal Maternal Smoking (reference: light or none)	1.54 (0.73-3.25)	0.70 (0.17-2.85)	**1.92 (1.00-3.66)**	1.76 (0.62-4.96)
Postnatal Maternal Smoking (reference: light or none)	1.92 (0.86-4.26)	2.56 (0.59-11.11)	1.67 (0.79-3.55)	1.17 (0.35-3.87)
Preterm Birth (reference: term)	**2.45 (1.09-5.50)**	1.69 (0.64-4.44)	0.78 (0.27-2.24)	0.63 (0.18-2.18)
Prenatal Maternal Vitamin Use (reference: none)	0.30 (0.10-0.92)	0.50 (0.10-2.41)	0.56 (0.16-1.97)	0.61 (0.13-2.87)
Breastfeeding (reference: less than 8 weeks or none)	1.02 (0.52-2.02)	1.00 (0.47-2.16)	0.92 (0.50-1.67)	1.12 (0.55-2.26)
Prenatal Maternal (reference: none) Moderate	1.67 (0.81-3.43)	1.58 (0.71-3.53)	1.44 (0.73-2.87)	1.85 (0.89-3.84)
Severe	2.41 (0.89-6.54)	1.69 (0.45-6.34)	**3.36 (1.45-7.79)**	**3.25 (1.16-9.13)**
Sex of the baby (reference: girl)	**1.99 (1.16-3.42)**	**2.99 (1.57-5.71)**	**1.66 (1.03-2.68)**	1.63 (0.94-2.84)
Possible Postpartum Depression (EPDS score) (reference: no depression)	1.27 (0.48-3.36)	0.90 (0.32-2.54)	1.05 (0.40-2.73)	0.75 (0.27-2.09)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child, duration exclusive breastfeeding and **potential postpartum depression**.

Table 10. *Maternal experience of childhood physical abuse and risk of wheeze and allergies in all children*

	Wheeze at age 3 Years		Allergies at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Physical Abuse before age 8 (reference: none)	1.76 (0.60-5.20)	1.99 (0.70-5.68)	1.34 (0.46-3.93)	1.02 (0.33-3.15)
Prenatal Maternal Smoking (reference: light or none)	1.54 (0.73-3.25)	0.69 (0.17-2.80)	**1.92 (1.00-3.66)**	1.60 (0.57-4.46)
Postnatal Maternal Smoking (reference: light or none)	1.92 (0.86-4.26)	2.70 (0.62-11.71)	1.67 (0.79-3.55)	1.12 (0.34-3.67)
Preterm Birth (reference: term)	**2.45 (1.09-5.50)**	**2.48 (1.07-5.69)**	0.78 (0.27-2.24)	0.75 (0.26-2.19)
Prenatal Maternal Vitamin Use (reference: none)	**0.30 (0.10-0.92)**	**0.26 (0.08-0.84)**	0.56 (0.16-1.97)	0.55 (0.15-1.99)
Breastfeeding (reference: less than 8 weeks or none)	1.02 (0.52-2.02)	1.41 (0.66-2.99)	0.92 (0.50-1.67)	1.24 (0.64-2.40)
Prenatal Maternal Distress (reference: none)				
Moderate	1.67 (0.81-3.43)	1.44 (0.66-3.17)	1.44 (0.73-2.87)	1.55 (0.76-3.14)
Severe	2.41 (0.89-6.54)	2.51 (0.87-7.28)	**3.36 (1.45-7.79)**	**3.28 (1.35-7.99)**
Sex of the baby (reference: girl)	**1.99 (1.16-3.42)**	**2.15 (1.21-3.83)**	**1.66 (1.03-2.68)**	**1.71 (1.03-2.82)**

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child and duration exclusive breastfeeding.

Table 10a. *Maternal experience of childhood physical abuse and risk of wheeze and allergies in all children*

	Wheeze at age 3 Years		Allergies at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Physical Abuse before age 8 (reference: moderate or none)	1.76 (0.60-5.20)	1.90 (0.60-5.99)	1.34 (0.46-3.93)	0.56 (0.12-2.58)
Prenatal Maternal Smoking (reference: light or none)	1.54 (0.73-3.25)	0.69 (0.17-2.85)	**1.92 (1.00-3.66)**	1.90 (0.66-5.42)
Postnatal Maternal Smoking (reference: light or none)	1.92 (0.86-4.26)	2.82 (0.63-12.54)	1.67 (0.79-3.55)	1.09 (0.32-3.70)
Preterm Birth (reference: term)	**2.45 (1.09-5.50)**	1.84 (0.71-4.74)	0.78 (0.27-2.24)	0.67 (0.20-2.29)
Prenatal Maternal Vitamin Use (reference: none)	0.30 (0.10-0.92)	0.49 (0.10-2.34)	0.56 (0.16-1.97)	0.59 (0.13-2.78)
Breastfeeding (reference: less than 8 weeks or none)	1.02 (0.52-2.02)	1.08 (0.50-2.30)	0.92 (0.50-1.67)	1.12 (0.55-2.27)
Prenatal Maternal Distress (reference: none) Moderate	1.67 (0.81-3.43)	1.58 (0.71—3.51)	1.44 (0.73-2.87)	1.96 (0.95-4.06)
Severe	2.41 (0.89-6.54)	1.64 (0.43-6.22)	**3.36 (1.45-7.79)**	**3.42 (1.22-9.65)**
Sex of the baby (reference: girl)	**1.99 (1.16-3.42)**	**2.94 (1.54-5.60)**	**1.66 (1.03-2.68)**	1.64 (0.94-2.85)
Possible Postpartum Depression (EPDS score) (reference: no depression)	1.27 (0.48-3.36)	0.94 (0.34-2.61)	1.05 (0.40-2.73)	0.79 (0.28-2.18)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, sex of child, duration exclusive breastfeeding and **potential postpartum depression**.

Table 11. *Maternal experience of multiple forms of adversity and sex specific risk of wheeze in toddlers*

		Girls at age 3 Years		Boys at age 3 years	
		Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
2 or More Early Life Adversity Experiences (reference: none)		**11.06 (3.40-35.93)**	**10.06 (2.77-36.52)**	1.83 (0.51-6.62)	1.27 (0.32-5.04)
Prenatal Maternal Smoking (reference: light or none)		0.40 (0.05-3.08)	0.14 (0.01-1.55)	**2.41 (1.02-5.69)**	0.99 (0.24-4.08)
Postnatal Maternal Smoking (reference: light or none)		0.53 (0.07-4.08)	1.89 (0.38-9.31)	3.38 (1.32-8.57)	3.39 (0.70-16.53)
Preterm Birth (reference: term)		3.04 (0.82-11.25)	3.53 (0.93-13.47)	2.04 (0.73-5.73)	1.78 (0.60-5.33)
Prenatal Maternal Vitamin Use (reference: none)		**0.14 (0.04-0.58)**	0.16 (0.04-0.71)	0.68 (0.08-5.80)	0.91 (0.09-8.85)
Breastfeeding (reference: less than 8 weeks or none)		2.06 (0.47-9.09)	3.07 (0.65-14.54)	0.81 (0.37-1.80)	0.96 (0.40-2.29)
Prenatal Maternal Distress (reference: none)	Moderate	1.44 (0.40-5.13)	1.53 (0.41-5.70)	1.79 (0.74-4.36)	1.24 (0.45-3.42)
	Severe	**4.41 (1.15-16.90)**	3.43 (0.81-14.52)	1.39 (0.30-6.41)	1.39 (0.27-7.10)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth and duration exclusive breastfeeding.

Table 11a. *Maternal experience of multiple forms of adversity and sex specific risk of wheeze in toddlers*

	Girls at age 3 Years		Boys at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
2 or More Early Life Adversity Experiences (reference: none)	**11.06 (3.40-35.93)**	**8.07 (1.82-25.80)**	1.83 (0.51-6.62)	1.40 (0.35-5.68)
Prenatal Maternal Smoking (reference: light or none)	0.40 (0.05-3.08)	0.24 (0.02-2.69)	**2.41 (1.02-5.69)**	0.82 (0.19-3.48)
Postnatal Maternal Smoking (reference: light or none)	0.53 (0.07-4.08)	2.40 (0.47-12.30)	**3.38 (1.32-8.57)**	2.68 (0.55-13.00)
Preterm Birth (reference: term)	3.04 (0.82-11.25)	2.96 (0.69-12.77)	2.04 (0.73-5.73)	1.28 (0.39-4.27)
Prenatal Maternal Vitamin Use (reference: none)	**0.14 (0.04-0.58)**	0.30 (0.30-2.95)	0.68 (0.08-5.80)	0.99 (0.11-9.28)
Breastfeeding (reference: less than 8 weeks or none)	2.06 (0.47-9.09)	1.74 (0.36-8.27)	0.81 (0.37-1.80)	0.86 (0.36-2.05)
Prenatal Maternal Distress (reference: none) Moderate	1.44 (0.40-5.13)	2.27 (0.58-8.83)	1.79 (0.74-4.36)	1.25 (0.46-7.02)
Severe	**4.41 (1.15-16.90)**	1.90 (0.21-16.96)	1.39 (0.30-6.41)	1.32 (0.25-7.02)
Possible Postpartum Depression (EPDS score) (reference: no depression)	**4.68 (1.20-18.28)**	**4.45 (1.10-18.10)**	0.48 (0.11-2.10)	0.31 (0.07-1.50)

Adjusted for prenatal maternal smoking, postnatal smoking, prenatal distress and vitamin use, preterm birth, duration exclusive breastfeeding **and possible postpartum depression**.

	Wheeze at age 3	Allergies at age 3
Psychological Abuse	-	+
Household Dysfunction	+	-
Neglect	-	-
Physical Abuse	-	-
Separation or Divorce	+ (for girls)	-
Sexual Abuse	-	+ (for boys)

Figure 3. Overall associations between adversity types and wheeze and allergy outcomes. A + sign denotes evidence of an association, a - sign marks no association.