"Associations Among Maternal Exposure to Prenatal and Lifetime Family Violence and Cord Blood IgE "

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BACKGROUND

Evidence linking psychosocial stress to the expression of asthma and atopy continues to grow. Research from animal studies suggest that experiencing high levels of *in utero* stress may prove especially critical for asthma development(Calvani, Alessandri, Sopo, Panetta, Tripodi, Torre, Pingitore, Frediani, and Volterrani 2004; Hessl, Dawson, Frey, Panagiotides, Self, Yamada, and Osterling 1998; Kurukulaaratchy, Waterhouse, Matthews, and Arshad 2005; Kurzius-Spencer, Halonen, Lohman, Martinez, and Wright 2005; Sanchez 2006; Sánchez, Noble, Lyon, Plotsky, Davis, Nemeroff, and Winslow 2005; Xu, Pekkanen, Jarvelin, Olsen, and Hartikainen 1999). No human studies to date, however, have examined the influence of prenatal stress and asthma risk in children or the intermediate mechanisms linking the two. Interest in this subject is motivated by enhanced understanding of the psycho-neuroimmunological (PNI) mechanisms implicated in asthma etiology and as well as an increasing effort to determine why asthma remains a leading cause of health disparities unexplained by physical environmental risk factors (Gold and Wright 2005; McEwen 2002; Wright, Cohen, and Cohen 2005; Wright, Rodriguez, and Cohen 1998).

Also unknown is the nature of the stressor(s) that would have the strongest effects. This study examines family violence experienced across the mother's life course as a key stressor that may play a role in asthma etiology in their children. We focus on violence both because of its high prevalence rate, and because, as a psychological stressor disproportionately affecting members of racial/ethnic minorities and those of lower SES (Cunradi, Ames, and Moore 2008; Cunradi, Caetano, and Schafer 2002; Fox, Benson, DeMaris, and Wyk 2002; Hazen and Soriano 2007), such exposures may in part explain

the excess burden of asthma in these populations. Furthermore, exposure to violence has been implicated in lasting key physiological disruptions likely underlying asthma etiology (Baum 1990).

The influence of violence may best be understood when considered as both an acute and chronic strain. Evidence from both animal models (Heim and Nemeroff 2002) and human studies (Gunnar and Donzella 2002) indicate that exposure to traumatic stress during early development may permanently alter physiological responses for the victims, with adverse health consequences extending into adulthood (McEwen 2002). Past and current stressors may operate synergistically or additively as they accumulate over the life course (Baum 1990; Pike, Smith, Hauger, Nicassio, Patterson, McClintick, Costlow, and Irwin 1997). Experiences of past violence not only increase the likelihood of subsequent victimization (Bowen, Heron, Waylen, and Wolke 2005; Saltzman, Johnson, Gilbert, and Goodwin 2003), but may also sensitize mothers to more proximal abuse exposure (i.e. during pregnancy) (Murburg 1997). Individuals with a history of assault, for instance, are more vulnerable to HPA dyssregulation and exhibit blunted cortisol levels in the face of current trauma, compared to those with no preexisting trauma history (Bremner and Vermetten 2001; Bryant, Harvey, Guthrie, and Moulds 2000; Resnick, Yehuda, Foy, and Pitman 1995; Saltzman, Holden, and Holahan 2005). Thus, a mother's remote exposure to violence (i.e. in childhood and/or adolescence) may prime one's body, enhancing vulnerability to proximal stressful experiences (Clougherty, Levy, Kubzansky, Ryan, Suglia, Canner, and Wright 2007; Murburg 1997; Wright in press).

Given these overlapping threads of evidence, it seems plausible that maternal exposure to violence may influence stress pathways in mothers that may have

implications for the child's immune development, even starting *in utero* (Wright in press; von Hertzen L 2002). Whether triggered by remote or proximal violent experiences, the disruption of biological systems during pregnancy may produce adverse health consequences transmitted to the next generation.

We tested this hypothesis by taking advantage of the Asthma Coalition on Community, Environment, and Social Stress (ACCESS), a prospective pregnancy cohort of women recruited from prenatal clinics throughout Boston in order to assess the role of early life exposure to both environmental determinants and psychosocial factors on asthma risk in their children. We examined the relationship between maternal experiences of violence during their life course and cord blood total IgE, an immunological biomarker of atopic asthma. This is important because elevated IgE levels are not only predictive of atopic asthma, but also are often detectable before the child becomes symptomatic (Halken 2003; Hansen, Halken, Host, Moller, and Osterballe 1993; Odelram, Bjorksten, Leander, and Kjellman 1995; Tariq, Arshad, Matthews, and Hakim 1999). Linking violence to this "asthma precursor" may illuminate key biological mechanisms through which violence may "get under the skin."

Specifically, the study addressed two research questions: first, is cord blood IgE levels significantly higher among women experiencing abuse during pregnancy (or most proximate to pregnancy), compared to their non-abused counterparts? Second, does a mother's cumulative exposure to violence throughout her life course (i.e. exposure during early childhood, teenage years, adulthood, during pregnancy) influence cord blood IgE levels?

LITERATURE REVIEW

The theoretical and empirical basis for my paper relies heavily on biomedical research on asthma, stress, atopy, and perinatal programming, and the transgernational transmission of trauma.stress effects. Given the complex and somewhat technical nature of this research, I provide a brief summary below of the most relevant physiological processes involved in the violence-IgE link.

Asthma Biology

Asthma is a disease typified by airway obstruction, airway inflammation, and heightened airway sensitivity to a range of stimuli (Burrows, Martinez, Cline, and Lebowitz 1995; Robinson, Hamid, Bentley, Ying, Kay, and Durham 1993; Wright 2005). Conceptualized as a disease of dysregulated immunity, most asthma involves allergy-mediated inflammation and the activation of specific T-helper cells (T_H2 cells). In a series of complex immunological events, activated T_H2 cells promote the production of immunoglobulin antibodies (IgE), which in turn recruit inflammatory cells implicated in allergic inflammation and atopic diseases (Platts-Mills, Ward, Sporik, Gelber, Chapman, and Heymann 1991; Rauh, Chew, and Garfinkel 2002; Sporik and Platts-Mills 2001).

Since asthma is a developmental disease, with most cases diagnosed by age 5 (Wright 1996; Wright 2005), the polarization of the atopic phenotype likely occurs in early childhood or *in utero*. Consequently, there is increasing interest in identifying aspects of the fetal environment that may alter neuro-immune expression and potentiate atopic disorders (Barker 1990; Osmond and Barker 2000; Roseboom, van der Meulen, Osmond, Barker, Ravelli, Schroeder-Tanka, van Montfrans, Michels, and Bleker 2000).

An extensive body of research suggests that the *in utero* environment may influence fetal development, a concept known as "perinatal programming." Numerous studies have found associations between prenatal factors and lifelong risk of developing coronary heart disease (Hales, Barker, Clark, Cox, Fall, Osmond, and Winter 1991; Rich-Edwards, Colditz, Stampfer, Willett, Gillman, Hennekens, Speizer, and Manson 1999; Roseboom et al. 2000); diabetes mellitus (Barker 1992; Levitt, Lambert, Woods, Hales, Andrew, and Seckl 2000), and hypertension (Barker 1990). Barker and colleagues have argued that adverse fetal conditions during late gestation may disturb the programming of blood pressure regulation, cholesterol metabolism, and glycemic control (Coe and Lubach 2003).

Notably, there is evidence that the asthma phenotype could also be programmed before birth. Studies report associations between maternal antibiotic use, probiotic use, and maternal infections during gestation and asthma risk. Other studies have found that maternal exposure to inhaled allergens prime fetal T cells toward an atopic phenotype (Wright, Rodriguez, and Cohen 1998).

Stress and Asthma

Beyond allergen exposure (Hoffjan, Nicolae, Ostrovnaya, Roberg, Evans, Mirel, Steiner, Walker, Shult, and Gangnon 2005) and gene-environment interactions (Cohen, Kessler, and Gordon 1995), psychosocial stress may play a role in asthma development and morbidity. Chronic stress is associated with asthma exacerbations in both cross-sectional (Sandberg, Jarvenpaa, Penttinen, Paton, and McCann 2004) and prospective studies (Lehrer, Isenberg, and Hochron 1993; Wright, Cohen, Carey, Weiss, and Gold 2002). Perceived stress has been linked to asthma symptoms (Isenberg, Lehrer, and

Hochron 1992), bronchoconstriction and reduced pulmonary flow rates (Gold and Wright 2005; Wright et al. 2002; Wright, Finn, Contreras, Cohen, Wright, Staudenmayer, Wand, Perkins, Weiss, and Gold 2004b). Stress may also play a role in asthma etiology (McEwen 2002).

One potential explanation for this association is that that the physiological processes triggered by stress directly heighten asthma morbidity/onset. According to the life stress model (Wright, Mitchell, Visness, Cohen, Stout, Evans, and Gold 2004a; Wright, Rodriguez, and Cohen 1998; Wright et al. 2004b), when individuals perceive themselves as being under stress, they experience a range of negative emotions, such as fear, anger, anxiety, and depression. Accompanying these emotional changes are a cascade of neuroendocrine and immunological reactions, including the dysregulation of the hypothalamic-pituitary-adrenocortisal (HPA) axis and the sympathetic and adrenomedullary (SAM) system (McEwen 2002). Though system dysregulation is useful for short-term immune, metabolic, and neural defense responses to stress, continuous or repeated activation of the stress response can result in long-term bodily damage (Wamboldt, Laudenslager, Wamboldt, Kelsay, and Hewitt 2003). Chronic stress may precipitate a state of hyporesponsiveness of the HPA axis, depressing the secretion of anti-inflammatory hormones (Buske-Kirschbaum, Fischbach, Rauh, Hanker, and Hellhammer 2004), heightening risk of atopic inflammation.

Stress and Perinatal Programming

Experiencing high levels of *in utero* stress may prove especially critical for asthma development (Wright et al. 2004b). Animal and human studies have found associations between perinatal stress and preterm and low birth weight (LBW) (Egliston,

McMahon, and Austin 2007; Van den Bergh, Van Calster, Smits, Van Huffel, and Lagae 2007), altered immune function (Hessl et al. 1998), and heightened stress reactivity (Calvani et al. 2004; Kurukulaaratchy, Waterhouse, Matthews, and Arshad 2005; Kurzius-Spencer et al. 2005; Xu et al. 1999). Stress-induced hormones such as cortisol may influence T helper cell phenotype differentiation in the fetal immune system, elevating IgE production, and leading to an increased risk of atopic asthma (Wright 2006). Emerging empirical evidence supports these claims. A 2004 study of caregiver stress and early childhood immune response found that higher stress in the 6 to 18 months after birth was associated with a higher IgE level and an atopic immune profile (Wright et al. 2004b)

Conceptual Framework Linking Violence to Asthma

If, as the above overview suggests, stress is a risk factor for asthma development, it follows that violence, a particularly high magnitude and pervasive stressor taxing vulnerable individuals, may trigger similar physiological reactions (Fick and Thomas 1995; Margolin and Gordis 2000; Selner-O'Hagan, Kindlon, Buka, Raudenbush, and Earls 1998). The conceptualization of violence as a stressor is based in trauma theory and an extensive literature on family violence (Baum 1990; Claussen and Crittenden 1991; De Bellis, Baum, Birmaher, Keshavan, Eccard, Boring, Jenkins, and Ryan 1999; Egeland, Sroufe, and Erickson 1983; Putnam and Trickett 1997; Wright 2006). All forms of abuse may have the distressing characteristics of being unpredictable, uncontrollable, and potentially threatening (Cicchetti, Rogosch, Lynch, and Holt 1993) Moreover, even sporadic or acute episodes of abuse can generate long-lasting stress responses for the

victims, in the form of intrusive thoughts and rumination (Baum 1990). Thus, victims of family violence are subject to chronic trauma and stress.

Because violence is a major life stressor, it may trigger physiological reactions characteristic of a "chronic stress response" (e.g., dysregulation of the HPA axis and the SAM system) (Baum 1990; Massey 2004; Murali and Chen 2005; Wilson, Kliewer, Teasley, Plybon, and Sica 2002; Wright 2006). Specifically, stress-induced disruption of the maternal HPA axis may elevate maternal IgE levels during pregnancy, which, in turn, may prime fetal sensitization to allergies and increase atopic risk (Wright, Cohen, and Cohen 2005; Wright 2005). Consequently, maternal experiences of violence may influence the infant's immunologic and neuroendocrine developmental processes, setting the stage for the inflammatory processes and altered reactivity to stimuli characteristic of chronic asthma (Wright et al. 2004b).

In this light, we propose the following hypotheses:

H1: Mothers exposure to intimate partner violence (IPV) during pregnancy and/or in the period prior to pregnancy (*proximal violence)* will predict higher cord blood IgE levels, even when controlling for other sources of stress and relevant confounders.

H2: Mothers cumulative lifetime exposure to family violence will predict higher cord blood IgE even when controlling for potential confounders. Specifically, more chronic exposure to family violence in mothers will be associated with increased cord blood IgE.

METHODS

Data

Data for this study come from the Asthma Coalition on Community, Environment, and Social Stress (ACCESS), a prospective pregnancy cohort of women recruited from prenatal clinics throughout Boston in order to assess the role of early life exposure to both environmental determinants and psychosocial factors on the rising childhood asthma burden in Boston urban communities. Mother-infant pairs were recruited during prenatal visits from August 2003 to January 2007. Pregnant women receiving prenatal care at Brigham & Women's Hospital, Boston Medical Center, three urban community health centers and women attending Women, Infants and Children (WIC) programs associated with the health centers in the Boston metropolitan area and one WIC program serving a large suburban population 20 miles south of Boston were eligible for enrollment. The project was designed to take advantage of the structure of the WIC programs given particular difficulties with recruitment and retention of study participants in this largely lower-income, ethnically diverse inner-city population who moved frequently and/or did not have telephones. Women enrolled in the WIC programs make monthly visits to pick up vouchers provided for food and childcare and are followed from 3 months to 5 years postnatally. Women who did not speak either English or Spanish and who were less than 18 years of age were excluded. Trained research assistants approached all women receiving prenatal care on selected clinic days that changed weekly depending on patient flow. At the time of this analysis, Project ACCESS had approached 2261 mothers, of whom 1,614 (71%) completed the screening questionnaire. After this screening, 1,239 (55% of those approached) agreed to participate in the longitudinal Project ACCESS cohort. Written informed consent was obtained in the subject's primary language (English or Spanish) and the study was

approved by the human studies committees at the Brigham and Women's Hospital and the Boston Medical Center. Of the subjects enrolled in the study, 643 (51%) had cord blood IgE available for their child. Of these 643 women, 191 were excluded because of missing data on the key predictor variables, resulting in a sample of 451 subjects (70%).

Use of this data set offers several advantages. The study contains a rich source of information about psychosocial factors and environmental factors associated with asthma, including socioeconomic status, interpersonal violence (sexual, physical, psychological), community violence, negative life events (unemployment, housing stress, relationship difficulties), and samples of in-home dust and cockroach allergen levels. Such extensive measures, in addition to the collected information about the mothers' medical histories, allow us to control for a range of confounding factors with greater accuracy than typically used. Moreover, because of the project's affiliation with the WIC programs, we have better access to hard-to-reach and typically underrepresented populations particularly vulnerable to asthma. The data also offer biomarkers of early-life asthma vulnerability, namely, IgE levels for a sub-cohort of women and their children. Finally, the study's longitudinal design enables us to establish temporal priority between maternal reports of violence and subsequent cord blood IgE levels.

MEASURES

Dependent Variable

Total serum IgE Levels. Serum samples from infant cord blood were analyzed for total IgE antibodies, reported in IU/mL. Various cut-off points have been used to define elevated IgE levels in cord blood that may more likely indicate increased asthma risk

(ranging from 0.2 to 0.77); (Hansen et al. 1993; Liu, Wang, Chuang, Ou, Hsu, and Yang 2003; Scirica, Gold, Ryan, Abulkerim, Celedón, Platts-Mills, Naccara, Weiss, and Litonjua 2007; Tariq, Arshad, Matthews, and Hakim 1999). However, because there is no established level for total cord blood IgE that consistently predicts asthma risk in epidemiologic studies, IgE levels were divided into tertiles, with serum levels at or above the upper tertile (0.77 IU/mL) considered to be "high."

Key Predictors – Violence Exposure Measures

Proximal and Lifetime Abuse History. Physical and sexual abuse was assessed using the Revised Conflict-Tactics Scale Short form (7), the most widely used reliable and validated instrument to identify intimate partner maltreatment. Respondents were asked about their abuse history during four periods: childhood (age 11 and below), adolescence (ages 12 to 17), adulthood before the pregnancy (18 and above), and during the index pregnancy. Abuse was defined as being pushed, grabbed or shoved; kicked, punched or bit; hit with something that hurt one's body; choked or burned; forced to have sexual activities; or experiencing other physical abuse, by one's partner (or parent, in the case of childhood).

Proximal Abuse: Given that a small number of women reported abuse at the time of interview during pregnancy (n=21) and a significant proportion of subjects abused during pregnancy also reported abuse during the period of adulthood just prior to the pregnancy (66%), we considered proximal abuse as (1) only occurring in pregnancy and (2) occurring either in pregnancy or adulthood prior to pregnancy. Other evidence also suggests that those abused just prior to pregnancy are likely to experience abuse at a

similar frequency and severity during the target pregnancy (Bowen, Heron, Waylen, and Wolke 2005; Saltzman, Johnson, Gilbert, and Goodwin 2003). In the latter case we do not know how recent the subject experienced abuse "in adulthood prior to pregnancy."

Lifetime history of abuse: We defined lifetime history of abuse based on the total number of time periods (1 through 4) in which a study participant reported experiencing abuse: childhood, adolescence, adulthood before this pregnancy, and during the index pregnancy. Because of the small cell sizes, the categories were then collapsed to create an ordinal variable (0=no abuse, 1=1-2 time periods, 2= 3 or more periods).

Control Variables

Sociodemographic Factors. We adjusted for a number of variables that have been associated with increased cord blood IgE in previous studies that may also be associated with violence exposure. Violence victimization is correlated with other markers of poverty and disadvantage that may also produce elevated IgE levels (Levin 1991). For example, minorities and individuals of low SES experience higher rates of family violence than their counterparts and are more likely to have elevated IgE cord blood levels (Scirica et al. 2007) or engage in asthma-inducing health behaviors (smoking) (Shohaimi, Luben, Wareham, Day, Bingham, Welch, Oakes, and Khaw 2003; Tseng, Yeatts, Millikan, and Newman 2001). Moreover, minorities and individuals of low SES are more likely to experience other stressors (i.e., community violence, poverty, food insecurity), (Williams and Jackson 2005) that may also heighten IgE levels (Pike et al. 1997; Wright et al. 2004b).

Given that race and/or socioeconomic status may confound the relationship between violence and IgE, our analysis controlled for maternal race (categorized as White/other, Black, or Hispanic), maternal education (in years), and maternal financial strain, a three-item summary index based on responses to the following questions: a) How difficult is it (1=not difficult at all, 5=extremely difficult), for you to live on your total household income right now? b) In the next two months, how likely is it (1=not at all likely, 5=extremely likely) that you and your family will experience actual hardships, such as inadequate housing, food, or medical attention? c) In the next two months, how likely is it that you and your family will have to reduce standard of living to the bare necessities in life? Scores ranged from 0 to 15, higher scores indicating greater economic hardship. Economic strain has been found to affect parent's psychological well-being in addition to other health outcomes (Conger, Conger, Elder Jr, Lorenz, Simons, and Whitbeck 1992).

Maternal Factors. In addition to standard sociodemographic factors, we also included other predictors of asthma and/or IgE, including gestational age at time of survey (measured in weeks), maternal age (in years), maternal smoking during pregnancy (coded as 1 if smoked during pregnancy child's sex (coded as 1 if male), and maternal history of atopic disease (defined as ever being diagnosed with asthma, hay fever, or eczema) (Scirica et al. 2007).

We also control for other negative life events that may confound the relationship between violence and IgE, using the Crisis in Family Systems (CRISYS) questionnaire, an instrument developed to capture the stressful life events of vulnerable and low-income communities (Shalowitz, Mijanovich, Berry, Clark-Kauffman, Quinn, and Perez 2006).

Participants indicated whether they experienced a list of events that span several domains (safety, finances, community career, death, relationships, medical issues, home issues, authority, drug use, child delinquency) in the last six months. The total number of events (with the exception of those relating to home safety, which will be excluded because of collinearity with current violence exposure) was summed to create a contemporary stressor score.

Environmental Factors. Environmental allergens tied to elevated IgE, such as cockroach and dust mite, are more prevalent in low-income areas with high crime rates (i.e. urban neighborhoods) (Wright and Subramanian 2007). Prenatal exposure to home allergens was operationalized through two dummy variables: dust mite allergen (defined as a detectable level [20ng/G] or greater of either Der p or Der f allergens were found in the home) and cockroach allergen (defined as a detectable level [.4 U/g] or greater of Bla g 2).

Childhood SES. Childhood SES is an important risk factor for adult respiratory and infectious diseases. Unfavorable early life SES has been shown to predict the exptression of proinflammatory phenotype in adolescencts(Chen, Hanson, Paterson, Griffin, Walker, and Miller 2006; Miller and Chen 2007) and is associated with a decreased resistance to upper respiratory infections (Cohen et al 2004 (Cohen, Doyle, Turner, Alper, and Skoner 2004)). Low SES is also a risk factor for intimate partner violence. We operationalized maternal childhood SES through home ownership (coded as 1 if the mother's parents owned their home during her childhood up to age 15 years and 0 if it was rented). Home ownership is a well-established indicator of income and

assets, and an especially good retrospective measure of childhood SES circumstances since adults can typically recall whether their parents owned or rented their homes.

ANALYTIC STRATEGY

The analysis proceeded in two stages. The first stage examined the association between proximal abuse and cord blood IgE levels. An initial binary logistic regression model estimated the unadjusted relationship between proximal abuse exposure and elevated IgE. Standard sociodemographic covariates and other confounders were added in a stepwise fashion to assess a) whether violence exposure is actually a proxy for demographic factors tied to asthma onset (i.e., poverty, race) and b) whether any association between violence exposure and IgE level is in part driven by correlated factors. We ran models using both definitions of proximal abuse (abuse in pregnancy versus abuse either in pregnancy or adulthood prior to pregnancy).

The second stage examined the relationship between lifetime abuse and cord blood IgE level. The analysis proceeded in a similar fashion, with the first model regressing IgE levels on the measure of chronic abuse, and subsequent models sequentially incorporating the following covariates: maternal age, race, education attainment, socioeconomic status, child's gender; maternal atopy, maternal smoking during pregnancy, and other negative life events; cockroach and dust mite allergens, and childhood SES. All results were presented in odds ratios.

RESULTS

Table 1 describes sample characteristics. As shown, 151 (33%) of the women had offspring with IgE levels at or above 0.77. The majority of the sample did not

experience proximal abuse; only five percent of the subjects reported abuse during pregnancy, a prevalence rate consistent with other hospital-or clinic-based samples of pregnant women.(Martin, Mackie, Kupper, Buescher, and Moracco 2001). Twenty percent reported abuse during pregnancy or adulthood, a prevalence rate found by researchers using national probability samples, which estimate the risk of victimization among all women or all women of childbearing age and samples of women who are pregnant (see Jasinski 2004 for a review). A substantial proportion (45%) of the sample experienced some abuse throughout their lifetime. The "chronicity" pattern was: one time period (22.6%); two time periods (13%); and 3 or more time periods (8.65%) The average subject was 27. 3 weeks pregnant at the time of interview, Hispanic, and relatively uneducated (64% had a high school degree or less). About half reported that their parents owned a home when they were growing up (53%). In terms of current maternal risk factors, approximately a third of the sample reported a lifetime diagnosis of maternal atopy (32%), ten percent smoked during pregnancy, and the majority reported 5 or more stressful live events based on the CRISYS. Finally, over half the sample had detectable allergen levels in their home.

Table 2 presents odds ratios of elevated cord blood IgE by mother's proximal abuse history, with columns A and B representing, respectively, abuse during pregnancy, and abuse during pregnancy or adulthood. Contrary to our hypothesis, neither measure of proximal abuse positively correlated with elevated IgE levels. Adjusting for standard sociodemographic controls and maternal risk factors had no effect on proximal violence. Maternal atopy and current financial strain yielded independent, positive effects on IgE

while childhood SES (as measured through home ownership) decreased the likelihood by around 40 percent.

Table 3 shows results from analyses on cord blood IgE and lifetime abuse history. The bivariate analyses revealed a gradient increase in risk of elevated IgE with each abuse rank order. Adjusting for standard sociodemographic factors (model 2), maternal factors (model 3), environmental factors (model 4), or childhood SES (model 5) produced no meaningful attenuation. Consistent with the findings of proximal abuse, maternal atopy and childhood SES were significant predictors of elevated IgE in the expected direction.

Figure 1 further illustrates the graded relationship between lifetime history of abuse and elevated IgE. Based on estimates from the fully adjusted model (5), the figure shows a gradient increase in the predicted probability of elevated IgE with each abuse category (P=.01).

DISCUSSION

The aim of this study was to examine the relationship between maternal experiences of violence during her life course and fetal cord blood IgE. Our results show a graded association between lifetime exposure to violence and cord blood IgE, a biological marker for atopic asthma. Greater exposure to violence throughout one's life course was independently associated with increased risk of offspring elevated IgE after simultaneously adjusting for maternal race, educational attainment, SES, maternal atopy, smoking behavior, other adverse life events, housing allergens, or childhood SES, suggesting that violence was not simply a marker for these other factors.

The gradient between maternal lifetime exposure to violence and offspring IgE indicates that the detrimental effects of family violence may not only accumulate over the mother's life course, but also transmit across generations through the fetal environment. These findings are consistent with an emerging literature linking violence to asthma (Clougherty et al. 2007; Wright 2006; Wright, Hanrahan, Tager, and Speizer 1997; Wright et al. 2004a; Wright and Steinbach 2001). Notably, our results provide some of the first empirical evidence that maternal experiences of violence may alter fetal immune developmental processes relevant to asthma etiology (Barker 1995; Barker, Gluckman, Godfrey, Harding, Owens, and Robinson 1993; Ben-Shlomo and Kuh 2002; Welberg and Seckl 2001).

Interestingly, we found no association between proximal abuse (pregnancy or pregnancy or adulthood) and elevated IgE in the unadjusted and adjusted models. One possibility is that acute abuse and chronic abuse have different biological consequences for elevated IgE. That is, the *cumulative* exposure to violence, rather than the *proximity* of the abuse to the index pregnancy, may be the most salient factor in influencing fetal development. This notion is theoretically consistent with our conceptualization of violence as a pervasive but extreme stressor. As with other life stressor, exposure to violence may trigger physiological reactions characteristic of a stress response (dysregulation of the HPA axis and the SAM system). While short-term dysregulation may be adaptive, the continuous or repeated activation of the stress response can result in long-term bodily damage. Though some studies reveal that sporadic or acute episodes of abuse can generate long-lasting responses for the victim (Baum 1990), other research indicates that the frequency of violent experiences over the life course is the most robust

predictor of adverse biological markers (Chen and Murali 2005). Such an interpretation would suggest that victimization need not occur *during* the index pregnancy in order to adversely affect the fetus. Likewise, for women with no prior history of violence exposure, physical/sexual abuse during pregnancy may have minimal consequences for cord blood IgE levels.

However, another possibility is that the results reflect a lack of statistical power. Recall that only 21 subjects reported abuse during pregnancy, a sample size too small to detect statistical significance. While the alternative definition of proximal abuse (during pregnancy and pregnancy versus adulthood) substantially increased the sample size of abused subjects, this definition was far less precise in capturing "proximal abuse" since it encompassed any abuse from age 18 onward, without any indication of its proximity to the index pregnancy. Thus, the absence of an effect may be reflective of data limitations rather than substantive issues. Further research using a greater sample size will prove useful in clarifying whether these results reflect substantive or statistical differences.

Independent of their abuse history, current SES, smoking behavior, or life stressors, subjects raised in homes owned by their parents were less likely to have offspring with elevated IgE, compared to those raised in rented homes. This is in agreement with other evidence linking unfavorable SES circumstances early in life (as measured by home ownership) with a heightened vulnerability to respiratory and cardiovascular diseases in adulthood (Chen, Fisher, Bacharier, and Strunk 2003; Chen et al. 2006; Cohen et al. 2004; Miller and Chen 2007), even when adjusting for health behaviors, life stress, or adult SES. Our findings are unique in suggesting that the physiological effects of childhood SES, at least in terms of elevated IgE, may have

transgenerational implications. While the mechanisms underlying this process are not well understood, extant research indicates that adverse early life SES may program biological systems, resulting in pro-inflammatory epigenetic processes that prime the body to later life respiratory infections or inflammatory diseases (Chen et al. 2006; Miller and Chen 2007) Additional research will be useful to further elucidate the socio-psycho-biological pathways linking maternal childhood SES and offspring-IgE.

The study has several limitations. The association between violence exposure and IgE may be due to residual confounding. Though the prospective study design and the use of statistical controls attempt to control for systematic differences between the "control" (i.e., those not exposed to violence) and the "treatment group" (those experiencing violence) or factors correlated with both IgE and violence exposure, unmeasured factors may nevertheless confound the violence-IgE association. Second, measures of violence victimization are self-reported and retrospective. Though several studies indicate the accuracy of retrospectively obtained abuse histories, the potential for recall bias remains (Brewin, Andrews, and Gotlib 1993; Maughan and Rutter 1997; Paivio 2001). Similarly, the use of survey questions, especially in such a sensitive area, raises the possibility of social desirability response bias. Third, because the study does not represent a random sample of mothers, the results may be subject to selection bias. All participants were recruited from either prenatal care units at hospitals or WIC sites. These mothers may differ systematically from those who do not receive prenatal care, are not participants in WIC, or chose to not participate in the survey. Therefore, the results of this sample may not be generalizable to these overlooked populations. Finally, measuring violence victimization is challenging. Any one type of abuse can range vastly

depending on the age of initial onset, the frequency, and chronicity. Though the use of widely accepted, validated scales of violence will hopefully minimize measurement error, we recognize that any survey-based measure of violence necessarily sacrifices the personally-tailored and fine-grained assessment of a clinical diagnosis.

Future research could build on these findings by examining prenatal exposure to family violence within the context of community-level physical and social stressors. Recent evidence suggests a synergistic effect between traffic-related air pollution and urban exposure to violence on urban asthma etiology (Clougherty et al. 2007). Additional studies should investigate whether *in utero* exposure to family violence operate multiplicatively with neighborhood violence such that victimized pregnant women living in socially toxic areas have offspring with the highest asthma rates.

Additional research should also consider the role of proximal and lifetime psychological abuse for asthma pathogenesis. Psychological maltreatment in the form of humiliation, isolation, and disempowerment within a relationship has been linked to post-traumatic stress disorder (PTSD) (Basile, Arias, Desai, and Thompson 2004) and other adverse physical outcomes (Coker, McKeown, and Alerts 2000), and may be just as damaging as other types of violence (Claussen and Crittenden 1991; Coker, McKeown, and Alerts 2000; Egeland, Sroufe, and Erickson 1983). Given that the co-occurrence of abuse types may be more detrimental to health than any single form, future research should test for potential independent, additive, and multiplicative influences of multiple abuse types.

CONCLUSION

While past research has identified associations between violence and asthma morbidity (Wright 2006; Wright, Hanrahan, Tager, and Speizer 1997; Wright et al. 2004a; Wright and Steinbach 2001), minimal evidence exists on the relationship between violence asthma etiology. Moreover, no studies to date have examined the influence of prenatal stress and asthma risk in children or the intermediate mechanisms linking the two. Our work therefore contributes to the existing literature by providing some of the first empirical evidence that chronic experiences of abuse may have transgenerational implications for asthma susceptibility. We demonstrate that the detrimental effects of violence may a) accumulate over the life course and b) transmit across generations through the fetal environment. Such research may prove useful in further understanding why asthma remains a leading cause of health disparities unexplained by physical environmental risk factors.

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Table 1. Summary Characteristics for ACCESS Sample (n=451)

Variables	N	Percent	Mean	SD	Range	
Elevated Cord Blood IgE *	151	33%	0.33	0.47		
Maternal Physical/Sexual Abuse						
Proximal Abuse History						
During Pregnancy	21	5%	0.05	0.21		
Adulthood (age 18-Pregnancy)	85	20%	0.20	0.40		
During Pregnancy and/or Adulthood	92	20%	0.20	0.40		
*Lifetime Abuse History***						
No Abuse	251	56%	-			
1-2 Time Periods	161	36%	-			
3 -4 Time Periods	39	9%	-			
Sociodemographic Factors						
Maternal Age (Years)	-		26.70	5.83	16.38	40.93
Gestational Age (Weeks)	-		29.28	7.60	8	41.14
Child's Sex (Male)	226	50%	0.50	0.50		
Maternal Race						
Non-Hispanic White	19	4%	-			
Non-Hispanic Black	125	28%	-			
Hispanic	265	59%	-			
Other	42	9%	-			
Maternal Education						
Less than 12th Grade	159	35%	-			
High School Degree	133	29%	-			
Some College +	132	29%	-			
Missing	27	6%	-			
Current SES			5.69	2.53	1	15
Financial Strain						
Maternal Risk Factors						
Maternal Atopy¶	146	32%	0.32	0.47		
Smoking During Pregnancy	56	13%	0.13	0.33		
Negative Life Events (CRISYS)			6.45	5.34	0	48
Environmental Risk Factors						
Detectable Dust Mite#	258	57%	0.57	0.50		
Detectible Cockroach##	82	18%	0.18	0.39		
Childhood SES						
Parents Owned Home	239	53%	0.53	0.49		

* Cord blood IgE $\geq$ .77 IU/mL (upper tertile)

**Defined during 4 periods: childhood up to age 11, adolescence ages 12-17, adulthood age 18 up to the pregnancy, and during pregnancy

¶Defined as ever being diagnosed with asthma, eczema, or allergies.

Defined as 20ng/G or greater of either Der p or Der f allergens.

Defined as .4 U/g or greater of Bla g allergen.

Table 2. Odds Ratios of Elevated Cord Blood IgE by Proximal Abuse History (n=450)

	Proximal Abuse Measure					
	A. Pregnancy			B. Pregnancy or Adulthood		
	N	Unadjusted	Adjusted	N	Unadjusted	Adjusted
Proximal Abuse History	21	1.51 (0.62 - 3.67)	1.93 (0.71 - 5.22)	92	1.36 (0.85 - 2.18)	1.29 (0.76 - 2.18)
Sociodemographic Factors						
Maternal Age (Years)			0.96 (0.93 - 1.00)			0.96 (0.92 - 1.00)
Gestational Age (Weeks)			0.99 (0.96 - 1.02)			0.99 (0.96 - 1.02)
Child's Sex						
Female			Ref			Ref
Male			1.49 (0.97 - 2.29)			1.48 (0.96 - 2.27)
Maternal Race						
Black			Ref			Ref
Non-Hispanic White			1.11 (0.38 - 3.25)			1.19 (0.41 - 3.47)
Hispanic			0.89 (0.31 - 2.59)			0.93 (0.32 - 2.72)
Other			0.70 (0.20 - 2.43)			0.76 (0.22 - 2.59)
Maternal Education						
Less than High School			Ref			Ref
High School Degree			0.98 (0.57 - 1.68)			0.98 (0.57 - 1.68)
Some College +			1.23 (0.68 - 2.22)			1.23 (0.68 - 2.22)
Current SES						
Financial Strain			1.10* (1.01 - 1.20)			1.10* (1.00 - 1.20)
Maternal Factors						

Table 2. Continued

Maternal Atopy	2.08** (1.32 - 3.28)	2.03** (1.29 - 3.20)
Smoking During Pregnancy	0.74 (0.38 - 1.46)	0.75 (0.38 - 1.48)
Other Negative Life Events (CRISYS)	0.96 (0.92 - 1.01)	0.96 (0.92 - 1.01)
Environmental Factors		
Detectable Dust Mite#	1.21 (0.74 - 1.98)	1.21 (0.74 - 1.97)
Detectible Cockroach##	1.19 (0.68 - 2.06)	1.17 (0.67 - 2.03)
Childhood SES		
Parents Owned Home	0.59* (0.37 - 0.94)	0.61* (0.39 - 0.97)

Note: Reference group in bracket. 95% confidence intervals in parentheses

** $p<0.01$, * $p<0.05$

Defined as 20ng/G or greater of either Der p or Der f allergens.

Defined as .4 U/g or greater of Bla g allergen.

Table 3. Odds Ratios of Elevated Cord Blood IgE by Lifetime Abuse History (n=451)

	1	2	3	4	5
Lifetime Abuse History[¶]	1.45* (1.08 - 1.95)	1.39* (1.01 - 1.91)	1.43* (1.03 - 2.00)	1.46* (1.04 - 2.05)	1.45* (1.03 - 2.04)
Sociodemographic Factors					
Maternal Age (Years)		0.95* (0.92 - 0.99)	0.96* (0.92 - 1.00)	0.96* (0.92 - 0.99)	0.96 (0.92 - 1.00)
Gestational Age (Weeks)		0.99 (0.96 - 1.02)	0.99 (0.96 - 1.02)	0.99 (0.96 - 1.02)	0.99 (0.96 - 1.02)
Child's Sex					
Female		Ref	-	-	-
Male		1.41 (0.94 - 2.12)	1.39 (0.92 - 2.12)	1.44 (0.94 - 2.20)	1.49 (0.97 - 2.29)
Maternal Race					
Black		Ref	-	-	-
Non-Hispanic White		1.31 (0.47 - 3.67)	1.23 (0.42 - 3.57)	1.23 (0.42 - 3.59)	1.27 (0.43 - 3.76)
Hispanic		1.03 (0.37 - 2.83)	0.92 (0.32 - 2.68)	0.93 (0.32 - 2.71)	1.04 (0.35 - 3.07)
Other		0.8 (0.24 - 2.62)	0.7 (0.21 - 2.42)	0.75 (0.22 - 2.61)	0.78 (0.23 - 2.72)
Maternal Education					
Less Than High School		Ref	-	-	-
High School Degree		1.03 (0.61 - 1.73)	0.96 (0.57 - 1.63)	0.97 (0.57 - 1.66)	0.98 (0.57 - 1.68)
Some College +		1.41 (0.80 - 2.49)	1.22 (0.69 - 2.18)	1.21 (0.67 - 2.19)	1.27 (0.70 - 2.30)
Current SES					
Financial Strain		1.08 (1.00 - 1.17)	1.09* (1.00 - 1.19)	1.10* (1.01 - 1.20)	1.09 (1.00 - 1.19)
Maternal Factors					
Maternal Atopy			1.96** (1.26 - 3.07)	2.00** (1.27 - 3.15)	1.98** (1.26 - 3.12)
Smoking During Preg.			0.78 (0.40 -	0.76 (0.39 -	0.75 (0.38 -

Table 3. Continued

		1.49)	1.47)
	1.52)		
Other Negative Life Events (CRISYS)	0.97 (0.93 - 1.01)	0.96 (0.91 - 1.00)	0.96 (0.91 - 1.00)
Environmental Factors			
Detectable Dust Mite#		1.12 (0.69 - 1.82)	1.18 (0.72 - 1.93)
Detectible Cockroach##		1.23 (0.71 - 2.14)	1.25 (0.72 - 2.18)
Childhood SES			
Parents Owned Home			0.63* (0.39 - 1.00)

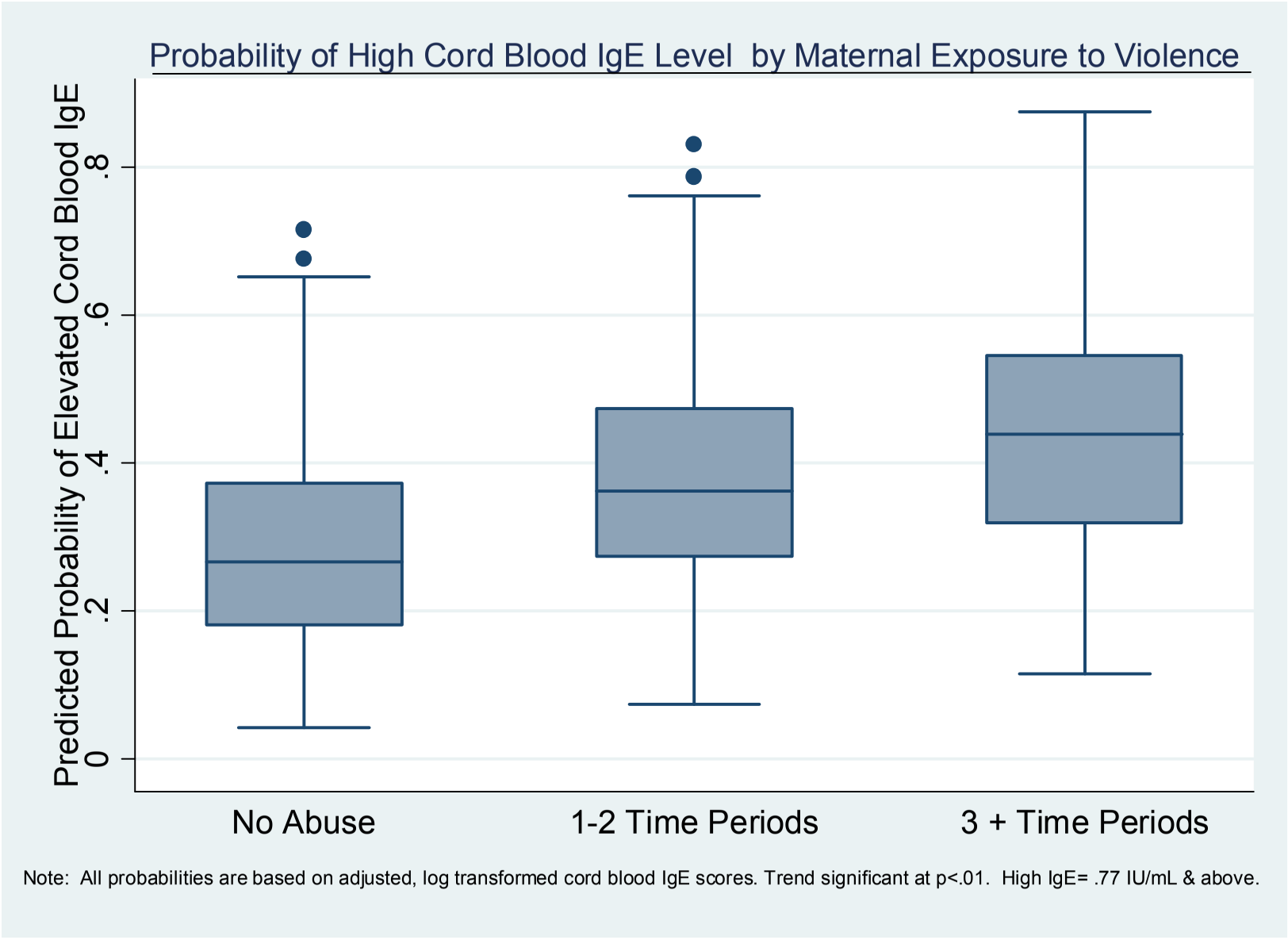
¶Lifetime abuse variable was considered as an ordinal variable, based on three levels (none, 1-2 periods, 3 or more periods).

** $p<0.01$, * $p<0.05$

Defined as 20ng/G or greater of either Der p or Der f allergens.

Defined as .4 U/g or greater of Bla g allergen.

Figure 1. Probability of Elevated CB IgE By Maternal Lifetime Exposure



Note: All probabilities are based on adjusted, log transformed cord blood IgE scores. Trend significant at p<.01. High IgE= .77 IU/mL & above.