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Maternal Intimate Partner Violence Exposure, Child Cortisol Reactivity and Child Asthma

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Abstract

Psychosocial stressors like intimate partner violence (IPV) exposure are associated with increased risk of childhood asthma. Longitudinal studies have not investigated the role of hypothalamic-pituitary-adrenal (HPA) axis reactivity (and associated alterations in cortisol relsease) in the child IPV exposure-asthma association. We sought to investigate this association, and to assess whether this relationship differs by child HPA reactivity. This secondary analysis used longitudinal cohort data from the Family Life Project. Participants included 1292 low-income children and mothers; maternal interview and child biomarker data, including maternal report of IPV and child asthma, and child salivary cortisol obtained with validated stress reactivity paradigms, were collected

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when the child was 7, 15, 24, 35, and 48 months. Using structural equation modeling, maternal IPV when the child was 7 months of age predicted subsequent reports of childhood asthma (B = 0.18, p = .002). This association differed according to the child's HPA reactivity status, with IPV exposed children who were HPA reactors at 7 and 15 months of age -- defined as a ≥ 10% increase in cortisol level twenty minutes post peak arousal during the challenge tasks and a raw increase of at least .02 ug/dl -- being significantly at risk for asthma (7 months: B = 0.17, p = .02; 15 months: B = 0.17, p = .02). Our findings provide support that children who are physiologically reactive are the most vulnerable to adverse health outcomes when faced with environmental stressors.

Keywords

intimate partner violence; asthma; longitudinal; cortisol

Asthma is a significant public health challenge, with ~9% of children diagnosed with this chronic condition (Myers & Tomasio, 2011). Asthma remains one of the top causes of pediatric ambulatory visits and hospitalizations, costing the health care system more than $15 billion annually (Clark, 2011). The development of asthma stems from a complex interaction of risk factors that has not been completely elucidated, though exposure to psychosocial stress is increasingly being implicated as a source of risk (Herman, 2011). The National Heart, Lung and Blood Institute (NHLBI) states that "stress can… possibly act as a risk factor for an increase in the prevalence of asthma" (p. 181), as well as a risk factor for asthma exacerbations ("National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma," 2007). NHLBI also acknowledges the role of psychosocial stress in asthma exacerbations (Sandberg et al., 2000).

Few psychosocial stressors have the potential to impact health more than intimate partner violence (IPV) exposure. Over 15 million children in the US are exposed to IPV each year, and children less than five are disproportionately represented in homes with IPV (Fantuzzo, 1997; McDonald, Jouriles, Ramisetty-Mikler, Caetano, & Green, 2006). Young children are dependent on their primary caregiver (Davies & Woitach, 2008); thus, their immediate safety may be threatened by IPV, and direct exposure to violence against a primary caregiver is distinctly traumatic (Davies & Cummings, 1994). Finally, in homes with IPV, care-giving relationships – an important buffer to the effects of stressors -- are often disrupted (Davies & Cummings, 1994; Johnson, Riley, Granger, & Riis, 2013).

The impact of family psychosocial stressors, like IPV, on children's asthma is related to alterations in children's stress response, particularly the hypothalamic-pituitary-adrenal (HPA) axis (Dougherty, Klein, Rose, & Laptook, 2011; Gump et al., 2009; Moss, Vanyukov, Yao, & Kirillova, 1999). The development of the HPA axis is under strong social regulation throughout early childhood (Dougherty et al., 2011; Evans & Kim, 2007). When children experience stressful events, the HPA axis is activated resulting in release of cortisol from the adrenal glands. Acute HPA axis activation is imperative in the short-term, allowing children to mobilize physiological resources to meet environmental challenges. In the long-term, however, repeated activation may lead to dysregulation and increased risk for

disease (M Gunnar & Quevedo, 2007; G Miller, Chen, & Cole, 2009; Wright, Cohen, & Cohen, 2005). HPA dysregulation due to chronic stress can lead to exaggerated or blunted cortisol reactivity, depending on the nature, timing, and severity of the stressor (GE Miller, Chen, & Zhou, 2007; Slopen, McLaughlin, & Shonkoff, 2014).

One way to measure the HPA axis is to assess salivary cortisol reactivity to a laboratory stressor (MR Gunnar, Talge, & Herrera, 2009). In young children, these stressors include exposure to a novel person or frustrating task (MR Gunnar et al., 2009). The limited number of studies exploring HPA reactivity to a laboratory stressor in children with and without IPV exposure have yielded mixed results, with some demonstrating exaggerated cortisol responses, while others demonstrate no difference between groups (Hibel, Granger, Blair, Cox, & Investigators, 2009, 2011).

With regard to asthma expression, chronic HPA activation and the associated cortisol release can impact neuroendocrine regulation of immune and inflammatory processes (Chen & Miller, 2007; Wright, 2011; Wright et al., 2005). Repeatedly activating the stress response system may trigger hormone release that favors T helper 2 cell (Th2) versus T-helper cell 1 (Th1) predominance (Wright et al., 2005). An imbalance between the cytokines associated with Th2 and Th1 lymphocytes has been associated with asthma development (Wright et al., 2005). In addition, Miller & Chen reported that asthmatic children experiencing chronic stress had a 5.5 fold reduction in glucocorticoid receptor mRNA expression (GE Miller & Chen, 2006). Diminished glucocorticoid receptor expression can lead to excessive inflammation and increased airway reactivity.

Although evidence links childhood IPV exposure and childhood asthma (Breiding & Ziembroski, 2011; Suglia, Enlow, Kullowatz, & Wright, 2009) and alterations in cortisol and asthma (Chen & Miller, 2007; Wright, 2011; Wright et al., 2005), we are not aware of literature investigating the role, over time, of cortisol reactivity in the association between IPV and child asthma in young children. We therefore conducted a secondary analysis using data collected as part of the Family Life Project (FLP) prospective cohort study which enrolled families at the time of a child's birth, with interview and/or biomarker data collected when the target child was 7, 15, 24, 35, and 48 months. Our objectives were to determine the association between reports of maternal IPV and childhood asthma, and to assess whether this association differed by child cortisol reactivity.

Methods

Human Subjects

The parent study and the current analyses were institutional review board approved. Participants enrolling in the initial FLP study provided written informed consent.

Study Design, Setting and Sample

This secondary analysis examined data collected for the FLP. Details of the FLP design have been described elsewhere (Blair et al., 2011; Hibel et al., 2009). FLP is a population-based longitudinal cohort study examining the multiple levels that influence the development of rural children. Complex sampling procedures were used to recruit a representative sample of

1292 families from North Carolina (NC) and Pennsylvania (PA) at the time of birth. Low-income families in NC and PA, and African American families in NC were over-sampled. In both states, recruitment occurred daily in hospitals from September 2003–September 2004 using a standardized protocol. The sample for the current study consisted of mothers who reported having a current partner, as IPV data were not collected for those indicating no partner.

Data Collection and Measurement

Research assistants visited families' homes when the target child was 7, 15, 24, 35, and 48 months. There was minimal attrition (2% attrition through 35 months and 11% at later interviews).

Structured data collection included maternal questionnaires and biological sample collection. Mothers independently read questionnaires and entered responses into a computer; questions were read privately to mothers with <8th grade reading level.

Independent Variable

IPV: At the 7, 15, 24, and 35 month home visits, IPV was measured using the 19-item Conflict Tactics Scale-Couple Form Revised (CTS-CF-R) which asks about behaviors used by partners in response to conflict (Straus, 1979). Adequate reliability, discriminant and predictive validity have been demonstrated (Straus, 1979; Straus & Gelles, 1999). The CTS-CF-R contains the following scales: verbal discussion, verbal aggression, and physical aggression. For this analysis, IPV was defined using the physical aggression items only because 86 to 94% of the sample reported exposure to verbal and/or physical aggression across time points, such that including both in the definition did not provide enough variability in the exposure variable to conduct analyses. Caregivers responded about their own and their partner's actions including never, once, twice, 3–5 times, 6–10 times, 11–20 times, and >20 times. Based on coding recommendations by CTS creators, these categorical responses were converted to counts as follows: 3–5 coded as 4; 6–10 as 8; 11–20 as 15; and > 20 as 25 (Straus & Gelles, 1999). Using these values, we created a count variable for the total number of acts of physical aggression at each time point.

Outcome Variable

Asthma Expression: At each interview, mothers were asked whether their child had asthma. Parental report of child asthma is used in myriad multi-state surveys, and has been positively associated with airway hyper-responsiveness (Suglia, Duarte, Sandel, & Wright, 2010). A composite outcome variable was created such that children were categorized as asthmatic if mothers answered positively at 15, 24, 35 or 48 months.

Grouping Variable

Child Cortisol Reactivity: Using Lab-TAB protocols, children participated in age-appropriate tasks designed to induce emotional stress; data in the current analyses come from the 7 and 15 month time points (Goldsmith, Reilly, Lemery, Longley, & Prescott, 1999; Voegtline, Stifter, & Investigators., 2010). Infant tasks included the barrier challenge, mask presentation, and arm restraint, with these tasks conducted sequentially. For example,

in the "barrier challenge," infants were allowed to play with a toy, after which the toy was removed and placed behind a plexiglass window such that the infant could see but no longer touch the toy. Toddler tasks included a toy removal task and mask presentation. If a child reached "peak arousal," defined as 20 seconds of hard crying, the tasks were stopped. Three saliva samples were collected: a pre-task sample prior to the start of the task battery, and 20 and 40 minutes after the final task (or after peak arousal if the tasks were stopped). The child's oral intake was restricted for 20 minutes prior to sample collection. Saliva was assayed for cortisol using a highly sensitive enzyme immunoassay and all samples were assayed in duplicate. Potential confounders were collected via questionnaire, including time of day, child age, and medication use in the past 48 hours. Cortisol reactivity was calculated as the change in cortisol from pre-task to 20-min post divided by the pre-task level to control for individual baseline differences.

Covariates

Demographics: Data on mother's age, race and cigarette use, and infant sex and age were collected at the first interview.

Maternal Depression: At the 7 month home visit, the psychometrically valid Brief Symptom Index (BSI) was administered to assess mental health symptoms in the past seven days (Derogatis, 2000). The depression sub-scale of the BSI is scored continuously with higher scores indicating more symptomatology.

Socioeconomic Status (SES): An SES risk index was created with one point for each of the following (Borstein & Bradley, 2003): maternal education high school or less, family income-to-needs ratio <200% of the poverty line, and single parent. Higher scores indicated greater socioeconomic risk.

Statistical Analyses

Preliminary analyses examined descriptive statistics for all variables. Non-maternal interview data were excluded, accounting for <4% of the sample. Although sampling weights were created, this study did not utilize weights due to use of a restricted subset of participants. To test the hypothesized relationship between IPV exposure and childhood asthma, analytic modeling proceeded in a structural equation modeling (SEM) framework which allows for simultaneous examination of reliability, validity, and potential associations among variables (e.g., measurement and structural models) (Little, 2013). All SEM models were performed in MPlus 5.21(Muthén & Muthén, 1998–2010) and utilized a full information maximum likelihood estimation approach to handle missing data, a robust, modern analytic approach that preserves the power in analysis of longitudinal data (Little, 2013). The significance level was set at $p < .05$.

The main predictor variable, maternal IPV, was modeled as a latent growth curve to allow for simultaneous examination of latent intercept (baseline levels) and slope (growth or change over time) parameters. The use of a latent growth curve modeling (LGCM) approach provides distinct advantages for this study over traditional lagged regression models by examining intra-individual change over time with simultaneous exploration of the potential

antecedents and consequences of change (Preacher, Wichman, MacCallum, & Briggs, 2008). The latent variable for IPV intercept loadings is modeled in such a way as to set the intercept at the baseline 7 month assessment (factor loadings all fixed at 1.0). The slope latent variable examined linear growth across the time points of 7 to 35 months (factor loadings set at 0, 1.0, 2.0 and 3.0). Alternative models were tested to assess potential nonlinear growth (e.g. first and last factor loadings for slope set at 0 and 1.0 while others are free). A negative binomial distribution was applied to model IPV count data which were characterized by over-dispersion. When using count data in SEM, MPlus does not provide typical fit statistics such as the comparative fit index or root mean square of approximation to evaluate model fit (Browne & Cudeck, 1993; Hu & Bentler, 1999). Thus, a series of nested models were examined, as well as model residuals, to evaluate fit. Within the nested model approach, absolute fit indices such as the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) are compared, with lower values indicating better fit. Extreme values on residuals also suggest poor model fit (West, Taylor, & Wu, 2012).

The main analytic model included maternal IPV growth parameters as latent predictors of childhood asthma. Maternal age, race, SES risk, cigarette use, depression at baseline, child sex and age were also included as manifest covariates. Potential shared method bias for models including maternal reports of both exposure and outcome were examined by correlating residual error terms for constructs measured by the same informant (Conway, 2004). Results of these analyses demonstrated standardized correlations ranging from .06 to .14, suggesting that minimal covariation exists between maternal report constructs and that associations between IPV and asthma are likely not affected by method bias (Kenny & Kashy, 1992). Given the dichotomous nature of the asthma outcome, the strength of the relationships among these variables was determined by *unstandardized* regression coefficients (B), which expresses relation in raw units. Unlike their standardized counterparts, coefficient sizes are not directly comparable to one another; therefore the largest B coefficient is not necessarily the largest effect.

Analyses for this study proceeded in a series of four steps. Potential associations of baseline IPV with covariates were examined first. Next, associations between baseline (intercept) IPV and child asthma were examined, followed by potential associations between growth (slope) of IPV over time and child asthma. Finally, associations between IPV and child asthma are examined in stratified models to determine if associations vary by child cortisol reactor status. Stratified models were created by child cortisol reactor status (reactor, non-reactor) at 7 and 15 months. Individuals were classified as "reactors" if they demonstrated a ≥ 10% increase in their cortisol level 20-min post peak arousal during the challenge task battery, relative to the pre-task baseline sample, *and* a raw increase of at least .02 ug/dl (Granger et al., 2012). Prior to stratification, cortisol reactor status was evaluated in terms of potential confounders including time of saliva collection, medication use in the past 48 hours, and child age. Models were compared for cortisol reactors and non-reactors to examine potential differences in effect size and statistical significance.

Results

From the total sample of 1292, our current analysis included 961 mothers; ~2% were excluded owing to due to non-maternal interviews with the remaining women not included due to reporting not having a partner. The mean age of included mothers was 25.8 years. Fifty-nine percent identified as Caucasian; the majority were low-income (63%), reporting a household income less than 200% of the federal poverty line (see Table 1).

The LGCM model for IPV growth with a negative binomial distribution provided an acceptable fit. Residuals were negligible for all analytic models. There was a significant mean linear decline in IPV over time with advancing child age from 7 to 35 months (latent mean $\mu = -0.37$, $p = .002$). Raw data showed that 34% at 7 months, 27% at 15 months, 24% at 24 months and 20% of the sample at 35 months reported exposure to IPV. Median IPV count levels were 6, 5.5, 6, and 4, respectively. IPV at the initial 7 month assessment was not associated with subsequent change in IPV over time (covariance of latent IPV intercept with latent IPV slope $\sigma_e = 0.30$, $p = .28$), however pairs of adjacent timepoints were positively associated indicating time to time stability in exposure ($rs = .33$ to $.49$, $ps < .0001$).

Asthma was observed for 9.6% (n=122) of the sample. Examining the impact of covariates, baseline IPV (intercept) was significantly associated with concurrent maternal depression (B = 0.12, $p < .001$; unstandardized regression weight [B]), younger maternal age (B = −0.08, $p < .001$), race (B = 1.41, $p < .001$), and greater SES risk (B = 0.44, $p = .001$). Child age and sex and maternal smoking were not associated with IPV ($p = .48$, $.90$, and $.13$, respectively). A significant direct relationship was observed between IPV at 7 months (intercept) and presence of asthma (B = 0.18, $p = .002$). The IPV slope (change in IPV over time) was not significantly associated with child asthma (B = −1.61, $p = .35$) indicating early IPV exposure during infancy (7 months) was predictive of subsequent asthma, but not change in IPV over time.

At 7 and 15 months, 42.4% and 43.7%, of children, respectively, were determined to be cortisol ‘reactors’. At the 7 month assessment, infants that were cortisol reactors were visited earlier in the day (*M diff* = 36 min; $t = 3.30$, $p = .01$) and were less likely to have taken medications in the past 48 hours ($\chi^2 = 5.39$, $p = .02$). Findings were not affected by the group differences reported here and were thus not included in subsequent analyses.

Stratified models revealed a differential relationship in associations between IPV intercept (7 months) and subsequent reports of childhood asthma by child cortisol reactivity. At both 7 and 15 months of age, early IPV exposure predicted asthma diagnosis only for children who were cortisol reactors in response to emotional challenge (7 months: B = 0.17, $p = .02$; 15 months: B = 0.17, $p = .02$).

Discussion

Our findings contribute to the mounting evidence linking early adversity to poor health, lending support to the ecobiodevelopmental model and other models that characterize disease risk as a function of early life environmental conditions as well as individual

differences in reactivity to those environments (Garner & Shonkoff, 2012; Shonkoff, Garner, Health, Committee on Early Childhood, & Pediatrics, 2012). In this secondary analysis, maternal IPV when the child was 7 months of age predicted reports of childhood asthma. This association differed by the child's cortisol reactivity status, with IPV exposed children deemed to be cortisol reactors at 7 and 15 months being significantly at risk.

Several studies have reported that IPV-exposed children were more likely than their peers to develop asthma (Subramanian, Ackerson, Subramanyam, & Wright, 2007; Suglia et al., 2010; Suglia et al., 2009). For example, Suglia found that IPV-exposed children were twice as likely as their peers to develop asthma (Suglia et al., 2009). These studies, however, have not examined physiological data that may provide insight about variation in susceptibility to environmental risk.

In contrast, we examined potential differences in outcome based on child cortisol reactivity. Our finding that IPV-exposed children who were cortisol reactors were at higher risk than non-reactors for incident asthma is consistent with the stress diathesis hypothesis (Belsky, Hsieh, & Crnic; Obradovic, Bush, Stamperdahl, Adler, & Boyce). The stress diathesis hypothesis posits that children who are reactive to stress (for example, as measured by cortisol output) early in life experience worse outcomes when raised in adversity than non-reactive children. Previous literature supports the role of physiological reactivity to stress as a potential moderator of the impact of early social environments and later health and developmental outcomes (Boyce & Ellis, 2005). For example, in one study, cortisol reactors exposed to high levels of family adversity were more likely to experience maladaptive patterns of behavior, compared to non-reactor children raised in similar circumstances (Obradovic et al., 2010).

With respect to asthma, dysregulation in the HPA axis likely alters inflammatory tone, particularly in response to stress, with previous studies demonstrating both exaggerated and blunted cortisol reactivity; these mixed findings may be partially explained by children's shift from exaggerated to blunted reactivity over time with exposure to chronic stressors (Ball, Anderson, Minto, & Halonen, 2006; Buske-Kirschbaum, Fischbach, Rauh, Hanker, & Hellhammer, 2004; Kelsay, Leung, Mrazek, & Klinnert, 2013). In a prospective study, Kelsay found that cumulative psychosocial risk in the first two years of life was associated with attenuated cortisol reactivity in late adolescence, but was not predictive of later asthma (Kelsay et al., 2013). In contrast, our results provide preliminary support for the idea that IPV may be associated with asthma development. The differences in findings may reflect different ages at assessment, or our ability to separate those who are cortisol reactors from those who are not.

A Centers for Disease Control and Prevention researcher commented that "the complexity of … the determinants of asthma's burden on individuals… demands a comprehensive approach [to intervention]" (p. S8; (Herman, 2011). Pediatric asthma interventions often do employ a multifaceted approach, focusing on education, medication management and reduction of allergen exposure. However, these interventions generally do *not* address cortisol response or, relatedly, potential psychosocial determinants of asthma (Butz et al., 2011; Karnick et al., 2007). Emerging evidence suggests that there are effective

interventions to mitigate familial psychosocial stressors (Cuijpers, Andersson, Donker, & van Straten, 2011; McFarlane et al., 2002; Sibinga et al., 2012). In addition, a recent systematic review examined 19 studies in which a psychosocial intervention was tested, and children's cortisol was assessed as an outcome; the authors concluded that 18 out of 19 of the interventions had a measurable impact on children's cortisol regulation or reactivity (Slopen et al., 2014). This study's findings support the need to consider adding these "missing pieces" to asthma interventions.

Several limitations should be noted. Asthma data were collected by maternal report, which may not be concordant with physician diagnosis. In addition, mothers were simply asked whether their child had "asthma," rather than being asked whether their child had wheezed or whether a doctor had ever told them that their child had asthma, or about their child's health care use related to asthma. However, the prevalence of asthma in our study sample (9.6%) closely parallels national statistics that indicate that 9.3% of US children currently have asthma (Bloom, Jones, & Freeman, 2012). In addition, numerous multi-state surveys use parental report of childhood asthma as an outcome and parental report has been positively associated with airway hyper-responsiveness (Suglia et al., 2010). Some researchers believe that wheeze in children < 5 years constitutes reactive airways, though NHLBI does not include a lower age limit for diagnosing asthma ("National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma," 2007). To date, most asthma disparities research has focused on urban children (Pesek et al., 2010). The degree to which asthma expression differs between urban and rural children remains controversial. The "hygiene hypothesis" suggests that early exposure to higher levels of microbes in rural children (e.g, exposure to farm animals) may be protective, while other studies report that rates of asthma may be similar for rural and urban children and that asthma severity actually may be greater for rural children (Frei et al., 2014; Pesek et al., 2010). Thus, while recruitment from rural populations limits generalizability, a strength of this study is that it uses information from an understudied yet potentially vulnerable population of children. In addition, by nature of definition of the IPV construct as exposure to partner violence, a portion of the total sample (n = 1292) was excluded from the current analysis (n=961) because they stated that they had no partner and thereby were not asked IPV questions; women were included, however, regardless of their marital status.

Conclusions

Our findings support the association between IPV exposure and asthma, and help to elucidate which children are at greatest risk using biological data. Future research should explore factors that predict which children are likely to be early cortisol "reactors" and the degree to which screening for cortisol reactivity is clinically relevant; and, whether integration of evidence-based asthma and psychosocial interventions leads to enhanced improvement in children's asthma.

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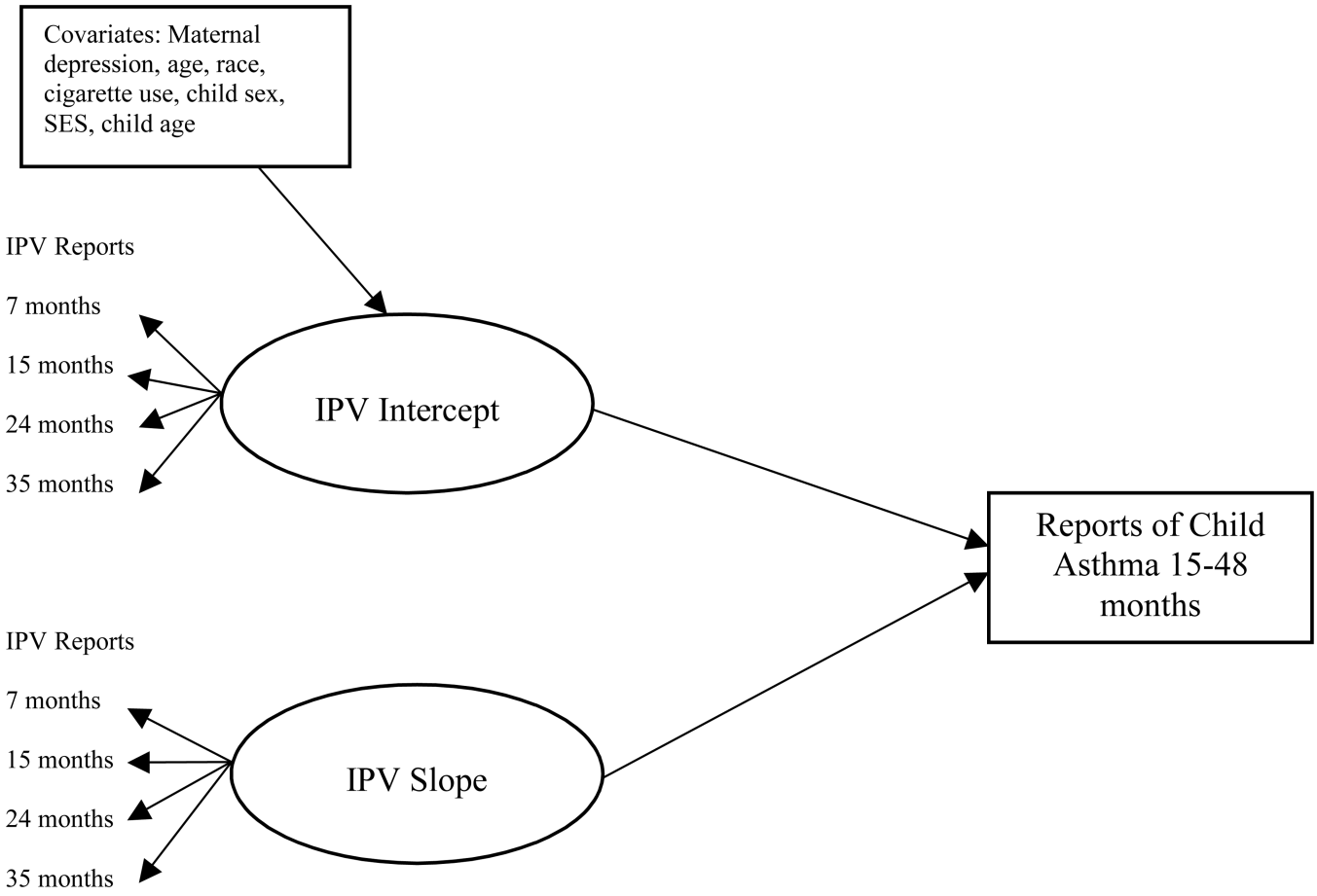

Figure 1.

Associations between IPV and child asthma expression*

*Figure depicts latent intercept and slope variables each constructed by 4 time points of data (7, 15, 24, 35 months). Loadings for intercepts (not shown) are all set so that the intercept models baseline levels (7 month) of IPV. Arrows leading to child asthma reports depict hypothesized associations between baseline (intercept) and growth (slope) of IPV with child asthma. *Note*: Stratified models with child cortisol reactivity not shown.

Table 1

Sociodemographic characteristics by intimate partner violence (IPV) exposure

	No IPV (*n* = 634)		IPV (*n* = 327)		
Variable	**%**	***M (SD)***	**%**	***M (SD)***	**diff** [a]
Maternal age, y		27.1 (5.7)		25.3 (5.7)	4.71*
Race					36.13*
Caucasian	73.6		54.4		
African-American	26.4		45.6		
SES risk index		0.8 (0.9)		1.2 (1.0)	−5.88*
Household income < 200% of the poverty line	53.1		66.3		14.18*
Maternal education ≤ high school	12.2		24.2		22.90*
Marital status single	32.3		55.3		47.56*
Child sex, male	53.0		49.9		0.86

[a] Group difference tested via *t*-test or chi-square as appropriate.

* $p < .001$

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