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Observed parent–child relationship quality predicts antibody response to vaccination in children

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ABSTRACT

Background: Quality of the parent–child relationship is a robust predictor of behavioral and emotional health for children and adolescents; the application to physical health is less clear. *Methods:* We investigated the links between observed parent–child relationship quality in an interaction task and antibody response to meningococcal conjugate vaccine in a longitudinal study of 164 ambulatory 10–11 year-old children; additional analyses examine associations with cortisol reactivity, BMI, and somatic illness. *Results:* Observed Negative/Conflict behavior in the interaction task predicted a less robust antibody response to meningococcal serotype C vaccine in the child over a 6 month-period, after controlling for socio-economic and other covariates. Observer rated interaction conflict also predicted increased cortisol reactivity following the interaction task and higher BMI, but these factors did not account for the link between relationship quality and antibody response. *Conclusions:* The results begin to document the degree to which a major source of child stress exposure, parent–child relationship conflict, is associated with altered immune system development in children, and may constitute an important public health consideration.

Decades of research document reliable links between parent–child relationship quality and an array of short- and long-term behavioral health outcomes in children, including psychiatric symptoms, relationship quality with peers, and educational and occupational success (Cui et al., 2010; Davidov and Grusec, 2006; DeGarmo et al., 1999; O'Connor, 2002; Patterson et al., 2010). These findings have shaped the development and dissemination of interventions to improve parent–child relationship quality (Scott et al., 2010; Webster-Stratton et al., 2004). The extent to which parent–child relationship quality – and interventions that target parent–child relationship quality – might also influence children's physical health is much less clear. Research of that kind is needed to identify potential sources of the wide variation in children's physical health, and to evaluate the broader clinical and public health implications of family-focused interventions. The current study of a diverse sample of pre-adolescent children contributes to this line of research by assessing the links between observed parent–child relationship quality and antibody response to immunization; additional analyses examine other biomarkers of health that are important outcomes and potential mediators of the antibody response, namely, cortisol reactivity, BMI, and somatic illness.

The hypothesis that (early) stress exposure compromises the function of multiple biological systems and may lead, in some cases, to illness is supported by numerous animal investigations (Lubach et al., 1995) and studies of adults (Lehman et al., 2009; Taylor et al., 2006). These findings converge with the well-documented social class gradients of health, in which social class, used as a proxy for stress exposure, predicts adult health outcomes

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(Cohen et al., 2006; Marmot et al., 1997) and support further studies of mediating mechanisms, such as inflammation and stress physiology (Cohen et al., 2012; McEwen, 2012). Significantly, it is not yet clear if stress exposure has reliable effects on children's somatic health, i.e., if there are *childhood-onset* effects on health associated with stress exposure. On the one hand, analyses of large-scale studies such as the National Health Interview Survey (Chen et al., 2006) indicate that parental reports of children's general health problems are more common in low social class strata. Somewhat stronger evidence derives from studies associating specific measures of stress with measured health biomarkers, including documented somatic illness (Caserta et al., 2008, 2011; Chen et al., 2010; Evans and Kim, 2007; Liang et al., 1997). Nonetheless, this area of study is at a nascent stage, as illustrated by the limited and inconsistent evidence so far reported, and the diversity in research methods employed (Broyles et al., 2012; Mills et al., 2013; O'Connor et al., 2013a; Slopen et al., 2012). Further research in this area is needed to clarify the nature of the effects, establish mechanisms of effect, and consider the applications to prevention and intervention.

In the current study we measure child stress exposure based on observed parent–child relationship quality for three reasons. First, a wealth of research indicates that parent–child relationship quality is among the most reliable predictors of behavioral health and mediates effects of distal risks, such as economic stress and family transitions (Burchinal et al., 2008; Conger et al., 1994; Hetherington et al., 1998; Simons et al., 1999). Second, if parent–child relationship quality did reliably predict childhood-onset health problems, then existing parenting and family interventions (Sanders et al., 2000; Scott et al., 2014; Webster-Stratton et al., 1989) might provide one strategy for promoting children's overall health. Third, experimental animal studies suggest that the caregiving environment may regulate multiple biological systems in the offspring, including aspects of immunology (Coe et al., 1992; Hofer, 1994; Laudenslager et al., 1985; Levine et al., 1984); these findings warrant concerted translational research.

Our primary health outcome focus is immune system function, and more specifically antibody response to immunization. Our study design capitalized on the natural experiment of immunization to examine parent–child relationship quality as a predictor of antibody response to the quadrivalent meningococcal polysaccharide-protein conjugate vaccine (MCV4). The meningococcal conjugate vaccine is now routinely administered at approximately 11 years of age in the US. We assessed parent–child relationship quality using observer reports of conflict and Warmth/Support in a moderately stressful problem-solving interaction as a predictor of subsequent antibody response following immunization.

Predicting antibody response to vaccine is an established experimental paradigm in animal (Laudenslager et al., 1988) and adult psychoneuroimmunology research (Glaser et al., 2000). For example, Glaser and colleagues (Glaser et al., 2000) showed that a high-stress group, caregivers of spouses with dementia, showed a more rapid 6-month decline in antibody concentrations to pneumococcal polysaccharide vaccine compared with those not currently caring for a spouse with dementia. Studies of adults have also demonstrated that several psychological factors, such as stress and negative affect, may alter immune response to other immunizations, such as hepatitis B vaccine (Marsland et al., 2001). Evidence that a history of stress exposure may compromise antibody response in children and adolescents is much more limited, and is so far based on quite diverse measures of risk exposure (Boyce et al., 1995; O'Connor et al., 2013b). We provide one of the first longitudinal studies to assess if quality of the parent–child relationship, as a key marker of child stress, predicts subsequent antibody response to vaccine at 4 weeks, 3 months, and 6 months post-vaccination.

Factors that may predict antibody response that may also be associated with parent–child relationship quality were also investigated. One of these was cortisol reactivity, which was assessed in response to the parent–child problem-solving stress paradigm. Cortisol, a steroid hormone that is the product of the hypothalamic-pituitary-adrenal (HPA) axis, plays a major role in stress regulation and metabolism. The relevance for the current study is that cortisol has well-known dynamic influences on multiple aspects of immune function (Vedhara et al., 1999), including in pediatric samples (Boyce et al., 1995). Additionally, cortisol reactivity has been incorporated in numerous developmental studies of child stress exposure and is perhaps the most frequently assessed biomarker in studies of parent–child relationship quality in young children (Hertsgaard et al., 1995; Spangler and Grossmann, 1993) and adolescents (Kobak et al., 2009; Spies et al., 2011); furthermore, it is considered in many health composites (Matthews and Gallo, 2011), such as allostatic load (Evans and Kim, 2012; Rogosch et al., 2011). We investigate the degree to which associations between parent–child relationship quality and antibody production may be mediated by alterations in cortisol production associated with parent–child relationship quality. Second, we examine BMI given the sizable research linking BMI to antibody production in both adults (Sheridan et al., 2012) and children (Halsey et al., 1999), and the links between parent–child and family relationship quality and child BMI (Anderson et al., 2012; Evans et al., 2012; Parks et al., 2012; Stenhammar et al., 2010; Wu et al., 2011). That is, like cortisol, BMI may be an important mediator of an association between parent–child relationship quality and antibody response; we test this hypothesis in the current study. Finally, we begin to consider specific clinical applications of antibody response by assessing a further index of immune function, physical illness. Illness was determined by active surveillance for an acute illness via biweekly phone calls and illness visits, an approach with methodological advantages over parental reports of general health. In a sample of 5–10 year-olds, Caserta et al. (2008) found that more frequent physical illness in younger children was predicted from parental psychiatric symptoms, an indirect index of caregiving stress. We expand this work by tracking illnesses over a 12-month period as predicted from observer reports of interaction quality of parents and children to the problem-solving stress paradigm.

In summary, the current study contributes to existing research by assessing observations of parent–child interactions, widely considered a measurement "gold standard" in developmental and clinical research, and their impact on vaccine response and other markers of children's physical health. Prior research in adults suggested that stress exposure, indexed by conflicted/negative parent–child relationship quality, would be associated with weaker vaccine responses, although no directly relevant pediatric data are available.

1. Material and methods

1.1. Sample and procedure

Children 9–10 years of age and a primary caregiver (in 89% the biological mother) were recruited by an invitation letter from three pediatric practices serving diverse populations in a medium-sized US city; the intent was to oversample families at high psychosocial risk. Interested families were subsequently screened by phone for eligibility. Children were eligible if they were free of chronic illness affecting immune function and were able to complete the research measures in English. Given the study's focus on vaccine responses, the assessment protocol was devised according to the standard US immunization schedule. Specifically, children were recruited