

# The associations between psychosocial stress and the frequency of illness, and innate and adaptive immune function in children<sup>☆</sup>

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Received 22 September 2007; received in revised form 15 January 2008; accepted 15 January 2008

Available online 4 March 2008

## Abstract

**Objective.** Family processes have a substantial impact on children's social and emotional well-being, but little is known about the effects of family stress on children's physical health. To begin to identify potential links between family stress and health in children, we examined associations between specific aspects of family psychosocial stress and the frequency of illnesses in children, measures of innate and adaptive immune function, and human herpesvirus 6 (HHV-6) reactivation.

**Study design.** Prospective study of 169 ambulatory school-age children and parents. Parents completed multiple assessments of stress at 7 sequential six-month visits and maintained weekly illness diaries for their children over three years using a thermometer to record fever. Children had blood obtained for HHV-6 and immune function studies at each visit including natural killer (NK) cell function and the percentage of CD4 and CD8 cells associated with immune control of cytomegalovirus (CMV).

**Results.** Parental psychiatric symptoms were associated with a higher frequency of illnesses: for each 1 U increase in symptom score children had an increased 1-year rate of total illnesses of 40% (rate ratio, 1.40; 95% CI, 1.06–1.85) and febrile illnesses of 77% (rate ratio, 1.77, 95% CI, 1.00–3.13). Parental psychiatric symptom scores were also associated with enhanced NK cell function (estimate, 0.15; 95% CI, 0.05–0.26) and increased percentages of CD8+CD28-CD57+ cells in the blood of CMV seropositive children (estimate, 2.57; 95% CI, 0.36–4.79). HHV-6 reactivation was not detected.

**Conclusions.** There is an association between specific psychosocial stress exposure and rates of illness and immune function in normally developing children.

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**Keywords:** Child health; Natural killer cells; Cytomegalovirus; Terminally differentiated T cells; Human herpesvirus-6

## 1. Introduction

Psychosocial stress adversely affects physical health. This connection has been demonstrated most convincingly in studies with diverse populations of adults, including an association between stress and an increased risk of mortality (Schulz and Beach, 1999; Ickovics et al., 2001). Psychosocial stress also has reproducible effects on the human immune system. Chronic stress experiences of adults are associated with decreases in natural killer (NK) cell

<sup>☆</sup> This work was supported by a Grant (RO1 HD 38938) from the National Institute of Child Health and Development and in part by a General Clinical Research (GCRC) Grant, 5 MO1 RR00044 from the National Center for Research Resources, NIH. Drs. Wang and Tu are supported by a Clinical Translational Science Institute award (1 ULI RR024160-01).

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cytotoxicity, lower antibody titers to influenza vaccine, diminished delayed type hypersensitivity responses, and decreased lymphocyte proliferation (Segerstrom and Miller, 2004; Glaser and Kiecolt-Glaser, 2005). An association between stress and reactivation of latent herpesviruses has also been demonstrated in adult populations suggesting that psychosocial factors functionally impact effective anti-viral immunity (Glaser and Kiecolt-Glaser, 2005). Evidence of decreases in both innate and antigen specific immune functions suggest that as stress becomes more chronic, an increasing number of components of the immune system are affected in potentially adverse ways (Segerstrom and Miller, 2004). Despite these findings, however, changes in immune function due to psychosocial stress are not reliably associated with disease susceptibility.

How findings from reports of stress and adult diseases apply to children remains to be determined. Although family stress is reliably associated with increases in children's risk for maladaptive social, emotional, and cognitive development (Conger et al., 1992; Masten et al., 1999; Costello et al., 2003), only limited research has examined how children's experiences of stress influences their health and immune function. There is a suggestion that stress may be associated with streptococcal pharyngitis and upper respiratory illnesses in children (Meyer and Haggerty, 1962; Graham et al., 1986; Clover et al., 1989; Cobb and Steptoe, 1998). However, few such studies have included measures of specific psychosocial stressors and health outcomes, or examined these links longitudinally.

The effect of psychosocial stress on the immune function of children, in particular, is under-explored. Preliminary reports suggest that the effects of stress on children's immunity may differ from adults. One recent report described an association in infants between parenting stress, parental unemployment, serious adverse events during the first year of life and the presence of high concentrations of autoantibodies associated with type-one diabetes (Sepa et al., 2005). Among young children predisposed to asthma, high levels of parent reported stress predicted greater atopic immune profiles, including increases in proliferative responses (Wright et al., 2004). Similarly, Chen and colleagues reported that high levels of stress among adolescents with histories of asthma predicted lower morning cortisol levels and higher stimulated cytokine responses indicative of elevations in both Th-2 and Th-1 responses (Chen et al., 2003). One of the hypothesized mechanisms by which psychosocial stress effects immune function and health is via activation of the hypothalamic–pituitary–adrenal (HPA) axis with dysregulation of cortisol secretion (Glaser and Kiecolt-Glaser, 2005; Flinn, 2006). The findings of Chen and colleagues are consistent with data demonstrating that chronic stress may decrease cortisol responses in children (Flinn, 2006). The immunological data provided by the studies outlined above are equally important, but have no ready interpretation, and they contrast—at least in principle—with the adult-based model that presumes that stress dampens immune function.

To expand on existing work linking stress and child health, we began a prospective, longitudinal study of a diverse cohort of school-age children. Our hypotheses were that elevated levels of specific psychosocial stresses would be associated with an increased number of illnesses and febrile illnesses in children, changes in specific immune system parameters involved in the control of viral replication, and increased rates of reactivation of human herpesvirus 6 (HHV-6). We focused on psychosocial stress in children's lives that are widely researched and repeatedly linked with children's behavioral adjustment; namely: parental psychiatric symptoms and functioning, stressful life events, and family conflict (Sameroff and Seifer, 1983). We hypothesized that these sources of stress may also predict physical health. In choosing immunological outcome variables, we considered both innate and antigen specific aspects of immune function involved in the control of common, persistent, viral infections. These included NK cell function as a measure of innate immune function, as changes are noted in these cells during chronic viral infections (Biron et al., 1999). There is also a well documented association between prior cytomegalovirus (CMV) infection and marked oligoclonal expansion of the CD8+CD57+ subset of T cells, which have of late been shown to be terminally differentiated CD8+ T cells that lack either the CD27 or CD28 surface marker (Wang et al., 1993; Wang and Borysiewicz, 1995; Batliwalla et al., 1996; Hooper et al., 1999; Kuijpers et al., 2003). We chose to measure the frequency of these cells as a marker of adaptive immune function, and hypothesized that the percentage of CD8+CD28–CD57+ cells would be increased in children with prior CMV infection living in environments with the highest degree of stress, reflecting episodic/sporadic viral antigen stimulation with the occurrence of CMV reactivation. As an indirect measure of antigen specific immune function, we also examined HHV-6 activity, as this virus is acquired by all children by three years of age and has been shown to reactivate and cause recurrent disease in immunocompromised hosts (Caserta et al., 2001).

A subset of results of the first 18 months of this study have been previously reported and demonstrated that children living with parents reporting increased levels of psychiatric symptoms in the context of family stress had more total illnesses and febrile illnesses over a one year period compared to children in less stressed families (Wyman et al., 2007). In addition, children living in families with higher stress had enhanced NK cell function over an 18-month period. This report extends these findings by defining more precisely the psychosocial factors associated with child health over the full three-year period of study and by examining child temperament as a moderating factor of family-stress illness relationships. The innate immune function outcome (NK cell function) that was measured in the children over the entire course of the study is now presented. In addition, this study extends outcomes to include an adaptive immunity measure not included in our prior report.

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