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Associations among Depression, Perceived Self-Efficacy and Immune Function and Health in Preadolescent Children

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Abstract

Experimental animal studies and adult research consistently show that stress exposure and/or psychological symptoms are associated with poorer health and immune function. The application to children is not yet clear, however, and we lack developmental models for studies in this area. The objective of this paper was to test the hypothesis that self-reported self-efficacy and depression, two markers of psychological well-being in children, would predict immunity and rate of illnesses. The data are based on a prospective study of 141 healthy, normally developing children aged 7 – 13 years who were recruited from an ambulatory pediatric setting. Children completed self-efficacy and depression measures and had blood obtained for IL-6 plasma levels and natural killer (NK) cell functional assays on three occasions, six months apart. Parents maintained weekly child illness diaries over one year, using a thermometer to record fever. Parent psychiatric symptoms and income were used as covariates. Results indicated that, across the three occasions of measurement collected over the one-year period, higher perceived self-efficacy was significantly associated with lower plasma IL-6 concentrations. There was no overall main effect of depressive symptoms on immune measures; however, for older girls, higher depression was associated with elevated NK cell cytotoxicity and an increased rate of total illnesses and febrile illnesses. The findings provide some of the first evidence that psychological processes are associated with immunity and health in a normally developing sample of pre-adolescents. Furthermore, the pattern of results suggests a modified model of a link between psychological well-being and immunological processes in children. These results build on and expand research on the notion of allostatic load, and develop a groundwork for developmental studies in this area.

Keywords

Self efficacy; depression; interleukin 6; children's health

Research findings suggest that depression and psychosocial stress may have an etiological role in diverse diseases in adulthood, including cardiovascular disease, chronic pain, stroke, diabetes mellitus, susceptibility to infectious diseases, and HIV disease progression (Cohen, Tyrrell, & Smith, 1991; Holahan, et al., 2010; Ickovics, et al., 2001; G. Miller, Chen, & Cole, 2009; Rozanski, Blumenthal, & Kaplan, 1999). These associations provide a basis for the allostatic load model, a leading framework for linking stress, health and development

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(Juster, McEwen, & Lupien, 2010). The pathophysiological mechanisms leading to such varied disease states are not fully elucidated, but considerable evidence points to inflammation as one likely mediator (Juster, et al., 2010; Karelina & DeVries, 2011). Whether or not the health impacts of depression and stress – and the underlying mechanisms – are apparent in childhood is not yet clear and represents a major developmental question with sizable public health implications. The current study is part of an ongoing effort to translate research on stress exposure and health outcomes from adults to children. Specifically, we examined the links between two indicators of psychological well-being in children, depression and self-efficacy, and markers of immune function and illnesses in a short-term longitudinal study of typically developing 7–13 year-old children.

Clinical and epidemiological studies provide robust evidence that psychosocial stress and depression are associated with changes in adult immune function (Musselman, Evans, & Nemeroff, 1998; Padgett & Glaser, 2003). Specifically, a recent meta-analysis involving over 400 subjects showed that levels of the pro-inflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were elevated in subjects with major depressive disorder compared to normal controls (Dowlati, et al., 2010). Additionally, elevated concentrations of IL-6 were reported in subjects with higher levels of stress associated with elevated blood pressure, and more severe symptoms during an upper respiratory infection (Brydon & Steptoe, 2005; Cohen, Doyle, & Skoner, 1999). Chronic psychosocial stress and depression may increase immune activation via greater glucocorticoid resistance (T. W. Pace & Miller, 2009; T. W. W. Pace, et al., 2006). Other studies suggest that depression may suppress immune activation, as shown in previous studies linking depression to reductions in lymphocyte proliferative responses to mitogens, natural killer cell (NK) activity, and cellular immunity to viruses (Irwin, 2002; Kronfol, 1983; Schleifer, Keller, & Bartlett, 2002). These apparently contradictory findings have not yet been reconciled, and underscore the need for further study.

Research translating the adult findings on depression or stress and immunity to pediatric samples is now underway (Worthman & Panter-Brick, 2008) but, to date, findings are limited, particularly with respect to specific mechanisms. Nevertheless, several reports link some aspect of general family stress to one or the other marker of immune functioning. Wolf et al. found that parent-reported perceived stress and depressive symptoms were associated with increased levels of the T helper cell type 2 (Th2) markers IL-4 and eosinophilic cationic protein in their children (Wolf, Miller, & Chen, 2008). Another indicator of family stress, harsh family climate in early childhood, was linked to a pro-inflammatory phenotype during adolescence (G. E. Miller & Chen, 2010). In a healthy ambulatory sample, we previously reported that parental psychiatric symptoms predicted elevated NK cell activity in their children and increased CD8+T cell responses to chronic viral stimulation with CMV(Caserta, et al., 2008).

The above findings support the broad hypothesis that stress may compromise health in children, but further research is needed to address several developmental questions not yet tackled in existing studies. One concerns the point in development at which reliable associations may be detected. Animal studies demonstrate that the effect of early stress exposure may have lasting impact on inflammatory markers (Hennessy, Deak, & Schiml-Webb, 2010) and that there are reliable links between behavior and immunity (Granger, Hood, Dreschel, Sergeant, & Likos, 2001), but the immune outcomes are, as in most human studies, limited to adulthood. Accordingly, it is not clear when in development a reliable impact on immune mechanisms can be detected. It may be that reliable links between stress exposure and immune outcomes are not detectable in younger children, perhaps because of greater immunological reserve that underlies resilience or because stress exposure effects are detectable only after prolonged, i.e., more chronic, stress exposure. The current study seeks

to address this question by testing whether one of the most reliable associations in adult psychoneuroimmunology, an association between IL-6 and self-reported depressive symptoms, is also found in young children.

A further developmental question for research is the identification of the risk phenotype that may associate with child immune function. Major depressive disorder, the focus of much of the adult work, is rare in pre-adolescent (especially pre-pubertal) children (Angold, Costello, Erkanli, & Worthman, 1999). Therefore, if inflammation were specifically associated with depression, then the link may not be detectable in pre-adolescent samples. In fact, studies of immune function and depressive symptoms in children and adolescents have yielded inconsistent findings. For example, whereas one study of 8 – 12 year-olds reported that major depression was associated with lower NK cell cytotoxity and increased concanavalin A (ConA) mitogen responses (Barlett et al., 1995), a different study of adolescents found major depression associated with increased NK cell activity, increases in circulating lymphocytes and lymphocyte subsets, and with lower ConA mitogen responses(S. J. Schleifer, et al., 2002). Still other studies found few differences on measures of immunity associated with depression (Birmaher, et al., 1994; Shain, et al., 1991; Targum, Clarkson, Magac-Harris, Marshall, & Skwerer, 1990). Small sample size and varying health status of participants may explain the discrepant findings so far reported. In any event, epidemiological data underscore the substantial role of age and sex on rates of depression (Angold, Costello, & Worthman, 1998), and point to these as likely moderators of a link with physical health. As a result, we consider age and sex as moderators of the link between depressive symptoms and immune markers.

Additionally, it may be that a number of psychological states predict inflammation, as suggested, for example, by the adult work on optimism and positive emotional style (Cohen, Doyle, Turner, Alper, & Skoner, 2003). We therefore also include in this study a measure of perceived self-efficacy, or positive beliefs in one's ability to enact actions in order to achieve desired goals (Bandura, 1977). Perceived self-efficacy is a predictor of positive social-emotional and behavioral functioning among at-risk or high-stress youth (Cowen, et al., 1997; Masten & Coatsworth, 1998; Wyman, Cowen, Work, & Parker, 1991). This study extends prior work on behavioral outcomes to immunity and health.

In summary, in the present study, as part of a developmental study of an allostatic load model, we sought to extend work on children's psychological well-being and health, and the mechanisms involved. Pediatric research has included a range of immune markers, some linked to particular disease states of the clinical samples studied; no particular or optimal set of immune markers is easily discernible from existing studies. Here, we include a common marker of inflammation, IL-6, and a frequently assessed indicator of immune activation, NK cell cytotoxicity. To examine whether the association with immune markers translate to health outcomes, we include a measure of illness, based on detailed diary data. These immune and health data were examined in relation to children's self-reports over a one-year period.

METHODS

Subject Enrollment and Protocol

Children ages 5 – 10 and their primary caregivers were recruited and enrolled between July 1, 2001 and June 30, 2003 from a population participating in a longitudinal study of childhood viral infections in the Division of Pediatric Infectious Diseases at the University of Rochester Medical Center. The children had initially been identified during visits to the emergency department or other pediatric services of the Golisano Children's Hospital at Strong in Rochester NY. One child per family (chosen based upon inclusion criteria and

previous participation in the prior study) was enrolled, and all children were well at the time of enrollment. Children with chronic diseases adversely affecting the immune system (e.g., those on chronic corticosteroid therapy) were excluded. The Research Subjects Review Board of the University of Rochester approved this study. All caregivers provided informed consent, and children provided verbal assent. A $45 honorarium was given to the family following each visit.

The full study protocol spanned a three-year period, and consisted of seven visits approximately six months apart. At each visit, blood samples were collected from children, and each child's vital signs, including height and weight, were measured. The enrolled parent supplied demographic information and completed several measures of family stress and perceived personal distress, including psychiatric symptoms. At each visit, the parent also provided an interim medical history of illnesses and other health conditions between visits, and reported any symptoms of illness in the child in the preceding two weeks (see Caserta et al., 2008). For the first two years of the study (visits 1 – 4), children engaged in quiet activities in a separate room while their parents were interviewed. Beginning at the fifth visit and continuing for the next year (Visits 5 – 7), children completed self-report measures of depression symptoms and self-efficacy (described below). The fifth visit was chosen to initiate the collection of child self-report data because it was presumed that the youngest children in the study (the youngest child was age 5 years at study visit 1) would not have been reliable reporters on all of the self-report measures at the earlier waves. The present study focuses on this one-year period during which child-report measures of depression and self-efficacy were obtained.

Illness Diary

At enrollment, parents were given a diary form and digital thermometer and instructed to record each week their child's health status, including temperatures associated with every instance of illness. Strict definitions of illnesses were not provided to parents. Rather, parents were asked to record all episodes they considered illnesses, all associated symptoms, and their child's corresponding temperature. Diaries were collected via mail on a monthly basis. If a diary was not returned, then a study nurse contacted the family by phone to collect the information. If a family could not be reached, the diary was updated at the next clinic visit. All of the illness records were reviewed by a pediatric infectious disease specialist who was not part of the study team and was kept unaware of all subject characteristics. That specialist coded each episode of illness to determine if the episode was consistent with an illness and to determine if multiple records from a 14-day time period reflected a single (e.g., a single viral upper respiratory tract infection recorded as a cold and sore throat) or multiple illnesses (e.g., viral URI and otitis media). Physical trauma, elective or orthopedic surgery, mental health/behavioral problems, constipation, and well child-care visits were not coded as illnesses. Allergies, asthma, eczema, and contact dermatitis were included. Over the 3-year study, 1,065 incidents were coded as separate illnesses and 330 were reported as febrile illnesses, with 230 temperatures recorded (Caserta et al., 2008). Fever was defined as a temperature >38°C. If the families reported fever but a temperature was not provided (i.e., temperature data were missing), then the illness was recorded as a febrile illness. If families reported a fever but the recorded temperature was ≤ 38°C, then the illness was recorded as without fever.

Laboratory Assays

NK cell cytotoxicity assays were performed on whole blood samples as previously reported (Bromelow, Galea-Lauri, O'Brien, & Souberbielle, 1998; Caserta, et al., 2008). The percent specific lysis was calculated as: 100 x (cpm experimental-cpm spontaneous)/(cpm maximum-cpm spontaneous) for each dilution of whole blood. The percent specific lysis at

each dilution was log transformed and linear regression was used to estimate the dilution that corresponded to 20% lysis, which was then used as an overall measure of NK cell cytotoxicity for each visit.

Plasma samples were assayed in duplicate using the Quantikine High Sensitivity (HS) ELISA kit for human IL-6 (R and D Systems, Minneapolis, MN) as per manufacturer's instructions (Kiecolt-Glaser, et al., 2011; Eisenberger, Inagaki, Mashal & Irwin, 2010).

Child Psychosocial Measures

At visits five through seven, the children completed the *Children's Depression Inventory-Short Form* (CDI-SF), (Kovacs, 1992). The self-report CDI-SF was designed for children from age 7 to 17 years and consists of 10 questions covering cognitive, affective and behavioral symptoms associated with depression. For each item, the child selects which of three descriptors spanning minimal to significant symptomotology best describes him/her in the past two weeks. The items originated from the longer, 27-item Children's Depression Inventory (Kovacs, 1992) and were selected based on a backward stepwise internal consistency reliability analysis. Higher CDI–SF scores reflect more depression symptoms. The 10 items had an alpha reliability coefficient of .80.

At visits five through seven, children also completed the *Perceived Self Efficacy Scale* (PSE; Cowen et al., 1991). This 14-item self-report measure assesses children's judgments about their ability to achieve their desired goals in common problem situations, spanning school challenges, peer and family conflicts, and being in new, unfamiliar situations. For each item, children rate their degree of certainty in achieving a desired outcome on a 3-point Likert scale (Not at all sure – Very sure). The measure is designed to assess a combination of self-efficacy beliefs and outcome expectations (Bandura & Cervone, 1983). The PSE scale has demonstrated adequate internal consistency and construct validity: higher scores are associated with positive behavioral and social-emotional functioning among children in general populations and among those exposed to chronic psychosocial adversity (Wyman, et al., 1999). An internal consistency coefficient of 0.59 was found for the present study. Higher PSE scores reflect greater perceived self-efficacy.

Covariates

Parent psychiatric symptoms were ascertained at each visit using the 51-item Brief Symptom Inventory (BSI) (Derogatis, 1992). The items assess nine symptom clusters including depression, anxiety, and psychoticism. For each item, the parent provides a severity rating of 0 to 4 based on the prior month. The total symptom score was used, which has been shown to be sensitive to changes in psychological status due to mental disorders and social-interpersonal events. Higher BSI total scores indicate more psychiatric symptoms. We used the BSI as a covariate in models testing associations between children's self-evaluations and health because of previous analyses indicating that parent-reported symptoms were a predictor of increased illnesses and altered immune function in children (Caserta, et al., 2008). In addition, we used family income as another covariate: total yearly family income was assessed at enrollment and at subsequent visits parents were asked to report any changes in income. Child age and sex were also included as covariates and moderators (see below).

Statistical Analysis

Analyses were performed with SAS (version 9.2, SAS Institute Inc, Cary, NC). Descriptive analyses were conducted to summarize the data using means, SD, frequency and percentage, as appropriate, and correlations were examined among the study variables. Mixed models were used to evaluate the relationships among the repeatedly measured variables of CDI-SF,

PSE, BSI and income. Patterns of attrition were examined and the assumption of Missing Completely at Random (MCAR) was tested. Plasma IL-6 concentration and NK cell function were log-transformed for normality model assumption and back transformed to the original metric for presentation.

To evaluate whether depression and self-efficacy were associated with the two immune function measures, plasma IL-6 concentration and NK cell function, longitudinal data analysis was performed using mixed models with random subject effects to account for within-subject correlation over time. Plasma IL-6 concentration and NK cell function assessed at visit 5 through visit 7 were the dependent variables. Depression (CDI-SF) and self-efficacy (PSE) prior to each visit were used as time-varying predictors. In addition to child age and sex, two additional covariates were added to the models – annual household income and parent psychiatric symptoms (BSI)- to account for well-established effects of those two family variables on child health and to better ascertain the unique contributions of children's self-reported depression and self-efficacy. Also included in each model was immune function at the prior visit (Visit 4) corresponding to the dependent variable (plasma IL-6 concentration or NK cell function) and whether an illness had been reported for the child in the preceding 14 days. Race/ethnicity was not found to be associated with either of the immune responses and, therefore, was not included as a covariate. BMI was added to the model testing plasma IL-6 concentrations to account for its association with plasma IL-6 concentration (Shelton & Miller, 2010). We tested for moderation effects of gender and age on the relationship between depression and immune function in two ways. First, we included both main effects and interaction terms in the regression model. Second, we examined separately the effects of depression on immune function by estimating models for four subgroups defined by age (older vs. younger) and sex in order to test our hypothesis that the adverse effects on health from depression would be greatest in older girls in our sample.

General Estimating Equation (GEE) (Zeger & Liang, 1986) with a log link function and Poisson errors was used to test the association of depression and self-efficacy with parent-reported child illnesses, as appropriate for the distribution of these count data. Depression and self-efficacy reported by children at visit 5 were the independent variables of primary interest in analyses predicting number of illnesses in the following year. In addition to children's age and sex, the other covariates in the model were: total illnesses reported by parents in the previous year (Visit 3 – 5) and the two indicators of family stress at visit 5: parent psychiatric symptoms (BSI) and annual household income. To account for seasonal effects on children's illnesses, the number of parent-reported illnesses between visit 5 and 7 was used as the dependent variable so that it covers one year. Actual length of reporting time was treated as the offset in the model to justify the variation of this variable among subjects. By using a prospective, longitudinal model (i.e., visit 5 CDI-SF and PSE predicting illnesses over the next year), the potential confounding effects of illness on children's depression and perceived self-efficacy were reduced. To examine whether the association was moderated by age and sex, interaction analyses were also performed and models were estimated separately for the four groups of children stratified by age (using the median age, 9.3 years) and sex; the association of depression and self-efficacy with febrile illness was analyzed in a similar manner. Whether or not the child had at least one reported febrile illness between visit 5 and 7 was used as dependent variable to fit a logistic model using GEE, with a logit link and binary error, with the same set of covariates and independent variables as in the model for total illnesses. Moderation effects of age and sex were also tested and age/sex subgroup analyses were conducted. Mediation analysis (Baron and Kenny, 1986) was performed to test if plasma IL-6 concentration and NK cell function mediated the relationship between depression and child illnesses.

RESULTS

Cohort description

Of 170 enrolled child-caregiver dyads, 141 were retained at the fifth visit when child depression and self-efficacy measures were first collected (Table 1). Ninety-three percent of the enrolled caregivers were female (mean age= 35 years; range: 21 – 73) and 89% were either the target child's biological or adoptive parent. A total of 120 subjects completed all seven visits (71% of enrolled). The reasons for leaving the study were non-compliance with follow-up visits (62%), self-withdrawal due to lack of interest (24%), and relocation away from area (14%). Sample attrition was unrelated to any measured child or parent characteristic, family income or family stress and personal distress measures completed by caregivers at enrollment. The assumption of data Missing Completely at Random (MCAR) was tested and found to be valid.

Preliminary analyses

Table 1 includes basic demographic data on the sample. Children's self-reported depression symptoms were moderately stable over the three visits spanning one year (visits 5 – 7), as shown by an intra-class correlation coefficient of 0.49 for CDI-SF scores (subject as the class). The intra-class correlation coefficient for perceived self-efficacy (PSE) scores was 0.26. Inter-correlations among the study variables at baseline were tested with Fisher's Z transformation test and are presented in Table 2. Children's depression symptoms and perceived self-efficacy scores were not significantly correlated. Parent self-reported BSI score and income were not associated with self-efficacy; BSI was positively correlated with child depression (correlation coefficient 0.28, $p < 0.01$); income was marginally negatively correlated with child self-reported depression scores (correlation coefficient −0.16, $p = 0.05$). Income was negatively associated with parent psychiatric symptoms (BSI total) (correlation coefficient −0.19, $p = 0.03$). Neither depression nor self-efficacy scores were associated with child sex. Baseline CDI-SF was correlated with child age, with older children having lower scores (correlation coefficient −0.22, $p = 0.01$).

Over the three visits (5 – 7), 372 plasma IL-6, and 353 NK cell assays from 138 individuals were collected for analysis. Two subjects' plasma IL-6 concentrations were excluded from analysis due to extreme outlying values. The intraclass correlation coefficients for plasma IL-6 concentration and NK cell function were 0.35 and 0.44 respectively, indicating moderate stability. Plasma IL-6 concentrations had an overall range of 0.12 – 11.50 pg/ml, and NK cell function ranged from 1.20 to 22.35 (dilution corresponding to 20% lysis). The total number of illnesses recorded between visit 5 and 7 were 190 and number of febrile illnesses were 38.

Children's self-report measures and immune responses: Perceived self-efficacy

Children reporting higher perceived self-efficacy had lower plasma IL-6 concentrations. After controlling for children's age, sex, BMI, parent psychiatric symptoms, family income, and previous IL-6 concentrations (visit 4), for each 1-U increase in PSE score, the $\log_{10}$ of plasma IL-6 concentration decreased by 0.01 pg/ml (95% CI, −0.02 – 0.00) (Table 3). The model indicated that children with higher BMI also had elevated plasma IL-6 concentrations over the one year period (for each 1-U increased in BMI the $\log_{10}$ of plasma IL-6 concentrations increased by 0.01 pg/ml (95% CI, 0.01 – 0.02); additionally, occurrence of illness in the two weeks before the study visit was associated with 0.08 U increase in $\log_{10}$ of plasma IL-6 (95% CI, 0.02 – 0.14). Estimates reported in Table 3 are based on $\log_{10}$ transformation because of the distribution of IL-6, but that makes interpretation of effect size difficult; accordingly, we also report, for illustrative purposes only, non-transformed estimates of the raw IL-6 scale for significant predictors: for self-efficacy, for each 1-U

increase in PSE score, the plasma IL-6 concentration decreased by 0.03 pg/ml; for each 1-U increase in BMI, the plasma IL-6 concentrations increased by 0.01 pg/ml; occurrence of illness in the two weeks before the study visit was associated with 0.32 U increase in plasma IL-6.

Perceived self-efficacy was not associated with NK cell function (p=0.27) or with illnesses (p=0.13) or febrile illnesses (p=0.07). Further analyses assessing interactions by age and sex did not detect any evidence of moderation. None of the two-way or three-way interactions were statistical significant (p>0.05).

Children's self-report measures and immune responses: Depressive symptoms

Over the one-year period, there was not a main effect association between depression and IL-6. Moderation analyses indicated no interactions: the lack of significant association between depression and IL-6 was consistent across age and sex and age X sex subgroups (younger female, p=0.82; younger male, p=0.94; older female, p=0.25; older male, p=0.81).

Children's NK cell function was not associated with depression scores in the full cohort over the one-year study, but there was evidence of moderation by age (using the median split) and sex. A stratified subgroup analyses showed that depression was positively associated with NK cell function in older girls but not in any of the other three groups (Table 4). Further analyses of the older girl subsample indicated that, after controlling for self-efficacy, parent psychiatric symptoms, family income, being sick in the prior 14 days, and previous NK cell function (visit 4), each 1-U increase in depression (CDI-SF) score increased the $\log_{10}$ of NK cell function by 0.02 U (95% CI, 0.00 – 0.04). For the non-transformed (raw) NK cell scale, each 1-U increase in depression increased NK cell function by 0.27. For younger females, older males and younger males, no association was found between self-reported depression and NK cell function.

Children's self-report measures and health

In the full cohort of children, neither PSE nor CDI-SF measured at visit five were associated with total illnesses over the subsequent one-year period (controlling for initial level of illnesses), nor with the likelihood of having a febrile illness. However, analyses stratified by age and sex showed that higher depression scores were associated with increased illnesses in the following year only among older girls (Table 5): each 1-unit increase in depression symptoms was associated an increased rate of total illnesses of 18% (rate ratio = 1.18; 95% CI, 1.07 – 1.30). Febrile illnesses, a subset of total child illnesses, showed the same effect: for older girls, higher depression scores predicted an increased risk of having at least one febrile illness during the next year (OR = 1.62, 95%CI, 1.05 – 2.49). There was no significant association between depression and illnesses found in the other groups. There was not a significant association between self-efficacy and illnesses in the same as a whole or when the sample was stratified by age and sex.

Mediation analyses were limited to older girls because it was only in the subsample of girls that we obtained links between depression and illness and depression and NK cell function. However, we found no evidence that the relationship between depression and illnesses were mediated by NK cell function.

DISCUSSION

In a prospective, one-year longitudinal study of a normative, healthy sample of pre-adolescent children, we found modest support for a link between psychological well-being and immune function and illness. The strongest link, observed in the entire cohort of children, was a negative association between self-efficacy and IL-6. Two further

associations were also detected, but only in older girls: depression was associated with increased NK cell function and with higher rates of illness.

The findings extend research on stress and health and allostatic load in children in several important ways. First, rather than rely on parent reports of stress, we included children's self-reports of well-being, indexed by efficacy and depressive symptoms as predictors of immunity and health. These two indicators of psychological well-being are widely researched in the developmental and clinical psychology literature as causes and effects of psychosocial stress and as predictors of long-term behavioral adjustment. We provide some of the only evidence thus far that these psychological measures also predict health outcomes in normally developing children. The self-report data also provide an extension to the prior research on stress and children's health, which has to date been dominated by parent reports of child stress exposure and, in some cases, inferred from parent self-report of their own psychological symptoms. The finding that children's own views of their ability to cope with stress predicted lower levels of IL-6 extends a considerable adult literature on psychological outlook and immunity. For example, positive emotional style, assessed by measures of extraversion, agreeableness, and positive relationship style is associated with fewer colds following respiratory viral challenge (Cohen, Alper, Doyle, Treanor, & Turner, 2006; Cohen, et al., 2003). Also, increased optimism was inversely associated with an IL-6 response to acute psychosocial stress (Brydon, Walker, Wawrzyniak, Chart, & Steptoe, 2009), whereas pessimism was associated with increased levels of IL-6, C reactive protein (CRP), and fibrinogen (Roy, et al., 2010). Coping, appraisal and other psychological resources and dispositions need also to be incorporated into models of stress and health in pediatric samples. Significantly, the prediction from self-efficacy to IL-6 was independent of parental symptoms, providing further support for the need to consider psychological processes within the child as distinct from general markers of stress exposure as reported on by parents.

Second, results from the study begin to piece together a developmental model of psychoneuroimmunology. On one hand, children who report greater ability to achieve desired results in common situations showed a healthier, and presumably more adaptive immunological profile and reduced levels of IL-6; evidence of positive psychological appraisal and coping was associated with reduced generalized inflammation, a prediction that comports easily with existing animal and adult work. On the other hand, in older girls (only), we found that depression was associated with increased NK cell function or cytotoxicity. That is congruent with our earlier finding that psychosocial stress as reported by parents predicted increased NK cell function (Caserta, et al., 2008). The extent to which the increased NK cell function associated with depression is compatible with or contradicts adult studies is confounded by the inconsistency across adult studies, with some reporting a decrease (Park, et al., 2006) but others reporting an increase (Ravindran, Griffiths, Merali, & Anisman, 1998; Seidel, et al., 1996) in NK cells in depression. These discrepancies may be resolved by attention to depression subtypes (Ravindran, et al., 1998), something that we were not able to investigate in our sample. In any event, it may be noteworthy that a link with NK cell function was found only in older girls, who may, by virtue of the age and sex effects on depression, present the most "adult-like" in terms of risk for depression. That a limited or focused effect of depression in older girls was also detected for illnesses also warrants consideration and implies, at a minimum, that age and sex may emerge as modifiers of the links between stress/psychological symptoms and immunity in pediatric samples. It is noteworthy that sex effects on the link between depression and immune markers have also been reported in adult studies (Brummett, et al., 2010; Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008). Further work that incorporates the hormonal and neurophysiological changes associated with puberty (e.g., Dahl & Gunnar, 2009) is needed to revise and expand a developmental model of psychoneuroimmunology.

A non-finding also deserves attention for what it may suggest about developmental influences and the detection of allostatic load in young people, namely, the lack of association between depression and IL-6. This lack of association in the current sample does contradict adult work that shows a reliable but small negative association between depressive symptoms and IL-6, as well as TNF-alpha, (Dowlati, et al., 2010), which was not assessed in the current study. This raises the possibility that, for reasons not yet clear, associations between behavioral/psychological well-being and IL-6 either may be less robust in children or slower to develop, perhaps requiring chronic stress or depression, a possibility implicit in the adult work and in the allostatic load model but not yet adequately tested. In other words, our findings on a pre-adolescent sample do not mimic in every way the patterns so far reported in adults.

Finally, we did not find evidence that changes in immune markers mediated the effects of depression on health outcomes. In fact, we found, in older girls, depression leading to both increased NK cell function and increased illness. It may be that the impact on immunity and on observable health outcomes are under different time course constraints; it is also likely that health outcomes are multiply determined and that any specific immune marker may not carry sufficient impact to alter a systemic illness.

Several limits of the study should be noted. Detailed data on pubertal development were not available in this study; more precise measurement of pubertal changes may help clarify the moderating influence of sex and age on depression and IL-6 and illnesses. The young age of the sample may also confound interpretations of age and sex; indeed, we did not detect strong age and gender effects on levels of depressive symptoms that are found in pubertal or adolescent samples. Additionally, the interpretation of depression symptoms should be considered in light of the generally non-clinical nature of symptoms and impairment; arguably, a strength of this study, which would increase its generalizability, is that we detected associations within a healthy sample, outside of the clinical extremes. Also, a variety of other potential markers of immunity that could have been assessed were not included. We targeted those that had a sizable adult literature, and so had a limited focus; analyses of a wider array of pro- and anti-inflammatory markers will be needed to develop a comprehensive developmental model of psychoneuroimmunology. Furthermore, although the study sample size was adequately powered for main effects analyses and compares favorably with studies in the area, the power to detect multi-way interactions was limited and the reliability of interactions is notably less robust than main effects. Therefore, despite the strong a priori case for analyzing data by age and sex, replication of these findings is necessary before drawing firm conclusions. Finally, we proposed directional hypotheses concerning within-individual change, derived from adult and animal work, that changes in depression and self-efficacy would be associated with immune markers, the dependent variable. It is plausible that the direction of effects is reciprocal, and the time course for charting the dynamic interplay between psychological well-being and health and immune markers requires further study. These limitations are offset by several strengths of the paper, including the longitudinal design with multiple occasions of measurement of psychological and immune data, and detailed health diary data verified, to a considerable extent, by medical investigators on the project.

Clinical implications of the findings are not yet clear, but promising. Perhaps the most obvious is the need to consider physical well-being in those children who report psychological distress, in both assessment and intervention. If further research also endorses links between psychological well-being and physical health in children, then this would provide a conceptual-biological basis for instituting an inter-disciplinary model for child health assessment, something that is not now widely established.

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References

Angold A, Costello EJ, Erkanli A, Worthman CM. Pubertal changes in hormone levels and depression in girls. Psychological Medicine. 1999; 29(5):1043–1053. [PubMed: 10576297]

Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychological Medicine. 1998; 28(1):51–61. [PubMed: 9483683]

Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychological Review. 1977; 84(2):191–215. [PubMed: 847061]

Birmaher B, Rabin BS, Garcia MR, Jain U, Whiteside TL, Williamson DE, et al. Cellular immunity in depressed, conduct disorder, and normal adolescents: role of adverse life events. Journal of the American Academy of Child and Adolescent Psychiatry. 1994; 33(5):671–678. [PubMed: 8056730]

Bromelow KV, Galea-Lauri J, O'Brien ME, Souberbielle BE. A highly sensitive whole blood natural killer cell assay. Journal of Immunological Methods. 1998; 217(1–2):177–184. [PubMed: 9776587]

Brummett BH, Boyle SH, Ortel TL, Becker RC, Siegler IC, Williams RB. Associations of depressive symptoms, trait hostility, and gender with C-reactive protein and interleukin-6 response after emotion recall. Psychosomatic Medicine. 2010; 72(4):333–339. [PubMed: 20190126]

Brydon L, Steptoe A. Stress-induced increases in interleukin-6 and fibrinogen predict ambulatory blood pressure at 3-year follow-up. Journal of Hypertension. 2005; 23(5):1001–1007. [PubMed: 15834286]

Brydon L, Walker C, Wawrzyniak AJ, Chart H, Steptoe A. Dispositional optimism and stress-induced changes in immunity and negative mood. Brain, Behavior and Immunity. 2009; 23(6):810–816.

Caserta MT, O'Connor TG, Wyman PA, Wang H, Moynihan J, Cross W, et al. The associations between psychosocial stress and the frequency of illness, and innate and adaptive immune function in children. Brain, Behavior and Immunity. 2008; 22(6):933–940.

Cohen S, Alper CM, Doyle WJ, Treanor JJ, Turner RB. Positive emotional style predicts resistance to illness after experimental exposure to rhinovirus or influenza a virus. Psychosomatic Medicine. 2006; 68(6):809–815. [PubMed: 17101814]

Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. Psychosomatic Medicine. 1999; 61(2):175–180. [PubMed: 10204970]

Cohen S, Doyle WJ, Turner R, Alper CM, Skoner DP. Sociability and susceptibility to the common cold. Psychological Science. 2003; 14(5):389–395. [PubMed: 12930466]

Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. New England Journal of Medicine. 1991; 325(9):606–612. [PubMed: 1713648]

Cowen EL, Wyman PA, Work WC, Kim JY, Fagen DB, Magnus KB. Follow-up study of young stress-affected and stress-resilient urban children. Development and Psychopathology. 1997; 9(3): 565–577. [PubMed: 9327240]

Dahl RE, Gunnar MR. Heightened stress responsiveness and emotional reactivity during pubertal maturation: Implications ofr psychopathology. Development and Psychopathology. 2009; 21(1):1–6. [PubMed: 19144219]

Derogatis, LR.; Dellapietra, L.; Kilroy, V., editors. Screening for psychiatric disorder in medical populations. Amsterdam: Elsevier; 1992.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biological Psychiatry. 2010; 67(5):446–457. [PubMed: 20015486]

Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and Social Experience: An Inflammatory Challenge Induces Feelings of Social Disconnection in Addition to Depressed Mood. Brain Behav Immun. 2010; 24(4):558–563. [PubMed: 20043983]

Granger DA, Hood KE, Dreschel NA, Sergeant E, Likos A. Developmental effects of early immune stress on aggressive, socially reactive, and inhibited behaviors. Development and Psychopathology. 2001; 13(3):599–610. [PubMed: 11523850]

Hennessy MB, Deak T, Schiml-Webb PA. Early attachment-figure separation and increased risk for later depression: potential mediation by proinflammatory processes. Neuroscience and Biobehavioral Reviews. 2010; 34(6):782–790. [PubMed: 20359585]

Holahan CJ, Pahl SA, Cronkite RC, Holahan CK, North RJ, Moos RH. Depression and vulnerability to incident physical illness across 10 years. Journal of Affective Disorders. 2010; 123(1–3):222–229. [PubMed: 19880190]

Ickovics JR, Hamburger ME, Vlahov D, Schoenbaum EE, Schuman P, Boland RJ, et al. Mortality, CD4 Cell Count Decline, and Depressive Symptoms Among HIV-Seropositive Women: Longitudinal Analysis From the HIV Epidemiology Research Study. Journal of the American Medical Association. 2001; 285(11):1466–1474. [PubMed: 11255423]

Irwin M. Psychoneuroimmunology of depression: clinical implications. Brain, Behavior, and Immunity. 2002; 16(1):1–16.

Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010; 35(1):2–16. [PubMed: 19822172]

Karelina K, DeVries AC. Modeling social influences on human health. Psychosomatic Medicine. 2011; 73(1):67–74. [PubMed: 21097660]

Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R. Childhood Adversity Heightens the Impact of Later-Life Caregiving Stress on Telomere Length and Inflammation. Psychosomatic Medicine. 2011; 73(1):16–22. [PubMed: 21148804]

Kovacs, M. The Children's Depression Inventory. New York, NY: Multi-health Systems; 1992.

Kronfol Z. Cancer and depression. British Journal of Psychiatry. 1983; 142:309. [PubMed: 6860884]

Masten AS, Coatsworth JD. The development of competence in favorable and unfavorable environments. Lessons from research on successful children. American Psychologist. 1998; 53(2): 205–220. [PubMed: 9491748]

Miller G, Chen E, Cole SW. Health Psychology: Developing Biologically Plausible Models Linking the Social World and Physical Health. Annual Review of Psychology. 2009; 60(1):501–524.

Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychological Science. 2010; 21(6):848–856. [PubMed: 20431047]

Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Archives of General Psychiatry. 1998; 55(7):580–592. [PubMed: 9672048]

Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling. Relevance to major depression. Annals of the New York Academy of Sciences. 2009; 1179:86–105. [PubMed: 19906234]

Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, et al. Increased Stress-Induced Inflammatory Responses in Male Patients With Major Depression and Increased Early Life Stress. American Journal of Psychiatry. 2006; 163(9):1630–1633. [PubMed: 16946190]

Padgett DA, Glaser R. How stress influences the immune response. Trends in Immunology. 2003; 24(8):444–448. [PubMed: 12909458]

Park EJ, Lee JH, Chae JH, Lee KH, Han SI, Jeon YW. Natural Killer T cells in patients with major depressive disorder. Psychiatry Research. 2006; 144(2–3):237–239. [PubMed: 17027089]

Ravindran AV, Griffiths J, Merali Z, Anisman H. Circulating lymphocyte subsets in major depression and dysthymia with typical or atypical features. Psychosomatic Medicine. 1998; 60(3):283–289. [PubMed: 9625215]

Roy B, Diez-Roux AV, Seeman T, Ranjit N, Shea S, Cushman M. Association of optimism and pessimism with inflammation and hemostasis in the Multi-Ethnic Study of Atherosclerosis (MESA). Psychosomatic Medicine. 2010; 72(2):134–140. [PubMed: 20100888]

Rozanski A, Blumenthal JA, Kaplan J. Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy. Circulation. 1999; 99(16):2192–2217. [PubMed: 10217662]

Schleifer SJ, Bartlett JA, Keller SE, Eckholdt HM, Shiflett SC, Delaney BR. Immunity in adolescents with major depression. Journal of the American Academy of Child and Adolescent Psychiatry. 2002; 41(9):1054–1060. [PubMed: 12218426]

Schleifer SJ, Keller SE, Bartlett JA. Panic disorder and immunity: Few effects on circulating lymphocytes, mitogen response, and NK cell activity. Brain, Behavior, and Immunity. 2002; 16(6):698–705.

Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H. Increased CD56+ natural killer cells and related cytokines in major depression. Clinical Immunology and Immunopathology. 1996; 78(1):83–85. [PubMed: 8599889]

Shain BN, Kronfol Z, Naylor M, Goel K, Evans T, Schaefer S. Natural killer cell activity in adolescents with major depression. Biological Psychiatry. 1991; 29(5):481–484. [PubMed: 2018821]

Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Progress in Neurobiology. 2010; 91(4):275–299. [PubMed: 20417247]

Steptoe A, O'Donnell K, Badrick E, Kumari M, Marmot M. Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: the Whitehall II study. American Journal of Epidemiology. 2008; 167(1):96–102. [PubMed: 17916595]

Targum SD, Clarkson LL, Magac-Harris K, Marshall LE, Skwerer RG. Measurement of cortisol and lymphocyte subpopulations in depressed and conduct-disordered adolescents. Journal of Affect Disorders. 1990; 18(2):91–96.

Wolf JM, Miller GE, Chen E. Parent psychological states predict changes in inflammatory markers in children with asthma and healthy children. Brain, Behavior and Immunity. 2008; 22(4):433–441.

Worthman CM, Panter-Brick C. Homeless street children in Nepal: use of allostatic load to assess the burden of childhood adversity. Dev Psychopathol. 2008; 20(1):233–255. [PubMed: 18211736]

Wyman PA, Cowen EL, Work WC, Hoyt-Meyers L, Magnus KB, Fagen DB. Caregiving and developmental factors differentiating young at-risk urban children showing resilient versus stress-affected outcomes: a replication and extension. Child Development. 1999; 70(3):645–659. [PubMed: 10368913]

Wyman PA, Cowen EL, Work WC, Parker GR. Developmental and family milieu correlates of resilience in urban children who have experienced major life stress. American Journal of Community Psychology. 1991; 19(3):405–426. [PubMed: 1892136]

Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986; 42(1):121–130. [PubMed: 3719049]

Table 1

Subject Characteristics

	Sample Characteristics (n = 141)	Self-Efficacy Mean (SD)	Depression Mean (SD)
Child's Race:			
White	67 (47%)	28.22 (4.35)	12.28 (2.28)
Black	40 (28%)	29.08 (3.67)	13.38 (4.11)
Hispanic	9 (6%)	28.78 (3.03)	13.44 (5.08)
Asian	4 (3%)	28.25 (6.13)	11.50 (1.91)
Biracial	21 (15%)	29.48 (4.73)	12.29 (2.49)
Child's Gender:			
Male	76 (54%)	29.08 (4.05)	12.92 (3.43)
Female	65 (46%)	28.23 (4.31)	12.32 (2.77)
Child's Age:			
7.1 – 9.3 Years	70 (50%)	28.70 (4.38)	13.34 (3.81)
9.4 – 13.1 Years	71 (50%)	28.68 (3.99)	11.96 (2.13)
Household Income:			
≤ $25K	52 (37%)	29.23 (4.21)	13.46 (4.08)
$26K–55K	48 (34%)	28.96 (4.59)	12.10 (2.51)
$56K–95K	27 (19%)	27.93 (3.12)	12.63 (2.26)
> $95K	14 (10%)	27.21 (4.19)	11.50 (1.74)

Note.

[1] Age and Income at time of first assessment of depression and self-efficacy. Age is presented at the median split (see details on age interactions).

Table 2

Pearson correlations among variables at visit 5

	CDI	EFFICACY	BSI	INCOME	AGE
CDI					
EFFICACY	0.03				
BSI	0.28*	−0.07			
INCOME	−0.16*	−0.12	−0.19*		
AGE	−0.22*	0.03	−0.09	0.11	

* P ≤ 0.05

Table 3

Adjusted mean differences in the $\log_{10}$ of IL-6 levels for study variables[1]

Variables	IL-6 Estimate		
	Estimate (95% CI)		P-value
Depression	0.00	−0.01, 0.01	0.83
Self-Efficacy	−0.01	−0.02, −0.00	0.03
BMI	0.01	0.01, 0.02	<0.01
Parent BSI	0.02	−0.04, 0.09	0.51
Income	−0.004	− 0.02, 0.01	0.58
Sick prior 14 days	0.08	0.02, 0.14	0.01

Abbreviations: BSI, Brief Symptom Inventory; CI, confidence interval; BMI, body mass index. For each variable, the estimates correspond to the change in log10 IL-6 level of 1-U increase.

[1]Analyses were adjusted for child age, sex, and prior IL6 levels (visit 4).

Table 4

Adjusted mean differences in the $\log_{10}$ of NK function for depression in females and males stratified by age[1]

Depression estimates by group	NK function		
	Estimate (95% CI)		P-value
Female Age ≤ 9.3 years	0.00	−0.02, 0.02	0.91
Male Age ≤ 9.3 years	0.01	−0.01, 0.02	0.36
Female Age > 9.3 years	0.02	0.00, 0.04	0.02
Male Age > 9.3 years	−0.02	−0.03, 0.01	0.37

For each variable, the estimates correspond to the change in log10 NK cell function of 1-U increase.

[1]Analyses were adjusted for child age, sex, parent psychiatric symptoms (BSI), income, and prior NK function.

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Table 5

Estimated rate ratios for the association between depression and total illnesses and febrile illnesses for females and males stratified by age[1]

	Total Illnesses			Febrile Illnesses		
Depression estimates by group	**RR**	**(95% CI)**	**P-value**	**RR**	**(95% CI)**	**P-value**
Female Age ≤ 9.3 years	0.95	0.84, 1.07	0.39	0.89	0.60, 1.30	0.54
Male Age ≤ 9.3 years	1.07	0.98, 1.16	0.12	1.06	0.89, 1.26	0.53
Female Age > 9.3 years	1.18	1.07, 1.30	<0.01	1.62	1.05, 2.49	0.03
Male Age > 9.3 years	1.01	0.84, 1.22	0.87	1.34	0.85, 2.12	0.21

Note: Outcome was febrile illness in 1-year period after assessment of depression and self-efficacy.

[1]Analyses were adjusted for child age, sex, parent psychiatric symptoms (BSI), income, and illnesses in the previous year.