Relationship of Early Life Stress and Psychological Functioning to Adult C-Reactive Protein in the Coronary Artery Risk Development in Young Adults Study

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Background: Low socioeconomic status (SES) and a harsh family environment in childhood have been linked to mental and physical health disorders in adulthood. The objective of the present investigation was to evaluate a developmental model of pathways that may help explain these links and to relate them to C-reactive protein (CRP) in the Coronary Artery Risk Development in Young Adults (CARDIA) dataset.

Methods: Participants (n = 3248) in the CARDIA study, age 32 to 47 years, completed measures of childhood SES (CSES), early family environment (risky families [RF]), adult psychosocial functioning (PsyF, a latent factor measured by depression, mastery, and positive and negative social contacts), body mass index (BMI), and C-reactive protein.

Results: Structural equation modeling indicated that CSES and RF are associated with C-reactive protein via their association with PsyF (standardized path coefficients: CSES to RF, RF to PsyF, PsyF to CRP, CSES to CRP, all p < .05), with good overall model fit. The association between PsyF and CRP was partially mediated by BMI (PsyF to BMI, BMI to CRP, both p < .05).

Conclusions: Low childhood SES and a harsh early family environment appear to be related to elevated C-reactive protein in adulthood through pathways involving psychosocial dysfunction and high body mass index.

Key Words: Stress, family, health, SES, comorbidities, HPA

Striking comorbidities have been observed between psychiatric illness and some chronic disorders such as hypertension, coronary heart disease (CHD), and compromised immunologic functioning (Barth et al 2004; Van Melle et al 2004). Understanding the mechanisms that link these processes is, therefore, an important research priority. C-reactive protein (CRP), a biomarker of inflammatory processes, may play an important role in these relations. C-reactive protein has been reliably related to depression (Suarez 2003; Jousilahti et al 2003; Hemingway et al 2003; Miller et al 2005) and to enhanced risk for cardiovascular disease (King et al 2004), among other disorders.

Our research has developed and tested a model that relates childhood stressors to risk for mental and physical health disorders in adulthood. The model maintains that the effects of early life stress are cumulative, adversely affecting psychosocial resources, as by contributing to low social support and risk for depression, which, in turn, may enhance risks for health disorders in adulthood. Specifically, we link low childhood socioeconomic status (SES) and risky family (RF) environment marked by harsh parenting to the development of negative affect and low social support as predictors of risk factors for mental and physical illness (Repetti et al 2002; Lehman et al 2005; Taylor et al 2004). In the present research, we explore whether this theoretical model explains significant variance in CRP, thereby clarifying both the psychosocial factors that contribute to elevated CRP and elucidating processes that may contribute to the comorbidities between mental and physical health more generally.

The model is presented in Figure 1 (which details both the model itself and the upcoming analyses). The first link in the model is childhood SES. Health-related risks of low SES begin in childhood (Francis et al 2000; Singer and Ryff 2000), and family environment is implicated in these processes (Repetti et al 2002). Substantial research links economic adversity in the family to a poor or deteriorating quality of parenting, including higher levels of family conflict, a harsh restrictive parenting style, and chaotic or neglectful parenting (Dodge et al 1994; Emery and Laumann-Billings 1998; Mcloyd 1998). In the model, childhood SES is temporally prior, has been tied to subsequent variables in the model, and is minimally affected by them in return; specifically, in addition to being related to parenting style, low childhood SES has been related to the development of depression (Gallo and Matthews 2003) and to problems in the enlistment and/or use of social support (Repetti et al 2002). Low socioeconomic status is associated with elevated CRP, and this association may contribute to the SES gradient in coronary heart disease and immune-related disorders (Owen et al 2003; Hemingway et al 2003).

The next variable in the model, risky early family environment, is temporally prior to the subsequent variables in the model and has been independently correlated with each of the subsequent steps as well. Early family environments marked by harsh or chaotic parenting are reliably associated with deficits in offspring emotion regulation skills, including both internalizing and externalizing behavior in children (Repetti et al 2002). A harsh early environment has been related to higher levels of depression (Repetti et al 2002); to lower levels of social support (Repetti et al 2002); to preclinical risk factors for illness, including elevated autonomic and cortisol responses to stress (Matthews et al 1996; Taylor et al 2004) and compromised metabolic functioning (Lehman et al 2005); and to major physical health disorders (Felitti et al 1998).

With respect to psychosocial functioning, the next step in the model, depression, has been tied to increased body mass index.
Methods and Materials

Participants

The research made use of the Year 15 CARDIA dataset (with the exception of childhood SES, which was measured at baseline). Coronary Artery Risk Development in Young Adults is an ongoing epidemiologic study in which African American and white participants from a broad range of SES backgrounds took part in six assessments over 15 years. The CARDIA study tracks predictors of coronary artery disease as young people transition to adulthood. To be enrolled, participants must have identified themselves as either black or white, had a permanent address in one of four urban areas (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; or Oakland, California), have been without symptoms of long-term disease or disability, and not have been pregnant (see Cutter et al 1991 and Friedman et al 1988 for further detail on the methodology of the CARDIA study). The original assessment was in 1985 to 1986 when participants were 18 to 30 years old. All procedures were approved by University of Alabama at Birmingham Institutional Review Board.

At the time of the most recent assessment (2000 to 2001), participants ranged in age from 32 to 47 years. Of the initial sample of 5115 participants, 3671 were examined at the Year 15 assessment. Participation among the living members of the original sample was 73.5% in Year 15; attrition analyses suggested that those who remained at Year 15 were more likely than the baseline sample to be white, well educated, older, and female. Those included in the final sample for this study had complete data on the eight measures used in the analyses, including a report of childhood socioeconomic status that was obtained during the 1985 to 1986 baseline assessment. The final sample consisted of 3248 participants: 625 African American men; 851 African American women; 846 white men; 946 white women. Participants with CRP values higher than 10 were excluded from all analyses, because extremely high CRP values likely indicate infection at the time of assessment.

Procedure

For the Year 15 CARDIA assessment, participants were asked not to exercise on the day of the examination, to fast for 12 hours, and to refrain from smoking for one half hour prior to the examination. The examination took approximately 3 hours, during which participants completed informed consent and provided blood and urine samples, blood pressure measurements, and anthropomorphic measurements. After being given a small snack, they participated in interviews concerning their health and completed a set of self-administered questionnaires, including the psychosocial and risky family measures used for this study.

Measures

Early Family Environment. The Risky Families questionnaire was adapted from an instrument developed by Felitti et al (1998). Respondents rated aspects of their family environment on 4-point scales from 1 (rarely or none of the time) to 4 (most or all of the time), including whether the individual felt loved and cared for; was shown physical affection; was verbally abused; was physically abused; lived with a substance abuser; lived in a well-organized, well-managed household; and whether family members knew what the child was up to. Because individual items differed in their variability, each item was z-scored before a composite measure was formed; Cronbach’s alpha was .77.
Higher values represent a riskier family environment; we observed the full range of possible values on this measure.

Psychosocial Functioning. Depression was assessed using the 20-item Center for Epidemiologic Studies Depression Scale (Radloff 1977). Possible values ranged from 0 to 60; we observed values from 0 to 54. Cronbach’s alpha was .89. Mastery was measured through the Personal Mastery Scale (Pearlin et al 1981), with response options ranging from 1 to 5. Cronbach’s alpha was .79, and observed values ranged from 1.3 to 5. Social contacts were assessed by an 8-item scale adapted from Schuster et al (1990) that included both supportive and unsupportive interactions. Four items comprised the positive social contacts (PSC) subscale (alpha = .83), and four items measured negative social contacts (NSC) (alpha = .72). The subscales were correlated (r = −.37, p < .001). Response scales for PSC and NSC ranged from 1 to 4, and values along that entire continuum were observed in this sample.

Childhood SES (CSES) was assessed at the baseline 1984 CARDIA assessment by using parental educational attainment as a proxy for CSES. Participants indicated the highest level of education obtained by the participant’s parents or primary caregivers. The mean of standardized z-scores of the primary male and female caregivers’ levels of education (r = .56, p < .001) was used as a measure of CSES.

Body Mass Index. To measure height, each participant stood against a wall, and a plane was used to form a right angle between the wall and the top of the head. All measurements were rounded to the nearest half centimeter. Weight was rounded to the nearest half pound. Lightweight attire and no shoes were worn during anthropomorphic measurements. To calculate BMI, pounds were converted to kilograms, and BMI was calculated to equal weight (in kilograms) divided by height squared (in meters). Observed BMI values in our sample ranged from 15.73 to 65.61.

C-Reactive Protein. Plasma samples were stored in a citrated vacutainer tube, centrifuged, and transferred to a cryovial for analysis by the University of Vermont. C-reactive protein was measured using the BNII nephelometer from Dade Behring (Deerfield, Illinois) utilizing a particle-enhanced immunonephelometric assay. The assay range was .175 to 1100 mg/L. Expected values for CRP in normal, healthy individuals are ≤5 mg/L. After excluding participants with extremely high CRP (n = 60), observed CRP values in the sample ranged from .24 to 9.98. Intra-assay coefficients of variation (CVs) ranged from 2.3% to 4.4%, and interassay CVs ranged from 2.1% to 5.7%.

Results

Table 1 presents summary statistics for our overall sample.

Statistical Analysis: Overview

To test whether the theoretical model shown in Figure 1 explained variability in C-reactive protein in the CARDIA dataset, a series of structural equation models using EQS 6.0 was conducted. The data were first evaluated for multivariate normality. Second, a latent psychosocial functioning factor was created by combining the measures of depression, mastery, and positive and negative social contact. It was tested first on the entire CARDIA sample, and then a multigroup analysis was conducted to test for invariance of the latent factor across the four race-sex subgroups. Third, the latent psychosocial factor was incorporated into a test of the whole model (shown in Figure 1) using the entire CARDIA sample. This model was also compared with an alternative model that gave psychosocial functioning (PsyF) causal priority to examine whether deficits in PsyF influenced the retrospective reporting of childhood family environment, which then influenced BMI and C-reactive protein. Fourth, the model in Figure 1 was tested through a series of multiple groups analyses to determine whether the model fit the data equally well for the four race-sex subgroups in the CARDIA sample.

Examination of Assumptions

To address skew, BMI and CRP were logarithmically transformed prior to their inclusion in analyses. However, because transformed data were still not normally distributed, multivariate outliers were examined, and robust standard errors were used for indices of model fit (Satorra and Bentler 1994). We used several indicators of model fit to determine the adequacy of the theoretical models. Models that fit the data had standardized discrepancies close to 0 and root mean-square error of approximation (RMSEA) of .05 or less; those with RMSEA lower than .08 were acceptable. Normed Fit Index (NFI) and Comparative Fit Index (CFI) estimates greater than .90 were indicators of acceptable model fit. The Satorra-Bentler scaled chi-square (Satorra and Bentler 1994) is also reported, although nonsignificance of the scaled chi-square value is an inappropriate criterion of model fit in the present analyses because of the large sample size. Model chi-square, NFI, CFI, and RMSEA are reported for each of the major analyses. When nested models are compared, a chi-square change statistic that accounts for the use of robust indicators is also presented (Satorra and Bentler 2001).

PsyF Confirmatory Factor Analysis

A confirmatory factor analysis was conducted to determine whether depression, mastery, positive and negative social contacts were appropriately modeled as indicators of a single latent factor of psychosocial functioning. An exploratory factor analysis, conducted for the entire sample as well as separately for each of the race-sex subgroups, indicated that a single factor was appropriate. The path to depression was fixed to 1, and depression and mastery were allowed to covary.1 This model fit the data

Table 1. Demographic, Psychosocial, and Physiological Characteristics of Participants

<table>
<thead>
<tr>
<th>Variables in the RF Model</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s Education (years)</td>
<td>13.15</td>
<td>2.24</td>
</tr>
<tr>
<td>Father’s Education (years)</td>
<td>13.23</td>
<td>2.57</td>
</tr>
<tr>
<td>Early Family Environment</td>
<td>1.66</td>
<td>.58</td>
</tr>
<tr>
<td>Depression</td>
<td>8.98</td>
<td>7.80</td>
</tr>
<tr>
<td>Mastery</td>
<td>4.11</td>
<td>.61</td>
</tr>
<tr>
<td>Positive Social Contacts</td>
<td>3.51</td>
<td>.56</td>
</tr>
<tr>
<td>Negative Social Contacts</td>
<td>2.05</td>
<td>.62</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>28.48</td>
<td>6.59</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>1.76</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Sample Descriptive Information (in 2000–2001)

| Age                        | 40.1  | 3.6   |
| Percent with College Degrees| 48.2  |       |
| Percent Income <$75,000     | 61.7  |       |

RF, risky family.
are shown above the diagonal in Table 2, and summary statistics suggested that conceptually important links were missing. Neither Lagrange multiplier tests nor standardized residuals computed for the final model indicated indicators of the latent (unmeasured) PsyF construct. Therefore, we repeated the SEM analysis but gave PsyF causal priority over RF. The fit of the alternative model was significantly poorer ($\chi^2 (2) = 30.91, p < .001$), and fit indices indicated that the alternative model was not as successful at explaining the data.

Multiple Groups Analyses of the RF Model

Several steps were used to determine whether the RF model differed significantly among the four race-sex subgroups. An initial analysis tested whether the model fit the data when the grouped structure was considered. This model did fit the data. Second, factor loadings were constrained to be equal across the four groups. This model was also supported. Third, all model paths were constrained to be equal. Lagrange multiplier tests indicated that the theorized model paths did not differ significantly among the four subgroups. However, these tests did not apply to the reconstruction of RF. Accordingly, we repeated the SEM analysis but gave PsyF causal priority over RF. The fit of the alternative model was significantly poorer ($\chi^2 (2) = 30.91, p < .001$), and fit indices indicated that the alternative model was not as successful at explaining the data.

Test of the RF Model

The correlation matrix of variables in the model is shown below the diagonal of Table 2. Model fit statistics for the model shown in Figure 1 indicated a good fit with the data ($Satorra-Bentler \chi^2 (16) = 87.69, p > .05; NFI = .97; CFI = .98; RMSEA = .03$) and required no post hoc modification to fit the data. (Note that the individual PsyF measures (e.g., depression) are to be interpreted as indicators of the latent (unmeasured) PsyF construct). Neither Lagrange multiplier tests nor standardized residuals suggested that conceptually important links were missing from the model. Standardized discrepancies for the final model are shown above the diagonal in Table 2, and summary statistics for model fit are shown in Table 3.

As shown in Figure 1, all of the links proposed in the risky families model were supported. As predicted, children from lower SES families were more likely to report growing up in a household characterized by harsh parenting. A risky early family environment was, in turn, associated with less adaptive psychosocial functioning. Psychosocial functioning, as indicated by depression, mastery, and low positive/high negative social contacts, predicted higher body mass index and increased levels of C-reactive protein. Childhood SES also predicted BMI, which was closely linked to C-reactive protein.

An alternative model addressed the possibility that a negative response bias (as embodied in the PsyF variable) might predict the reconstruction of RF. Accordingly, we repeated the SEM analysis but gave PsyF causal priority over RF. The fit of the alternative model was significantly poorer ($\chi^2 (2) = 30.91, p < .001$), and fit indices indicated that the alternative model was not as successful at explaining the data.
indicate that links from PsyF to BMI $[\chi^2 (1) = 5.72, p < .02]$, and from CSES to BMI $[\chi^2 (1) = 10.67, p < .01]$ differed among the four subgroups. Specifically, the link from CSES to BMI was significantly less important for African American men and women than for white men and women, whereas the path between PsyF and BMI was less important for the male subgroups than for the two female subgroups. Because of these differences, a final multigroup model allowed the CSES to BMI and the PsyF to BMI paths to vary freely. This model was a good fit with the data $[\text{Satorra-Bentler} \chi^2 (79) = 142.48, p < .05; \text{CFI} = .96; \text{CFI} = .96; \text{RMSEA} = .016]$ and was a significant improvement over the previous model $[\chi^2 (6) = 25.01, p < .01]$.

**Discussion**

We proposed a theoretical developmental model to address the robust relations between a harsh early environment in childhood and mental and physical health outcomes in adulthood (Repetti et al 2002). We hypothesized that one underlying mechanism may be elevated C-reactive protein, which has been tied to both depression and to physical health outcomes. To test the model, we related childhood SES and risky family background to elevations in C-reactive protein via psychosocial functioning and body mass index. The model was supported and accounted for 21% of the variance in CRP. The model was largely supported for all four subgroups of white and African American men and women as well. The significance of the findings lies in the ability of the model to explain how developmentally early psychosocial processes may predict a significant biological risk factor later in life: The results not only clarify how childhood SES and family background may contribute to elevations in C-reactive protein but also clarify how psychosocial factors, including depressive symptomatology, mastery, and social support, influence these pathways.

Low childhood SES affected early family environment directly and adversely. A risky family environment, as predicted, was strongly related to indicators of psychosocial functioning, including depression, mastery (negatively), and social support (negatively), consistent with previous evidence (Taylor et al 2004; Lehman et al 2005). The pathway from body mass index to C-reactive protein was very strong, whereas the pathways from psychosocial functioning to CRP, both directly and indirectly through BMI, were less strong. Nonetheless, the evidence is consistent with the prediction that psychosocial variables, including family environment and psychological and social functioning, play a role in developing risk factors prognostic for illness, specifically BMI and C-reactive protein. Of Note, these results are also consistent with the conclusions of Miller et al (2003) that depressive symptoms promote weight accumulation (as opposed to a model which maintains that inflammatory molecules arising from expanded adipose tissue promote depressive symptoms).

The results are also generally consistent with models that emphasize the cumulative significance of stress exposure on mental and physical health outcomes across the life span (McEwen 1998). As previous research has noted (Allen et al 1997), processes underlying chronic illness can begin in early childhood, and the present results suggest that both low SES in childhood and a stressful early family environment can contribute to these accumulating risks.

**Limitations**

There are several limitations to the present findings. The model does not include variability in CRP that is due to genetic factors or unmeasured health behaviors. Genetic factors are estimated to account for 13% to 30% of the intradividual variability in CRP (Pankow et al 2001). Second is the fact that, with the exception of childhood SES, the data are largely cross-sectional, not longitudinal. Consequently, we have inferred causal paths from correlational data. Experimental tests of these hypotheses are not feasible except with animals, and even within the constraints of structural equation modeling, inferring causality from correlational evidence has attendant risks. Third, reconstructions of family environments may include an emotional overlay, contributing to response bias that may influence relations among model variables. However, the instrument on which our assessment of family environment is based (Felitti et al 1998) has demonstrated a dose-response relationship to a broad array of hard health outcomes (e.g., cancer, CHD), and a response bias is highly unlikely to yield such effects. Nonetheless, to further assess this possibility, we evaluated the fit of an alternative model that gave psychosocial functioning priority to see if it explained the reconstruction of childhood events. This model was a weak fit to the data. We note that this alternative model has been ruled out in other tests of the risky families model as well (Taylor et al 2004; Lehman et al 2005). Alterations in sample composition due to attrition is also a limitation, resulting in an underrepresentation of African American men in the sample. Nonetheless, the model was largely supported in all race-sex subgroups.

Finally, it should be noted that C-reactive protein is only one marker of inflammation and its relation to disease is still incompletely understood. Nonetheless, it is regarded as the most clinically useful inflammatory marker tied to cardiovascular risk (King et al 2004), and its relation to depression makes it an excellent candidate for exploring comorbidities between mental and physical disorders. Clinical implications of these findings should be drawn with caution, as CRP is a single risk factor for mental and physical health disorders. Nonetheless, the results point to the importance of intervening early with troubled families, especially with respect to the psychosocial sequelae that may result from problematic family dynamics. Early interventions aimed at poor psychosocial functioning (Rozanski and Kubzansky 2005) and at weight control would appear to be especially promising. Targeting depressive symptomatology early may help to avoid the cascade of mental and physical health risks that follow.

**Conclusions**

This study suggests that low SES and a harsh family environment in childhood may be related to inflammatory processes in adulthood via psychosocial functioning (depression, mastery, social support) and body mass index. The results underscore the potential role of childhood SES and early family environment in a trajectory of emotional distress, poor social functioning, obesity, and inflammatory processes in later years. As such, the results have implications for understanding the development of psychological distress, for understanding comorbidities involving mental and physical illness, and for understanding SES-related gradients in mental and physical health disorders. In addition,
the results suggest the potential value of intervening with troubled families to enhance the likelihood of improving offspring long-term mental and physical health.

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