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Child Abuse Is Related to Inflammation in Mid-life Women: Role of Obesity

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Abstract

Objective—Elevated inflammation biomarkers are associated with incident cardiovascular disease. Several studies suggest that childhood abuse may be associated with inflammation later in life. This study examined whether childhood abuse predicted elevated levels of C reactive protein (CRP) and whether the association was due to body size.

Methods—Participants were 326 (104 Black, 222 White) women from the Pittsburgh site of the Study of Women's Health Across the Nation (SWAN). SWAN included a baseline assessment of premenopausal or early perimenopausal women in midlife (mean age = 45.7), and CRP, depressive symptoms, body mass index (BMI), and other covariates were measured over 7 annual follow-up visits. The Childhood Trauma Questionnaire, a standardized measure that retrospectively assesses abuse and neglect in childhood and adolescence, was administered at year 8 or 9 of follow-up.

Results—Approximately 37% of the participants reported a history of abuse or neglect. Generalized estimating equations showed that sexual and emotional abuse, emotional and physical neglect, and the total number of types of abuse were associated with higher CRP levels over 7 years, adjusting for race, age, education, smoking status, use of hormone therapy, depressive symptoms, occurrence of heart attack or stroke, and medications for hypertension. The coefficients for indirect effects for emotional and sexual abuse, physical neglect, and total number of types of abuse on CRP levels through BMI were significant. A history of emotional abuse and neglect was related to percent change in CRP over the 7 years but not through percent change in BMI over the 7 years.

Conclusion—A history of childhood abuse and neglect retrospectively reported is related to overall elevated inflammation in mid-life women, perhaps through obesity. A history of some types of abuse and neglect (emotional) may be related to change in inflammation, independent of simultaneously measured change in BMI.

Keywords

childhood abuse; neglect; inflammation; obesity; women

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Introduction

Abuse and neglect in childhood are unfortunately quite common. Among over 9,000 women enrolled in a health maintenance organization, 27% reported physical abuse, 25% sexual abuse, and 13% emotional abuse (Dube et al., 2001). In the Nurses' Health Study, 53% reported physical abuse and 33% reported sexual abuse in childhood or adolescence (Boynton-Jarrett et al., 2011). Furthermore, the mental health consequences of childhood abuse and neglect can be long lasting. They are associated with risk for depression, post-traumatic stress disorder, and alcohol and substance abuse (Brewin et al., 2000; Simpson and Miller, 2002; Widom et al., 2007). Several epidemiological studies suggest that early abuse may also increase risk for later diabetes, cardiovascular disease (CVD), and clustering of CVD risk factors (Danese et al., 2009; Rich-Edwards et al., 2012; Rich-Edwards et al., 2010). Early abuse combined with other adverse childhood circumstances, including violence against mother and household members with psychiatric illness and prison records, were associated with an elevated prevalence of diabetes, stroke, and heart disease (Felitti et al., 1998).

Low grade systemic inflammation in the absence of acute infection is associated with diverse health outcomes, including diabetes, CVD, and clustering of CVD risk factors (Kaptoge et al., 2010; Libby, 2002; Ridker, 2007; Ridker et al., 2002). As noted by the National Institute of Aging 2007 Strategic Directions, "inflammation may increase susceptibility to and rate of progression of age-related pathologies … independent of overt disease". A nonspecific marker of inflammation, C-reactive protein (CRP), is considered to be a useful biomarker for identifying individuals who are at high risk for later CVD (Pearson et al., 2003). Perhaps early child abuse and neglect are related to later risk for CVD and other chronic diseases in part through inflammation generally and CRP specifically.

Few studies have evaluated whether child abuse and neglect are related to CRP and most have examined abuse combined with other childhood stressors. In a large population-based study of English children, those who experienced more types of adverse events (physical and sexual abuse, foster care, separated from mother and father) summed across ages 1.5 through age 8 were more likely to have higher CRP levels as teenagers (Slopen et al., 2010). In men and women enrolled in the Dunedin New Zealand Study, prospectively measured childhood maltreatment (at least 2 of the following: physical and sexual abuse, maternal rejection, harsh discipline, caregiver changes) was associated with a 1.61 risk for having CRP levels > 3 mg/dl at age 32 (Danese et al., 2007). A follow-up analysis showed that those who were depressed and maltreated (N=27) were at particularly high risk for elevated CRP (Danese et al., 2008). Similarly, in a small sample of 12-year-old children, those who were physically maltreated and depressed were more likely to have elevated CRP levels (Danese et al., 2011). In the Nurses' Health Study II, sexual abuse as an adolescent, but not physical abuse as a child or adolescent, was related to CRP levels. Thus, further investigation of the independent effects of abuse and neglect on CRP is needed.

Adipose tissue, once considered only an energy storage depot, is a metabolically active organ with the capacity to secrete a range of inflammatory factors, which are associated with vascular injury, and lead to production of acute phase proteins in the liver, such as CRP. A recent meta-analysis reported that maltreatment in childhood is related to risk for obesity in adulthood (Danese and Tan, 2013). Similarly, exposure to more types of violence at home or in the neighborhood, including physical and sexual abuse, is related to risk for obesity (Midei and Matthews, 2011). Some studies of abuse and maltreatment found that the associations with inflammation were reduced to nonsignificance with statistical adjustments for body mass index (BMI) simultaneous with other health behaviors (Bertone-Johnson et al., 2012), whereas others did not adjust specifically for obesity. For example, in the

Dunedin Study, adjustments were made for the presence of elevated CVD risk, defined as having least 3 of 6 CVD risk factors: overweight, high blood pressure, high total cholesterol, low high-density cholesterol, high glycated hemoglobin, and low VO_2max adjusted for body weight (Danese et al., 2007). Taken together, these findings raise the possibility that child maltreatment influences inflammation primarily through increased risk for obesity.

The current study aims to test the hypothesis that childhood abuse and neglect are associated with CRP levels over time among women during mid-life aging, a time of increasing obesity. We also explore whether abuse and neglect are associated with change in CRP levels in midlife. We previously reported that physical abuse and sexual abuse predicted obesity and central adiposity in the same sample of mid-life women (Midei et al., 2010). Thus, we evaluated whether any observed associations between childhood abuse and neglect and CRP are reduced significantly by adjustment for body size. Second, we examine whether depressive symptoms may exacerbate the effects of childhood maltreatment, given the pattern of results obtained in the Dunedin Study. Third, we examine race differences because blacks have elevated CRP levels (Matthews et al., 2005) and the Midlife in the United States Survey (MIDUS) found that blacks, but not whites, who report more early life stressors have elevated inflammatory markers (Slopen et al., 2010).

Method

Participants

Participants were from the Pittsburgh site of the Study of Women's Health Across the Nation (SWAN), a multi-site, community-based, cohort investigation of menopause and aging, who also participated in the Mental Health ancillary study starting in 1996-1997. Participants were eligible for inclusion in SWAN if they were 42 to 52 years old, had at least one menstrual period in the past three months, were not using oral contraceptives or other female reproductive hormones, had not undergone a hysterectomy or bilateral oophorectomy, and were not pregnant or breast-feeding. Each site was required to recruit approximately 450 women, including white women and one designated minority group, in the case of Pittsburgh, women who self-identified as Black. All instruments and study protocol were approved by the University of Pittsburgh Institutional Review Board, and written informed consent was obtained from all participants.

Of the 463 Pittsburgh SWAN participants eligible for the Mental Health Study, 96% enrolled (n = 443). The Mental Health Study retention rate was approximately 82% through follow-up visit 9 (n = 365). At visit 8 or 9, 342 completed the Childhood Trauma Questionnaire (CTQ; Bernstein 1994, 2003). Nine women who completed the CTQ did not have CRP data and seven women who had a heart attack or stroke at study entry were excluded from the analysis. Thus, the final analytic sample included 326 women (104 Black, 222 White). Relative to those not in the analysis, those in the analytic sample were more likely to be white, better educated, premenopausal, and nonsmokers, *p*s < .05 and they tended to have a lower BMI at baseline, $p = .06$.

Procedure

SWAN and Mental Health Study baseline assessments were conducted in 1996 and 1997. SWAN participants completed self-administered and interviewer-administered questionnaires and a physical examination at the SWAN baseline and annually (+/− three months) thereafter. Core SWAN data collection provided CRP data at baseline and selected visits (visits 1, 3, 4, 5, 6, 7) due to the cost of assays. Visit 7 was completed in 2003-2004. The Mental Health Study provided childhood abuse data (measured by the CTQ) from visits 8 or 9 (through 2006).

Measures

Childhood abuse—Childhood abuse was assessed using the short form of the CTQ, a self-report instrument that assesses physical, sexual, and emotional abuse and physical and emotional neglect. Subjects rated statements about childhood experiences on five-point Likert-type scales ("never true" to "very often true"). Items were summed to yield scores on the five types of abuse and neglect. Clinical cut-off scores have been validated and have sensitivity and specificity at 0.85 or higher relative to clinical interview (therapists' ratings of childhood maltreatment) (Bernstein et al., 2003; Walker et al., 1999). Scores above these cutoff scores were classified as positive for abuse or neglect. The number of types of abuse was also calculated based on the clinical cutoffs. The CTQ has strong test-retest reliability and convergent validity with clinical interview and therapist ratings (Bernstein et al., 1994; Bernstein et al., 2003;Walker et al., 1999). Responses from SWAN participants showed that the CTQ had strong internal consistency, Cronbach's α = 0.80-0.94 for the subscales in this investigation.

Inflammation—At each visit, blood was drawn in the morning after fasting. CRP-hs was measured using an ultra-sensitive rate immunoephelometry method (Dade-Behring, Marburg, Germany) at the central SWAN laboratory, Medical Research Laboratory, Cincinnati Ohio, a Center for Disease Control-certified laboratory. This method is based on monitoring light scattering during agglutination of CRP to polystyrene particles coated with monoclonal antibodies to CRP. The sensitivity of the assay (lowest detectable concentration) was 0.03 mg/dl. The coefficients of variation at CRP concentrations of 0.05 and 2.2 mg/dl were 10-12% and 5-7%, respectively.

Covariates—Race was self-identified as white/Caucasian or black/African American. Educational attainment was measured at the baseline visit and women were categorized as having a 4 year college degree or more or less than a college degree. Cigarette smoking was assessed by the item, "Since your last study visit, have you smoked cigarettes regularly (at least one cigarette a day)?" A positive response to this item indicated a current smoker. Smoking status was measured at baseline and each follow-up visit. Depressive symptom levels were assessed at each visit by the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977). This is a 20-item scale measuring depressive symptoms with four-level responses indicating frequency of experiencing each symptom in the past week. Scores were dichotomized with those scoring at or above 16 being classified as potentially clinically depressed. The CES-D has well-established reliability (Cronbach's alpha=.85) and has been shown to correlate well with other depressive symptom questionnaires and with interview assessments of severity of depression. Menopausal status was assessed at every visit and women were classified as premenopausal (bleeding in the last 3 months with no cycle irregularity in the previous 12 months), early perimenopausal (bleeding in the last 3 months with some change in cycle regularity in the last 12 months), late perimenopausal (bleeding >3 months ago but within the last 12 months), postmenopausal (12 months or more of no menses not due to hysterectomy), hysterectomy, and unknown (hormone therapy or other circumstance interfering with ability to characterize bleeding patterns). These categories were collapsed into pre- or early peri-menopause vs others at each visit. Height and weight (without shoes) were measured at each visit and BMI calculated (kg/m^2). An updated medical history was taken at each visit, including new diagnoses, current medications, and hormone therapy. Among medications reported for diabetes or insulin, heart disease, arthritis, lipid lowering, anticoagulants, and hypertension, only medications for hypertension were related to CRP, $p < .20$, so they were included in the model. Medications were verified by examination of the medication containers in the clinic by the interviewers or participants reading labels to the interviewer on the telephone. Medical history was not verified against medical records. Only 2 women reported heart disease or

stroke during the follow-up period. Results were the same with and without this covariate in the model.

Statistical Analyses

CRP values were skewed and were log transformed for analyses after removal of values > 10 mg/dl (evidence of acute infection). Generalized estimating equations (GEE) were used to test the primary hypotheses where predictors were abuse types measured continuously and number of types of abuse above the clinical cutoffs and the outcomes were logged CRP levels. Model 1 adjusted for race, with age at each exam as a time varying covariate; model 2 in addition adjusted for educational attainment and time varying covariates of smoking, use of hormone therapy, menopausal status, hypertensive medication, CES-D scores, and occurrence of heart attack or stroke. The final model included the above covariates and BMI. Tests for mediation were conducted by calculating indirect effect estimates for BMI, which describes the degree of mediation that occurred, i.e. the proportion of the association between abuse and CRP that is explained by BMI. The standard error of the indirect effect was calculated by the multivariate delta method (MacKinnon et al., 2002; Sobel, 1982). Secondary analyses were conducted using clinical cutoffs for each type of abuse to dichotomize women into two groups accordingly. We also tested whether abuse history had a stronger effect among women who were depressed, CES-D scores ≥ 16, blacks, and those with a higher BMI, with interaction terms between abuse history and each of the moderator variables. Finally, to address whether abuse history predicted change in CRP over time (as opposed to elevated CRP levels over time), we conducted GEE analyses predicting percent change from baseline to each visit in CRP [logged (percent change from baseline to each visit + 100)] with sets of same models described above, except for substituting BMI percent change from baseline to each visit as the time varying covariate In lieu of BMI.

Results

Sample Characteristics

By design approximately a third of the women were black and all were middle-aged (Table 1). The sample was fairly well educated, on average overweight, and a quarter had elevated CES-D scores at baseline. Nearly 40% had at least one type of abuse or neglect above clinical cutoffs, with the most common being emotional abuse, followed by physical abuse. As reported elsewhere (Midei et al. 2010), the only type of abuse that varied by race was physical abuse with blacks reporting higher rates. At study entry, C-reactive protein levels were on average rather high, with about 1/3 (N=97) of the women having values ≥ 3 mg/dl.

Over the 7 years of follow-up, there was a modest but significant annual increase in logged CRP values, $b = .04$ (.01), $p < .0001$, with mean annual percent change from baseline (SD) = 13.5 (36.6) mg/dl, and median annual percent change (IQR) = 3.2 (−6.5, +16.7) from baseline to each annual observation of a woman. (Note that CRP values > 10 mg/dl are excluded from these calculations). The Pearson correlation coefficients (concurrent) between BMI and CRP varied from rs= .39 to .48 within the years.

History of Abuse and Neglect in relation to C-Reactive Protein Levels across Time

Women who reported exposure to greater emotional abuse, sexual abuse, emotion neglect, and physical neglect as children had elevated CRP levels over the 7 years of follow-up in mid-life (Table 2; model 1). These relationships were apparent with adjustments for ethnicity, education, and time varying covariates of smoking, hormone therapy use, CES-D scores, and BP medication (model 2). Furthermore, women who reported more types of abuse or neglect above clinical cutoffs had elevated CRP levels with covariate adjustments.

Examination of the associations of CRP with dichotomized CTQ scores showed that women who reported any abuse or neglect (model 2, $p < .02$) and women who reported emotional neglect (model 2, $p = .004$) were particularly likely to have elevated CRP scores (data not shown).

The significant covariates in model 2 were race (black), older age, lower education, hormone therapy use, hypertensive medication, and occurrence of heart attack or stroke.

Influence of Body Mass Index on Associations with C-Reactive Protein Levels across Time

With an equivalent set of covariates as in model 2 but without history of abuse or neglect in the model, BMI was a strong predictor of CRP levels over time, [*b* (standard error) = 0.10 (.01), p < .0001].

With the addition of BMI to model 3, the associations between history of abuse or neglect and CRP were no longer significant (Table 2). The indirect effects of abuse and neglect on CRP through BMI were significant for sexual abuse [effect (95% confidence intervals) = .03 (.01, .05)], physical neglect [.05 (.01, .08)], and total number of types of abuse [.07 (.02, .13)] and approached significance for emotional abuse [.02 (.00, .04)]. The percent of the effect of abuse and neglect mediated by BMI was 111.3%, 97.8%, 88.8%, and 66.4%, respectively. Note that the percent can be greater than 100% if the direct and indirect effects have opposite signs.

The association of any abuse or neglect above the clinical cutoffs with CRP levels over time also became nonsignificant when BMI was added to model 3, $p = .36$, with tests of the indirect effects of any abuse or neglect on CRP through BMI being significant, [effect = .17, (.04, .29)]. Women who reported a history of emotional neglect above the clinical cutoff had elevated CRP scores with BMI in model 3, $p = .05$.

There were no significant interactions between abuse and neglect, measured either continuously or categorically, and depressive symptoms or race. There were no significant interactions with BMI.

To illustrate the results another way, logistic regression showed that women with any abuse/neglect above the clinical cutoff were 58 percent more likely to have CRP levels > 3 mg/dl over the follow-up; this association became nonsignificant with the addition of BMI to the model (Figure 1).

History of Abuse and Neglect in relation to Change in C-Reactive Protein over Time

With an equivalent set of covariates as in model 2 but without history of abuse or neglect in the model, annual percent change in BMI predicted annual percent change in CRP over time, [$b = .04$ (.004) p < .0001].

Women who reported more emotional abuse and neglect had greater percent change in CRP over time (Table 3; model 1). This association remained significant in analyses adjusted for all covariates (model 2) and for percent change in BMI over time (model 3). Sexual and physical abuse and total number of types of abuse were unrelated.

Analyses using clinical cutoffs for emotional abuse and neglect approached statistical significance in model 1, ps < .09 and .08 respectively, but were nonsignificant in models 2 and 3 (data not shown). Tests for interactions with race, depressive symptoms, and BMI percent change showed one significant effect out of 72 tests.

Discussion

Consistent with our study hypotheses, women who reported having experienced childhood abuse and neglect had elevated levels of CRP over an 8 year follow-up period. These relationships were largely accounted for by elevated BMI in these women. In this sample, there was no indication that the influence of early childhood abuse and neglect were stronger in women who also had elevated depression scores. Furthermore, race did not influence the pattern of results, even though black women had higher scores on physical abuse and on CRP levels (Matthews et al., 2005).

We did find some evidence that women who reported a history of greater emotional abuse and neglect specifically experienced increases in CRP over the observation period. Furthermore, these increases were not accounted for by increases in BMI measured at the same time points. Perhaps the findings for change in CRP were not as consistent across types of abuse and neglect as were the results for levels of CRP because the magnitude of change in CRP was modest by mid-life and the negative effects on inflammation may have started closer in time to abuse exposure.

Study strengths include repeated assessments of CRP levels over time; inclusion of both black and white women in the study; a well validated and widely used assessment method for abuse and neglect; analyses restricted to women who were free from CHD and stroke at study entry; and statistical adjustment for medications and hormone use in the models, as appropriate. Limitations are that the findings can only be generalized to women, not to men. The association between abuse and obesity is also stronger in women than in men (Danese and Tan, 2013). While our study was longitudinal in design, the assessment of abuse and neglect was necessarily retrospective. Typically abuse and neglect are under-reported so there may have been false negatives among our participants. As in many observational studies, the women who left the study by the time of the years 8 and 9 follows-up were less educated, more obese, and depressed, impacting the results in unknown ways. Finally, our study only examined one inflammatory marker, CRP, and did not measure other important cytokines that may act as pathways connecting adipose tissue and acute phase reactants produced in the liver or be impacted by childhood history of abuse and neglect.

Nonetheless, our study shows that middle-aged women with a childhood history of abuse and neglect have elevated levels of inflammation over time and that inflammation is largely accounted for by BMI. Women with such a history are at elevated risk for multiple chronic diseases that have an inflammatory pathophysiology, and inflammatory pathways may be involved in understanding the links between abuse and CVD risk and diabetes, specifically. Our findings suggest that mid-life women with an abuse history may benefit from weight reduction and obesity prevention programs in addition to supportive therapy to help mitigate the long-term impact of early abuse history.

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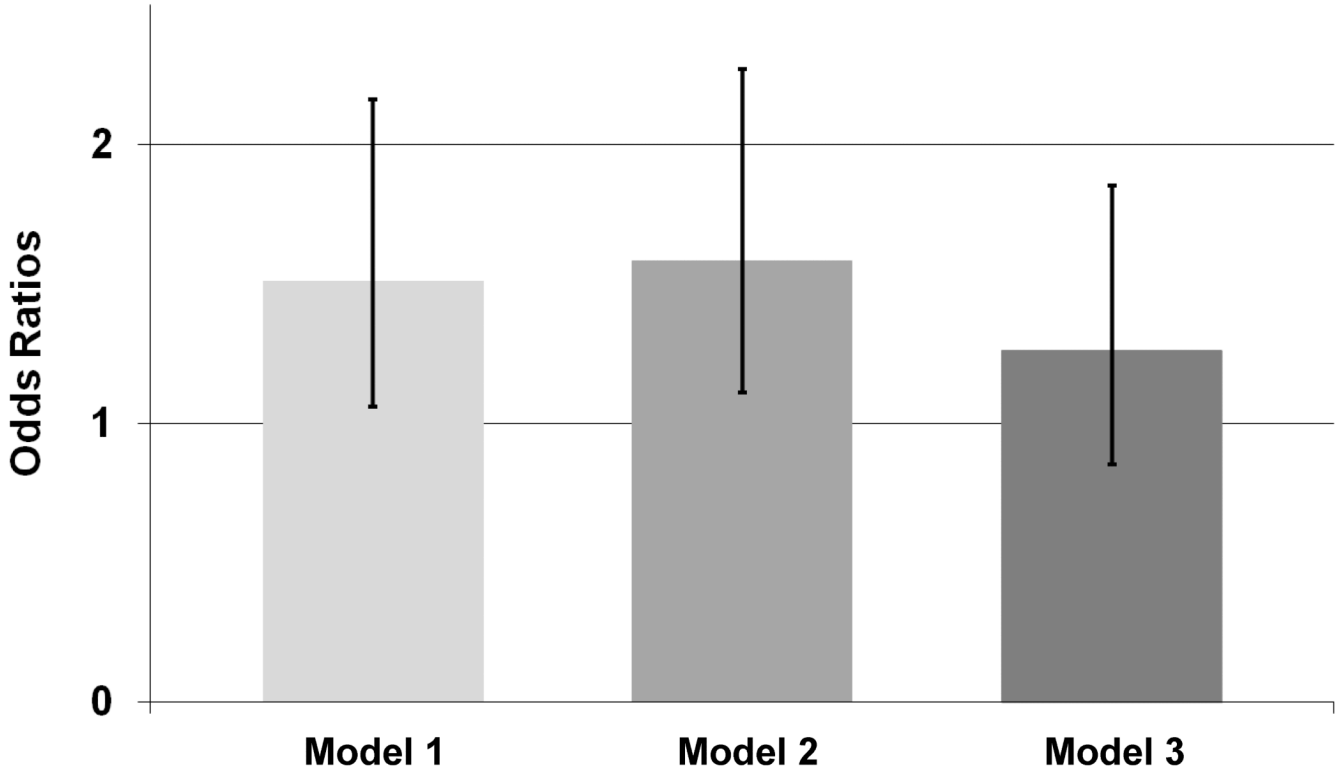

Figure 1.
Odds ratios associated with history of child/abuse and neglect and CRP > 3 mg/dl over 7 years.
Model 1, adjusted for age and race; model 2 added smoking status, education, use of hormone therapy, CES-Depression scores, menopausal status, and use of hypertensive medication; model 3 added BMI.

Table 1

Sample characteristics of women enrolled at baseline and child abuse/neglect history scores

Characteristic		
Mean (SD)[a] Age (years)		45.7 (2.5)
Ethnicity % (N)		
Black		31.9 (104)
White		68.1 (222)
Educational attainment (years) % (N)		
< college		58.0 (189)
≥ college		42.0 (137)
CES-Depression ≥ 16 % (N)		23.2 (71)
Mean (SD) Body mass index (kg/m^2)		28.1 (6.0)
Mean (SD) C-reactive protein (mg/dl)		2.5 (2.5)
Child abuse type:		
Physical	Mean (SD)	6.5 (2.8)
	% (N) above cutoff	16.9 (55)
Sexual	Mean (SD)	6.3 (3.6)
	% (N) above cutoff	13.9 (45)
Emotional	Mean (SD)	7.7 (4.0)
	% (N) above cutoff	19.9 (65)
Physical neglect	Mean (SD)	6.1 (2.1)
	% (N) above cutoff	15.7 (51)
Emotional neglect	Mean (SD)	8.2 (3.9)
	% (N) above cutoff	7.4 (24)
Total number of types of abuse % (N) above cutoff		
	0	62.6 (204)
	1	18.7 (61)
	2	8.9 (29)
	3	4.6 (15)
	4	2.8 (9)
	5	2.5 (8)

[a](SD)= Standard Deviation

Table 2

Regression estimates from generalized linear regression models on logged C-reactive protein levels across 7 years by child abuse/neglect history

	Model 1		Model 2		Model 3	
	b (SE)[a]	p-value	b (SE)	p-value	b (SE)	p-value
Abuse Type						
Sexual	.03 (.01)	.02	.03 (.01)	.02	.00 (.01)	.87
Physical	.03 (.02)	.10	.03 (.02)	.15	.00 (.02)	.90
Emotional	.02 (.01)	.04	.03 (.01)	.03	.01 (.01)	.36
Emotional Neglect	.03 (.01)	.04	.03 (.01)	.04	.02 (.01)	.16
Physical Neglect	.05 (.02)	.03	.05 (.02)	.03	.00 (.02)	.90
Total number of types of abuse	.08 (.04)	.05	.08 (.04)	.04	.01 (.04)	.74

Model 1: age, ethnicity

Model 2: + education, smoking status, HT use, CES-D, menopausal status, heart attack/stroke, medications for hypertension

Model 3: + body mass index

[a](SE)= Standard Error

Table 3

Regression estimates from generalized linear regression models on logged annual percent change from baseline in C-reactive protein across 7 years by child abuse/neglect history

	Model 1		Model 2		Model 3	
	b (SE)[a]	p-value	b (SE)	p-value	b (SE)	p-value
Abuse Type						
Sexual	.02 (.01)	.15	.02 (.01)	.16	.01 (.01)	.13
Physical	.03 (.02)	.11	.02 (.02)	.15	.02 (.02)	.28
Emotional	.03 (.01)	.001	.03 (.01)	.002	.02 (.01)	.005
Emotional Neglect	.03 (.01)	.01	.02 (.01)	.02	.02 (.01)	.02
Physical Neglect	.00 (.02)	.94	.00 (.02)	.85	−.01 (.02)	.78
Total number of types of abuse	.07 (.04)	.07	.06 (.04)	.10	.04 (.04)	.28

Model 1: age, ethnicity

Model 2: + education, smoking status, HT use, CES-D, menopausal status, heart attack/stroke, medications for hypertension

Model 3: + percent annual change from baseline body mass index

[a](SE)= Standard Error