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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 pre-menopausal or early peri-menopausal women in mid-life (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.

1. Introduction

Abuse and neglect in childhood are unfortunately quite common. Among over 9000 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, 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 non-specific marker of inflammation, C-reactive

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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 two 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 twelve-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 non-significance 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_2 max 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 mid-life. 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 Mid-life 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).

2. Method

2.1. 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 42–52 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, pre-menopausal, and non-smokers, p's < .05 and they tended to have a lower BMI at baseline, $p = .06$.

2.2. 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 (±3 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).

3. Measures

3.1. 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 cutoff 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, 2003;Walker et al., 1999). Responses from SWAN participants showed that the CTQ had strong internal consistency, Cronbach's $\alpha = 0.80–0.94$ for the subscales in this investigation.