Published in final edited form as:
*Am J Prev Med*. 2012 December ; 43(6): 611–620. doi:10.1016/j.amepre.2012.08.014.

# Inflammation and Early-Life Abuse in Women

**Elizabeth R. Bertone-Johnson, ScD**, **Brian W. Whitcomb, PhD**, **Stacey A. Missmer, ScD**, **Elizabeth W. Karlson, MD**, and **Janet W. Rich-Edwards, ScD**
Division of Biostatistics and Epidemiology (Bertone-Johnson, Whitcomb), University of Massachusetts, Amherst; Channing Laboratory, Department of Medicine (Missmer, Karlson), Rich-Edwards) Brigham and Women's Hospital and Harvard Medical School; Department of Epidemiology (Missmer, Rich-Edwards), Harvard School of Public Health, Boston, Massachusetts

## Abstract

**Background—**Abuse in childhood and adolescence may affect risks of diabetes and cardiovascular disease later in life. Although mechanisms underlying these relationships are unclear, chronic stress may lead to dysregulation of immune function and chronic inflammation.

**Purpose—**To evaluate associations between early-life physical and sexual abuse and blood levels of inflammatory markers in adulthood among 702 members of the Nurses' Health Study II.

**Methods—**Abuse in childhood (before age 11 years) and adolescence (ages 11–17 years) was self-reported in 2001. Plasma samples collected in 1996–1999 were assayed for C-reactive protein (CRP); interleukin (IL)-6; and the soluble fraction of tumor necrosis factor alpha receptor 2 in 2001, 2009 and 2010.

**Results—**Mean age at blood collection was 43.9 years. Moderate or severe physical abuse was reported by 35.3% of participants; 22.7% reported unwanted sexual touching and 9.8% reported forced sex. Plasma levels of CRP and IL-6 were higher in women reporting sexual abuse in adolescence compared to those reporting no abuse ($p$=0.04 and 0.03, respectively) in analyses adjusted for confounders including age and childhood adiposity. Inflammatory marker levels were similarly elevated in women reporting sexual abuse during childhood, but results were not significant. Relationships largely persisted after further adjustment for potential mediators such as adult BMI and smoking. Physical abuse during childhood and/or adolescence was not consistently associated with inflammatory marker levels.

**Conclusions—**Chronic inflammation may be one mechanism through which sexual abuse may affect future risk of physical and psychological disorders.

## Introduction

Abuse in childhood and adolescence is common[1, 2] and may have lasting implications for emotional and physical health. Results from a small number of prospective studies suggest that women with a history of physical and/or sexual abuse in childhood or adolescence have higher rates of chronic diseases later in life, including diabetes, cardiovascular disease



Address correspondence to: Elizabeth R. Bertone-Johnson, ScD, University of Massachusetts, Arnold House, 715 North Pleasant Street, Amherst MA 01003-9304. ebertone@schoolph.umass.edu.



No financial disclosures were reported by the authors of this paper.

(CVD), and depression.[2–8] A relationship between abuse and chronic disease may be explained in part through dysregulation of immune function leading to chronic inflammation, as suggested by laboratory experiments in humans and animal studies.[9, 10] Despite compelling evidence from animal studies, few studies have evaluated whether abuse in childhood is associated with increased levels of markers of inflammation in adulthood. Further, it is unknown whether higher levels of inflammation may be explained largely by greater rates of smoking, obesity and other behavioral factors more common among adult women with abuse histories, rather than by long-lasting physiologic changes in immune function resulting from abuse.

An evaluation was made of the association of self-reported history of physical and sexual abuse during childhood and adolescence and markers of inflammation during adulthood among a subset of participants in the Nurses' Health Study II. It was hypothesized that women reporting severe physical and/or sexual abuse in early life would have higher levels of inflammation markers in adulthood compared to women not reporting abuse, and that positive associations would be largely attenuated after adjustment for mediating factors including smoking, alcohol use, and obesity.

## Methods

### Study Population

The Nurses' Health Study II (NHS2) is a cohort of 116,678 U.S. female registered nurses aged 25–42 years who responded to a mailed questionnaire in 1989 and provided information on their medical history and health-related behaviors, such as use of oral contraceptives, pregnancy history, and smoking status. Cohort members have completed questionnaires every 2 years thereafter to update information on risk factors and to identify new diagnoses of disease. The protocol for this study was approved by the IRB at Brigham and Women's Hospital.

Between 1996 and 1999, members of the NHS2 who had not previously reported a diagnosis of cancer were invited to provide a blood sample ($n$=92,888). Details of this collection have been reported previously.[11] Briefly, women were asked to collect two timed blood samples during the menstrual cycle or a single untimed sample, depending on their menopausal status and use of exogenous hormones.

Participants were provided with supplies and asked to collect their own samples and return them to the laboratory via overnight courier. Women recorded current and recent medication use, current weight, fasting status, and the time of day of sample collections. Frozen water bottles were included to keep samples cool during shipping. When samples were received, they were centrifuged, separated into blood components, and archived at −130°C or colder in continuously monitored nitrogen freezers. Samples were ultimately received from 29,613 women. Women who provided blood samples were very similar to the entire NHS2 cohort in terms of age, smoking status, BMI, and other factors.[11]

Women included in the present analysis were controls from nested case–control studies of inflammation markers and incidence of endometriosis ($n$=568) and rheumatoid arthritis ($n$=141) in the NHS2. Endometriosis study controls were randomly chosen from among premenopausal women with no reported diagnosis of endometriosis before 2009, an intact uterus, and no history of cancer other than nonmelanoma skin cancer. Rheumatoid arthritis study controls were randomly chosen from among women with no self-reports of the disease or other connective tissue disease through 2005 and no history of cancer except nonmelanoma skin cancer.[12]

### Measurement of Inflammatory Factors

Plasma samples assayed were either luteal phase or untimed. All assays were performed in 2001 and 2009 (rheumatoid arthritis controls) and 2010 (endometriosis controls). C-reactive protein (CRP) was measured using a high-sensitivity latex-enhanced immunonephelometric assay on a BNII analyzer. Interleukin (IL)-6 was measured by a quantitative sandwich enzyme immunoassay technique. The soluble fraction of tumor necrosis factor alpha receptor 2 (sTNFR2) was measured by ELISA using immobilized monoclonal antibody to human sTNFR2. For all control groups, coefficients of variation (CV) for CRP were <5%. CVs for IL-6 were 11.7% and 8.1%, and for sTNFR2 were 4.9% and 6.8%, for rheumatoid arthritis and endometriosis, respectively.

### Assessment of Abuse

In 2001, a violence questionnaire was mailed to 91,286 NHS2 members to measure physical and sexual abuse at three different time periods: before age 11 years, during ages 11–17 years, and during adulthood.[13] Completed questionnaires were returned by 68,518 (75.0%) participants. Questions on childhood physical abuse were adapted from the Revised Conflict Tactics Scale.[14]

Women were asked: “Did a parent, step-parent or other adult guardian ever: spank you for discipline; push, grab or shove you; kick, bite or punch you; hit you with something that hurt your body; choke or burn you; or physically attack you in some other way.” Response options included never, once, a few times, more than a few times. Four categories of physical abuse were derived, based on the most-severe level of abuse reported at each time period.[3] “None” corresponded to no reported physical abuse. “Mild” included being pushed, grabbed or shoved one or more times; being kicked, bitten or punched once; or being hit with something once. “Moderate” included being hit with something more than once; or being physically attacked once. “Severe” included being kicked, bitten or punched; physically attacked more than once; or ever choked or burned. The question on spanking for discipline was not included in the abuse categorization.

Questions on inappropriate sexual touching or forced sex were adapted from the Sexual Experiences Survey.[15] Questions were: “Were you ever touched in a sexual way by an adult or an older child, or were you forced to touch an adult or an older child in a sexual way when you did not want to?” and “Did an adult or older child ever force you or attempt to force you into any sexual activity by threatening you, holding you down, or hurting you in some way when you did not want to?” Response options for these questions were: “No, this never happened”; “Yes, this happened once”; or “Yes, this happened more than once.” Sexual abuse during childhood and adolescence was categorized as follows: “None” when there was no report of sexual abuse; “Unwanted sexual touching” if any unwanted sexual touching but no forced sexual activity was reported; and “Forced sex” if forced sexual activity was reported one or more times. As with physical abuse, women were assigned to categories based on the most-severe level of abuse reported at each time period.[3]

### Assessment of Other Factors

The 1989 NHS2 questionnaire measured age, age at menarche, and race/ethnicity. Age at blood collection was calculated based on dates of birth and receipt of blood samples. Information on number of full-term pregnancies, age at first birth, menopausal status, and smoking status was collected at baseline and then updated every 2 years. Socioeconomic factors including mother’s education, father’s education, household income, and home ownership when the participant was an infant were assessed in 2005. Physical activity was measured asking women how much time was spent weekly participating in specific recreational activities. Medication use, including antidepressants, was assessed from 1993

onward. Information on food and nutrient intake was collected by a validated semi-quantitative foods frequency questionnaire,[16] and was used to estimate glycemic load, glycemic index, and intake of crude fiber. All nutrients were adjusted for total energy intake using the residual method.[17]

Participants reported their height at baseline and reported current weight on each biennial questionnaire, which was used to calculate BMI. In addition, at baseline participants were shown diagrams of female body figures and asked to identify which best represented their body at age 5 years (range from 1=very thin to 9=extremely obese). Responses were used to derive somatogram score.[18]

For analysis, covariates were classified into two groups following the method used by Rich-Edwards et al (2010).[3] Fixed characteristics and characteristics during early childhood or adolescence (i.e., prior to or contemporaneous with abuse) were considered potential confounders. These included race/ethnicity, maternal and paternal education levels, income and home ownership during infancy, and somatotype at age 5 years.

Characteristics that could vary between childhood or adolescence and the time of blood collection and that could plausibly be affected by abuse history[13] were considered potential mediators. For these factors, assessments made closest in time to blood collection were used. Factors evaluated included age at blood collection; BMI (as assessed in 1999); smoking status (1999); task hours of physical activity in METs (1997); age at menarche (1989); alcohol intake (1999); number of cigarettes smoked per day (1999); antidepressant use (1999); abuse occurring between ages 18 and 19 years; and dietary intake of crude fiber, glycemic index, and glycemic load (1999).

### Statistical Analysis

Data analyses were conducted in 2011–2012. Age-adjusted participant characteristics by level of abuse were compared with *F*-tests. General linear models were used to assess the relationship of abuse history and inflammation marker levels, and least-square means are presented. In order to meet model assumptions, inflammatory factor levels were log-ransformed, and results were then exponentiated to yield geometric means. To determine if associations varied by timing of abuse, abuse occurring during childhood and adolescence were evaluated separately, as well as combined.

Three analyses for each association were conducted. Model 1 adjusted for age and control type (endometriosis vs rheumatoid arthritis) only. Model 2 adjusted for age, control type, and confounders, as described above. Model 3 adjusted for age and control type, confounders, and mediators, as described above. For both Models 2 and 3, variables were included in the final model if they were associated with one or more types of abuse, or with one or more markers of inflammation at $p<0.05$, after adjustment for other factors in the model. For each inflammation marker, the covariate that was the strongest mediator of the observed association was identified by adding and removing each term from the fully adjusted model to identify the factors responsible for the greatest change in mean marker levels. Finally, to evaluate potential interaction between abuse types, participants were classified into four categories based on combined history of moderate or severe physical abuse and forced sex (neither, physical abuse only, forced sex only, both physical abuse and forced sex) for each of the two time periods.

## Results

The 702 NHS2 participants included were similar to the main NHS2 cohort in terms of prevalence of smoking in 1999 (10.1% vs 9.6%); mean alcohol intake (2.0 vs 2.0 grams per

day); antidepressant use (9.9% vs 9.5%); and mean BMI (25.8 vs 26.5 and other factors. However, mean age of the subsample was slightly higher in the overall cohort (mean age=48.9 years vs 44.3 years in 1999).

Age-adjusted characteristics of participants by self-reported history of physical abuse and sexual abuse in either childhood or adolescence are presented in Table 1. Moderate or severe physical abuse was reported by 35.5% ($n$=248) of participants. Unwanted sexual touch was reported by 22.6% ($n$=159) of women and 9.8% ($n$=69) reported forced sex. The prevalence of abuse reported by the subsample was comparable to that reported by all NHS2 members who completed the violence questionnaire (moderate to severe physical abuse=35.0%; unwanted sexual touching=22.2%; forced sex=11.3%).

Women reporting severe physical abuse were more likely to be current smokers and use antidepressants than women reporting no abuse, and reported a lower level of maternal and paternal education. Women reporting forced sex were more likely to be current smokers than those reporting no sexual abuse and less likely to consume 15 or more grams of alcohol daily. Mean level of physical activity was higher in women with a history of sexual abuse than those reporting no sexual abuse. Among women reporting severe physical abuse, 58.5% also reported sexual abuse, compared to 23.4% of women not reporting physical abuse. Of women reporting sexual abuse, approximately 46% also reported moderate or severe physical abuse.

Levels of CRP and sTNFR2 did not vary linearly by level of physical abuse during either childhood or adolescence, although differences across levels of physical abuse in childhood were significant for sTNFR2. In age-adjusted analyses (Model 1), IL-6 levels varied somewhat by physical abuse during adolescence, with the highest levels among those reporting severe abuse ($p$=0.06; Table 2). Results were marginally significant after adjusting for confounders including race and somatotype at age 5 years (Model 2; $p$=0.05), and were attenuated after adjustment for mediating factors including BMI, smoking, physical activity and alcohol use (Model 3; $p$=0.11).

Levels of CRP and IL-6 were generally higher in women reporting a history of unwanted sexual touching and forced sex compared to women not reporting sexual abuse (Table 3). Overall, associations were stronger for abuse occurring during adolescence than that occurring during childhood. For example, after adjustment for confounders (Model 2), mean CRP levels in women reporting unwanted touching and forced sex in adolescence were 0.92 and 1.02 mg/L, respectively, compared to 0.68 in women with no abuse history ($p$=0.04). Mean IL-6 levels in women reporting forced sex were 1.36 pg/mL, compared to 1.03 in women reporting no abuse and 1.07 in women reporting touching only ($p$=0.03). Mean sTNFR2 levels were modestly higher in women reporting forced sex during childhood, but results did not reach significance.

Adjustment for mediating factors such as adult BMI and smoking status (Model 3) attenuated the relationship between sexual abuse and CRP levels. The mediating factor explaining the largest proportion of the relationship was BMI. Associations remained marginally significant for IL-6 ($p$=0.06). Alcohol intake was the most substantial mediator of the relationship between sexual abuse and IL-6 levels.

In analyses of effect modification between types of abuse, CRP levels did not differ across combined categories of moderate to severe physical abuse and forced sex at either age (Table 4). Levels of IL-6 and sTNFR2 were highest among women reporting both types of abuse during adolescence, although interactions were not significant and power for these comparisons was low ($p$ for interaction from Model 2: 0.22 for IL-6 and 0.08 for sTNFR2).

## Discussion

These analyses are among the first to separately consider the relationship of early-life physical and sexual abuse in childhood and in adolescence with levels of inflammation markers in adulthood. Sexual abuse, especially during adolescence, was associated with levels of inflammation in adulthood. Levels of CRP and IL-6 were 20%–50% higher in women reporting forced sex than those reporting no sexual abuse. This level of effect is comparable to those of established cardiovascular risk factors in women, including current smoking and physical inactivity,[19] and translates into an approximately 40%–60% higher risk of coronary heart disease.[20] These associations were mediated in part by factors known to be associated with abuse, including adult BMI and alcohol intake. However, these mediators did not explain all of the observed associations, especially for IL-6.

Stressful early-life events, including physical and sexual abuse, may alter the normal stress responses of the hypothalamic-pituitary-adrenal (HPA) axis.[9, 21] Persistent stimulation of the HPA axis and prolonged elevation of cortisol may lead to disruption of immune function. In animals, the pro-inflammatory effect of maternal separation and other early-life psychological stressors is well established.[22, 23] Stress responses may remain heightened even years after the original trauma or stressor.[21] In human experiments, chronic stress is associated with heightened response to immune challenge (i.e., lipopolysaccaride injection)[10] and to psychosocial stress.[24]

For example, Heim et al (2000) compared HPA axis responsiveness to a public speaking and mental arithmetic task in women reporting a history of childhood physical and/or sexual abuse versus no history.[24] Women with early-life stress had higher plasma adrenocorticotropic hormone peak levels than controls both during and following the stressor. Stress reactivity was further heightened among women with abuse history who were currently experiencing major depressive disorder.

These findings are consistent with those of the few other observational studies of childhood abuse, inflammation and chronic disease risk. In the Dunedin Multidisciplinary Health and Development study, childhood maltreatment was associated with higher risk of elevated CRP levels (>3 mg/dL) at age 32 years, independent of behavioral factors including adult smoking, physical activity and BMI, as well as childhood SES and birth weight.[5] Childhood abuse history was also associated with greater risk of depression in this cohort.[6]

In the population for the current study, early-life physical and sexual abuse have been associated with higher risk of coronary heart disease and stroke,[7] type 2 diabetes[3] and uterine leiomyoma[4] during adulthood. In these studies and the current analysis, observed associations for each outcome largely persisted after adjustment for adult BMI, smoking and other mediating factors. Although a large number of confounders and mediators were controlled for, it is still possible that some degree of residual confounding by measured and/or unmeasured factors persists.

In the current study, the association between sexual abuse and inflammation markers was slightly stronger for abuse occurring during adolescence than that occurring during childhood. For example, CRP levels were approximately 50% higher in women reporting forced sex in adolescence compared to those not reporting sexual abuse, and forced sex in childhood was associated with 30% higher CRP levels. Previous studies of depression have suggested that the pubertal transition, when estrogen and testosterone production increase in girls, may be a time of particular vulnerability to the adverse effects of stress.[25, 26] Others have reported that abuse onset during early adolescence may be a stronger predictor of adverse health outcomes later in life than abuse occurring later.[27, 28] The effect of timing of early-life stress on immune function warrants further study.

To our knowledge, few previous studies have separately evaluated the association of childhood physical abuse and sexual abuse on adult health outcomes. The potential for sexual and physical abuse to have differing effects is supported by studies of abuse and early menarche.[8, 29, 30] In the Black Women's Health Study, women reporting a history of sexual abuse had a significant 25%–46% higher risk of menarche before age 12 years compared to those not reporting abuse.[29] In contrast, history of physical abuse was not associated with age at menarche. The current results are also consistent with previous studies in the NHS2 reporting stronger associations between sexual abuse and risk of type 2 diabetes[3] and CVD[7] than physical abuse. Additional work is needed to disentangle the potentially differential effects of physical and sexual abuse on stress reactivity, immune function, and chronic disease risk.

In the current study, abuse history was self-reported on validated questionnaires in 2001. Self-report of childhood abuse is likely more accurate than objective reports (i.e., police records), as only a small proportion of cases are reported to authorities. The measures used in the current study have good validity and reliability.[31] Further, the levels of abuse reported here are comparable to those in other surveys using similar instruments.[1, 2] Childhood abuse history as measured by our questionnaire predicted multiple outcomes associated with abuse in other studies[32, 33] and in the current population, including prevalence of cigarette smoking, antidepressant use and adult revictimization.[13] Ultimately, any under-report of abuse would likely lead to attenuation of relationships with inflammatory markers, rather than amplification.

Although inflammatory markers measured in a single plasma sample were used as markers of chronic inflammation, these factors appear stable over time. For example, intraclass correlations for plasma cytokine levels in 82 men with plasma samples measured 4 years apart were high (CRP=0.67; IL-6=0.47; sTNFR2=0.78);[34] however, some degree of error in the measurement of laboratory values may have affected the ability to detect modest associations, and may have attenuated results. One-time measures of inflammatory markers have also been associated with long-term risk of diabetes[35] and coronary heart disease.[36] Although this analysis has evaluated CRP, IL-6 and sTNFR2 levels individually, there are complex biological interactions among inflammatory factors involved in the immune response. Further, this analysis was not able to evaluate specific molecular pathways linking abuse history to effects on individual inflammatory markers. Future analyses with larger sample sizes are needed to fully explore these important issues.

The current findings provide further evidence[37–39] that abuse during adolescence and possibly childhood has potential long-term implications for physical and psychological health. These results suggest that early-life sexual abuse may affect adulthood levels of inflammatory markers as much as established cardiovascular risk factors such as smoking. Chronic inflammation is one mechanism potentially explaining observed higher risks of CVD, diabetes and depression among women with a history of abuse.

## Acknowledgments

This work was supported by Public Health Services grants CA50385, AR049880, HD057201 and HL064108 from the NIH, DHHS.

## References

1. Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: Results from the Adverse Childhood Experiences study. Am J Psychiatry. 2003; 160(8):1453–1460. [PubMed: 12900308]

2. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. Am J Prev Med. 1998; 14(4):245–258. [PubMed: 9635069]
3. Rich-Edwards JW, Spiegelman D, Lividoti Hibert EN, et al. Abuse in childhood and adolescence as a predictor of type 2 diabetes in adult women. Am J Prev Med. 2010; 39(6):529–536. [PubMed: 21084073]
4. Boynton-Jarrett R, Rich-Edwards JW, Jun HJ, Hibert EN, Wright RJ. Abuse in childhood and risk of uterine leiomyoma: The role of emotional support in biologic resilience. Epidemiology. 2011; 22(1):6–14. [PubMed: 21068667]
5. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA. 2007; 104(4):1319–1324. [PubMed: 17229839]
6. Danese A, Moffitt TE, Harrington H, et al. Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 2009; 163(12):1135–1143. [PubMed: 19996051]
7. Rich-Edwards JW, Mason S, Rexrode K, et al. Physical and sexual abuse in childhood as predictors of early onset cardiovascular events in women. Circulation. 2012
8. Bensley L, Van Eenwyk J, Wynkoop Simmons K. Childhood family violence history and women's risk for intimate partner violence and poor health. Am J Prev Med. 2003; 25(1):38–44. [PubMed: 12818308]
9. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007; 298(14): 1685–1687. [PubMed: 17925521]
10. Miller GE, Rohleder N, Cole SW. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. Psychosom Med. 2009; 71(1):57–62. [PubMed: 19073750]
11. Tworoger SS, Sluss P, Hankinson SE. Association between plasma prolactin concentrations and risk of breast cancer among predominately premenopausal women. Cancer Res. 2006; 66(4):2476–2482. [PubMed: 16489055]
12. Karlson EW, Chibnik LB, Tworoger SS, et al. Biomarkers of inflammation and development of rheumatoid arthritis in women from two prospective cohort studies. Arthritis Rheum. 2009; 60(3): 641–652. [PubMed: 19248103]
13. Jun HJ, Rich-Edwards JW, Boynton-Jarrett R, Austin SB, Frazier AL, Wright RJ. Child abuse and smoking among young women: The importance of severity, accumulation, and timing. J Adolesc Health. 2008; 43(1):55–63. [PubMed: 18565438]
14. Straus, MA.; Gelles, RH. Physical violence in American families: Risk factors and adaptations to violence in 8145 families. New Brunswick, NJ: Transaction Publishing; 1990.
15. Koss MP, Oros CJ. Sexual experiences survey: A research instrument investigating sexual aggression and victimization. J Consult Clin Psychol. 1982; 50(3):455–457. [PubMed: 7096751]
16. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122(1):51–65. [PubMed: 4014201]
17. Willett, WC. Nutritional epidemiology. 2nd edition. New York: Oxford University Press; 1998.
18. Field AE, Franko DL, Striegel-Moore RH, Schreiber GB, Crawford PB, Daniels SR. Race differences in accuracy of self-reported childhood body size among white and black women. Obes Res. 2004; 12(7):1136–1144. [PubMed: 15292478]
19. Bermudez EA, Rifai N, Burning J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol. 2002; 22:1668–1673. [PubMed: 12377747]
20. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incidence coronary heart disease. Prospective analysis from the Women's Health Initiative Observational Study. JAMA. 2002; 288(8):980–987. [PubMed: 12190368]
21. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. Dev Psychobiol. 2010; 52(7):671–690. [PubMed: 20882586]
22. Hennessy MB, Schiml-Webb PA, Deak T. Separation, sickness, and depression: A new perspective on an old animal model. Curr Dir Psychol Sci. 2009; 18(4):227–231. [PubMed: 20221300]

23. Hennessy MB, Deak T, Schiml-Webb PA. Early attachment-figure separation and increased risk for later depression: Potential mediation by proinflammatory processes. Neurosci Biobehav Rev. 2010; 34(6):782–790. [PubMed: 20359585]
24. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000; 284(5):592–597. [PubMed: 10918705]
25. Ge X, Conger RD, Elder GH Jr. Pubertal transition, stressful life events, and the emergence of gender differences in adolescent depressive symptoms. Dev Psychol. 2001; 37(3):404–417. [PubMed: 11370915]
26. Angold A, Costello EJ, Erkanli A, Worthman CM. Pubertal changes in hormone levels and depression in girls. Psychol Med. 1999; 29(5):1043–1053. [PubMed: 10576297]
27. Thornberry TP, Ireland TO, Smith CA. The importance of timing: The varying impact of childhood and adolescent maltreatment on multiple problem outcomes. Dev Psychopathol. 2001; 13(4):957–979. [PubMed: 11771916]
28. Kaplow JB, Widom CS. Age of onset of child maltreatment predicts long-term mental health outcomes. J Abnorm Psychol. 2007; 116(1):176–187. [PubMed: 17324028]
29. Wise LA, Palmer JR, Rothman EF, Rosenberg L. Childhood abuse and early menarche: Findings from the black women's health study. Am J Public Health. 2009; 99(Suppl 2):S460–S466. [PubMed: 19443822]
30. Zabin LS, Emerson MR, Rowland DL. Childhood sexual abuse and early menarche: The direction of their relationship and its implications. J Adolesc Health. 2005; 36(5):393–400. [PubMed: 15837343]
31. Follingstad DR, Bradley RG, Laughlin JE, Burke L. Risk factors and correlates of dating violence: The relevance of examining frequency and severity levels in a college sample. Violence Vict. 1999; 14(4):365–380. [PubMed: 10751045]
32. Smith PH, White JW, Holland LJ. A longitudinal perspective on dating violence among adolescent and college-age women. Am J Public Health. 2003; 93(7):1104–1109. [PubMed: 12835193]
33. Humphrey JA, White JW. Women's vulnerability to sexual assault from adolescence to young adulthood. J Adolesc Health. 2000; 27(6):419–424. [PubMed: 11090744]
34. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among U. S. men and women. Circulation. 2003; 108(2):155–160. [PubMed: 12821543]
35. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes. 2004; 53(3):693–700. [PubMed: 14988254]
36. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med. 2004; 351(25):2599–2610. [PubMed: 15602020]
37. Fleming RM. The Fleming Unified Theory of Vascular Disease: A Link Between Atherosclerosis, Inflammation, and Bacterially Aggravated Atherosclerosis (BAA). Angiol. 2000; 51(8):87–89.
38. Fleming RM, Boyd L, Forster M. Reversing Heart Disease in the New Millennium - The Fleming Unified Theory. Angiol. 2000; 51(10):617–629.
39. Fleming, RM. Chapter 64: The Pathogenesis of Vascular Disease. In: Chang, JC., editor. Textbook of Angiology. New York: Springer Verlag; 1999. p. 787-798.

**Table 1**

Age-adjusted[a] characteristics of participants by physical and sexual abuse history, Nurses' Health Study II

| Characteristic | Childhood and/or Adolescent Physical Abuse | | | | | Childhood and/or Adolescent Sexual Abuse | | | |
|---|---|---|---|---|---|---|---|---|---|
| | none *n*=328 | mild *n*=126 | moderate *n*=186 | severe *n*=62 | *p*-value | none *n*=474 | touch only *n*=159 | forced sex *n*=69 | *p*-value |
| Age at blood collection, years | 42.7 (4.9) | 42.1 (4.7) | 42.9 (4.5) | 43.7 (4.6) | 0.17 | 42.8 (4.8) | 42.6 (4.5) | 41.9 (4.2) | 0.45 |
| Somatotype at age 5 years | 2.5 (0.07) | 2.7 (0.11) | 2.6 (0.09) | 2.8 (0.15) | 0.10 | 2.6 (0.06) | 2.4 (0.10) | 2.7 (0.14) | 0.23 |
| BMI in 1999 | 26.0 (0.4) | 25.9 (0.6) | 26.3 (0.5) | 27.0 (0.8) | 0.65 | 26.1 (0.3) | 26.0 (0.5) | 26.8 (0.7) | 0.61 |
| BMI at age 18 years | 21.1 (0.2) | 21.4 (0.3) | 21.3 (0.2) | 21.2 (0.4) | 0.79 | 21.1 (0.2) | 21.3 (0.3) | 21.6 (0.4) | 0.39 |
| Physical activity in 1997 (METs/week) | 19.8 (4.6) | 18.3 (7.1) | 28.9 (5.9) | 13.7 (9.8) | 0.43 | 15.9 (3.9) | 34.3 (6.3) | 29.9 (9.4) | 0.02 |
| Age at menarche, years | 12.4 (1.4) | 12.5 (1.5) | 12.5 (1.5) | 12.7 (1.6) | 0.51 | 12.5 (0.07) | 12.5 (0.1) | 12.1 (0.2) | 0.12 |
| Alcohol intake in 1999 (grams/day) | 1.9 (0.07) | 2.3 (0.10) | 2.1 (0.09) | 2.1 (0.14) | 0.06 | 2.0 (0.06) | 2.1 (0.09) | 1.9 (0.14) | 0.28 |
| White race | 97.1% | 97.3% | 97.3% | 90.7% | 0.09 | 96.8% | 97.9% | 93.0% | 0.19 |
| Current smoking in 1999 | 30.8% | 36.6% | 45.8% | 53.3% | 0.0003 | 35.2% | 39.8% | 54.2% | 0.01 |
| Antidepressant use in 1999 | 10.0% | 9.5% | 7.1% | 26.1% | 0.0002 | 9.6% | 11.5% | 16.9% | 0.16 |
| >15 grams/day alcohol in 1999 | 4.2% | 7.4% | 5.0% | 5.3% | 0.59 | 4.3% | 9.0% | 1.7% | 0.03 |
| Mom > high school education | 34.8% | 30.4% | 23.56% | 24.3% | 0.05 | 30.6% | 27.3% | 32.2% | 0.69 |
| Dad > high school education | 40.8% | 35.6% | 27.0% | 38.2% | 0.02 | 36.9% | 33.1% | 38.7% | 0.62 |
| Moderate–severe physical abuse | | | | | | 30.3% | 45.9% | 47.0% | 0.0002 |
| Sexual abuse[b] | 23.4% | 33.1% | 35.8% | 58.5% | <0.0001 | | | | |

[a] All characteristics standardized by age at blood collection. M (SE) reported for all factors except age at blood draw, for which SD is reported.

[b] Includes unwanted touching and forced sex

## Table 2

Inflammatory Factors by History of Childhood and Adolescent Physical Abuse, Nurses' Health Study II, geometric M (95% CI)

| | | CRP (mg/L) | | | IL-6 (pg/mL) | | | sTNFR2 (pg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] |
| **Physical Abuse (child and/or adolescent)** | | | | | | | | | | |
| None | 328 | 0.70 (0.45, 1.07) | 0.74 (0.46, 1.27) | 0.64 (0.41, 1.02) | 1.12 (1.01, 1.24) | 1.05 (0.90, 1.23) | 0.96 (0.81, 1.12) | 955 (918, 994) | 944 (887, 1004) | 945 (884, 1009) |
| Mild | 126 | 0.69 (0.43, 1.11) | 0.74 (0.43, 1.26) | 0.70 (0.43, 1.14) | 1.10 (0.95, 1.26) | 1.02 (0.85, 1.22) | 0.97 (0.81, 1.16) | 1003 (952, 1057) | 991 (923, 1063) | 1004 (933, 1081) |
| Moderate | 186 | 0.72 (0.46, 1.11) | 0.74 (0.44, 1.25) | 0.63 (0.40, 1.01) | 1.12 (0.99, 1.27) | 1.05 (0.88, 1.25) | 0.98 (0.82, 1.17) | 997 (951, 1045) | 984 (919, 1052) | 994 (926, 1068) |
| Severe | 62 | 0.69 (0.40, 1.18) | 0.71 (0.39, 1.28) | 0.56 (0.33, 0.95) | 1.24 (1.03, 1.48) | 1.15 (0.93, 1.43) | 1.04 (0.85, 1.28) | 949 (885, 1018) | 940 (866, 1020) | 941 (865, 1023) |
| | | $p$=0.99 | $p$=0.98 | $p$=0.69 | $p$=0.68 | $p$=0.68 | $p$=0.76 | $p$=0.11 | $p$=0.14 | $p$=0.03 |
| **Physical Abuse (child)** | | | | | | | | | | |
| None | 355 | 0.69 (0.45, 1.06) | 0.75 (0.45, 1.26) | 0.64 (0.40, 1.01) | 1.11 (1.00, 1.23) | 1.04 (0.89, 1.22) | 0.95 (0.81, 1.12) | 952 (916, 990) | 939 (883, 999) | 940 (880, 1004) |
| Mild | 108 | 0.68 (0.43, 1.10) | 0.72 (0.42, 1.24) | 0.70 (0.43, 1.13) | 1.12 (0.96, 1.29) | 1.03 (0.85, 1.24) | 0.99 (0.82, 1.19) | 1016 (962, 1074) | 1002 (932, 1077) | 1017 (944, 1096) |
| Moderate | 182 | 0.73 (0.47, 1.13) | 0.75 (0.44, 1.26) | 0.62 (0.39, 1.00) | 1.13 (1.00, 1.27) | 1.05 (0.88, 1.25) | 0.98 (0.82, 1.16) | 995 (949, 1042) | 980 (916, 1048) | 987 (919, 1060) |
| Severe | 57 | 0.72 (0.42, 1.26) | 0.76 (0.41, 1.38) | 0.59 (0.35, 1.01) | 1.26 (1.04, 1.53) | 1.18 (0.95, 1.47) | 1.06 (0.86, 1.31) | 957 (890, 1030) | 945 (870, 1030) | 944 (866, 1029) |
| | | $p$=0.97 | $p$=0.99 | $p$=0.83 | $p$=0.61 | $p$=0.59 | $p$=0.64 | $p$=0.06 | $p$=0.07 | $p$=0.01 |
| **Physical Abuse (adolescent)** | | | | | | | | | | |
| None | 496 | 0.69 (0.46, 1.06) | 0.75 (0.45, 1.23) | 0.63 (0.40, 0.99) | 1.11 (1.01, 1.23) | 1.05 (0.90, 1.22) | 0.96 (0.82, 1.13) | 964 (929, 1000) | 949 (894, 1007) | 952 (892, 1016) |
| Mild | 94 | 0.74 (0.46, 1.19) | 0.77 (0.45, 1.33) | 0.71 (0.44, 1.14) | 1.04 (0.89, 1.21) | 0.97 (0.80, 1.18) | 0.92 (0.76, 1.11) | 1026 (968, 1088) | 1009 (936, 1087) | 1015 (940, 1097) |
| Moderate | 73 | 0.68 (0.41, 1.13) | 0.72 (0.41, 1.26) | 0.61 (0.37, 1.01) | 1.17 (0.98, 1.38) | 1.10 (0.90, 1.35) | 1.02 (0.84, 1.25) | 965 (904, 1030) | 950 (878, 1028) | 958 (882, 1040) |
| Severe | 41 | 0.74 (0.40, 1.35) | 0.77 (0.40, 1.50) | 0.54 (0.30, 0.97) | 1.44 (1.16, 1.79) | 1.34 (1.05, 1.72) | 1.19 (0.94, 1.50) | 1000 (920, 1086) | 984 (895, 1082) | 984 (895, 1083) |
| | | $p$=0.97 | $p$=0.99 | $p$=0.67 | $p$=0.06 | $p$=0.05 | $p$=0.11 | $p$=0.14 | $p$=0.16 | $p$=0.11 |

CRP, C-reactive protein; IL-6, interleukin-6; sTNFR2, soluble tumor necrosis factor receptor 2

[a] *n* for IL-6 and sTNFR2 analyses=702–704; total *n* for CRP=599–602; two women responded to question on adolescent abuse but not childhood abuse

[b] Adjusted for age (at blood draw) and control type (endometriosis control vs rheumatoid arthritis control)

[c] Additionally adjusted for confounders, including white race, somatotype at age 5 years, maternal education, and paternal education.

[d] Additionally adjusted for mediators, including BMI (1999), cigarettes smoked/day (1999), METs/week of physical activity (1997), alcohol intake (1999), crude fiber intake (1999), glycemic load (1999), antidepressant use (1999) and age at menarche.

**Table 3**

Inflammatory Factors by History of Childhood and Adolescent Sexual Abuse, Nurses' Health Study II, geometric M (95% CI)

| | CRP (mg/L) | | | | IL-6 (pg/mL) | | | sTNFR2 (pg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n*[a] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators *d* | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] |
| **Sexual Abuse (child and/or adolescent)** | | | | | | | | | | |
| none | 474 | 0.63 (0.42, 0.96) | 0.66 (0.40, 1.09) | 0.58 (0.37, 0.91) | 1.10 (1.00, 1.22) | 1.03 (0.88, 1.21) | 0.95 (0.81, 1.12) | 973 (937, 1010) | 959 (902, 1019 | 965 (903, 1031) |
| touching only | 159 | 0.75 (0.48, 1.16) | 0.78 (0.46, 1.32) | 0.67 (0.42, 1.06) | 1.10 (0.97, 1.24) | 1.04 (0.87, 1.24) | 0.96 (0.81, 1.15) | 973 (927, 1021) | 958 (894, 1027) | 968 (900, 1041) |
| forced sex | 69 | 0.91 (0.55, 1.49) | 0.92 (0.53, 1.59) | 0.76 (0.46, 1.24) | 1.34 (1.13, 1.59) | 1.25 (1.02, 1.53) | 1.12 (0.92, 1.37) | 988 (926, 1056) | 975 (901, 1056) | 972 (895, 1056) |
| | | *p*=0.08 | *p*=0.10 | *p*=0.12 | *p*=0.06 | *p*=0.08 | *p*=0.10 | *p*=0.89 | *p*=0.87 | *p*=0.97 |
| **Sexual Abuse (child)** | | | | | | | | | | |
| none | 562 | 0.65 (0.43, 0.99) | 0.68 (0.41, 1.13) | 0.59 (0.37, 0.93) | 1.11 (1.01, 1.22) | 1.05 (0.89, 1.22) | 0.96 (0.82, 1.13) | 965 (931, 1001) | 950 (895, 1009) | 955 (894, 1020) |
| touching only | 99 | 0.76 (0.48, 1.21) | 0.80 (0.47, 1.38) | 0.70 (0.43, 1.14) | 1.10 (0.95, 1.27) | 1.05 (0.86, 1.27) | 0.99 (0.82, 1.19) | 990 (935, 1048) | 975 (905, 1050) | 986 (912, 1065) |
| forced sex | 42 | 0.88 (0.51, 1.54) | 0.89 (0.49, 1.64) | 0.72 (0.42, 1.23) | 1.34 (1.09, 1.66) | 1.26 (0.99, 1.60) | 1.11 (0.88, 1.39) | 1039 (959, 1125) | 1023 (934, 1122) | 1011 (921, 1109) |
| | | *p*=0.26 | *p*=0.31 | *p*=0.25 | *p*=0.18 | *p*=0.21 | *p*=0.31 | *p*=0.15 | *p*=0.14 | *p*=0.20 |
| **Sexual Abuse (adolescent)** | | | | | | | | | | |
| None | 564 | 0.65 (0.43, 0.98) | 0.68 (0.42, 1.12) | 0.60 (0.39, 0.94) | 1.10 (1.00, 1.21) | 1.03 (0.88, 1.20) | 0.96 (0.82, 1.13) | 973 (939, 1009) | 958 (903, 1016) | 967 (906, 1031) |
| touching only | 99 | 0.89 (0.54, 1.45) | 0.92 (0.52, 1.62) | 0.69 (0.42, 1.14) | 1.14 (0.99, 1.33) | 1.07 (0.88, 1.30) | 0.96 (0.80, 1.16) | 981 (927, 1039) | 965 (896, 1040) | 959 (888, 1036) |
| forced sex | 40 | 1.01 (0.58, 1.76) | 1.02 (0.56, 1.88) | 0.84 (0.4, 1.45) | 1.46 (1.18, 1.82) | 1.36 (1.07, 1.74) | 1.22 (0.96, 1.55) | 972 (894, 1057) | 958 (872, 1053) | 954 (865, 1053) |
| | | *p*=0.03 | *p*=0.04 | *p*=0.15 | *p*=0.03 | *p*=0.03 | *p*=0.06 | *p*=0.95 | *p*=0.96 | *p*=0.92 |

CRP = C-reactive protein; IL-6 = interleukin-6; sTNFR2 = soluble tumor necrosis factor receptor 2

[a] *n* for IL-6 and sTNFR2 analyses= 702–704; total *n* for CRP = 599–602; two women responded to question on adolescent abuse but not childhood abuse

[b] Adjusted for age (at blood draw) and control type (endometriosis control vs rheumatoid arthritis control)

[c] Additionally adjusted for confounders, including white race, somatotype at age 5 years, maternal education and paternal education.

[d] Additionally adjusted for mediators, including BMI (1999), cigarettes smoked/day (1999), METs/week of physical activity (1997), alcohol intake (1999); crude fiber intake (1999); glycemic load (1999); antidepressant use (1999); and age at menarche.

**Table 4**

Inflammatory Factors by Combined History of Childhood and Adolescent Physical and Sexual Abuse, Nurses' Health Study II, geometric M (95% CI)

| | | CRP (mg/L) | | | IL-6 (pg/mL) | | | sTNFR2 (pg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n*[a] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] | Age-adjusted[b] | Adjusted for age and confounders[c] | Adjusted for age, confounders and mediators[d] |
| **Physical and Sexual Abuse (child)** | | | | | | | | | | |
| Neither | 441 | 0.66 (0.43, 1.02) | 0.71 (0.43, 1.19) | 0.64 (0.40, 1.01) | 1.10 (0.99, 1.21) | 1.03 (0.88, 1.21) | 0.95 (0.81, 1.12) | 962 (927, 999) | 947 (890, 1007) | 953 (891, 1018) |
| Physical abuse only[e] | 218 | 0.70 (0.45, 1.08) | 0.71 (0.43, 1.20) | 0.60 (0.38, 0.95) | 1.14 (1.01, 1.28) | 1.07 (0.90, 1.27) | 0.99 (0.83, 1.17) | 983 (940, 1029) | 968 (906, 1034) | 975 (909, 1046) |
| Forced Sex only | 22 | 0.89 (0.46, 1.72) | 0.93 (0.46, 1.86) | 0.76 (0.41, 1.39) | 1.31 (0.99, 1.73) | 1.25 (0.92, 1.68) | 1.10 (0.83, 1.45) | 1065 (957, 1187) | 1051 (936, 1180) | 1030 (919, 1155) |
| Physical abuse and Forced Sex | 20 | 0.89 (0.42, 1.86) | 0.88 (0.40, 1.93) | 0.72 (0.90, 1.43) | 1.39 (1.03, 1.87) | 1.27 (0.92, 1.75) | 1.11 (0.82, 1.51) | 1010 (901, 1133) | 993 (878, 1124) | 986 (871, 1117) |
| *p* for difference in means[f] | | 0.62 | 0.74 | 0.74 | 0.28 | 0.32 | 0.46 | 0.20 | 0.20 | 0.34 |
| *p* for interaction[g] | | 0.90 | 0.90 | 0.98 | 0.90 | 0.94 | 0.91 | 0.35 | 0.34 | 0.39 |
| **Physical and Sexual Abuse (adolescent)** | | | | | | | | | | |
| Neither | 568 | 0.68 (0.45, 1.03) | 0.71 (0.43, 1.16) | 0.61 (0.39, 0.96) | 1.10 (1.00, 1.21) | 1.02 (0.88, 1.19) | 0.95 (0.81, 1.11) | 977 (943, 1013) | 961 (906, 1020) | 967 (906, 1031) |
| Physical abuse only[e] | 95 | 0.66 (0.40, 1.06) | 0.68 (0.39, 1.18) | 0.58 (0.36, 0.95) | 1.19 (1.02, 1.38) | 1.11 (0.92, 1.35) | 1.04 (0.86, 1.25) | 970 (915, 1028) | 954 (866, 1028) | 963 (892, 1040) |
| Forced Sex only | 22 | 0.96 (0.50, 1.84) | 1.03 (0.51, 2.07) | 1.07 (0.57, 2.01) | 1.24 (0.93, 1.64) | 1.16 (0.86, 1.57) | 1.12 (0.84, 1.51) | 913 (819, 1017) | 899 (799, 1011) | 898 (796, 1014) |
| Physical abuse and Forced Sex | 18 | 1.07 (0.51, 2.25) | 0.99 (0.45, 2.16) | 0.60 (0.30, 1.20) | 1.81 (1.32, 2.48) | 1.66 (1.18, 2.31) | 1.35 (0.97, 1.86) | 1055 (934, 1191) | 1040 (913, 1183) | 1031 (903, 1178) |
| *p* for difference in means[f] | | 0.33 | 0.41 | 0.16 | 0.02 | 0.01 | 0.04 | 0.34 | 0.35 | 0.39 |
| *p* for interaction[g] | | 0.74 | 0.99 | 0.18 | 0.17 | 0.22 | 0.68 | 0.07 | 0.08 | 0.10 |

CRP = C-reactive protein; IL-6 = interleukin-6; sTNFR2 = soluble tumor necrosis factor receptor 2

[a] *n* for IL-6 and sTNFR2 analyses = 702–704; total *n* for CRP = 599–602; two women responded to question on adolescent abuse but not childhood abuse

[b] Adjusted for age (at blood draw) and control type (endometriosis control vs rheumatoid arthritis control)

[c] Additionally adjusted for confounders, including white race, somatotype at age 5 years, maternal education and paternal education.

[d] Additionally adjusted for mediators, including BMI (1999), cigarettes smoked/day (1999), METs/week of physical activity (1997), alcohol intake (1999), crude fiber intake (1999), glycemic load (1999), antidepressant use (1999) and age at menarche.

[e] Physical abuse rated as moderate or severe

[f] *p*-value comparing geometric means across four categories

[g] *p*-value for multiplicative interaction term from linear model including dichotomous terms for moderate–severe physical abuse (v. none or mild) and forced sex (vs none or unwanted touching).