# Childhood Abuse and Elevated Markers of Inflammation in Adulthood: Do the Effects Differ Across Life Course Stages?

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## Abstract

Research indicates that victims of childhood abuse have an increased risk of developing immune-related disorders in adulthood. Elevated markers of inflammation under stressful conditions have been considered as a plausible explanation for the high prevalence of such disorders among victims. Most studies related to health disparities have focused on the effects of SES differences on health outcomes, but little research has investigated whether the effects of early life adversity on inflammatory markers vary across age groups. Guided by life course and selective mortality approaches, this study investigates the associations between childhood abuse and inflammatory markers in adulthood and the extent to which the effects of childhood abuse on inflammatory markers vary over the life course. Moreover, this study evaluates the extent to which these associations are mediated by four plausible pathways: sleep problems, body mass index (BMI), perceived stress, and family social ties. Data come from a biomarker study of the National Survey of Midlife Development in the United States (MIDUS, n = 1,255). I use three inflammatory biomarkers: interleukin (IL)-6, C-reactive protein (CRP), and fibrinogen. To test the selective mortality hypothesis, I consider both all-cause mortality and attrition between the surveys of MIDUS I and MIDUS II. Using latent class analysis, I identify five distinct profiles of childhood abuse. To assess the age-related patterns of inflammatory markers associated with the experience of childhood abuse, the five abuse groups are categorized into two groups: no abuse and abuse. I find significant main effects and age-by-abuse interaction effects on inflammatory markers. In the younger age groups (ages 34-44 and 45-54), victims of childhood abuse have elevated markers of inflammation for all three biomarkers, compared to non-victims. Yet, there are no significant effects of childhood abuse on elevated markers of inflammation in the older age groups (ages 55-64 and 65-84). Victims of childhood abuse, compared to non-victims, have greater mortality and attrition rates between MIDUS I and MIDUS II, suggesting selective mortality might contribute to a reduced gap in the markers of inflammation between the victims and non-victims in the older age groups. High BMI, poor sleep quality, and weak family social ties partially explain why the experience of childhood abuse increases the levels of inflammatory markers. High BMI, in particular, is the most significant mediator for all the inflammatory biomarkers. My findings highlight the importance of life course stages in understanding the effects of childhood abuse and its adverse health consequences. Targeted interventions to prevent the consequences of childhood abuse need to be started at an early age in order to help reduce the risk that individuals will develop chronic diseases through elevated markers of inflammation in adulthood.

**Keywords**

stress; childhood abuse; inflammation; age; sleep problems; body mass index; social ties; perceived stress

## Introduction

A life course perspective on health emphasizes the importance of early life experiences in the development of chronic diseases in adulthood (Kuh et al. 2003). Numerous studies have indicated that traumatic stress in early life, such as childhood abuse, increases the risk of developing various chronic diseases. Both clinic- and population-based studies have reported that victims of childhood abuse are particularly susceptible to developing disorders, such as allergies and asthma (Felitti et al. 1998; Lanier et al. 2010), autoimmune disorders (Dube et al. 2009), and osteoarthritis (Fuller-Thomson et al. 2009). Stress-induced immune dysfunction and unregulated inflammation may explain the elevated risk of developing these types of diseases among victims of childhood abuse. Chronic stress and/or traumatic stress interfere with the activation of the parts of the brain which are associated with the secretion of the stress hormone cortisol, one of the most important anti-inflammatory hormones. Abnormal cortisol levels, due to chronic and/or traumatic stress, can lead to a high concentration of inflammation biomarkers, such as interleukin (IL)-6 and C-reactive protein (CRP) in the body (Kiecolt-Glaser et al. 2003). Elevated inflammation levels play important roles in developing various chronic diseases (e.g., cancer and cardiovascular diseases) and in increasing the mortality rate (Danesh et al. 1998; Harris et al. 1999).

An emerging body of research has demonstrated the associations between early life adversities (e.g., childhood abuse and living with a substance abuser) and elevated markers of inflammation in both young adulthood (Danese et al. 2007; Taylor et al. 2006) and midlife (Slopen et al. 2010). The associations are consistently significant even after controlling for potential confounders and mediators (e.g., demographics, socioeconomic status [SES]). While timely public interventions play a major role in reducing health inequalities and may decrease the overall cost of care, few researchers have studied whether the effect of childhood abuse on physiological dysregulation (e.g., inflammation) varies over the life course.

Selective mortality and "age-as-leveler" theories suggest that differences in health status by SES are the largest at middle age and converge in later years, perhaps due to premature death among individuals of lower SES or due to biological fragility among old people regardless of their SES (House et

al. 2005). Similarly, disparities in levels of inflammatory markers between victims and non-victims of childhood abuse might be narrower with age. Victims of childhood abuse, compared to non-victims, are less likely to achieve higher SES (Currie and Widom 2010), and they are more likely to experience subsequent negative life events (e.g., incarceration) (Widom and Maxfield 2001). Given these cumulative life burdens and physiological loads, victims of childhood abuse, compared to non-victims, might have elevated markers of inflammation at earlier ages and may die younger. Accordingly, disproportionate attrition rates due to illness and premature death might eventually reduce the gap in levels of inflammatory markers between victims and non-victims of childhood abuse in old age.

In addition, psychological and behavioral factors might contribute to understanding the association between childhood abuse and elevated markers of inflammation. The literature documents that unhealthy conditions, including poor sleep quality (Friedman et al. 2005a), elevated perceived stress (McDade et al. 2006), high body weight (Visser et al. 1999), and small social networks (Loucks et al. 2006), are particularly associated with a high concentration of inflammatory markers in the body (Kiecolt-Glaser et al. 2003). Victims of childhood abuse are more likely to experience these unhealthy conditions (Bentley and Widom 2009; Danese et al. 2009; Gotlib and Wheaton 1997; Greenfield et al. 2011). Although previous research on childhood abuse and inflammation (Danese et al. 2009; Slopen et al. 2010) has included some of these factors as either mediators or controls, to my knowledge no research has studied the extent to which sleep quality and the quality of adult social relationships are potential mediators that link childhood abuse to levels of inflammatory markers. Additionally, most prior studies that link childhood abuse to elevated markers of inflammation are limited to samples consisting of young adults. Further research is needed to understand the diverse mechanisms in older adults.

Using data from the National Survey of Midlife Development in the U.S. (MIDUS), my study aims to address three issues which have not been fully investigated in prior studies. First, I investigate the effects of childhood abuse on levels of inflammatory markers in midlife and beyond. I also test whether the effects of childhood abuse decrease in magnitude, or even disappear, with an increase in age. Finally,

I examine multiple pathways which might connect childhood abuse to levels of inflammatory markers in adulthood.

## Background

According to a life course perspective on chronic disease, childhood experiences play an important role in the development of adult diseases (Kuh et al. 2003). Research has demonstrated that individuals who experience adversities in childhood (e.g., poverty, family violence) have an increased risk of developing various chronic diseases, such as psychological disorders, cardiovascular diseases, diabetes, and cancer. In particular, victims of childhood abuse, compared to non-victims, have an elevated risk of developing such chronic diseases even after controlling for poor family environments in childhood (Springer 2009). Both clinic- and population- based studies have indicated that victims of childhood abuse are especially vulnerable to certain types of diseases over the life course, such as asthma in childhood (Lanier et al. 2010), autoimmune diseases in adulthood (Dube et al. 2009), and multiple sclerosis in adulthood (Spitzer et al. 2012). These types of diseases are directly or indirectly related to altered immune function, such as abnormally enhanced or prolonged inflammation, in response to stressful conditions. This evidence raises a question: how does the experience of childhood abuse influence the immune system and ultimately increase susceptibility to such diseases?

### *Stress and Inflammation*

According to theories related to stress and immunity, psychological stress and negative emotions can alter activities in important brain structures, including the hippocampus and amygdala; the hippocampus is related to the intake and interpretation of sensory stimuli while the amygdala is associated with the generation of emotions based on appraisals (Lovallo 2005). Through these mechanisms, stress stimulates two brain systems, the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) axis, which release diverse stress hormones, for example, adrenocorticotrophine (ACTH) and cortisol (Lovallo 2005). These hormones ultimately influence immune function in two different ways: 1) by directly interacting with immune cells which have stress hormone receptors and 2)

by indirectly inducing the production of cytokines (Glaser and Kiecolt-Glaser 2005). Thus, the regulation of stress hormones plays a role in controlling immune functions, including the inflammatory process.

Generally, inflammation is a series of processes that fight against the invasion of viruses or bacteria, detecting invading pathogens, accumulating white blood cells at the site of infection, eliminating the pathogens, and repairing tissue damage. The entire process is orchestrated by inflammatory cytokines (e.g., interluekin-1ß, IL-6, tumor necrosis factor-α), which are molecules secreted by white blood cells. However, without regulation, healthy tissues are damaged by the secretion of massive amounts of inflammatory cytokines; extreme levels of cytokines can even be lethal (e.g., toxic shock syndrome) (Lovallo 2005).

Animal studies show that secretion of the stress hormone cortisol is associated with inflammatory response. After a prolonged period of hyperactivity of the HPA axis, due to chronic or extreme stress, the HPA axis becomes prone to "down-regulate" in response to stress (Gómez et al. 1996), and this hypo-activity of the HPA axis results in the secretion of lower levels of stress hormones (Moncek et al. 2001), which eventually leads to the development of severe chronic inflammation of the joints, such as arthritis (Sternberg et al. 1989). These findings suggest that unregulated inflammation occurs under extreme stress through the dysregulation of stress hormones.

Moreover, research documents significant associations between life stress and altered immune function in humans. The experience of chronic stress and/or negative life events is significantly associated with elevated levels of inflammatory cytokines. For example, older adults who take care of spouses with dementia display increased levels of interleukin (IL)-6, one of the well-known cytokines that increases inflammatory processes (Kiecolt-Glaser et al. 2003). Another study shows that parents who have been caring for children with cancer display a diminished suppression of IL-6 in a glucocorticoid sensitivity test, which suggests that chronic stress might impair some immune functions through cortisol dysregulation (Miller et al. 2002). Childhood abuse has also been implicated in these associations.

### *The Associations between Childhood Abuse and Elevated Markers of Inflammation*

Studies show that there are significant associations between early life adversities and elevated levels of single and/or multiple inflammatory markers, including IL-6, CRP, and fibrinogen in adulthood. For example, a prospective longitudinal study shows that childhood abuse and neglect are significantly associated with increased levels of inflammation markers (CRP and fibrinogen) in young adulthood (age 32 years); the association between childhood abuse and high sensitive CRP levels remains significant, even after accounting for potential confounders, including early life risks (low birth weight and childhood SES), perceived adult stress, adult health, and health behaviors (Danese et al. 2007). A study, based on a retrospective report of early life adversities, shows that low SES and harsh family environments in childhood (e.g., living with a substance abuser and/or experiencing physical and/or emotional abuse) are significantly related to elevated CRP in young adulthood (average age 40) through pathways involving psychological problems and a high body mass index (BMI) (Taylor et al. 2006).

Another retrospective study indicates that experiencing more stressors throughout childhood and adolescence (e.g., abuse, poverty, dropping out of school, parental alcoholism) is associated with higher levels of multiple inflammatory markers (e.g., IL-6, CRP, fibrinogen) in midlife (average age 56) for African Americans but not for Whites. The significant effects of early life adversities on the elevated markers of inflammation among African Americans either is reduced or disappears after accounting for several factors encountered throughout adulthood, including stressful life events, health conditions, and risky health behaviors (Slopen et al. 2010), suggesting that later negative life events and unhealthy habits in adulthood contribute to part of the association between childhood abuse and levels of inflammatory markers. These three studies show important evidence of the associations between childhood abuse and inflammation, yet, Danese et al. (2007) and Taylor et al. (2006) are limited to a sample which includes only young adults and Slopen et al. (2010) and Taylor et al. (2006) use multiple generic adversities in childhood as a predictor. It is important to replicate these studies using a sample of individuals with different ages and to disentangle the effects of childhood abuse on inflammation from the effect of other childhood adversities (e.g., poverty). Thus, the first hypothesis I test is:

**Hypothesis 1**: The experience of childhood abuse will be associated with elevated levels of inflammatory markers among adults (ages 34-84), even after controlling for adverse childhood environments.

*Do the Effects of Childhood Abuse on Elevated Markers of Inflammation Vary over the Life Course?*

Little research has paid attention to whether the effects of childhood abuse on elevated markers of inflammation are consistent across different age groups. Research indicates that elevated levels of inflammation predict an increased risk of morbidity (Danesh et al. 1998) and mortality (Alley et al. 2007). Therefore, because individuals who were abused during childhood have elevated markers of inflammation, they are at increased risk of death, which might eventually lead to decreasing age variations in the gap of levels of inflammatory markers between victims and non-victims of childhood abuse across the life course. Selective mortality theory helps us to understand the potential age patterns of the effects of childhood abuse on levels of inflammatory markers. According to this hypothesis, differences in health status by SES are the largest at around middle age and then are narrowed in old age or disappear in later old age (Crimmins et al. 2009; House et al. 2005). In other words, health and mortality differentials at earlier ages lead to a nonrandom selection by SES, which eventually results in a decrease in health inequality in later life. Thus, some of the victims of childhood abuse who were exposed to several negative events and who have low SES and weak social ties might have a greater risk of premature death, which might eventually reduce the differences in inflammation levels between victims and non-victims of childhood abuse in old age. Thus, I would suggest a second two-fold hypothesis:

**Hypothesis 2a**: Disparities in levels of inflammatory marker between victims and non-victims of childhood abuse will narrow with increasing age.

**Hypothesis 2b**: Victims of childhood abuse, compared to non-victims, will have greater attrition rates due to death, which may explain why the gap in levels of inflammatory markers between victims and non-victims diminishes in old age.

*Psychosocial and Behavioral Pathways Linking Childhood Abuse and Elevated Markers of Inflammation*

Numerous studies have documented that victims of childhood abuse have a greater chance of having various unhealthy conditions and engaging in unhealthy behaviors, which are known risk factors for elevated markers of inflammation. Based on the literature, I consider four plausible psychosocial and behavioral pathways linking childhood abuse to elevated markers of inflammation: sleep quality, perceived stress, body mass index, and family social ties.

First, *poor sleep quality*, which is common among victims of childhood abuse (Greenfield et al. 2011), increases levels of inflammatory markers for both healthy and unhealthy individuals over different ages. For instance, people with obstructive sleep apnea, a sleep disorder characterized by abnormal pauses in breathing or instances of abnormally low breathing during sleep, tend to have elevated CRP levels (Shamsuzzaman et al. 2002). In healthy young women, self-reported poor sleep quality is associated with increased levels of CRP, but there is no significant association between poor sleep quality and IL-6 (Okuna et al. 2009). For women aged 61-90, poor sleep quality is significantly associated with elevated levels of IL-6 (Friedman et al. 2005a). Accordingly, individuals with a history of childhood abuse might have elevated markers of inflammation due to trouble sleeping, yet to my knowledge no prior study investigates the extent to which sleep problems mediate the association. Following from these prior findings, I propose a first hypothesis related to these plausible pathways:

> **Hypothesis 3a**: Poor sleep quality will mediate the positive association between childhood abuse and elevated levels of inflammatory markers.

Second, high levels of *perceived stress* might link the experience of childhood abuse to elevated levels of inflammatory markers. Research indicates that long-term caregivers (ages 55 to 89), who take care of spouses who have dementia, report significantly more perceived stress and loneliness than non-caregivers, and they have elevated levels of IL-6 compared to their counterparts (Kiecolt-Glaser et al. 2003). Another study indicates that more perceived stress is significantly related to elevated levels of CRP

in middle-aged and older adults (ages 52 to 72), even after accounting for demographic characteristics and health behaviors (McDade et al. 2006).

Individuals who were abused during childhood appear to experience high levels of stress in adulthood (Hyman et al. 2007). Research indicates that individuals who are exposed to adverse circumstances in early life have a greater risk of being exposed to additional adversities in later life, namely stress proliferation (Pearlin et al. 2005), which might increase sensitivity to stressful situations and cause elevated markers of inflammation. Danese et al. (2007) find that the experience of childhood abuse predicts both increased levels of CRP and high levels of perceived stress for young adults (average age of 32). Yet, perceived stress does not operate as a significant mediator in the association between childhood abuse and increased levels of CRP for these young adults when demographic characteristics (e.g., SES, gender) and medications are accounted for (Danese et al. 2007). Since negative life events and stress accumulate with age, it is necessary to replicate the Danese et al. (2007) study in older populations. Thus, I hypothesize a second mediating association:

> **Hypothesis 3b**: High perceived stress will mediate the positive association between childhood abuse and elevated levels of inflammatory markers.

Third, *BMI* is significantly associated with elevated markers of inflammation. Research finds that obese people are more likely to be in a state of chronic inflammation, as indicated by elevated inflammatory markers, such as IL-6 and CRP (Dandona et al. 2004). For example, young adults (age 17-39) who are overweight or obese are more likely to have elevated CRP levels than those who have healthier body weights (Visser et al. 1999). A prior study finds that BMI mediates the association between early life adversity (e.g., childhood abuse) and elevated markers of inflammation (e.g., IL-6) for African Americans in midlife (Slopen et al. 2010). Another study finds that early life adversity (e.g., physical and emotional abuse) appears to be significantly associated with elevated CRP through high BMI (Taylor et al. 2006). These studies show that experiencing multiple early life stressors is

significantly associated with elevated markers of inflammation through high BMI, yet it is hard to specify which form(s) of early stressors play(s) a significant role in increasing inflammation.

Research shows that victims of childhood abuse have an increased risk of being overweight and obese after controlling for early life environments, negative coping skills, and unhealthy habits (Bentley and Widom 2009). Thus, individuals who experienced childhood abuse, regardless of other early life adversities (e.g., poverty), might have elevated markers of inflammation due to uncontrolled body weight. Accordingly, I hypothesize a third mediating association:

> **Hypothesis 3c**: High BMI will mediate the positive association between childhood abuse and elevated levels of inflammatory markers.

Finally, the stress-buffering hypothesis (Cohen and Wills 1985) indicates that strong or high-quality social ties operate as protectors from the potential pathogenic effects of stressful life events. That is, strong social ties and support mitigate the effects of stressful events on perceived stress and helps individuals utilize positive coping skills and health-promoting behaviors in order to relieve stress (Cohen 2004). Studies find that poor emotional relationships and social isolation are associated with elevated markers of inflammation. For example, for women in midlife and old age, a high degree of social engagement buffers the effect of poor sleep quality on elevated markers of inflammation, decreasing levels of IL-6 (Friedman et al. 2005a). Another study shows that for both men and women in midlife (average age 62), the size of their social network, measured by the Berkman–Syme Social Network Index (Berkman and Syme 1979), is inversely associated with levels of inflammatory markers (e.g., IL-6); the association remain significant for men but not for women even after adjusting for potential confounders (e.g., BMI and SES) (Loucks et al. 2006). Individuals with a history of childhood abuse, in general, may have insufficient social resources (e.g., poor marital quality and social isolation) (Gotlib and Wheaton 1997) that might further increase their vulnerability to stressful situations. In contrast, sufficient social ties and the utilization of social resources may operate as countervailing factors protecting against life's stressors even for victims of childhood abuse and may help them avoid having elevated markers of

inflammation. Based on extensive evidence in the literature, I propose a final hypothesis for the mediating associations:

> **Hypothesis 3d**: Strong social ties will attenuate the positive association between childhood abuse and levels of inflammatory markers.

## Data and Methods

### *Sample*

The sample for my study (n=1,255) comes from two subsamples of the Midlife Development in the United States (MIDUS) biomarker study: one from the respondents who participated in both the MIDUS I (1995-1996) and MIDUS II (2004-2005) surveys, and the other from a supplementary sample of African Americans from Milwaukee, Wisconsin (2004-2005), called the Milwaukee sample. The data for the biomarker study came from a two-day data-collection protocol at the General Clinical Research Center (GCRC). The data were collected between 2004 and 2009. Participants stayed overnight at the GCRC and completed the protocol with a clinician. This special module includes diverse biomarkers and a detailed medical history as well as more comprehensive questions regarding childhood abuse than those in MIDUS I. The data collection for MIDUS was approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison.

MIDUS is a national study of health and aging among U.S. residents, aged 25 to 74 (b. 1920-1970), who were first interviewed between 1995 and 1996 (n = 7,108). The baseline study included a national sample, which was obtained through random digit dialing (RDD), and consists of respondents, siblings of many respondents (13% of the MIDUS I sample), and a national sample of twins (24% of the MIDUS I sample) of the same age range as the national RDD sample. Respondents were limited to English speaking, non-institutionalized adults. A longitudinal follow-up of the MIDUS sample was conducted 10 years after the baseline assessment (2004-2005). At that point, a supplemental sample of 592 African Americans from Milwaukee, Wisconsin was recruited in order to investigate health in a highly segregated U.S. city. MIDUS II assessed a wide array of psychological constructs and

demographic characteristics as well as extensive health measures. Based on the primary survey, four additional projects (Daily Diary Study, Cognitive Function, Bioindicators, and Neuroscience) were conducted to explore the biopsychosocial pathways to various health outcomes (Love et al. 2010).

Of those who initially responded to the questions in the MIDUS I, 70% were interviewed in the MIDUS II and 21% of the MIDUS II sample (n =1,054) and 39 % of Milwaukee sample (n = 201) attended the clinical examination, resulting in a total of 1,255 respondents. Compared to the respondents in the primary national sample (MIDUS I), those in this subsample had higher levels of education and personal income, visited doctors more frequently, and maintained an overall healthier life style (e.g. non-smokers). They were, however, similar to the other respondents in terms of demographic (e.g., age, gender, and marital status) and health characteristics (for a more detailed description of the study, consult Love et al. 2010).

***Measures***

***Dependent Variables.*** On the basis of prior research on inflammatory markers, I select three of the commonly used biomarkers for inflammation (IL-6, CRP, and fibrinogen) and the summary of these markers, called the inflammatory index. CRP and fibrinogen are molecules produced in the liver in response to IL-6 (Friedman and Herd 2010). Like IL-6, high levels of CRP and fibrinogen are clinical signals of elevated risk of inflammation in the body (Danesh et al. 1998). Fasting serum samples are assayed for CRP, IL-6, and fibrinogen, based on the manufacturer guidelines (Dade Behring Inc., Deerfield, IL for CRP and fibrinogen; R&D Systems, Minneapolis, MN for IL-6). Immunonephelometric assay is performed for the citrated plasma CRP and fibrinogen assay and enzyme-linked immunosoben assay is performed for the IL-6 assay. For all three inflammation markers, the laboratory intra- and inter-assay coefficients of variance are in acceptable ranges (< .13%) (Ryff et al. 2010). IL-6 (*mean* = 3.04; SD = 3.04; *skewness* = 3.32) and CRP (*mean* = 3.02; SD = 4,02; *skewness* = 5.78) are log-transformed to improve the normality of the distribution, which is consistent with prior studies (Danese et al. 2007; Slopen et al. 2010). The inflammatory index is a summary of the high risk cut offs of the three inflammatory markers and ranges from 0 to 3: CRP (≥ 3.0 mg/L), fibrinogen ( ≥ 341 mg/dL for men and

≥ 411 mg/dL for women) and the top quartile of the IL-6 level distribution ( > 3.47pg/dL). Tetrachoric correlations between these three markers range from .49 to .57. Research indicates that top 25% of IL-6 and high CRP ( ≥ 3.0 mg/L) are associated with mortality in the elderly (age 65+) (Harris et al. 1999) and coronary health disease for all adults (Danesh et al. 1998).

***Independent Variable.*** *Childhood abuse history***.** Childhood abuse is used as a key indicator of traumatic stress during childhood. The Childhood Trauma Questionnaire (CTQ; Bernstein and Fink 1998) is used to evaluate the severity of physical, emotional, and sexual abuse up to the age of 16. The CTQ is a well-validated questionnaire that contains 25 items divided among five subscales to assess the three different types of abuse (physical, emotional, and sexual) and two different types of neglect (physical and emotional). It also includes a three-item scale for minimization and denial to identify respondents who are more likely to underreport negative events in childhood (e.g., "I had the best family in the world"). Respondents answered questions about childhood abuse/neglect and minimization/denial, which were measured on a scale ranging from 1 = "never true" to 5 = "very often true". Based on the 15 CTQ items, including the three types of abuse, and on the composite score from the three minimization/denial items, I conduct latent class analysis (LCA) and create five classes of childhood abuse history (for details about latent classes of childhood abuse, see Chapters 2 and 3). Since the sample size is too small to test the age-by-abuse interaction effects for all the LCA classes, I create a dichotomous measure of childhood abuse: *no abuse* (65%) vs. *abuse* (35%) including the four abuse classes from the LCA (see note 2).

***Psychosocial and Behavioral Mediators.*** *Sleep Quality.* The Pittsburgh Sleep Quality Inventory (Buysse et al. 1989), which is one of the most widely used subjective sleep quality scales of measurement based on respondents' self-reports, is used to evaluate sleep difficulties. This includes seven sleep components: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbance, 6) use of sleep medications, and 7) daytime dysfunction. The response to items for each component ranges from 0 to 3, with the higher scores indicating poorer subjective sleep quality. I use a summary index of the seven sleep components as a measure of sleep quality, ranging from 0 to 21, which is consistent with the measures used in prior studies (Friedman et al. 2005a; Okuna et al. 2009).

*Body Mass Index* (BMI) is based on the data (body weight (kg)/ [height (m)]$^2$) measured by the GCRC staff. BMI is used as a continuous variable (*Mean* = 29.77; SD = 6.62), which is consistent with prior studies (Slopen et al. 2010; Taylor et al. 2006). The 10-item *perceived stress* scale (Cohen et al. 1983) assesses the degree to which participants were consciously aware that their daily lives were unpredictable, uncontrollable, and overloaded with life stress during the week prior to the interview. Participants rated each item from never (=1) to very often (=5). A composite scale score of the 10 items ranges from 10 to 50, a higher score indicating higher levels of perceived stress (*Mean* = 22.24; SD = 6.36; alpha =.86). *Family social ties,* which does not include spouse/partner, is a 6-item scale combining the two items about "support given to family" (family rely on respondents for help with serious problems and family discuss their worries with respondents), and four items about "strain given to family" (making too many demands on family, criticizing family members, letting family down when they are counting on respondents, and getting on family's nerves). The 6 items are coded consistently, with a high score signifying high levels of "family affectual solidarity" (1 = not at all through 4 = a lot). The scale of family social ties is constructed by calculating the mean of the values of the 6 items ranging from 1 to 4 (*Mean* = 3.43; SD = .37). I did not include strain or support given to a spouse/partner as a part of family social ties since 35% of respondents did not have a spouse/partner (31% of non-victims and 43% of victims). Prior studies indicate that strong social ties are associated with health-promoting behaviors and positive health outcomes (Grzywacz and Marks 1999; Kawachi and Berkman 2001).

***Control Variables.*** To thoroughly test and describe age variation in the effect of childhood abuse on inflammation, I use two different measures of the ages of the respondents at the time of MIDUS II (34-84 years old): a linear covariate for testing the age-by-abuse interaction effect and a categorical variable (ages 34-44, 45-54, 55-64, and 65-84) for better visualizing the age-by-abuse interaction effect. The first age category (ages 34-44) is made up in order to compare findings in the current study and those in prior studies on early life adversities in young adulthood (Danese et al. 2009; Taylor et al. 2006). The second and third categories (ages 45-54 and ages 55-64) are selected based on a prior study based on the selective mortality hypothesis (Robert et al. 2009). Given a small sample size for older people (age 65+),

particularly for victims of childhood abuse (14% of the sample), the fourth category of age consists of all respondents who are age of 65 or older.

In order to disentangle the effects of childhood abuse on inflammation from other early life adversities and potential confounders, this study includes five sets of covariates: demographic characteristics, such as SES and marital status (Friedman and Herd 2010; Loucks et al. 2006; O'Connor et al. 2009), childhood environment (Slopen et al. 2010), chronic diseases (Alley et al. 2007), as well as medications, which are significantly related to inflammation markers. Demographic variables include gender (1 = female), race/ethnicity (white/non-white) and current marital status (married/cohabiting = 1 vs. separated, divorced, widowed, or never married = 0) at the time of the Bioindicators assessment. SES is assessed by the participants' educational attainment (less than high school [reference], high school, college, more than maters' degree).

For the childhood contexts, I use the highest level of parental (mother's or father's) education (less than high school [reference], high school, more than high school), whether the respondents lived with both their biological parents until the age of 16 (yes/no), and whether the family was on welfare or Aid to Dependent Children (ADC) during childhood (yes/no).

History of chronic disease indicates whether the respondents have experienced a stroke or have either diabetes or cancer (yes/no). I include the use of four types of medication: blood pressure medication (yes/no), cholesterol-lowering medication (yes/no), steroids (yes/no), and antidepressants (yes/no), as inventoried by the GCRC staff. I adjust for use of these medications based on research showing the effect of these medications on circulation of inflammatory markers

***Attrition.*** To assess the selective mortality hypothesis, I make two dichotomous indicators of attrition rates: all causes of attrition (yes/no) and all causes of mortality (yes/no), to examine whether the abused survivors were more likely than the non-abused respondents to fail to participate in the 2004 survey (MIDUS II) (see note 1). These two indicators are consistent with a prior study regarding non-random attrition for victims of childhood abuse (Springer 2009). I use self-reported mental health, physical health, demographics, and childhood contexts as controls for the attrition test.

***Analytic Strategy***

After the LCA of childhood abuse, analyses are carried out in four stages: 1) bivariate analyses for characteristics of victims and non-victims of childhood abuse; 2) multivariate analyses in order to test the age-by-abuse interaction effects; 3) mediation modeling to identify potential mediators; and 4) supplementary analyses to test the selective mortality hypothesis.

In order to carry out subsequent analyses, in the first stage, I conduct bivariate analyses to evaluate whether the childhood abuse groups differ in potential mediators and controls. In the second stage, to examine the age variations in the associations between childhood abuse and inflammation outcomes, I first test the main effects of childhood abuse on each inflammation marker after adjusting for all controls. Second, I include the interaction term between childhood abuse and the linear measure of age. To understand the pattern of the effects of childhood abuse on inflammation by age, I graph the mean values of each individual inflammation maker within the abuse groups and the four age groups (ages 34-44, 45-54, 55-64, and 65-84) with a 95% confidence interval (CI). Multivariate ordinary least squares (OLS) and zero-inflated Poisson regression are used to determine the associations between childhood abuse and linear inflammatory markers (logged IL-6, logged CRP, and fibrinogen) and a count measure of the inflammatory index, respectively.

In the third stage, I test the effects of potential mediators (Baron and Kenny 1986), examining the extent to which each mediator significantly accounts for the association between childhood abuse and risk of elevated inflammation levels. The four sets of mediators enter into the model, separately. To check whether the mediators carry the effects of childhood abuse to elevated markers of inflammation, I use a Sobel test (Sobel 1982). Finally, in case there are significant age-by-abuse interaction effects on inflammatory markers, I conduct a supplementary analysis for a selective mortality hypothesis to investigate whether abused respondents were more likely than non-abused ones to fail to participate in the 2004 survey (MIDUS II) and whether the higher attrition rates of abused individuals are due to mortality.

The percentage of missing data is less than 13 percent when I apply listwise deletion. I impute the missing data under the missing-at-random (MAR) assumption (Allison 2001) in order to alleviate the

potential statistical power issues in subsequent analyses. All variables, except the dependent variables and a mediator (social support from family, missing n = 6), are included in the imputation procedure. The analyses are carried out using Mplus 6.0 (Muthén and Muthén 2008; Muthén and Muthén 2010) and STATA 11.0 (STATA Corp, 2010). To correct intra-class correlation due to some respondents being from the same family (e.g., twins or siblings, 12.61% in the biomarker study), I apply robust standard error estimation.

## Results

### *Characteristics of Abuse and No Abuse Respondents*

Table 1 summarizes the results of the bivariate analyses for the characteristics of the abuse group (35% of the respondents) and no-abuse group (65% of the respondents). Individuals with a history of childhood abuse, compared to those who did not experience it, are younger ($Mean_{abuse} = 51.89$ vs. $Mean_{no\ abuse} = 55.93$); there are significant age variations in the two groups. In particular, the individuals who are between 65 and 84 make up 25% of the no-abuse group, while individuals between these ages represent 14% of the abuse group, suggesting there might be a non-random selection bias due to the experience of childhood abuse or cohort differences in reporting rates of childhood abuse. In addition, individuals with a history of childhood abuse tend to be less educated, and they are more likely to be female and non-white. The former are more likely to have grown up in families on welfare and are less likely to have lived with parents until age 16. The mean inflammatory markers for individuals in the abuse group are significantly higher for IL-6 and CRP, and the inflammation index; yet, there is no significant difference between those in the abuse and no-abuse groups for fibrinogen ($p = .23$). Regarding the potential mediators, the individuals in the abuse group have significantly poorer sleep quality, higher perceived stress, higher BMI, and lower levels of family social ties, compared to those not abused.

[Table 1 about here]

### *Levels of Inflammatory Markers by Abuse and Age*

In the baseline models (in Table 2), I test the first and second hypotheses regarding whether individuals who experienced childhood abuse have elevated markers of inflammation and whether the

effects of childhood abuse on elevated markers of inflammation vary by age after adjusting for all controls. I find that there is not a significant main effect of childhood abuse on inflammatory markers (see model 1 of Table 2), however a main effect emerges when the age-by-abuse interaction term is added into the models (see model 2 of Table 2), indicating that the effects of childhood abuse on levels of inflammatory makers are not consistent across ages. These life course patterns would have been concealed in a model that failed to evaluate such interaction effects. Figures 1 through 4 illustrate the means of inflammatory markers by abuse and age groups, after adjusting for all controls. Specifically, Figure 1 shows that the experience of childhood abuse is significantly associated with elevated levels of IL-6 for the two younger age groups (ages 34-44 and 45-54) but not for two older age groups (ages 55-64 and 65-84). In the younger age groups, the difference in IL-6 levels between the abuse and no-abuse groups is wider for the 34-44 age group (difference $_{ages\ 34\text{-}44}$ = .32) than the 45-54 age group (difference $_{ages\ 45\text{-}55}$ = .16). Between the ages of 55-64, there is no significant difference in IL-6 levels between those in the abuse and no-abuse groups. Between the ages of 65-84, the pattern reverses; those in the no-abuse group have greater IL-6 levels than those in the abuse group, although the difference is not significant.

[Figures 1 and 2 about here]

The results of CRP and fibrinogen shown in Figures 2 and 3, respectively, show similar patterns to IL-6, except that the fibrinogen levels at ages 65-84 are significantly higher for individuals in the no-abuse group compared to those in the abuse group. Finally, Figure 4 shows that the experience of childhood abuse is significantly associated with elevated levels of the inflammatory index for the three youngest age groups (ages 34-44, 45-54, and 55-64), but the association is inversely related for the oldest group (ages 65-84). Overall, the results in Figures 1 through 4 indicate that a difference in levels of inflammatory markers exists depending on whether the individuals experienced abuse or not; the difference is largest at ages 34-44, smaller at ages 45-54, much smaller at ages 55-64, and disappears between the ages of 65-84.

[Figure 3 and 4 about here]

***Plausible Pathways Linking Childhood Abuse and Elevated Markers of Inflammation***

Models 3 to 6 of Table 3 show whether the four hypothesized pathways, including poor sleep quality, perceived stress, BMI, and family social ties, explain the association between childhood abuse and levels of inflammatory markers. Model 3 shows that the effects of childhood abuse on all inflammatory outcomes are attenuated after including sleep quality, but the main effects and the interaction effect are still significant. The Sobel tests show that poor sleep quality significantly links childhood abuse to two elevated inflammatory makers: CRP (Sobel test $p < .05$) and the inflammatory index (Sobel test $p < .05$) but not to fibrinogen (Sobel test $p = .49$) and IL-6 (Sobel test $p = .07$). Model 4 includes perceived stress as a mediator; there are no significant main effects of perceived stress on any of the four inflammatory markers. Changes in the estimated main effects and the interaction effect on inflammatory markers are small or change little before and after including perceived stress. These findings indicate that perceived stress does not mediate the associations between childhood abuse and elevated markers of inflammation in adulthood. In Model 5, including BMI as a mediator, all parameter estimates for the main effects of childhood abuse on levels of inflammatory markers are reduced significantly. Results of the Sobel tests indicate that BMI significantly mediates the associations between childhood abuse and all inflammatory markers (all Sobel tests $p < .01$). Model 6 includes social ties as a mediator. After including the mediator, the main effects of childhood abuse on inflammatory markers are reduced substantially but are still significant. Results of the Sobel tests show that family social ties significantly mediates the association between childhood abuse and elevated IL-6 (Sobel test $p < .05$) but not for fibrinogen levels (Sobel test $p = .06$) and other two inflammatory markers.

Overall, this series of mediation models suggests that the associations between childhood abuse and risk of elevated markers of inflammation partially operate through the effects of childhood abuse on sleep quality, BMI, and/or family social ties. BMI, in particular, is the strongest mediator for all the inflammatory markers.

[Table 2 about here]

***Supplemental Analyses: Selective Mortality Theory***

To expand on the results regarding age variation on the effect of childhood abuse, I examine whether the abused survivors were more likely than the non-abused respondents to fail to participate in the 2004 survey (MIDUS II) The results in Table 3 show that the respondents who reported having experienced physical abuse have greater rates of attrition in the 2004 survey (OR = 1.16, 95% CI = 1.01-1.35), compared to the non-abused respondents, after adjusting for controls. In addition, individuals with a history of physical abuse are more likely to leave the 2004 survey due to death (OR = 1.33, 95% CI = 1.03-1.71). There are no age-by-abuse interaction effects on both risk of attrition and risk of death. That is, the attrition rates and death rates are greater for abused individuals than for non-abused respondents, yet the association does not vary significantly by age. These findings indicate selective mortality might contribute to a reduced gap in the levels of inflammatory markers between victims and non-victims in the older age groups.

[Table 3 about here]

## Discussion

My study demonstrates that the experience of childhood abuse increases levels of inflammatory markers in adulthood; I find that there are substantial age variations in levels of the markers between the abuse and no-abuse groups. In the younger age groups (ages 34-44 and 45-54), abused individuals, compared to non-abused ones, have elevated levels of IL-6, CRP, and fibrinogen, and they also have a higher inflammatory index, a summary of these three markers. The differences in levels of inflammatory markers between the two groups are larger for ages 34-44 than for ages 45-54. However, the effects of childhood abuse on most measures of inflammatory markers are no longer statistically significant and even reverse in the older age groups (ages 55-64 and 65-84). Overall, my findings are consistent with those in a prior study showing the effects of childhood abuse on elevated markers of inflammation in young adulthood (Danese et al. 2007). While the Danese et al. (2007) study is limited to a sample with a cohort of children born in the 1970s in New Zealand, my study uses a U.S. nationally representative sample including various cohorts of individuals born between 1920 and 1975. My study reveals that the

effects of childhood abuse on elevated markers of inflammation are present only for young adults or adults in early midlife.

The difference in levels of inflammatory markers across age groups within the abuse/no-abuse groups supports the selective mortality hypothesis. The patterns of age-by-abuse interactions in levels of inflammatory markers are similar to the findings in age-by-SES interactions in health outcomes in prior studies (Crimmins et al. 2009). Yet, while SES disparities in health outcomes are the largest around middle age, narrow in old age, and disappear in later old age, disparities in levels of inflammatory markers within the abuse/no-abuse groups are the largest in young adulthood, narrow in midlife, and disappear in old age. Given the cumulative life adversities and low SES achievements that the individuals with a history of childhood abuse have experienced (Currie and Widom 2010; Maxfield and Widom 1996), they might suffer cognitive impairment, physical limitations, and chronic diseases at earlier ages, which can eventually lead to higher mortality rates throughout the life course. These factors might be a reason why the difference in levels of inflammatory markers between these two groups does not exist beyond midlife.

Although cross-sectional data show that patterns of levels of inflammatory markers vary across the life course, research has pointed out that cohort effects might confound these differences (House et al. 2005). Because public attention on childhood abuse and neglect has increased and cultural definitions of abuse have changed over recent decades, individuals in older cohorts might not view corporal punishment (e.g., being punished with hard objects or spanking) as abuse, whereas younger cohorts might report it as abuse. On the other hand, older cohorts might consider the experience of childhood abuse as a stigma, so they may be more likely to underreport their experience of childhood abuse. Thus, cohort differences in the definition of childhood abuse might lead to a bias in the findings regarding the age patterns of inflammation between victims and non-victims of childhood abuse. Due to the nature of the data, this study does not separate the age effect from the cohort effect. Future studies need to consider both the cohort and age effects when addressing childhood abuse and health consequences over the life course.

The findings from supplementary analyses somewhat confirm the selective mortality hypothesis. Abused individuals are more likely to fail to participate in the second wave of the MIDUS study, and one reason is due to higher mortality among abused individuals between 1994 and 2004. I assume risk of death might be greater for abused individuals in old adulthood, compared to in young adulthood, and that might be a plausible explanation for why the effects of childhood abuse on markers of inflammation disappear in later midlife and old age. However, I do not find an age-by-abuse interaction effect on either the attrition or death rates, perhaps because I use short-term longitudinal data including diverse cohorts. On the other hand, it is possible that individuals who experience childhood abuse and survive until old age might have biological robustness and/or resilience, which might help them overcome the harm from childhood abuse.

In additional supplementary analyses, interestingly, I find that there is an age-by-abuse interaction effect on family social ties. An increase in family social ties by age is more dramatic for victims of childhood abuse than non-victims. That is, disparities in social ties between the abuse and no-abuse groups are largest in the 34-44 age group; these disparities are smaller with advancing age (data available upon request). In the 65-84 age group, there is no significant difference in family social ties between victims and non-victims. Given the association between strong family social ties and health-promoting behaviors (Grzywacz and Marks 1999), the fact that victims of childhood abuse do not have higher levels of inflammatory markers than non-victims in old age might be explained by similarities in the degree of family social ties within each group. Future research needs to apply advanced analysis (e.g., a mediated moderation analysis) to thoroughly investigate these associations.

Findings in the mediation analysis indicate that high BMI, poor sleep quality, and weak family social ties partially explain the pathways through which the experience of childhood abuse increases levels of inflammatory markers. Amid the mediators, high BMI plays a major role linking the experience of childhood abuse to elevated markers of inflammation. Since heavy people tend to have sleep apnea, which compromises their sleep quantity and quality (Wolk et al. 2003), BMI may be a more powerful predictor than sleep. There is also a possibility of reverse causality. That is, the experience of childhood

abuse may increase levels of inflammatory markers, and elevated markers of inflammation may increase the risk of being obese. Recent research indicates either that there is a positive association between levels of cytokines in early life and the development of obesity and type 2 diabetes, or that there are common factors (e.g., poor diet) which cause both obesity and elevated markers of inflammation (Litonjua and Gold 2008). Therefore, individuals with a history of childhood abuse might have elevated markers of inflammation via either pathway. It is necessary for future research to include more time points to assess the temporal order between potential mediators and outcomes.

There appears to be an independent association between childhood abuse and levels of inflammatory markers even after accounting for various confounders and mediators. For example, all variables, including childhood abuse, explain up to 26% of the variation of CRP levels. Unobserved and unmeasured factors in this study might potentially explain the rest of the variation. These might include common genetic predictors, maternal nutrition during pregnancy, birth weight, and infant weight gain (Barker et al. 2002). Unhealthy behaviors over the life course, including insufficient exercise, sedentary activity, poor diet, smoking, and alcohol use, might also explain why abused individuals have elevated levels of inflammatory markers. Being exposed to poor physical environments (e.g., crowded or poor housing conditions, and toxic exposures) (Cohen et al. 2010) might also increase the risk of being exposed to pathogens and elevate the markers of inflammation for abused individuals. Additionally, given the strong association between early life and adult victimization (Bensley et al. 2003), elevated markers of inflammation in adulthood might be explained by the experience of abusive relationships in adulthood (e.g., intimate partner violence). Accordingly, future research should consider investigating the extent to which these multiple factors lead to elevated markers of inflammation in victims of abuse.

***Limitations and Future Directions***

This study has limitations that should be noted. When analyzing the age-by-abuse interaction effects in a relatively small sample, I combine all four abuse groups generated by the LCA into one group, called abuse. Therefore, I do not consider multiple subtypes of abuse or the severity of abuse. In addition, given the relatively small size of the sample, I merge all individuals who are 65 or older into one group

(ages 65-84). Future studies need to replicate my study with larger samples, examining various types of childhood abuse across multiple age groups.

Research on the selective mortality hypothesis demonstrates that disparities in health conditions by SES disappear in later old age (House et al. 2005). Individuals who experience abuse as children and survive into later old age might have biological robustness, as well as psychological resiliency; experiencing hardships in early life might help them resist or deal better with later life hardships, such as the death of friends and family members or the need to care for an ill or disabled spouse, which are common difficulties for older people (Glass et al. 1997). Little research has investigated how long abused individuals will live, and if they are still alive in midlife and beyond, what are the conditions which made them resilient. Some survivors of childhood abuse might develop skills in mobilizing resources, avoiding stressful situations, and adopting positive coping strategies (Walsh et al. 2010) that eventually operate as protective resources against stressors and physiological burdens and increase the individuals' longevity and quality of life. Future studies should explore these factors to better understand the long-term effects of childhood abuse on lifelong health.

Moreover, since the questions about abuse were asked in midlife and required retrospective evaluations of experiences that may have occurred as much as 50 years earlier, a recall bias in reporting childhood abuse must be considered. There might be a possibility that individuals with mood disorders might exaggerate or misrepresent the adversities they experienced during childhood (Widom and Morris 1997). Yet, memories of specific childhood experiences (e.g., positive relationships, negative events, parental discipline) are highly stable (Yancura and Aldwin 2009), and recollections of traumatic events in childhood tend to be fairly accurate (for a review, see Hardt and Rutter 2004). In supplementary analyses, I also find both strong correlation and consistency between reports of physical abuse that were measured at MIDUS I and MIDUS II, with a 10-year gap. In addition, I find no interaction effect of depression diagnosis (in MIDUS II) in the association between reports of physical abuse, possibly indicating that depression does not significantly affect the repeated reports of physical abuse over the 10-year span. Given the use of slightly different measures at the two periods, the measures of self-reported childhood

abuse in this study appear quite reliable. In addition, research on stressful events, subjective responses to these events, and the various strategies employed to cope with them has pointed out the importance of considering an individual's subjective perceptions of stressors (Lazarus and Folkman 1984). That is, the way that victims of childhood abuse assess the adversity of early life events might explain whether they adopt negative or positive coping strategies and their concomitant health consequences.

Despite these limitations, there is much to be learned from this study. Overall, my findings highlight the importance of life course stages in understanding the effects of childhood abuse and its adverse health consequences. In order to help reduce the risk of developing chronic diseases through elevated markers of inflammation in adulthood, targeted interventions to prevent the consequences of childhood abuse (e.g., developing both positive emotional resources and close social ties and controlling body mass index) need to be started at an early age. Furthermore, understanding the complex mechanisms (e.g., the biological, cognitive, emotional, social and behavioral pathways) linking early life adversities to later health outcomes can shed light on how to improve social services and public health interventions for those who have experienced such adversities during childhood.

**Notes**

1. For the supplementary analyses of attrition rates, I use severe physical abuse measured in MIDUS I. Severe physical abuse consists of five items from Conflict Tactics Inventory (CTI): 1) kicked, bit, or hit you with a fist; 2) hit or tried to hit you with something; 3) beat you up; 4) choked you; and 5) burned or scalded you. Severe physical abuse is coded as a dichotomous variable, 1 indicating that individuals reported "often" or "sometimes" to any of the five CTI items and 0 indicating the others ("rarely" and "never"). Cohen's kappa between severe physical abuse (MIDUS I) and physical abuse (MIDUS II) is .84.5%, indicating a very good agreement ( > .81%) and Tetrachoric correlation is .76.

2. Most victims of childhood abuse experienced multiple forms of abuse with different degree, yet most previous studies have been limited to a measure representing a single type of childhood abuse (e.g., emotional, physical, or sexual abuse). Consistent with prior studies (e.g., Greenfield et al 2011), I conduct latent class analysis and create and five distinct groups of childhood abuse. Due to the statistical power issue in analyzing age-by-abuse interaction terms, I categorize these five groups into two general groups: *abuse* vs. *no abuse*, including four abused groups. For the sensitivity test, I generate a dichotomous measure of childhood abuse, called *anyabuse* (yes = 1 / no = 0): 1 including respondents who answered "sometimes, often, or, very often true" to any of the 15 CTQ items and 0 including respondents who answered "rarely or never true" to all of the 15 CTQ items. Any abuse consists of 53% respondents who reported any type of childhood abuse. I use a dichotomous measure generated by LCA analysis since *anyabuse* (53%) seems to overestimate the prevalence of childhood abuse in the population and 100% of the individuals who are categorized *abuse* also belong to *anyabuse*.

## References


Alley, Dawn E., Eileen Crimmins, Karen Bandeen-Roche, Jack Guralnik, and Luigi Ferrucci. 2007. "Three-year change in inflammatory markers in elderly people and mortality: the Invecchiare in Chianti study." *Journal of the American Geriatrics Society* 55:1801-7.

Allison, Paul D. 2001. *Missing data*, Vol. 136: Sage Publications, Inc.

Barker, David J., Johan G. Eriksson, Tom Forsén, and Clive Osmond. 2002. "Fetal origins of adult disease: strength of effects and biological basis." *International Journal of Epidemiology* 31:1235-39.

Baron, Reuben M. and David A. Kenny. 1986. "The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations." *Journal of Personality and Social Psychology* 51:1173-82.

Bensley, Lillian, Juliet Van Eenwyk, and Katrina Wynkoop Simmons. 2003. "Childhood family violence history and women's risk for intimate partner violence and poor health." *American Journal of Preventive Medicine* 25:38-44.

Bentley, Tyrone and Cathy S. Widom. 2009. "A 30-year follow-up of the effects of child abuse and neglect on obesity in adulthood." *Obesity* 17:1900-5.

Berkman, Lisa F. and S. Leonard Syme. 1979. "Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents." *American Journal of Epidemiology* 109:186-204.

Bernstein, David and Laura Fink. 1998. *Manual for the childhood trauma questionnaire*. New York The Psychological Corporation, San Antonio.

Buysse, Daniel J., Cahrles F. Reynolds, 3rd, Timothy H. Monk, Susan R. Berman, and David J. Kupfer. 1989. "The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research." *Psychiatry Research* 28:193-213.

Cohen, Sheldon. 2004. "Social relationships and health." *American Psychologist* 59:676-84.

Cohen, Sheldon, Denise Janicki-Deverts, Edith Chen, and Karen A. Matthews. 2010. "Childhood socioeconomic status and adult health." *Annals of the New York Academy of Sciences* 1186:37-55.

Cohen, Sheldon, Tom Kamarck, and Robin Mermelstein. 1983. "A global measure of perceived stress." *Journal of Health and Social Behavior* 24:385-96.

Cohen, Sheldon and Thomas A. Wills. 1985. "Stress, social support, and the buffering hypothesis." *Psychological Bulletin* 98:310-57.

Crimmins, Eileen M., Jung K. Kim, and Teresa E. Seeman. 2009. "Poverty and biological risk: the earlier "aging" of the poor." *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 64:286-92.

Currie, Janet and Cathy S. Widom. 2010. "Long-term consequences of child abuse and neglect on adult economic well-being." *Child Maltreatment* 15:111-20.

Dandona, Paresh, Ahmad Aljada, and Arindam Bandyopadhyay. 2004. "Inflammation: the link between insulin resistance, obesity and diabetes." *Trends in Immunology* 25:4-7.

Danese, Andrea, Terrie E. Moffitt, HonaLee Harrington, Barry J. Milne, Guiherme Polanczyk, Carmine M. Pariante, Richie Poulton, and Avshalom Caspi. 2009. "Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers." *Archives of Pediatrics and Adolescent Medicine* 163:1135-43.

Danese, Andrea, Carmine M. Pariante, Avshalom Caspi, Alan Taylor, and Richie Poulton. 2007. "Childhood maltreatment predicts adult inflammation in a life-course study." *Proceedings of the National Academy of Sciences* 104:1319-24.

Danesh, John, Rory Collins, Paul Appleby, and Richard Peto. 1998. "Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies." *JAMA: The Journal of the American Medical Association* 279:1477-82.

Dube, Shanta R., Delisa L. Fairweather, Willima S. Pearson, Vincent J. Felitti, Reber F. Anda, and Janet B. Croft. 2009. "Cumulative childhood stress and autoimmune diseases in adults." *Psychosomatic Medicine* 71:243-50.

Felitti, Vincent J., Robert F. Anda, dale Nordenberg, David F. Williamson, Alison. M. Spitz, Valerie Edwards, Mary P. Koss, and James S. Marks. 1998. "Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study." *American Journal of Preventive Medicine* 14:245-58.

Friedman, Elliot M., Mary S. Hayney, Gayle D. Love, Heather L. Urry, Melissa A. Rosenkranz, Richard J. Davidson, Burton H. Singer, and Carol D. Ryff. 2005. "Social relationships, sleep quality, and interleukin-6 in aging women." *Proceedings of the National Academy of Sciences of the United States of America* 102:18757-62.

Friedman, Elliot M. and Pamela Herd. 2010. "Income, education, and inflammation: differential associations in a national probability sample (The MIDUS Study)." *Psychosomatic Medicine* 72:290-300.

Fuller-Thomson, Esme., Maria Stefanyk, and Sarah Brennenstuhl. 2009. "The robust association between childhood physical abuse and osteoarthritis in adulthood: findings from a representative community sample." *Arthritis Care and Research* 61:1554-62.

Glaser, Ronald and Janice K. Kiecolt-Glaser. 2005. "Stress-induced immune dysfunction: implications for health." *Nature Reviews Immunology* 5:243-51.

Glass, Thomas A, Stanislav V. Kasl, and Lisa F. Berkman. 1997. "Stressful life events and depressive symptoms among the elderly. Evidence from a prospective community study." *Journal of Aging and Health* 9:70-89.

Gómez, Francisca , Abdelialil Lahmame, E. Ronald de Kloet, and Antonio Armario. 1996. "Hypothalamic-pituitary-adrenal response to chronic stress in five inbred rat strains: differential responses are mainly located at the adrenocortical level." *Neuroendocrinology* 63:327-37.

Gotlib, Ian H. and Blair Wheaton. 1997. "Stress and adversity over the life course." Campbrige University Press.

Greenfield, Emily A., Chioun Lee, Elliot L. Friedman, and Kristen W. Springer. 2011. "Childhood abuse as a risk factor for sleep problems in adulthood: evidence from a U.S. national study." *Annals of Behavioral Medicine* 42:245-56.

Grzywacz, Joseph G. and Nadine F. Marks. 1999. "Family solidarity and health behaviors." *Journal of Family Issues* 20:243-68.

Hardt, Jochen and Michael Rutter. 2004. "Validity of adult retrospective reports of adverse childhood experiences: review of the evidence." *Journal of Child Psychology and Psychiatry* 45:260-73.

Harris, Tamara B, Luigi Ferrucci, Russell P Tracy, M.Chiara Corti, Sholom Wacholder, Walter H Ettinger Jr, Harley Heimovitz, Harvey J Cohen, and Robert Wallace. 1999. "Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly." *American Journal of Medicine* 106:506-12.

House, James. S., Paula. M. Lantz, and Pamela Herd. 2005. "Continuity and change in the social stratification of aging and health over the life course: evidence from a nationally representative longitudinal study from 1986 to 2001/2002 (Americans' Changing Lives Study)." *The Journals of Gerontology: Series B: Psychological Sciences and Social Sciences* 60 Spec No 2:15-26.

Hyman, Scott M., Prashni Paliwal, and Rajita Sinha. 2007. "Childhood maltreatment, perceived stress, and stress-related coping in recently abstinent cocaine dependent adults." *Psychology of Addictive Behaviors* 21:233-38.

Kawachi, Ichiro and Lisa F. Berkman. 2001. "Social ties and mental health." *Journal of Urban Health* 78:458-67.

Kiecolt-Glaser, Janice K., Kristopher J. Preacher, Robert C. MacCallum, Cathie Atkinson, William B. Malarkey, and Ronald Glaser. 2003. "Chronic stress and age-related increases in the proinflammatory cytokine IL-6." *Proceedings of the National Academy of Sciences of the United States of America* 100:9090-95.

Kuh, Diana, Yoav Ben-Shlomo, John Lynch, Johan Hallqvist, and Chris Power. 2003. "Life course epidemiology." *Journal of Epidemiology and Community Health* 57:778-83.

Lanier, Paul, Melissa Jonson-Reid, Mary J. Stahlschmidt, Brett Drake, and John Constantino. 2010. "Child maltreatment and pediatric health outcomes: a longitudinal study of low-income children." *Journal of Pediatric Psychology* 35:511-22.

Lazarus, Richard S. and Susan Folkman. 1984. *Stress, appraisal, and coping*. New York: Springer Publishing Company.

Litonjua, Augusto A. and Diane R. Gold. 2008. "Asthma and obesity: common early-life influences in the inception of disease." *Journal of Allergy and Clinical Immunology* 121:1075-84; quiz 85-6.

Loucks, Eric B., Lisa M. Sullivan, Ralph B. D'Agostino, Sr., Martin G. Larson, Lisa F. Berkman, and Emelia J. Benjamin. 2006. "Social networks and inflammatory markers in the Framingham Heart Study." *Journal of Biosocial Science* 38:835-42.

Lovallo, William R. 2005. *Stress & health: Biological and psychological interactions*: Sage Publications, Inc.

Love, Gayle D., Teresa E. Seeman, Maxine Weinstein, and Carol D. Ryff. 2010. "Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context." *Journal of Aging and Health* 22:1059-80.

Maxfield, Michael G. and Cathy S. Widom. 1996. "The cycle of violence: revisited 6 years later." *Archives of Pediatrics and Adolescent Medicine* 150:390-95.

McDade, Thomas W., Louise C. Hawkley, and John T. Cacioppo. 2006. "Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study." *Psychosomatic Medicine* 68:376-81.

Miller, Gregory E, Sheldon Cohen, and A. Kim Ritchey. 2002. "Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model." *Health Psychology* 21:531-41.

Moncek, Fedor, Richard Kvetnansky, and Daniela Jezova. 2001. "Differential responses to stress stimuli of Lewis and Fischer rats at the pituitary and adrenocortical level." *Endocrine Regulations* 35:35-41.

Muthén, Linda K. and Bengt O. Muthén. 2008. *Mplus User's Guide: Statistical Analysis with Latent Variables*. Los Angeles, CA: Muthén & Muthén.

—. 2010. *Mplus Version 6.0. Computer file*. Los Angeles, CA: Muthén and Muthén.

O'Connor, Mary-Frances, Julie E. Bower, Hyong Jin Cho, J. David Creswell, Stoyan Dimitrov, Mary E. Hamby, Michael A. Hoyt, Jennifer L. Martin, Theodore F. Robles, Erica K. Sloan, KaMala S. Thomas, Michael R. Irwin, and G. A. Aarons. 2009. "To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers." *Brain, Behavior, and Immunity* 23:887-97.

Okuna, Michele L., Mary Coussons-Readb, and Martica Halla. 2009. "Disturbed sleep is associated with increased C-reactive protein in young women." *Brain, Behavior, and Immunity* 23:351-54.

Pearlin, Leonard I., Scott Schieman, Elena M. Fazio, and Stephen C. Meersman. 2005. "Stress, health, and the life course: some conceptual perspectives." *Journal of Health and Social Behavior* 46:205-19.

Robert, Stephanie A., Dasha Cherepanov, Mari Palta, Nancy Cross Dunham, David Feeny, and Dennis G. Fryback. 2009. "Socioeconomic status and age variations in health-related quality of life: results from the national health measurement study." *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences* 64:378-89.

Ryff, Carol D., Teresa Seeman, and Maxine Weinstein. 2010. "Blood, Urine, and Saliva Data Documentation." *National Survey of Midlife Development in the United States (MIDUS II): Biomarker Project, 2004-2009*. Ann Arbor, Michigan: Inter-university Consortium for Political and Social Research (ICPSR).

Shamsuzzaman, Abu S.M., Mikolaj Winnicki, Paola Lanfranchi, Robert Wolk, Tomas Kara, Valentina Accurso, and Virend K. Somers. 2002. "Elevated C-reactive protein in patients with obstructive sleep apnea." *Circulation* 105:2462-64.

Slopen, Natalie, Tene T. Lewis, Tara L. Gruenewald, Mahasin S. Mujahid, Carol D. Ryff, Mujahid A. Albert, and David R. Williams. 2010. "Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey." *Psychosomatic Medicine* 72:694-701.

Sobel, Michael E. 1982. "Asymptotic confidence intervals for indirect effects in Structural Equation Models." Pp. 290-312 in *Sociological Methodology*, vol. 13, edited by L. S. Washington, DC: American Sociological Association.

Spitzer, Carsten, Miriam Bouchain, Liza Y. Winkler, Katja Wingenfeld, Stefan M. Gold, Hans Joergen Grabe, Sven Barnow, Christian Otte, and Christoph Heesen. 2012. "Childhood trauma in multiple sclerosis: a case-control study." *Psychosomatic Medicine* 74:312-18.

Springer, Kristen W. 2009. "Childhood physical abuse and midlife physical health: Testing a multi-pathway life course model." *Social Science and Medicine* 69:138-46.

Sternberg, Esther M., Joanna M. Hill, George P. Chrousos, Themis Kamilaris, Samuel J. Listwak, Philip W. Gold, and Ronald L. Wilder. 1989. "Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats." *Proceedings of the National Academy of Sciences of the United States of America* 86:2374-78.

Taylor, Shelley E., Barbara J. Lehman, Catarina I. Kiefe, and Teresa E. Seeman. 2006. "Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study." *Biological Psychiatry* 60:819-24.

Visser, Marjolein, Lex M. Bouter, Geraldine M. McQuillan, Mark H. Wener, and Tamara B. Harris. 1999. "Elevated C-reactive protein levels in overweight and obese adults." *JAMA: The Journal of the American Medical Association* 282:2131-35.

Walsh, Kate, Michelle A. Fortier, and DiLillo Dilillo. 2010. "Adult coping with childhood sexual abuse: a theoretical and empirical review." *Aggression and Violent Behavior* 15:1-13.

Widom, Cathy S. and Michael G. Maxfield. 2001. *An update on the "cycle of violence"*. Washington, D.C.: U.S. Dept. of Justice, Office of Justice Programs, National Institute of Justice.

Widom, Cathy S. and Suzanne Morris. 1997. "Accuracy of adult recollections of childhood victimization: Part 2. childhood sexual abuse." *Psychological Assessment* 9:34-46.

Wolk, Robert, Abu S. Shamsuzzaman, and Virend K. Somers. 2003. "Obesity, sleep apnea, and hypertension." *Hypertension* 42:1067-74.

Yancura, Loriena A. and Carolyn M. Aldwin. 2009. "Stability and change in retrospective reports of childhood experiences over a 5-year period: findings from the Davis Longitudinal Study." *Psychology and Aging* 24:715-21.

Table 1 Bivariate Analysis for Abuse and No Abuse Respondents

| | Abuse (n = 437) Mean (SD) | No Abuse (n = 818) Mean (SD) | Total (n = 1,255) Mean (SD) | $\chi^2$ (df) or t-test (df) |
|---|---|---|---|---|
| Inflammatory markers | | | | |
| IL-6 (mg/L) | 3.26 (3.25) | 2.93 (2.93) | 3.04 (3.04) | -1.82 (1241) |
| CRP (pg/dL) | 3.34 (4.88) | 2.86 (4.71) | 3.02 (4.78) | -1.68 (1233) |
| FGN (mg/dL) | 353.09 (84.43) | 346.72 (89.57) | 348.92 (87.85) | -1.21(1233) |
| Inflammatory index (0-3) | .90 (1.01) | .75 (.97) | .80 (.99) | -2.41 (1232)* |
| Potential mediators | | | | |
| Poor sleep quality (0-21) | 7.41 (3.94) | 5.63 (3.36) | 6.25 (3.67) | -10.31(1253)*** |
| Perceived Stress Scale (10-50) | 24.68 (0.34) | 20.94 (0.19) | 22.24 (0.18) | -3.80 (1252)*** |
| Body mass index (kg/m$^2$) | 30.73 (7.68) | 29.25 (5.93) | 29.77 (6.63) | -8.43 (1253)*** |
| Family social ties | | | | |
| (1= not at all – 4 = a lot) | 3.31(0.40) | 3.49 (0.34) | 3.43 (0.37) | 8.46 (1247) |
| Covariates | | | | |
| Age (34-84) | 51.89 (10.55) | 55.93 (12.05) | 54.52 (11.71) | 5.91(1253)*** |
| Age groups | | | | |
| 34-44 | 22 | 27 | 23 | 29.90 (3)*** |
| 45-54 | 26 | 35 | 29 | |
| 55-64 | 28 | 24 | 27 | |
| 65-84 | 25 | 14 | 21 | |
| Female | 68 | 51 | 57 | 31.24 (1)*** |
| White | 73 | 81 | 78 | 10.27 (1)** |
| Parental education | | | | |
| Less than high school | 28 | 24 | 25 | 2.57 (2) |
| High school | 34 | 34 | 34 | |
| More than high school | 38 | 42 | 41 | |
| Living with parents until age 16 | 71 | 81 | 77 | 13.7 (1)*** |
| Family on welfare in childhood | 16 | 6 | 9 | 36.9 (1)*** |
| Married/cohabitating | 57 | 69 | 65 | 15.5 (1)*** |
| Education | | | | |
| High school or less | 31 | 26 | 28 | 11.6 (3)** |
| Less than college | 33 | 28 | 30 | |
| College | 16 | 22 | 20 | |
| MA or more | 19 | 23 | 22 | |
| Chronic diseases [a] | 24 | 28 | 27 | 2.23 (2) |
| Medications | | | | |
| Antihypertension | 35 | 37 | 37 | 0.46 (1) |
| Anticholesterol | 24 | 30 | 28 | 5.37 (1)* |
| Steroids | 14 | 11 | 12 | 1.22 (1) |

*Note*: [a] chronic diseases indicate whether the respondents have experienced a stroke or have either type 2 diabetes or cancer.

Table 2 Main and Mediation Effects of Childhood Abuse on Inflammatory Markers through Plausible Pathways

| | IL-6 (log) n = 1,239 | CRP (log) n = 1,231 | Fibrinogen n = 1,231 | Inflammation Index n = 1,230 |
|---|---|---|---|---|
| Model 1. Baseline Model | | | | |
| Abuse | .06 (.05) | .05 (.07) | .91 (5.14) | .08 (.07) |
| Age | .01 (.002)*** | -.005 (.003) | .82 (.26)** | .003 (.003) |
| Model fit | $R^2$ = .150 | $R^2$ = .103 | $R^2$ = .117 | $\chi^2$ (df) = 145 (17) |
| Model 2. Interaction Model | | | | |
| Abuse | .49 (.21)* | .92 (.35)** | 64.12 (23.78)** | .80 (.35)* |
| Age | .01 (.002)*** | .0003 (.004) | 1.19 (.30)*** | .008 (.004)* |
| Abuse × Age | -.008 (.004)* | -.02 (.006)** | -1.19 (.44)** | -.01 (.006)* |
| Model fit | $R^2$ = .153 | $R^2$ = .108 | $R^2$ = .122 | $\chi^2$ (df) = 146 (18) |
| Model 2. Poor Sleep | | | | |
| Abuse | .46 (.21)* | .87 (.35)** | 62.92 (23.88)** | .75 (.36)* |
| Age | .01 (.002)*** | .001 (.004) | 1.20 (.30)*** | .008 (.004)* |
| Abuse × Age | -.008 (.004)* | -.02 (.006)** | -1.18 (.44)** | -.01 (.006)* |
| Poor Sleep Quality | .01 (.006)† | .02 (.01)* | .49 (.71) | .02 (.009)* |
| Model fit | $R^2$ = .156 | $R^2$ = .113 | $R^2$ = .122 | $\chi^2$ (df) = 153 (19) |
| Model 3. Perceived Stress | | | | |
| Abuse | .48 (.21)* | .95 (.34)** | 64.15 (23.77)** | .79 (.35)* |
| Age | .10 (.002)*** | -.00004 (.004) | 1.19 (.30)*** | .008 (.004)* |
| Abuse × Age | -.008 (.004)* | -.02 (.006)** | -1.19 (.44)** | -.01 (.006)* |
| Perceived Stress | .001 (.003) | -.005 (.006) | -.007 (.38) | .001(.005) |
| Model fit | $R^2$ = .153 | $R^2$ = .109 | $R^2$ = .122 | $\chi^2$ (df) = 147 (19) |
| Model 4. BMI | | | | |

| | | | | |
|---|---|---|---|---|
| Abuse | .42 (.21)* | .79 (.31)** | 57.52 (22.77)* | .65 (.35) |
| Age | .01 (.002)*** | .005 (.004) | 1.42 (.29)*** | .01 (.004)** |
| Abuse × Age | -.008 (.004)* | -.02 (.006)** | -1.14 (.43)** | -.01 (.006) |
| BMI | .03 (.003)*** | .07 (.005)*** | 3.48 (.43)*** | .05 (.004)*** |
| Model fit | $R^2$ = .223 | $R^2$ = .257 | $R^2$ = .182 | $\chi^2$ (df) = 338 (19) |
| | | | | |
| Model 5. Family Social Ties | | | | |
| Abuse | .43 (.21)* | .88 (.35)* | 57.31 (23.87)* | .73 (.35)* |
| Age | .01 (.002)*** | .0002 (.96) | 1.18 (.30)*** | .008 (.004) |
| Abuse × Age | -.007 (.004) | -.02 (.006)* | -1.11 (.44)* | -.01 (.006) |
| Family Social Ties | -.12 (.06)* | -.09 (.09) | -13.50† | -.15 (.09) |
| Model fit | $R^2$ = .156 | $R^2$ = .109 | $R^2$ = .125 | $\chi^2$ (df) = 147 (19) |

*Note*. All control variables (demographics, childhood environments, chronic diseases, SES, and medications) are adjusted for the models.
*$p$ < .05; ** $p$ <.01; *** $p$ <.001.

Table 3 Risks of Attrition and Mortality by Abuse and No-abuse Groups between MIDUS I (1994) and MIDUS II (2004)

| | Odds of Attrition (n = 5,814) | | Odds of Death (n = 5,814) | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Severe physical abuse in childhood | 1.16* | (1.00-1.33) | 1.33* | (1.04-1.71) |
| Demographics | | | | |
| Age | .93* | (.87-.98) | 2.82*** | (2.45-3.26) |
| Female | .77** | (.68-.88) | .75* | (.60-.93) |
| White | .45** | (.37-.54) | 1.00 | (.67-1.51) |
| Childhood context | | | | |
| Parental education | | | | |
| Less than high school (Reference) | 1.00 | | 1.00 | |
| High school | .84* | (.72-98) | .94 | (.73-1.21) |
| More than high school | .64* | (.54-.75) | .96 | (.73-1.27) |
| Family on welfare in childhood | 1.29* | (1.02-1.63) | 1.25 | (.83-1.88) |
| Health status (MIDUS I) | | | | |
| Physical health | .75*** | (.70-.81) | .51 | (.45-.57)*** |
| Mental health | 1.01 | (.94-1.09) | 1.21 | (1.07-1.38)** |
| $\chi^2$ (df) | 240.55 (9) | | 528.42 (9) | |

*$p < .05$; ** $p < .01$; *** $p < .001$.

Figure 1 IL-6 Mean Levels by Abuse and Age Groups (birth year)

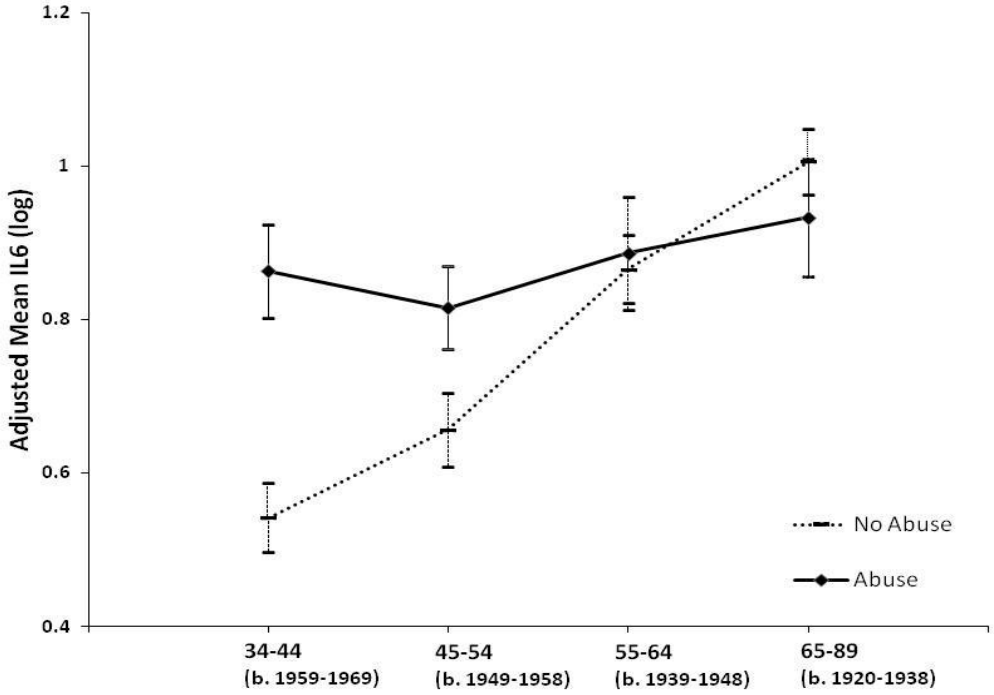

Figure 2 CRP Mean Levels by Abuse and Age Groups (birth year)

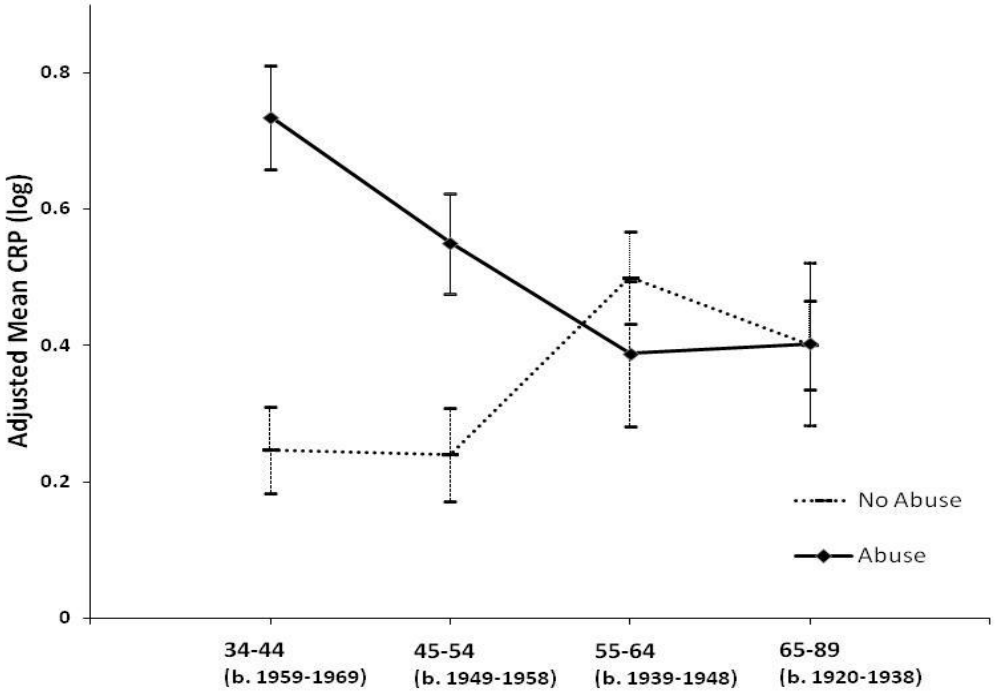

Figure 3 Fibrinogen Mean Levels by Abuse and Age Groups (birth year)

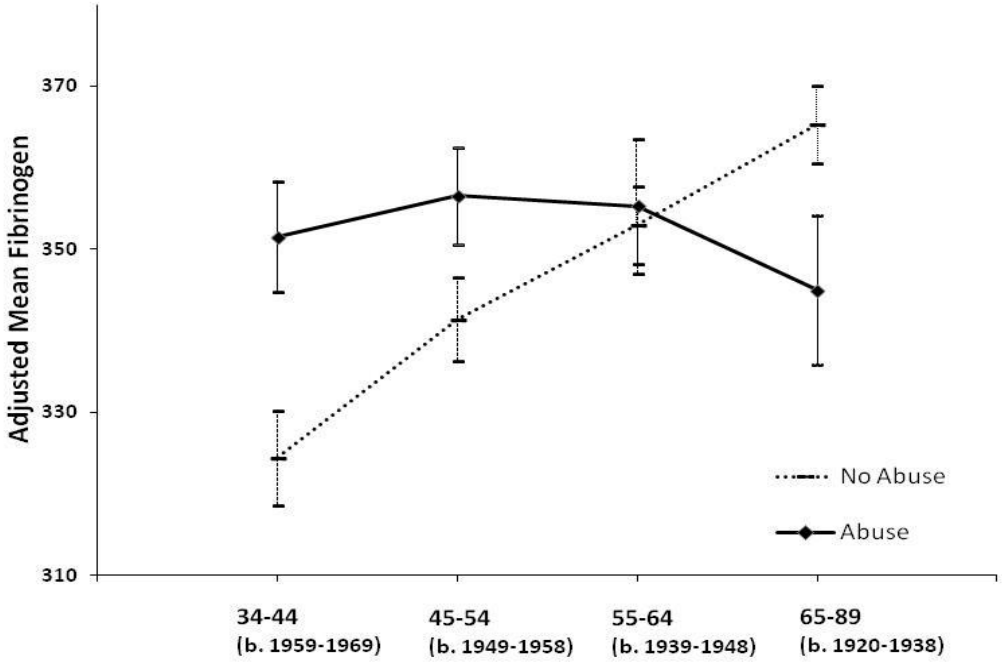

Figure 4 Summary Scores of Inflammatory Markers by Abuse and Age Group (birth year)