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Biological and behavioral mechanisms underlying childhood physical abuse and age-related disease: Borderline personality pathology and inflammation

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Biological and Behavioral Mechanisms Underlying Childhood Physical Abuse and Age-Related Disease: Borderline Personality Pathology and Inflammation

by

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ABSTRACT OF THE DISSERTATION

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Background: The frequent comorbidity of psychiatric and physical health conditions may be partially attributable to early life stress-related changes in inflammatory signaling and behavior (e.g., borderline personality pathology, health behaviors) that reciprocally maintain and enhance their effects on overall health.

Methods: Using data from older adults (n=1,630) who participated in the ongoing longitudinal St Louis Personality and Aging Network (SPAN) study, we examined associations between childhood physical abuse, borderline pathology, inflammation markers (i.e., interleukin 6, c-reactive protein), health behaviors, and physical health. Morning fasting serum IL-6 and CRP were assayed from a subset of participants (n=791). Borderline pathology factor scores were computed using interviews as well as self- and informant-reports across the course of the study. Physical health, health behaviors, and additional covariates (e.g., medication class usage) were also assessed.

Results: IL-6 was associated with higher BPD symptomatology, greater exposure to childhood physical abuse, worse physical health, and lower preventative health behaviors. Similar findings for CRP emerged, though its association with childhood physical abuse was not robust to covariate

inclusion. An integrated model suggests an indirect pathway of exposure to childhood physical abuse, greater BPD symptomology, reduced preventative health behaviors, elevated IL-6, and worse health outcomes.

Conclusions: These findings suggest that physical abuse during childhood may be predictive of later poor physical health through behavioral (i.e., borderline pathology, reduced preventative health behaviors), and biological (i.e., inflammation) pathways.

1. Introduction

The effects of adversity during childhood have a lingering impact on psychological and physical health that extends into adulthood and later life (Afifi et al., 2011; Elwenspoek, Kuehn, Muller, & Turner, 2017; Miller, Chen, & Parker, 2011; Newnham & Janca, 2014). For instance, estimates suggest that early life stress is associated with a substantial portion of psychiatric disorders (45% of childhood onset disorders and 26-32% of adolescent/adult-onset disorders; (Green et al., 2010)) and greater odds of physical illness ((Murphy, Cohn, & Loria, 2017); e.g., cardiovascular disease: OR: 1.3-1.7; (Dong et al., 2004)). Further, the severity of early abuse has been shown to have a dose-dependent relationship with severity of symptomatology in disorders such as borderline personality pathology (Widom, Czaja, Paris, 2009). However, the potential pathways that may contribute to the comorbidity of mental and physical health conditions and their frequent association with early life stress, remain poorly understood. Influential theoretical work pioneered by Miller, Chen and Parker suggests that psychiatric and physical health comorbidities may be partly attributable to early life stress-related changes in inflammation (e.g., a proinflammatory phenotype) and behavior (e.g., impulsivity, reduced preventative health behaviors) that reciprocally maintain and enhance their collective effects on general health (Miller et al., 2011; Nusslock & Miller, 2016).

Borderline personality pathology (BPP), which consists of pervasive affective instability, environmental reactivity, inconsistency in self-image, interpersonal dysfunction, and high levels of impulsivity, may contribute to early life stress-related physical ailments in later life. The characteristic symptomatology of borderline personality pathology, most notably emotion dysregulation and impulsivity, can serve as an analog for the behavioral proclivities proposed to exacerbate pro-inflammatory tendencies in the Miller, Chen, and Parker model. First, borderline

personality has been robustly linked to childhood maltreatment and abuse (e.g., ORs of 2.04-2.47; (Afifi et al., 2011)). Second, BPP is commonly comorbid with internalizing and externalizing psychopathology as well as physical health conditions [e.g., cardiovascular disease, diabetes, obesity, and arthritis (Dixon-Gordon, Whalen, Layden, & Chapman, 2015; El-Gabalawy, Katz, & Sareen, 2010; Powers & Oltmanns, 2013)], somatic syndromes [e.g., fibromyalgia and chronic fatigue (Frankenburg & Zanarini, 2004)], and subjective health complaints (Powers & Oltmanns, 2013). Relatedly, it represents a general factor of personality pathology (Sharp et al., 2015). As such, it may represent a critical clinical construct with widespread implications for understanding comorbidity, similar to findings supporting a unifactoral model (e.g., p factor) of non-personality psychopathology (Lahey et al., 2012). Third, consistent with theoretical arguments suggesting that preventative health behaviors may be an intervening behavioral mechanism through which psychopathology and inflammation are related (Miller et al., 2011), BPP is associated with reduced preventative health behavior (e.g., reduced exercise (Keuroghlian, Frankenburg, & Zanarini, 2013)), which has independently been linked to elevated inflammation and worse physical health (Dankelm, Loenneke, & Loprinzi, 2017; Hamer et al., 2012). Fourth, the limited data examining inflammation in the context of borderline personality disorder suggests that it is associated with elevated systemic inflammation [however, we are aware of 3 studies which have examined borderline personality disorder, only within the context of comborbid depression (Kahl et al., 2006; Kahl et al., 2009; Kahl et al., 2005)]. Collectively, guided by theoretical models (Miller et al., 2011), these data raise the intriguing possibility that childhood abuse may precipitate the development of borderline personality pathology which, in turn, may contribute to reduced preventative healthcare, increased inflammation, and worse physical health later in life.

Using data (n=1,630) from adults ages 60-72 who have participated in the ongoing longitudinal St Louis Personality and Aging Network (SPAN) study (Oltmanns, Rodrigues, Weinstein, & Gleason, 2014), we examined associations between childhood physical abuse, borderline personality pathology, inflammation markers (i.e., IL-6 and CRP), preventative health behaviors, and a global index of physical health. We hypothesized that childhood abuse would be indirectly linked to worse physical health through borderline pathology expression and associated lower health behaviors and elevated inflammation. Based on meta-analytic evidence that physical abuse in childhood is linked to elevations in IL-6, but not CRP, we expected that the link between childhood physical abuse and inflammation would be stronger for IL-6, and potentially absent with CRP (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016).

For additional rationale and discussion of literature linking childhood maltreatment to inflammation, borderline pathology, and physical health see Appendix Item 1.

2. Methods and Materials

2.1 Participants and Procedure

The SPAN study is an ongoing longitudinal protocol assessing a wide range of personality, health, social, and biological characteristics in a representative community sample of 1,630 older adults (ages 55-65 at baseline) residing in the St. Louis, Missouri area (Iacovino, Bogdan, & Oltmanns, 2016). Recruitment details are provided in **Supplemental Material**. Each participant completed a 3-hour in-person assessment at baseline (N=1630; baseline), and at 2 subsequent follow-up (FU) in-person sessions (FU5, FU10; a 3rd is currently ongoing). Participants were also asked to complete a short sequence of mailed or online FU questionnaires every 6 months after entering the

study. All participants consented to the SPAN protocol, which was approved by the Washington University in St. Louis Institutional Review Board. They received $20 remuneration for the blood draw, as well as $60 for each in-person session and $10 for each mailed or online follow-up questionnaire completed. Participants (90%, n=1,467) also identified an individual that knew them well and could describe their personality to serve as their informant. Informants completed online or mailed questionnaires about each participant's personality (see **Supplemental Material** for additional details).

2.2 Measures

2.2.2 Borderline Personality Factor Scores

Borderline pathology was assessed using a dimensional approach from multiple perspectives (i.e., clinician, self, and informant ratings) to improve our coverage of subthreshold presentations of borderline pathology. Consistent with recent findings highlighting the merit in using unidimensional definitions for psychopathologic phenotypes (Lahey et al., 2012), we adopted a dimensional as opposed to a categorical (i.e., presence of diagnosis) approach to model borderline pathology across our non-selected community sample. Relative to a categorical approach, dimensional approaches to measure borderline personality pathology have garnered evidence of better reliability and clinical utility leading to their inclusion in Section III ("emerging measures and model" of the Fifth Edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-5) (Morey, Skodol, & Oldham, 2014; Morey et al., 2012; Clark, 2007; Widiger & Trull, 2007). Further, in light of evidence that many people exhibit at least some personality pathology symptoms (Oltmanns et al., 2014), and that subthreshold BPD-related symptoms are associated with psychosocial impairment (Ellison, Rosenstein, Chelminski, Dalrymple, & Zimmerman, 2016; Zimmerman, Chelminski, Young, Dalrymple, & Martinez, 2013), scores were treated continuously

to retain variation at subthreshold diagnostic levels. We included informant reports because they add unique information about an individual's personality that the participant may be unable or unwilling to report (Oltmanns & Turkheimer, 2009) and they are predictive of physical health outcomes over and above self-report (Jackson, Connolly, Garrison, Leveille, & Connolly, 2015; Kneip et al., 1993). Clinician ratings of borderline pathology were acquired using the Structured Interview for DSM-IV Personality (SIDP-IV; (Pfohl, Blum, & Zimmerman, 1997)); self- and informant reports were collected using the Revised NEO Personality Inventory (NEO PI-R; (Costa & McCrae, 1992)) and the Multisource Assessment of Personality Pathology (MAPP; (Oltmanns & Turkheimer, 2006)). Please see **Supplemental Material** for descriptions of these measures.

We performed an exploratory structural equation modeling (ESEM) analysis on BPD scores derived from interview (SIDP-IV) and self- and informant (NEO PI-R and MAPP) data collected at the Baseline, FU5, and FU10 assessments using maximum likelihood estimation in MPlus 7.3 (Muthén & Muthén, 1998-2012; additional details are provided in **Supplemental Material**). We hypothesized a one-factor model to account for the correlations among the 15 BPD measures (i.e., self and informant report and clinician ratings across Baseline, FU5, and FU10 assessment times). The unifactoral model was the best fit of the data, (RMSEA = .056, CFI = .976, TLI = .955) which according to conventional criteria is a good fit (Hu & Bentler, 1999). Factor loadings ranged from .45 to .70. Factor scores were estimated and saved for use in all subsequent analyses.

2.2.3 Childhood Physical Abuse

The 28-item Childhood Trauma Questionnaire (CTQ; (Bernstein et al., 2003; Scher, Stein, Asmundson, McCreary, & Forde, 2001)) was used to retrospectively assess emotional, physical,

and sexual abuse as well as emotional and physical neglect before the age of 17. Our decision to focus specifically on childhood physical abuse was two-fold. First, meta-analytic findings suggest that trauma type differentially impacts inflammatory signaling and that childhood physical abuse is associated with circulating IL-6 but not CRP levels (Baumeister et al., 2016). Second, autobiographical memory research finds that physically painful life events are more deeply encoded and therefore are more easily recollected than less physically threatening experiences (Rubin & Kozin, 1984). Additionally, older adults have a greater propensity for recalling more emotionally positive than negative events (Kennedy, Mather, & Carstensen, 2004; Schlagman, Schulz, & Kvavilashvili, 2006). Accordingly, identifying neglect may be more difficult within our older cohort, while autobiographic memories associated with physical trauma may be more likely to be preserved due to their increased salience. This is supported by evidence that discrepancies between prospective and retrospective reports of early life stress occur most in the detection of less severe (i.e., single occurrence or less physically evident) cases of maltreatment (Shaffer, Huston, & Egeland, 2008).

2.2.4 Global Physical Health and Health Behaviors

Global physical health was assessed at FU10 and baseline using the physical health composite (i.e., physical functioning, role limitations due to physical problems, pain, and general health perceptions) of the 36-item Health Status Inventory (Hays & Morales, 2001). The Health Status Inventory is a 36-item questionnaire that assesses subjective physical and mental health. It provides scores on 8 health constructs, including physical functioning, role limitations due to physical/emotional problems, pain, general health perceptions, emotional wellbeing, social functioning, and energy. The present study used the physical health composite, which is comprised

of the four weighted subscales: physical functioning, role limitations due to physical problems, pain, and general health perceptions.

Preventative health behaviors were assessed at FU10 using the 40-item Health Behavior Checklist (Vickers, Conway, & Hervig, 1990). Factor analytic evidence supports a two-factor model composed of preventative (i.e., avoiding or minimizing effects of accidents and maintaining or enhancing wellness) and risk-taking behavior (i.e., risk taking behaviors and substance use). Due to the strong association between preventative health behaviors and inflammation (Yates et al., 2008; Anderson et al., 2012; Richard, Couture, Desroches, & Lamarche, 2013; Dimitrov et al., 2006), we used this variable in our study.

2.2.5 IL-6 and CRP

Morning fasting blood samples were collected between 7:30-10:00 am via peripheral (primarily antecubital) venipuncture in an independent session closely following the SPAN FU10 assessment from consenting participants (n=791). Samples were processed according to standard operating procedures before being stored at -80º C (Tuck et al., 2009)**.**

IL-6 and CRP were assayed in duplicate using commercially available enzyme-linked immunosorbent assays (IL-6: Quantikine HS Human IL-6 ELISA, R&D Systems, Minneapolis, MN, USA; CRP: EIA-3954 High Sensitivity C-Reactive Protein ELISA DRG International Inc., USA). Intra- (IL-6: 5%, CRP: 4%) and inter- (IL-6: 14%, CRP: 13%) assay coefficients of variation were acceptable. Samples producing unreliable measures (i.e., intra-assay CVs >20%) of IL-6 (N=38; 4.8%) or CRP (N=22; 2.8%), even after being reassayed in duplicate were excluded leaving 753 and 769 measured data points for IL-6 and CRP, respectively.

2.2.6 Other Relevant Covariates

Age at the blood draw session was calculated using the participants' date of birth and the date of their blood draw appointment. Body Mass Index (***BMI***) and Mean Arterial Pressure (***MAP***) were directly measured (Life Source model UA-789) at the blood draw appointment. ***Medication*** use was assessed using lists of all current prescription drugs, over the counter medications, and supplements provided by participants at the FU10 interview and phlebotomy session. Medications were logged within the following medication classes: statin (n=307), beta blocker (n=172), calcium blocker (n=161), ACE inhibitor (n=303), benzodiazepines (n=50), hormonal medications (n=72), aspirin (n=296), prescription pain killer (n=98), NSAID (n=155), steroid medication (n=102), anti-depressant medication (i.e., a TCA, SSRI, or SNRI; n=175). Average hours of sleep per night and caffeine use (e.g., number of caffeinated beverages consumed in the average day) were assessed at the phlebotomy session. ***Baseline physical health*** was assessed at baseline assessment time using the health status inventory (the same measure used as our FU10 outcome variable). Depressive symptoms were measured at the FU10 session using the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). History of ever being a ***regular smoker*** (0 vs 1) was assessed at baseline.

2.3 Statistical Analyses

To maintain data variability but minimize the influence of extreme outliers, all outlier values on predictor variables of interest were winsorized to ±3 SDs before conducting analyses. Further, consistent with prior literature, inflammation markers (i.e., IL-6, CRP) were log transformed prior to analyses. All predicted associations were tested using bivariate correlations with listwise deletion. Benjamini-Hochberg false-discovery rate (fdr) was used to adjust for multiple comparisons. All analyses other than the simple bivariate correlations and demographic

comparisons were conducted using maximum likelihood (ML) estimation in M*plus* to retain missing data points. Any associations involving inflammation markers with evidence of significant bivariate correlation were further tested using a series of linear regressions with the following 20 covariates: age at blood draw, sex, self-reported ethnicity (i.e., white/not-white, Black/not-Black; Hispanic/not-Hispanic), BMI, MAP, sleep, caffeine, and medication class usage (see list in covariate section). Regressions not involving inflammation markers included the following 5 covariates: sex, white/not white, black/not black, Hispanic/not Hispanic, age. Our hypothesized mediational model included all 20 covariates included in our inflammation analyses on all paths (see also **Figure 1**). This analysis was repeated in 3 additional forms: (1) with the addition of baseline physical health and lifetime regular smoking status as a covariate, (2) with the analysis just mentioned but using listwise deletion, and (3) with no covariates. As reported in the **Supplemental Material**, these different analytic approaches yielded a consistent pattern of results.

3. Results

3.1 Participants Characteristics and Associations with Variables of Interest

Supplemental Tables 7.1-7.3 detail participant characteristics on demographic and study-relevant assessments as well as their associations with our variables of interest (i.e., childhood physical abuse, borderline factor scores, IL-6, CRP, health behaviors, and global physical health). Briefly, self-reported ethnicity was significantly associated with all variables of interest except preventative health behaviors (**Supplemental Table 1**). Relative to all others and European-Americans, African-Americans had higher inflammation and reported greater childhood abuse as well as more physical health problems and reduced preventative health behaviors, but had lower BPD factor scores. Given the negative relationship with borderline pathology, separate serial mediation analyses were conducted in the African American (n=153) and European American subsamples (n=430; Supplemental Table 7.8-7.9). Compared to men, women had higher levels of CRP and engaged in more preventative health behaviors (**Supplemental Table 7.2**).

3.2 Elevated Inflammation: A Putative Pathway Linking Childhood Abuse, Borderline Personality Pathology, and Health Behavior to Physical Health

Bivariate correlations between childhood physical abuse, borderline personality pathology preventative health behaviors, IL-6, CRP, and physical health are presented in **Table 1** with correction for multiple testing. Below we describe FDR-corrected correlations of hypothesized and other notable associations as well as these results when considering our covariates, and finally, our integrated mediational model.

Table 3.1: Correlation matrix for variables of interest

	IL-6	CRP	Childhood Physical Abuse	Borderline Pathology	Preventative Health Behaviors
Childhood Physical Abuse	0.126** (n=738)	0.080* (n=754)	--	--	--
Borderline Pathology	0.165** (n=753)	0.092* (n=769)	0.256** (n=1052)	--	--
Preventative Health Behaviors	-0.302** (n=738)	-0.218** (n=754)	-0.081* (n=1050)	-0.256** (n=1052)	--
Physical Health	-0.346**** (n=732)	-0.289*** (n=748)	-0.200** (n=1038)	-0.380**** (n=1039)	0.341*** (n=1038)

p-FDR is denoted as follows: * $p<10^{-4}$; ** $10^{-4}<p<10^{-11}$; *** $10^{-11}<p<10^{-15}$; **** $p>10^{-21}$

Childhood Physical Abuse was predictive of elevated borderline personality pathology, while being negatively associated with physical health and unrelated to preventative health behaviors. The association between childhood physical abuse and IL-6 was not robust to the inclusion of borderline pathology (β=0.009, p=0.83), consistent with the meditational model presented below. ***Borderline Personality Pathology*** was associated with reduced preventative health behaviors and worse physical health. ***Preventative health behaviors*** were positively correlated with physical health. ***IL-6*** and ***CRP*** were both associated with increased childhood physical abuse and borderline personality pathology while being negatively correlated with preventative health behaviors and physical health. Suggestive of unique associations between borderline pathology and inflammation, these associations were robust to the additional inclusion of either childhood abuse (IL-6: β= 0.11, p=0.004; CRP: β= 0.11, p=0.005) or depression (IL-6: β= 0.07, p=0.02; CRP: β= 0.06, p=0.05, which was also uniquely associated with inflammation; **Supplemental Figure 2**). As depicted in **Table 3.2**, all of these associations were robust to the inclusion of our covariates, with the exception of the link between childhood physical abuse and CRP, which was reduced to a trend. As a result of meta-analytic evidence that CRP is not

associated with childhood physical abuse (Baumeister et al., 2016) as well as the lack of an association between childhood physical abuse and CRP after accounting for covariates in our sample, we did not include CRP in our mediational models.

Our mediational model provides support for a serial indirect association wherein childhood physical abuse is indirectly linked to worse physical health in later-life through increased borderline pathology, reduced preventative health behavior, and increased inflammation (**Figure 1; Supplemental Table 7.4**). This indirect association remained significant when baseline physical health and lifetime regular smoking status were added to the model, when this analysis was conducted using listwise deletion, or when no covariates were included (**Supplemental Table 7.5-7.7)**. Of note, when examined our analyses within our ethnicity subsamples (African American and European American), the serial meditational model was only significant in European Americans (Indirect Effect: maximum likelihood estimate: B= -0.07, CI= [-0.15, -0.02]; listwise deletion: B= -0.02, CI= [-0.21, -0.003]), because borderline personality pathology was not predictive of preventative health behaviors nor was preventative health behaviors predictive of inflammation within the African American subsample (Indirect Effect: maximum likelihood estimate: B= -0.02, CI= [-0.14, 0.03]; listwise deletion: B= -0.02, CI= [-0.21, 0.002]). However, within the African American subsample, the pathways in the model, though non-significant, were consistent with our hypothesized direction. Therefore, it is possible that given the small sample size of the African American subsample (Total sample: 1630; African American subsample: n=516 [with measured biomarkers, n=130]; European American subsample: n=1061 [with measured biomarkers, n=542]; Other subsample: n=56 [with measured biomarkers, n=18]), we were unpowered to detect meaningful effects. Analyses examining the interactive effect of African American ethnicity and variables of interest revealed a significant effect of preventative health

behaviors x African American ethnicity on physical health (maximum likelihood estimate: B=1.41, p=0.01; **Supplemental Table 7.8**). Follow up analyses revealed that this effect was significant in both the European American (maximum likelihood estimate: B=0.02, p<0.001; listwise deletion: B= 1.71, p<0.001) and African American subsamples (maximum likelihood estimate: B=0.02, p=0.005; though not significant in listwise deletion: B=1.21, p=0.15), though the effect is slightly larger for European Americans.

Figure 3.1: Serial Mediation Model of Child Abuse, BPD, Preventative Health Behaviors, and IL-6 Predicting Physical Health

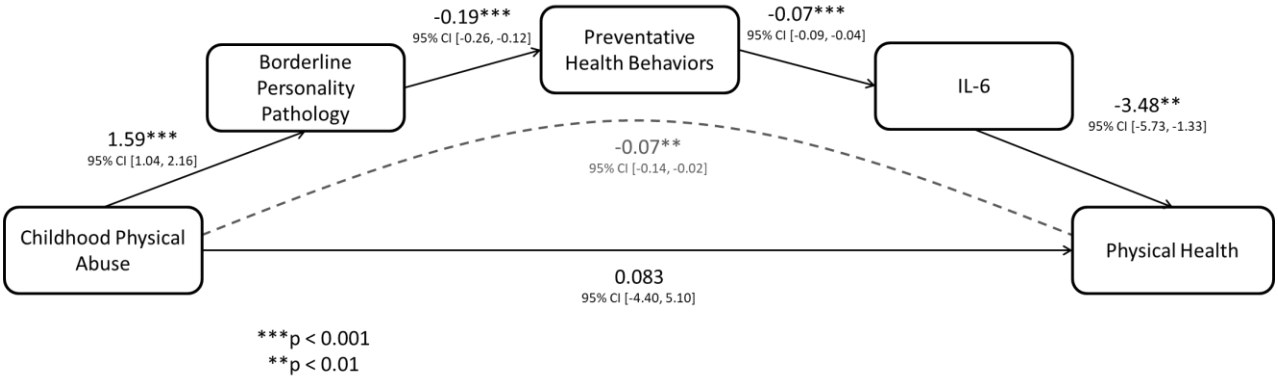

Figure 3.1: The relationship between childhood abuse (i.e., physical and sexual abuse) and worse physical health in later life is accounted for by borderline personality pathology, preventative health behaviors, and IL-6. BPD mediated the association between childhood physical abuse and elevated IL-6. Preventative health behaviors mediated the link between BPD and inflammation, and inflammation indirectly linked BPD with worse physical health. An integrated model suggests an indirect pathway between childhood abuse, greater BPD symptomology, reduced preventative health behaviors, elevated IL-6, and worse health outcomes. Covariates included, age, sex, 19 medication classes, mean arterial pressure, caffeine consumption, sleep, baseline physical health, and smoking (see Covariate section). The association between childhood abuse and physical health (C pathway, -4.401, p = 0.05) was entirely accounted for by this indirect pathway Effects represent unstandardized coefficients with bootstrapped 95% confidence intervals.

Table 3.2: Regressions Predicting Variables of Interest When Accounting for all Covariates and Using Full Information Maximum Likelihood Estimation

	IL-6[a]	CRP[a]	Childhood Physical/Sexual Abuse[b]	Borderline Pathology[b]	Preventative Health Behaviors[b]

Childhood Physical Abuse	**0.08***	0.032	--	**--**	**--**
Borderline Pathology	**0.12****	**0.10***	**0.23*****	--	**--**
Preventative Health Behaviors	**-0.22*****	**-0.16*****	-0.04	**-0.26*****	--
Physical Health	**-0.19*****	**-0.18*****	**-0.11*****	**-0.41*****	**0.33*****

***p≤0.001; **p≤0.01; *p≤0.05

Effect represents standardized beta values.

[a]Analyses involving inflammation markers included the following covariates: sex, white/not white, black/not black, Hispanic/not Hispanic, age, mean arterial pressure, sleep, caffeine, BMI, statin (n=307), beta blocker (n=172), calcium blocker (n=161), ACE inhibitor (n=303), benzodiazepines (n=50), hormonal medications (n=72), aspirin (n=296), prescription pain killer (n=98), NSAID (n=155), steroid medication (n=102), anti-depressant medication (i.e., a TCA, SSRI, or SNRI; n=175).

[b]Analyses involving only non-inflammatory variables included the following covariates: sex, white/not white, black/not black, Hispanic/not Hispanic, age

4. Discussion

The high comorbidity between mental and physical health conditions (Barnett et al., 2012; Quirk et al., 2016), and their unequivocal association with early life stress (1-4), suggest that common underlying pathways shaped by early life stress may underlie their expression. Our study examined whether borderline personality pathology, health behaviors, and inflammation indirectly link childhood physical abuse to physical health in a large sample (n=1,630) of aging adults. Three findings within our study are particularly noteworthy. First, we find evidence that borderline pathology is associated with heightened inflammation (i.e., IL-6 and CRP; (17-19)) and that these associations are present even when considering childhood physical abuse or depression. Second, IL-6, but not CRP (when considering potential confounding covariates), was associated with childhood abuse, consistent with recent meta-analytic evidence (Baumeister et al., 2016). While the association between CRP and childhood physical abuse was trending in our sample after accounting for potential confounding covariates, this correlation may indeed reflect a meaningful association that could be uncovered in future prospective studies before medication use and other related factors develop (e.g., obesity). Third, and most importantly, we find evidence for an indirect pathway wherein childhood physical abuse is indirectly linked to worse physical health in later-life through increased borderline personality pathology, reduced preventative health behavior, and increased inflammation (**Figure 1**). Broadly, these results are consistent with theoretical work advanced by Miller, Chen, and Parker (2011) that adversity encountered in childhood leads to biological (e.g., pro-inflammatory responsivity) and behavioral (e.g., emotion dysregulation, impulsivity) programming that initiates, maintains, and exacerbates chronic inflammation to increase risk for later age-related disease. In particular, our data provide evidence that it is plausible that childhood physical abuse may promote the development of borderline

personality pathology, which, through reduced preventative health behavior, increases inflammation signaling and risk for later age-related physical disease.

Consistent with a developing literature, borderline pathology was related to worse physical health (7-11), as well as increased inflammation (17-19). We are only aware of three prior studies of borderline personality pathology and inflammation (17-19), which found evidence of increased inflammation, and in particular IL-6 levels, among patients with comorbid borderline personality disorder and major depressive disorder (17-19). Our study critically extends this work by showing that borderline personality pathology present in the general population is associated with elevated IL-6 and CRP, and further, that these relationships are present even after accounting for depressive symptoms (17-19), and childhood physical abuse. Thus, our data suggest that borderline personality pathology, even in subclinical forms, has unique assocaitions with inflammation beyond its common comorbidity with childhood adversity and depressive symptoms, and that such increased inflamamtion may arise from borderline personality pathology associated reductions in prevenative health behaviors (El-Gabalawy et al., 2010; Frankenburg & Zanarini, 2004), to increase risk for age-related physical health conditions.

Collectively, our data are consistent with speculative theory that early life stress-related behavioral proclivities may serve to initiate, maintain, and enhance risk for age-related physical health problems through inflammatory effects. A critical issue unaddressed by our data is whether inflammation linked to physical abuse during childhood may elicit borderline personality pathology, the expression of which may further exacerbate greater systemic inflammation. While there is evidence to support such bidirectional associations between inflammation and psychopathology as well as related behavior (e.g., impulsivity (Miller et al., 2011); reward dysfunction (Treadway et al., 2017)), such data do not exist for borderline personality pathology

specifically. We are unable to test such a model in our data because it requires measures across the entire lifespan (e.g., inflammation markers assessed during childhood prior to the development of borderline personality characteristics), that are unavailable in our sample.

It is important to consider the limitations of this study in its interpretation. First, our mediational model implies a direction of effect. While these models were built based upon prior evidence supporting their directionality (Miller et al., 2011), as well as their temporal assessment in our study, the lack of multiple measures for each phenotype (e.g., inflammation) across the lifespan did not permit us to evaluate whether change in each variable temporally precedes change in another. However, given our lifecourse perspective, to truly inform such temporality, we would need such measures across the entire lifespan, including childhood. For our model, we temporarily anchor childhood adversity (collected at FU10) as preceding borderline pathology (collected at baseline, FU5, and FU10, and stable across time) and inflammation (collected at FU10) based on foundational literature [e.g., ELS predicting BPD symptomatology (Hiraoka et al., 2016; Zanarini et al., 1997) and inflammation in adulthood (Danese et al., 2008; Danese, Pariante, Caspi, Taylor, & Poulton, 2007)]. Further, though the preventative health, inflammation, and physical health variables were not temporally discernable based on timing of data collection (FU10), we posited directionality guided by theoretical hypotheses (Miller, Chen, and Parker, 2011) and extant literature suggesting the effect of preventative health behaviors on both inflammation and physical health (Yates et al., 2008; Anderson et al., 2012; Richard, Couture, Desroches, & Lamarche, 2013)). Moreover, we were able to include our physical health composite as assessed during our baseline visit as a covariate, suggesting that our observed effects are not attributable to preexisting health problems. In addition to constraining conclusions about temporality, estimates generated by our mediational model may be biased because components in our mediational model (e.g.,

retrospective report of ELS, inflammation, preventative health behaviors, and physical health) were collected at the same time point (Maxwell & Cole, 2007).

Notably, additional pathways to poor health must be considered. For example, in addition to our serial meditational model, we found that baseline physical health also indirectly links childhood physical abuse to later physical health problems. This pathway may represent the presence of an additional pathway to poor health, but may also reflect the same serial indirect pathway occurring at an earlier time (e.g., it is possible that BPP pathology, preventative health behaviors and inflammation occurring prior to the baseline health assessment provide an indirect link). Additionally, when examining our model within the ethnicity subsamples, we found that the indirect effect was only significant in the European American subsample and not the African American subsample (though the non-significant effect was in the same direction). Upon further examination, we found a significant moderation of ethnicity on the relationship between preventative health behaviors and physical health in both ethnicity subsamples, though the effect was slightly stronger for European Americans. This result, along with an independent finding in this sample showing that increased inflammation (CRP) in African Americans was entirely accounted for by comparably reduced caffeine use (increased caffeine intake was associated with reduced CRP levels) by African Americans (C: B=0.10, CI= [0.01, 0.19]; C' (pathway after accounting for indirect effect): B= 0.14, p=0.16; Indirect Effect: B=0.12, CI= [0.01, 0.31]), suggests that cultural influences (e.g., food/beverage consumption) may be an example of an independent pathway to poor health above personality considerations.

Second, consistent with literature showing that BPD "matures out" with age (Shea et al., 2009; Zanarini, Frankenburg, Reich, & Fitzmaurice, 2012), only 0.4% of our sample met diagnostic (e.g., DSM-5) criteria for BPD, which is less than an epidemiological study identifying

a prevalence rate of 2.7% (NESAR: (Tomko, Trull, Wood, & Sher, 2014)). Despite evidence that certain maladaptive personality traits are less common in older adulthood, previous research using data from the SPAN study shows that these traits continue to contribute unique variance to the prediction of stressful life events, marital satisfaction and physical health in later life (Gleason, Weinstein, Balsis, & Oltmanns, 2014). BPD, in particular, exhibits associations with negative health perceptions and increased healthcare utilization at six-month follow-up in this sample (Powers & Oltmanns, 2013), and is related to arthritis and heart disease, with obesity partially mediating these associations (Powers & Oltmanns, 2013). Additionally, focusing on an older adult sample was important for the purposes of our study as it afforded us the unique opportunity to explore the physical health issues related to the aging immune system, which leads to greater susceptibility to illness and increased frequency of new health problems onset.

Third, our measure of childhood physical abuse was measured using retrospective self-report, which may introduce error in report. However, these concerns are likely overstated, particularly given findings that there is less discrepancy between prospective and retrospective reports of ELS when asked to recount more salient or severe events (Kennedy et al., 2004), such as physical abuse, as well as the demonstrated convergent validity with clinican-rated childhood abuse interviews (Scher et al., 2001). Further, identified reporting bias tends to lead to underreporting of maltreatment (Hardt & Rutter, 2004; Shaffer et al., 2008), thereby introducing noise into our model and likely reducing our power to detect associations. Finally, when interpreting the current results, it is important to recognize that a representative community sample does not mean a sample devoid of pathology. Forty-four percent of the current sample indicated that they "received treatment for a mental disorder or advice from a mental health professional on problems in life" at some point in their lifetime (Lawton & Oltmanns, 2013). At the same time,

clinical samples would likely exhibit greater psychiatric medication usage and comorbidity between BPD and other psychiatric conditions, making it harder to control for the effects of these sample characteristics. Additionally, our findings using a dimensional approach to personality pathology highlight the fact that, even in individuals who exhibit subthreshold levels of BPD symptoms, these effects on preventative health behaviors and physical health outcomes are significant. Although we consider the representativeness of the current sample as a strength of the current analyses, it will be important to replicate these results in a clinical sample with greater rates of individuals who meet full criteria for BPD.

Limitations notwithstanding, our results support theory positing that childhood stress-related immune function plays an important role in the development of comorbid mental health and physical health disorders (Miller & Blackwell, 2006; Nusslock & Miller, 2016). The observed indirect association suggests that borderline personality pathology and related preventative health behavior as well as inflammation may represent behavioral and biological mechanisms linking childhood physical abuse to poor physical health in later life. As such, these represent potential therapeutic targets to reduce the impact of childhood adversity on later health.

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Appendix 1

Behavioral and pathophysiological mechanisms of childhood abuse

Human and non-human animal studies have produced a wealth of results documenting the plethora of lasting negative effects of early life stress (e.g., childhood physical abuse)(Miller, Chen, & Parker, 2011), ranging from mental health to physical health problems. For example, childhood maltreatment is a reliable predictor of borderline personality pathology (Hiraoka et al., 2016; Zanarini et al., 1997) and a documented risk factor for age-related diseases, such as neurological disorders and cardiovascular disease (Wegman & Stetler, 2009). Given the broad and lingering consequences of early adversity, it is important to characterize the mechanisms, such as biological embedding, through which early life stress promotes risk for physical and psychiatric diseases.

Biological embedding of childhood adversity

The biological embedding of childhood adversity model (Miller et al., 2011) offers a compelling, integrated framework for how the effects of early stress persists across the lifespan. This theory posits that adversity in childhood, a period of enhanced plasticity and marked sensitivity to environmental inputs, leads to biological (e.g., pro-inflammatory responsivity) and behavioral (e.g., emotion dysregulation, impulsivity) programming that maintains and exacerbates chronic inflammation, which cumulatively drives the pathogeneses of mental and physical disease states.

Childhood Adversity and Immune Function

Evidence shows that children exposed to maltreatment have higher levels of inflammatory cytokines, including CRP and IL-6 (Danese et al., 2011). Further, this pattern of elevated inflammation extends through adulthood, with findings in adults with histories of childhood

abuse mirroring the results in children (Danese et al., 2008). Importantly, these associations are above and beyond potential confounding factors, including psychiatric diagnosis, suggesting a unique effect of childhood adversity on a lasting elevated inflammation profile.

These stress-related elevations in immune function associated with childhood adversity may initially represent adaptive responding to environmental threat. As the mediator of a wide-range of functions, including defense against pathogens as well as behavioral modifications that affect mood, energy, and cognition to facilitate recovery from infection, the proliferation of pro-inflammatory cytokines in response to a stressor would be of great importance in the face of acute and time-limited stressors (e.g., fight or flight from a predator) (Segerstrom & Miller, 2004). However, as patterns of immune functioning are established in early childhood (Finch & Crimmins, 2004), these early experiences promote a tendency for a heightened inflammatory response. Results from a prospective study of inflammation in adolescents,(Miller et al., 2011) showing that pro-inflammatory (e.g., IL-6) response becomes increasingly greater over time, supports this hypothesis that early trauma would promote the propagation of an increased responsivity of the immune system to later challenges

Further lending evidence to the pro-inflammatory tendencies programming hypotheses, both physical health conditions (Maggio, Guralnik, Longo, & Ferrucci, 2006; Ridker, Hennekens, Buring, & Rifai, 2000; Ridker, Rifai, Stampfer, & Hennekens, 2000) and mental health disorders (e.g., comorbid depression and borderline personality disorder (Kahl et al., 2006; Kahl et al., 2009; Kahl et al., 2005)), which are linked to exposure to early adversity (Hiraoka et al., 2016; Mock & Arai, 2010; Wegman & Stetler, 2009; Zanarini et al., 1997) , are associated with elevated inflammation. Notably, the association between inflammation and psychopathology is shown to be exacerbated by the presence of childhood adversity (Danese et

al., 2008). Collectively, these data suggest that chronic elevated inflammation may link childhood abuse, borderline personality pathology and physical health outcomes.

Borderline personality disorder, physical health, and inflammation

As with childhood abuse, borderline personality pathology is also associated with later stress- and age-related physical health conditions, such as cardiovascular disease, diabetes, obesity, and arthritis (El-Gabalawy, Katz, & Sareen, 2010; Powers & Oltmanns, 2013), somatic syndromes (e.g., fibromyalgia and chronic fatigue (Frankenburg & Zanarini, 2004)), as well as subjective health complaints (Powers & Oltmanns, 2013). Further, though only examined in the context of depression, there is some initial evidence (Kahl et al., 2006; Kahl et al., 2009; Kahl et al., 2005) suggesting that elevated inflammation, in particular IL-6, may play a critical role in this relationship between physical and mental health.

Preventative health behaviors, borderline personality pathology, inflammation, and physical health

In addition to the proposed immune function changes, the biological embedding model proposes that certain "behavioral proclivities" develop in response to early adversity serve to maintain and further exacerbate the chronic inflammation tendencies promoted by these same childhood experiences (Miller et al., 2011). Borderline personality pathology, characterized by pervasive affective instability, interpersonal dysfunction, and high levels of impulsivity, encompasses those behaviors identified in the model. According to the theory, behaviors such as emotion dysregulation and impulsivity may impact the development of healthy relationships and increase engagement in unhealthy lifestyles choices, which in turn will amplify the chronic inflammation predisposition.

Childhood adversity is associated with later maladaptive health behaviors, including alcohol dependence, illicit drug use, and infrequent exercise (Felitti et al., 1998; Lovallo, 2013). Impulsivity is similarly linked to poor health behaviors such as disinhibited eating (Yeomans, Leitch, & Mobini, 2008), risky sexual behaviors (Atkins, 2008), and alcohol, drug, and tobacco use (Robbins & Bryan, 2004). In line with this literature, individuals with borderline personality pathology are more likely to engage in poorer health-related lifestyle behaviors, such as tobacco use, increased substance use, reduced exercise; (El-Gabalawy et al., 2010; Frankenburg & Zanarini, 2004), as well as potentially acutely harmful behaviors, such as medical self-sabotage (e.g., misuse of prescription medication (Sansone, Mclean, & Wiederman, 2008)) and suicidal and non-suicidal self-injury (Black, Blum, Pfohl, & Hale, 2004). Given the profound impact that preventative health behaviors (e.g., regular exercise (Yates et al., 2008), healthy diet (Anderson et al., 2012; Richard, Couture, Desroches, & Lamarche, 2013), and balanced sleep (Dimitrov et al., 2006)) have on physical health and inflammation, the associated reduction of preventative health behaviors in individuals with borderline personality pathology presumably add to their biologically embedded pro-inflammatory predisposition.

Specific Aims

Despite findings from independent studies supporting individual components [either the biological (e.g., pro-inflammatory responsivity) or behavioral (e.g., emotion dysregulation, impulsivity)] of the biological embedding of childhood adversity theory (Miller et al., 2011), few studies concurrently evaluate the links between psychopathology symptomatology, early life adversity, physical health factors, and inflammation (Hepgul et al., 2012; Taylor, Lehman, Kiefe, & Seeman, 2006). Here, I present a study aimed at examining each of these proposed links in a model within a representative community sample.

Using data (n=1,630) from adults ages 60-72 who have participated in the ongoing longitudinal St Louis Personality and Aging Network (SPAN) study (Oltmanns, Rodrigues, Weinstein, & Gleason, 2014), we examined associations between childhood abuse (i.e., physical and sexual), borderline personality pathology, inflammation markers (i.e., IL-6 and CRP), preventative health behaviors, and a global index of physical health.

Aim 1: Examine the associations between childhood physical abuse, borderline personality pathology, and inflammation markers (i.e., IL-6 and CRP). Findings from a recent meta-analysis (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016) suggest potential specificity of trauma exposure, such that different types of childhood trauma may be associated with different aspects of inflammatory dysregulation. The meta-analysis revealed that childhood physical abuse were associated with significantly increased IL-6 and TNF-α, but not CRP; whereas CRP was significantly associated with parental absence in childhood. Based on these findings, we expected that the link between childhood physical abuse and inflammation would be stronger for IL-6, and potentially absent with CRP (Baumeister et al., 2016).

Aim 2: Examine the associations between childhood physical abuse, borderline personality pathology, and inflammation markers (i.e., IL-6 and CRP), preventative health behaviors, and a global index of physical health. Given the proposed theory suggesting preventative health behaviors as an behavioral link between psychopathology and inflammation (Miller et al., 2011), and independent studies examining some but not all components of the proposed theory (6-11; 14-19), we propose an integrated model of these associations. Specifically, we hypothesized that childhood abuse would be indirectly linked to worse physical health through borderline pathology expression and associated lower health behaviors and elevated inflammation.

Appendix References

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SUPPLEMENTAL INFORMATION

7.1 Supplemental Methods

7.1.2 Recruitment

Participants were recruited using listed phone numbers that were crossed with current census data in order to identify households with at least one member in the eligible age range. When more than one person in a household was in the target age range, the conservative Kish method (Kish, 1949) was used, which enables the random selection of one individual from the household (i.e., sampling without replacement). If the target refused to participate, other eligible residents were not included. Individuals were excluded if they lacked a permanent residence, could not read at a 6th-grade level, or had active psychotic symptoms

7.1.3 Informants

Participants identified an informant that knew them well and could describe their personality. Ninety percent of the participants had an associated informant consent to the SPAN protocol and complete the baseline assessment (n = 1,467). Informants were majority female (68%, n = 1,004) and European-American (67%, n = 979). Ages ranged between 18 and 92 (M = 55, SD = 11.4), and informants had known the participant for an average of 32 years (SD = 15). In terms of their relationship with the participant, most of the informants were a spouse or romantic partner (48%, n = 702), followed by other family members (28%, n = 404), friends (22%, n = 328), with the remaining informants consisting of neighbors, coworkers, or other acquaintances (2%, n = 33). Informants completed questionnaires through the mail or online. They received $30 remuneration for questionnaires completed during a follow-up in which the participant had an in-person session, and $10 for all other follow-up questionnaires.

7.1.4 Borderline Pathology Assessment Measures

Clinical Interview: The SIDP-IV is a semi-structured interview in which trained interviewers rate 80 items corresponding to criteria of the 10 PDs on a scale of 0 (no pathology present) to 3 (pathology strongly present). SIDP scores were treated continuously by summing responses across the 9 BPD criteria. All interviews were conducted by graduate students in clinical psychology and trained undergraduate research assistants and interrater reliability ratings from a selected subsample of 265 video-recorded interviews was excellent (intraclass correlation coefficient: 0.77); Oltmanns et al., 2014).

Self and Informant Report: The NEO PI-R (Form S for self; Form R for informant) consists of 240-items assessing the five domains of neuroticism, extraversion, openness, agreeableness, and conscientiousness, as well as six lower-order facets within each domain. NEO PI-R borderline pathology scores were generated independently for self and informant report by summing anxiety, angry hostility, depression, impulsiveness, vulnerability, openness to feelings, openness to actions, compliance (reverse scored), and deliberation (reverse scored) facet scale scores (Miller, Reynolds, & Pilkonis, 2004). The MAPP is an 80-item measure of personality pathology based on lay translations of DSM-IV PD diagnostic criteria. Self- and informant MAPP BPD scores were calculated by summing responses across the 9 BPD items

7.1.5 Borderline Personality Disorder Factor Scores

We performed an exploratory structural equation modeling analysis in Mplus 7.3 using maximum likelihood estimation on BPD scores derived from interview (SIDP-IV) and self- and informant (NEO PI-R and MAPP) data collected at the Baseline, FU5, and FU10 assessments. We hypothesized a one-factor model to account for the correlations among the 15 BPD measures.

However, because the unique components of the same measure administered on different occasions are likely to be correlated, we included them in the a priori model. An evaluation of model fit with these correlated residuals resulted in an improvement in fit as compared to a baseline model without them (RMSEA = .115, CFI = .867, TLI = .813 vs. RMSEA = .184, CFI = .588, TLI = .520) but still does not provide an acceptable fit to the data. Modification indices suggested that the error terms correlated across method (e.g., participant MAPP with NEO, informant MAPP with NEO), and were therefore estimated in a subsequent model. This resulted in very good to excellent model fit (RMSEA = .056, CFI = .976, TLI = .955) according to conventional criteria (Hu & Bentler, 1999). Factor loadings in this model ranged from .45 to .70. Factor scores were estimated and saved for use in all subsequent analyses.

7.2 Supplemental Results

In addition to findings reported in the manuscript using maximum likelihood (ML) estimation in M*plus*, the model was also tested using listwise deletion (n=613) in SPSS using the PROCESS macro (Hayes, 2013), which produced similar results, as reported below.

Figure 7.1: Serial Mediation Model

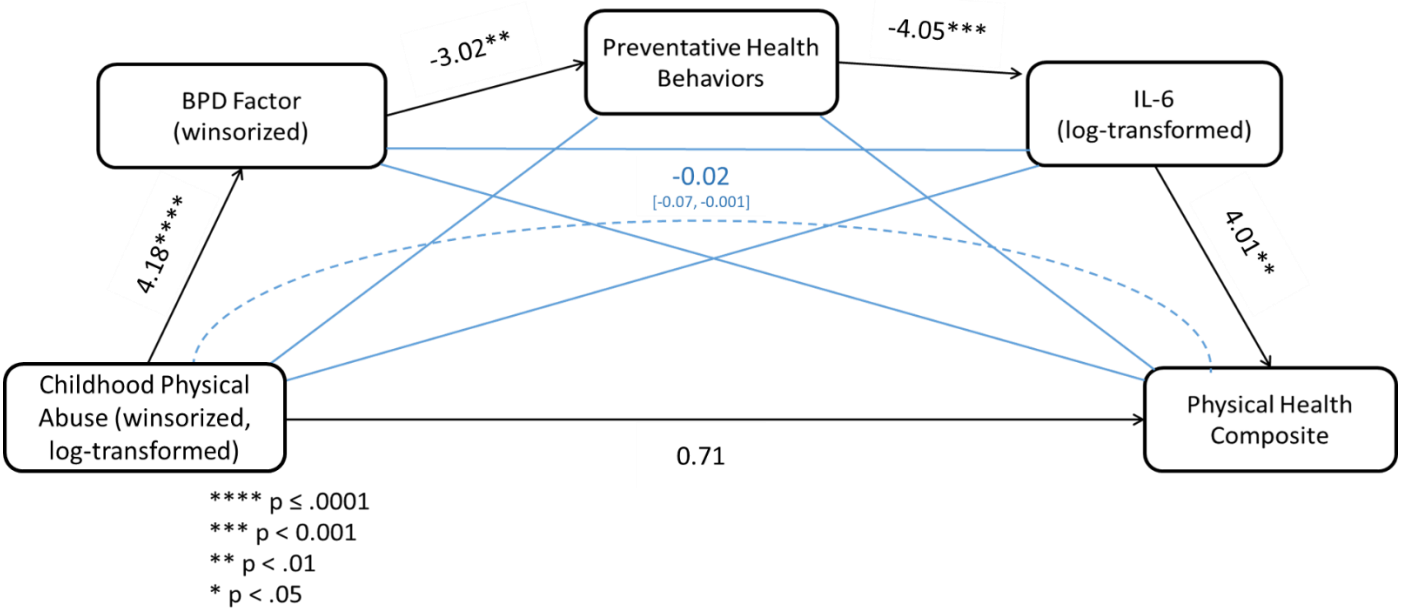

Figure 7.1. The relationship between childhood abuse (i.e., physical and sexual abuse) and worse physical health in later life is accounted for by borderline personality pathology, preventative health behaviors, and IL-6. An integrated model suggests an indirect pathway between childhood abuse, greater BPD symptomology, reduced preventative health behaviors, elevated IL-6, and worse health outcomes. Covariates included, age, sex, 19 medication classes, caffeine consumption, sleep, smoking, and baseline health. Pathways represent non-standardized coefficients. The association between childhood abuse and physical health was entirely accounted for by this indirect pathway (without BPD, preventative health behaviors, and IL-6, this association was significant at t= -2.58, p= 0.01).

Figure 7.2: Association Between Inflammation and Depression

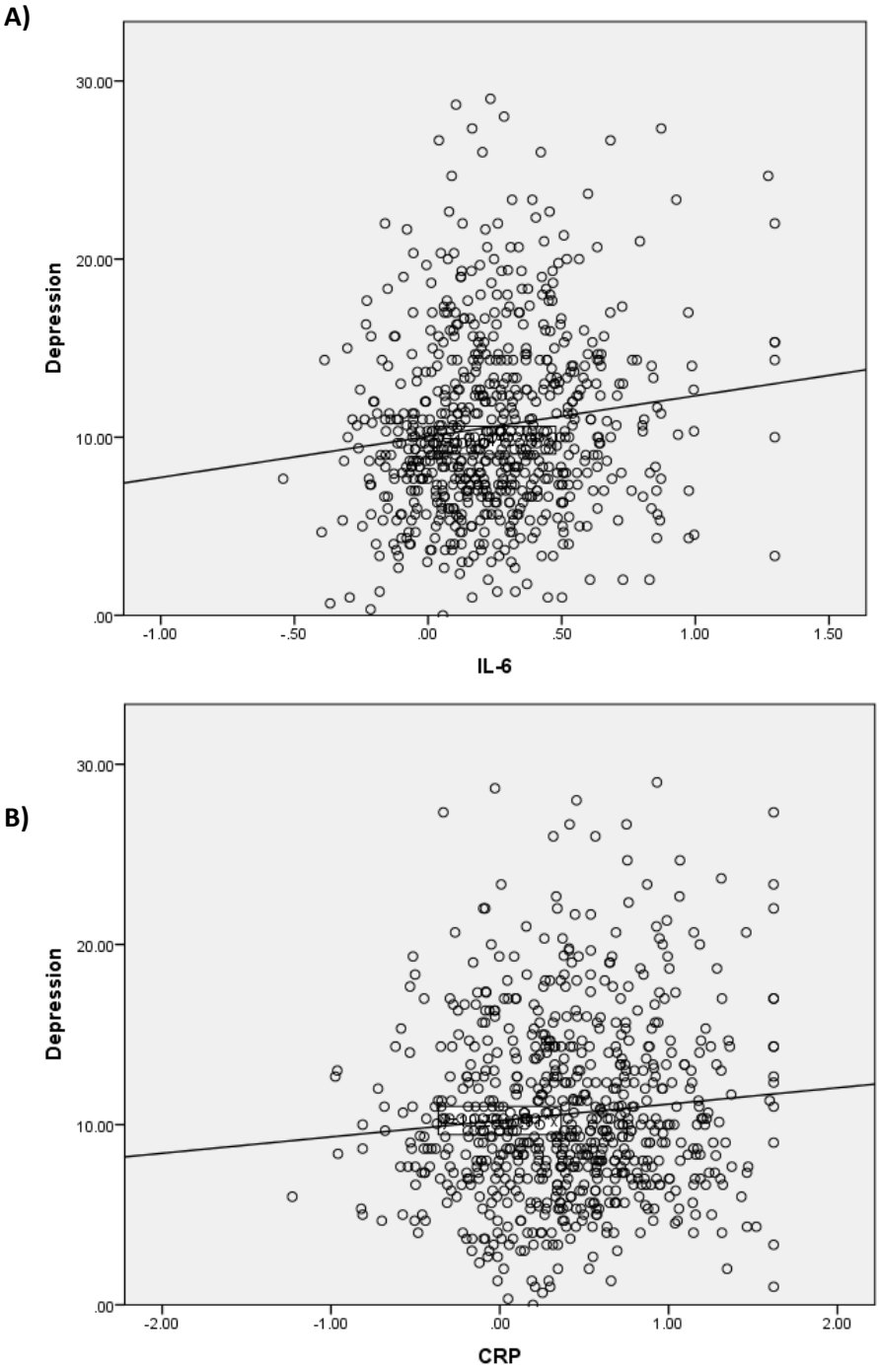

Figure 7.2. There was a significant positive association between depression and **A)** IL-6 (β=0.099, p=0.019), and **B)** CRP (β=0.103, p=0.017) were found, after inclusion of covariates.

Table 7.1: Associations with Ethnicity

	European American Total n=1061			African American Total n= 516			Hispanic Total n= 39			Total n=		
	N	Mean(SD)	t/ χ^2	n	Mean(SD)	t/ χ^2	N	Mean(SD)	t/ χ^2	n	Mean(SD)	Timepoint
Covariates of Interest												
IL-6	542	0.23(0.28)	-3.91***	195	0.32(0.29)	3.40**	18	0.28(0.23)	0.30	753	0.26(0.29)	FU10
CRP	551	0.35(0.51)	-5.02***	201	0.56(0.51)	4.73***	18	0.51(0.39)	0.82	769	0.41(0.52)	FU10
Childhood Physical Abuse	744	1.06(1.54)	-9.93***	284	0.88(0.14)	9.47***	22	.82(0.11)	0.32	1052	0.81(0.13)	B
Borderline Pathology	1061	0.01(1.02)	0.63	516	-0.06(1.04)	-1.48	30	-0.14(0.79)	-0.570	1630	-.00001(1.04)	B,FU5,FU10
Preventative Health Behaviors	742	0.83(0.90)	4.61***	286	-0.20(0.91)	-4.30***	22	-0.22(0.81)	-1.11	1053	-0.01(0.92)	FU10
Physical Health	741	60.93(8.91)	6.51***	274	56.29(11.05)	-6.03***	20	62.75(6.62)	2.10	1039	59.57(9.81)	FU10
Covariates of No Interest												
Age	570	65.92(2.87)	-0.01	204	66.02(2.97)	0.59	18	65.17(2.38)	-1.12	791	65.92(2.89)	FU10
Gender (# women)	577	54.38% women	χ^2=0.29	291	56.40% women	χ^2=0.72	13	43.33% women	χ^2=1.69	1617	54.9% woman	FU10
BMI	654	29.40(6.56)	-4.27***	251	31.60(7.17)	4.28***	18	32.45(5.52)	1.85	924	.02(6.91)	FU10
Beta Blockers	617	0.18(0.39)	-2.01*	225	0.25(0.44)	2.20**	18	0.11(0.32)	-1.16	860	0.20(0.40)	FU10
Calcium Channel Blockers	617	0.13(0.34)	-5.97***	225	0.33(0.47)	5.77***	18	0.11(0.32)	-0.84	860	0.19(0.39)	FU10
Statins	617	0.36(0.48)	-0.04	225	0.38(0.49)	0.76	18	0.22(0.43)	-1.34	860	0.36(0.48)	FU10
ACE/ARBs	617	0.32(0.24)	-2.85**	225	0.44(0.50)	3.28**	18	0.22(0.43)	-1.29	860	0.35(0.48)	FU10
Benzodiazepines	617	0.06(0.24)	1.01	225	0.04(0.21)	-1.10	18	0.06(0.24)	-0.05	860	0.06(0.23)	FU10
Hormone Medications OC/HT	617	0.10(0.29)	2.25*	225	0.05(0.23)	-2.17	18	0.00(0.00)	-8.87***	860	0.08(0.28)	FU10
Aspirin	617	0.34(0.48)	-0.22	225	0.35(0.48)	0.09	18	0.44(0.51)	0.91	860	0.34(0.48)	FU10
Rx Pain	617	0.10(0.30)	-2.05*	225	0.15(0.36)	1.88*	18	0.00(0.00)	-10.53***	860	0.11(0.32)	FU10

Non-Steroidal Anti-Inflammatory Drugs	617	0.19(0.39)	1.18	225	0.16(0.36)	-1.16	18	0.17(0.38)	-0.153	860	0.18(0.39)	FU10
Steroid Medications	617	0.11(0.31)	-1.16	225	0.14(0.35)	1.21	18	0.06(0.24)	-0.84	860	0.12(0.32)	FU10
Antidepressants	617	0.23(0.42)	2.94**	225	0.14(0.35)	-3.13**	18	0.17(0.38)	-0.84	860	0.20(0.40)	FU10
Mean Arterial Pressure	626	101.19 (13.75)	-4.25***	244	106.01 (15.59)	4.52***	18	107.37 (10.26)	-0.39	888	102.50(14.38)	FU10
Baseline Physical Health	1040	60.99(8.72)	9.68***	501	55.63(11.12)	-9.20***	29	62.66(6.38)	2.90**	1578	59.14(9.97)	FU10
Sleep	490	7.10(1.10)	9.27***	187	6.03(1.47)	-8.79***	17	7.26(0.97)	2.01	694	6.79(1.30)	FU10
Caffeine	490	2.52(1.69)	7.25***	187	1.54(1.42)	-7.57***	17	2.24(2.03)	-0.04	694	1.55(0.50)	FU10
Smoking	1061	3.23(5.41)	-0.45	516	3.24(6.02)	-0.16	30	3.40(5.19)	0.13	1630	3.24(5.69)	B

*p<0.05, **p<0.01, ***p<0.001

Timepoint at which variable assessed is denoted as follows: B= Baseline; FU5= Follow up 5; FU10= Follow up 10. All analyses conducted using listwise deletion.

Table 7.2: Associations with Gender

	Women Total n=		Men Total n=		
	n	Mean(SD)	N	Mean(SD)	t/ χ^2
Covariates of Interest					
IL-6	410	0.25(0.28)	343	0.27(0.30)	-1.10
CRP	414	0.48(0.53)	355	0.33(0.49)	4.19***
Childhood Physical Abuse	572	6.85(2.75)	480	6.86(2.35)	0.90
Borderline Pathology	887	30.04(1.05)	730	-0.04(1.04)	-1.53
Preventative Health Behaviors	571	0.08(0.86)	481	-0.12(0.96)	3.36**
Physical Health	563	59.16(9.99)	476	60.06(9.58)	-1.48
Covariates of No Interest					
Age	426	65.97(2.92)	365	65.87(2.87)	0.50
European American	577	54.38% EA	484	45.62% EA	χ^2=0.29
African American	291	56.40% AA	225	43.60% AA	χ^2=0.72
Hispanic Ethnicity	13	43.33% His	17	56.67% His	χ^2=1.69
BMI	499	30.91(7.90)	425	28.98(5.36)	4.38
Beta Blockers	467	0.21(0.41)	393	0.19(0.40)	0.44
Calcium Channel Blockers	467	0.21(0.41)	393	0.17(0.37)	1.52
Statins	467	0.32(0.47)	393	0.40(0.49)	-2.24*
ACE/ARBs	467	0.32(0.47)	393	0.39(0.49)	-2.08*
Benzodiazepines	467	0.07(0.26)	393	0.40(0.20)	1.75
Hormone Medications OC/HT	467	0.11(0.32)	393	0.05(0.22)	3.30**
Aspirin	467	0.30(0.46)	393	0.40(0.49)	-3.27**
Rx Pain	467	0.14(0.35)	393	0.08(0.28)	2.59*
Non-Steroidal Anti-Inflammatory Drugs		0.22(0.41)	393	0.14(0.35)	3.06**
Steroid Medications	467	0.15(0.36)	393	0.08(0.28)	2.95**
Antidepressants	467	0.27(0.45)	393	0.12(0.33)	5.86***
Mean Arterial Pressure	477	101.00 (14.64)	411	104.24(13.88)	-3.37**
Baseline Physical Health	865	58.57(10.2)	712	59.82(9.61)	2.49*
Sleep	371	6.80(1.31)	323	6.78(1.29)	0.23
Caffeine	371	2.17(1.65)	323	2.34(1.70)	-1.36
Smoking	887	3.09(5.48)	730	3.48(5.97)	1.37

*p<0.05, **p<0.01, ***p<0.001. All analyses conducted using listwise deletion.

Table 7.3: Sample Demographics and Associations with Model Variables

		Correlations (r) with variables of interest:					
Variable	**N or Mean ± Std Dev**	**IL-6**	**CRP**	**Physical Abuse**	**BPD**	**Physical Health**	**Prevent Health Behaviors**
White/not White	1061	-0.14***	-0.18***	-0.30***	0.02	0.22***	0.14***
Black/not Black	516	0.12***	0.17***	0.29***	-0.04	-0.20***	-0.13***
Hispanic/not Hispanic	30	0.01	0.03	0.01	-0.02	0.05	-0.03
Gender (N men)	730	-0.04	0.15***	-0.03	-0.04	-0.05	0.10**
Age	65.92 ± 2.89	-0.01	0.02	-0.06	-0.09*	0.10**	0.08*
BMI	30.02 ± 6.91	0.32***	0.42***	0.05	0.09**	-0.33***	-0.21***
Beta Blockers	172	0.15***	0.08*	0.07	0.02	-0.20***	-0.01
Calcium Channel Blocker	161	0.14***	0.14***	0.08*	-0.02	-0.16***	-0.02
Statins	307	0.12***	0.02	0.04	0.05	-0.10**	-0.03
ACE/ARBs	303	0.17***	0.16***	0.05	0.04	-0.19***	-0.04
Benzodiazepines	50	0.04	0.01	0.003	0.22***	-0.16***	-0.03
Hormone medications OC/HT	72	-0.14***	-0.08*	0.07*	0.02	0.09**	0.11***
Aspirin	296	0.09*	0.04	-0.01	-0.04	-0.14***	-0.02
Rx Pain	98	0.24***	0.12***	0.05	0.08*	-0.34***	-0.02
Non-Steroidal Anti Inflammatory Drugs	155	0.01	0.02	-0.06	0.08**	-0.14***	0.03
Steroid Medications	102	0.08*	0.10**	-0.01	0.07	-0.13***	0.05
Antidepressants	175	0.11**	0.06	0.09*	0.31***	-0.27***	-0.10**
Mean Arterial Pressure	102.50 ± 14.38	0.06	0.09*	0.04	-0.003	-0.10**	-0.05
Baseline Physical Health	59.14 ± 9.97	-0.26***	-0.20***	-0.19***	-0.36***	0.71***	-0.27***
Sleep	6.79 ± 1.30	-0.14***	-0.10**	-0.21***	-0.12**	0.23***	0.18***
Caffeine	2.25 ± 1.68	-0.02	-0.13**	-0.06	0.07	0.03	-0.06
Smoking	3.24 ± 5.69	0.20***	0.11**	0.16***	0.38***	-0.49***	-0.29***

***p≤0.001; **p≤0.01; *p≤0.05. All analyses conducted using listwise deletion.

Table 7.4: Serial Mediation Model of Child Abuse, BPD, Preventative Health Behaviors, and IL-6 Predicting Physical Health Using Full Information Maximum Likelihood Estimation

	Borderline Pathology		Preventative Health Behaviors		IL-6		Physical Health	
	B	P	B	P	b	p	b	P
Gender	**-0.25**	**<0.01**	**0.20**	**<0.01**	-0.03	0.16	-0.22	0.68
European American	-0.32	0.21	0.17	0.37	-0.07	0.38	2.60	0.14
African American	**-0.52**	**0.04**	-0.08	0.69	-0.06	0.46	0.45	0.81
Hispanic Ethnicity	-0.18	0.20	-0.13	0.42	<0.01	0.98	**3.35**	**0.05**
Age	-0.02	0.20	0.01	0.25	>-0.01	0.85	**0.28**	**<0.01**
BMI	0.01	0.02	-0.03	<0.01	**0.01**	**<0.01**	**-0.22**	**<0.01**
Beta Blockers	0.01	0.93	0.06	0.49	0.04	0.08	**-2.25**	**<0.01**
Calcium Channel Blockers	-0.13	0.12	0.08	0.35	0.04	0.20	-0.64	0.44
Statins	0.06	0.42	-0.02	0.75	0.03	0.14	0.48	0.43
ACE/ARBs	-0.04	0.59	0.07	0.31	0.02	0.50	-1.36	0.31
Benzodiazepines	**0.64**	**<0.01**	0.06	0.64	-0.02	0.63	-1.36	0.31
Hormone Medications OC/HT	0.03	0.79	0.23	0.04	**-0.09**	**0.01**	-0.42	0.66
Aspirin	**-0.20**	**<0.01**	-0.04	0.62	>-0.01	0.88	-1.16	0.06
Rx Pain	-0.01	0.94	0.05	0.62	**0.17**	**<0.01**	**-5.88**	**<0.01**
Non-Steroidal Anti-Inflammatory Drugs	0.14	0.12	0.08	0.33	-0.03	0.18	-1.23	0.09
Steroid Medications	0.09	0.41	**0.20**	**0.05**	-0.04	0.27	-0.87	0.35
Antidepressants	0.70	<0.01	**-0.18**	**0.04**	0.01	0.68	**-2.26**	**<0.01**
Mean Arterial Pressure	<0.01	0.97	<0.01	0.86	<0.01	0.84	-0.02	0.45
Sleep	**-0.10**	**<0.01**	0.08	<0.01	>-0.01	0.59	0.53	0.07
Caffeine	0.03	0.30	-0.04	0.06	>-0.01	0.75	0.14	0.50
Child Abuse	**1.59**	**<0.01**	0.26	0.24	0.13	0.06	-0.02	0.97
Borderline Pathology	--	--	**-0.19**	**<0.01**	0.02	0.11	**-2.23**	**<0.01**
Prevent Health Behaviors	--	--	--	--	**-0.07**	**<0.01**	**1.91**	**<0.01**
IL-6	--	--	--	--	--	--	**-3.48**	**<0.01**
Indirect Effect							**-0.07**	

b = unstandardized beta coefficient. The 95% CI for the indirect effect was -0.14, -0.02.

Table 7.5: Serial Mediation Model of Child Abuse, BPD, Preventative Health Behaviors, and IL-6 Predicting Physical Health Including Baseline Physical Health and Lifetime Regular Smoking Status as Covariates (N=1,630)

	Borderline Pathology		Preventative Health Behaviors		IL-6		Physical Health	
	B	**P**	**B**	**p**	**B**	**p**	**B**	**P**
Gender	**-0.34**	**<0.001**	**0.20**	**0.001**	-0.03	0.16	0.12	0.78
European American	-0.23	0.37	0.14	0.46	-0.07	0.39	1.69	0.25
African American	**-0.52**	**0.04**	-0.08	0.69	-0.06	0.47	0.60	0.70
Hispanic Ethnicity	-0.14	0.30	-0.15	0.36	0.002	0.97	1.78	0.14
Age	-0.02	0.11	**0.02**	**0.015**	-0.001	0.80	**0.23**	**0.004**
Baseline Physical Health	--	--	--	--	--	--	**0.54**	**<0.001**
Ever Reg. Smoker	**0.30**	**<0.001**	**-0.22**	**<0.001**	0.02	0.39	-0.26	0.55
BMI	**0.01**	**0.01**	**-0.03**	**<0.001**	**0.05**	**0.08**	**-0.14**	**0.001**
Beta Blockers	0.03	0.74	0.05	0.56	0.04	0.20	-1.04	0.09
Calcium Channel Blockers	-0.14	0.10	0.09	0.28	0.03	0.20	-0.23	0.75
Statins	0.03	0.68	-0.01	0.94	0.03	0.15	-0.04	0.94
ACE/ARBs	-0.02	0.82	0.06	0.39	0.02	0.49	0.10	0.85
Benzodiazepines	**0.64**	**<0.001**	0.03	0.82	-0.02	0.68	-1.77	0.07
Hormone Medications OC/HT	-0.01	0.94	**0.27**	**0.02**	**-0.09**	**0.01**	0.07	0.92
Aspirin	**-0.17**	**0.03**	-0.05	0.51	-0.002	0.91	-0.25	0.68
Rx Pain	0.04	0.71	0.04	0.66	**0.16**	**<0.001**	**-3.07**	**0.002**
Non-Steroidal Anti-Inflammatory Drugs	**0.17**	**0.05**	0.06	0.46	-0.03	0.21	-0.25	0.68
Steroid Medications	0.10	0.37	0.20	0.06	0.04	0.26	-0.40	0.62
Antidepressants	**0.71**	**<0.001**	-0.19	0.03	0.01	0.68	**-1.61**	**0.02**
Mean Arterial Pressure	-0.001	0.67	0.001	0.61	<0.001	0.81	-0.03	0.21
Sleep	**-0.14**	**<0.001**	**0.09**	**<0.01**	-0.004	0.64	0.19	0.41
Caffeine	0.013	0.64	-0.03	0.16	-0.002	0.75	0.06	0.74
Child Abuse	**1.40**	**<0.001**	0.34	0.12	**0.13**	**0.07**	1.16	0.50
Borderline Pathology			**-0.16**	**<0.001**	0.02	0.17	**-0.76**	**0.003**
Prevent Health Behaviors					**-0.06**	**<0.001**	**1.17**	**<0.001**
IL-6							**-2.67**	**0.01**
INDIRECT EFFECT							**-0.04**	

b = unstandardized beta coefficient. The 95% CI for the indirect effect was -0.09, -0.01.

Table 7.6: Serial Mediation Model of Child Abuse, BPD, Preventative Health Behaviors, and IL-6 Predicting Physical Health Using Listwise Deletion (N=598)

	Borderline Pathology		Preventative Health Behaviors		IL-6		Physical Health	
	B	**P**	**b**	**p**	**b**	**p**	**B**	**P**
Gender	-0.40	0.50	0.13	0.07	-0.04	0.06	0.63	0.26
European American	-0.01	0.98	**0.45**	**0.04**	-0.07	0.34	1.12	0.53
African American	-0.34	0.08	0.31	0.17	-0.06	0.42	-0.03	0.99
Hispanic Ethnicity	-0.10	0.60	-0.15	0.49	0.005	0.95	0.78	0.65
Age	-0.007	0.50	0.003	0.75	-0.001	0.84	**0.29**	**<0.01**
Baseline Physical Health	**-0.01**	**<0.01**	**0.02**	**<0.01**	-0.001	0.32	**0.52**	**<0.01**
Ever Reg. Smoker	**0.25**	**<0.01**	**-0.25**	**<0.01**	-0.01	0.76	0.25	0.65
BMI	0.004	0.35	**-0.02**	**<0.01**	**0.01**	**<0.001**	**-0.14**	**<0.01**
Beta Blockers	-0.003	0.98	-0.01	0.87	0.03	0.33	-0.83	0.23
Calcium Channel Blockers	-0.13	0.10	0.15	0.07	0.04	0.13	-0.18	0.79
Statins	0.03	0.64	-0.004	0.96	0.04	0.13	0.07	0.91
ACE/ARBs	-0.11	0.13	0.05	0.50	-0.01	0.57	-0.15	0.81
Benzodiazepines	**0.50**	**<0.01**	0.09	0.53	-0.06	0.19	**-2.29**	**0.05**
Hormone Medications OC/HT	-0.08	0.46	**0.29**	**0.02**	-0.07	0.07	0.32	0.74
Aspirin	-0.13	0.06	0.02	0.75	-0.005	0.84	-0.34	0.57
Rx Pain	-0.14	0.19	**0.27**	**0.02**	**0.16**	**<0.001**	**-3.64**	**<0.01**
Non-Steroidal Anti-Inflammatory Drugs	**0.17**	**0.04**	0.12	0.16	**-0.07**	**0.02**	-0.17	0.81
Steroid Medications	-0.09	0.37	0.10	0.30	0.03	0.37	-0.50	0.54
Antidepressants	**0.55**	**<0.01**	-0.08	0.41	0.02	0.55	**-2.28**	**<0.01**
Mean Arterial Pressure	-0.001	0.70	-0.0003	0.90	-0.0001	0.87	**-0.04**	**0.04**
Sleep	-0.04	0.13	**0.07**	**0.01**	-0.0004	0.97	0.11	0.62
Caffeine	-0.001	0.98	-0.03	0.11	-0.003	0.60	0.02	0.89
Child Abuse	**1.04**	**<0.01**	0.002	0.99	**0.18**	**0.04**	1.54	0.48
Borderline Pathology			**-0.13**	**0.03**	0.02	0.20	**-0.78**	**0.03**
Prevent Health Behaviors					**-0.05**	**<0.001**	**1.36**	**<0.01**
IL-6							**-3.14**	**0.03**
INDIRECT EFFECT							**-0.02**	

b = unstandardized beta coefficient. The 95% CI for the indirect effect was -0.09, -0.01.

Table 7.7: Serial Mediation Model of Child Abuse, BPD, Preventative Health Behaviors, and IL-6 Predicting Physical Health with No Covariates (N=1,630)

	Borderline Pathology		Preventative Health Behaviors		IL-6		Physical Health	
	B	**P**	**b**	**P**	**b**	**p**	**B**	**P**
Child Abuse	**1.86**	**<0.01**	-0.18	0.38	**0.23**	**<0.01**	-3.50	0.13
Borderline Pathology	--	--	**-0.22**	**<0.01**	**0.02**	**0.05**	**-2.71**	**<0.01**
Prevent Health Behaviors	--	--	--	--	**-0.09**	**<0.01**	**2.06**	**<0.01**
IL-6	--	--	--	--	--	--	**-8.35**	**<0.01**
Indirect Effect							**-0.17**	**<0.01**

b = unstandardized beta coefficient. The 95% CI for the indirect effect was -0.47, -0.16.

Table 7.8: Interaction between African American (AA) ethnicity and Childhood Abuse, BPD, Preventative Health Behaviors, and IL-6 Predicting Physical Health using Maximum Likelihood Estimates (N=1,630)

	Borderline Pathology		Preventative Health Behaviors		IL-6		Physical Health	
	B	**P**	**b**	**P**	**b**	**p**	**B**	**P**
Child Abuse x AA	0.38	0.57	0.84	0.06	0.20	0.19	0.81	0.53
Borderline Pathology x AA	--	--	0.11	0.17	-0.02	0.39	-0.83	0.09
Prevent Health Behaviors x AA	--	--	--	--	-0.004	0.89	**1.41**	**0.01**
IL-6 x AA	--	--	--	--	--	--	2.43	0.29
Indirect Effect							-0.02	

b = unstandardized beta coefficient. The 95% CI for the indirect effect was -0.14, 0.03.

7.3 Supplemental References

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