NEUROBIOLOGICAL CORRELATES OF STRESS AND THE PATHOPHYSIOLOGY OF DEPRESSION: ASSOCIATIONS AMONG SOCIAL VICTIMIZATION, IL-6, CRP, AND BDNF VAL66MET

by

ALLYSON A. ARANA

Presented to the Faculty of the Graduate School of

The University of Texas at Arlington in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS AT ARLINGTON

SEPTEMBER 2016

Copyright © by ALLYSON A. ARANA 2016

All Rights Reserved

Acknowledgements

First and foremost, this dissertation would not have been possible without the generous contributions by the Jerry M. Lewis MD Mental Health Research Foundation and the University of Texas at Arlington Center of Excellence for the Study of Health and Chronic Illnesses. I would also like to thank the parents and children of the Dallas/Fort Worth area for taking the time to participate in this study.

To the undergraduate research assistants in the lab, as well as my fellow graduate students, past and present (Erin Boyd, Maria Guarneri-White, Erika Venzor, Priya Iyer-Eimerbrink, Sarah Lee, and Norma Garza): thank you for being an incredible support system throughout the past five years. And to my mentor, Lauri Jensen-Campbell: thank you for always having my back and always pushing me to be a better researcher and statistician. I couldn't have asked for a better boss and labmates.

I would like to thank my committee members, Angela Liegey Dougall, Jeff Gagne, Robert Gatchel, and Jared Kenworthy for their continued guidance throughout this process and graduate school in general. A big thanks also goes out to Melissa Muenzler and Kim Bowles from the Andy Baum Memorial Bioassay Laboratory for teaching me the assays and taking the time to give me help and advice.

Finally, thank you to my loved ones: momma, dad, my sisters, friends, and Jesse (and Tuff) for their unconditional love and putting up with my crazy schedule for the past five years. This dissertation is dedicated to my little sisters and niece – Yoko, Anna, Demz, and Mila – thanks for always challenging me and inspiring me to be a better role model; I hope all of you get to follow your passion and do what you love.

September 9, 2016

Abstract

NEUROBIOLOGICAL CORRELATES OF STRESS AND

THE PATHOPHYSIOLOGY OF DEPRESSION:

ASSOCIATIONS AMONG SOCIAL VICTIMIZATION, IL-6, CRP, AND BDNF

Allyson A. Arana, PhD

The University of Texas at Arlington, 2016

Supervising Professor: Lauri A. Jensen-Campbell

Peer victimization, a common psychosocial stressor in adolescence, is linked to adverse health outcomes ranging from depression to changes in biological functioning. Social victimization is particularly harmful given the importance placed on peer relations and social status during this developmental period. This dissertation evaluated the associations among social victimization, physical health, psychological health, the BDNF Val66Met polymorphism, and inflammatory biomarkers (IL-6 and CRP) in a diverse sample of adolescents (N = 254). Social victimization was related to depressive symptoms, health problems, and inflammation, partially replicating a previous study. BDNF Val66Met moderated the link between social victimization and health outcomes, such that the association was stronger for homozygous Val teens. Additionally, social victimization was related to negative health consequences regardless of social bullying in moderated multiple regression analyses. Finally, the role of gender as a moderator was explored, with results indicating that female victims, male bully-victims, and female Met carriers generally reported worse outcomes. These results underscore the importance of accounting for social, biological, and genetic factors related to depressive symptoms and health outcomes.

Table of Contents

List of Tables and Figures

Chapter 1:

Introduction

The impact of psychosocial stress on adolescents' psychological and physical health has been well documented. Teens who face persistent interpersonal difficulties often experience anxiety, depressive symptoms, physical health problems, and lower self-esteem (e.g., Brendgen & Vitaro, 2008; Lopez & DuBois, 2005; Prinstein & Akins, 2004). Chronic psychosocial stress has also been found to elicit changes in biological functioning, particularly in the neuroendocrine, immune, and neurotrophic systems (Duman & Monteggia, 2006; Fuligni et al., 2009; Miller, Chen, & Zhou, 2007), and evidence suggests that these physiological changes may be associated with outcomes like depression and somatic complaints (Calabrese, Molteni, Racagni, & Riva, 2009; Dantzer, 2009). Moreover, genetic polymorphisms that influence these biological mechanisms may moderate the relationship between stress and health (Hosang, Shiles, Tansey, McGuffin, & Uher, 2014). This dissertation examined the relationships among psychosocial stress, health outcomes, genetic influences, and biological functioning within a peer victimization framework.

Peer victimization is a common source of psychosocial stress during childhood and adolescence – as many as one out of three students report either being victimized, bullying others, or both (Hong & Espelage, 2012). Its links to adverse outcomes have led many researchers and organizations to declare bullying a public health issue (Dale, Russell, & Wolke, 2014). Defined as the repeated exposure to the intentionally aggressive actions of one's peers and characterized by a real or perceived imbalance of power between the two parties (Olweus, 1993), peer victimization encompasses a wide array of experiences that range from physical aggression to more subtle attacks aimed at one's relationships and social standing. Though early research focused more on the

former (e.g., Olweus, 1978), recent work suggests that relational or social victimization may actually be more physically and psychologically harmful (Iyer-Eimerbrink, Scielzo, & Jensen-Campbell, 2015; Murray-Close et al., 2014; Zimmer-Gembeck, Trevaskis, Nesdale, & Downey, 2014). A construct proposed by Crick and Grotpeter (1995), relational aggression aims to harm one's peer relationships through acts such as social exclusion, spreading rumors, and manipulating social interactions. Social aggression attempts to expand on this construct by also including gossip, verbal rejection, and other acts intended to lower one's social standing, self-esteem, or both (Galen & Underwood, 1997).

The prevalence and efficacy of social forms of aggression may be developmentally influenced. As physical aggression is seen as less socially acceptable, teens find subtler ways to harass one another and social bullying emerges as a more viable option (Hinduja & Patchin, 2010; Wang, Iannotti, & Nansel, 2011). Additionally, due to the increased importance that adolescents place on their peer relationships, this type of victimization may be especially salient (Harris, 1995). Studies on gender differences in social victimization have yielded conflicting results, with some reporting that girls are socially bullied more frequently than are boys, and others showing no difference; however, girls tend to worry about and be more negatively affected by social victimization compared to boys (Crick, Casas, & Nelson, 2002; Paquette & Underwood, 1999). On the other hand, boys and girls alike participate in social bullying: females aggress against other females as a form of social competition for status and/or mates (see Vaillancourt, 2013, for a review), while it may manifest itself more as social dominance in males (Pellegrini & Bartini, 2001). These practices – collectively dubbed *social combat* by Faris and Felmlee (2014) – are almost seen as normative behaviors and affect even popular or high-status youth. Indeed, relational aggression was found to be increasingly predictive

of perceived popularity in a longitudinal examination of early adolescents, suggesting that these behaviors are valued in the peer group and reinforced by social benefits (Cillessen & Mayeux, 2004).

Given the nature of social competition during adolescence, it comes as no surprise that social victimization and social bullying are significantly correlated with one another (Putallaz et al., 2007; Sullivan, Farrell, & Kliewer, 2006). Though few studies focus specifically on social bully-victims (i.e., individuals who are socially victimized by and socially bully others), research on bully-victims in general indicates that they may be at a greater risk for negative consequences due to their dual roles as both victim and aggressor (Pellegrini, 1998). They fare even worse than "pure" victims in many outcomes, including depression, anxiety, post-traumatic stress symptoms, and physical health complaints (e.g., Arana, 2015; Haynie et al., 2001; Idsoe, Dyregrov, & Idsoe, 2012; Kaltiala-Heino, Rimpelä, Rantanen, & Rimpelä, 2000; Nansel, Craig, Overpeck, Saluja, & Ruan, 2004). The dearth of work concentrating on social or relational bully-victims coincides with a lack of published research on social bullies themselves – gaps in the literature that this dissertation aimed to explore.

However, research has established a robust link between social victimization and maladjustment, particularly depressive symptoms and physical health problems. The two are closely related, as symptoms of depression include somatic components, such as fatigue, appetite changes, and sleep disturbances (American Psychiatric Association , 2013). In a longitudinal study, Rosen and colleagues (2009) found that students who reported persistent social victimization from ages 9 to 13 experienced continuously elevated levels of anxious depression, withdrawn depression, and somatic complaints. Additionally, a recent meta-analysis showed an overall positive relationship between social victimization and anxiety, depression, and loneliness (Iyer-Eimberbrink, Scielzo, &

Jensen-Campbell, 2015). For the two former outcomes, social victimization was actually a stronger predictor than was physical victimization. Similarly, relational victimization was found to have a stronger association with somatic complaints one semester later, even after controlling for gender, grade, baseline somatic complaints, and previous victimization experiences (Nixon, Linkie, Coleman, & Fitch, 2011).

The effects of social victimization also extend into the biological realm, with the hypothalamic-pituitary-adrenal (HPA) axis being a prominent topic in recent work. The HPA axis responds to environmental stressors with a cascade involving the secretion of corticotrophin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland, and glucocorticoids (such as cortisol) from the adrenal glands (for more detail, see Miller, Chen, & Zhou, 2007). The consequences of altered HPA axis functioning include (but are certainly not limited to) symptoms of depression, anxiety, and physical health problems like obesity and metabolic syndrome (Dallman et al., 2007; Maniam, Antoniadis, & Morris, 2014; Pariante & Lightman, 2008; Tronche et al., 1999). Blunted cortisol reactivity has been found in relationally bullied adolescents, even when accounting for the effects of physical victimization, life stress, and depressive symptoms (Calhoun et al., 2014). Moreover, verbal peer victimization was linked to hyposecretion of cortisol in a non-clinical sample of adolescents (Vaillancourt et al., 2008). These findings not only highlight the gravity of the consequences associated with social victimization, but also have generated interest in examining other biological mechanisms that may be affected. After all, given that many facets of the human body's stress response are closely intertwined, it follows that chronic peer victimization may wield some influence on other biological systems.

Stress, Inflammation, and Depression

This dissertation focused on the effects of social peer victimization on two biomarkers frequently studied in the context of stress, but rarely examined with respect to peer victimization: interleukin-6 and C-reactive protein.

Interleukin-6 (IL-6) is an inflammatory cytokine secreted by T-cells, macrophages, adipocytes, and a variety of other immune and nonimmune cells to activate the inflammatory response. Its secretion is governed primarily by a feedback loop involving the HPA axis (for more detail, see Chrousos, 1995; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). Glucocorticoids (such as cortisol) typically inhibit the expression of the IL-6 gene, thus suppressing production of IL-6. However, chronic stress and the resulting chronic activation of the HPA axis can lead to glucocorticoid receptor resistance, in which excess adrenocortical output causes desensitization and inhibits receptors' ability to transduce signals. Under these conditions, the expression of IL-6 is no longer suppressed and production of IL-6 increases. In turn, IL-6 activates the HPA axis and elevates the concentration of corticotropin and cortisol.

In addition to its effects on the neuroendocrine system, IL-6 also stimulates the production of C-reactive protein (CRP) from the liver. CRP has been linked to the pathogenesis of atherosclerosis and has shown utility as a marker for cardiovascular risk (Pasceri, Willerson, & Yeh, 2000; Ridker, Hennekens, Buring, & Rifai, 2000). Together, IL-6 and CRP have been studied as indicators of inflammation in response to persistent exposure to stress. Links between early-life stress and elevated circulation levels of IL-6 and CRP have been found in samples of adolescents, as well as adults (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Miller & Chen, 2010). A recent prospective study also found that greater cumulative stress exposure in childhood (e.g., physical or

sexual abuse, separation from parents, foster care) predicted higher levels of both IL-6 and CRP up to seven years later (Slopen, Kubzanksky, McLaughlin, & Koenen, 2013).

Though considerable evidence links stress to inflammation, it is important to note that only three studies to date have examined the association between peer victimization (as a psychosocial stressor) and inflammation. Being bullied in childhood predicted increased CRP in adulthood while controlling for BMI, substance use, physical health status, and exposure to other childhood trauma in one study (Copeland et al., 2014), as well as higher CRP, fibrinogen levels, BMI, and waist-to-hip ratio in a similar study one year later (Takizawa, Danese, Maughan, & Arsenault, 2015). Additionally, Arana and colleagues (in press) found that social and physical forms of peer victimization were differentially associated with IL-6 and CRP in a cross-sectional study on a diverse sample of adolescents, such that social victimization predicted greater inflammation and physical victimization shared an inverse relationship with inflammatory markers. This dissertation aimed to address a gap in the literature by attempting to replicate the findings from the latter study.

In addition to being useful markers of stress, circulating levels of IL-6 and CRP have also been implicated in the pathophysiology of depressive symptoms. This development has blossomed rather recently, as researchers have shown increasing interest in unraveling the biological underpinnings of what was originally considered to be a purely psychological ailment. The inflammatory theory, or *social signal transduction theory*, as most recently outlined by Slavich and Irwin (2014), hypothesizes that social-environmental stress upregulates inflammatory processes, which in turn stimulate changes in behavior that include common symptoms of depression such as anhedonia, fatigue, and social-behavioral withdrawal. Human and animal studies alike have shown that administration of pro-inflammatory cytokines elicits these behaviors, and that

antidepressant medications can alleviate these symptoms (Castanon, Bluthé, & Dantzer, 2001; De La Garza, 2005; Eisenberger et al., 2010; Hannestad, DellaGioia, & Bloch, 2011).

The theory is also supported by findings that depressed individuals exhibit higher circulating levels of inflammatory markers compared to nondepressed individuals (see Dowlati et al., 2010, for a review), though many believe the link between inflammation and depression to be bidirectional (e.g., Copeland, Shanahan, Worthman, Angold, & Costello, 2012; Gimeno et al., 2009; Messay, Lim, & Marsland, 2012). Increases in cytokine production are also associated with sickness behavior (see Dantzer & Kelley, 2007, for a review), which may account for some of the somatic symptoms experienced by depressed individuals. Furthermore, systemic inflammation has been linked to a heightened risk of physical health problems that frequently co-occur with depression such as metabolic syndrome, inflammatory bowel disease, and coronary heart disease (Barth, Schumacher, & Herrmann-Lingen, 2004; Graff, Walker, & Bernstein, 2009; Pan et al., 2012).

In sum, inflammatory mechanisms appear to be associated with both chronic stress and depressive symptomatology. Though this study did not directly test this theory, it suggests that bullied children would experience depressive symptoms and increased concentrations of inflammatory markers.

Genetic Influences on the Stress-Health Link: BDNF Val66Met

Brain-derived neurotrophic factor (BDNF) is a protein from the neurotrophin family that plays a role in the development, survival, and function of neurons. Its activity-dependent modulation of neuronal structure and function suggests that it may be a useful

tool in examining synaptic plasticity in response to environmental influences (Bramham & Messaoudi, 2005).

The *neurotrophic theory of depression*, first described by Duman, Heninger, and Nestler (1997), posits that depression is associated with aberrant neurogenesis due to lower expression of BDNF, particularly in brain regions known to regulate emotion and memory, such as the hippocampus. A meta-analysis of imaging studies showed that patients suffering from depression had lower hippocampal volume compared to healthy controls (Campbell, Marriott, Nahmias, & MacQueen, 2014). Research has also shown that antidepressant-free depressed patients exhibit lower concentrations of BDNF when compared to non-depressed individuals as well as depressed patients being treated with anti-depressant medication (see Molendijk et al., 2014). Furthermore, evidence suggests that BDNF levels significantly increase following anti-depressant treatment, and changes in depression scores are correlated with changes in BDNF concentration (Brunoni, Lopes, & Fregni, 2008). Given the role the hippocampus plays in memory and attention, it comes as no surprise that BDNF has also been implicated in attention problems in children and adults alike (e.g., Amiri et al., 2013; Corominas-Roso et al., 2013).

A single nucleotide polymorphism (SNP) in the BDNF gene, Val66Met (rs6265), has been shown to influence the activity of the BDNF protein. This SNP results in the substitution of valine (Val) to methionine (Met) in the pro-domain at codon 66, which is thought to affect the activity-dependent secretion of BDNF such that the Met allele is associated with reduced BDNF (Egan et al., 2003). Numerous studies have shown a relationship between BDNF Val66Met and depression, though the malleable genotype (Val/Val or Met carrier) varies throughout the literature (e.g., Kourmouli et al., 2013; Lavebratt, Åberg, Sjöholm, & Forsell, 2010; Montag, Weber, Fliessbach, Elger, & Reuter, 2009; Schumacher et al., 2005). Furthermore, BDNF Val66Met interacts with life

stressors to predict depressive symptoms (Carver, Johnson, Joormann, LeMoult, & Cuccaro, 2011; Gutierrez et al., 2015; Hosang, Shiles, Tansey, McGuffin, & Uher, 2014).

Similarly, the extant work regarding BDNF and attention problems contains mixed results, with some studies suggesting Met as the risk allele, some with Val as the risk allele, and others showing no relationships (e.g., Bergman, Westberg, Lichtenstein, Eriksson, & Larsson, 2011; Cho et al., 2010; Liu et al., 2014). Indeed, these conflicting findings serve as grounds for further investigation into the influence of the BDNF Val66Met polymorphism on health outcomes. This dissertation aimed to fill this gap in the literature by addressing these effects within a peer victimization framework using a sample of diverse adolescents.

Current Study

The present study aimed to build upon previous work on psychosocial stress, psychological and physical health outcomes, biological markers of inflammation, and the influence of the BDNF Val66Met SNP. Considering the evidence of the impact of chronic stress on health outcomes, it follows that social peer victimization, a common stressor in adolescence, would also produce similar outcomes.

Aim 1

First, I attempted to replicate the results of Arana and colleagues (in press) by testing the differential effects of social and physical victimization on various health outcomes in a subsample of early adolescents (rather than mid to late adolescents, as was done in the previous paper). Specifically, I expected that social victimization would be associated with more depressive symptoms, physical health problems, and higher concentrations of IL-6 and CRP. I also attempted to replicate Arana and colleagues'

findings that social victimization was indirectly linked to increased IL-6 and CRP via depressive symptoms.

Aim 2

Using a combined sample of early and middle/late adolescents, I examined the influence of the BDNF Val66Met polymorphism on the relationship between social victimization and depressive symptoms, physical health, attention problems, and inflammation, with the expectation that the Met allele would be associated with worse outcomes due to the literature on how possessing the Met allele is related to lower BDNF secretion.

Aim 3

Furthermore, I tested the hypothesis that social bully-victims would experience higher levels of depressive symptoms, physical health symptoms, attention problems, and inflammation by evaluating the interaction between social victimization and social bullying. I also analyzed a three-way interaction with BDNF Val66Met, social victimization, and social bullying to determine if the aforementioned relationships were stronger for adolescents with at least one Met allele.

Chapter 2:

Method

Participants

The sample was recruited through the local school district's mailing list, various youth organizations, local churches, and word of mouth. Flyers containing information about the study and a link to an online interest form were also posted at local businesses (e.g., restaurants, coffee shops, gyms, etc.). A total of 254 students (6th through 12th grade, age 11 to 19) visited the Personality and Social Behavior laboratory at the University of Texas at Arlington to participate in the study. The sample was ethnically diverse (5% Asian, 12% Black/African-American, 55% White/Anglo-American, 25% Hispanic/Latino, 3% other), consistent with the demographic characteristics of the area. For multiple regression analyses with sr^2 = .10 at α = .05 (two-tailed) and power = .80, a minimum of 73 participants was required (Cohen, 1988). Furthermore, a sample of 115 was required to evaluate indirect effect/mediation models using bias-corrected bootstrapping with *a* and *b* path estimates of .26 to .39 and power = .80 (Fritz & McKinnon, 2007). To detect a moderator with a standardized effect (β) of .20 at high (.975) power, a sample of at least 200 would be required (Champoux & Peters, 1987).

Data were collected during two waves: from December 2012 to June 2013 (wave 1; n = 98) and again from October 2013 to June 2016 (wave 2; n = 156). Although both waves were similar in terms of gender and ethnic makeup, wave 1 (M_{age} = 15.94; range = 13-19) contained significantly older (p < .001) adolescents than did wave 2 (M_{age} = 13.54; range = 11-18). The sample from the first wave was used in the Arana et al. (in press) paper; thus, we used only the 2013-2016 sample in the replication analyses (Aim 1). For all new analyses (i.e., Aims 2 and 3), the whole sample (N = 254) was utilized. The data

collection materials and procedure relevant to this study were virtually identical in both collection waves.

Materials

Peer Victimization and Bullying

The Direct and Indirect Aggression Scale (DIAS; Bjorkvist, Lagerspetz, & Osterman, 1992) victim and bully versions examined how frequently one experiences or commits aggressive acts. Items included physical (e.g., "How often are you hit by/do you hit others?"), verbal (e.g., "How often are you insulted by/do you insult others?"), and indirect (e.g., "How often are you ignored by/do you insult others?") forms of aggression (see Appendix for full list of items). Each version consisted of 24 items (α for victimization = .89; α for bullying = .82), scored on a Likert-type scale from 1 ("never") to 5 ("very often"). Parents also completed these questionnaires with respect to their child's experiences and behaviors (α for victimization = .95; α for bullying = .92).

The Children's Self-Experiences Questionnaire (CSEQ; Crick & Grotpeter, 1996) is a 15-item survey assessing relational victimization (e.g., "How often do other kids leave you out on purpose when it is time to play or do an activity?"), overt victimization (e.g., "How often do you get hit by another kid at school?"), and prosocial help (e.g., "How often does another kid give you help when you need it?") experienced by the child. Both the child (α = .72) and the parent (α = .78) completed this measure.

Physical and Psychological Health

The Child Behavior Checklist (CBCL; Achenbach, 1991) is a parent questionnaire for examining problems in 6- to 18-year-olds over the past six months. The anxious depression, withdrawn depression, somatic complaints, and attention problems subscales were utilized in this study. The possible responses are 0 ("not true"), 1

("somewhat or sometimes true"), and 2 ("very true or often true"). The Youth Self-Report (YSR; Achenbach, 1991) is a self-report scale for 11- to 18-year-olds containing approximately the same items and was completed by the participant (see Appendix). Parent and child scores were correlated for anxious depression (r = .36, p < .001), withdrawn depression (r = .30, p < .001), somatic complaints (r = .36, p < .001), and attention problems (r = .35, p < .001), and were averaged prior to analysis.

The Center for Epidemiological Studies Depression Scale for Children (CESD; Weissman, Orvaschel, & Padian, 1980) is a 20-item self-report scale (α = .76) that measures depressive symptoms in children, particularly how they have felt and acted within the past week. Sample items include: "I was bothered by things that usually don't bother me," "I didn't sleep as well as I usually sleep," and "I did not feel like eating, I wasn't very hungry" (see Appendix for complete list). Items were measured on a Likert-type scale, from 1 ("not at all") to 4 ("a lot"), with possible scores ranging from 20 to 80.

Participants completed the Health Outcomes Scale (Knack, Jensen-Campbell, & Baum, 2011), which includes 29 questions on frequency and 29 questions regarding the severity of their health problems, including extreme fatigue, nausea, sleep problems, fever, headaches, chest pains, and visits to the nurse or doctor (see Appendix). Frequency items are rated from 0 ("not at all") to 4 ("all the time") and severity items are rated from 0 ("does not hurt at all") to 4 ("unbearable pain"). Parents completed the same measure, answering questions about their child's health. Cronbach's α ranged from .86 to .90 for all scales. Parent and child responses were correlated (r = .27, p < .001) and were averaged prior to analysis.[1] Previous research has found little differences between

[1] Analyses conducted using parent-report and child-report outcome variables (separately) produced similar results to the composite variables.

parent and child reports as outcome measures (e.g., Lereya, Copeland, Costello, & Wolke, 2015).

Physical Assessments

Researchers recorded the adolescent's height, weight, neck circumference, waist circumference, and hip circumference during the lab visit. The waist-to-height ratio (WtHR), a reliable measure of abdominal obesity, was used as a covariate given its connections to depression, health, and inflammation (McElroy et al., 2004; Von Eyben et al., 2003; Wisse, 2004). Research has demonstrated that WtHR is a better predictor of cardiovascular risk factors in children compared to BMI and does not rely on age or sex references (Kahn et al., 2014; Savva et al., 2000).

Participants also completed a 5-item pubertal development scale in which they were asked about the development of their growth in height, body hair, skin changes, breast development and menstruation (girls only), and facial hair and voice deepening (boys only). Cronbach's α was .88 for girls and .86 for boys. Scores were standardized for comparison between genders.

Blood Collection and Plasma Biomarker Assays

Blood samples were taken from the adolescents via antecubital venipuncture by a certified phlebotomist. Approximately 5-7mL were taken during the second in-lab session, which was scheduled at the same time of day for each participant (from 4 to 7 pm) in order to control for diurnal patterns. The sample was then centrifuged and about 3mL of plasma was extracted and stored at -80°C until analysis.

Samples were centrifuged at 1100RPM at 18C for 10 minutes no more than two hours after the blood draw. Up to 3.6mL of plasma was extracted from each sample and stored at -78C until ready for assay. Plasma IL-6 and CRP were analyzed using quantitative solid-phase sandwich ELISAs, which provide high specificity; since two

antibodies are used, the antigen/analyte is specifically captured and detected. The Quantikine Human IL-6 (R&D Systems Product D6050) and high-sensitivity CRP (R&D Systems Product DCRP00) kits were chosen due to their commercial availability and wide use in peer-reviewed academic publications.

In short, 96-well microplates were coated with a monoclonal antibody specific to IL-6 or CRP. Standards (human IL-6 or CRP, in a buffered protein base) and samples were pipetted into the wells, and the immobilized antibody bound to its respective biomarker. The plate was covered and allowed to incubate at room temperature for two hours, then the wells were aspirated and washed. Next, a conjugate (antibody) was added to each well, and the plate was covered and incubated at room temperature. After the wells were aspirated and washed to remove any unbound enzyme-antibody reagent, the substrate solution was added to each well and the plates were incubated in room temperature away from light. Finally, an amplifier solution (IL-6 only) and a stop solution (sulfuric acid; used in both assays) were added to each well. The color in each well developed in proportion to the amount of IL-6 or CRP in the sample. After 30 minutes, the intensity of the color was measured using a microplate reader at 450nm with wavelength correction set to 570nm (for CRP; readings were done at 490nm with a correction of 690nm for IL-6). All samples were run in duplicate.

Saliva Collection and DNA Genotyping

Saliva samples were collected with the Oragene DISCOVER (OGR-500) tubes by DNA Genotek (Ottawa, ON, Canada). The participant filled the tube using the passive drool method until saliva reached the marked line (2mL). The sample was then capped, releasing a reagent into the saliva that preserves the sample and allowed for storage at room temperature until analysis.

A total of 251 saliva samples were obtained (three participants had difficulty producing saliva) and sent to DNA Genotek (Ottawa, ON, Canada) for extraction and genotyping analyses. DNA was extracted from a 700µL aliquot of the saliva collected in the Oragene tubes using the prepIT-L2P validated protocol. The samples were then genotyped for BDNF Val66Met (rs6265) using the TaqMan single tube assay. The TaqMan assay is an allele discrimination assay using polymerase chain reaction (PCR) amplification and a pair of fluorescent dye detectors that target the SNP. One fluorescent dye is attached to the detector that is a perfect match to the first allele (e.g., an "A" nucleotide) and a different fluorescent dye is attached to the detector that is a perfect match to the second allele (e.g., a "C" nucleotide). During PCR, the polymerase releases the fluorescent probe into solution where it is detected using endpoint analysis in a Life Technologies, Inc. (Foster City, CA, USA) 7900HT Real-Time instrument. Primers and probes were obtained through Life Technologies design and manufacturing. Genotypes were determined using Life Technologies' Taqman Genotyper v1.0.1 software.

The genotype distribution (158 Val/Val, 84 Val/Met, 8 Met/Met) matched the expected allelic distribution (80% Val, 20% Met; Egan et al., 2003) and was in the Hardy-Weinberg equilibrium, $\chi^2(1, N = 251) = 0.60$, $p = .438$. Gene-by-environment (GxE) analyses focused on two groups: homozygous Val ($n = 158$), and Met carriers ($n = 92$).

Procedure

During the recruitment and sign-up period, parents of participants were notified of the blood extraction process and the questionnaires their children would be asked to complete. Participants and their parent were both provided with and asked to sign written informed consent and assent forms upon arrival at the lab for the first session. Approval

from the Institutional Review Board (IRB) at the University of Texas at Arlington was obtained prior to the initiation of this study.

Participation consisted of two sessions, both taking place at the Personality and Social Behavior Lab at UTA. During Session 1, participants completed a series of online questionnaires that assessed victimization, depression, and physical health. Their accompanying parent or guardian also completed a set of questionnaires evaluating their child's victimization and physical health. These questionnaires were delivered concurrently but separately so that the two parties did not influence each other's responses. The adolescents then had a small saliva sample taken for DNA and were instructed on how to collect salivary cortisol at home as part of a larger study; the latter was not used in the present study. The researcher paid them for their participation in this session ($10.00 for the parent, $20.00 for the child), which lasted approximately 60 to 90 minutes.

The parent and adolescent returned to UTA for Session 2, which took place approximately one week after Session 1. Once at the laboratory, the parent and child completed surveys about their interpersonal relationships and social support (not used in this study), as well as the Achenbach measures (the CBCL for the parent and the YSR for the child), which assessed the adolescent's internalizing and externalizing problems. After both parties completed these questionnaires, a research assistant escorted the child to the blood extraction laboratory located on the 5th floor of the Life Sciences Building. A certified phlebotomist briefed the participant about the blood collection procedure prior to collecting the sample via antecubital venipuncture. Per the IRB protocol, phlebotomists were required to stop the procedure if the participant withdrew assent and were also limited to a maximum of two attempts in order to limit any discomfort felt by the participant. Once a sample was obtained, the participant returned

to the lab for debriefing and payment ($30.00 for the parent and $40.00 for the adolescent, for a total of $100.00 for the pair's participation in this study). Session 2 lasted approximately 45 to 60 minutes.

The blood samples were then taken to the Andy Baum Memorial Bioassay Clinical Research Laboratory, where the phlebotomist extracted and stored the plasma. Concentrations of IL-6 and CRP were determined using commercially available enzyme-linked immunosorbence assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA). Saliva samples were shipped to DNA Genotek (Ottawa, ON, Canada) for DNA extraction and BDNF Val66Met genotyping.

Analytical Plan

The first set of hypotheses focused on replicating the findings of Arana et al. (in press) using a subset of my sample (the second wave of data, which was not used in the previous paper and contains a younger sample). A series of iterative multiple regression analyses were conducted in SPSS Version 20 (IBM, 2011) to determine the relationships between social and physical victimization and health outcomes (Aim 1). Specifically, age, gender, WtHR, pubertal status, and physical victimization were included in the first block of predictors, social victimization in the second step, and depressive symptoms, physical health, IL-6, and CRP as outcomes separately.

Next, I examined the indirect effect of social victimization on IL-6 via depressive symptoms. This model was extended to include CRP as the outcome, with depression and IL-6 as mediating variables, in that order. Age, gender, WtHR, pubertal status, and physical victimization were included in the models as covariates. These analyses were performed using the PROCESS Macro in SPSS (Hayes, 2013), which allows for the estimation of path coefficients in a variety of mediational and conditional process models. Indirect effects were estimated using bias-corrected bootstrapping procedures with 1000

samples, as bootstrapping does not assume normality among sampling distributions of the indirect effects (Hayes, 2009). Although these data are cross-sectional in nature and we cannot definitively establish causal links, indirect effect analyses can provide support for one path model over another (Shrout & Bolger, 2002). As such, I also tested the indirect effect of social victimization on depressive symptoms via inflammation.

My remaining hypotheses utilized the combined sample of 254 adolescents. For Aim 2, I examined the influence of BDNF Val66Met on the relationships between social victimization and negative outcomes (i.e., depressive symptoms, frequency and severity of physical health symptoms, attention problems, and inflammatory markers) by testing the interaction between social victimization and BDNF in a moderated regression model in SPSS PROCESS. Age, gender, pubertal status, and WtHR were entered as covariates in the model. The Johnson-Neyman regions of significance were determined using the recommendations outlined by Roisman and colleagues (2012) and the online application by Fraley (2012).

Similarly, I used PROCESS to assess the hypothesis that those who score highly in both social victimization and social bullying (i.e., social bully-victims) would report poor health outcomes (Aim 3). As bully-victims appear to comprise a small percentage (2-10%) of the population (Solberg, Olweus, & Endresen, 2007), the sample size of this current study would not produce a sufficient group of bully-victims, and conducting person-centered analyses (particularly when the expected effect size is low) requires larger cells to maintain adequate power (VanVoorhis & Morgan, 2007). Thus, these analyses employed a variable-centered approach in which social bullying and victimization were treated as continuous variables. I tested the interaction between social victimization and social bullying on depressive symptoms, physical health, attention problems, and inflammation, as well as a three-way interaction between social

victimzation, social bullying, and Val66Met (to determine if the associations were stronger for Met carriers). As done previously, age, gender, pubertal status, and WtHR were entered as covariates.

Preliminary Analyses

Blood Sample Collection Rates

Venipuncture is commonly seen as a painful experience during which about two-thirds of children feel significant distress (Fradet, McGrath, Kay, Adams, & Luke, 1990; Taddio et al., 2012). Although researchers notified parents of the blood collection aspect of the study and were careful in briefing the participants when they came into the lab, a blood sample was not obtained from 64 (25%) of the adolescents due to refusal of assent or difficulty obtaining a sufficient volume for analysis. This success rate of 75% (n = 190) is comparable to previous studies involving venipuncture on children (Hammond, Chinn, Richardson, & Rona, 1994; Schober et al., 2003). Blood collection success/failure was not significantly related to gender (p = .146), age (p = .796), WtHR (p = .969), social victimization (p = .115), social bullying (p = .207), depressive symptoms (p = .166), or physical health (p = .171).

Creating Victimization and Bullying Scores

Peer victimization and bullying scores were determined using principal components analysis with PROMAX rotation, which allows factors to correlate with one another. Although the DIAS is structured to produce three subscales (physical, verbal, and indirect) and the CSEQ includes two victimization-related subscales (relational and overt), research suggests that there are two main types of victimization/bullying (social and physical) as verbal victimization can either be social or physical in nature (see Rosen, Beron, & Underwood, 2013). The principal components analysis revealed two

factors: (1) social victimization (relational/indirect/verbal), and (2) physical victimization (overt/physical/verbal), which together accounted for 87.85% of the variance (see Table 1). The two factors were correlated with one another (r = .60), consistent with previous work (Guarneri-White, Knack, & Jensen-Campbell, 2015). I also conducted a principal components analysis for bullying and obtained similar results; the two factors (social and physical bullying) accounted for 89.64% of the variance and were correlated with one another (r = .36).

Overall, gender-specific, and genotype-specific descriptive statistics can be found in Table 2. Zero-order correlations between the study variables for the whole sample are found in Table 3.

Table 1: *Principal Components Analysis Factor Loadings for Peer Victimization and Bullying*

	Social	Physical
Victimization		
Indirect	1.03	-0.12
Relational	0.92	0.00
Verbal	0.65	0.35
Physical	-0.13	1.03
Overt	0.12	0.87
% of Variance	71.51	16.34
Bullying		
Indirect	0.99	-0.17
Verbal	0.80	0.24
Physical	-0.03	1.00
% of Variance	62.83	26.82

Note. A PROMAX rotation was utilized. The values from the pattern matrix are presented. N = 254.

Table 2. *Descriptive Statistics by Gender and Genotype Group*

Variable	Overall (*N* = 254)	Gender		BDNF	
		Boys (*n* = 107)	Girls (*n* = 147)	Val/Val (*n* = 159)	Met carriers (*n* = 92)
Social Victimization	0.00 (1.00)	-0.21 (0.90)	0.15 (1.04)**	0.07 (1.09)	-0.11 (0.82)
Physical Victimization	0.00 (1.00)	0.25 (1.16)**	-0.18 (0.82)	0.10 (1.13)	-0.15 (0.71)
Social Bullying	0.00 (1.00)	-0.19 (0.95)	0.13 (1.02)*	0.03 (1.06)	-0.04 (0.89)
Age	14.47 (2.22)	14.50 (2.32)	14.44 (2.14)	14.53 (2.13)	14.40 (2.36)
Pubertal development	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	-0.01 (0.97)	0.06 (1.02)
WtHR	.47 (0.09)	.47 (0.10)	.47 (0.09)	.47 (0.09)	.46 (0.10)
Frequency	45.46 (7.57)	43.20 (5.87)	47.10 (8.24)***	45.94 (8.26)	44.68 (6.28)
Severity	39.01 (6.02)	37.36 (5.01)	40.22 (6.41)***	39.15 (6.44)	38.82 (5.34)
Depressive Symptoms	36.00 (10.85)	33.13 (9.47)	38.09 (11.34)***	35.57 (11.04)	36.86 (10.66)
Anxious Depression	4.21 (3.46)	3.06 (2.48)	5.04 (3.83)***	4.20 (3.63)	4.17 (3.21)
Withdrawn Depression	2.86 (2.15)	2.68 (2.08)	2.99 (2.20)	2.87 (2.21)	2.80 (2.08)
Somatic Complaints	2.80 (2.34)	2.11 (2.04)	3.31 (2.41)***	2.89 (2.53)	2.65 (1.95)
Attention Problems	4.91 (3.18)	5.08 (3.26)	4.79 (3.13)	5.14 (3.22)	4.48 (3.13)
IL-6 (log)	0.14 (0.34)	0.09 (0.35)	0.18 (0.34)	0.13 (0.37)	0.14 (0.29)
CRP (log)	2.66 (0.64)	2.63 (0.63)	2.67 (0.66)	2.67 (0.65)	2.59 (0.59)

Note. Asterisks indicate a significant difference between groups (with asterisks in the column with higher values). Standard deviations are given in parentheses. *N* = 254.

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

Table 3. *Correlations Between Study Variables*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	-														
2. Gender	-.01	-													
3. Puberty	.73***	.004	-												
4. WtHR	-.04	.02	-.02	-											
5. Social Vic.	-.12*	.19**	-.15**	.07	-										
6. Physical Vic.	-.37***	-.22***	-.31***	.09	.60***	-									
7. Social Bul.	.06	.16**	.04	.05	.72***	.37***	-								
8. Frequency	-.01	.26***	.001	.20**	.37***	.12	.33***	-							
9. Severity	-.11	.24***	-.10	.16**	.46***	.22***	.35***	.75***	-						
10. Depressive Sx	.06	.23***	.08	.14*	.41***	.16*	.26***	.45**	.38***	-					
11. Anxious Dep.	.12	.28***	.09	.09	.37***	.08	.30***	.56***	.48***	.53***	-				
12. Withdrawn Dep.	.20**	.07	.17**	.15*	.19**	.01	.18**	.37***	.26***	.53***	.60***	-			
13. Somatic Comp.	-.05	.25***	-.06	.11	.36***	.15*	.32***	.60***	.49***	.41***	.60***	.45***	-		
14. Attention Prob.	-.08	-.05	-.07	.17**	.31***	.31***	.27***	.25***	.24***	.33***	.40***	.35***	.36***	-	
15. IL-6	-.27***	.14	-.16*	.30***	-.01	.06	-.09	.07	.06	.09	.01	.07	.03	.000	-
16. CRP	-.04	.03	-.04	.33***	.05	-.04	-.001	.17	.04	.13	.03	.07	.05	.02	.51***

Note. Sx = symptoms. Gender is coded with "1" for boys and "2" for girls. $N = 254$. *** $p < .001$; ** $p < .01$; * $p < .05$

Chapter 3:

Results

Aim 1: Replication Analyses

The first aim of this present study was to replicate my previous work (Arana et al., in press), which found that social victimization uniquely predicted negative health outcomes and higher levels of inflammatory markers. In the Wave 2 sample of early adolescents, those who were socially victimized reported more frequent and severe health problems, depressive symptoms (CESD), anxious depression, and somatic complaints even after controlling for the effects of physical victimization, age, WtHR, pubertal status, and gender (Table 4). However, social victimization was inversely related to IL-6 concentration and not significantly associated with CRP.

Being physically victimized was significantly associated with higher levels of IL-6, in contrast with the original study. Additionally, physical victimization was unrelated to frequency, severity, CESD scores, anxious and withdrawn depressive symptoms, somatic complaints, and CRP concentration.

Overall, this set of predictors was able to account for 8% to 23% of the variance in all outcomes, with social victimization explaining unique variance in all but two (withdrawn depressive symptoms and CRP). Like the original study, WtHR was the strongest predictor of IL-6 and CRP (ΔR^2 = .07 and .10, respectively).

Table 4: *Social Victimization Predicting Health Outcomes*

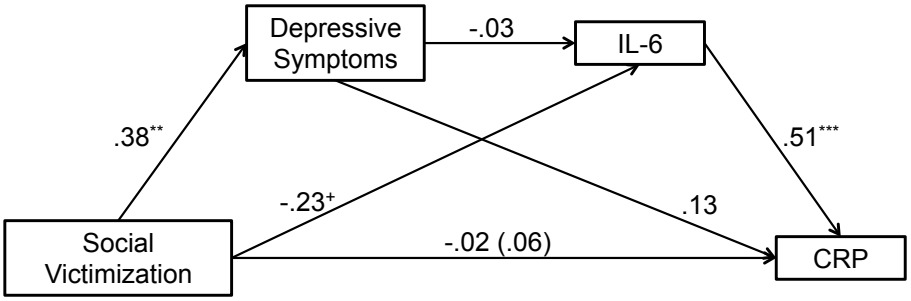
	Frequency	Severity	CESD	Anxious Dep.	Withdrawn Dep.	Somatic Complaints	IL-6	CRP
Step 1								
Physical Vic.	.06 (.003)	.20 (.03)*	.26 (.05)**	.12 (.01)	.05 (.002)	.11 (.01)	.11 (.01)	-.05 (.002)
Age	-.01 (.001)	-.09 (.004)	.14 (.01)	.10 (.004)	.22 (.02)	.03 (.000)	-.04 (.001)	-.10 (.004)
WtHR	.12 (.01)	.10 (.01)	.14 (.02)	.02 (.000)	.12 (.01)	.06 (.004)	.25 (.06)**	.31 (.09)**
Gender	.21 (.04)*	.26 (.06)**	.25 (06)**	.22 (.05)**	-.03 (.001)	.23 (.05)**	.12 (.01)	-.01 (.000)
Puberty	-.02 (.000)	-.03 (.001)	.13 (.01)	-.01 (.000)	.04 (.001)	-.06 (.000)	.06 (.002)	-.06 (.002)
Step 2								
Physical Vic.	-.21 (.02)	-.13 (.01)	-.01 (.000)	-.10 (.004)	-.07 (.002)	-.15 (.01)	.33 (.04)*	-.02 (.000)
Age	-.02 (.000)	-.10 (.004)	.13 (.01)	.10 (.004)	.22 (.02)	.03 (.000)	-.03 (.000)	-.09 (.004)
WtHR	.12 (.01)	.10 (.01)	.13 (.02)	.00 (.000)	.11 (.01)	.04 (.002)	.27 (.07)**	.31 (.10)**
Gender	.06 (.003)	.08 (.005)	.11 (.01)	.10 (.01)	-.09 (.01)	.09 (.01)	.24 (.04)	.01 (.000)
Puberty	-.03 (.000)	-.04 (.001)	.12 (.01)	-.02 (.000)	.03 (.000)	-.07 (.002)	.07 (.003)	-.06 (.002)
Social Vic.	.38 (.07)**	.46 (.10)***	.38 (.07)***	.32 (.05)**	.17 (.01)	.36 (.06)**	-.30 (.05)*	-.05 (.001)
Model R^2	.13**	.23***	.21***	.10*	.08	.12**	.13**	.12*

Note. Numbers given are beta coefficients, and numbers in parentheses represent squared semipartial correlations.
Wave 2 (N = 156) was used for these analyses.
*** $p < .001$; ** $p < .01$; * $p < .05$; Bonferroni's adjustment for multiple comparisons ($p = .05$) $\alpha = .014$.

I also examined the indirect effect of social victimization on IL-6 via depressive symptoms. Socially bullied adolescents reported more depressive symptoms (β = .38, *p* = .002), but depressive symptoms did not significantly predict levels of IL-6 (β = -.03, *p* = .707). Although the overall model explained 11.4% of the variance in IL-6, *F*(6, 110) = 2.36, *p* = .035, the indirect effect of social victimization on IL-6 was not significant, β = -.01, bootstrap *SE* = .04, bootstrap 95% CI [-.09, .06]. As the relationship between depression and IL-6 is likely bidirectional, I also tested the effect of social victimization on depressive symptoms via IL-6, with similar results: the overall model explained 18.9% of the variance in depressive symptoms, *F*(6, 110) = 4.28, *p* = .006, but social victimization did not indirectly influence depressive symptoms, β = .01, bootstrap *SE* = .03, bootstrap 95% CI [-.03, .09].

Finally, I tested the model from the original study with social victimization as the predictor, CRP as the outcome, and depressive symptoms and IL-6 as serial mediators. Social victimization predicted depressive symptoms (β = .38, *p* = .002), but depressive symptoms were not associated with IL-6 (β = -.03, *p* = .707). IL-6 was significantly related to CRP levels (β = .51, *p* < .001). Approximately 29.3% of the variance in CRP was accounted for by the overall model, *F*(7, 109) = 6.44, *p* < .001, though a significant indirect effect of social victimization on CRP via depressive symptoms and IL-6 was not replicated, β = -.01, bootstrap *SE* = .02, bootstrap 95% CI [-.05, .03]. However, social victimization did indirectly predict CRP via IL-6 in this model, β = -.12, bootstrap *SE* = .06, bootstrap 95% CI [-.26, -.01] (see Figure 1).

Figure 1. *Indirect Effect Model from Social Victimization to CRP*



Note. All values are standardized regression coefficients (β). The direct effect of social victimization on CRP (i.e., controlling for depressive symptoms, IL-6, and model covariates) is given in parentheses. $N = 156$. *** $p < .001$; ** $p < .01$; * $p < .05$; + $p < .10$

Aim 2: Moderating Effects of BDNF Val66Met

In the larger sample of adolescents ($N = 254$), I evaluated the moderating effect of BDNF on the victimization-health link. BDNF Val66Met significantly moderated the relationship between social victimization and frequency of health problems; contrary to expectations, this association was stronger for adolescents homozygous for the Val allele. A summary of these results can be found in Table 5. The Johnson-Neyman method determined that the region of significance had a lower boundary of -3.71 (not pictured in graph, as social victimization Z-scores below -2 were not observed in these data) and upper boundary of .31, indicating that Val/Val and Met carrier adolescents only differed in their reported frequency of health outcomes at above-average levels of social victimization (see Figure 2). At average or below-average levels of social victimization, the BDNF genotype groups were not significantly different from one another.

The interaction between social victimization and BDNF Val66Met was also related to symptoms of anxious depression and somatic complaints. Again, these

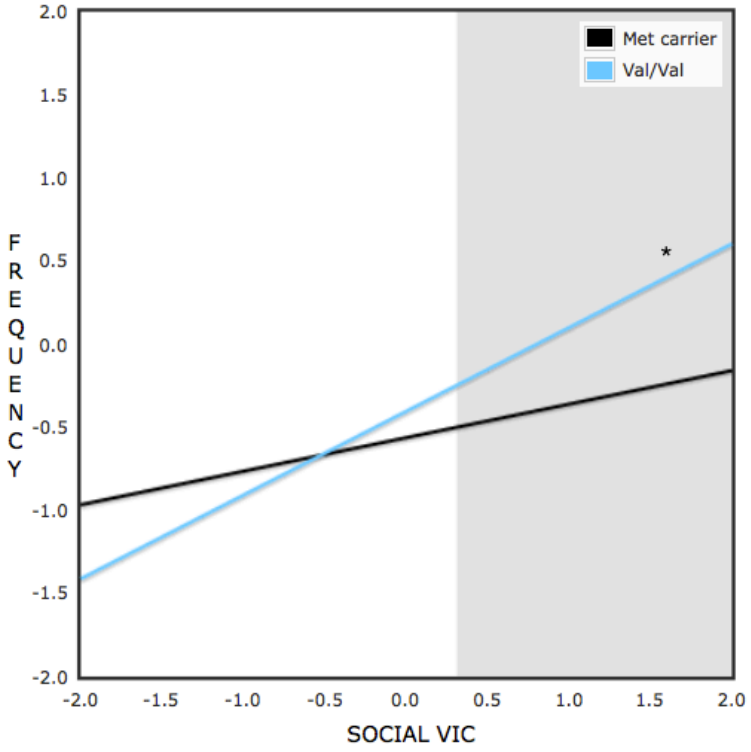
relationships were stronger for Val/Val teens compared to Met carriers. The effect of BDNF genotype was significant when social victimization *Z*-scores fell outside the region of [-2.05, 1.70] for anxious depression (Figure 3) and [-9.60, .61] for somatic complaints (Figure 4). Val/Val and Met carrier adolescents only differed in somatic complaints at above-average levels of social victimization, and at very high levels of social victimization for anxious depression. At average or low levels of social victimization, the BDNF groups did not significantly differ.

Table 5. *The Interaction Effects of Social Victimization and BDNF Val66Met*

	Frequency	Severity	CESD	Anxious Dep.	Withdrawn Dep.	Somatic Complaints	Attention Prob.	IL-6	CRP
Age	-.04 (.09)	-.09 (.09)	.03 (.09)	.07 (.07)	.13 (.07)	-.04 (.08)	-.01 (.08)	-.25 (.10)*	-.05 (.10)
Gender	.30 (.13)*	.24 (.13)	.29 (.13)*	.28 (.11)*	-.01 (.12)	.29 (.12)*	-.06 (.12)	.39 (.15)*	-.04 (.16)
WtHR	.17 (.06)**	.13 (.06)*	.11 (.06)*	.05 (.05)	.11 (.05)*	.05 (.05)	.11 (.05)*	.31 (.07)***	.35 (.07)***
Physical Vic	-.14 (.09)	-.09 (.09)	-.03 (.09)	-.08 (.07)	-.05 (.08)	-.07 (.07)	.13 (.08)	.15 (.10)	-.11 (.11)
Puberty	.04 (.08)	.00 (.08)	.11 (.08)	.04 (.07)	.07 (.07)	.00 (.07)	.03 (.07)	.06 (.10)	-.02 (.10)
Social Vic	.80 (.20)***	.67 (.20)***	.60 (.20)**	.66 (.17)***	.31 (.17)	.60 (.17)***	.25 (.18)	-.38 (.22)	.04 (.23)
BDNF	-.14 (.12)	-.03 (.12)	.16 (.12)	-.02 (.10)	.01 (.11)	-.10 (.10)	-.09 (.11)	.04 (.14)	-.06 (.15)
Social Vic X BDNF	-.31 (.13)*	-.15 (.13)	-.15 (.13)	-.25 (.11)*	-.08 (.12)	-.25 (.12)*	-.07 (.12)	.15 (.15)	.01 (.16)
Model R^2	.23***	.26***	.23***	.23***	.12***	.18***	.14***	.21***	.13**

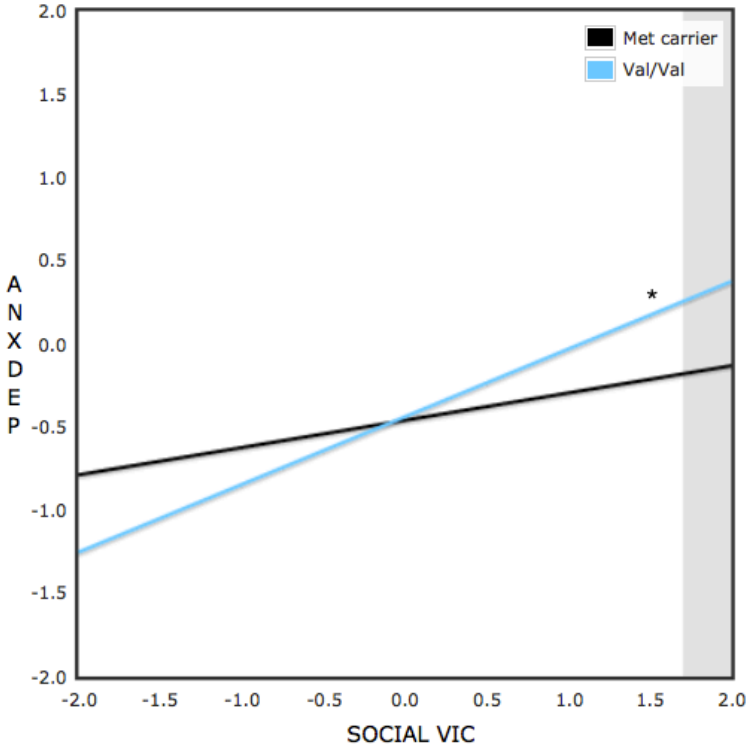
Note. Numbers given are beta coefficients, and numbers in parentheses represent standard errors.
Combined Waves 1 and 2 (N = 254) were used for these analyses.
*** $p < .001$; ** $p < .01$; * $p < .05$; Bonferroni's adjustment for multiple comparisons α = .014.

Figure 2. *Social Victimization × BDNF on Frequency of Health Problems*



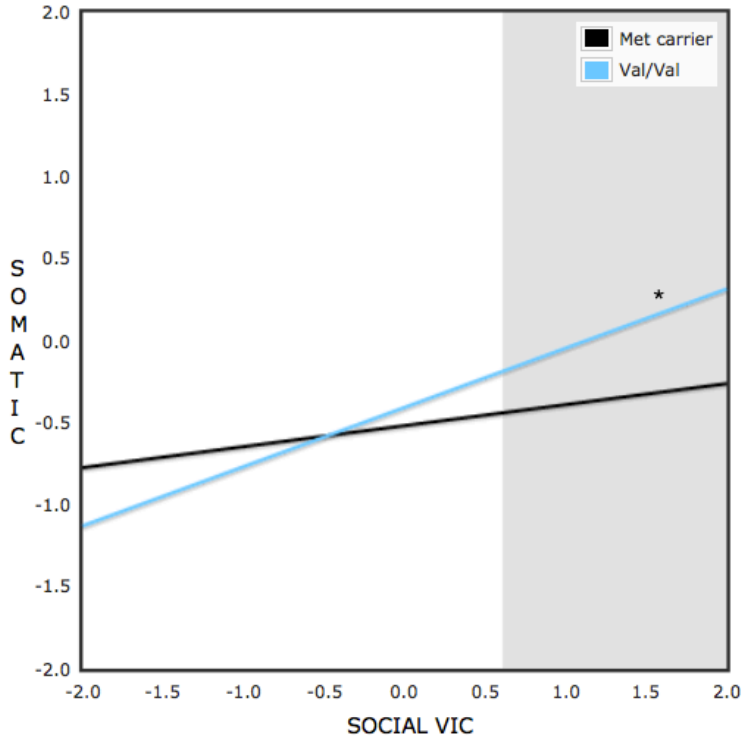
Note. Both axes represent standardized (*Z*) scores. The Johnson-Neyman regions of significance are shaded in gray. $N = 254$. $^{*}p < .001$.

Figure 3. *Social Victimization × BDNF on Anxious Depression*



Note. Both axes represent standardized (*Z*) scores. The Johnson-Neyman regions of significance are shaded in gray. $N = 254$. $^{*}p < .001$.

Figure 4. *Social Victimization × BDNF on Somatic Complaints*



Note. Both axes represent standardized (*Z*) scores. The Johnson-Neyman regions of significance are shaded in gray. $N = 254$. $^{*}p < .001$.

Aim 3: Bully-Victims and BDNF Val66Met

In order to examine at the health outcomes of social bully-victims, I tested the interaction between social victimization and social bullying using a moderation analysis and controlled for age, gender, and WtHR. Although the overall models were able to explain 12% to 25% of the variance (Table 6), the interaction was not significant for health problems, depressive symptoms, anxious depression, somatic complaints, and inflammation, and was only marginally related to withdrawn depression (p = .089). For withdrawn depression symptoms (and the majority of the other outcomes), the effects of social victimization were higher for those that scored high on social bullying, though the difference did not reach statistical significance. In sum, social victimization was related to poor health outcomes regardless of social bullying. These results remained unchanged when physical victimization, physical bullying, and pubertal status were also used as covariates. The results from the simpler model are presented in Table 6.

Similarly, I analyzed the effects of a three-way interaction between social victimization, social bullying, and BDNF groups on these outcomes. The variance accounted for by the overall models ranged from 13% to 25%, but the three-way interaction uniquely explained less than 1% in each model (Table 7). The results were similar when controlling for physical victimization and physical bullying. In short, my hypotheses regarding social bully-victims and BDNF were not supported by these data.

Table 6. *The Interaction Effects of Social Victimization and Social Bullying*

	Frequency	Severity	CESD	Anxious Dep.	Withdrawn Dep.	Somatic Complaints	Attention Prob.	IL-6	CRP
Age	.01 (.08)	-.06 (.08)	.05 (.08)	.10 (.07)	.14 (.07)	-.02 (.07)	-.05 (.07)	-.30 (.09)**	-.01 (.10)
Gender	.38 (.12)**	.31 (.06)**	.33 (.12)**	.35 (.10)***	.03 (.10)	.31 (.10)**	-.16 (.10)	.34 (.14)*	.09 (.14)
WtHR	.17 (.06)**	.12 (.06)*	.11 (.06)*	.05 (.05)	.11 (.05)*	.05 (.05)	.12 (.05)*	.30 (.07)***	.34 (.07)***
Puberty	.03 (.08)	-.01 (.08)	.12 (.08)	.03 (.07)	.06 (.07)	-.02 (.07)	.01 (.07)	.06 (.10)	-.01 (.10)
Social Vic	.25 (.08)**	.36 (.08)***	.48 (.08)***	.24 (.07)**	.10 (.07)	.12 (.07)	.16 (.07)*	-.02 (.10)	.05 (.10)
Social Bullying	.10 (.08)	.07 (.08)	-.10 (.08)	.02 (.07)	.04 (.07)	.14 (.07)*	.13 (.07)	-.14 (.09)	-.11 (.10)
Social Vic X Social Bullying	-.01 (.05)	.01 (.05)	-.04 (.05)	.06 (.04)	.07 (.04)	.04 (.04)	-.01 (.04)	.04 (.06)	.03 (.06)
Model R^2	.20***	.25***	.23***	.21***	.12***	.17***	.13***	.20***	.12**

Note. Numbers given are beta coefficients, and numbers in parentheses represent standard errors.
Waves 1 and 2 (N = 254) were both used for these analyses.
*** $p < .001$; ** $p < .01$; * $p < .05$; Bonferroni's adjustment for multiple comparisons α = .014.

Table 7. *The Interaction Effects of Social Bully-Victims and BDNF*

	Frequency	Severity	CESD	Anxious Dep.	Withdrawn Dep.	Somatic Complaints	Attention Prob.	IL-6	CRP
Age	.00 (.08)	-.06 (.08)	.06 (.08)	.10 (.07)	.14 (.07)	-.03 (.07)	-.06 (.08)	-.30 (.09)**	-.12 (.10)
Gender	.40 (.12)***	.32 (.12)**	.32 (.12)**	.35 (.10)***	.03 (.10)	.34 (.10)**	-.14 (.11)	.28 (.14)*	.06 (.14)
WtHR	.17 (.06)**	.13 (.06)*	.12 (.06)*	.05 (.05)	.10 (.05)	.05 (.05)	.12 (.05)*	.30 (.07)***	.37 (.07)***
Puberty	.03 (.08)	-.01 (.08)	.11 (.08)	.04 (.07)	.06 (.07)	-.01 (.07)	.03 (.07)	.06 (.10)	.00 (.10)
Social Vic	.45 (.25)	.43 (.25)	.56 (.25)*	.49 (.21)*	.18 (.22)	.40 (.22)	.11 (.22)	-.26 (.28)	-.19 (.30)
Social Bullying	.29 (.23)	.10 (.23)	-.04 (.24)	.00 (.21)	-.06 (.21)	.13 (.21)	.43 (.22)*	-.06 (.27)	.07 (.28)
BDNF	-.20 (.14)	-.06 (.14)	.13 (.14)	-.04 (.12)	.05 (.13)	-.14 (.12)	-.18 (.13)	.08 (.16)	-.13 (.17)
Vic X Bullying X BDNF	.13 (.15)	.11 (.15)	.10 (.15)	.09 (.13)	-.01 (.13)	.10 (.13)	.12 (.14)	-.08 (.17)	.21 (.18)
Model R^2	.22***	.25***	.24***	.23***	.13**	.19***	.15***	.21***	.14**

Note. Numbers given are beta coefficients, and numbers in parentheses represent standard errors.
Waves 1 and 2 (N = 254) were both used for these analyses.
*** $p < .001$; ** $p < .01$; * $p < .05$; Bonferroni's adjustment for multiple comparisons α = .014.

Supplementary Analyses

Social Victimization × BDNF Val66Met × Gender

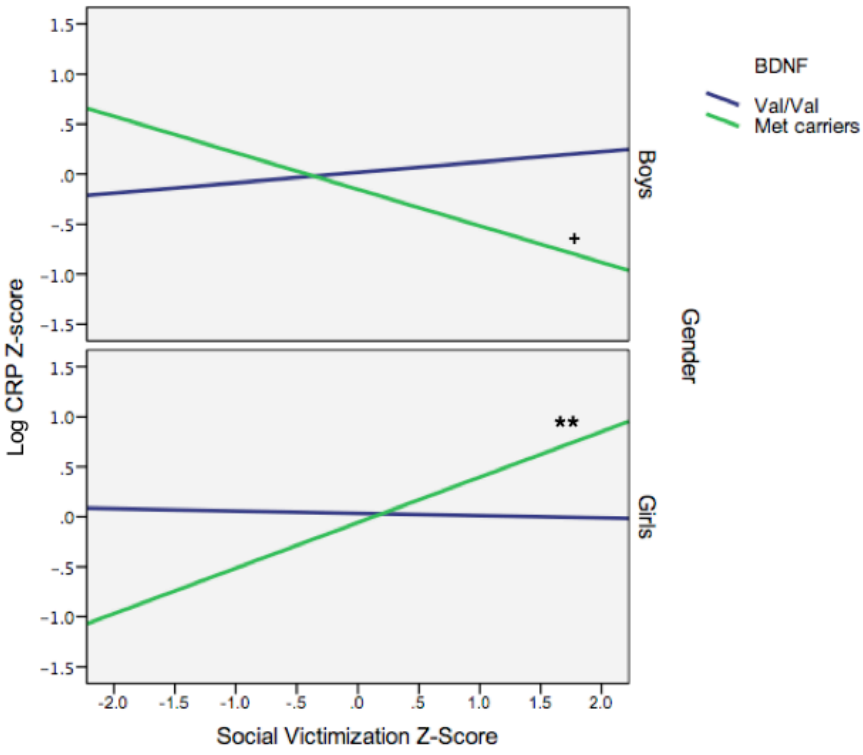
In addition to the Aim 2 analyses, I also tested the effects of a three-way interaction between social victimization, BDNF, and gender on physical and psychological health outcomes while controlling for the effects of physical victimization, age, WtHR, and pubertal status. The three-way interaction was only marginally related to severity of health problems (p = .080) and symptoms of withdrawn depression (p = .067), but was significantly associated with circulating levels of CRP, explaining 4.6% of the variance (Table 8). For girls with at least one Met allele, social victimization predicted higher levels of CRP; this relationship was not significant for girls homozygous for the Val allele or for boys (Figure 5). Social victimization, BDNF genotype, and gender did not interact to significantly predict any of the other health outcomes.

Table 8. *The Interaction Effects of Social Victimization, BDNF, and Gender*

	Frequency	Severity	CESD	Anxious Dep.	Withdrawn Dep.	Somatic Complaints	Attention Prob.	IL-6	CRP
Age	-.04 (.09)	-.09 (.09)	.02 (.09)	.07 (.08)	.12 (.08)	-.04 (.08)	-.01 (.08)	-.26 (.10)*	-.04 (.10)
Gender	.15 (.06)**	.12 (.06)*	.11 (.06)	.04 (.05)	.10 (.05)	.05 (.05)	.11 (.05)*	.31 (.07)***	.37 (.07)***
WtHR	-.13 (.09)	-.11 (.09)	-.05 (.09)	-.08 (.08)	-.06 (.08)	-.07 (.08)	.12 (.08)	.13 (.11)	-.05 (.11)
Puberty	.03 (.08)	.00 (.08)	.11 (.08)	.04 (.07)	.07 (.07)	.00 (.07)	.04 (.07)	.06 (.10)	.01 (.10)
Social Vic	-.26 (.61)	-.18 (.60)	.25 (.61)	.11 (.53)	-.52 (.54)	.75 (.54)	.42 (.55)	-.32 (.68)	.56 (70)*
BDNF	-.26 (.41)	-.32 (.41)	.33 (.42)	.28 (.36)	.25 (.37)	-.07 (.37)	.23 (.38)	-.43 (.48)	-.23 (.49)
Gender	.17 (.360	-.06 (.36)	.39 (.37)	.52 (.31)	.15 (.32)	.31 (.32)	.21 (.33)	-.03 (.42)	-.03 (.44)
Social Vic X BDNF X Gender	-.44 (.26)	-.45 (.26)	-.26 (.27)	-.25 (.23)	-.45 (.23)	.05 (.23)	.00 (.24)	-.03 (.30)	.92 (.31)**
Model R^2	.24***	.27***	.24***	.23***	.13***	.18***	.15***	.21***	.18***

Note. Numbers given are beta coefficients, and numbers in parentheses represent standard errors.
Waves 1 and 2 (N = 254) were both used for these analyses.
*** $p < .001$; ** $p < .01$; * $p < .05$; Bonferroni's adjustment for multiple comparisons α = .014.

Figure 5. *Social Victimization × BDNF × Gender on CRP Levels*



Note. $N = 254$. $^{**}p < .01$; $^{*}p < .05$; $^{+}p < .10$

Social Victimization × Social Bullying × Gender

Although the interaction between social victimization and social bullying did not uniquely predict any of the physical and psychological health outcomes, gender was a significant predictor in the majority of those models. To further examine the role of gender, I conducted a moderation analysis with the interaction between social victimization, social bullying, and gender (with age and WtHR as covariates). This three-

way interaction was significantly associated with frequency of health problems, depressive symptoms, and levels of CRP (Table 9).

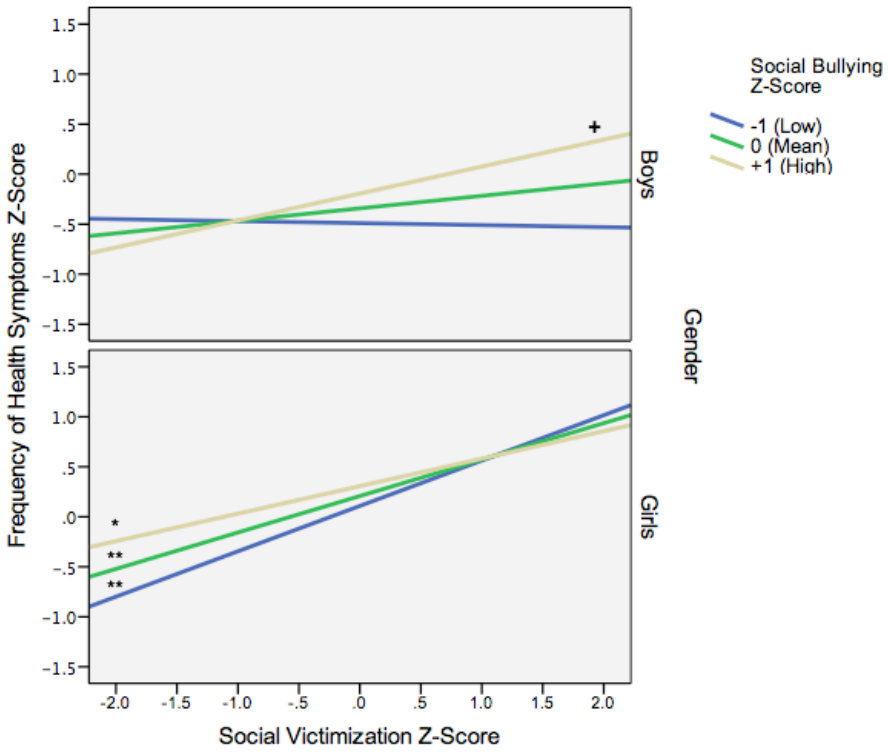
Specifically, the relationship between social victimization and frequency of health problems was strongest for girls who scored low on bullying. This link was weaker but still significant for girls who were high on bullying. Social victimization had no significant effect on boys' frequency of health problems when they were at low or average levels of bullying, and only a marginal effect on boys high on bullying (Figure 6). For depressive symptoms, social victimization was a significant predictor for girls regardless of bullying and for boys who were at average or high levels of bullying. However, these effects were strongest for girls who scored low on bullying and boys who scored high on bullying (Figure 7). Social victimization also interacted with social bullying to predict circulating levels of CRP. For girls, this relationship was significant and positive at both low and mean levels of bullying (albeit slightly stronger for the former). Social victimization was inversely associated with CRP for boys who were low on bullying (Figure 8). Thus, there is some support for the hypothesis that the bully-victim interaction varies by gender, such that girls are more affected by their victim status, and boys are worse off when high on both bullying and victimization.

Table 9. *The Interaction Effects of Social Victimization, Bullying, and Gender*

	Frequency	Severity	CESD	Anxious Dep.	Withdrawn Dep.	Somatic Complaints	Attention Prob.	IL-6	CRP
Age	-.01 (.08)	-.08 (.08)	.02 (.08)	.09 (.07)	.13 (.07)	-.03 (.07)	-.05 (.07)	-.30 (.08)**	-.03 (.10)
Gender	.16 (06)** .	.13 (.06)*	.11 (.06)	.06 (.05)	.11 (.05)*	.06 (.05)	.11 (.05)*	.28 (.07)***	.30 (.07)***
WtHR	.03 (.08)	.00 (.08)	.12 (.08)	.04 (.07)	.06 (.07)	-.01 (.07)	.02 (.07)	.07 (.10)	-.02 (.10)
Puberty	-.11 (.29)	.42 (.29)	.55 (.29)	.37 (.25)	.29 (.25)	.29 (.25)	.28 (.26)	-.03 (.33)	-.68 (.34)*
Social Vic	.21 (.29)	-.01 (.28)	-.02 (.28)	-.17 (.25)	-.02 (.25)	-.07 (.25)	.27 (.26)	.23 (.32)	.72 (.33)*
Social Bullying	.55 (.14)***	.41 (.14)**	.55 (.14)***	.40 (.12)**	.11 (.12)	.34 (.12)**	-.10 (.12)	.40 (.16)*	.27 (.17)
Gender	-.23 (.11)*	-.16 (.11)	-.36 (.11)**	-.07 (.10	-.13 (.10)	-.04 (.10)	-.11 (.10)	-.11 (.13)	-.27 (.10)*
Vic X Bullying X Gender	.23***	.26***	.26***	.21***	.13***	.17***	.14***	.21***	.17***
Model R^2	-.01 (.08)	-.08 (.08)	.02 (.08)	.09 (.07)	.13 (.07)	-.03 (.07)	-.05 (.07)	-.30 (.08)**	-.03 (.10)

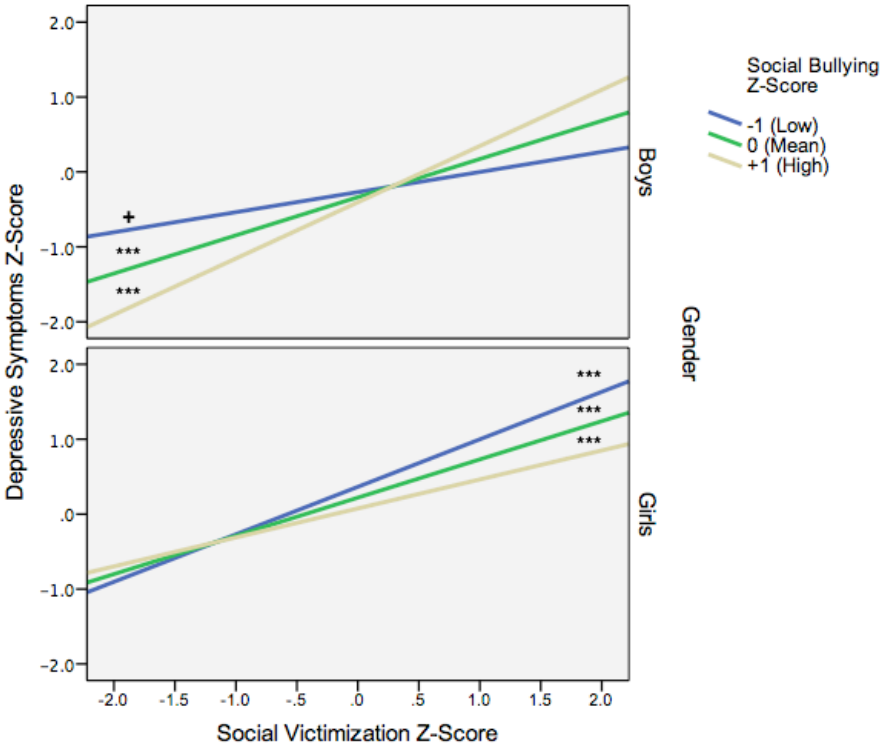
Note. Numbers given are beta coefficients, and numbers in parentheses represent standard errors.
Waves 1 and 2 (N = 254) were both used for these analyses.
*** $p < .001$; ** $p < .01$; * $p < .05$; Bonferroni's adjustment for multiple comparisons α = .014.

Figure 6. *Bully-Victims × Gender on Frequency of Health Problems*



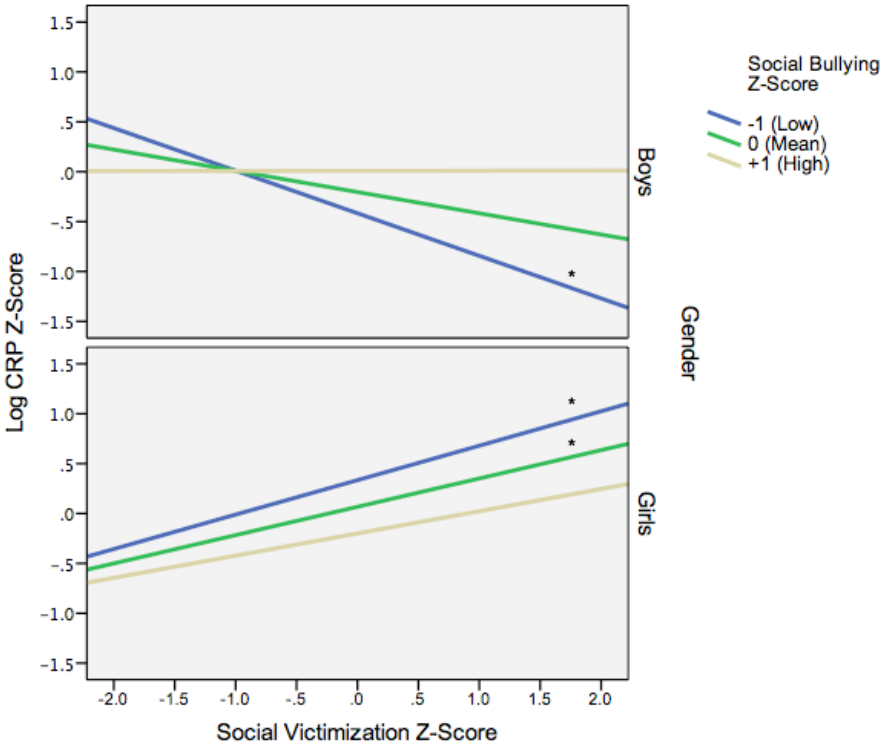
Note. $N = 254$. $^{***}p < .001$; $^{**}p < .01$; $^{*}p < .05$; $^{+}p < .10$

Figure 7. *Bully-Victims* × *Gender on Depressive Symptoms*



Note. $N = 254$. $^{***}p < .001$; $^{**}p < .01$; $^{*}p < .05$; $^{+}p < .10$

Figure 8. *Bully-Victims* × *Gender on CRP*



Note. $N = 254$. $^{***}p < .001$; $^{**}p < .01$; $^{*}p < .05$; $^{+}p < .10$

Chapter 4:

Discussion

Social victimization is a common form of peer harassment for adolescents, and has been tied to numerous health consequences. The overall purpose of this dissertation was to evaluate the influence of social victimization on physical health, psychological health, and inflammation, as well as the moderating effect of the BDNF Val66Met polymorphism in a diverse sample of adolescents.

Replicating Previous Findings

My first aim was to replicate the findings from my previous work (Arana et al., in press), which found that social victimization uniquely predicts depressive symptoms, physical health complaints, and inflammation. This replication utilized the same assessments and procedure as the original paper, but involved a younger sample of adolescents and included additional measures of depressive symptoms and physical health. The majority of the hierarchical regression analyses produced similar results to the original work: social victimization uniquely predicted more frequent and severe health problems, higher symptoms of depression and anxious depression, and more somatic complaints (while controlling for physical victimization, age, gender, and WtHR). These results are also consistent with previous studies on social or relational peer victimization, internalizing problems, and somatic complaints (e.g., Fitzpatrick & Bussey, 2014; Marshall, Arnold, Rolon-Arroyo, & Griffith, 2015; Rosen et al., 2009).

However, unlike the original paper, social victimization significantly predicted *lower* levels of IL-6. This finding also conflicts earlier studies linking psychosocial stress to increased IL-6 in adults (Carpenter et al., 2010; Pace et al., 2006). A possible reason

for these results could be the anti-inflammatory properties of glucocorticoids. While the literature supports the idea that psychosocial stress-induced hypercortisolism can lead to glucocorticoid resistance and increased production of IL-6 (Miller, Cohen, & Ritchey, 2002), one key function of glucocorticoids is to inhibit IL-6 and other inflammatory cytokines (Barnes, 1998). This immunosuppression model is corroborated by findings that psychosocial stress raises the risk for inflammation-related illnesses such as upper respiratory infections (Cohen, Tyrrell, & Smith, 1991). Moreover, glucocorticoid resistance has typically been observed in adults experiencing extreme or prolonged periods of stress, such as experiencing over four years of social isolation (Cole et al., 2007) and parenting a child with cancer (Miller, Cohen, & Ritchey, 2002). The sample in this present study was significantly younger than that of the original paper, so they may not have experienced stress to the extent necessary to manifest glucocorticoid resistance. In short, it is possible that these socially victimized teenagers have higher cortisol, which in turn suppress (rather than increase) levels of IL-6. Unfortunately, cortisol levels were not assessed as part of this dissertation and this hypothesis could not be tested. Additionally, the non-significant relationship between social victimization and CRP (as well as the inverse relationship between social victimization and IL-6) likely contributed to the inability to replicate the indirect effect of social victimization to inflammation via depressive symptoms that was found in the original paper.

Another important factor to consider is the significant age gap between the replication sample and the original sample. Two years, especially during adolescence, can encompass vast differences in terms of physical, social, cognitive, and emotional development. It is possible that social victimization affects younger and older teens differently, as it becomes more prevalent in late adolescence when the social groups are more exclusive and better developed (see Archer & Coyne, 2005, for a review).

Compared to older teens, early adolescents may not yet have the societal structures in place that truly make social victimization harmful. Indeed, a longitudinal study found that increases in social victimization (over the course of two years) predicted more physical and psychological health consequences in adolescents (Iyer-Eimerbrink & Jensen-Campbell, 2016).

The disparity between my findings in this dissertation and those from my previous study brings to mind an important discussion in the field of psychological research today: replication (or lack thereof). In a study that conducted 100 replications of studies from three psychology journals, only 36% of the replications had significant results (compared to 97% of the original studies) and 38% of the effects were subjectively judged as successfully replicating the previous findings (Open Science Collaboration, 2015). Other examinations of replication rates yielded similar results (e.g., Makel, Plucker, & Hegarty, 2012). Some reasons behind the "replication crisis" include a lack of transparency in published work (McNutt, 2014), the bias to publish novel findings rather than replications (Neuliep & Crandall, 1993), and even the possibility that most published research findings are false and therefore inherently irreproducible (Ioannidis, 2005).

Many scientists argue that falsification, a core tenet of science, is not as simple as completely discarding a hypothesis after a "failed" replication, but instead should be a process in which we continue to test theories until reproducible effects that refute the particular theory are observed (Laws, 2016; Popper, 1959). Maxwell, Lau, and Howard (2015) agree and argue that multiple replication studies are required, however frustrating that may be for those who seek quick and simple answers to complex scientific questions. Though this present study has the advantage of being a replication that used the same assessments and procedures as the original paper, the fact that some of the results seem to be at odds with the original should serve as an impetus rather than a

deterrent for future study. To quote Laws (2016): “a ‘failed’ replication is not, in itself, an answer to a question, but a further question” (p. 1).

BDNF Val66Met as a Moderator

The remainder of this dissertation involved novel analyses using the larger sample of adolescents. For my second set of hypotheses, I tested the moderating effects of the BDNF Val66Met polymorphism on the association between social victimization and health outcomes. Significant results were obtained for frequency of health symptoms, anxious depression, and somatic complaints, such that the relationship was stronger for Val/Val adolescents. Furthermore, the interaction effects suggest differential susceptibility, with homozygous Val teens experiencing less frequent health symptoms, anxious depression symptoms, and somatic complaints at low levels of social victimization, and more negative outcomes at higher levels of social victimization. These findings are consistent with studies that link chronic stress to more depressive symptoms in Val/Val adults (Jiang, Brummett, Babyak, Siegler, & Williams, 2013) as well as adolescent Val carriers (Chen & McGue, 2013) with similar differential susceptibility patterns. Additionally, Duncan and colleagues (2009) found that the Val/Val genotype was associated with higher total scores on the Beck Depression Inventory (BDI-II), as well as higher scores on the cognitive-affective and somatic-vegetative factors of the BDI, when compared to carriers of the Met allele. The only published work on peer victimization and BDNF Val66Met also found that the Val allele is linked to greater sensitivity to victimization (Gottfredson, Foshee, Ennett, Haberstick, & Smolen, 2015), which corroborates the findings in this dissertation.

However, the general literature on BDNF Val66Met and which is the risk or malleable allele is mixed (see Hosang et al., 2014, for a review), and at first glance, it

appears that this dissertation only adds to a list of contradictory findings. Indeed, many studies show that the Met allele is associated with decreased activity-dependent secretion of BDNF (e.g., Chen et al., 2004; Egan et al., 2003), which is implicated in the pathophysiology of depressive symptoms. A closer look suggests that the effects of BDNF vary based on its location in the neural circuitry. In the hippocampus, BDNF has anti-depressant effects, evidenced by studies that show decreased hippocampal volume and lower BDNF levels in depressed individuals (Gatt et al., 2009; Hariri et al., 2003; Lee, Kim, Park, & Kim, 2007). Conversely, BDNF in the ventral tegmental area (VTA)-nucleus accumbens (NAc) pathway is linked to a depression-like phenotype (De Vry et al., 2016; Eisch et al., 2003). Thus, it is within the realm of possibility that homozygous Val teens (who theoretically have higher levels of BDNF secretion compared to their Met carrier counterparts) would actually exhibit more depressive symptoms.

This assertion is supported by the fact that the VTA-NAc pathway (also referred to as the mesolimbic or reward pathway) is activated by aversive stimuli such as aggression and social subordination (Louillot, Le Moal, & Simon, 1986; Tidey & Miczek, 1996). Berton and colleagues (2006) used a social defeat paradigm in which mice experienced ten daily sessions of social aggression followed by continuous contact with their aggressor. Defeated mice displayed aversive responses when introduced to an unfamiliar mouse, whereas non-defeated mice behaved socially. After four weeks, defeated mice still exhibited dramatic social avoidance as well as an activated pattern of gene expression in NAc neurons. However, locally deleting the BDNF gene in the VTA reversed the effects of social defeat on the NAc (i.e., similar to an anti-depressant effect). Although this study was based on a rodent model, the social defeat paradigm used shares striking similarities with the experience of peer victimization in humans. This dissertation adds support to the theory that BDNF activity in the mesolimbic pathway may

be a key mediator of depressive symptoms and makes a case for the future study of this topic.

Bully-Victim Outcomes

For my last set of hypotheses, I evaluated the impact of being a bully-victim on health outcomes. I utilized a variable-centered approach with the interaction of the continuous variables of social victimization and social bullying as the predictor. Social bullying did not moderate the effect of social victimization on any of the tested outcomes, contrary to expectations. Yet, the lack of significant interactions does not negate the effects of being a social bully-victim. In fact, the conditional effects for all of the outcomes except for inflammation were significant and positive for teens who scored highly on bullying. Thus, these results suggest that while being a social bully-victim is associated with poor outcomes, it is not necessarily worse than only being socially victimized. Although studies on overall bully-victims have found that they often experience higher levels of depression and physical health problems compared to other children (for a review, see Arana, 2015), the limited literature on social/relational/indirect bully-victims shows a similar pattern to the present findings (Marini, Dane, Bosacki, & Cura, 2006; Wang, Nansel, & Iannotti, 2011). It is possible that other factors may be able to assist in differentiating the group of social bully-victims from other teens involved in social peer victimization; gender was used in supplementary analyses and will be discussed later in this section.

I also assessed the three-way interaction between social victimization, social bullying, and BDNF and its effect on health outcomes. The interaction between social victimization and social bullying was not moderated by BDNF genotype, and this combination did not account for more than 1% of the variance in any of the models.

Theoretically speaking, some allelic variants should leave certain individuals differentially susceptible to chronic psychosocial stress, like in the case of BDNF Val66Met or the short allele of the serotonin transporter gene 5-HTTLPR (e.g., Benjet, Thompson, & Gotlib, 2010; Sudgen et al., 2010). However, there are currently no published studies on bully-victim outcomes (social or otherwise) and BDNF Val66Met (or any other SNPs), so it remains to be seen whether specific genetic polymorphisms play a role in the bully-victim interaction. A twin study by Ball and colleagues (2008) found that children's tendency to be a bully-victim was influenced almost solely by heritable factors, though the specific genotypes were not assessed. Perhaps a closer evaluation of the traits that contribute to a child's role as a bully-victim could provide clues to the genetic influences behind their health outcomes.

Given the gender differences in social victimization and health outcomes, I conducted supplementary analyses on Aims 2 and 3 using gender as an additional moderator. The three-way interaction of social victimization, BDNF Val66Met, and gender significantly predicted circulating levels of CRP. Interestingly, teens with the Met allele were more susceptible to the effects of stress: the relationship between social victimization and CRP was strongest and positive for Met carrier girls and negative for Met carrier boys. Generally, females tend to exhibit higher levels of inflammation and a more pronounced immune response to stress relative to males (Lakoski et al., 2006; Shames, 2002). Studies have also shown that estrogen modulates BDNF expression as well as inflammatory markers (see Sohrabji & Lewis, 2006, for a review). Conversely, testosterone levels are negatively correlated with obesity and inflammatory biomarkers (Mogri, Dhindsa, Quattrin, Ghanim, & Dandona, 2013), though there is a notable paucity of research on the interactions between testosterone and BDNF in human subjects. Nevertheless, these results hint at a sexually dimorphic effect of BDNF genotype on

stress and inflammation. More research is needed to better elucidate the potential influence of gonadal hormones on these complex relationships.

This study also filled a gap in the sparse literature on social bully-victims. Differences between boys and girls emerged when examining the three-way interaction between social victimization, social bullying, and gender. Boys who were high on social bullying were more sensitive to the effects of being socially victimized, such that social bully-victims (i.e., high on both social victimization and social bullying) reported the most depressive symptoms and most frequent health problems, and social bullies (i.e., high on social bullying but low on social victimization) reported the least. For girls, the pattern was different. Generally, social victimization predicted more frequent health problems and higher levels of depressive symptoms regardless of bullying scores. The differences between slopes in the three-way interaction models were not addressed as part of this paper; future studies should follow the recommendations for a slope-difference test as outlined by Dawson and Richter (2006). The effects of differential susceptibility were far less pronounced than they were for boys, and girl social bully-victims (as well as girl social bullies, to a smaller extent) still experienced negative outcomes.

While it is evident that teen boys and girls use social aggression at comparable rates, physical forms of aggression tend to be employed more often by boys (Juvonen, Wang, & Espinoza, 2013). Boys who are social bully-victims are likely involved in more negative peer interactions in general, and masculine acts of social aggression (e.g., taunting, “punking,” or “smack talk”) may escalate into physical altercations (Phillips, 2007). Though this study did not directly examine the effects of physical victimization, it was significantly higher in boys compared to girls and was correlated with social victimization, social bullying, and many negative outcomes. Therefore, it could be that the consequences faced by male bully-victims are at least partly driven by their

participation in physical forms of aggression. These findings highlight the need to consider both physical and social types of aggression when evaluating bully-victims, especially for boys.

Faris and Felmlee (2014) argue that participating in "social combat" is an instrumental part of social climbing for both teen boys and girls. Their study on over 4000 8th-10th graders found that social victimization and its negative consequences are exacerbated as teens jockey for status until a prominent level is reached and they are "above the fray." Additionally, the positive association between social aggression and popularity is stronger for boys, and the negative link between social aggression and social preference (i.e., being liked by peers) is greater for girls (Andreou, 2006; Vaillancourt & Hymel, 2006). Thus, it could be that boys who frequently engage in social bullying enjoy high levels of status, are less socially victimized, and ultimately report fewer negative outcomes, while girl social bullies may be popular but are less liked by their peers. Girls who are social bully-victims find themselves in a middle ground between victims and bullies; they are competing for social status and experience adverse outcomes, but may benefit from having close friendships, which are shown to buffer against the effects of victimization and low peer acceptance (Hodges, Boivin, Vitaro, & Bukowski, 1999; Waldrip, Malcolm, & Jensen-Campbell, 2008). On the other hand, girls who are socially victimized but do not bully others are probably unpopular and may not have the advantage of having close friends or social support.

When evaluating the three-way interaction between social victimization, social bullying, and gender on CRP levels, a pattern of gender differences emerged similar to the previous analysis on social victimization, BDNF, gender, and CRP. Social victimization was significantly related to CRP; this was negative for boys who were low on bullying and positive for girls at average and low levels of bullying. In other words,

socially victimized boys exhibited low concentrations of CRP, and socially victimized girls reported higher concentrations of CRP. As previously mentioned, males and females tend to differ in their overall levels of inflammation as well as their inflammatory responses to stress. Specifically, female sex hormones enhance and male hormones suppress the immune reaction to trauma (see Choudhry, Bland, & Chaudry, 2006; Chrousos, 2010). Studies have also shown that males experience a decrease in markers of inflammation in response to a psychosocial stressor while females show an increase, though these effects were only observed in the short period following the task (Prather et al., 2009). The limited literature on peer victimization and inflammation did not stratify analyses by gender (i.e., Arana et al., in press; Copeland et al., 2014; Takizawa et al., 2015), so it remains unclear if the gender-differentiated patterns uncovered in this study are consistently present in the context of bullying. However, this dissertation provides support for sexually dimorphic inflammatory responses, a topic that warrants additional investigation.

Limitations and Future Directions

This findings in this dissertation should be interpreted in light of the study's limitations. These data are cross-sectional in nature, and causal links can not be inferred from the analyses. The possibility of bidirectional relationships should be considered, particularly given the findings that suggest depressed, hyperactive, and lonely children and adolescents are often the target of school bullies (Busch et al., 2015; Sweeting, Young, West, & Der, 2006; van den Eijnden et al., 2014). Also, this study only examined BDNF Val66Met (rs6265), though there are other SNPs that have been studied in relation to psychological disorders and stress vulnerability, such as G-712A, C270T, rs11030102, rs11030101, rs56164415, and rs2049046 (van Winkel et al., 2014; Zhang et al., 2006).

Furthermore, research on the interaction between BDNF polymorphisms and other SNPs (particularly 5-HTTLPR) has produced promising findings (e.g., Cicchetti & Rogosch, 2014; Kim et al., 2007). The need to account for the interaction between multiple candidate genes is underscored by the fact that models using BDNF as a moderator in the present study were unable to account for more than a miniscule amount of variance. Indeed, the inconsistencies in GxE studies has prompted other researchers to seek out polygenic explanations (Peyrot et al., 2014).

The scientific community has recently become more critical about GxE research and its shortcomings (see Dick et al., 2015, for a review), some of which are applicable to this current study. For one, effect sizes in GxE tend to be overestimated, leading to inadequate sample sizes and power; Dick et al. insist that sample sizes less than 1000 are "grossly underpowered," (p. 6). Properly modeling a genotype with small samples can also be problematic, especially when homozygotes are grouped with heterozygotes (as was done here with the Val/Met and Met/Met groups to form the Met carrier group). Although this is a fairly common practice in BDNF Val66Met research (e.g., Carver, Johnson, Joormann, LeMoult, & Cuccaro, 2011; Mata, Thompson, & Gotlib, 2010), the potential of obfuscating complex associations remains. Moreover, the choice, conceptualization, and measurement of the environment aspect of GxE can be challenging. This dissertation focused on a well-defined chronic early-life stressor (social peer victimization) and reported its psychometric properties, but it is likely that different types of stress are relevant for different genes and disorders, and it is plausible that BDNF Val66Met is not the best candidate gene for these models. Finally, the GxE model must be properly specified, which means to include quadratic terms if the relationship is non-linear, and to include gene-by-covariate and environment-by-covariate terms when controlling for potential confounds. ~~Incidentally, the latter suggestion would necessitate a~~

~~large sample, a limitation of this study addressed previously.~~ Future work should address these methodological considerations and include the ~~proper~~ additional variables for model specification. Though the state of GxE research may seem bleak in light of these concerns, not all researchers agree with the criticisms, and many researchers do believe that many of these issues can be corrected and genetic association research has many potential uses (Colhoun, McKejgue, & Smith, 2003).

Research on relational/social victimization is a growing area that undoubtedly deserves the attention it is receiving. Unlike the traditional notion of overt and physical bullying, social bullying often flies under the radar of parents and educators, and is even rewarded with social status in some settings. Future work should focus on the aspects of the social milieu that condones and encourages such aggressive behavior. Bystanders and witnesses, who may play a role in the problem by providing assistance and attention to the bullies, should be a target of forthcoming research and intervention efforts. Additionally, the correspondence between the results from this study and Faris and Felmlee's (2014) social combat framework suggests that social status may contribute to victimization rates and outcomes. Much of the previous literature has operated under the assumption that only weaker and low-status peers are the target of harassment, but popular teens are affected as well. By taking into account the role of social combat, researchers can better understand the processes underlying the development of adverse effects, and more comprehensive interventions can be designed to serve the whole student population. Furthermore, the findings in this dissertation point to age and/or pubertal status as possible moderators of the victimization-health link. Changes in social environments, peer dynamics, and physical maturation are inextricably linked to adolescent development, and could provide some important nuance when considering how peer relationships affect teens' well-being.

Conclusion

This study aimed to evaluate the impact of social peer victimization on a number of physical and psychological health outcomes. Though I was able to partially replicate previous work on systemic inflammation (Arana et al., in press), these findings underscore the intricacy of the human stress response and the demand for additional study in this field. It is evident that the influence of psychosocial stress on depressive symptoms and systemic inflammation likely cannot be explained by one singular theory, but these results also strengthened the support for the social victimization-health link. Additionally, this dissertation is the first to examine the interaction between social victimization and the BDNF Val66Met polymorphism, and contributed to the contentious debate about which is the more malleable allele. Given the relatively nascent state of BDNF research and the complex nature of neurotrophic activity, forthcoming work should focus on the involvement of various neural pathways in the pathophysiology of depressive symptoms. Finally, I was able to elucidate some important gender differences concerning social victimization, social bullying, and health outcomes. These findings highlight the value of not only controlling for gender, but also considering it as an important moderator of psychosocial processes in adolescence.

Appendix A:

Survey Materials

Direct and Indirect Aggression Scale – Victim Version

(DIAS-VS; Bjorkvist, Lagerspetz, & Osterman, 1992)

Directions**:** Answer each question by bubbling in the answer that seems to most closely tell you about how your classmates behave toward you.

Scale
1 = Never
2 = Seldom
3 = Sometimes
4 = Quite often
5 = Very often

1. How often are you hit by other classmates?
2. How often are you shut out of the group by other classmates?
3. How often do other classmates yell at you or argue with you?
4. How often do classmates become friends with another classmate as a kind of revenge?
5. How often are you kicked by other classmates?
6. How often are you ignored by other classmates?
7. How often are you insulted by other classmates?
8. How often do classmates who are angry with you gossip about you?
9. How often are you tripped by other classmates?
10. How often do classmates tell bad or false stories about you?
11. How often do classmates say they are going to hurt you?
12. How often do classmates plan to secretly bother you?
13. How often are you shoved by other classmates?
14. How often do classmates say bad things about you behind your back?
15. How often are you called names by other classmates?
16. How often do classmates tell others “Let’s not be friends with him/her!”?
17. How often do other classmates take things from you?
18. How often do classmates tell your secrets to a third person?
19. How often are you teased by other classmates?
20. How often do classmates write small notes where you are criticized?
21. How often are you pushed down to the ground by other classmates?
22. How often do other classmates criticize your hair or clothing?
23. How often do other classmates pull at you?
24. How often do classmates who are angry with you try to get others to dislike you?

Note. Parent-report scale contains identical items with wording that indicates the questions are about the child.

Direct and Indirect Aggression Scale – Bully Version

(DIAS-BV; adapted from Bjorkvist, Lagerspetz, & Osterman, 1992)

Directions**:** Answer each question by bubbling in the answer that seems to most closely tell you about how you behave toward other people.

Scale
1 = Never
2 = Seldom
3 = Sometimes
4 = Quite often
5 = Very often

1. How often do you hit other people?
2. How often do you shut other people out of the group by ignoring them?
3. How often do you yell at other people or argue with them?
4. How often do you become friends with another classmate as a kindof revenge on another person?
5. How often do you kick other people?
6. How often do you ignore other people?
7. How often do you insult other people?
8. How often do you gossip about people you are angry with?
9. How often do you trip other people?
10. How often do you tell bad or false stories about other people?
11. How often do you say you are going to hurt other people?
12. How often do you plan to secretly bother other people?
13. How often do you shove other people?
14. How often do you say bad things about other people behind their backs?
15. How often do you call other people names?
16. How often do you tell other people, “Let’s not be friends with him/her!” about another person?
17. How often do you take things from other people?
18. How often do you tell other people’s secrets to a third person?
19. How often do you tease other people?
20. How often do you write notes where other people are criticized?
21. How often do you push other people down to the ground?
22. How often do you criticize other people’s hair or clothing?
23. How often do you pull at other people (their clothes, hair, etc.)?
24. How often do you try to get others to dislike people with whom you are angry?

Note. Parent-report scale contains identical items with wording that indicates the questions are about the child.

Center for Epidemiological Studies Depression Scale for Children

(CESD; Weissman, Orvaschel, & Padian, 1980)

Directions: Below is a list of the ways you might have felt or acted. Please check how much you felt this way during the past week.

Scale

0 = Not at all
1 = A little
2 = Some
3 = A lot

1. I was bothered by things that usually don't bother me.
2. I did not feel like eating, I wasn't very hungry.
3. I wasn't able to feel happy, even when my family or friends tried to help me feel better.
4. I felt like I was just as good as other kids.
5. I felt like I couldn't pay attention to what I was doing.
6. I felt down and unhappy.
7. I felt like I was too tired to do things.
8. I felt like something good was going to happen.
9. I felt like things they did before didn't work out right.
10. I felt scared.
11. I didn't sleep as well as I usually sleep.
12. I was happy.
13. I was more quiet than usual.
14. I felt lonely, like I didn't have any friends.
15. I felt like kids I know were not friendly or that they didn't want to be with me.
16. I had a good time.
17. I felt like crying.
18. I felt sad.
19. I felt people didn't like me.
20. It was hard to get started doing things.

Children's Self-Experiences Questionnaire

(CSEQ; Crick & Grotpeter, 1996)

Directions**:** Here is a list of things that sometimes happen to kids your age at school. How often do they happen to you school?

Scale: 1 never 2 almost never 3 sometimes 4 almost all the time 5 all the time

1. How often does another kid give you help when you need it?
2. How often do you get hit by another kid at school?
3. How often do other kids leave you out on purpose when it is time to play or do an activity?
4. How often does another kid yell at you and call you mean names?
5. How often does another kid try to cheer you up when you feel sad or upset?
6. How often does a kid who is mad at you try to get back at you by not letting you be in their group anymore?
7. How often do you get pushed or shoved by another kid at school?
8. How often does another kid do something that makes you feel happy?
9. How often does a classmate tell lies about you to make other kids not like you anymore?
10. How often does another kid kick you or pull your hair?
11. How often does another kid say they won't like you unless you do what they want you to do?
12. How often does another kid say something nice to you?
13. How often does a kid try to keep others from liking you by saying mean things about you?
14. How often does another kid say they will beat you up if you don't do what they want you to do?
15. How often do other kids let you know that they care about you?

Major Changes to Dissertation

While conducting the enzyme-linked immunosorbence assays (ELISA) to determine plasma concentration of brain-derived neurotrophic factor (BDNF), I encountered a series of problems that rendered my data unusable. In short, the second round of centrifugation as recommended by the manufacturers of the ELISA kits was unable to produce platelet-poor plasma (which is required for this specific assay), and multiple freeze-thaw cycles occurred while trying to obtain valid results, causing the cells to lyse. Thus, the results (after running several plates in duplicate) were inconsistent and the researchers from the Genomics Core Facility and Andy Baum Memorial Laboratory strongly advised against using these data.

However, BDNF has also been studied with regard to single nucleotide polymorphisms (SNPs) that can affect gene expression. Specifically, a SNP in the BDNF gene Val66Met (rs6265) has been shown to influence the activity of the BDNF protein. This SNP results in the substitution of valine (Val) to methionine (Met), which affects the activity-dependent secretion of BDNF such that the Met allele is associated with reduced BDNF (Egan et al., 2003). Numerous studies have shown a relationship between the Met allele (either Val/Met or homozygous Met/Met) and depression (e.g., Lavebratt, Åberg, Sjöholm, & Forsell, 2010; Montag, Weber, Fliessbach, Elger, & Reuter, 2009; Schumacher et al., 2005). Furthermore, BDNF Val66Met interacts with life stressors to predict depressive symptoms (Carver, Johnson, Joormann, LeMoult, & Cuccaro, 2011; Hosang, Shiles, Tansey, McGuffin, & Uher, 2014). The link between the Met allele and attention problems is not quite as well-defined, with some studies suggesting Met as the risk allele, some with Val as the risk allele, and others showing no relationships (e.g., Bergman, Westberg, Lichtenstein, Eriksson, & Larsson, 2011; Cho et al., 2010; Liu et al., 2014); however, one could argue that these contradicting findings serve as grounds for the continued study of the role of the BDNF gene.

Therefore, in lieu of studying differences in BDNF concentration, I will be examining the links between the BDNF Val66Met polymorphism and social peer victimization within the framework of my previously approved dissertation proposal. Aim 1 will not be affected, as it deals exclusively with replicating the findings from Arana et al. (in press). For Aim 2, I will conduct a series of moderation analyses evaluating the effect of the interaction between BDNF Val66Met and social victimization on depressive symptoms, physical health problems, attention problems, and inflammation, with the expectation that the Met allele would be associated with worse outcomes. Finally, for Aim 3 I will look at the effect of a three-way interaction between BDNF Val66Met, social victimization, and social bullying on the aforementioned outcomes to examine whether social bully-victims with the Met allele fare worse than those homozygous for the Val allele. The appropriate changes will be made to the introduction and method sections. The title will be changed to "Neurobiological Correlates of Stress and the Pathophysiology of Depression: Associations Among Social Victimization, IL-6, CRP, and BDNF Val66met." These changes and new analyses are made possible by a contribution from the University of Texas at Arlington Center of Excellence for the Study of Health and Chronic Illnesses.

References

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 profile* (p. 288). Burlington, VT: Department of Psychiatry, University of Vermont.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Amiri, A., Parizi, G. T., Kousha, M., Saadat, F., Modabbernia, M. J., Najafi, K., & Roushan, Z. A. (2013). Changes in plasma Brain-derived neurotrophic factor (BDNF) levels induced by methylphenidate in children with Attention deficit–hyperactivity disorder (ADHD). *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *47*, 20-24.

Andreou, E. (2006). Social preference, perceived popularity and social intelligence relations to overt and relational aggression. *School Psychology International*, *27*(3), 339-351.

Arana, A.A. (2015). *Health Outcomes of Bully-Victims: A Review*. Unpublished manuscript, University of Texas at Arlington, Arlington, Texas.

Arana, A.A., Boyd, E.Q., Guarneri-White, M.E., Iyer-Eimerbrink, P.A., Dougall, A.L., & Jensen-Campbell, L.A. (in press). The impact of social and physical peer victimization on systemic inflammation in adolescents. *Merrill-Palmer Quarterly*. Accepted June 2016.

Arana, A.A. & Jensen-Campbell, A.A. (2015). Do bully-victims have the worst outcomes? Manuscript in preparation.

Archer, J., & Coyne, S. M. (2005). An integrated review of indirect, relational, and social aggression. *Personality and Social Psychology Review*, *9*(3), 212-230.

Aureli, A., Del Beato, T., Sebastiani, P., Marimpietri, A., Melillo, C. V., Sechi, E., & Di Loreto, S. (2010). Attention-deficit hyperactivity disorder and intellectual disability: a study of association with brain-derived neurotrophic factor gene polymorphisms. *International journal of immunopathology and pharmacology*, *23*(3), 873-880.

Ball, H. A., Arseneault, L., Taylor, A., Maughan, B., Caspi, A., & Moffitt, T. E. (2008). Genetic and environmental influences on victims, bullies and bully-victims in childhood. *Journal of Child Psychology and Psychiatry*, *49*(1), 104-112.

Barnes, P. J. (1998). Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clinical science*, *94*(6), 557-572.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic medicine*, *66*(6), 802-813.

Benjet, C., Thompson, R. J., & Gotlib, I. H. (2010). 5-HTTLPR moderates the effect of relational peer victimization on depressive symptoms in adolescent girls. *Journal of Child Psychology and Psychiatry*, *51*(2), 173-179.

Bergman, O., Westberg, L., Lichtenstein, P., Eriksson, E., & Larsson, H. (2011). Study on the possible association of brain-derived neurotrophic factor polymorphism with the developmental course of symptoms of attention deficit and hyperactivity. *International Journal of Neuropsychopharmacology*, *14*(10), 1367-1376.

Berton, O., McClung, C. A., DiLeone, R. J., Krishnan, V., Renthal, W., Russo, S. J., ... & Monteggia, L. M. (2006). Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science*, *311*(5762), 864-868.

Björkqvist, K., Lagerspetz, K. M. J., & Österman, K. (1992). Direct and indirect aggression scales (DIAS). *Vasa, Findland: Abo Academi University, Department of Social Sciences*.

Bramham, C. R., & Messaoudi, E. (2005). BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Progress in neurobiology*, *76*(2), 99-125.

Brendgen, M., & Vitaro, F. (2008). Peer rejection and physical health problems in early adolescence. *Journal of Developmental & Behavioral Pediatrics*, *29*(3), 183-190.

Brunoni, A. R., Lopes, M., & Fregni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *International Journal of Neuropsychopharmacology*, *11*(8), 1169-1180.

Busch, V., Laninga-Wijnen, L., van Yperen, T. A., Schrijvers, A. J. P., & De Leeuw, J. R. J. (2015). Bidirectional longitudinal associations of perpetration and victimization of peer bullying with psychosocial problems in adolescents: A cross-lagged panel study. *School Psychology International*, 0143034315604018.

Calabrese, F., Molteni, R., Racagni, G., & Riva, M. A. (2009). Neuronal plasticity: a link between stress and mood disorders. *Psychoneuroendocrinology*, *34*, S208-S216.

Calhoun, C. D., Helms, S. W., Heilbron, N., Rudolph, K. D., Hastings, P. D., & Prinstein, M. J. (2014). Relational victimization, friendship, and adolescents' hypothalamic–pituitary–adrenal axis responses to an in vivo social stressor. *Development and psychopathology*, *26*(03), 605-618.

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2014). Lower hippocampal volume in patients suffering from depression: a meta-analysis. *American Journal of Psychiatry*.

Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology*, *35*(13), 2617-2623.

Carver, C. S., Johnson, S. L., Joormann, J., LeMoult, J., & Cuccaro, M. L. (2011). Childhood adversity interacts separately with 5-HTTLPR and BDNF to predict lifetime depression diagnosis. *Journal of affective disorders*, *132*(1), 89-93.

Castanon, N., Bluthé, R. M., & Dantzer, R. (2001). Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1β in the rat. *Psychopharmacology*, *154*(1), 50-60.

Champoux, J. E., & Peters, W. S. (1987). Form, effect size and power in moderated regression analysis. *Journal of Occupational Psychology*, *60*(3), 243-255.

Chen, J., Li, X., & McGue, M. (2013). The interacting effect of the BDNF Val66Met polymorphism and stressful life events on adolescent depression is not an artifact of gene–environment correlation: Evidence from a longitudinal twin study. *Journal of Child Psychology and Psychiatry*, *54*(10), 1066-1073.

Chen, Z. Y., Patel, P. D., Sant, G., Meng, C. X., Teng, K. K., Hempstead, B. L., & Lee, F. S. (2004). Variant brain-derived neurotrophic factor (BDNF)(Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *The Journal of Neuroscience*, *24*(18), 4401-4411.

Cho, S. C., Kim, H. W., Kim, B. N., Kim, J. W., Shin, M. S., Chung, S., ... & Chung, U. S. (2010). Gender-specific association of the brain-derived neurotrophic factor gene with attention-deficit/hyperactivity disorder. *Psychiatry investigation*, *7*(4), 285-290.

Choudhry, M. A., Bland, K. I., & Chaudry, I. H. (2006). Gender and susceptibility to sepsis following trauma. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *6*(2), 127-135.

Chrousos, G. P. (1995). The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. *New England Journal of Medicine*, *332*(20), 1351-1363.

Chrousos, G. P. (2010). Stress and sex versus immunity and inflammation. *Sci. Signal.*, *3*(143), pe36-pe36.

Cicchetti, D., & Rogosch, F. A. (2014). Genetic moderation of child maltreatment effects on depression and internalizing symptoms by 5-HTTLPR, BDNF, NET, and CRHR1 genes in African-American children. *Development and psychopathology*, *26*, 1219.

Cillessen, A. H., & Mayeux, L. (2004). From censure to reinforcement: Developmental changes in the association between aggression and social status. *Child development*, *75*(1), 147-163.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd Edition). Hillsdale, NJ: Lawrence Earlbaum Associates.

Cohen, S., Tyrrell, D. A., & Smith, A. P. (1991). Psychological stress and susceptibility to the common cold. *New England journal of medicine*, *325*(9), 606-612.

Cole, S. W., Hawkley, L. C., Arevalo, J. M., Sung, C. Y., Rose, R. M., & Cacioppo, J. T. (2007). Social regulation of gene expression in human leukocytes. *Genome biology*, *8*(9), 1.

Colhoun, H. M., McKeigue, P. M., & Smith, G. D. (2003). Problems of reporting genetic associations with complex outcomes. *The Lancet*, *361*(9360), 865-872.

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A., & Costello, E. J. (2012). Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. *Biological psychiatry*, *71*(1), 15-21.

Copeland, W. E., Wolke, D., Lereya, S. T., Shanahan, L., Worthman, C., & Costello, E. J. (2014). Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. *Proceedings of the National Academy of Sciences*, *111*(21), 7570-7575.

Corominas-Roso, M., Ramos-Quiroga, J. A., Ribases, M., Sanchez-Mora, C., Palomar, G., Valero, S., ... & Casas, M. (2013). Decreased serum levels of brain-derived neurotrophic factor in adults with attention-deficit hyperactivity disorder. *International Journal of Neuropsychopharmacology*, *16*(6), 1267-1275.

Crick, N. R., Casas, J. F., & Nelson, D. A. (2002). Toward a more comprehensive understanding of peer maltreatment: Studies of relational victimization. *Current Directions in Psychological Science*, *11*(3), 98-101.

Crick, N. R., & Grotpeter, J. K. (1995). Relational aggression, gender, and social-psychological adjustment. *Child development*, *66*(3), 710-722.

Crick, N.R., & Grotpeter, J.K. (1996). Children's treatment by peers: Victims of relational and overt aggression. *Development and Psychopathology*, *8*, 367–380.

Dale, J., Russell, R., & Wolke, D. (2014). Intervening in primary care against childhood bullying: an increasingly pressing public health need. *Journal of the Royal Society of Medicine*, 0141076814525071.

Dallman, M. F., Akana, S. F., Pecoraro, N. C., Warne, J. P., la Fleur, S. E., & Foster, M. T. (2007). Glucocorticoids, the etiology of obesity and the metabolic syndrome. *Current Alzheimer Research*, *4*(2), 199-204.

Danese, A., Pariante, C. M., Caspi, A., Taylor, A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences*, *104*(4), 1319-1324.

Dantzer, R. (2009). Cytokine, sickness behavior, and depression. *Immunology and allergy clinics of North America*, *29*(2), 247-264.

Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, behavior, and immunity*, *21*(2), 153-160.

Dawson, J. F., & Richter, A. W. (2006). Probing three-way interactions in moderated multiple regression: development and application of a slope difference test. *Journal of Applied Psychology*, *91*(4), 917.

De La Garza, R. (2005). Endotoxin-or pro-inflammatory cytokine-induced sickness behavior as an animal model of depression: focus on anhedonia. *Neuroscience & Biobehavioral Reviews*, *29*(4), 761-770.

De Vry, J., Vanmierlo, T., Martínez-Martínez, P., Losen, M., Temel, Y., Boere, J., ... & Prickaerts, J. (2016). TrkB in the hippocampus and nucleus accumbens differentially modulates depression-like behavior in mice. *Behavioural brain research*, *296*, 15-25.

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., ... & Sher, K. J. (2015). Candidate gene–environment interaction research reflections and recommendations. *Perspectives on Psychological Science*, *10*(1), 37-59.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctot, K. L. (2010). A meta-analysis of cytokines in major depression. *Biol Psychiatry, 67*(5), 446-457. doi: 10.1016/j.biopsych.2009.09.033

Duman, R. S., Heninger, G. R., & Nestler, E. J. (1997). A molecular and cellular theory of depression. *Archives of general psychiatry*, *54*(7), 597-606.

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological psychiatry*, *59*(12), 1116-1127.

Duncan, L. E., Hutchison, K. E., Carey, G., & Craighead, W. E. (2009). Variation in brain-derived neurotrophic factor (BDNF) gene is associated with symptoms of depression. *Journal of affective disorders*, *115*(1), 215-219.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., ... & Lu, B. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257-269.

Eisch, A. J., Bolanos, C. A., de Wit, J., Simonak, R. D., Pudiak, C. M., Barrot, M., ... & Nestler, E. J. (2003). Brain-derived neurotrophic factor in the ventral midbrain–nucleus accumbens pathway: a role in depression. *Biological psychiatry*, *54*(10), 994-1005.

Eisenberger, N. I., Berkman, E. T., Inagaki, T. K., Rameson, L. T., Mashal, N. M., & Irwin, M. R. (2010). Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biological psychiatry*, *68*(8), 748-754.

Elzinga, B. M., Molendijk, M. L., Voshaar, R. C. O., Bus, B. A., Prickaerts, J., Spinhoven, P., & Penninx, B. J. (2011). The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val66Met. *Psychopharmacology*, *214*(1), 319-328.

Faris, R., & Felmlee, D. (2014). Casualties of Social Combat: School Networks of Peer Victimization and Their Consequences. *American Sociological Review*, *79*(2), 228-257.

Fitzpatrick, S., & Bussey, K. (2014). The Role of Perceived Friendship Self-efficacy as a Protective Factor against the Negative Effects of Social Victimization. *Social Development*, *23*(1), 41-60.

Fradet, C., McGrath, P. J., Kay, J., Adams, S., & Luke, B. (1990). A prospective survey of reactions to blood tests by children and adolescents. *Pain*, *40*(1), 53-60.

Fraley, R. C. (2012). Probing Interactions in Differential Susceptibility Research. Retrieved from http://www.yourpersonality.net/interaction/ros2.pl

Fritz, M. S., & MacKinnon, D. P. (2007). Required sample size to detect the mediated effect. *Psychological science*, *18*(3), 233-239.

Fuligni, A. J., Telzer, E. H., Bower, J., Cole, S. W., Kiang, L., & Irwin, M. R. (2009). A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. *Psychosomatic Medicine*, *71*(3), 329.

Galen, B. R., & Underwood, M. K. (1997). A developmental investigation of social aggression among children. *Developmental psychology*, *33*(4), 589.

Gatt, J. M., Nemeroff, C. B., Dobson-Stone, C., Paul, R. H., Bryant, R. A., Schofield, P. R., ... & Williams, L. M. (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular psychiatry*, *14*(7), 681-695.

Gimeno, D., Kivimaki, M., Brunner, E. J., Elovainio, M., De Vogli, R., Steptoe, A., ... & Ferrie, J. E. (2009). Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological medicine*, *39*(3), 413.

Gottfredson, N. C., Foshee, V. A., Ennett, S. T., Haberstick, B., & Smolen, A. (2015). Genetic heterogeneity in adolescents' depressive symptoms in response to victimization. *Journal of Clinical Child & Adolescent Psychology*, *44*(5), 762-774.

Graff, L. A., Walker, J. R., & Bernstein, C. N. (2009). Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflammatory bowel diseases*, *15*(7), 1105-1118.

Gutierrez, B., Bellon, J. A., Rivera, M., Molina, E., King, M., Marston, L., ... & Monton-Franco, C. (2015). The risk for major depression conferred by childhood maltreatment is multiplied by BDNF and SERT genetic vulnerability: a replication study. *Journal of Psychiatry and Neuroscience*, *40*(3), 187-197.

Hammond, J., Chinn, S., Richardson, H., & Rona, R. (1994). Response to venepuncture for monitoring in primary schools. *Archives of disease in childhood*, *70*(5), 367-372.

Hannestad, J., DellaGioia, N., & Bloch, M. (2011). The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology*, *36*(12), 2452-2459.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *The Journal of neuroscience*, *23*(17), 6690-6694.

Harris, J. R. (1995). Where is the child's environment? A group socialization theory of development. *Psychological review*, *102*(3), 458.

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Communication Monographs, 76*(4), 408-420. doi: 10.1080/03637750903310360

Hayes, A. F. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford Press.

Haynie, D. L., Nansel, T., Eitel, P., Crump, A. D., Saylor, K., Yu, K., & Simons-Morton, B. (2001). Bullies, victims, and bully/victims: Distinct groups of at-risk youth. *The Journal of Early Adolescence*, *21*(1), 29-49.

Hinduja, S., & Patchin, J. W. (2010). Bullying, Cyberbullying, and Suicide. *Archives of Suicide Research, 14*(3), 206-221. doi: 10.1080/13811118.2010.494133

Hodges, E. V., Boivin, M., Vitaro, F., & Bukowski, W. M. (1999). The power of friendship: protection against an escalating cycle of peer victimization. *Developmental psychology*, *35*(1), 94.

Holt, M. K., Kaufman Kantor, G., & Finkelhor, D. (2008). Parent/child concordance about bullying involvement and family characteristics related to bullying and peer victimization. *Journal of School Violence*, *8*(1), 42-63.

Hong, J. S., & Espelage, D. L. (2012). A review of research on bullying and peer victimization in school: An ecological system analysis. *Aggression and Violent Behavior*, *17*(4), 311-322.

Hosang, G. M., Shiles, C., Tansey, K. E., McGuffin, P., & Uher, R. (2014). Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. *BMC medicine*, *12*(1), 1.

Idsoe, T., Dyregrov, A., & Idsoe, E. C. (2012). Bullying and PTSD symptoms. *Journal of abnormal child psychology*, *40*(6), 901-911.

Ioannidis, J. P. (2005). Why most published research findings are false. *PLoS Med*, *2*(8), e124.

Iyer-Eimerbrink, P.A. & Jensen-Campbell, L.A. (2016). The Long-Term Consequences of Peer Victimization on Physical and Psychological Health: A Longitudinal Study. Unpublished manuscript.

Iyer-Eimerbrink, P.A., Scielzo, S., & Jensen-Campbell, L.A. (2015). Impact of Social and Relational Victimization on Depression, Anxiety, and Loneliness: A Meta-Analytic Review. *Journal of Bullying and Social Aggression,* 11/2015, 1.

Jiang, R., Brummett, B. H., Babyak, M. A., Siegler, I. C., & Williams, R. B. (2013). Brain-derived neurotrophic factor (BDNF) Val66Met and adulthood chronic stress interact to affect depressive symptoms. *Journal of psychiatric research*, *47*(2), 233-239.

Juvonen, J., Wang, Y., & Espinoza, G. (2013). Physical aggression, spreading of rumors, and social prominence in early adolescence: reciprocal effects supporting gender similarities?. *Journal of youth and adolescence*, *42*(12), 1801-1810.

Kaltiala-Heino, R., Rimpelä, M., Rantanen, P., & Rimpelä, A. (2000). Bullying at school—an indicator of adolescents at risk for mental disorders. *Journal of adolescence*, *23*(6), 661-674.

Kahn, H. S., Jago, R., Foster, G. D., McMurray, R. G., Buse, J. B., Stadler, D. D., ... & HEALTHY Study Group. (2014). Cardiometabolic risk assessments by body mass index z-score or waist-to-height ratio in a multiethnic sample of sixth-graders. *Journal of obesity*, *2014*.

Kim, J. M., Stewart, R., Kim, S. W., Yang, S. J., Shin, I. S., Kim, Y. H., & Yoon, J. S. (2007). Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. *Biological psychiatry*, *62*(5), 423-428.

Knack, J. M., Jensen-Campbell, L. A., & Baum, A. (2011). Worse than sticks and stones? Bullying is associated with altered HPA axis functioning and poorer health. *Brain and cognition*, *77*(2), 183-190.

Kourmouli, N., Samakouri, M., Mamatsiou, A., Trypsianis, G., Livaditis, M., & Veletza, S. (2013). Effect of BDNF Val66Met and serotonin transporter 5-HTTLPR polymorphisms on psychopathological characteristics in a sample of university students. *Psychiatric genetics*, *23*(5), 188-197.

Ladd, G. W., & Kochenderfer-Ladd, B. (2002). Identifying victims of peer aggression from early to middle childhood: analysis of cross-informant data for concordance, estimation of relational adjustment, prevalence of victimization, and characteristics of identified victims. *Psychological assessment*, *14*(1), 74.

Lakoski, S. G., Cushman, M., Criqui, M., Rundek, T., Blumenthal, R. S., D'Agostino, R. B., & Herrington, D. M. (2006). Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal*, *152*(3), 593-598.

Lavebratt, C., Åberg, E., Sjöholm, L. K., & Forsell, Y. (2010). Variations in FKBP5 and BDNF genes are suggestively associated with depression in a Swedish population-based cohort. *Journal of affective disorders*, *125*(1), 249-255.

Laws, K. R. (2016). Psychology, replication & beyond. *BMC psychology*, *4*(1), 1.

Lee, B. H., Kim, H., Park, S. H., & Kim, Y. K. (2007). Decreased plasma BDNF level in depressive patients. *Journal of affective disorders*, *101*(1), 239-244.

Lereya, S. T., Copeland, W. E., Costello, E. J., & Wolke, D. (2015). Adult mental health consequences of peer bullying and maltreatment in childhood: two cohorts in two countries. *The Lancet Psychiatry*, *2*(6), 524-531.

Li, H., Liu, L., Tang, Y., Ji, N., Yang, L., Qian, Q., & Wang, Y. (2014). Sex-specific association of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and plasma BDNF with attention-deficit/hyperactivity disorder in a drug-naïve Han Chinese sample. *Psychiatry research*, *217*(3), 191-197.

Lopez, C., & DuBois, D. L. (2005). Peer victimization and rejection: Investigation of an integrative model of effects on emotional, behavioral, and academic adjustment in early adolescence. *Journal of Clinical Child and Adolescent Psychology*, *34*(1), 25-36.

Louilot, A., Le Moal, M., & Simon, H. (1986). Differential reactivity of dopaminergic neurons in the nucleus accumbens in response to different behavioral situations. An in vivo voltammetric study in free moving rats. *Brain research*, *397*(2), 395-400.

Makel, M. C., Plucker, J. A., & Hegarty, B. (2012). Replications in psychology research how often do they really occur?. *Perspectives on Psychological Science*, *7*(6), 537-542.

Maniam, J., Antoniadis, C., & Morris, M. J. (2014). Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes. *Frontiers in endocrinology*, *5*.

Marini, Z. A., Dane, A. V., Bosacki, S. L., & Cura, Y. L. C. (2006). Direct and indirect bully-victims: differential psychosocial risk factors associated with adolescents involved in bullying and victimization. *Aggressive Behavior*, *32*(6), 551-569.

Marshall, N. A., Arnold, D. H., Rolon-Arroyo, B., & Griffith, S. F. (2015). The association between relational aggression and internalizing symptoms: A review and meta-analysis. *Journal of Social and Clinical Psychology*, *34*(2), 135.

Mata, J., Thompson, R. J., & Gotlib, I. H. (2010). BDNF genotype moderates the relation between physical activity and depressive symptoms. *Health Psychology*, *29*(2), 130.

Maxwell, S. E., Lau, M. Y., & Howard, G. S. (2015). Is psychology suffering from a replication crisis? What does "failure to replicate" really mean?. *American Psychologist*, *70*(6), 487.

McElroy, S. L., Kotwal, R., Malhotra, S., Nelson, E. B., Keck, P. E., & Nemeroff, C. B. (2004). Are mood disorders and obesity related? A review for the mental health professional. *The Journal of clinical psychiatry*, *65*(5), 634-651.

McNutt, M. (2014). Reproducibility. *Science*, *343*(6168), 229-229.

Messay, B., Lim, A., & Marsland, A. L. (2012). Current understanding of the bi-directional relationship of major depression with inflammation. *Biol Mood Anxiety Disord*, *2*(1), 4.

Miller, G. E., & Chen, E. (2010). Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. *Psychological science*, *21*(6), 848–856.

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychology*, *21*(6), 531.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological bulletin*, *133*(1), 25.

Mogri, M., Dhindsa, S., Quattrin, T., Ghanim, H., & Dandona, P. (2013). Testosterone concentrations in young pubertal and post-pubertal obese males. *Clinical endocrinology*, *78*(4), 593-599.

Molendijk, M. L., Spinhoven, P., Polak, M., Bus, B. A. A., Penninx, B. W. J. H., & Elzinga, B. M. (2014). Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N= 9484). *Molecular psychiatry*, *19*(7), 791-800.

Montag, C., Weber, B., Fliessbach, K., Elger, C., & Reuter, M. (2009). The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. *Psychological medicine*, *39*(11), 1831-1839.

Murray-Close, D., Crick, N. R., Tseng, W. L., Lafko, N., Burrows, C., Pitula, C., & Ralston, P. (2014). Physiological stress reactivity and physical and relational aggression: The moderating roles of victimization, type of stressor, and child gender. *Development and psychopathology*, *26*(03), 589-603.

Nansel, T. R., Craig, W., Overpeck, M. D., Saluja, G., & Ruan, W. J. (2004). Cross-national consistency in the relationship between bullying behaviors and psychosocial adjustment. *Archives of pediatrics & adolescent medicine*, *158*(8), 730-736.

Neuliep, J. W., & Crandall, R. (1993). Reviewer bias against replication research. *Journal of Social Behavior and Personality*, *8*(6), 21.

Nixon, C. L., Linkie, C. A., Coleman, P. K., & Fitch, C. (2011). Peer relational victimization and somatic complaints during adolescence. *Journal of adolescent health*, *49*(3), 294-299.

Olweus, D. (1978). *Aggression in the schools: Bullies and whipping boys*. Hemisphere.

Olweus, D. (1993). Victimization by Peers: Antecedents and Long-Term Outcomes. *Social Withdrawal, Inhibition, and Shyness in Childhood*, 315.

Open Science Collaboration. (2015). Estimating the reproducibility of psychological science. *Science*, *349*(6251), aac4716.

Pace, T. W., Mletzko, T. C., Alagbe, O., Musselman, D. L., Nemeroff, C. B., Miller, A. H., & Heim, C. M. (2006). Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *American Journal of Psychiatry*.

Pan, A., Keum, N., Okereke, O. I., Sun, Q., Kivimaki, M., Rubin, R. R., & Hu, F. B. (2012). Bidirectional Association Between Depression and Metabolic Syndrome A systematic review and meta-analysis of epidemiological studies. *Diabetes care*, *35*(5), 1171-1180.

Papanicolaou, D. A., Wilder, R. L., Manolagas, S. C., & Chrousos, G. P. (1998). The pathophysiologic roles of interleukin-6 in human disease. *Annals of internal medicine*, *128*(2), 127-137.

Paquette, J. A., & Underwood, M. K. (1999). Gender differences in young adolescents' experiences of peer victimization: Social and physical aggression. *Merrill-Palmer Quarterly (1982-)*, 242-266.

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. *Trends in neurosciences*, *31*(9), 464-468.

Pasceri, V., Willerson, J. T., & Yeh, E. T. (2000). Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation*, *102*(18), 2165-2168.

Pellegrini, A. D. (1998). Bullies and victims in school: A review and call for research. *Journal of Applied Developmental Psychology*, *19*(2), 165-176.

Pellegrini, A. D., & Bartini, M. (2001). Dominance in early adolescent boys: Affiliative and aggressive dimensions and possible functions. *Merrill-Palmer Quarterly*, *47*(1), 142-163.

Peyrot, W. J., Milaneschi, Y., Abdellaoui, A., Sullivan, P. F., Hottenga, J. J., Boomsma, D. I., & Penninx, B. W. (2014). Effect of polygenic risk scores on depression in childhood trauma. *The British Journal of Psychiatry*, *205*(2), 113-119.

Phillips, D. A. (2007). Punking and bullying strategies in middle school, high school, and beyond. *Journal of Interpersonal Violence*, *22*(2), 158-178.

Popper, K. R. (1959). The logic of scientific discovery. *London: Hutchinson*.

Prather, A. A., Carroll, J. E., Fury, J. M., McDade, K. K., Ross, D., & Marsland, A. L. (2009). Gender differences in stimulated cytokine production following acute psychological stress. *Brain, behavior, and immunity*, *23*(5), 622-628.

Prinstein, M. J., & Aikins, J. W. (2004). Cognitive moderators of the longitudinal association between peer rejection and adolescent depressive symptoms. *Journal of abnormal child psychology*, *32*(2), 147-158.

Putallaz, M., Grimes, C. L., Foster, K. J., Kupersmidt, J. B., Coie, J. D., & Dearing, K. (2007). Overt and relational aggression and victimization: Multiple perspectives within the school setting. *Journal of School Psychology*, *45*(5), 523-547.

Ridker, P. M., Hennekens, C. H., Buring, J. E., & Rifai, N. (2000). C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New England Journal of Medicine*, *342*(12), 836-843.

Rigby, K., & Slee, P. T. (1991). Bullying among Australian school children: Reported behavior and attitudes toward victims. *The journal of social psychology*, *131*(5), 615-627.

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis–stress: Recommendations for evaluating interaction effects. *Development and psychopathology*, *24*(02), 389-409.

Rosen, L. H., Beron, K. J., & Underwood, M. K. (2013). Assessing peer victimization across adolescence: Measurement invariance and developmental change. *Psychological assessment*, *25*(1), 1.

Rosen, L. H., Underwood, M. K., Beron, K. J., Gentsch, J. K., Wharton, M. E., & Rahdar, A. (2009). Persistent versus periodic experiences of social victimization: Predictors of adjustment. *Journal of abnormal child psychology*, *37*(5), 693-704.

Savva, S. C., Tornaritis, M., Savva, M. E., Kourides, Y., Panagi, A., Silikiotou, N., ... & Kafatos, A. (2000). Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. *International journal of obesity*, *24*(11), 1453-1458.

Schober, S. E., Sinks, T. H., Jones, R. L., Bolger, P. M., McDowell, M., Osterloh, J., ... & Joseph, C. B. (2003). Blood mercury levels in US children and women of childbearing age, 1999-2000. *Jama*, *289*(13), 1667-1674.

Schumacher, J., Jamra, R. A., Becker, T., Ohlraun, S., Klopp, N., Binder, E. B., ... & Zobel, A. (2005). Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. *Biological psychiatry*, *58*(4), 307-314.

Shames, R. S. (2002). Gender differences in the development and function of the immune system. *Journal of Adolescent Health*, *30*(4), 59-70.

Shrout, P. E., & Bolger, N. (2002). Mediation in experimental and nonexperimental studies: New procedures and recommendations. *Psychological Methods, 7*(4), 422-445. doi: 10.1037//1082-989x.7.4.422

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological bulletin*, *140*(3), 774.

Slopen, N., Kubzansky, L. D., McLaughlin, K. A., & Koenen, K. C. (2013). Childhood adversity and inflammatory processes in youth: a prospective study. *Psychoneuroendocrinology*, *38*(2), 188-200.

Sohrabji, F., & Lewis, D. K. (2006). Estrogen–BDNF interactions: implications for neurodegenerative diseases. *Frontiers in neuroendocrinology*, *27*(4), 404-414.

Solberg, M. E., Olweus, D., & Endresen, I. M. (2007). Bullies and victims at school: Are they the same pupils?. *British Journal of Educational Psychology*, *77*(2), 441-464.

Sugden, K., Arseneault, L., Harrington, H., Moffitt, T. E., Williams, B., & Caspi, A. (2010). Serotonin transporter gene moderates the development of emotional problems among children following bullying victimization. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(8), 830-840.

Sullivan, T. N., Farrell, A. D., & Kliewer, W. (2006). Peer victimization in early adolescence: Association between physical and relational victimization and drug use, aggression, and delinquent behaviors among urban middle school students. *Development and psychopathology*, *18*(01), 119-137.

Sweeting, H., Young, R., West, P., & Der, G. (2006). Peer victimization and depression in early–mid adolescence: A longitudinal study. *British journal of educational psychology*, *76*(3), 577-594.

Taddio, A., Ipp, M., Thivakaran, S., Jamal, A., Parikh, C., Smart, S., ... & Katz, J. (2012). Survey of the prevalence of immunization non-compliance due to needle fears in children and adults. *Vaccine*, *30*(32), 4807-4812.

Takizawa, R., Danese, A., Maughan, B., & Arseneault, L. (2015). Bullying victimization in childhood predicts inflammation and obesity at mid-life: a five-decade birth cohort study. *Psychological medicine*, 1-11.

Tidey, J. W., & Miczek, K. A. (1996). Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. *Brain research*, *721*(1), 140-149.

Tronche, F., Kellendonk, C., Kretz, O., Gass, P., Anlag, K., Orban, P. C., ... & Schütz, G. (1999). Disruption of the glucocorticoid receptor gene in the nervous system results in reduced anxiety. *Nature genetics*, *23*(1), 99-103.

Vaillancourt, T., Duku, E., Decatanzaro, D., Macmillan, H., Muir, C., & Schmidt, L. A. (2008). Variation in hypothalamic–pituitary–adrenal axis activity among bullied and non-bullied children. *Aggressive Behavior*, *34*(3), 294-305.

Vaillancourt, T., & Hymel, S. (2006). Aggression and social status: The moderating roles of sex and peer-valued characteristics. *Aggressive Behavior*, *32*(4), 396-408.

van den Eijnden, R., Vermulst, A., van Rooij, A. J., Scholte, R., & van de Mheen, D. (2014). The bidirectional relationships between online victimization and psychosocial problems in adolescents: A comparison with real-life victimization. *Journal of youth and adolescence*, *43*(5), 790-802.

VanVoorhis, C. R. W., & Morgan, B. L. (2007). Understanding power and rules of thumb for determining sample sizes. *Tutorials in Quantitative Methods for Psychology*, *3*(2), 43-50.

van Winkel, M., Peeters, F., van Winkel, R., Kenis, G., Collip, D., Geschwind, N., ... & Myin-Germeys, I. (2014). Impact of variation in the BDNF gene on social stress sensitivity and the buffering impact of positive emotions: replication and extension of a gene–environment interaction. *European Neuropsychopharmacology*, *24*(6), 930-938.

Von Eyben, F. E., Mouritsen, E., Holm, J., Montvilas, P., Dimcevski, G., Suciu, G., ... & Von Eyben, R. (2003). Intra-abdominal obesity and metabolic risk factors: a study of young adults. *International journal of obesity*, *27*(8), 941-949.

Waldrip, A. M., Malcolm, K. T., & Jensen-Campbell, L. A. (2008). With a little help from your friends: The importance of high-quality friendships on early adolescent adjustment. *Social Development*, *17*(4), 832-852.

Wang, J., Nansel, T. R., & Iannotti, R. J. (2011). Cyber and traditional bullying: Differential association with depression. *Journal of Adolescent Health*, 48(4), 415-417.

Weissman, M. M., Orvaschel, H., & Padian, N. (1980). Children's Symptom and Social Functioning Self-Report Scales Comparison of Mothers' and Children's Reports. The Journal of Nervous and Mental Disease, 168(12), 736-740.

Wisse, B. E. (2004). The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *Journal of the American Society of Nephrology*, *15*(11), 2792-2800.

Zhang, H., Ozbay, F., Lappalainen, J., Kranzler, H. R., van Dyck, C. H., Charney, D. S., ... & Gelernter, J. (2006). Brain derived neurotrophic factor (BDNF) gene variants and Alzheimer's disease, affective disorders, posttraumatic stress disorder, schizophrenia, and substance dependence. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *141*(4), 387-393.

Zimmer-Gembeck, M. J., Trevaskis, S., Nesdale, D., & Downey, G. A. (2014). Relational victimization, loneliness and depressive symptoms: Indirect associations via self and peer reports of rejection sensitivity. Journal of youth and adolescence, 43(4), 568-582.

Biographical Information

Allyson Arana, a native of Quezon City, Philippines, graduated with Honors from Southern Methodist University in Dallas, Texas with a Bachelor of Arts in Psychology and minor in Chemistry in 2010. In 2011, she began her graduate career at the University of Texas at Arlington under the supervision of Dr. Lauri Jensen-Campbell. Allyson received her Master of Science in Experimental Psychology in 2013, and her Ph.D. in Psychological Science in 2016 from UTA.

She currently teaches at Texas A&M University - San Antonio, and is also completing a postdoctoral research fellowship in statistics at the US Army Institute of Surgical Research in San Antonio, Texas.