Posttraumatic Stress Symptoms and Pain: Examining Models of Co-Occurrence with Twin Analyses

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Clinical Psychology by Sheeva Mariam Mostoufi

Committee in charge:

University of California, San Diego

Professor Niloofar Afari, Chair
Professor Steven R. Thorp
Professor Julie L. Wetherell

San Diego State University

Professor Joseph M. Price
Professor Scott C. Roesch

2015
The Dissertation of Sheeva Mariam Mostoufi is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

[Signatures]

Chair

University of California, San Diego
San Diego State University
2015
# TABLE OF CONTENTS

Signature Page ............................................................................................................ iii

Table of Contents....................................................................................................... iv

List of Figures............................................................................................................. v

List of Tables............................................................................................................ vi

Acknowledgements................................................................................................... vii

Vita.............................................................................................................................. viii

Abstract of the Dissertation..................................................................................... ix

Chapter 1: Introduction............................................................................................. 1

Chapter 2: Methods.................................................................................................. 23

Chapter 3: Results.................................................................................................... 38

Chapter 4: Discussion............................................................................................... 48

References .................................................................................................................. 72

Appendix A................................................................................................................ 90
LIST OF FIGURES

Figure 2.1: Univariate ACE model ................................................................. 99

Figure 2.2: Bivariate Cholesky model ......................................................... 100

Figure 2.3: MZ twin differences cross-lagged model in PTSS and migraine headache symptoms for Two Time Points ......................................................... 101

Figure 3.1: Path coefficients for best-fitting (AE) bivariate model for males ........ 102

Figure 3.2: Path coefficients for best-fitting (AE) bivariate model for females .... 103

Figure 3.3: Cross-lagged model for MZ twin differences in PTSS and migraine headache symptoms across two time points for males ........................................ 104

Figure 3.4: Cross-lagged model for MZ twin differences in PTSS and migraine headache symptoms across two time points for females ................................. 105
LIST OF TABLES

Table 3.1: Demographic characteristics of twins for aim 1 (Time 1) ......................... 90

Table 3.2: Means and standard deviations for study variables used for aim 1 (Time 1) .................................................................................................................. 91

Table 3.3: Phenotypic, twin, and cross-twin, cross trait correlations between IES and MSQ scores within male and female twins by zygosity ................................................. 92

Table 3.4: Univariate structural equation models of IES and MSQ scores for male and female twins ........................................................................................................... 93

Table 3.5: Bivariate structural equation models of IES and MSQ in male and female twin pairs .................................................................................................................. 94

Table 3.6: Trait-specific and shared additive genetic and environmental variances for best-fitting (AE) bivariate model in male and female twin pairs ........................... 95

Table 3.7: Demographic characteristics for MZ twins for aim 2 (Time 1 and Time 2) .......................................................................................................................... 96

Table 3.8: Individual level and twin difference scores for IES and MSQ by sex at Time 1 and Time 2 ............................................................................................................ 97

Table 3.9: MZ difference score correlations for males and females at Time 1 and Time 2 ....................................................................................................................... 98
ACKNOWLEDGMENTS

This research was supported by National Institutes of Health awards R01AR051524 (Niloofar Afari, Ph.D.) and RC2HL103416 (Dedra Buchwald, MD).

Chapters 1 through 4, in part is currently being prepared for submission for publication of the material: Mostoufi, S. M., Gasperi, M., Godfrey, K. M, Strachan, E., Buchwald, D & Afari, N. “Posttraumatic stress disorder symptoms and migraine headache: Examining models of co-occurrence with twin analyses.” The dissertation author was the primary investigator and author of this material.
VITA

2008 Bachelor of Science, The Ohio State University

2011 Master of Science, San Diego State University

2015 Doctor of Philosophy, University of California, San Diego and San Diego State University

PUBLICATIONS (Selected)


ABSTRACT OF DISSERTATION

Posttraumatic Stress Symptoms and Pain: Examining Models of Co-Occurrence with Twin Analyses

by

Sheeva Mariam Mostoufi

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2015
San Diego State University, 2015

Professor Niloofar Afari, Chair

A large body of research exists on the prevalence and impact of PTSD symptoms assessed in relation to a specific traumatic event, as well as on posttraumatic stress symptoms (PTSS) which refers to the presence of posttraumatic stress symptoms without measurement of a specific traumatic event. Migraine headache is one example of a moderately heritable chronic pain condition which has been found to co-occur with PTSD and PTSS. However, there is a dearth of scientific evidence to either support or refute any proposed models of co-occurrence. The specific aims of this study were to: 1) examine the extent to which shared genetic contributions convey a shared vulnerability to the association between PTSS and migraine headache symptoms (MHS); and 2) use longitudinal twin data to estimate the direction of the relationship between PTSS and
MHS. Already available data, as of November 2013, was used from the University of Washington Twin Registry community-based sample of adult twin pairs. To address aim 1, 3,369 MZ and DZ pairs with complete data from the Registry at Time 1 were included in the analyses. To address aim 2, 1,134 MZ pairs with complete data from the Registry at both Time 1 and Time 2 were included in the analyses. A modest phenotypic association was found between PTSS and migraine headache for males and females. Bivariate analyses revealed that the proportion of the phenotypic association attributable to additive genetics that are common to both PTSS and MHS was an estimated 38% in males and 68% in females. The cross-lagged MZ twin difference model did not find PTSS at Time 1 to be directly related to MHS at Time 2 in both males and females or vice versa. Findings from both aims suggest that there is a modest overlap in genetic influences common to both PTSS and MHS in males and females, that this overlap is potentially more substantial in females, rather than one condition directly influencing the other. Understanding the underlying mechanisms that link PTSD or PTSS and chronic pain conditions such as migraine can provide insight into the development of tailored psychological and pharmacological interventions.
CHAPTER 1:
INTRODUCTION

Posttraumatic stress disorder (PTSD) is a clinically impairing disorder characterized by symptoms of re-experiencing, hyper-arousal, numbing and avoidance in response to an emotionally traumatic event (American Psychiatric Association, 2013). A large body of research exists on the prevalence and impact of PTSD symptoms assessed in relation to a specific traumatic event, as well as on posttraumatic stress symptoms (PTSS) which refers to the presence of posttraumatic stress symptoms without measurement of a specific traumatic event (Breslau, 2001; Dobie et al., 2004; Magruder et al., 2004; Sareen et al., 2007; Villano et al., 2007). In addition, a growing body of literature has established a consistent association between PTSD or PTSS and chronic pain conditions such as migraine headache, the co-occurrence of which is associated with higher rates of disability (Afari et al., 2009; Peterlin et al., 2009). Despite the consistent association between PTSD or PTSS and chronic pain conditions, the nature and mechanisms of the relationship are not well understood. Several theoretical models have been proposed (Asmundson, Coons, Taylor, & Katz, 2002; Asmundson & Katz, 2009; Sharp & Harvey, 2001), but none have been rigorously examined. Given the evidence that these conditions are moderately heritable (Afifi, Asmundson, Taylor, & Jang, 2010; True et al., 1993; Plesh, Noonan, Buchwald, J., & Afari, 2012; Nielsen, Knudsen, & Steingrimsdo´ttir, 2012), the existing literature has paid little attention to the potential role of shared genetic factors in the co-occurrence of PTSD or PTSS and chronic pain conditions (Burris, Cyders, de Leeuw, Smith, & Carlson, 2009; Jenewein, Wittmann, Moergeli, Creutzig, & Schnyder, 2009; Ramchand, Marshall, Schell, & Jaycox, 2008).
Further, the vast majority of the research has been cross-sectional (Afari, Wen, Buchwald, Goldberg, & Plesh, 2008; Burris et al., 2009) and unable to address questions of causality.

The present study used longitudinal data from the large community-based University of Washington Twin Registry to investigate the co-occurrence of PTSS with one specific chronic pain condition, migraine headache. Twin studies are a staple in the field of behavioral genetics and can be used to estimate heritability as well as the extent to which the co-occurrence of two conditions or traits is influenced by shared genetic factors. Additionally, twin studies with longitudinal data can shed light on causal relationships in the absence of randomized experimental designs. This study ascertained the extent to which shared genetic influences convey a shared vulnerability to the co-occurrence of PTSS and migraine headache. We also determined if current PTSS is directly related to the development of migraine headache symptoms. Estimating the shared genetic influences on PTSS and migraine headache can help in identifying some of the biological underpinnings of these conditions and lead to the development of targeted interventions. Additionally, examining the direction of the relationship has implications for developing better tailored prevention and treatment strategies. In the sections below, we review the relevant literature on the co-occurrence of PTSD or PTSS with chronic pain conditions, and specifically migraine headache. We then provide an overview of the theoretical models of co-occurrence as well as the use of twin methodology. Finally, we summarize the limitations of the existing literature and outline the specific aims of this study.

Posttraumatic stress disorder and symptoms
PTSD is a major public health concern that affects about 9% of the general population (Breslau, 2001; Hidalgo & Davidson, 2000). Nearly 6% of males and 12% of females exhibit a lifetime history of PTSD in the general population (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) and nearly half of psychiatric outpatients suffer from this debilitating condition (Villano et al., 2007). PTSD also has been associated with greater utilization of healthcare services by veterans (Schnurr, Friedman, Sengupta, Jankowski, & Holmes, 2000) and the onset of other deleterious conditions such as major depression, alcohol abuse or dependence, several physical disorders, and suicidal behavior (Breslau, 2001; Sareen et al., 2007). While a large body of literature exists on the prevalence and impact of PTSD symptoms assessed in relation to a specific traumatic event, there is also a substantial literature examining the influence of PTSS, which refers to the presence of posttraumatic stress symptoms without measurement of a specific traumatic event. For instance, PTSS has been shown to be associated with physical and mental health problems as well as poorer health-related quality of life in veteran patients in primary care (Magruder et al., 2004) and female veterans (Dobie et al., 2004).

As an aside, there is substantial literature suggesting that PTSD is highly comorbid with depression (Creamer, Burgess, & McFarlane, 2001; Kessler et al., 1995). However, there are also data suggesting that PTSD and depression have a shared vulnerability (Breslau, Davis, Peterson, & Schultz, 2000; Koenen et al., 2008) and that when occurring concurrently and chronically, they become very difficult to differentiate (O'Donnell, Creamer, & Pattison, 2004). In addition, depression symptoms have been shown to mediate the relationship between PTSD and pain interference in chronic pain.
patients (Morasco et al., 2013), further suggesting that depression and PTSD are not only highly comorbid, but potentially may be similar constructs.

Finally, vulnerability to PTSD symptoms has also been found to be moderately heritable, with genetic factors accounting for 25-38% of the variance in PTSD symptoms (Afifi et al., 2010; Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993). Family studies have also found a higher prevalence of PTSD in family members with PTSD, suggesting both a genetic and common environmental influence on the development of PTSD (Koenen, Nugent, & Amstadter, 2008). Therefore, it is important that a comprehensive study of PTSD or PTSS consider the role of genetic and familial factors.

**Chronic pain conditions**

Chronic pain, defined as pain lasting longer than 3 months (Cherry, Burt, & Woodwell, 2003; Gureje, Simon, & Von Korff, 2001), impairs the physical, psychological, and social functioning of individuals (Blyth, 2008; Hardt, Jacobsen, Goldberg, Nickel, & Buchwald, 2008; Manchikanti, Singh, Datta, Cohen, & Hirsch, 2009; Ratcliffe, Enns, Belik, & Sareen, 2008). Pain is the most common symptom for which patients seek medical care (Nawar, Niska, & Xu, 2007), and an estimated $61.2 billion per year is lost due to lost productivity among individuals experiencing common pain conditions in the work force such as headache (Stewart, Ricci, Chee, Morganstein, & Lipton, 2003). The pervasiveness of experiencing pain also negatively impacts the emotional, cognitive, biological, psychological, and social functioning of individuals from the young to the elderly (Hardt et al., 2008; Manchikanti et al., 2009).
Migraine headache

One particularly pervasive chronic pain condition is migraine headache. The classification of migraine headache is typically based on attack frequency and headache duration (Lipton, 2011). Chronic migraine (CM) is defined as a complication of headache attacks which occur more days than not in a one month period, lasting for a duration of greater than or equal to four hours, while episodic migraine (EM) lasts for a similar duration but occurs fewer than 15 days per month (Lipton, 2011). The general prevalence of migraine headache based on a U.S. population-based survey is 11.8% (17.3% of females; 5.7% of males) with approximately 1% meeting criteria for CM (Buse et al., 2012; Lipton et al., 2007), which is consistent with worldwide ranges of CM ranging from 1-3% (Natoli et al., 2010; Scher, Stewart, Liberman, & Lipton, 1998). Compared to individuals experiencing EM, those meeting survey criteria for more severe forms of migraine headache such as CM were found to be slightly older, have higher body mass index, were less likely to be employed full time and twice as likely to be disabled (Buse, Manack, Serrano, Turkel, & Lipton, 2010). Migraine conditions such as CM have been shown to be substantially disabling and associated with more headache-related disability, poorer health related quality of life, and higher rates of co-morbid respiratory disorders, cardiovascular risk factors including hypertension and obesity, as well as psychiatric conditions such as depression and anxiety (Buse et al., 2010; Buse et al., 2012). Further, a substantial proportion of those who could potentially benefit from preventative treatment for severe forms of migraine headache, do not receive it (Lipton et al., 2007).

A multitude of mechanisms have been indicated in the development of migraine. Recent models of migraine suggest that neurological changes and biochemical
abnormalities may contribute to the transformation of EM to CM (Aurora, Kulthia et al., 2011; Bigal & Lipton, 2008). These models demonstrate the neurological components uniquely influencing migraine headache relative to other chronic pain conditions. Bigal & Lipton (2008) hypothesize that migraine may lead to changes in the central nervous system such as changes in nociceptive thresholds leading to allodynia, and physiological changes in pain pathways such as repeated central sensitization episodes leading to neuronal damage around or near periaqueductal gray matter in the brain, an area that influences pain modulation. Further, chronic migraine has been associated with changes in cortical processing, which is associated with the emotional and attentive components of pain (de Tomasso, et al., 2005), frontal lobe dysfunction as indicated through neuropsychological tests (Mongini, Keller, et al., 2005), disturbed brainstem functioning (Obermann et al., 2006), as well as chronically low levels of system 5-HT (serotonin), which may predispose individuals to develop migraine headaches (Ferrari & Saxena, 2003). Together, these studies suggest that there are neurological mechanisms that maybe uniquely associated with the progression of migraine.

While a handful of genetic polymorphisms are found to be related to the development of several pain conditions such as CWP, temporomandibular pain, musculoskeletal pain, and migraine headache (Diatchenko et al., 2006; Diatchenko et al., 2006; Diatchenko, Eröz, Bahadir, Dikici & Tasdemir, 2014; Nackley, Tchivileva, Shabalina, & Maixner, 2007; Holliday et al., 2010; Holliday et al., 2009; Holliday et al., 2010; Slade et al., 2007), evidence from twin studies also indicate that the overlap of multiple chronic pain conditions is substantially mediated by genetic and familial factors (Fillingim, Wallace, Herbstman, Ribeiro-Dasilva, & Staud, 2008; Kato, Sullivan,
Evengard, & Pedersen, 2006; Kato, Sullivan, & Pedersen, 2010; Williams, Spector, & MacGregor, 2010). A recent review of twin studies found migraine headache and tension-type headache to exhibit 40-45% heritability (Nielsen, Knudsen, & Steingrímsdóttir, 2012). Specifically, additive genetics have been found to contribute to 49% of the variance in migraine headache in females and 38% of the variance in males (Plesh et al., 2012; Svensson, Larsson, Waldenlind, & Pedersen, 2003). A study examining the importance of shared rearing environment for lifetime migraine found that shared rearing environment did not play a significant role in the development of lifetime migraine, suggesting that family similarity in migraine may be largely due to genetic factors (Svensson et al., 2003). Therefore, there is a need to consider the role of genetic influences in the development of chronic pain conditions and specifically, migraine headache.

The co-occurrence of PTSD or PTSS with pain conditions and migraine headache

Although individually impairing, a growing body of literature has documented that PTSD or PTSS and chronic pain conditions often occur concurrently (Afari et al., 2006; Afari et al., 2008; Asmundson, Bonin, Frombach, & Norton, 2000; Asmundson, et al., 2002; Otis et al., 2010; Schur et al., 2007; Sharp, 2004). For example, of individuals seeking treatment for chronic pain due to a motor vehicle accident, nearly 50% present with PTSD symptoms as well (Hickling, Blanchard, Silverman, & Schwarz, 1992). Pain also has been found to be the most frequently reported physical symptom in individuals with PTSD (McFarlane, Atchison, Rafalowicz, & Papay, 1994). Individuals with co-occurring PTSD and chronic pain report higher ratings of psychiatric distress, greater disability, lower ratings of mental health confidence, and more intense pain compared to
those with only a single condition (Geisser, Roth, Bachman, & Eckert, 1996; Palyo & Beck, 2005; Villano et al., 2007). Further, individuals with comorbid chronic pain and self-reported PTSS endorse significantly more maladaptive coping strategies and beliefs about pain compared to those with chronic pain alone (Alschuler & Otis, 2011).

There is also a growing literature on the co-occurrence of PTSD or PTSS and migraine headache (Afari et al., 2009; Peterlin, Nijjar, & Tietjen, 2011; Peterlin et al., 2009). With migraine headache, lifetime and one year prevalence of PTSD was significantly higher in individuals with EM and CM compared to those without headache, and remained significant after adjusting for depression, general anxiety, and substance use (Peterlin et al., 2011). Individuals with PTSD and migraine headache also have been shown to experience more headache-related disability, even after adjusting for demographics and depression (Peterlin et al., 2009), and were more frequently diagnosed with alexithymia (Balaban et al., 2012). Further, an increased prevalence of PTSD and migraine headache has been found across multiple cohorts including pain clinic patients (Peterlin et al., 2009), veterans (Afari et al., 2009), medical students (Balaban et al., 2012), and population-based samples (Peterlin et al., 2011). In addition, of those reporting EM and PTSD, 69.2% reported experiencing PTSD symptoms prior to developing severe or frequent headaches (Peterlin et al., 2011). Although this study was cross-sectional and therefore causality could not be formally assessed, this pattern may suggest PTSD is a vulnerability factor to the development of migraine headache (Peterlin et al., 2011).

Given, the growing co-occurrence of PTSD and migraine there is a need to explore potential mechanisms that may underlie the development and maintenance of
these co-occurring disorders. Recent reviews have proposed a number of mechanisms that may uniquely influence the development of PTSD and migraine headache such as hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system dysfunction, an increase in pro-inflammatory cytokins, a possible role of serotonin (Juang & Yang, 2014; Peterlin et al., 2011), and sex hormones such as estrogen (Peterlin, Katsnelson, & Calhoun, 2009). These studies suggest that there are underlying mechanisms that maybe specific to the development and maintenance of PTSD and migraine.

Twin designs have been used to explore the relationship between psychological trauma and a number of physical health conditions such as coronary heart disease, hypertension, respiratory conditions, persistent skin conditions, gastrointestinal disorders, hearing problems, temporomandibular pain, chronic widespread pain, and urological symptoms (Afari et al., 2008; Arguelles et al., 2006; Eisen et al., 1998; Schur et al., 2007; Wright et al., 2010; Vaccarino et al., 2013). Studies utilizing twin designs to examine the association between PTSS and specific chronic pain conditions such as temporomandibular pain and urological symptoms suggest partial explanation of these associations maybe be due to shared familial and genetic effects (Afari et al., 2008; Wright et al., 2010), however, a significant association between PTSS and the presence of chronic widespread pain has been found in a sample of twins, even after adjusting for demographic variables and depression, that was not explained by shared familial or genetic vulnerability to these conditions (Arguelles et al., 2006). These findings suggest a need to further examine possible underlying genetic or familial influence that may be a vulnerability to both PTSS and different physical health conditions.
Studies have also used twin methodologies to examine migraine headache symptoms and its co-occurrence with mental health symptoms and traits such as depression, anxious depression, and neuroticism (Schur, Noonan, Buchwald, Goldberg, & Afari, 2009; Ligthart & Boomsma, 2012; Ligthart, Nyholt, Penninx, & Boomsma, 2010). Twin studies have found that the comorbidity of migraine headache and depression may be attributed to shared genetic risk factors (Schur et al., 2009), a genetic correlation between migraine and anxious depression has been documented (Ligthart et al., 2010), and a co-twin control study of monozygotic and dizygotic twin pairs suggests that neuroticism and migraine headache maybe partially explained by the same genetic and unique environmental factors, and that neurotic personality may increase the risk of developing migraine headache (Ligthart & Boomsma, 2012). These findings suggest underlying shared genetic vulnerability to migraine and other mental health conditions.

However, despite the consistent association of PTSD or PTSS and migraine headache, the examination of genetic and familial factors in PTSD and other disease states, as well as the role of genetic and familial factors on migraine and other mental health conditions, there is a dearth of research accounting for the role of shared genetic and familial factors on the PTSS or PTSD and migraine relationship.

In sum, the drastic and damaging impact of PTSD, PTSS and chronic pain conditions such as migraine headache on individuals and society makes these conditions major public health concerns. Given the frequent co-occurrence and detrimental physical and psychological influence of PTSD, PTSS, and chronic pain conditions such as migraine headache, and the unique mechanisms associated with the co-occurrence of PTSD and migraine headache, it is important to better understand the nature and
mechanisms of the link in order to adequately treat these highly comorbid disorders (Asmundson et al., 2002; Otis, Keane, & Kerns, 2003; Sharp & Harvey, 2001).

**Overview of theoretical models of co-occurrence**

Despite the consistent association between PTSD or PTSS and chronic pain conditions such as migraine headache, there is very little insight into why these conditions are linked and what mechanisms underlie the relationship. Several theoretical explanations have been proposed to explain why this relationship develops and persists. Although these models focus on PTSD and pain generally, they can easily be extended to encompass the link between PTSS and specific pain conditions such as migraine headache. The relationship between PTSD or PTSS and chronic pain is complex and likely involves elements of all of the proposed mechanisms. However, there is a dearth of literature to either support or refute any of these models.

*Shared vulnerability model*

One possible model is that PTSD and chronic pain both result from a shared genetic or other vulnerability factor known as the shared vulnerability model (Asmundson et al., 2002; Asmundson & Katz, 2009). This model suggests that the vulnerability may predispose individuals to develop both PTSD and chronic pain when exposed to certain environmental conditions such as a traumatic experience and/or injury. That is, this model suggests that the traumatic and/or physically painful experiences may interact with the vulnerability, likely genetically influenced, eliciting a negative emotional response, which then activates a variety of physiological, behavioral, and cognitive consequences that may later lead to the development of either or both PTSD and chronic pain.
For example, one potential vulnerability factor to developing both PTSD and chronic pain conditions is exposure to traumatic experiences specifically associated with physical injury. Severe injuries after exposure to bombings, or serious motor vehicle accidents have been associated with developing PTSD symptoms (Blanchard, Hickling, Taylor, Loos, Forneris, & Jaccard, 1996; Verger et al., 2004) as well as with chronic pain conditions such as low back pain and headache (Berglund, Alfredsson, Jensen, Cassidy, & Nygren, 2001; Cassidy, Carroll, Côté, Berglund, & Nygren, 2003; Ruff, Ruff, & Wang, 2008).

Although several studies have controlled for the confounding effects of shared genetic and familial factors in the relationship between PTSS and specific pain conditions (Afari, et al., 2008; Arguelles, et al., 2006; Schur, et al., 2007; Wright, et al., 2010), and the relationship between migraine headache and other mental health conditions (Schur, et al., 2009; Ligthart & Boomsma, 2012; Ligthart, et al., 2010), no studies to date have directly examined whether there is a shared genetic contribution to PTSS and migraine headache. Determining the shared genetic covariance is an essential first step in future research to identify specific genetic polymorphisms that lead to the co-occurrence of these conditions.

*PTSD and pain causal model*

Another proposed model is that PTSD causes the experience of chronic pain or vice versa (Asmundson et al., 2002). Although there is limited research exploring this model, two longitudinal studies have found that PTSD symptoms significantly impact the development of chronic pain symptoms in both individuals injured in an accident and victims of community violence, suggesting that PTSD symptoms precede and
significantly influence pain intensity (Jenewein et al., 2009; Ramchand et al., 2008). Stress has also been discussed as a preceding factor and trigger for the development of headache (Nash & Thebarge, 2006). Findings from a community-based study also suggest that anxiety may precede and potentially predict the development of migraine headache (Breslau, Chilcoat, & Andreski, 1996), and that increased frequency and magnitude of stressful life events may be associated with the development of clinical headaches (De Benedittis, Lorenzetti, & Pieri, 1990). Alternately, increased reports of pain after injury have been associated with greater risk of developing PTSD (Norman, Stein, Dimsdale, & Hoyt, 2008).

Given these discrepant findings and limited research, there is a need to further clarify if causal relationships between PTSD or PTSS and specific pain conditions exist and the nature of this relationship. However, very few studies have rigorously addressed this model and the vast majority of research has been cross-sectional (Afari et al., 2008; Burris et al., 2009) or limited in scope (Burris et al., 2009; Jenewein et al., 2009; Ramchand et al., 2008). Further elaboration on the direction of the relationship with specific chronic pain conditions like migraine headache, while accounting for the influence of shared genetic factors will provide invaluable information on how to approach treatment and prevention of these disorders, as well as help guide the further development of theoretical models of how these disorders co-occur.

*Mutual maintenance models*

Two additional models have been proposed asserting that symptoms of PTSD and chronic pain influence and maintain each other. The first model of mutual maintenance suggests that the physiological, affective, cognitive and behavioral components of PTSD
and chronic pain mutually maintain both sets of symptoms (Sharp & Harvey, 2001). This model identifies seven specific mechanisms through which mutual maintenance is hypothesized to occur through multiple, often bi-directional pathways. These factors include attentional and reasoning biases, anxiety sensitivity, reminders of the trauma, avoidance coping of pain and anxiety, depression, increased pain perception, and the additional cognitive demands of both PTSD and pain symptoms limiting the ability to employ adaptive cognitive strategies to mitigate symptoms (Sharp & Harvey, 2001). For instance, factors such as an attentional bias toward a pain sensation in an individual with PTSD may amplify pain sensations into chronic pain, while chronic pain symptoms can act as a reminder of a trauma experience together maintaining the symptoms of PTSD and chronic pain. The cognitive, affective and behavioral components of chronic pain, together with the physiological, affective and avoidance components of PTSD may exacerbate and maintain each other perpetuating an individual’s overall level of distress and disability (Asmundson & Katz, 2009; Sharp & Harvey, 2001).

Another model that has been developed to explain the mutual maintenance of PTSD and chronic pain is the perpetual avoidance model (Liedl & Knaevelsrud, 2008). This model asserts that dysfunctional cognitive processing during and after a traumatic event perpetuates an increase in physiological arousal symptoms and behavioral avoidance. The hyper-arousal symptoms and avoidance of activities then perpetuate an increase in pain sensations and fear of pain-related activities ultimately compounding the symptoms of PTSD and pain (Liedl & Knaevelsrud, 2008).

Limited research supports aspects of these mutual maintenance models. For example, a longitudinal study of trauma service patients reporting primarily motor
vehicle accidents, found that the relationship between pain 1 week post-injury and pain at 12 months was mediated by arousal symptoms at 3 months, while the relationship between arousal and re-experiencing symptoms at 3 months were mediated by pain symptoms at 3 months, suggesting that PTSD and pain maintain each other (Liedl et al., 2009). In an investigation of factors related to poorer daily functioning in chronic pain patients having experienced at least one traumatic event, higher levels of pain, hyper-arousal symptoms of PTSD, and pain avoidance behaviors were together associated with poorer daily functioning (Cho, Heiby, McCracken, Moon, & Lee, 2011).

Preliminary work examining the treatment of PTSD and chronic pain also suggests that multiple factors associated with mutual maintenance models may be associated with improvements in symptoms of both PTSD and pain. For instance, addressing physical activity and hyper-arousal symptoms through biofeedback was found to improve coping strategies related to PTSD and chronic pain (Liedl et al., 2011), and reductions in physiological arousal and reactivity were associated with reduced PTSD symptoms and improvements in functioning in a trauma-focused cognitive behavioral treatment for PTSD and chronic whiplash (Dunne, Kenardy, & Sterling, 2012). Although preliminary research suggests some evidence for components of these mutual maintenance models, there is a need to further examine the mechanisms that are proposed.

**Twin designs**

Twin studies have long been a staple in the field of behavioral genetics. Twin designs are extremely versatile and can be used to a) estimate heritability, or the importance of genetic and familial factors on health through classical twin studies, and b)
control for genetic and familial contributions with co-twin control studies, in order to examine the direct link between two traits or conditions which can help to establish cause and effect relationships in the absence of randomized experimental designs.

*Classical twin design*

One prominent method of estimating heritability is through the use of classical twin designs. Monozygotic (MZ) twins share 100% of their genes and dizygotic (DZ) twins share, on average, 50% of their genes. When twins are raised together, both MZ and DZ pairs are assumed to have shared a common familial environment and are extraordinarily well matched for numerous childhood/adolescent exposures. Greater phenotypic similarity in MZ twins compared to DZ twins suggests a genetic component to a trait or condition (Schur et al., 2009). Relying on these assumptions about the percentage of shared genes for MZ and DZ pairs allows for the estimation of the heritability of certain traits, and the estimation of the shared heritability between two traits. Heritability is determined by biometrical genetic analysis in which sources of variance in a condition or trait are decomposed into additive genetic (A or heritability), shared/common environment (C or familial), and unique environmental (E) influences which includes error variance. The utility of the classical twin designs has been widely discussed (Turkheimer, D'Onofrio, Maes, & Eaves, 2005). Therefore, the classical twin design can be used to explore the relative importance of genetic and familial factors on the relationship between two traits of interest.

*Co-twin control design*

In addition to estimating heritability, twin studies also have the capability to address the “chicken-egg” issue of whether an observed symptom or abnormality is a
result of, or a risk factor for a particular condition. Therefore, twin studies can potentially estimate the extent that a relationship between two factors are accounted for by non-shared environmental factors and make inferences about causation by controlling for the influence of additive genetic and shared environmental factors (Kremen, Koenen, Afari, & Lyons, 2012; McGue, Osler, & Christensen, 2010). Two commonly used twin designs to address this issue are the co-twin control design and the cross-lagged monozygotic twin differences design.

The co-twin control or discordant twin-pairs design involves utilizing MZ twin pairs who are discordant for a particular exposure such as trauma, and for a particular outcome, such as PTSD. The comparison of co-twins discordant for the exposure is inherently controlled for shared genetic and familial influences and can allow for inferences about whether an exposure like trauma is a risk factor for developing an outcome of interest such as PTSD. A proposed model of a typical co-twin control design would involve four participant groups including 1) the exposed twin who developed the outcome of interest such as a trauma-exposed twin who developed PTSD, 2) their “high risk” non-trauma exposed twin, 3) a trauma exposed twin who did not develop PTSD and 4) their co-twin who was neither trauma-exposed or developed PTSD (Kremen et al., 2012). Research using the co-twin control design has enabled the differentiation of pre-existing risk factors for PTSD such as smaller hippocampal volume (Gilbertson et al., 2002) from other factors that were primarily found in twins following a diagnosis of PTSD such as certain neurocognitive functioning (Gilbertson et al., 2006), coronary heart disease (Vaccarino et al., 2013) and pain (Boscarino, Forsberg, & Goldberg, 2010;
Co-twin designs enable the ability to make inferences about whether certain exposures act as risk factors for an outcome of interest or follow the exposure.

Similar to co-twin control designs, cross-lagged monozygotic twin differences designs capitalize on the fact that MZ twin pairs share 100% of their genes and shared environment (assuming they were reared together). But unlike co-twin designs, the longitudinal cross-lagged design has the additional strength of examining symptom differences over time. By examining MZ twin differences on symptoms longitudinally, the MZ twin difference design also accounts for genes and shared environmental factors, and it can be assumed that any existing differences are associated with unique environmental factors (Burt, McGue, Iacono, & Krueger, 2006). By utilizing the MZ twin difference design longitudinally, specifically using cross-lagged analyses, inferences about causation can be made by addressing two common alternative explanations for causation in observational research, reverse causation and confounding (McGue et al., 2010). A prospective, longitudinal, cross-lagged MZ twin difference design addresses these alternative explanations by first accounting for the order of occurrence between two factors, such as PTSS and pain over time, and by controlling for the confounds of genetics and shared environment on the relationship of interest (Burt, McGue, & Iacono, 2009; Burt et al., 2006). The longitudinal, cross-lagged MZ twin difference design has been used to determine a relationship between the non-shared environmental factor of adolescent externalizing behaviors and increased deviant peer affiliation over time, regardless of genetic predisposition (Burt et al., 2009). This finding exemplifies the power of longitudinal studies of MZ twins in examining possible cause and effect
relationships, short of randomized experimental designs that are often ethically and logistically unfeasible (Spector & Hochberg, 1994).

**Summary and limitations of previous research**

Several investigations into the epidemiology and detrimental effects of PTSD or PTSS and chronic pain have been conducted, but unfortunately, our understanding and treatment of co-occurring PTSD or PTSS and chronic pain conditions remains incomplete. Further, few investigations have examined the relationship between PTSD, PTSS and the specific chronic pain condition of migraine headache. Theoretical explanations have been proposed that both result from a shared genetic or other vulnerability factor, one directly causes the other, or the physiological, affective, and behavioral components of PTSD and chronic pain mutually maintain both sets of symptoms. The link between PTSD or PTSS and chronic pain conditions such as migraine headache is likely a complex interaction of genetic, physiological, psychological, and environmental factors. However, transformational progress in understanding the nature and mechanisms of this relationship has been hampered by several factors. First, despite the proposed theoretical models, there is a general dearth of literature that examines the specific mechanisms that may best explain the relationship. Second, most studies that have explored this relationship are cross-sectional in nature, limiting the ability to infer any causal relations. Third, the handful of longitudinal studies that have examined the relationship between PTSD or PTSS and chronic pain conditions, have been limited in scope by not accounting for the role of genetic and familial factors. To date, the preponderance of investigations of the relationship between PTSD or PTSS and chronic pain conditions have been conducted with singletons (Afari et al., 2009;
Asmundson et al., 2000; Peterlin et al., 2011; Peterlin et al., 2009), where it is impossible to determine the potential role of genetic factors. The few longitudinal studies have not controlled for genetic and familial factors that may contribute to the relationship between PTSD, PTSS, pain, and their correlates (Burris et al., 2009; Jenewein et al., 2009). Further, the limited studies with twins were cross-sectional, where the findings are correlational (Afari et al., 2008; Arguelles et al., 2006; Schur et al., 2007; Wright et al., 2010). Finally, the proposed theoretical models of co-occurring PTSD and chronic pain describe chronic pain conditions broadly, and have yet to examine the relationship between PTSD or PTSS with specific chronic pain conditions. A recent meta-analysis examining the relationship between psychological trauma, and PTSD with functional somatic syndromes found the strength of the trauma and somatic syndrome relationship to vary by type of syndrome (Afari et al., 2014), suggesting that the relationship between traumatic experiences, PTSD, and PTSS may vary by pain condition. Considering the co-occurrence and substantial disability associated with co-occurring PTSD, PTSS, and migraine headache symptoms and hypothesized mechanisms underlying the development of PTSD, PTSS or migraine headache symptoms that may differ from other pain conditions (Afari et al., 2009; Juang & Yang, 2014; Peterlin et al, 2011; Peterlin et al., 2009), examining the specific chronic pain condition of migraine headache is an important step in examining proposed models of co-occurrence and understanding the nature and mechanisms of the co-occurrence of PTSS with a specific chronic pain condition.

This study was uniquely situated to use longitudinal data from a genetically-informative sample to provide further insights into the relationship between PTSS and
migraine headache symptoms. These data were used to assess the shared genetic contribution to the relationship, and to examine the potential causal links between these conditions. It was important to first determine whether a shared genetic contribution exists in the relationship of PTSS with migraine headache symptoms. Assuming that there is a shared genetic contribution, it is necessary to then control for the confounding effects of the shared genetic and environmental influences to determine whether there is also a unique causal relationship between PTSS and migraine headache in order to gain further insight into the relationship between PTSS and migraine headache. Given the likely complexity of the link between PTSS and chronic pain conditions as exemplified by the proposed mutual maintenance models, ascertaining the shared genetic vulnerability in addition to the examining the direction of the relationship are two of the first steps in furthering our understanding of the co-occurrence of PTSS and chronic pain conditions.

**Specific aims**

This study ascertained the extent to which shared genetic influences convey a shared vulnerability to the co-occurrence of PTSS and migraine headache. We also examined if current PTSS is directly related to the development of migraine headache symptoms. Estimating the shared genetic influences on the association between PTSS and a specific chronic pain condition can help in identifying some of the biological underpinnings of the PTSS and migraine headache co-occurrence, and lead to the development of targeted interventions. Additionally, examining the direction of the relationship has implications for developing better tailored prevention and treatment strategies.
Because sex differences in PTSD (lifetime prevalence of 10% in females and 5% in males) (Kessler et al., 1995) and migraine headache (lifetime prevalence of 17% in females; 5.7% in males) (Buse et al., 2012) have been previously established, our a priori decision was to conduct sex-stratified analyses to address aims 1 and 2. The separate analyses for male and female twins can facilitate more accurate interpretation of the findings. Thus, our specific aims were to:

1. **Examine the extent to which shared genetic contributions convey a shared vulnerability to the association between PTSS and migraine headache symptoms.** Data from 3,369 MZ and DZ twin pairs were used to first conduct univariate genetic analyses to determine the proportion of variance accounted for by genetic factors in each of the set of symptoms separately. Once univariate models were established for PTSS and migraine headache symptoms individually, bivariate biometrical genetic analyses were conducted to estimate the extent of shared genetic vulnerability to PTSS and migraine headache symptoms association. We hypothesized that there was a significant shared genetic influence on the association of current PTSS and migraine headache symptoms.

2. **Estimate the direction of the relationship between PTSS and migraine headache symptoms.** Longitudinal data from 1,134 MZ twin pairs were examined in cross-lagged twin differences analyses. We hypothesized that consistent with a causal model of PTSD and pain, current PTSS will be directly related to the development of migraine headache symptoms.

This chapter is currently being prepared for submission for publication of the material. Mostoufi, S. M., Gasperi, M., Godfrey, K. M, Strachan, E., Buchwald, D & Afari, N. The dissertation author was the primary investigator and author of this material.
CHAPTER 2:
METHODS

Study overview

This study used data available from the University of Washington Twin Registry to examine the nature and mechanisms of the link between PTSS and migraine headache symptoms. The twin design, with both MZ and DZ twin pairs, permits the examination of the shared genetic vulnerability in this relationship, and the use of longitudinal data with MZ twin pairs allowed us to precisely control for individual genetic and familial factors while testing for the causal link between PTSS and migraine headache symptoms. The approach and hypotheses were guided by two prominent theoretical models that have been proposed to explain the association between PTSD and pain. The findings from this study can provide insight into the mechanisms that may underlie the co-occurrence of PTSS and migraine headache, and guide future research to either support or refute, and ultimately refine existing theoretical models of PTSD and pain.

Sample and setting

Background and procedures

The University of Washington Twin Registry was established in 2001 to study the genetic and non-genetic factors that affect health and illness. The Registry is an ongoing collection of twins identified from the Washington State Department of Licensing (DOL). Given that the state of Washington determines driver license identification numbers based on a person’s last name and date of birth, making it likely for twins to have the same driver license numbers, every applicant is asked if they are a member of a twin pair in order to avoid duplicate license numbers. Beginning in 1998, negotiations began with
the DOL and the Washington State Attorney General to access all DOL records and begin a twin registry. Based on these negotiations, the names, contact information, and demographic information of twins 18 years of age and older who are identified through the DOL database are received each week by the Registry. Identified twins are then sent an invitation packet to provide consent and complete a brief survey that collects information on physical and psychological health status, sociodemographics, and zygosity ascertained by a set of standardized questions known to classify zygosity correctly approximately 95% of the time (Miller, 1987). This registry data collection has been fully approved by both the University of Washington Institutional Review and the office of the Washington State Attorney General.

A recent NIH Grand Opportunity grant allowed the Registry to conduct a comprehensive survey of all twins in the Registry that began in 2010 to provide follow-up data on key assessment domains. Therefore, data on current PTSS, and migraine headache symptoms were available from the brief initial Registry survey (Time 1: collected on a rolling basis from 2001- November 2013) and the comprehensive follow-up survey (Time 2: collected on a rolling basis from 2010 - November 2013).

Participants and exclusion criteria

Both members of the pair must have completed the survey to become Registry members, and all twins included in the registry have been reared together until age 15. As of November 2013, 15,722 individual twins (7,861 twin pairs) have become members of the Registry; on average, about 200 twin pairs are enrolled per month. All Registry members are adults, fluent in English, and live in the United States. One member has lived in Washington State at some time in his or her life. Based on the November 2013
dataset for the overall Registry, twins were 38 years old on average, 95% had a high school education or higher, 42% were married, 87% were White, 52% were MZ, and half were female. As of November 2013, 7,468, individual twins (3,734 twin pairs) have completed the comprehensive follow-up survey (Time 2). The demographic characteristics of these respondents are similar to the characteristics of the broader Registry. Twins were 41 years old on average, close to 97% had a high school education or higher, 48% were married, 92% were white, 57% of respondent pairs were MZ and 55% were female. Data from Time 1 were used to address aim 1 and data from Time 1 and 2 were used to address aim 2. Twin pairs with unclear zygosity, all male/female DZ twin pairs, and all pairs in which one twin had not completed a measure of interest (measure inclusion criteria described below), were excluded from the final analyses for Aim 1 and Aim 2. Both MZ and DZ twin pairs were included in the final analyses for Aim 1; only MZ twins pairs were included in the final analyses for Aim 2. Two twin pairs reported inconsistent times of assessment at Time 1 and Time 2 and were excluded from the Aim 2 analyses. Given the epidemiological approach of this study to look broadly at the relationship between PTSS and migraine headache symptoms in a population-based sample, all twin pairs who met study inclusion criteria were included in the final analyses.

**Measures**

*Current posttraumatic stress symptoms (PTSS)*

The Impact of Events Scale (IES) was used at both Time 1 and Time 2 to assess for current symptoms resulting from a traumatic event (Horowitz, Wilner, & Alvarez, 1979). The IES captures qualities of conscious experiences that encompass stressful life
events, such as bereavement or personal injuries from accidents, violence, illness, or surgery (Horowitz et al., 1979). In previous studies, the IES was strongly correlated with a diagnosis of PTSD (Taal & Faber, 1997) even though the IES measures only the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) intrusion and avoidance symptom criteria for PTSD (Association, 1994). The IES is a well-known and often used measure of PTSS, primarily in population-based studies as recently as 2013 (Lukaschek et al., 2013). Sundin & Horowitz (2002) review of the psychometric properties of the IES have determined it to be a valid screening measure for PTSD given its stable factor structure, convergent validity with a PTSD diagnosis, and its clinical use in treatment studies. The IES total score was found to be significantly correlated with PTSD diagnosis determined by structured clinical interview for PTSD in a mixed military and civilian population ($r = .81$) (Neal et al., 1994). As a screening measure for PTSD, the sensitivity of the IES ranges from .94 - 1.00 and the specificity ranges from .78 - .84 (Wohlfarth, van den Brink, Winkel, & ter Smitten, 2003). The IES has also been utilized with a variety of adult populations including Vietnam theater veterans (Tichenor, Marmar, Weiss, Metzler, 1996), assault survivors (Elliot & Briere, 1995) and natural disaster survivors (Johnson et al., 1997). It is important to note that the IES does not query about the type or timing of a traumatic event that would be useful in describing the sample of twins but is not essential in addressing the aims of this study.

Only 11 of the original 15 items of the IES were collected based on the cluster analysis conducted by Horowitz et al. (1979) which found 4 items to be poorly correlated with the intrusion and avoidance subscales. IES items included 4 response categories coded as ($0 = \text{not at all}$, $1 = \text{rarely}$, $3 = \text{sometimes}$, $5 = \text{often}$), and a sum score was
calculated with values ranging from 0-55. Based on the strategy described in Arguelles et al., (2006), only twins who answered at least 6 of the 11 items were included in the final analyses, and the participants average score was imputed for the missing values (based on recommendations of Ware et al., 1980). For example, if a participant did not answer 1 IES item, the mean score of the remaining 10 items was imputed for the 1 missing item. Internal consistency was high for IES in our sample (Cronbach's alpha = .90).

Current migraine headache symptoms

The Migraine Screen Questionnaire (MSQ) was collected at Time 1 and Time 2 to capture current symptoms consistent with migraine headache. The MSQ was initially developed using the criteria from the International Headache Society (Lainez et al., 2005). It consists of 5-items that assess for the frequency and intensity of migraine headache for durations between 4 hours and 3 days, and for symptoms such as nausea, sensitivity to light/noise, and disability. This instrument exhibits 93% sensitivity and 81% specificity for migraine headache, and a Cronbach’s alpha coefficient of .82 (Lainez et al., 2005). The MSQ has also been shown to exhibit strong psychometric properties for the early detection and assessment of migraine in primary care settings (Lainez et al., 2010). Only participants who responded to all 5 MSQ items at Time 1 and Time 2 were included in the final analyses and a sum score was calculated with values ranging from 0-5. Internal consistency was high for MSQ in our sample (Cronbach's alpha = .80).

Current depression symptoms

The Patient Health Questionnaire (PHQ-2) was collected at Time 1 and Time 2. The PHQ-2 was adapted from the PHQ-9 and is a 2-item measure of depressive symptoms that inquires about the frequency of depressed mood and anhedonia over a 2
week period. The PHQ-2 exhibits 83% sensitivity and 92% specificity for major depression (Kroenke, Spitzer, & Williams, 2003). PHQ-2 items included 4 response categories coded as (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day), and a sum score was calculated with values ranging from 0-6. Only participants who responded to both PHQ-2 items at Time 1 and Time 2 were included in the analyses. Internal consistency was high for PHQ-2 in our sample (Cronbach's alpha = .83).

**Data analytic plan**

*Analysis overview*

A variety of analytic techniques specific to working with twin studies such as bivariate biometrical genetic models with structural equation modeling (SEM) and cross-lagged twin differences analyses were used to address the specific aims of this study. The primary interest across all of these analyses was to examine IES scores as the primary independent variable and MSQ scores as the dependent variable. These measures were treated as continuous variables. Distributions of study variables were examined for normality preceding all analyses. First, we conducted exploratory analyses to determine if the PHQ-2 as a measure of depression should be used in the main study analyses. These exploratory analyses examined the components of posttraumatic stress symptoms by conducting an exploratory factor analysis with the IES and PHQ-2 items. Next, descriptive statistics were used to assess the distributions of demographic and study variables under investigation for both aims 1 and 2, and to determine appropriate covariates. Finally, the main sets of analyses for aim 1 and aim 2 focused on PTSS (factor determined based on exploratory factor analysis), and migraine headache symptoms.
Descriptive analyses, correlations, and exploratory factor analyses were conducted using Statistical Package for Social Sciences (SPSS) 20.0 software (IBM, Inc). All SEM and path analytic approaches were conducted using Mplus (version 6) (Muthén & Muthén, 1998-2011).

*Exploratory analyses for PTSS factor*

Given the substantial literature documenting the high comorbidity of depression and PTSD, we first examined the association of IES with PHQ-2 scores. If significantly associated, we then conducted an exploratory factor analysis (EFA), with IES items and PHQ-2 items to determine the components of PTSS and account for its potential shared factor structure with depression. This approach is consistent with the National Institute of Mental Health (NIMH) strategic plan’s call to classify psychopathology based on dimensions of observable behavior and neurobiological measures. The Research Domain Criteria project (RDoC) aims to cut across disorders and provide a more integrative understanding of psychopathology (Simmons & Quinn, 2014).

Before conducting the EFA, the PHQ-2 and IES items were first examined for normality and determined to be positively skewed after the examination of histograms, skew, and kurtosis. Items were then log-transformed before examining in the EFA. The EFA was conducted with a principal axis factoring (PAF) extraction method, using direct oblimin rotation to examine the factor structure of the IES and PHQ-2 items, specifying two factors. EFA was the selected approach because it is designed for exploring items where there is limited theoretical basis for specifying a priori the number of identified factors in the data with the items of interest and to reveal any latent variables that may influence the identified items to covary (Costello & Osborne, 2005; Floyd & Widaman,
Costello & Osborn (2005) recommend large sample sizes for EFA procedures, and therefore Time 1 data was used to conduct the EFA ($n = 6,738$). The items comprising the PTSS factor identified based on this EFA were then included in the PTSS variable in the aim 1 and aim 2 analyses.

Analyses for aim 1

**It is hypothesized that there is a significant shared genetic influence on the association of current PTSS and migraine headache symptoms.**

The time 1 IES and MSQ score distributions were first examined and determined to be positively skewed after examination of histograms, skew, and kurtosis. All variables were log-transformed to adjust for the non-normal distribution of the observed variables. Chronbach’s alpha was calculated for each of the study measures to examine internal consistency. T-test statistical analyses examined group differences on log-transformed IES, MSQ, and PHQ-2 by physician diagnosis (to examine validity of the measures), as well as by gender, and zygosity, and were also conducted separately for each set of twins (i.e., all Twin A’s and Twin B’s separately) due to non-independence of twin pairs. Additionally, it is recommended in classical twin study designs that analyses adjust for age and sex given the twin similarity on these variables, which may lead to an overestimation of effects (McGue & Bouchard, 1994). As stated before, all primary analyses were sex-stratified so there was no need to adjust for sex. The log-transformed study variables were adjusted for the influence of age using linear regression, and the standardized residuals were used in the final analyses (McGue & Bouchard, 1994).

Given that MZ twins share 100% of their genes, and DZ twins share, on average 50%, the variance in an observed phenotype can be estimated in terms of additive genetic
(A), common environmental (C), and non-shared/unique environmental and measurement error (E) influences using SEM. We initially examined the overall sample phenotypic association between age-corrected IES and MSQ scores. To further evaluate the association between PTSS and migraine headache symptoms, we then examined three specific types of correlations between the age-corrected IES and MSQ scores: phenotypic, twin, and cross-twin cross-trait. Phenotypic correlations evaluated the relationship between the IES and MSQ scores at the individual level. Twin correlations assessed the within-pair similarity and were calculated separately in MZ and DZ pairs. A pattern of MZ within-pair correlation larger than the DZ twin correlation suggests a genetic influence on the trait. Cross-twin, cross-trait correlations estimated the strength of the association between IES score in Twin A with MSQ score in twin B as well as IES score in twin B with MSQ score in Twin A in MZ and DZ pairs. A pattern of MZ cross-twin cross-trait correlation larger than the DZ twin correlation is suggestive of a genetic influence on the association between two traits.

SEM techniques for univariate and bivariate biometrical genetic analyses were conducted including both MZ and DZ twin pairs (Neale & Cardon, 1992). All models were estimated using maximum likelihood (ML) estimation. First, SEM techniques were used to estimate the univariate model for the influence of A, C, and E on IES and MSQ scores separately (Eaves, Last, Young, & Martin, 1978; Neale & Cardon, 1992; Prescott, 2004). Figure 2.1 shows an example of the univariate model in which the variance in an observed variable such as IES score is modeled as the contribution of three underlying latent factors. In an observed variable such as IES score, A, C, and E (including measurement error), represent the latent factors’ relative contribution to the variance in
IES score, while the lower case a, c and e represent the corresponding parameter estimates.

In building the univariate ACE models, the loadings were constrained to be equal for MZ and DZ twins, and latent factors were assumed to be uncorrelated within individual twins. Latent variable variances were set to 1, and latent variable means were set to 0. Models were fit assuming across twin pair an additive genetic correlation of 1.0 for MZ twins and .5 for DZ twins (Falconer & Mackay, 1996), a shared environmental correlation of 1.0 for all twins (since all of the Registry twins were reared together) and a unique environmental correlation of 0 for all twins (Boardman, Alexander, & Stallings, 2011). The parameter estimates are factor loadings that describe the relative contribution of the latent factors to the total variance of the observed phenotype.

The fit of the full ACE univariate model was first evaluated by estimating parameters, 95% confidence intervals, and goodness-of-fit statistics. The fit of reduced models in which all variance is attributable to genetic and specific environmental factors (AE), common and specific environmental factors (CE), and specific environmental factors (E) were then compared to the full ACE univariate model using a likelihood ratio test and by assessing model fit statistics such as Akaike's Information Criteria (AIC) (Akaike, 1987) with lower AIC values indicating a better fitting model. Parameters were excluded if doing so did not significantly influence the model fit ($p < .05$) based on likelihood ratio tests. Finally, the proportions of variance due to additive genetics, common environment, and non-shared/unique environmental (and measurement error) were presented from the best-fitting final model for IES and MSQ scores separately.
(Neale, & Cardon, L., 1992; Prescott, 2004). Confidence intervals (95%) are shown in parentheses.

After the univariate models were established for IES and MSQ scores, and genetic and common environmental contributions had been determined for each individual phenotype, bivariate SEM with a full Cholesky decomposition was used to estimate shared genetic and environmental contributions to both IES and MSQ scores. The bivariate SEM with a full Cholesky decomposition specified a general multivariate covariance structure and enabled both specific and shared influences between IES and MSQ scores to be estimated (Schur et al., 2009). The decomposition of the variance-covariance matrix of observed IES and MSQ scores is obtained by regression of the observed measures on the latent factors. An example of the bivariate full Cholesky decomposition model is represented by Figure 2.2 for one twin in the pair. The model partitions variance into common latent factors \((A_1, C_1, E_1)\) that influence both IES and MSQ scores, and unique latent factors that only influence the MSQ scores \((A_2, C_2, E_2)\). Coefficients \((a_{11}, c_{11}, e_{11})\) represent the factor loadings for IES scores to the common latent factors, coefficients \((a_{21}, c_{21}, e_{21})\) represent the factor loadings for the common latent factors to the MSQ scores, and coefficients \((a_{22}, c_{22}, e_{22})\) represent the factor loadings of unique latent factors to the MSQ scores. Latent variable variances were set to 1, and latent variable means were set to 0.

Model fitting followed a similar approach to the univariate models. We began with the full ACE bivariate model and estimated the percentage of variance that the A, C, and E parameters explain in IES scores and which concomitantly explain variance in the A, C, and E components of MSQ scores. A series of reduced models (AE, CE, and E, as
described above), were fit to the data and compared to the full ACE bivariate model to determine the best fitting and most parsimonious model. The best-fitting model was identified by excluding parameters that did not significantly influence the model fit based on the AIC (Akaike, 1987), with lower AIC values indicating a better fitting model, and on likelihood ratio tests \((p < .05)\). Goodness-of-fit statistics were presented for the full and reduced bivariate models of IES and MSQ scores. Standardized path estimates, trait-specific and shared variance components were presented for the best-fitting model.

Estimates of the genetic correlation coefficient \((r_g)\), independent of the heritability of the two traits, and the environmental correlations \((r_e, r_c)\) were conducted. A genetic correlation of 1.0 would indicate that the traits are influenced by the same genes, while a genetic correlation of 0 would indicate that the two traits are influenced by completely different genes. (Tarnoki et al., 2013). The environmental correlations indicate how much of the shared and unique environmental influences on the two traits are the same in both IES and MSQ scores. Standard procedures for estimating 95% correlation coefficient confidence intervals (CI) were utilized by conducting \(z'\) transformations of calculated \(r'\)'s, computing the confidence intervals in terms of \(z'\) and transforming the \(z'\) computed confidence intervals back to \(r\) for interpretation (Cohen, Cohen, West, & Aiken, 2003).

By considering the proportion of variance due to additive genetics in IES and MSQ scores determined from the bivariate cholesky decomposition, we were then able to address our primary question and determine the proportion of the total phenotypic correlation \((r_p)\) that was due to additive genetic factors that influence both IES and MSQ scores.

*Analyses for aim 2*
It is hypothesized that consistent with a causal model of PTSD and pain, current PTSS will be directly related to the development of migraine headache symptoms.

The multivariate analytic strategy to address aim 2 was based on those proposed by Burt and colleagues (Burt, McGue, Krueger, & Iacono, 2005) and implemented in a number of longitudinal MZ twin differences studies (Burt, McGue, & Iacono, 2009, 2010; Burt et al., 2006; Burt et al., 2005; Spanos, Klump, Burt, McGue, & Iacono, 2010). Given that MZ twins share 100% of their genes and 100% of their shared environment (assuming they were reared together), differences between these twins on an observed trait cannot be confounded by these factors and can only be attributed to direct influences (and measurement error). Therefore, phenotypic differences of MZ twins on any measure reflect differences in the twin pair’s non-shared environment (plus measurement error), and a “direct estimate” of unique environmental influences on an observed phenotype (Burt et al., 2006). Further, utilizing a longitudinal cross-lagged design enables the examination of causal relationships between two variables (Burt et al., 2006).

Consequently, utilizing a longitudinal cross-lagged MZ twin difference design enables us to directly evaluate the strength of the causal model between IES and MSQ scores by giving a “direct estimate” of unique environmental influences on each variable (i.e., IES and MSQ scores) by examining their relationship longitudinally.

First, within-pair differences were defined by difference scores calculated between Twin A’s and Twin B’s scores on all measures. While the absolute value of the difference represents the true magnitude of difference in the twin pair, signed differences were used in the analyses to examine the direction of significant effects (i.e. Twin A - Twin B) since difference scores could be positively or negatively signed. The sign of the
effect could then be interpreted with positive path coefficients indicating that a twin with more of one trait also demonstrated more of the other trait (Burt et al., 2009).

Descriptive statistics assessed the distributions of demographic and difference score variables for the MZ sample with both Time 1 and Time 2 data that was used to address aim 2. Difference score variables were determined to be normally distributed based on examination of histograms, skew, and kurtosis.

Since there was pair to pair variation in the measurement interval between Time 1 and Time 2 assessment ranging from 2 months to 2.5 years, the length of time between Time 1 and Time 2 assessments was examined as a potential covariate for aim 2 analyses. The measurement interval for length of time between assessments was fixed at the pair level (i.e., the interval was determined by calculating the average length of time between assessments for each twin pair). Additionally, age was examined as a covariate that may influence the relationship of PTSS with migraine headache symptoms. The Pearson product-moment correlation coefficients of age and length of time between assessments with IES and MSQ scores at Time 2 were examined to determine if either should be used as a covariate.

Correlations were then computed between IES and MSQ within-pair differences across the two time points, at the pair level. Non-significant correlations indicate the absence of shared unique environmental influences on the association. The cross-lagged MZ twin difference model was fit in Mplus with data entered at the pair level (i.e., variable difference scores), an example of which is presented in Figure 2.3. ML estimation was used to fit models. A multi-step strategy was used by first examining the within-pair cross-sectional associations for Time 1 (i.e., \( r_1 \)), then within-pair cross-
sectional associations for Time 2 (i.e., r2). Next, the cross-lagged associations were examined to determine if within-pair differences on IES at Time 1 predicted within-pair differences in MSQ at Time 2 (i.e., b12), or if within-pair differences on MSQ at Time 1 predicted within-pair differences on IES at Time 2 (i.e., b21). Additionally, the within-trait stabilities over time (e.g., stability of IES and MSQ from Time 1 to Time 2) were examined (i.e., b11, b22).

If differences in IES at Time 1 are significantly related to MSQ differences at Time 2, it can be concluded that PTSS is a risk factor for migraine headache symptoms. Alternately, if MSQ differences at Time 1 are significantly related to IES differences at Time 2, increases in PTSS may be a consequence of migraine headache. Finally, if both sets of associations are significant, we can infer that there is a feedback loop between higher levels of both symptoms, suggesting possible mutual maintenance. Because the cross-lagged models of MZ twin pair differences control for genetic and familial contributions, pre-existing associations, and the stability of differences in each trait over time, they provide a very strong test of causality within a longitudinal design (Burt, et al., 2006).

This chapter is currently being prepared for submission for publication of the material. Mostoufi, S. M., Gasperi, M., Godfrey, K. M, Strachan, E., Buchwald, D & Afari, N. The dissertation author was the primary investigator and author of this material.
CHAPTER 3:
RESULTS

Participant characteristics for exploratory analyses and aim 1 (Time 1)

Table 3.1 presents demographic characteristics of 6,738 twins (3,369 pairs) with complete data from the twin registry at Time 1, and who met all study criteria for inclusion in the analyses. Study sample included 2,452 male twins (1,226 twin pairs), and 4,286 female twins (2,143 pairs) of which 70% were MZ and 30% were DZ for both males (MZ: 1,704 twins [852 pairs]; DZ: 748 individuals [374 pairs]) and females (MZ: 3,020 twins [1,510 pairs]; DZ: 1,266 twins [633 pairs]). Twins on average were 41 years old, 48% were married, 91% identified as White, over 95% reported having a obtained a high school diploma or higher level of education, and over 82% of individuals reported having a yearly income of $20,000 or more.

Means and standard deviations of IES, MSQ, and PHQ-2 are presented in Table 3.2. Individuals reporting a doctor’s diagnosis of PTSD reported significantly greater IES scores ($p < .001$); similarly those reporting a doctor’s diagnosis of migraines ($p < .001$) or depression ($p < .001$) also reported significantly higher MSQ and PHQ-2 scores, respectively in both twins A and B. These findings lent some support to the validity of these measures. Both twins A ($p < .001$), and twins B ($p < .001$) significantly differed by sex on both IES and MSQ scores, supporting our a priori decision to conduct sex-stratified analyses. However, while twins B demonstrated significant mean differences on the PHQ-2 ($p = .043$), twins A did not ($p = .355$). No significant differences in study variables were found between MZ and DZ twins in either male or female twins.

Exploratory analyses for PTSS factor
The phenotypic association of PTSS and depression was examined and consistent with previous literature, greater IES scores were found to be significantly related to greater PHQ-2 scores ($r = .322, p < .001$). We then examined the underlying components and dimensionality of PTSS and depression symptoms by conducting an exploratory factor analysis (EFA) with the IES and PHQ-2 items. The EFA of the IES and PHQ-2 items suggested that a 2-factor solution best explained the data. The variance explained by the solution was 53.8%, and the two factors individually accounted for 45.4%, and 8.4% of the variance, respectively. An item was considered a component of an identified factor if it had a loading of $|.4|$ or greater on one factor and $|.3|$ or less on the other factor. Using the pattern matrix for interpretation, the 11 observed IES items loaded on the first factor (values ranged from .54 to .85) and the two observed PHQ-2 items loaded on the second factor (values ranged from .77 to .85). Correlation among these factors was: Factor 1, Factor 2 = .398. Therefore, we determined that IES items and PHQ-2 items were clearly loading on separate factors and consistent with our initial hypotheses to examine specifically PTSS as our construct of interest, we conducted the remainder of the analyses for aim 1 and aim 2 with the original 11 IES items included as the PTSS variable.

**Aim 1: Shared genetic influence on the PTSS and migraine headache symptoms relationship (Time 1)**

*Correlations and associations*

The overall phenotypic correlation ($r_p$) between IES and MSQ scores in the sample was $r_p = .194$ for males ($p < .001$), and $r_p = .177$ for females ($p < .001$). After establishing a significant overall phenotypic association, we then examined the
phenotypic, twin, and cross-twin cross-trait correlations by zygosity (Table 3.2).

Phenotypic within pair correlations ranged from $r = .170$ to $.173$ in MZ male twins, and from $r = .253$ to $.235$ in DZ male twins, and from $r = .178$ to $.194$ in MZ female twins and from $r = .130$ to $.179$ in DZ female twins. In both males and females, larger MZ than DZ twin correlations were found for IES (males: $MZr = .286$ vs. $DZr = .096$; females: $MZr = .280$ vs. $DZr = .151$) and MSQ (males: $MZr = .313$ vs. $DZr = .119$; females: $MZr = .420$ vs. $DZr = .118$), suggestive of genetic influence on both traits in males and females.

Higher cross-twin, cross-trait correlations were demonstrated in males ($MZrs = .047$ to $.086$ vs. $DZrs = -.031$ to $.061$) and females ($MZrs = .126$ to $.139$ vs. $DZrs = -.006$ to $.019$), suggesting shared genetic factors may influence the association between the two traits in both males and females.

Univariate analyses

The full ACE model was estimated for variance and covariance, and then compared to more restrictive AE, CE, and E models, with lower AIC indicating better model fit. Table 3.3 shows the model fit statistics for the univariate analyses in males and females. Out of the nested models, the best-fitting model yielding the lowest AIC values for IES and MSQ scores in males and females were the AE models indicating no significant contribution of C (common environmental influences) on these phenotypes. While the proportion of the variance in IES scores accounted for by additive genetic influences was similar for males and females, the contribution of additive genetic influences in MSQ scores varied by sex. Specifically, 28% of the variance in IES scores was due to additive genetic influences and the remaining 72% was due to unique environmental influences including error for both males and females. For migraine
headache symptoms, the estimates revealed that in males, 31% of the variance in MSQ scores was due to additive genetics and 69% was due to unique environmental factors including error, while in females, 41% of the variance in MSQ scores was due to additive genetics and 59% was due to unique environmental factors.

Bivariate structural equation modeling

The full ACE bivariate SEM was estimated and then compared to more restrictive AE, CE, and E models to determine the most parsimonious model, with lower AIC indicating better model fit. Table 3.4 shows the model fit statistics for the bivariate analyses in males and females. Out of the nested models, the best-fitting, most parsimonious models were the AE bivariate models, which included only shared additive genetics and shared unique environmental influences. This pattern of results was the same for males and females, though the proportion of variance explained by genetic factors varied. The standardized path coefficients for the AE bivariate models are presented separately for males (Figure 3.1) and females (Figure 3.2).

Consistent with the best-fitting univariate models, the AE bivariate models indicate that shared familial influences do not contribute to the phenotypic variance in IES and MSQ scores or to the phenotypic covariance in males and females. In males, we estimated that of the total genetic variation in IES scores, only about 7% of the additive genetic component of IES scores was shared with MSQ scores. There was a greater overlap of environmental influences contributing to both traits in which about 12% of the unique environmental component of IES scores was estimated as being common with MSQ scores in males. Further, of the phenotypic covariance of IES and MSQ scores in males, an estimated 38% was accounted for by additive genetic influences shared by the
two traits, and the rest, about 62% of the covariance was accounted for by unique environmental influences and error (Table 3.6).

In females, we estimated that of the total genetic variation in IES scores, about 12% of the additive genetic component of IES was shared with MSQ. The overlap of environmental influences contributing to both traits was minor, with only about 6% of the unique environmental component of IES estimated as being common with MSQ. Further, of the phenotypic covariance of IES and MSQ scores in females, an estimated 68% was accounted for by additive genetic influences shared by the two traits, and the rest, about 32%, was accounted for by unique environmental influences and error (Table 3.6).

The genetic correlation coefficient ($r_g$) and environmental correlation coefficient ($r_e$) in males and females were estimated, followed by calculating the proportion of the phenotypic association between IES and MSQ scores due to additive genetic effects. In males, the genetic correlation coefficient was $r_g = .251$ (95% CI, .214 – .287), and the environmental correlation was $r_e = .177$ (95% CI, .139 – .215), suggesting minimal influence of the same genes and environmental factors on these two traits. In males, 38% of the phenotypic correlation between IES and MSQ scores was due to additive genetic factors that influence both PTSS and migraine headache symptoms.

In females, the genetic correlation coefficient was $r_g = .354$ (95% CI, .328 – .379), while the environmental correlation was $r_e = .087$ (95% CI, .058 – .116), suggesting minimal influence of the same genes and little influence of the same environmental factors on IES and MSQ scores. In females, it was estimated that about 68% of the phenotypic correlation between IES and MSQ scores was due to additive genetic factors that influence both PTSS and migraine headache symptoms.
In sum, the PTSS and migraine headache phenotypes were weakly associated in both males and females; however, for males 38% of this association was due to additive genetic factors that influence both set of symptoms, and for females 68% of this association, was due to additive genetic factors that influence both symptoms.

Due to the documented high comorbidity of PTSD and migraine with depression, we also conducted exploratory analyses controlling for PHQ-2 scores in our bivariate models. A similar pattern of findings was found where out of the nested models, the best-fitting, most parsimonious models were the AE bivariate models, which included only shared additive genetics and shared unique environmental influences for both males and females. The AE bivariate models indicate that after controlling for PHQ-2 scores shared familial influences do not contribute to the phenotypic covariance in males and females. However, although diminished, a similar pattern of findings was determined with the proportion of the phenotypic association explained by genetic factors varying by sex after controlling for PHQ-2 scores. Specifically, for males 14% of this association was due to additive genetic factors that influence both set of symptoms after controlling for PHQ-2 scores, and for females 55% of this association, was due to additive genetic factors that influence both symptoms after controlling for PHQ-2 scores.

Participant characteristics for aim 2 (Time 1 and 2)

Table 3.7 presents demographic characteristics of 2,268 MZ twins (1,134 pairs) with complete data from the Registry at both Time 1 and Time 2, and who met all study criteria for inclusion in the analyses. Study sample included 782 male MZ twins (381 twin pairs), and 1,506 female MZ twins (753 twin pairs). At time 1, MZ twins on average were 39 years old, 46% were married, 92% identified as White, approximately 95%
reported having obtained a high school diploma or higher level of education, and over 84% of individuals reported having a yearly income of $20,000 or more. At time 2, MZ twins on average were 40 years old, 47% were married, 92% identified as White, approximately 96% reported having obtained a high school diploma or higher level of education, and over 84% of individuals reported having a yearly income of $20,000 or more. Average length of time between assessments for the overall sample was approximately 8 months and ranged from about 2 months to 2.5 years. For males the average length of time between assessments was approximately 8 months and ranged from about 3 months to 2.1 years; for females, length of time was approximately 8 months and ranged from about 2 months to 2.6 years.

Internal consistency was high in our sample for IES and MSQ at Time 1 (IES Cronbach's alpha = .88; MSQ Cronbach’s alpha = .80) and Time 2 (IES Cronbach's alpha = .86; MSQ Cronbach’s alpha = .80). As with the initial analyses for aim 1, individuals reporting a doctor diagnosis of PTSD in the aim 2 sample reported significantly greater PTSS ($p < .001$) and individuals reporting a doctor diagnosis of migraine headache reported significantly greater migraine headache symptoms ($p < .001$) in both twins A and B at both time points. IES and MSQ scores for both twins A ($p < .001$), and twins B ($p < .001$) significantly differed by sex.

**Descriptive PTSS and migraine headache symptom information**

Table 3.8 presents mean level of IES and MSQ scores at Time 1 and Time 2 for males and females at both the individual level, and the pair level. Average twin difference scores did not significantly differ by sex or over time. Difference scores presented in Table 3.8 indicate absolute values of the difference scores. However, to interpret the
direction of examined effects, all following analyses were conducted on signed twin difference scores.

**Aim 2: Estimate the direction of the relationship between PTSS and migraine headache symptoms (Time 1 and 2)**

*Covariates*

Age and length of time between assessments were examined as potential covariates for aim 2 analyses by examining their association with IES and MSQ difference scores at time 2. Neither age nor length of time between assessments were significantly associated with the IES difference score variable at Time 2 in males (age: \( p = .169 \); time between assessments: \( p = .213 \)) or females (age: \( p = .978 \); time between assessments: \( p = .562 \)). Similarly, neither age nor length of time between assessments were significantly associated with the MSQ difference score variable at Time 2 in males (age: \( p = .922 \); time between assessments: \( p = .305 \)) or females (age: \( p = .479 \); time between assessments: \( p = .942 \)). These initial findings ruled out both age and length of time between assessments as covariates; therefore, neither was included in the cross-lagged MZ twin difference model.

*Correlations*

At the individual level, the phenotypic correlations between IES and MSQ scores at time 1 were \( r = .237 \) (\( p < .001 \)) in MZ males and \( r = .187 \) (\( p < .001 \)) in MZ females, and at time 2 were \( r = .221 \) (\( p < .001 \)) in MZ males, and \( r = .162 \) (\( p < .001 \)) in MZ females. Table 3.9 presents correlations between IES and MSQ difference scores across time points. The difference score associations indicate within-trait stability across time points in males (IES: \( r = .40 \); MSQ: \( r = .540 \)) and females (IES: \( r = .315 \); MSQ: \( r = .678 \)) after
accounting for genetic and familial factors. The within-time, cross-trait difference score associations were moderately related at both time points in males ($rs = .140 - .167$) and females ($rs = .015 - .124$) suggesting a modest association between IES and MSQ difference scores cross-sectionally. Further, the modest cross-time, cross-trait association in males ($r = .112$) and females ($r = .077$) suggests unique environmental influences on the association between MSQ difference scores at Time 1 and IES difference scores at Time 2.

**Multivariate modeling**

Figure 3.3 presents the standardized path estimates for the cross-lagged MZ twin difference model of IES and MSQ twin difference scores in males. The percentage of the variance accounted for by each path was determined by squaring the path coefficients (Burt et al., 2009). Twin differences in IES scores demonstrated significant stability across time points and time 1 IES difference scores predicted 15% of the variance in IES difference scores at time 2 (i.e. b11). Twin differences in MSQ scores also demonstrated significant stability over time (i.e., b22) and time 1 difference scores predicted 29% of the variance at time 2. IES twin difference scores at time 1 did not significantly predict MSQ difference scores at time 2 (i.e., b12), accounting for less than 1% of the variance in MSQ difference scores at time 2. Similarly, MSQ difference scores at time 1 also did not significantly predict IES difference scores at time 2 (i.e. b21), accounting for less than 1% of the variance in IES difference scores at time 2.

Figure 3.4 presents the standardized path estimates for the cross-lagged MZ twin difference model of IES and MSQ twin difference scores in females. IES twin differences at time 1 and time 2 (i.e. b11), demonstrated significant stability across time points and
Time 1 predicted 10% of the variance at time 2. The MSQ twin difference scores also demonstrated significant stability over time (i.e., b22) and time 1 predicted 46% of the variance at time 2. The IES difference scores at time 1 did not significantly predict MSQ difference scores at time 2 (i.e., b12), accounting for less than 1% of the variance in MSQ difference scores at time 2. While the path coefficient examining MSQ difference scores at time 1 significantly predicted IES difference scores at time 2 (i.e., b21, Figure 3.4 $p = .037$), it only accounted for .05% of the variance in IES difference scores at time 2.

This chapter is currently being prepared for submission for publication of the material. Mostoufi, S. M., Gasperi, M., Godfrey, K. M, Strachan, E., Buchwald, D & Afari, N. The dissertation author was the primary investigator and author of this material.
CHAPTER 4:
DISCUSSION

The overall goal of this study was to use a large and longitudinal dataset from the community-based University of Washington Twin Registry to investigate hypothesized models of co-occurring PTSS with one specific chronic pain condition, migraine headache. The first aim focused on the shared vulnerability model by examining the extent to which shared genetic contributions may convey a shared vulnerability to the association between PTSS and migraine headache symptoms. The second aim centered on the causal model by using longitudinal twin data to estimate the relationship between PTSS and migraine headache symptoms controlling for the confounding effects of shared genetic and environmental influences. Findings from analyses to address both aims of the study provide general support for a shared genetic vulnerability to PTSS and migraine headache symptoms, rather than one condition directly influencing the other. Specifically, these findings suggest that there is a modest overlap in genetic influences common to both PTSS and migraine headache symptoms in males and females, and that this overlap is potentially more substantial in females. Below, we discuss each of the findings in detail.

Additive genetic contribution to PTSS and migraine headache symptoms

PTSS and migraine headache association

We found a modest but significant phenotypic association between PTSS and migraine headache symptoms in both males and females. Previous studies have typically examined prevalence rates based on diagnoses, consistently reporting a higher prevalence of migraine headache in those diagnosed with PTSD (Afari, et al., 2009; Peterlin et al.,
However, few studies have explicitly examined the association between PTSD symptoms or PTSS and migraine headache symptoms using continuous measures to examine the strength of symptom association. Consistent with our findings, one study found a modest association between PTSD symptoms and headache-related symptoms with PTSD symptoms accounting for a modest amount of variance in measures of headache frequency (4.1%), headache severity (2.2%), and headache-related disability (4.2%) (Smitherman & Kolivas, 2013), among individuals who met criteria for migraine headache. However, the modest phenotypic association in our study may have been partially due to the use of a community-based sample in which PTSD and migraine headache status were not assessed. Although there is some evidence supporting a modest association between PTSD, PTSS, and migraine headache symptoms there is a need to further explore these symptom associations in clinical populations.

**Heritability of PTSS and migraine headache**

PTSS was found to be moderately heritable in both males and females. Our findings also indicated no significant contribution of common environmental influences on the variance in PTSS or migraine headache symptoms in either males or females. These findings are consistent with previous literature examining the heritability of PTSD symptoms and symptom clusters with heritability ranging from 25-38% in both a male Vietnam Era Twin Registry sample (True et al., 1993), and a male and female twin community sample (Stein et al., 2002). These findings also are consistent with previous work indicating no significant contribution of common environmental influences on the variance in PTSD (Stein et al., 2002). Migraine headache symptoms were also found to be moderately heritable, but with females exhibiting greater heritability (41%) then males
Previous studies have reported mixed findings on sex differences in migraine headache heritability. Some studies have noted sex differences reporting additive genetics to account for 44-49% of the variance in migraine headache in females and 38% of the variance in males (Plesh et al., 2012; Schur et al., 2009; Svensson et al., 2003). However, one study found that while the prevalence of migraine headache is consistently greater in females, there was no evidence for different genes contributing to the liability to migraine by sex, or of sex differences in additive genetic influences in migraine (Mulder et al., 2011). Previous studies have also shown no significant contribution of shared familial environmental influences to the variation in migraine headache symptoms (Mulder et al., 2011; Schur et al., Svensson et al., 2003). Therefore, consistent with previous literature, our findings suggest that PTSS is moderately heritable, and with similar heritability for males and females. However, our findings suggest that migraine may be potentially more heritable in females than in males which is consistent with some previous literature, but evidence of sex differences in the heritability of migraine are generally more mixed. Therefore, there is a need to further explore sex differences in migraine heritability, and other potential mechanisms that maybe contributing to potential sex differences in the heritability of migraine headache.

*Shared additive genetic influence on current PTSS and migraine headache symptoms association*

The primary goal of aim 1 was to determine the extent to which the covariance and the association between PTSS and migraine headache symptoms were accounted for by shared genetic and environmental influences. A small genetic correlation between PTSS and migraine headache symptoms in both males and females suggested that some
shared additive genetic factors were possibly influencing PTSS and migraine headache symptoms. Further, a moderate proportion of the phenotypic association between PTSS and migraine headache symptoms was due to additive genetics factors that influence both traits, but the proportion of this association that was due to additive genetic factors was larger in females (68%) than in males (38%). These findings suggest that although the association between PTSS and migraine headache symptoms is weak in this sample for both males and females, there is substantial overlap between additive genetic factors that contribute to both PTSS and migraine headache symptoms, and that this overlap is potentially greater in females than males. The very weak unique environmental correlations in both males and females also indicate that unique environmental influences on PTSS and migraine headache were essentially non-shared. Further, our exploratory analyses indicate that after controlling for depression in these models, the influence of additive genetic factors that are common to both traits diminished somewhat, but that consistent with our previous findings, the remaining overlap is greater in females then males. These preliminary findings highlight the importance of considering the role of depression in disentangling the relationship between PTSD or PTSS and migraine headache in future studies.

To our knowledge, this is the first study to examine the relative contribution of additive genetics and environmental factors to the co-occurrence of PTSS and migraine headache symptoms. Our findings are consistent with previous studies that have found the co-occurrence of migraine headache and other mental health conditions such as depression, anxious depression and neuroticism to be partially explained by shared additive genetic and unique environmental factors (Schur et al., 2009; Ligthart et al.,
2010; Ligthart et al. 2012). Specifically, similar to our findings, 54% of the covariance between migraine and anxious depression was explained by shared genetic factors in female twin pairs (Ligthart et al., 2010), and 59% of the covariance between migraine and neuroticism was explained by shared genetic factors in males and females. Further, the genetic correlation was estimated at .30 between migraine and anxious depression (Ligthart et al., 2010), and .27 between neuroticism and migraine (Ligthart & Boomsma, 2012), suggesting a relatively weak, but similar influence in strength of common genes on migraine and these mental health related traits and conditions.

Our findings also support previous literature examining the association between PTSS and other specific pain conditions such as chronic widespread pain and temporomandibular pain that are known to be comorbid with migraine headache (Arguelles et al., 2006, Afari et al., 2008 & Plesh et al., 2012) as well as pain conditions that may not regularly co-occur with migraine headache (Wright et al., 2010). These studies, albeit using different methodology, found evidence of shared familial confounding (i.e., a combination of both genetic and common family environment) in the relationship between PTSS and pain conditions, while we found no influence of shared familial environment on the association or covariance of PTSS and migraine headache. Our differing results are likely due to the use of our analytic strategy in which we could parse genetic and common environmental influences. Nonetheless, these findings together with the previous research provide support for the shared vulnerability model of the PTSD and pain relationship. This model proposed that vulnerability factors that may be genetic, biological, physiological, psychological, and/or behavioral in nature, interact with certain environmental conditions such as trauma exposure to potentially predispose
individuals to developing both PTSD and pain (Asmundson et al., 2002; Asmundson & Katz, 2009). There is a need to further examine shared vulnerability factors underlying PTSD and migraine headache, and how they may potentially interact with environmental influences such as trauma exposure. There is also a need to determine whether these mechanisms differentially influence the PTSD and pain relationship by sex.

**Estimating the direction of the relationship between PTSS and migraine headache symptoms**

The second aim of this study was to examine the causation hypothesis of the association between PTSS and migraine headache symptoms by using an MZ-twin difference cross-lagged model with data at two time points. This design enabled us to estimate the direct influence of PTSS on migraine headache symptoms over time. However, the cross-lagged analyses revealed little support of a causal relationship between PTSS and migraine headache symptoms given that PTSS at time 1 accounted for less than 1% of the variance in migraine headache symptoms at time 2, and a similar pattern was found in migraine headache symptoms at time 1 predicting PTSS at time 2. This pattern of findings was found in both male and female MZ twin pairs. Although in females, the path where migraine headache symptoms at time 1 predicted PTSS symptoms at time 2 was significant ($p = .037$), migraine headache symptoms predicted less than 1% of the variance in PTSS symptoms. Given the similarities in regression coefficients in males and females, the statistical significance in females may have been due to the large sample size of female MZ twins (i.e., potentially over-powered). Despite the statistical significance in females, the magnitude of the cross-time cross-trait
associations for both PTSS and migraine headache symptoms were so small that the associations were likely to be clinically unimportant.

To our knowledge, this is the first study to use the cross-lagged twin differences strategy to examine the causal model of PTSD and pain with migraine headache symptoms. While our findings are supportive of Asmundson and colleagues’ assertion that there is limited evidence supporting the causal model of PTSD and pain, a handful of previous studies have reported that PTSD symptoms preceded the development of severe or frequent headaches (Peterlin et al., 2011), and preceded pain intensity after injury (Jenewein, et al., 2009; Ramchand, et al., 2008). Our findings are also in contrast to a study demonstrating the opposite relationship with pain post-injury conveying greater risk of developing PTSD symptoms (Norman, Stein, Dimsdale, & Hoyt, 2008).

Our lack of support for the causal model may be due to our use of a generally healthy community sample and possible lack of variability in symptomatology. However, these findings may also point to a need to explore other factors that may contribute to both PTSD and migraine headache and other pain conditions and maintain their association. In fact, the support we found for the shared vulnerability model (aim 1) is not mutually exclusive of the mutual maintenance model of PTSD and pain comorbidity (Asmundson et al., 2002), and together with the lack of support for the causal model (aim 2), point to a need to examine mutual maintenance factors. Future studies should examine the PTSD and migraine headache symptom relationship in clinical samples, as well as explore the influence of mutual maintenance factors (Asmundson et al.2002; Sharp & Harvey, 2001).

Summary of findings
We found that additive genetic influences contribute to the association between PTSS and migraine headache symptoms in males and females, particularly in females, and did not find substantial association between PTSS and migraine headache symptoms over time. Together these findings provide support for a shared genetic vulnerability to the PTSS and migraine headache symptoms relationship. Further exploration is needed of specific genetic, biological, physiological, psychological, and behavioral vulnerability factors underlying these conditions, and how they may differ by sex. In addition, we found that unique environmental factors did explain some proportion of the phenotypic covariance and association in males and females. Although the unique environmental factor includes error, this finding suggests that future studies should consider unique environmental factors, such as exposure to trauma that may be risk factors for the development of both PTSS and migraine headache symptoms. Further, the findings from this study indicate that there may be sex differences in the development of PTSS or PTSD and migraine headache, and that the influence of underlying mechanisms may differ by sex. Finally, while our findings lend preliminary support to the shared vulnerability model of PTSD and pain, these findings do not preclude the possibility of mutual maintenance factors that may influence PTSD or PTSS and migraine headache symptoms, and the need to examine these factors in clinical samples.

**Future directions**

*Genetic vulnerability factors*

While our study suggests that additive genetic factors contribute to the association between PTSS and migraine headache, we are unable to make any conclusions about specific genes that may underlie these conditions. Behavioral genetic twin designs enable
us to estimate the contribution of shared additive genetic, familial and unique environmental factors on two conditions but they cannot identify the specific genes and genetic polymorphisms that are potentially contributing to the development of two conditions. Identifying specific genes linked to behavioral disorders is a complex undertaking given that behavioral disorders are typically polygenic (Noble, 2003). The genetic and neurobiological factors underlying PTSD and migraine headache are unclear and have not been rigorously examined empirically. However, monoaminergic mechanisms in the brain such as serotonin and dopamine have been proposed as possible underlying mechanisms influencing the association between migraine and PTSD (Peterlin et al., 2011; Juang & Yang, 2014).

Association studies have examined candidate genes from the dopamine and serotonin systems in both PTSD (Afifi et al., 2010; Koenan et al., 2007), and migraine (Maher & Griffiths, 2011; Marziniak, Mössner, Schmitt, Lesch, & Sommer, 2005; Ogilvie et al., 1998). Candidate genes, and specifically the D2 dopamine receptor (DRD2) of the dopamine system, have been extensively examined across a range of neuropsychiatric disorders (Noble, 2003). Candidate genes from the dopamine system have been identified in individuals having migraine with aura (Peroutka, Wilhoit, & Jones, 1997), and in individuals with comorbid migraine with aura, anxiety disorders, and major depression (Peroutka, Price, Wilhoit, & Jones, 1998). However, findings on dopamine system candidate genes in PTSD have been mixed. For instance, the D2 dopamine receptor gene (DRD2) was identified in individuals with PTSD at a significantly great frequency compared to those who did not have PTSD (Comings,
Muhleman, & Gysin, 1996), while another study did not find an association with the dopamine system candidate gene and PTSD (Gelernter et al., 1999).

In contrast, serotonin system genes such as 5-HTT and 5-HTTLPR gene polymorphisms have been associated with the development of PTSD (Afifi et al., 2010; Koenen et al., 2007), and migraine headache (Marziniak, Mössner, Schmitt, Lesch, & Sommer, 2005; Ogilvie et al., 1998). Juang & Yang (2014) hypothesize that dysfunction in the serotonin system could be an underlying mechanism associated with co-occurring PTSD and migraine with aura. In addition to serotonin system candidate genes being identified in both migraine and PTSD, there is evidence of serotonin system involvement based on response to treatment. That is, medications that act on serotonin transmission pharmacologically including triptans, and selective serotonin 5-HT1B/1D agonists are typically the first line of treatment in migraine (Ferrari, Goadsby, Roon, Lipton, 2002; Gibson, 2012) and selective serotonin re-uptake inhibitors (SSRI) are commonly used in PTSD (Gibson, 2012; Ipser, Seedat, & Stein, 2006; Schur et al., 2009). Therefore, further exploration of the dopamine and serotonin systems and other potential candidate genes may be a preliminary step in understanding the etiology of co-occurring PTSD and migraine headache.

(Environmental risk factors: The role of trauma of exposure)

A diagnosis of PTSD requires exposure to a specific environmental factor, a traumatic event (American Psychological Association, 2013). Traumatic experiences such as childhood maltreatment and abuse, combat related injury, and motor vehicle accidents also have been associated with a higher prevalence of migraine and other headaches (Tietjen, et al., 2010, Afari et al., 2009; Berglund., Alfredsson, Jensen,
Cassidy, & Nygren, 2001). However, examining the influence of trauma exposure on the development of migraine has yielded mixed findings. Smitherman et al. (2013) did not find trauma exposure to significantly predict migraine headache, even when 7 out of 10 individuals examined reported experiencing a criterion A trauma. These authors concluded that it is the development and severity of PTSD symptoms that is associated with migraine headache rather than trauma exposure. A similar pattern of findings indicated that the prevalence of trauma exposure in individuals with recurrent headache was similar to that of other chronic masticatory muscle pain patients and non-patient populations (de Leeuw, Schmidt, & Carlson, 2005). It has also been reported that the number of traumas directly experienced was associated with migraine headache, suggesting a need to examine the influence of specific trauma types and the nature of trauma exposures on the development of migraine headache (Smitherman et al., 2013). In addition, CM patients having experienced at least one traumatic event reported more re-experiencing and avoidance symptoms compared to individuals with EM and trauma exposure (Corchs et al., 2011). These differential findings suggest a need to unravel the complex relationship between traumatic experiences, PTSD, and migraine.

Interestingly, there is evidence suggesting that traumatic event exposure itself also exhibits moderate heritability. Exposure to combat trauma in a sample of male twins from the Vietnam Era Twin Registry was found to be 35-47% heritable (Lyons et al., 1993). Stein et al., (2002) examined the heritability of assaultive traumatic events (robbery, being held captive, being beaten up, and sexual assault) and non-assaultive traumatic events (sudden death of a family member, motor vehicle accident, fire, tornado, flood, or earthquake). The experience of assaultive trauma was found to be moderately heritable
(20%), while non-assaultive trauma was influenced exclusively by shared and unique environmental factors. Further, the unique environmental influences on assaultive and non-assaultive trauma were essentially uncorrelated (shared environmental correlation of .31, unique environmental correlation of -.20), indicating that the environmental influences on assaultive and non-assaultive trauma were largely independent of each other (Stein et al. 2002). In addition, genetic influences on exposure to assaultive trauma substantially overlapped with genetic influences on PTSD symptoms (Stein et al., 2002). Taken together, these findings indicate that assaultive and combat-related trauma, which have been shown to be associated with increased prevalence of migraine headache, are moderately heritable and are worthy of investigation as a potential source of shared vulnerability between PTSD and migraine headache.

Given the complex nature of PTSD and migraine headache, there are also likely interactions between different genes (gene-gene interaction), as well as interactions between genes and the environment (gene-environment interaction) in which the influence of environmental exposure is moderated by genotype (Moffitt, Caspi, & Rutter, 2005). There are likely gene-environment interactions that are contributing to each and potentially both of these conditions. Although exposure to trauma has been shown to be prevalent in individuals with migraine, there are no studies to our knowledge that have considered gene-environment interactions in migraine. There is, however, evidence of significant gene-environmental interactions in PTSD, many of which have involved the serotonin transporter (5 serotonin transporter-linked polymorphic region [HTTLPR]) genotype, in which genotype moderated whether exposure to an environmental stressor
increased or decreased the likelihood of PTSD symptoms (Afifi et al., 2010; Koenen et al., 2008).

In sum, there is a need to examine and understand the nature and extent of the influence of trauma exposure on PTSD and migraine headache, as well as the genetic and environmental influence of specific trauma types. There may be pre-existing vulnerability factors that influence the selection of environments that may lead to PTSD and migraine headache or other chronic pain conditions. Additionally, studies of gene-environment interaction can likely lead to a better understanding of both genetic and environmental vulnerability factors for PTSD and migraine headache and other pain conditions.

Sex differences in vulnerability factors

Several studies have documented sex differences in the prevalence of PTSD and migraine headache in which females have a higher rate of PTSD (Kessler et al, 1995) and migraine headache symptoms (Carlson et al, 2013, Lipton et al., 2002) than males for each of these conditions. Although empirically evaluating sex differences in the association between PTSS and migraine headache symptoms was outside the scope of this study, our findings do indicate a potentially differential contribution of shared additive genetic and unique environmental factors to the PTSS and migraine headache association in females than males. Therefore, when examining vulnerabilities and mechanisms underlying the PTSS, PTSD, and migraine headache association, it may be important to consider the role of sex differences.

Little is known about the potential sex differences in the mechanisms underlying the PTSD and migraine association. Some likely potential mechanisms that may influence the sex differences in the PTSD and migraine headache association are sex
hormones such as estrogen, differential hypothalamic-pituitary-adrenal (HPA) axis response to stress (Juang & Yang, 2014; Peterlin et al., 2011a), and personality traits such as neuroticism.

It has been hypothesized that estrogen, which is associated with the modulation of serotonin, may play a role in the development of migraine headache and stress-related disorders (Peterlin et al., 2009). Many women diagnosed with migraine headache report experiencing attacks around menses when estrogen levels decline (Baskin & Smitherman, 2009), and low estrogen levels have been associated with deficits in fear extinction, suggesting that low estrogen may be a vulnerability factor for developing PTSD in women (Glover et al., 2012). HPA axis dysfunction has also been associated with both PTSD and migraine headache. Specifically, individuals with migraine have been shown to exhibit elevated baseline levels of cortisol in the morning and evening compared to controls (Patacchioli, et al., 2006), and individuals with PTSD exhibit higher cortisol levels following exposure to a traumatic stressor compared to controls (Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003). There are also some documented sex differences in HPA axis response to stress such as males exhibiting a greater cortisol response to achievement-related stressors, while females exhibit a greater cortisol response to social rejection-related stressors (Stroud, Salovey, & Epel, 2002). Understanding the role of sex hormones and potential differences in how HPA axis responses to stress may differ between males and females may shed light on sex-specific mechanisms that underlie the co-occurrence of PTSD and migraine headache. Considering the life-stage and hormonal cycle of females may also be imperative in understanding sex differences in PTSD and migraine headache.
Another vulnerability factor that may mediate the genetic influence on the development of PTSD and migraine headache is personality, specifically the trait of neuroticism. A co-twin control study with MZ and DZ twins discordant for neuroticism found preliminary support for neuroticism increasing the risk of migraine headache (Ligthart & Boomsma, 2012). Neuroticism has also been associated with the development of PTSD (Cox, MacPherson, Enns, & McWilliams, 2004; Perrin et al., 2014). Further, females have been shown to exhibit higher scores in neuroticism compared to males (Jorm, 1987; Breslau, 2009), and neuroticism has been shown to predict relative risk for migraine headache in females but not for males (Breslau et al., 1996). Neuroticism also has been shown to be moderately heritable (Jang, Livesley, Vernon, 1996). Therefore, future studies should also examine neuroticism as a potential shared vulnerability factor in the development of PTSD and migraine headache, with the potential of explaining sex differences.

*Mutual maintenance factors*

We did not find support for a causal model of PTSS serving as a risk factor for the development of migraine headache, instead supporting the hypothesis that pre-existing vulnerabilities may be linked to the development of PTSS and migraine headache symptoms. These findings do not preclude the possibility that once comorbid, shared psychological and/or behavioral factors may maintain both conditions (Asmundson et al., 2002). The mutual maintenance models assert that physiological, affective, cognitive, and behavioral components may mutually maintain and compound symptoms of PTSD and chronic pain (Sharp & Harvey, 2001; Liedl & Knaevelsrud, 2008). Although many mechanisms have been proposed to explain possible mutual maintenance of PTSD and
chronic pain, there is research support for a handful of common factors that may link PTSD with migraine headache. These include avoidant strategies, sleep disturbance, and depression.

Avoidance of trauma reminders is included in the diagnostic criteria for PTSD (American Psychiatric Association, 2013) and is a primary focus of treatment in interventions such as prolonged exposure for PTSD (Foa, Davidson, & Francis, 2002). However, there is also some evidence that migraine chronicity is associated with the use of more avoidant coping strategies (Radat et al., 2009), and it has also been suggested that the avoidance of migraine triggers may exacerbate migraine symptoms (Martin, 2000). Further behavioral treatments that address the avoidance of triggers have been recommended to promote a more integrated approach to migraine care (Pistoia, Sacco, & Carolei, 2013).

An additional shared trigger for both PTSD and migraine is sleep disturbance (Kelman, 2007; Maher, Rego, & Asnis, 2006; Tran & Spierings, 2013). Sleep problems have been shown to impact the development and symptom severity of PTSD, and to be a potential risk factor for migraine onset (Maher, Rego, & Asnis, 2006; Tran & Spierings, 2013). Cognitive behavioral treatments for sleep and nightmares have shown promise in addressing PTSD symptoms (Margolies, Rybarczyk, Vrana, Leszczyszyn, & Lynch, 2013), and while cognitive behavioral treatments for sleep have not been examined in migraine patients, a recent pilot study found significant reductions in headache severity after a brief behavioral sleep modification intervention (Calhoun & Ford, 2007).

Another important consideration in understanding the development and maintenance of PTSD or PTSS and migraine, is the role of depression. While
depression’s comorbidity with PTSD (Creamer et al., 2001; Kessler et al., 1995) and migraine (Breslau, Lipton, Stewart, Schultz, Welch, 2003; Ligthart et al., 2010) has been widely studied, the role of depression in the migraine and PTSS or PTSD association is unclear and requires further exploration. In one diathesis-stress model of depression and pain, depression and other psychopathology is hypothesized to follow the onset of pain (Dersh, Polatin, Gatchel, 2002). However, there is also evidence of depression increasing the risk of CM onset in individuals diagnosed with EM (Ashina et al., 2012), as well as a bidirectional relationship between depression and migraine (Breslau et al., 2003; Breslau et al., 2000). A recent study presented evidence that individuals with comorbid major depression disorder and migraine were more genetically similar to those with major depression disorder compared to those diagnosed with only a migraine disorder (Ligthart et al., 2014). Further, the depression and PTSD comorbidity has been shown to be largely explained by common genetic influences and a substantial genetic overlap, while environmental influences appear to be less related and more specific to each disorder (Koenen et al., 2008). In addition, depression symptoms have also been shown to mediate the relationship between PTSD and pain interference in chronic pain patients, (Morasco et al., 2013). Interestingly, the findings from our EFA with IES and PHQ-2 items determined two separate PTSS and depression factors. However, our measure of depression included only 2 items which assess for depressed mood and anhedonia, and the IES items only assess for intrusion and avoidance symptoms of PTSD, excluding other contributing factors to both conditions such as difficulties with sleep and concentration (American Psychiatric Association, 2013). Therefore, addressing the role of depression in the PTSD and migraine relationship may require considering physician
confirmed diagnoses in clinical samples addressing the full range of symptoms associated with PTSD and depression.

Taken together, the role of depression in the PTSD and migraine relationship is likely complex and requires further examination with comprehensive assessments and more rigorous statistical approaches. It is possible that PTSD, depression, and migraine headache share a preexisting vulnerability and/or genetic similarity; however, depression may also exacerbate and contribute to the maintenance of both conditions (Asmundson et al., 2002). Promising areas for unraveling the co-occurrence of PTSD and migraine headache are in continued exploration of potentially common factors such as avoidance, sleep, depression and others that maintain both conditions in clinical samples. However, it also is important to consider the role of additive genetic and shared environmental influences on these factors as well. It is possible that much of what maintains the phenotypic expression of PTSD and migraine headache symptoms are based on the activation of pre-existing genetically-based vulnerabilities by environmental stressors that are common to all of these factors.

**Implications**

There is an emerging literature on the co-occurrence of PTSD or PTSS and migraine headache, as well as in the disability and functional impairments linked to these conditions (Afari et al., 2009; Peterlin et al., 2011; Peterlin et al., 2009) Finding evidence for shared genetic influences on PTSS and migraine headache has important implications for guiding future research to identify some of the specific genetic, biological, physiological, psychological, and behavioral underpinnings of these conditions, and how they may function differently by sex. These findings also have clinical implications for
encouraging clinicians across disciplines to engage in thorough assessments in clinical settings for the co-occurrence of PTSD and pain conditions such as migraine headache, to facilitate timely diagnoses of both conditions and targeted treatment approaches. While there are no studies to our knowledge that have examined the efficacy of treating co-occurring PTSD and migraine headache specifically, there are some preliminary, but promising studies examining the feasibility and clinical benefit of integrated cognitive behavioral approaches to PTSD and pain (Otis, Keane, Kerns, Monson, & Scioli, 2009) and a collaborative approach including behavioral activation (Plagge, Lu, Lovejoy, Karl, & Dobscha, 2013) with patients diagnosed with co-occurring PTSD and chronic pain. Working across disciplines with clinical populations to understand the underlying etiology and maintenance of co-occurring PTSS or PTSD and migraine headache and other pain conditions may provide insight into developing more tailored psychological and pharmacological intervention strategies.

**Strengths and limitations**

To our knowledge, this study is the first to examine whether there is a shared genetic contribution to the relationship between PTSS and migraine headache symptoms, and to examine a potential causal link between these conditions. Theoretical models such as the shared vulnerability, causal, and mutual maintenance models have been proposed to explain the development and maintenance of the PTSD and pain relationship (Asmundson, Coons, Taylor, & Katz, 2002; Asmundson & Katz, 2009; Liedl & Knaevelsrud, 2008; Sharp & Harvey, 2001). There is, however, a lack of research empirically testing these models in specific pain conditions. This study is one of the first to empirically examine components of these proposed models, and to provide preliminary
support for a potential shared genetic vulnerability to the association between PTSS and migraine headache symptoms. Strengths of this study include the large community-based sample of twins, longitudinal nature of the data, and the availability of a large sample of MZ twin pairs to examine the potential causal dynamics between PTSS and migraine headache symptoms. Additional strength of this study are the use of continuous measures to examine a range of PTSS and migraine headache symptoms, and the use of screening measures that are most likely to be used with a clinical population.

There are, however, several limitations to this study. First, the measurement of PTSS through the IES was not linked to a specific traumatic event. Previous studies have found the IES measure to be strongly correlated with a diagnosis of PTSD (Taal & Faber, 1997), and we found significantly higher IES symptoms in those with a self-reported diagnosis of PTSD compared to those without PTSD diagnosis, providing some evidence for the validity of the IES as a measure of PTSD symptoms. However, we were unable to confirm whether individuals in the sample met criteria for a PTSD diagnosis, and whether our findings are generalizable to those with a confirmed PTSD diagnosis. Therefore in this study the IES may be conceptualized as measuring a “trait” or a general response to a stressor rather than a specific response to a specific traumatic event (Afari et al., 2008). Further, the IES only assesses symptoms experienced over the last 7 days and does not provide information about lifetime PTSD. To determine the generalizability of our findings to the association between PTSD and migraine headache, it is imperative to replicate and examine whether there is a shared genetic vulnerability, as well as whether there is a causal relationship with interview- and clinician-confirmed PTSD diagnosis.
Further it is important to examine potentially differential influences of lifetime PTSD on these associations compared to those experiencing current PTSD symptoms.

Second, the MSQ, our migraine headache symptom measure, was essentially a screening tool which assessed for the presence of five specific migraine-related symptoms, and did not fully assess for International Classification of Headache Disorders (2004) diagnostic criteria. The MSQ has been shown to facilitate early detection of migraine headache in primary care settings (Lainez et al., 2010), and we found that those reporting migraine headache diagnosis from a physician also had significantly higher MSQ scores compared to those without a physician diagnosis. However, it is unclear whether individuals in our sample would have met criteria for a migraine diagnosis without more formal and comprehensive assessment. Further, there was limited range in the MSQ scores (ranging from 0-5), which may have restricted variability and especially affected the results of the cross-lagged difference score analyses. The MSQ also does not differentiate between CM and EM. Individuals diagnosed with CM typically present with multiple comorbid disorders such as anxiety and depressive disorders compared to individuals diagnosed with EM (Ferrari et al., 2007). Therefore, future studies should replicate these findings with physician confirmed migraine headache, and also examine different headache types to determine whether findings are specific to one headache type or generalize across CM, EM, and other forms of headache.

Third, we had a disproportionately larger number of female twin pairs and fewer male pairs. This was especially problematic in the cross-lagged MZ twin differences analyses, where the small number of male pairs (n = 381 pairs) may have affected our power to detect a relationship between PTSS and migraine headache symptoms over time.
in men. However, our findings with female MZ twin pairs with a much larger sample size (n = 753 pairs) were similar and did not point to a substantial relationship between PTSS and migraine headache symptoms over time. Therefore, it is likely that our findings are sound. Nonetheless, sample size and power considerations are important to future studies, especially those examining the relationship between PTSD or PTSS and migraine headache over time.

Fourth, we did not find a significant role for the length of time between assessments (ranging from 2 months to 2 years), likely due to a restricted range of time between the time 1 and time 2 assessments. A recent meta-analysis of delayed-onset PTSD, or the onset of PTSD more than 6 months following a traumatic event, found that on average 24.5% of all PTSD cases investigated meet criteria for delayed-onset PTSD (Utzon-Frank et al., 2014). Therefore, it is important for future longitudinal studies to account for the amount of time between trauma exposure and PTSD symptoms, and to assess for PTSD symptoms specifically 6 months or more after the event to improve the likelihood of detecting PTSD and its comorbidities.

Fifth, as is consistent with most volunteer twin registries, we had an overrepresentation of MZ twins (70%) in the dataset used to address aim 1. Although no significant differences on our study variables were found based on zygosity, the disproportionate zygosity representation may have led to biases in our heritability estimates, potentially limiting the generalizability of our findings. However, the pattern of findings indicating higher MZ correlations in PTSS and migraine headache, suggestive of genetic influences on the phenotypes, is consistent with previous findings on the heritability of PTSS and migraine headache (True et al., 1993, Stein et al., 2002; Plesh et
al., 2012; Schur et al., 2009; Svensson et al., 2003). Nonetheless, it is important to replicate our findings in samples with more equal representation of MZ and DZ twin pairs to validate our findings.

Finally, this study focused on a large, relatively young, and generally healthy epidemiological sample of twins. We likely had limited variation of PTSS or migraine headache symptoms in this sample which may have influenced are ability to detect a direct relationship between these two conditions across Time 1 and Time 2 in our cross-lagged model. Therefore, it is important that future studies examine the PTSS and migraine headache symptoms relationship in clinical populations with greater symptom variation to determine whether our findings are relevant to more symptomatic populations. Further, our sample was primarily white and educated which may limit the generalizability of our findings to other populations.

Conclusions

Despite its limitations, this study provides preliminary support for the shared vulnerability model. We demonstrated that the association between PTSS and migraine headache symptoms is influenced by additive genetic factors that are common to both PTSS and migraine headache. Further, additive genetic factors appear to influence this relationship to a greater extent in females. This study did not find support for a causal model of PTSS and migraine headache. After controlling for the influence of shared familial and genetic factors on the PTSS and migraine association, PTSS accounted for a very small proportion of the variance in migraine headache symptoms, nor did migraine headache symptoms account for a significant amount of the variance in PTSS symptoms over time, in either males or females. These findings suggest that pre-existing genetic,
biological, physiological, psychological, and behavioral vulnerability factors may play a role in the PTSD or PTSS and migraine headache association. These pre-existing factors are also likely influenced by trauma exposure, and there is a need to consider the role of trauma exposure and trauma type in understanding the link between PTSS or PTSD and migraine headache. The influence of these pre-existing mechanisms may also differ by sex, which should be examined empirically. Further, exploration of potential mutual maintenance factors such as avoidance, sleep, and depression in clinical populations may also be an important future direction in understanding the association between PTSS or PTSD and migraine headache or other pain conditions, and whether these factors exacerbate both conditions. The present study is an initial step in understanding the complex underpinnings of co-occurring PTSD or PTSS with pain and specifically migraine headache; future research is needed to further explore the development and maintenance of these conditions to ultimately aide in the development of targeted prevention and treatment approaches.

This chapter is currently being prepared for submission for publication of the material. Mostoufi, S. M., Gasperi, M., Godfrey, K. M, Strachan, E., Buchwald, D & Afari, N. The dissertation author was the primary investigator and author of this material.
REFERENCES


7, 286-299.


general population study. Social Psychiatry and Psychiatric Epidemiology, 48, 525-532.


Martin, P. R. (2000). Headache triggers: To avoid or not to avoid, that is the question. Psychology and Health, 15, 801-809.


APPENDIX A:

Table 3.1: Demographic characteristics of twins for aim 1 (Time 1)

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 6738 )</td>
<td>( n = 2452 )</td>
<td>( n = 4286 )</td>
</tr>
<tr>
<td></td>
<td>(3369 pairs)</td>
<td>(1226 pairs)</td>
<td>(2143 pairs)</td>
</tr>
<tr>
<td><strong>Age in years, ( M(SD) )</strong></td>
<td>41 (17.8)</td>
<td>41 (18.6)</td>
<td>40 (17.3)</td>
</tr>
<tr>
<td><strong>Zygosity, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td><strong>Marital Status, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>33</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Married</td>
<td>48</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Widowed</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Divorced</td>
<td>9</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Separated</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Living with partner</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td><strong>Race/Ethnicity, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Native American</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>White</td>
<td>91</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Education, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known/attended</td>
<td>.3</td>
<td>.5</td>
<td>.2</td>
</tr>
<tr>
<td>Grades 1-8</td>
<td>.2</td>
<td>.3</td>
<td>.1</td>
</tr>
<tr>
<td>Grades 9-11</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Grade 12/High school diploma/GED</td>
<td>19</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Some college</td>
<td>26</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Associate degree</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>24</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>17</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td><strong>Income, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Less than $20,000</td>
<td>14</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>$20,000-$29,000</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>$30,000-$39,000</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>$40,000-$49,000</td>
<td>7</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>$50,000-$59,000</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>$60,000-$69,000</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>$70,000-$79,000</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>$80,000 and above</td>
<td>37</td>
<td>42</td>
<td>34</td>
</tr>
</tbody>
</table>
Table 3.2: Means and standard deviations for study variables used for aim 1 (Time 1)

<table>
<thead>
<tr>
<th>Measure, $M (SD)$</th>
<th>All participants $n = 6738$ twins (3369 pairs)</th>
<th>Male $n = 2452$ twins (1226 pairs)</th>
<th>Female $n = 4286$ twins (2143 pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IES</td>
<td>16.4 (13.2)</td>
<td>13.9 (13.0)</td>
<td>17.8 (13.2)</td>
</tr>
<tr>
<td>MSQ</td>
<td>.96 (1.44)</td>
<td>.59 (1.08)</td>
<td>1.16 (1.57)</td>
</tr>
<tr>
<td>PHQ-2</td>
<td>.72 (1.19)</td>
<td>.68 (1.14)</td>
<td>.74 (1.21)</td>
</tr>
</tbody>
</table>

*Note.* IES = Impact of Event scale; MSQ = Migraine Screen Questionnaire; PHQ-2 = Patient Health Questionnaire
Table 3.3: Phenotypic, twin, and cross-twin, cross trait correlations between IES and MSQ scores within male and female twins by zygosity

<table>
<thead>
<tr>
<th>Twin A</th>
<th>Twin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>IES</td>
<td>MSQ</td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td><strong>Monozygotic</strong></td>
<td></td>
</tr>
<tr>
<td>Twin A</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>1</td>
</tr>
<tr>
<td>MSQ</td>
<td>.170**</td>
</tr>
<tr>
<td>Twin B</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>.286**</td>
</tr>
<tr>
<td>MSQ</td>
<td>.047</td>
</tr>
<tr>
<td><strong>Dizygotic</strong></td>
<td></td>
</tr>
<tr>
<td>Twin A</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>1</td>
</tr>
<tr>
<td>MSQ</td>
<td>.251**</td>
</tr>
<tr>
<td>Twin B</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>.096</td>
</tr>
<tr>
<td>MSQ</td>
<td>.061</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td><strong>Monozygotic</strong></td>
<td></td>
</tr>
<tr>
<td>Twin A</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>1</td>
</tr>
<tr>
<td>MSQ</td>
<td>.194**</td>
</tr>
<tr>
<td>Twin B</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>.280**</td>
</tr>
<tr>
<td>MSQ</td>
<td>.139**</td>
</tr>
<tr>
<td><strong>Dizygotic</strong></td>
<td></td>
</tr>
<tr>
<td>Twin A</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>1</td>
</tr>
<tr>
<td>MSQ</td>
<td>.130**</td>
</tr>
<tr>
<td>Twin B</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>.151**</td>
</tr>
<tr>
<td>MSQ</td>
<td>.019</td>
</tr>
</tbody>
</table>

*p < .05, **p < .01

Note. All variables were log-transformed and regressed on age to control for age effects. + indicate phenotypic correlations (i.e., IES twin A with MSQ twin A). Twin correlations are italicized (i.e., IES Twin A with IES Twin B). Cross-twin, cross-trait correlations are bolded (i.e., IES Twin A with MSQ Twin B).
Table 3.4: Univariate structural equation models of IES and MSQ for male and female twins

<table>
<thead>
<tr>
<th>Model</th>
<th>Additive Genetic (A)</th>
<th>Common Environment (C)</th>
<th>Unique Environment (E)</th>
<th>χ²</th>
<th>Diff</th>
<th>df</th>
<th>P value</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>.28 (.22, .32)</td>
<td>0 (0, .20)</td>
<td>.72 (.67, .77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td><strong>.28 (.23, .33)</strong></td>
<td>-</td>
<td>.72 (.67, .77)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td>-2.00</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>-</td>
<td>.23 (.19, .28)</td>
<td>.77 (.72, .81)</td>
<td>5</td>
<td>1</td>
<td>.02</td>
<td>6.92</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>-</td>
<td>1.0 (1.0, 1.0)</td>
<td>38</td>
<td>2</td>
<td>&lt;.001</td>
<td>72.2</td>
<td></td>
</tr>
<tr>
<td>MSQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>.31 (.26, .36)</td>
<td>0 (0, .17)</td>
<td>.69 (.64, .74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td><strong>.31 (.26, .36)</strong></td>
<td>-</td>
<td>.69 (.64, .74)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td>-2.00</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>-</td>
<td>.25 (.21, .30)</td>
<td>.75 (.70, .79)</td>
<td>6</td>
<td>1</td>
<td>.014</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>-</td>
<td>1.0 (1.0, 1.0)</td>
<td>46</td>
<td>2</td>
<td>&lt;.001</td>
<td>88.1</td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>.26 (.13, .43)</td>
<td>.02 (.00, .38)</td>
<td>.72 (.68, .76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td><strong>.28 (.25, .32)</strong></td>
<td>-</td>
<td>.72 (.68, .76)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td>1.93</td>
<td>7</td>
</tr>
<tr>
<td>CE</td>
<td>-</td>
<td>.24 (.01, .28)</td>
<td>.77 (.73, .79)</td>
<td>4</td>
<td>1</td>
<td>.04</td>
<td>6.88</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>-</td>
<td>1.0 (1.0, 1.0)</td>
<td>68</td>
<td>2</td>
<td>&lt;.001</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>MSQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>.41 (.37, .44)</td>
<td>0 (0, .05)</td>
<td>.59 (.56, .63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td><strong>.41 (.37, .44)</strong></td>
<td>-</td>
<td>.59 (.56, .63)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>-</td>
<td>.33 (.30, .37)</td>
<td>.67 (.64, .70)</td>
<td>22</td>
<td>1</td>
<td>&lt;.001</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>-</td>
<td>1.0 (1.0, 1.0)</td>
<td>148</td>
<td>2</td>
<td>&lt;.001</td>
<td>294</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* aACE refers to a model that includes additive genetics (A), common environment (C), and unique environment (E), AE only includes additive genetics and unique environment, and CE only includes common and unique environment. Nested models are compared to full ACE model.

b Proportion of variance caused by additive genetics, shared environment, and unique environment according to each model.

Akaikie’s information criterion (AIC) is a global measure of goodness of fit; the best-fitting and most parsimonious models are shown in bold.

*Note.* All variables were log-transformed and regressed on age to control for age effects. NS = not significant.
Table 3.5: Bivariate structural equation models of IES and MSQ in male and female twin pairs

<table>
<thead>
<tr>
<th>Model*</th>
<th>Test of Model Fit</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shared component</td>
<td>-2 ll</td>
<td>$\chi^2$</td>
<td>Diff df</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>6483.846</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AE</td>
<td>6483.846</td>
<td>3</td>
<td>NS</td>
<td>13.95</td>
<td>-6.001</td>
</tr>
<tr>
<td>CE</td>
<td>6493.823</td>
<td>9.977</td>
<td>3</td>
<td>.02</td>
<td>-5.163</td>
</tr>
<tr>
<td>E</td>
<td>6567.198</td>
<td>83.35</td>
<td>6</td>
<td>.01</td>
<td>154.7</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>11948.349</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AE</td>
<td>11948.767&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.418</td>
<td>3</td>
<td>.93</td>
<td>-5.163</td>
</tr>
<tr>
<td>CE</td>
<td>11975.329</td>
<td>26.98</td>
<td>3</td>
<td>&lt;.01</td>
<td>47.96</td>
</tr>
<tr>
<td>E</td>
<td>12161.529</td>
<td>213.2</td>
<td>6</td>
<td>&lt;.01</td>
<td>414.4</td>
</tr>
</tbody>
</table>

*ACE refers to a model that includes additive genetics (A), common environment (C), and unique environment (E). AE only includes additive genetics and unique environment, and CE only includes common and unique environment. Nested models are compared to full ACE model.

<sup>a</sup>Akaike’s information criterion (AIC) is a global measure of goodness of fit; the best-fitting and most parsimonious model is shown in bold based on AIC and likelihood ratio test. NS = not significant.
Table 3.6: Trait-specific and shared additive genetic and environmental variances for best-fitting (AE) bivariate model in male and female twin pairs

<table>
<thead>
<tr>
<th>Trait Specific</th>
<th>Male</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additive Genetic (A)</td>
<td>Common Environment (C)</td>
<td>Unique Environment (E)</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>.28 (.26,.30)</td>
<td>-</td>
<td>.72 (.70,.74)</td>
<td></td>
</tr>
<tr>
<td>MSQ</td>
<td>.31 (.28,.34)</td>
<td>-</td>
<td>.69 (.66,.72)</td>
<td></td>
</tr>
<tr>
<td>Shared*</td>
<td>.38 (.28,.42)</td>
<td>-</td>
<td>.62 (.57,.72)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trait Specific</th>
<th>Female</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additive Genetic (A)</td>
<td>Common Environment (C)</td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>.28 (.26,.30)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MSQ</td>
<td>.41 (.38,.42)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Shared*</td>
<td>.68 (.65,.74)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* Proportion of shared variance. IES = Impact of Event Scale; MSQ = Migraine Screening Questionnaire.
**Table 3.7: Demographic characteristics for MZ twins for aim 2 (Time 1 and Time 2)**

<table>
<thead>
<tr>
<th>Marital Status, %</th>
<th>All participants</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 2268 (1134 twin pairs)</td>
<td>n = 762 (381 twin pairs)</td>
<td>n = 1506 (753 twin pairs)</td>
</tr>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
<td>Time 1</td>
</tr>
<tr>
<td>Single</td>
<td>37</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>Married</td>
<td>46</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Widowed</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Divorced</td>
<td>9</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Separated</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lives with partner</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Race/Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Native American</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>White</td>
<td>92</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known/attended</td>
<td>.4</td>
<td>.4</td>
<td>.7</td>
</tr>
<tr>
<td>Grades 1-8</td>
<td>.0</td>
<td>.1</td>
<td>0</td>
</tr>
<tr>
<td>Grades 9-11</td>
<td>4</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Grade 12/High school diploma/GED</td>
<td>19</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Some college</td>
<td>27</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Associated degree</td>
<td>8</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>23</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Income, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Less than $20,000</td>
<td>13</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>$20,000-$29,000</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>$30,000-$39,000</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>$40,000-$49,000</td>
<td>7</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>$50,000-$59,000</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>$60,000-$69,000</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>$70,000-$79,000</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>$80,000 and above</td>
<td>36</td>
<td>37</td>
<td>44</td>
</tr>
</tbody>
</table>
### Table 3.8: Individual level and twin difference scores for IES and MSQ by sex at Time 1 and Time 2

<table>
<thead>
<tr>
<th></th>
<th>Individual Scores</th>
<th>Twin Difference scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 2268 )</td>
<td>( n = 1134 ) pairs</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>13.0</td>
<td>12.7</td>
</tr>
<tr>
<td>MSQ</td>
<td>.605</td>
<td>1.13</td>
</tr>
<tr>
<td>Time 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>13.4</td>
<td>12.1</td>
</tr>
<tr>
<td>MSQ</td>
<td>.700</td>
<td>1.17</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>17.6</td>
<td>13.1</td>
</tr>
<tr>
<td>MSQ</td>
<td>1.18</td>
<td>1.55</td>
</tr>
<tr>
<td>Time 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>17.5</td>
<td>12.1</td>
</tr>
<tr>
<td>MSQ</td>
<td>1.26</td>
<td>1.61</td>
</tr>
</tbody>
</table>

**Note.** Means and standard deviations for the variables at the individual level are presented on the left. MZ twin difference scores are presented on the right, in absolute value so as to highlight the true magnitude of twin differences. Final analyses were conducted on signed MZ twin differences to examine the direction of any significant effects. M = Mean; SD = Standard Deviation; Min = minimum; Max = maximum. IES = Impact of Event Scale; MSQ = Migraine Screening Questionnaire.
Table 3.9: MZ difference score correlations for males and females at Time 1 and Time 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.Time 1 IES</td>
<td>1</td>
<td>.402** +</td>
<td>.140**</td>
<td>.087</td>
</tr>
<tr>
<td>2.Time 2 IES</td>
<td>.402** +</td>
<td>1</td>
<td>.112*</td>
<td>.167**</td>
</tr>
<tr>
<td>3.Time 1 MSQ</td>
<td>.140**</td>
<td>.112*</td>
<td>1</td>
<td>.540** +</td>
</tr>
<tr>
<td>4.Time 2 MSQ</td>
<td>.087</td>
<td>.167**</td>
<td>.540**</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.Time 1 IES</td>
<td>1</td>
<td>.315** +</td>
<td>.015</td>
<td>-.019</td>
</tr>
<tr>
<td>2.Time 2 IES</td>
<td>.315** +</td>
<td>1</td>
<td>.077*</td>
<td>.124**</td>
</tr>
<tr>
<td>3.Time 1 MSQ</td>
<td>.015</td>
<td>.077*</td>
<td>1</td>
<td>.678** +</td>
</tr>
<tr>
<td>4.Time 2 MSQ</td>
<td>-.19</td>
<td>.124*</td>
<td>.678** +</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note*: Within-time cross-trait correlations are italicized. Cross-time, cross-trait correlations are bolded. + Indicates within time, within-trait correlations. IES = Impact of Event Scale; MSQ = Migraine Screening Questionnaire. *\( p < .05\), **\( p < .01\).
Figure 2.1: Univariate ACE model.

*Note.* A = Additive genetic influences, C = common environmental influences, E = Unique environmental influences; a, c, and e = parameter estimates for latent variables A, C, and E, respectively. Latent variable variances are fixed at 1.
Figure 2.2: Bivariate Cholesky model.

Note. This model is shown for one individual. A = Additive genetic influences, C = common environmental influences, E = Unique environmental influences. Common latent factors (A₁, C₁, E₁) contribute to variation in PTSS and migraine headache symptoms, while unique latent factors (A₂, C₂, E₂) contribute to variation in migraine headache. Coefficients (a₁₁, c₁₁, e₁₁), represent the path estimates for common latent factors acting on PTSS. Coefficients (a₂₂, c₂₂, e₂₂) represent the path estimates from unique latent factors acting on migraine headache symptoms. Coefficients (a₂₁, c₂₁, e₂₁) represent the path estimates for common latent factors acting on migraine headache symptoms. Specifically, a₂₁ represents additive genetic covariance between PTSS and migraine headache symptoms, c₂₁ represents the common environmental covariance between PTSS and migraine headache symptoms, and e₂₁ represents the unique environmental covariance between PTSS and migraine headache symptoms. Latent variable variances are fixed at 1.
Figure 2.3: MZ twin Differences cross-lagged model in PTSS and migraine headache symptoms for 2 time points

*Note.* Cross-time paths (i.e., standardized regression coefficients) are indicated by “b.” Within-time correlations are indicated by “r.” The residual variance in PTSS and migraine headache symptoms at time 2 are represented by an “e.”
Figure 3.1: Path coefficients for best-fitting (AE) bivariate model for males.

Note. A = Additive genetic influences, C = common environmental influences, E = Unique environmental influences. Coefficients and 95% confidence intervals represent the path estimates for common and unique latent factors to PTSS and migraine headache phenotypes.
Figure 3.2: Path coefficients for best-fitting (AE) bivariate model for females

Note. A = Additive genetic influences, C = common environmental influences, E = Unique environmental influences. Coefficients and 95% confidence intervals represent the path estimates for common and unique latent factors to PTSS and migraine headache phenotypes.
Figure 3.3: Cross-lagged model for MZ twin differences in PTSS and migraine headache symptoms across 2 time points for males

Note. Path estimates presented correspond to those in Figure 2.3. The path estimate b11 represents the stability of PTSS twin differences over time, b22 represents the stability of migraine headache symptoms twin differences over time, b12 represents the association between PTSS differences at time 1 and migraine headache symptoms differences at time 2, and b21 represents the association between migraine headache symptoms differences at time 1 and PTSS symptoms differences at time 2. All b paths are standardized regression coefficients. The correlation labels r1 represents the correlation between PTSS and migraine headache symptoms twin differences at time 1, and r2 represents the residual correlation between PTSS and migraine headache symptoms twin differences at time 2, controlling for the time 1 contributions.

For single-headed arrows (i.e., paths), the standardized regression coefficients are presented. For double-headed arrows, the correlations are presented. * Indicates that Path estimate is significant at $p < .05$, and ** indicates that path estimate is significant at $p < .01$. 
Figure 3.4: Cross-lagged model for MZ twin differences in PTSS and migraine headache symptoms across 2 time points for females

*Note.* Path estimates presented correspond to those in Figure 2.3. The path estimate $b_{11}$ represents the stability of PTSS twin differences over time, $b_{22}$ represents the stability of migraine headache symptoms twin differences over time, $b_{12}$ represents the association between PTSS differences at time 1 and migraine headache symptoms differences at time 2, and $b_{21}$ represents the association between migraine headache symptoms differences at time 1 and PTSS symptoms differences at time 2. All $b$ paths are standardized regression coefficients. The correlation labels $r_1$ represents the correlation between PTSS and migraine headache symptoms differences at time 1, and $r_2$ represents the residual correlation between PTSS and migraine headache symptoms differences at time 2, controlling for the time 1 contributions.

For single-headed arrows (i.e., paths), the standardized regression coefficients are presented. For double-headed arrows, the correlations are presented. * Indicates that Path estimate is significant at $p < .05$, and ** indicates that path estimate is significant at $p < .01$. 