# A MULTILOCUS APPROACH TO EXAMINING GENETIC SUSCEPTIBILITY TO STRESS AND DEPRESSION AMONG YOUNG ADULTS

by

Emily E. Thaw

2020

A thesis submitted to the Faculty of Graduate and Postdoctoral Affairs in partial fulfilment of the requirements for the degree of

Master of Science

in

Neuroscience

Carleton University

Ottawa, Ontario

## Abstract

Depression is thought to arise from a combination of stressful experiences and genetic susceptibility as it has been shown that genes regulating the hypothalamus pituitary adrenal (HPA)-axis, not only modulate physiological stress reactivity, but have likewise been associated with depressive phenotypes. To explore genetic susceptibility, we examined the relation between a validated multilocus genetic profile score (MGPS), comprising genes that regulate HPA axis activity, with mental health outcomes and peripheral biomarkers levels in the context of stressful life experiences. We observed interactions between the MGPS score with traumatic experiences revealing that when individuals were exposed to high levels of trauma, those with lower MGPS, displayed higher stress, depressive, and anxiety symptoms. This study calls attention to the importance of environmental factors when examining genetic susceptibility to mental illnesses. Ultimately, these data suggest that experiences of trauma could potentially "set boundaries" on the impact of genes, overriding genetic predisposition to depression.

**Acknowledgments**

For the last several years I have been surrounded by the kindest, most supportive, inspiring human beings and I owe thanks to so many within the Carleton community. First and foremost, my incredible supervisor and role model Dr. Robyn McQuaid. I want to express my sincerest appreciation and gratitude to you as you have been an unfathomable source of guidance and encouragement. You consistently go out of your way to support, teach and motivate with kindness, deep consideration and patience. You have helped me to grow as well as to reach goals I never thought possible. I want you to know how truly blessed I feel having had the opportunity to learn from you. I would also like to express deep gratitude to my Co-supervisor Dr. Kim Matheson. Not only do you always take time to provide thoughtful feedback, but you have also been a source of support and considerable knowledge. Additionally, without you believing in me and introducing me to the McQuaid Lab none of this work would have been possible.

A thank you is owed to my committee members Dr. Hymie Anisman and Dr. Alfonso Abizaid. Your expert advice, time, support and ability to make me laugh is so appreciated and has been invaluable. It has been such a pleasure to work with you both! Thank you as well to my external examiner, Dr. Danyluck for taking time to join my committee. Finally, thank you to Dr. Patterson for your time and agreeing to chair my defense.

Thank you to all the members of the McQuaid Lab. It has been an honour to work with such an incredible group of people. Everyone on this amazing team of people has played an important role in making this work possible. A special thanks to Sabina Franklyn who helped lead the collection of this data and has been a wonderful colleague and friend.

To my friends and family – there is no way I would have made it through this degree without you (especially you Mom). Nana, Dad, Diane, Roy, Thally, Jordan, Leah and Beth – I love you and thank you. Finally, to my best friend and partner Nick your unwavering support, encouragement, kindness, and belief in me made this possible, I love you and I am so grateful for all that you do!

## Table of Contents

## List of Tables

## List of Figures

## List of Appendices

**A Multilocus Approach to Examining Genetic Susceptibility to Stress and Depression Among Young Adults**

Stressful experiences, particularly those encountered in early life, are strong predictors of the later development of mental health disorders, such as depression (Afifi et al., 2014; Wiens et al., 2020). Stress exposure initiates a cascade of biological responses including the activation of the hypothalamic-pituitary-adrenal axis (HPA-axis) and inflammatory pathways (Haapakoski et al., 2015) (Chrousos, 2009). Chronic activation of these pathways has been linked with depressive symptoms, as individuals with depression often display heightened levels of peripheral inflammation (Himmerich et al., 2019; Schmidt et al., 2014; Zou et al., 2018) and excessive dysregulation in glucocorticoid levels (McEwen, 2017; Yaribeygi et al., 2017). Moreover, depression is thought to arise from a combination of stressful experiences and genetic susceptibility (Dunn et al., 2015; Kim et al., 2019). Genes that regulate the HPA-axis, not only modulate physiological stress reactivity (Weeger et al., 2020), but have likewise been associated with depressive phenotypes (De la Cruz-Cano, 2017; Peng et al., 2018). Furthermore, single nucleotide polymorphisms (SNPs) on HPA-axis related genes serve to moderate associations between stressful life events and depressive illness (Kohrt et al., 2015; Normann & Buttenschøn, 2020). However, various limitations exist when considering the contribution of single SNPs in the relation between stressors and mental health outcomes, thus, taking a multilocus approach might be more profitable (Dick et al., 2015; Starr & Huang 2019; Starr et al., 2020). Multilocus genetic profile scores (MGPS), which use an additive approach by combining SNPs across multiple HPA-axis related genes to inform genetic susceptibility (Pagliaccio et al., 2015; Starr et al., 2020), have been linked to elevated cortisol levels (Pagliaccio et al., 2015), as well as interactions with stressful experiences to explain hippocampal and amygdala volumes, and

mental health outcomes among children and young adolescents (Starr & Huang, 2019). Currently, it is uncertain whether HPA MGPS will be tied to elevated peripheral biomarkers, such as cortisol levels to explain depressive symptoms among an emerging adult (18-25 years) 'at risk' population. This study will examine associations between MGPS with mental health outcomes and peripheral biomarker levels and will further assess these relationships in the context of early stressful life experiences.

**Biological Stress Response**

The HPA axis represents a complex, self-regulating neuroendocrine system, responsible for the coordination of an individual's response to stress (Chrousos, 2009). Upon activation by a stressor, neurons in the paraventricular nucleus of the hypothalamus (PVN) secrete corticotropin-releasing hormone (CRH) from terminals in the median eminence. CRH travels to the anterior portion of the pituitary gland stimulating the production and release of adrenocorticotropin (ACTH) into the blood stream. Once in circulation, ACTH travels to the adrenal cortex where it binds, effectively causing the release of glucocorticoids, or cortisol in humans (McEwen, 2002). Glucocorticoids have widespread effects throughout the central and peripheral nervous system. They target several organ systems, tissues and ultimately regulate inhibitory control over the HPA-axis. Negative feedback, within the axis, is mediated by cortisol binding to low-affinity glucocorticoid receptors (GRs), known as NR3C1, and high-affinity mineralocorticoid receptors (MRs), known as NR3C2, blunting the release of CRH and ACTH. Glucocorticoids are tightly interconnected with the immune as well as the endocrine system and are thought to play a fundamental role in maintaining allostasis (Chrousos, 2009; Yaribeygi et al., 2017).

Acute exposure to stress can be adaptive and sustainable for limited periods of time; however, more chronic activation of the HPA-axis can have significant deleterious effects

(McEwen, B. S. 2017; Yaribeygi et al., 2017) contributing to adaptation exhaustion (Wilkinson & Gooyer, 2011). Under these conditions, allostatic measures are no longer able to fluctuate appropriately to meet the demands of a chronically challenging environment and can lead to pathology. Interestingly, the impact of chronic stress is influenced by external factors (i.e., predictability, controllability, duration and intensity) as well as internal factors (i.e., biological age, genetic background, ability to cope) that together govern aspects of the stress response (Anisman, & Merali, 1999). The stress response is further influenced by events that take place early in life, as stressors during this time can increase the likelihood of stress-induced sensitization, resulting in exaggerated responses to later stressful events, and increased risk for mental health disorders in young adulthood (LeMoult et al., 2019) and later in life (Bandoli et al., 2017; Wesarg et al., 2020).

**HPA-axis Dysregulation and Early Life Stress**

Several studies have shown that cortisol levels are elevated in adolescents that have a history of exposure to abuse, neglect and other traumatic experiences, compared to those with no such history (Delahanty et al., 2005; Linares et al., 2013; Sanz-Martin et al., 2019). Indeed, a strong positive relationship exists between elevated cortisol and early life trauma experiences among adults (Butler et al., 2017). In contrast, it has also been shown that older adolescents and adults who retrospectively reported chronic stress experiences of abuse, neglect and trauma, displayed lower levels of cortisol (Elzinga et al., 2008; Pan et al., 2018; Duncko et al., 2019; Gerritsen et al., 2009). Interestingly, cortisol hyposecretion in adults that have encountered early life adversities, has been documented during periods of low stress (Carpenter et al., 2011) as well as under various challenges (Bunea et al., 2017; Elzinga et al., 2008; O'Connor et al., 2018) and throughout the day (Gerritsen et al., 2009; Power et al., 2012). Cortisol hyposecretion is thought

to be a compensatory response to repeated exposure of severe stress and hyperactivity (Heim et al., 2008), in which the HPA-axis adjusts to prolonged periods of cortisol hypersecretion by blunting cortisol reactivity resulting in low circulating levels of glucocorticoids and hyposecretion (Heim et al., 2008). In this case, the diminished activity seen in hyposecretion is suggested to be protective in nature (Agorastos et al., 2018). To date both hypersecretion and hyposecretion are associated with adverse childhood events and trauma.

Dysfunctional glucocorticoid signaling may be a fundamental mechanism through which stress leads to altered gene expression and pathophysiology related to mental illness (Cattaneo et al., 2016; Heim & Binder, 2012). Chronic exposure to early life stress can reduce the expression of glucocorticoid receptors (GR) and upregulate expression of the co-chaperone gene FKBP5 (Cattaneo et al, 2016). Under normal circumstances, when glucocorticoids bind to their receptor, the receptor gets released from the FKBP5 chaperone complex and translocates into the nucleus. Once in the nucleus, the receptor complex can modulate transcription on target genes through transcription factors (Binder, 2009). Upregulation of FKBP5 limits GR activity by inhibiting translocation of the receptor complex into the nucleus (Binder, 2009). In fact, together with early life traumatic experiences, genetic variants of the FKBP5 gene modified cortisol reactivity (Buchmann et al., 2014), and psychiatric symptoms (Comasco et al., 2015). It has been suggested that altered GR expression may be a key player in the moderation of downstream biological changes seen in mood disorders (Cattaneo et al., 2016).

**Trauma, Early Life Stress and Mental Health**

Substantial evidence indicates that trauma and early life stress are strong predictors of poor mental health in adulthood (Afifi et al., 2014; Wiens et al., 2020; Yang et al., 2020). Indeed, individuals with mood disorders tend to report a higher frequency of adverse life experiences and

trauma compared to the general population (Jaworska-Andryszewska & Rybakowski, 2019). Moreover, patients with major depressive disorders display distinctive biological and clinical differences depending on whether or not they have experienced traumatic events (Hatcher et al., 2019; Huh et al., 2017; Parsaik et al., 2017; Paterniti et al., 2017). It is well understood that in early life, stress timing is a critical factor for future mental health risk (Lupien et al., 2009). In this regard, stress during adolescence has a more profound impact on the HPA-axis compared to similar exposure to stress as an adult (Lupien et al., 2009). Moreover, traumatic events and adverse experiences during adolescence may put young adults at an increased risk for psychological impairments (De Berardis et al., 2020, Ford et al., 2006). This finding is especially problematic given that several studies within university student cohorts, have found that between 52- 84% of individuals reported experiencing at least one traumatic event (Artime et al., 2019; Ford et al., 2006; Voth Schrag & Edmond, 2018). Indeed, and as in other populations, stress and traumatic experiences among university students have been linked with increases in depression, anxiety, suicidal ideation and risk-taking behaviours (Eisenberg et al., 2007; Green et al., 2005; Lu et al., 2020).

**Depression**

While depression can occur at any age (Cheung & Dewa, 2006), adolescence and emerging adulthood is a period of particular vulnerability, as the onset of anxiety and depression tends to occur during this time (Patten et al., 2017). According to the 2012 Canadian Community Health Survey-Mental Health, individuals who are 15-24 years of age have the highest rates of anxiety and mood disorders compared to all other age groups (Statistics Canada, 2013). As such, approximately 11% of individuals aged 15 to 24 years in Canada experience depression in their lifetime; 7% in the past 12 months, and these rates are significantly higher for young females

(Findlay, 2017). Moreover, rates of depression and co-morbid anxiety among university students are estimated to be as high as 34% (Btsika, 2012). Indeed, increases in stress and stressful circumstances have been attributed to the development of mental illnesses among student cohorts. Among the factors identified, shifting support networks (Spence et al., 2020), academic stress (Sharma et al., 2021), pressure to succeed (Beiter et al., 2015), social factors (Othaman et al., 2019), independent living (Spence et al., 2020) and post-graduation plans (Beiter et al., 2015) have been highlighted as some of the most significant sources of distress contributing to the development of mental health symptomology among students.

**Monoamine Hypothesis of Depression**

The pathophysiology of depression has been traditionally focused on the monoamine neurotransmitters serotonin and norepinephrine (Boku et al., 2018). The monoamine hypothesis of depression suggests that depressed individuals have low levels of monoamines, resulting in depressive symptoms (Hirschfeld, 2000). This was further supported by evidence that depressed individuals who received antidepressant pharmacotherapy, such as selective serotonin re-uptake inhibitors (SSRI's) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) increased their monoamine levels and in turn, decreased their depressive symptoms (Arroll et al., 2005). SSRIs and SNRIs have played a fundamental role in understanding the neurobiology of depression and today are still the primary action of antidepressants. While some individuals do have improvement in their symptoms, most will not experience a clinical benefit for some time (2 - 4weeks) and for others there will be no benefit at all (Boku et al., 2018, Chen et al., 2020, Nemeroff, 2007). These findings suggest additional mechanisms and pathways are contributing to the etiology of depression, including the involvement of neurotrophic factors (Khan et al., 2019; Kishi et al., 2018; Levy et al., 2018; Mondal & Fatima, 2019; Yang et al., 2020), gut

microbiota (Flux & Lowry, 2020; Liang et al., 2018; Macedo et al., 2017), and as discussed briefly, there is extensive support for the role of stress and immune processes in depression (Engler et al., 2017; Giallusis et al., 2020; Haroon et al., 2018; Liu et al., 2019; Mac Giollabhui et al., 2020; Slavicfh et al., 2014).

**HPA-Axis Activity in Depression**

Stress and dysregulation within the HPA-axis has been recognized as a significant contributing factor to the development, severity and relapse of depression in adolescence and young adulthood (Jokinen et al., 2009; Juruena et al., 2020; Kim et al., 2020). In fact, adolescent depression has been associated with atypical responses in dexamethasone suppression testing (Guerry & Hastings, 2011; Lopez-Duran et al., 2009) and greater cortisol awakening responses (Kuhlman et al., 2020). Additionally, the cumulative impact of stressful experiences, measured through hair cortisol levels was positively associated with an increase in depressive symptoms, and found to moderate the relationship between recent life stress as well as depressive symptoms in adolescent populations (Shapero et al., 2019). Interestingly, recent studies have demonstrated a curvilinear relationship between hair cortisol concentrations and depressive symptoms in adolescents, such that both high cortisol and low cortisol levels were related to depressive symptoms (Ford et al., 2019; Morris et al., 2017). Expanding on this finding, it was reported that affective symptoms of depression related more closely to higher cortisol reactivity whereas neurovegetative symptoms of depression predicted lower cortisol reactivity in adolescents (Morris et al., 2017). Therefore, considering specific depressive phenotypes might help elucidate the cortisol-depression link.

**Inflammation and Depression**

Inflammation can play a fundamental role in the pathophysiology of depressive disorders (Dantzer et al., 2008). Indeed, depressed individuals have elevated inflammatory markers such as C-reactive protein (CRP) and pro-inflammatory cytokines including interleukin (IL)-6, IL-1B, tumor necrosis factor (TNF)-a (Haapakoski et al., 2015; Himmerich et al., 2019; Schmidt et al., 2014; Zou et al., 2018). Longitudinal research shows that higher systemic inflammation during childhood is associated with an increase in depressive symptoms during young adulthood (Khandaker et al., 2014). This link is not just correlational as administering pro-inflammatory cytokines to adults (e.g., during the course of treatment for hepatitis C and for some types of cancer) induces symptoms of depression, an effect that could be reversed by antidepressants (Dantzer et al., 2008). Likewise, a recent study demonstrates that coupling antidepressant treatment with an adjunct anti-inflammatory treatment among depressed individuals with raised serum levels of pro-inflammatory cytokines, increased antidepressant treatment responsiveness (Arteaga-Henriquez et al., 2019). Several other studies have shown that the addition of anti-inflammatory medications help to improve depressive symptoms (Fourrier et al., 2018; Kappelmann et al., 2018).

Inflammatory processes interact with many other biological systems, including monoamine and HPA activity. In fact, cytokines can stimulate HPA-axis activity whereas glucocorticoids are potent anti-inflammatory regulators. However, given that some depressed individuals display chronically high levels of glucocorticoids (Pariante, 2017) as well as inflammatory factors (Haapakoski et al., 2015; Himmerich et al., 2019; Schmidt; Zou et al., 2018), this begs the question as to how heightened inflammation and elevated cortisol co-occur. In this regard, acute administration of cytokines has been shown to elevate ATCH and cortisol in

the plasma of humans (Benson et al., 2017, Cassidy et al., 2002, Pace et al., 2007). However, excessive cortisol release due to HPA-axis hyperactivation, as in the context of chronic stress, can result to glucocorticoid resistance, rendering glucocorticoid action ineffective and the subsequent upregulation of immune activity (Cohen et al., 2012; Palumbo et al., 2020). Moreover, on a more fundamental level, interplay between the immune system and the HPA-axis may be further implicated in the pathogenesis of depression by the genes that regulate these systems.

**Genetic Basis of Depression**

Twin studies indicate that up to 40% of the depressive illnesses are heritable (Dunn et al., 2015). While genes alone are not shown to directly cause the onset of depression, possessing certain genes or gene variants, known as single nucleotide polymorphisms (SNP)s can serve as a risk factor for the development of depression (Kim et al., 2019). In this regard, a meta-analysis demonstrated an association between the glucocorticoid receptor gene *$NR_3C1$* SNP, rs41423247 with depression (Peng et al., 2018), and between variants of the *$NR_3C1$*gene with recurrent depressive episodes (Galecka et al., 2013). Moreover, variants in genes that encode CRH receptors, specifically *$CRHR_1$* and *$CRHR_2$,* were associated with treatment resistant depression (Fischer et al, 2019), suicidal behaviour (De la Cruz-Cano, 2017) and stress reactivity (Weeger et al., 2020). This risk is further compounded by the fact that certain genes increase the likelihood that environmental stress or adverse experiences could trigger the onset of depressive illness (Assary et al., 2018).

**Gene x Environment interactions -targets in the HPA-axis**

Several studies have revealed Gene x Environment interactions wherein SNPs within the HPA-axis moderate the stress-depression link (DeYoung et al., 2011, Sanabrais-Jiménez et al.,

2019). For instance, the association between stress induced cortisol reactivity and cognition strongly depend on genetic variants within the *$NR_3C1$* and *$NR_3C2$* genes (Plieger et al., 2018). Likewise, a study conducted by De Rijk et al, reported an association between the *$NR3C_2$* polymorphism (rs5522) and heightened cortisol reactivity after an in-lab stress test. In this regard, participants carrying Met/Met alleles and Val/Met alleles displayed significantly lower HPA-axis reactivity compared to Val/Val variant carriers (De Rijik et al., 2006). Beyond the $NR_3C$ genes, associations between early life trauma, depressive scores and awakening cortisol response were found to be moderated by variants in the *FKBP5* gene (rs9296158) (Kohrt et al., 2015). Similarly, *FKBP5* gene variants (rs9296158, rs4713916) have been associated with elevated depression scores and lower mean cortisol levels in individuals exposed to childhood maltreatment (Collip et al., 2013). Moreover, a recent systematic review reported that genetic variation of multiple SNPs across four HPA-axis related genes, including *CRHR1, FKBP5, NR3C1* and *NR3C2*, were found to influence the effects of maltreatment on depressive scores (Normann & Buttenschøn, 2020).

**Diathesis Stress and Differential Susceptibility- Context Matters**

The Diathesis-Stress model highlights vulnerability and has been guiding the theoretical basis of Gene x Environment studies for decades (Colodro-Conde et al., 2018; Flett et al., 1995). Within this model, individual "diathesis" or biological vulnerabilities, such as genetic factors, are thought to lead to the development of pathology when they interact with adverse experiences or environmental stressors (Broerman, 2020; Monroe & Simons, 1991). Additionally, this model suggests that individuals who are not negatively impacted by adverse events are resilient, due to protective factors such as social support or not carrying 'vulnerable' allele variants (Broerman, 2020; Monroe & Simons, 1991). While investigating gene variants within the stress diathesis

model is certainly important, one limitation is that it does not consider or account for alternative explanations, outside of a vulnerability viewpoint. According to the Differential Susceptibility perspective proposed by Belsky, certain gene variants might not be more vulnerable, but rather more influenced by or susceptible to environments 'for better or for worse' (Belsky & Puless, 2009). From this perspective, individuals with specific genes might show the greatest responses to both a positive and/or negative environment. Interestingly, in line with the differential susceptibility hypothesis, it was found that genetic susceptibility may contribute to the heterogeneity seen in the efficacy of therapeutic interventions (Bakermans-Kranenburg & Van Ijebndoorn, 2015; Belsky &Van Ijzendoorn, 2017). In addition, within this framework it has been shown that certain gene variants display enhanced sensitivity to various environments including early life stress (McQuaid et al., 2019), social rejection stress (McQuaid et al., 2015), and parenting experiences (Olofsdotter et al., 2018; Zhang et al., 2016) to influence a range of mental health and behavioural outcomes (Nilsson & Aslund. 2017; Zhang & Cao et al., 2016).

**Genetic Approaches to Understanding Depression**

Over the last two decades, single-candidate gene studies have significantly contributed to our understanding of mental illnesses such as depression. However, due to replication issues, there are concerns about false positives in this field (Border et al., 2019), in many cases this is the result of underpowered studies (Dick et al., 2015; Duncan & Keller, 2011). Moreover, given the complex biological mechanisms that underly mental illness, selecting an appropriate single SNP on a single gene that accounts for large portions of variation seen in complex pathological phenotypes, is unlikely (Dick et al., 2015; Border & Keller, 2017; Border et al., 2019; Munafò et al., 2014). Rather, many genes are likely contributing to small effects instead of single genes contributing to large ones (Culverhouse et al., 2018). Thus, in the last decade a large number of

genome-wide association studies have been conducted in relation to mental health outcomes, including depression (Dunn et al., 2015). Genome-wide studies have several advantages including identifying novel trait-variant associations, and discovering previously unsuspected biological mechanisms (Tam et al., 2019). However, they also have a number of limitations including the requirement for a very large sample size, the need to apply stringent p-value corrections to account for the vast number of genes assessed, often leaving few significant targets and the extensive expense involved in conducting these studies (Tam et al., 2019). Therefore, a number of studies have instead employed techniques to assess hypothesis driven multi-locus genetic approaches, which can address some of the issues in single-candidate gene and genome-wide studies (Starr & Huang 2019; Starr et al., 2020).

**Multilocus Genetic Approaches to Understanding Depression**

The genetic basis of depression is known to be complicated involving multiple genes at multiple loci (Shadrina et al., 2018). Various phenotypes that contribute to the heterogeneity of depression are thought to result from interlocus interactions (Shadrina et al., 2018). One common approach to explore polygenetic links to mental health is through the creation of haplotypes (Gao et al., 2009). A haplotype consists of alleles at multiple linked loci on the same chromosome, which are thought to be inherited together (Gao et al., 2009). Evidence suggests that using haplotypes to examine environmental interactions, is more powerful than using individual markers, specifically in the analysis of complex traits and disorders (Shadrina et al., 2018).

Association studies have found that a *CRHR1* haplotype comprising the rs7209436, rs110402, rs242924 SNPs impacted cortisol reactivity to an in-lab psychosocial stress test (Mahon et al., 2013, Sheikh et al., 2013). Additionally, studies examining various different haplotypes combining SNPs across the *CRHR1* gene (rs4792887, rs110402, rs242939,

rs1876831 and rs16940665) found an elevated risk for depression (Liu et al., 2006, Normann & Buttenschøn, 2020; Wasserman et al., 2009). A recent study revealed that individuals with SNPs in the *CRHR1* and *CRHR2* genes were at an increased risk of a suicide attempt when they also experienced physical neglect, emotional and/or sexual abuse (Sanabrais-Jiménez et al., 2019). Interestingly, a *CRHR1* haplotype comprising the rs110402, rs242924, rs7209436 SNPs was identified as potentially having protective effects against the risk of depression in childhood trauma exposed individuals (Kranzler et al., 2011; Polanczyk et al., 2009). However, these data conflict with a report that these *CRHR1* haplotypes in combination with environmental adversity was associated with increased risk of depressive illness (Davis et al., 2018). It is likely that various types of maltreatment and experiencing severe maltreatment are differentially moderated by these CRHR1 haplotypes to understand depression (DeYoung et al., 2011).

*NR3C2* and *NR3C1* gene haplotypes strongly influenced the associations between cortisol reactivity and cognition during acute stress (Plieger et al., 2018). Likewise, the *NR3C1* haplotypes comprising rs258747, rs6196, rs258813, rs6195 and rs9324924, rs7701443, rs4244032 SNPs were associated with an increased risk for hospital admissions due to depressive symptoms (Lahti et al., 2011). Interestingly, *NR3C2* gene haplotypes have been negatively associated with depression and cognitive vulnerability traits (e.g., rumination and hopelessness) in women (Klok et al., 2011). Likewise, the *NR3C2* haplotype comprising the rs5522 and rs2070951 SNPs was found to reduce depression susceptibility in women, conferring the notion of sex specific protective effects (Endedijk et al., 2020, Vinkers et al., 2015).

Given the function of *FKBP5,* which modulates GR activity, particular attention has been directed towards several haplotypes on the *FKBP5* gene in relation to mood disorders, especially among individuals who have experienced adversity. For example, a recent meta-analysis found

that individuals exposed to early life adversity, who also carry the T-allele of rs1360780, C-allele of rs3800373 and T-allele of rs9470080 SNPs on the *FKBP5* gene, had a higher risk of developing depression (Wang et al., 2018). Other variations in *FKBP5* genes regarded as "risk haplotypes" interacted with maltreatment and stress increasing susceptibility to depressive symptoms in adolescents (Kang et al., 2020; Yaylaci et al., 2017), anxiety in females exposed to violence (Isaksson et al., 2016) and depression and anxiety in non-clinical populations (de Castro-Catala et al., 2017).

**Multilocus Genetic Profile Scores**

An alternative approach to examining haplotypes, uses a polygenetic 'estimate' or scored approach. MGPS are created for individuals using an additive approach, combining alleles across multiple SNPs. Thus, only candidates with strong associations to behavioural and psychological phenotypes are selected, contributing to a strong biological hypothesis (Starr & Huang 2019, Starr et al., 2020). MGPSs hold higher statistical power compared to examining individual SNPs alone, which enhances predictive validity (Dick et al., 2015, Starr & Huang 2019, Starr et al., 2020). In this regard, Pagliaccio et al, combined 10 SNPs across four genes related to the HPA-axis (*CRHR*$_1$, *NR3C*$_2$, *NR3C*$_1$ and *FKBP5*), and found that MGPS predicted increased cortisol levels in lab-based stress tests among children (3-5 years old). Additionally, this same MGPSs combined with early life stress/traumatic events predicted hippocampal and amygdala volumes (Pagliaccio et al., 2014). These results demonstrate that considering multilocus genetic profiles together with early environment relates to variations in cortisol reactivity and limbic brain structures that reflect phenotypes typically seen in adulthood depression (Pagliaccio et al., 2014; 2015). Moreover, among young adolescents (age 14-17 years), this HPA MGPS moderated the relation between environmental stressors and depressive symptoms, such that adolescents with

higher MGPS and stress scores had the highest depression (Starr & Huang, 2019). Similarly, the MGPS interacted with childhood adversity to explain interpersonal dependant stress (Huang & Starr, 2020), revealing that adversity exposed adolescents with higher MGPS were more likely to encounter stress generating events triggered in part by the individual, such as disruptions in social relationships. In both of these studies, the MGPS effect accounted for more variance in the outcomes compared to individual SNPs alone (Huang & Starr, 2020; Starr & Huang, 2019).

Together these studies assessing the 10 SNP MGPS developed by Pagliaccio are more in-line with a risk or vulnerability perspective, revealing higher MGPS scores equate to increased vulnerability. However, another study examining MGPS comprising SNPs that regulate the HPA axis, showed contrasting effects. Namely, in the context of high levels of trauma, it was individuals with lower polygenic susceptibility that reported significantly higher depressive symptoms, an effect that was not observed among individuals with higher genetic 'risk' (Mullins et al., 2016). This study highlights that additional research is needed to better delineate the relationship between genes, environmental influence and the development of pathology. However, it is suggested that physiological compensatory mechanisms, age associated patterns of responding and developed coping abilities (Choi et al.,2019; Lussier et al., 2020; Starr et al., 2019) all may be driving the differential trajectories influencing mental health outcomes.

To date, there are only a handful of studies that have examined the 10 SNP MGPS created by Pagliaccio et al. None of which have focused on the emerging adult age group (considered between 18-25 years old). Emerging adulthood, which coincides with the age of university, is considered an at-risk population with estimates suggesting as many as one in three students have a mental health disorder (Auerbach et al., 2018). There is a need to identify factors that contribute to the increased risk of depression and/or anxiety experienced among emerging

adults. Thus, the overarching purpose of the current study was to examine the MGPS that comprises 10 SNPs on genes that regulate HPA-axis functioning (*CRHR1, NR3C2, NR3C1,* and *FKBP5*) among university students in relation to depressive and anxiety symptoms, as well as cortisol levels in the context of traumatic experiences. Specifically, we examined the moderating role of MGPS when considering the relations between early trauma experiences with mental health symptoms and peripheral cortisol profiles**.** We hypothesized that in the context of trauma, MGPS will interact with previous trauma scores moderating the relationship to mental health symptoms and cortisol levels; however, given the complex nature of gene x environment interactions, including the mixed evidence surrounding a vulnerability versus susceptibility perspective of HPA related MGPS, it was uncertain whether higher or lower MGPS would be most susceptible to trauma and thereby display exaggerated depression, anxiety and cortisol scores.

## Methods

### Participants

Carleton University first- and second-year undergraduate students between the ages of 17-29 years were recruited through SONA, the universities online computerized system. A wide range of participants with both normative mood and mental health symptomologies were present in the current sample. As such, all participants who met the age criteria, regardless of a current or past mental health conditions, were eligible to participate.

### Procedure

All procedures in the current study were approved by the Carleton University Research Ethics Board-B (Appendix A). Upon arrival to the laboratory, participants reviewed and

completed an informed consent package (Appendix B). Following the informed consent, participants were provided with a questionnaire booklet to complete, which was comprised of demographics and other scales of interest including the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Depression and Anxiety Stress Scale (DASS), and the short form of the Childhood Trauma Questionnaire (CTQ) (Appendix C). Once the booklet was completed participants provided a saliva sample for genotyping. Following completion of the saliva sample, participants' eligibility to provide a blood sample, for cortisol determination, was assessed (Appendix D). If participants were willing to provide a blood sample and met eligibility criteria (i.e. are not extremely nervous, have had blood drawn previously and have never had any complications, and are not taking any anti-inflammatory medication), they were given an additional informed consent form, specific to the blood draw (Appendix E). Upon signing the blood consent form, a registered phlebotomist collected a small blood sample. At the end of the laboratory session, an oral debriefing took place and participants were given an additional written debriefing form that included information about available mental health resources/supports on campus and within the Ottawa region (Appendix F). Laboratory sessions were conducted at the same time every day, between 1200h and 1530h to control for hormone diurnal patterns. Lastly, for their participation, all participants received a 2% course credit.

**Genotyping**

Samples for genotyping were collected using Saliva DNA Collection and Preservation Devices (Norgen Biotek Croporation, Thorold, Ontario, Canada). Genomic DNA was extracted from the sample collection kit in accordance with the manufacturer's instructions and diluted to approximately equal concentrations (20 ng/μL). Specific SNPs were chosen to develop the MGPs HPA risk score developed by Pagliaccio et al. 2014, including SNPs on the: FKBP5 gene,

rs1360780; CRHR1 gene, rs110402, rs4792887, rs242941, rs1876828, rs242939; NR3C1 gene, rs41423247, rs10482605, rs10052957; and NR3C2 gene, rs5522. Samples were sent for genotyping to McGill University and Génome Québec Innovation Centre (Montreal, Canada). A multiplex PCR was performed on 20ng of template genomic DNA in a 5uL reaction mixture containing: 0.1uL (0.5 U) HotStar Taq enzyme (QIAGEN), 0.625uL of 10X HotStar Buffer, 0.325uL of 25mM (total) MgCl2, 0.25uL of 10mM dNTP mix, 0.55uL of forward and reverse primer pool (1uM) and 1.15uL of water. The amplification cycling: 95c 15min, 45x (95c 20sec, 56c 30sec, 72c 60sec), 72c 3min, hold 4c. PCR reactions are run on QIAxcel (QIAGEN) to assess the amplification (1uL of PCR in 9uL of DNA Dilution Buffer (QIAGEN)). This is followed by a shrimp-alkaline-phosphatase treatment to remove the unused nucleotides  Next, a primer extension reaction (iPLEX Gold) is performed with 0.94uL of extension primer mix, 0.2uL of iPlex Terminator, 0.2uL of iPlex Buffer, 0.041uL of iPlex Thermo Sequenase and 0.619uL of water. The products are desalted using 6mg of resin (Agena Bioscience) and spotted on a 384-point SpectroCHIP (Agena Bioscience) using a nanodispenser. The distinct masses were determined by mass-spectrometry and data were analyzed using MassARRAY Typer Analyser software. Genotyping calls were revised and attributed using the Agena TYPER software. Primer sequences are found in Table 1.

**Table 1:**

*Gene Primer Sequences*

| Genes | Forward | Reverse | Probe |
|---|---|---|---|
| FKBP5 | rs1360780: ACGTTGGATGAGCTGCAAGTCCCCAAAATT | rs1360780: ACGTTGGATGTGCCAGCAGTAGCAAGTAAG | rs1360780: GCTTTCACATAAGCAAAGTTA |
| CRHR1 | rs110402: ACGTTGGATGGGCATTTTCTAAACACAGAGG | rs110402: ACGTTGGATGAACCTTCCACAGAGCAAGAG | rs110402: cccgccACACAGAGGACTGGTGTTG |
| | rs4792887: ACGTTGGATGCCCAGAGAAGCCCTTGACT | rs4792887: ACGTTGGATGTGGCCAGCAGATGGAAAGTG | rs4792887: ggggCAGTGTGGCCAAGATC |
| | rs242941: ACGTTGGATGGGCTTGGCAGCTGCTAAGG | rs242941: ACGTTGGATGAAGAGTGGACAGACAAGCC | rs242941: cccacccaTGAAGAGGCTGCCCCCAC |
| | rs1876828: ACGTTGGATGAGCAGCATACCCCTAGGGAC | rs1876828: ACGTTGGATGGATTGTCTAGAGCCTTCTCC | rs1876828: ggaaCCCTAGGGACCTAGGA |
| | rs242939: ACGTTGGATGTGAGTTGGTCACTCCTTCAC | rs242939: ACGTTGGATGACAGGGCCATGACCACAGAC | rs242939: ggtgCACTCCTTCACTTGGAA |
| NR3C1 | rs41423247: ACGTTGGATGTAGACACAGGTCTTGCTCAC | rs41423247: ACGTTGGATGTTTTGCACCATGTTGACACC | rs41423247: gggAGACAAGTTATGTCTGCTGAT |
| | rs10482605: ACGTTGGATGTTGGTGACGCTTGGCAACTG | rs10482605: ACGTTGGATGAGAGAGACCAGGTCGGCCC | rs10482605: CAACTCCCCAGGAAAA |
| | rs10052957: ACGTTGGATGCAGAGGTGGAAATGAAGGTG | rs10052957: ACGTTGGATGGACTCAATGTTATTATAACCC | rs10052957: gggaAAGGTGATGTATTCAGACTCA |
| NR3C2 | rs5522: ACGTTGGATGTGCAAACAGACGGGCTTTTC | rs5522: ACGTTGGATGTTATGTCTGACTCTGGGAGC | rs5522: ccgggACATGATAGGGCTTTTAACAA |

**Multilocus Genetic Profile Scores**

To create the total MGPS score, Table 2 comprises the scoring values developed by Pagliaccio et al. 2014.

**Table 2:**

*Single Nucleotide Polymorphism Numeric Values for MGPS*

| ***Gene*** | ***SNP*** | ***Alleles*** | ***MGPS Coding*** |
|---|---|---|---|
| *FKBP5* | *rs1360780* | *C >T* | *CC = 0, CT = 1, TT = 1* |
| *CRHR1* | *rs110402* | *C >T* | *CC = 0, CT = 0, TT = 1* |
| *CRHR1* | *rs4792887* | *C >T* | *CC = 0, CT = .5, TT = 1* |
| *CRHR1* | *rs242941* | *G >T* | *GG = 0, GT = 1, TT = 1* |
| *CRHR1* | *rs1876828* | *G >A* | *GG = 0, GA = 1, AA = 1* |
| *CRHR1* | *rs242939* | *A >G* | *AA = 0, GA = 1, GG = 1* |
| *NR3C1* | *rs41423247* | *G >C* | *GG = 0, GC = 1, CC = 1* |
| *NR3C1* | *rs10482605* | *T >C* | *TT = 1, CT = 0, CC = 0* |
| *NR3C1* | *rs10052957* | *G >A* | *GG = 0, GA = 0, AA = 1* |
| *NR3C2* | *rs5522* | *A >G* | *AA = 0, GA = 1, GG = 1* |

*Table 2: Alleles = Alleles present in current sample (Major > Minor)*
*Coding = Numeric values given to genes to make up MGPS*

**Measures**

***Depressive symptoms.*** Depressive symptoms were assessed using the 21-item version of the Beck Depression Inventory or BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) All items range from low (score of 0) to high (score of 3) depressive symptoms. This included one item assessing suicide ideation. Items in this scale were assessed by summing scores for a total depression score ($\alpha$ =.88)

***Anxiety symptoms*.** Anxiety symptoms were assessed using the 21-item version of the Beck Anxiety Inventory or BAI (Beck & Steer, 1990). The BAI is a scale used to assess symptoms of anxiety that have caused disturbances in the past week (i.e., current symptoms of anxiety). All 21 items are scored on a range from 0-3, 0 indicating that they have not experienced that symptom in the past week and 3 suggesting that they experienced that symptom frequently. Items in this scale were assessed by summing scores for a total anxiety score. ($\alpha$ =.89)

***Depression anxiety stress scale.*** Depression, anxiety and stress symptoms were assessed using the 21-item Depression, Anxiety and Stress Scale, version 21 or DASS-21 (Lovibond & Lovibond, 1995). The DASS-21 assesses 3 areas of symptoms that are common to mood, anxiety and stress disorders. The 21 items are separated into 3 scales. The first scale assesses negative emotional states associated with depression (e.g. dysphoria, hopelessness, devaluation of life, self-depreciation, lack of interest/involvement, anhedonia, and inertia). The second assesses negative emotional states associated with anxiety (e.g. autonomic arousal, skeletal muscle effects, situational anxiety, and the subjective experience of anxious affect). The third assesses negative emotional states associated with stress by asking questions regarding levels of chronic non-specific arousal (e.g. difficulty relaxing, nervous arousal, impatience, irritability and

agitation). For the current study, the stress subscale was of interest, and was assessed by summing scores for a total stress score ($\alpha$ =.87).

***Previous Trauma Experiences.*** Previous experiences of adversity were assessed using the 25-item Childhood Trauma Questionnaire or CTQ-Short Form (Bernstein et al., 1994). The CTQ assesses traumatic experiences that occurred prior to the age of 18. The 25 items are separated into categories assessing various forms of trauma such as physical abuse ($\alpha$ =.86), emotional abuse ($\alpha$ =.85), sexual abuse ($\alpha$ =.86) and emotional neglect ($\alpha$ =.93). A total trauma score will be assessed through summing total scores to represent an overall total trauma score ($a$ = .90) in addition to each separate subscale score.

**Blood Collection**

Participant blood samples were collected into chilled EDTA coated Vacutainer tubes by a registered nurse/phlebotomist. Upon collection, blood samples were immediately placed on ice and centrifuged for 20 minutes at 4°C and 1000g. Plasma was then aliquoted into Eppendorf tubes and frozen at -80°C until required for cortisol assays. See Appendix (G) for complete blood sampling information, including amounts collected.

***Cortisol assay.*** Plasma cortisol was determined in duplicates by radioimmunoassay (RIA) using a Cortisol Coated Tube RIA kit (125I) obtained from MP Biomedicals LLC. The assay was performed according to the manufacturer's instructions. The inter- and intra-assay variability is expected to be less than 10% and the minimum detectable concentration was 16 µg/dL.

**Statistical Analyses**

Statistical analyses were performed using IBM SPSS Statistic Premium for Mac 26.0 (SPSS Science, Chicago, Illinois, USA). Statistical significance was determined at $p < .05$ (two-

tailed). In order to clean data, all items were checked for out of range scores due to human error in data entry as well as all outliers (+/- 3.29) were brought into range for the analyses. Two members of the research group reviewed the data as it required manual entry into SPSS. To begin the data analysis, we ran descriptive statistics on participant demographics. Chi Squares were conducted to examine ethnicity differences according to genotype distribution. Due to significant population stratification effects (described in detail in Appendix H), the largest homogeneous ethnic group, European/White individuals was retained to assess relationships with MPGS scores. Pearson correlation analyses were performed to examine the direct associations between MGPSs with mental health symptoms, and cortisol levels. Moderation analyses were conducted using model #1 in PROCESS (Hayes, 2012) to examine if MGPS moderates the relation between experiences of trauma with mental health symptoms and cortisol levels.

# Results

## Participant Demographic Information

The current study comprised 505 undergraduate students with a mean age of 19.36 years (SD = 2.12, Range = 17-29). Of participants, 22.6% identified as male (*n* = 114), 76.8% as female (*n* = 388) and 0.6% as gender non-conforming (*n* = 3). Various socioeconomic backgrounds were reported by participants, with 14.2% (*n* = 72) reporting an annual household income of less than $45,000, 38.4% reporting an income between $45,000 and $105,000 (*n* = 194), and 25.9% reporting an income above $105,000 (*n* = 131). Furthermore, this sample included a diverse range of self-reported ethnicities with the majority 60.2 % identifying as White/European (*n* = 304), followed by 10.5 % Black (e.g., African, Haitian, Jamaican, Somali; *n* = 53), 7.7% Arab/West Asian (e.g., Armenian, Egyptian, Iranian, Lebanese, Moroccan; *n* = 39), 5.9% Asian (e.g., Chinese, Japanese, Korean; *n* = 30), 5.7% South Asian (e.g., East Indian, Pakistani, Punjabi, Sri Lankan; *n* = 29) and 8% reported a mixed ethic background (*n* = 40).

## Mental Health and Traumatic Experiences

Over one third of the undergraduate sample (34.5%) self-reported having a current mental health condition. Of those who reported having a mental health condition 82.2% (*n* = 143) were female and 16.1% (*n* = 28) were male. Of those with a mental health condition, 40.8% reported anxiety, 29.3 % reported having comorbid anxiety and depression, 15.5% reported depression, and 14.3% reported struggling with other conditions. In line with these findings, approximately twenty percent of participants *(n* = 100) reported receiving treatments for a mental health condition. Specific treatments, reported by participants, can be found in Table 3.

**Table 3:**

*Self-Reported Mental Health Conditions and Treatment*

| **Mental Health Variables** | *n* | % |
|---|---|---|
| Current mental health condition | 174 | 34.5 |
| Currently being treated for a mental health condition | 100 | 19.6 |
| **Treatment Type** | | |
| Anti-depressant medication | 24 | 4.7 |
| Therapy | 22 | 4.3 |
| Therapy + medication | 18 | 3.5 |
| Anti-anxiety medication | 2 | 0.4 |
| Other | 29 | 5.7 |

Approximately 43.5% ($n$ = 219) of our sample reported experiencing some form of trauma before the age of 18 years. Among females, 42.6% ($n$ = 165), reported experiencing abuse and/or neglect, whereas of males, 45.6% ($n$ = 52) experienced these events, an effect that did not significantly differ, $t(499) = -.27$, $p = .35$. In terms of specific forms of trauma, 40.3% ($n$ = 203) of participants reported experiences of emotional abuse. Of those that identified as female, 41.3% ($n$ = 160) reported experiencing emotional abuse, and of males, 36% ($n$ = 41) reported trauma in the form of emotional abuse, which did not differ significantly $t(499) = 1.26$, $p = .15$. Twenty percent of students reported trauma in the form of physical abuse, in which, significantly more males experienced physical abuse (28.9%, n = 33), compared to females 17.3% ($n$ = 67), $t(499) = -2.24$, $p = .003$. Moreover, approximately one forth, 24% ($n$ = 121) of students reported experiences of sexual abuse, which was higher among females 27.6% ($n$ = 107) than males 11.4% ($n$ = 13), $t(499) = 3.36$, $p = <.001$. Lastly, when examining emotional neglect, 43.5% ($n$ = 219) of students reported this experience, which affected a similar proportion of females 42.4% ($n$ = 164) and males 46.5% ($n$ = 53), $t(499) = -.78$, $p = .44$.

**Genotype Distributions**

**Ethnicity and Effects of Population Stratification**

As previously reported, the current study of 505 individuals comprised an ethnically diverse sample. Due to known issues surrounding population stratification in genetics, we first examined genotype distribution on each individual SNP according to ethnicity and found significant chi-squares for 8 of the 10 SNPs assessed (shown in Table 4). Ideally, if population stratification was not present, a mixed ethnic sample could have been used for MGPS analyses. In this regard, it would have been of particular interest to assess the influence of genotype across ethnic groups, however, this was precluded owing to the small number of participants in each

ethnic minority group. Moving forward, for analyses assessing relationships to the MGPS, only the largest homogenous ethnic sample could be used, which comprised $n$ = 282 White/European individuals. For detailed information on ethnicity according to genotype distributions, see Appendix H.

**Table 4:**

*SNP Genotype Distribution According to Ethnicity*

| SNP | $X^2$ | *df* | *n* | *p* |
|---|---|---|---|---|
| FKBP5 – rs1360780 | 21.51 | 16 | 448 | .16 |
| CRHR1- rs110402 | 123.06 | 16 | 475 | <.001 |
| CRHR1_rs4792887 | 73.98 | 16 | 492 | <.001 |
| CRHR1_rs242941 | 85.65 | 16 | 483 | <.001 |
| CRHR1_rs1876828 | 60.42 | 16 | 490 | <.001 |
| CRHR1_rs242939 | 93.45 | 16 | 495 | <.001 |
| NR3C1_rs41423247 | 40.39 | 16 | 483 | .001 |
| NR3C1_rs10482605 | 36.71 | 16 | 463 | .002 |
| NR3C1_rs10052957 | 26.82 | 16 | 453 | .04 |
| NR3C2_rs5522 | 16.28 | 16 | 483 | .43 |

**Final Sample SNP Distributions**

Table 5 includes the genotype distributions for the final sample retained for examination of relationships.

**Table 5:**

*Final Sample Genotype Distributions of HPA-Axis SNPs*

| SNP | Major Allele *n* (%) | Heterozygote *n* (%) | Minor Allele *n* (%) | Missing Data *n* (%) |
|---|---|---|---|---|
| FKBP5 - rs1360780 | 138 (45.4) | 109 (35.9) | 22 (7.2) | 35 (11.5) |
| CRHR1- rs110402 | 95 (31.3) | 147 (48.4) | 42 (13.8) | 20 (6.6) |
| CRHR1- rs4792887 | 240 (78.9) | 54 (17.8) | 4 (1.3) | 6 (2) |
| CRHR1- rs242941 | 123 (40.5) | 144 (47.4) | 25 (8.2) | 12 (3.9) |
| CRHR1- rs1876828 | 175 (57.6) | 106 (34.9) | 15 (4.9) | 8 (2.6) |
| CRHR1- rs242939 | 255 (83.9) | 43 (14.1) | --- (0) | 6 (2) |
| NR3C1- rs41423247 | 120 (39.5) | 131 (43.1) | 38 (12.5) | 15 (4.9) |
| NR3C1- rs10482605 | 206 (67.8) | 66 (21.7) | 9 (3) | 23 (7.6) |
| NR3C1- rs10052957 | 129 (42.4) | 122 (40.1) | 25 (8.2) | 28 (9.2) |
| NR3C2- rs5522 | 227 (74.7) | 59 (19.4) | 5 (1.6) | 13 (4.3) |

**MGPS Scores**

HPA-axis genetic profile scores were computed following procedures outlined in the work of Pagliaccio et al. (2014), and in Table 2. SNPs were coded to reflect the presence (1) or absence (0) of previously identified 'vulnerable' genotypes. Additionally, (.5) codes were assigned to heterozygotes when allelic rather than genotypic effects were anticipated. Participant's SNP codes were then summed to create a total MGPS score, where a higher MGPS reflected more genetic 'risk'. The MGPS had a possible range from 0-10, however, in the current sample the actual range was 1- 6.5 (M = 3.72, SD = 1.093). Upon calculating the MGPS for each participant, up to 2 missing genotypes (20%) per participant were allowed, which was in-line with the protocol developed by prior MGPS methods (Pagliaccio et al., 2014, Starr & Huang 2019, Starr et al., 2020). A breakdown of the MGPS distributions for participants are shown in Table 6.

**Table 6:**

Sample Distribution of Multilocus Genetic Profile Scores

| **Multilocus genetic profile scores** | ***n*** | **%** |
|---|---|---|
| 1 – 1.5 | 4 | 1.3 |
| 2 – 2.5 | 34 | 11.2 |
| 3 – 3.5 | 91 | 29.9 |
| 4 – 4.5 | 95 | 31.3 |
| 5 – 5.5 | 51 | 16.9 |
| 6 – 6.5 | 7 | 2.3 |

**Correlations**

Relationships between multilocus genetic profile scores (MGPS) and total scores of depression (BDI), anxiety (BAI), stress (DASS-Stress), previous trauma experiences (CTQ) and cortisol levels, are highlighted in Table 7. As expected, depression, anxiety, stress and all forms of trauma were positively associated with one another. Cortisol did positively relate, albeit weakly to anxiety scores. However, no associations were found between the MGPS and cortisol levels or mood scores, although the MGPS tended to have a weak negative association with anxiety scores, $p = .06$.

**Table 7:**

*Zero-Order Pearson Correlations Between Multilocus Genetic Profile Scores, Mood, Psychosocial and Biological Measures.*

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. MGPS | ____ | | | | | | | | | |
| 2. Anxiety | -.110 | ____ | | | | | | | | |
| 3. Depression | -.029 | .606** | ____ | | | | | | | |
| 4. Stress | -.057 | .641** | .688** | ____ | | | | | | |
| 5. Total Trauma | .020 | .188** | .344** | .307** | ____ | | | | | |
| 6. Emotional Abuse | -.054 | .188** | .281** | .267** | .871** | ____ | | | | |
| 7. Physical Abuse | .008 | .207** | .220** | .232** | .652** | .543** | ____ | | | |
| 8. Sexual Abuse | .082 | .178** | .197** | .209** | .463** | .273** | .288** | ____ | | |
| 9. Emotional Neglect | .019 | .136** | .355** | .268** | .844** | .663** | .387** | .207** | ____ | |
| 10. Cortisol | -.125 | .160* | .095 | .111 | .035 | .072 | -.065 | .149 | -.027 | ____ |

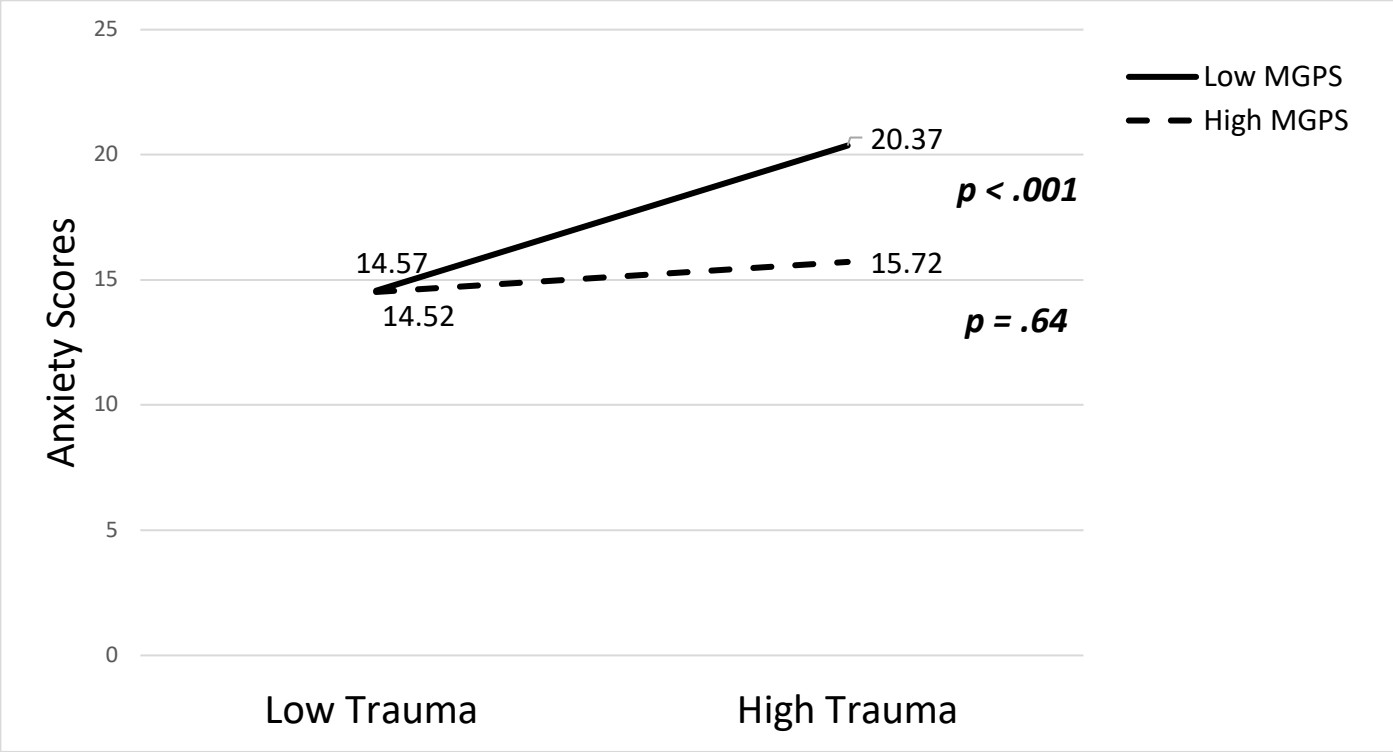
**p < .05, **p < 0.01*

**Moderation Analyses**

To examine whether MGPS scores would relate to outcomes of interest in the context of traumatic experiences, moderation analyses were conducted. For anxiety symptoms, while the overall model was significant, $R^2 = 0.56$, $F_{(3, 277)} = 5.48$, $p = 0.001$, likely due to the strong association between total trauma scores and anxiety symptoms in this model, $p = .008$, the Trauma x MGPS interaction only approached significance, $p = .053$. As shown in Figure 1, at low levels of trauma, anxiety scores were also fairly low regardless of MGPS scores. However, in the context of high levels of trauma, individuals with low MGPS scores displayed significantly elevated anxiety scores, $p < .001$, an effect not found for individuals with high MGPS scores, $p = .64$. It was also of interest to assess whether specific forms of trauma would interact with MGPS scores to understand anxiety. When assessing these relationships, only emotional neglect significantly interacted with MGPS to predict anxiety, see Table 8 for detailed statistics on each type of trauma assessed.

**Figure 1.**

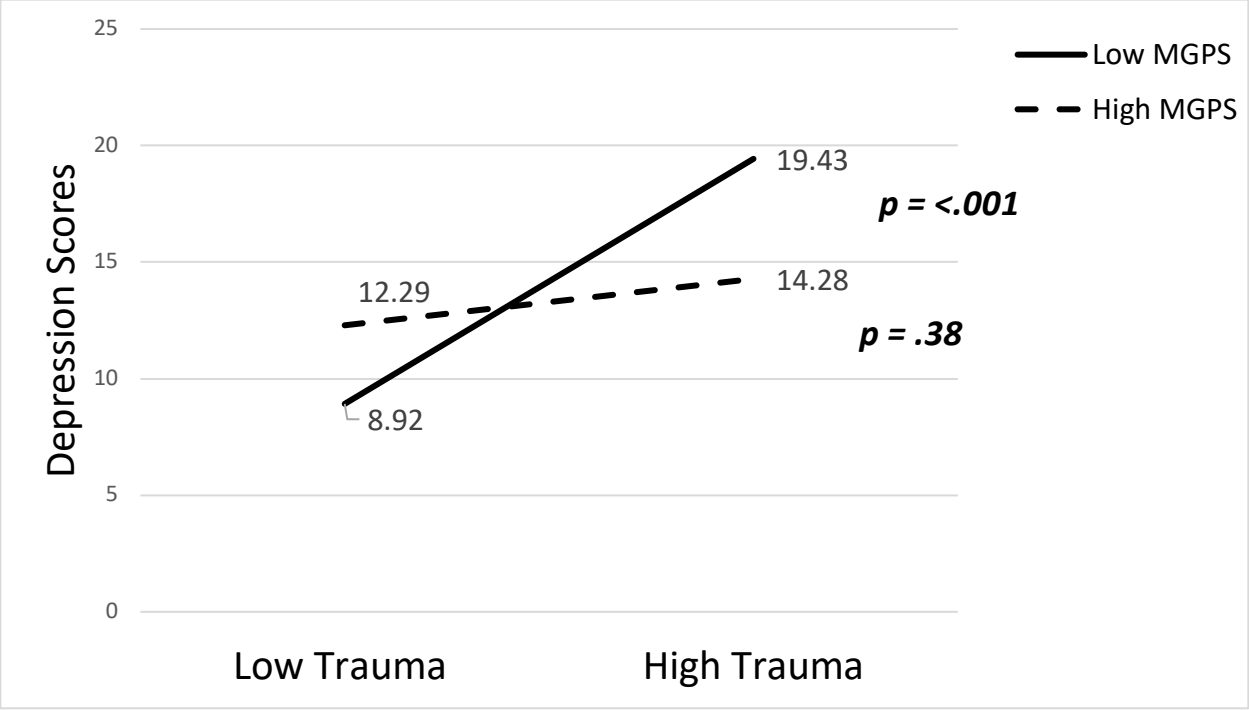
*Interaction Between MGPS and Total Trauma Scores in Relation to Anxiety Scores.*



In addition to anxiety, moderation analyses were used to explore if MGPS scores would relate to depressive symptoms among individuals with experiences of trauma. Upon examining total trauma scores, the overall model was significant $R^2 = .180$, $F_{(3, 277)} = 20.35$, $p < 0.001$. More specifically, the Trauma x MGPS interaction was significant, $p <. 001$. As shown in Figure 2, as trauma scores increased depression scores were appreciably higher among individuals with lower MGPS scores, $p <. 001$. This effect was not observed among individuals with high MGPS scores $p = .38$. In line with these findings, when assessing the different types of traumatic events experienced, MGPS scores moderated the association between each form of trauma to depression symptoms (Table 8).

**Figure 2.**

Interaction *Between MGPS and Total Trauma Scores in Relation to Depression Scores.*



It was also of interest to examine if MGPS scores would relate to stress levels in the context of earlier traumatic events. A moderation analysis revealed a significant overall model, $R^2 = 0.105$, $F_{(3, 277)} = 10.87$, $p < 0.001$. Furthermore, a significant interaction between total trauma x MGPS scores existed, $p = .006$. As shown in Figure 3, individuals with low MGPS report experiencing significantly higher levels of stress in the context of high trauma, $p < 0.001$ whereas those with higher genetic profile scores do not show this significant increase in stress when encountering high levels of trauma, $p = .25$. When further exploring this relationship according to the different types of trauma, it was found that MGPS scores only moderated the relation between emotional neglect and stress scores (Table 8).

**Figure 3.**

*Interaction Between MGPS and Low and High levels of Trauma in Relation to Stress Scores.*

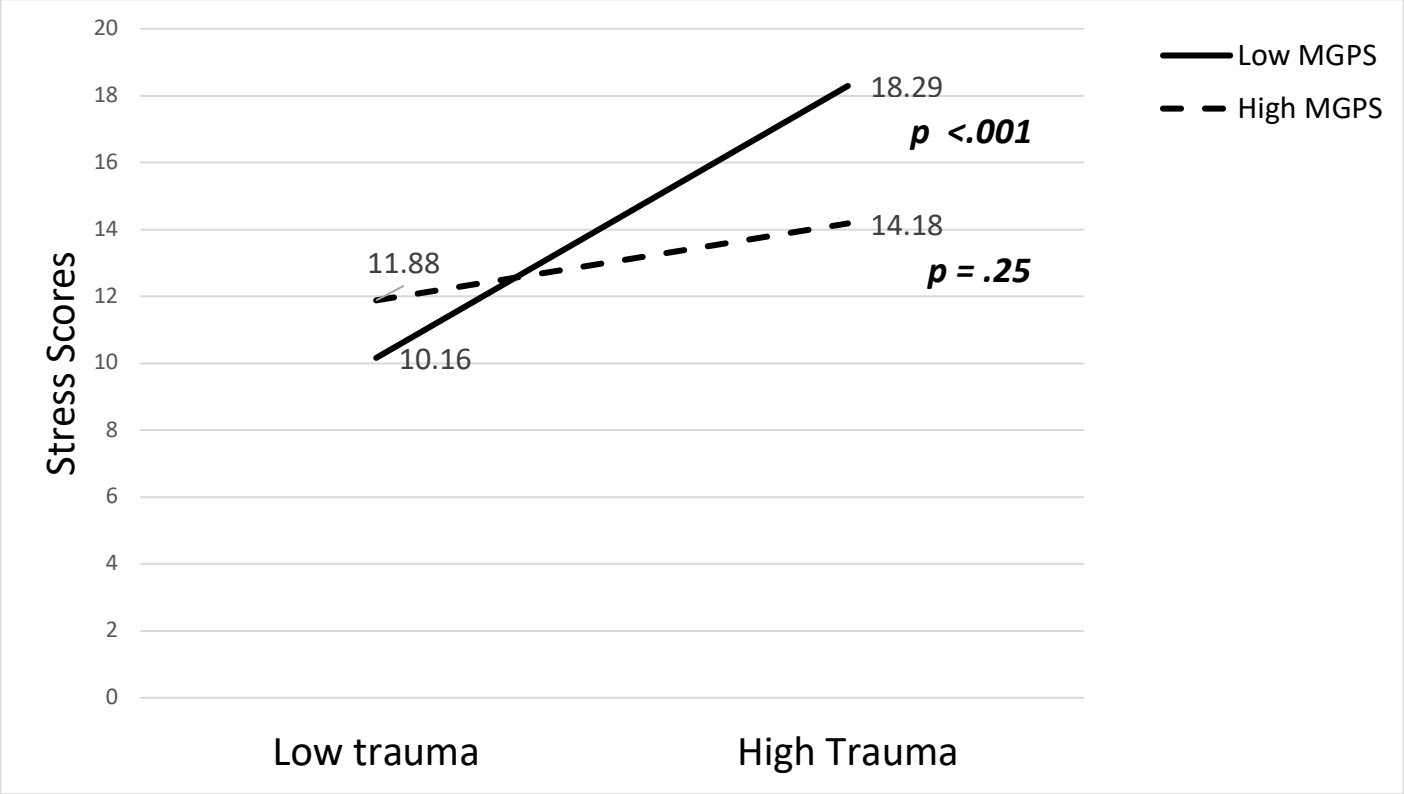


**Table 8:**

*Moderation Analyses for MGPS x Trauma Subscales on Anxiety, Depression, and Stress Outcomes*

| **Trauma Subscales** | $R^2_{Change}$ | *F* | *df* | *p* |
|---|---|---|---|---|
| **Anxiety** | | | | |
| Total Trauma x MGPS | .01 | 3.79 | 1, 277 | **.05*** |
| Physical Abuse x MGPS | .01 | 3.24 | 1, 277 | .07 |
| Emotional Abuse x MGPS | .002 | .64 | 1, 277 | .42 |
| Sexual Abuse x MGPS | .002 | .65 | 1, 277 | .42 |
| Emotional Neglect x MGPS | .02 | 4.51 | 1, 277 | **.03**** |
| **Depression** | | | | |
| Total Trauma x MGPS | .06 | 19.10 | 1, 277 | **< .001***** |
| Physical Abuse x MGPS | .03 | 9.05 | 1, 277 | **.002***** |
| Emotional Abuse x MGPS | .04 | 11.16 | 1, 277 | **.001***** |
| Sexual Abuse x MGPS | .02 | 5.07 | 1, 277 | **.03**** |
| Emotional Neglect x MGPS | .04 | 12.83 | 1, 277 | **< .001***** |
| **Stress** | | | | |
| Total Trauma x MGPS | .02 | 7.42 | 1, 277 | **.006***** |
| Physical Abuse x MGPS | .004 | 1.26 | 1, 277 | .26 |
| Emotional Abuse x MGPS | .01 | 3.49 | 1, 277 | .06 |
| Sexual Abuse x MGPS | .005 | 1.53 | 1, 277 | .21 |
| Emotional Neglect x MGPS | .03 | 10.56 | 1, 277 | **.003***** |

*$p \leq .05$, **$p \leq 0.05$, *** $p \leq 0.001$*

Lastly, it was of interest to examine whether MGPS scores would relate to cortisol levels in the context of traumatic experiences, as such a final moderation analysis was conducted. For cortisol levels, the overall model was not significant, $R^2 = 0.023$, $F_{(3, 136)} = .937$, $p = .424$, nor was there an interaction between total trauma x MGPS interaction to explain cortisol, $p = .56$. As this association was not close to significance, specific subtypes of trauma were not assessed further in relation to cortisol and the MGPS.

## Discussion

### Depression Anxiety and Trauma

In the present study, a current mental health diagnosis was reported by approximately thirty five percent of undergraduate students. This finding was not surprising as reports indicate that young adults aged 18 to 24 years report the highest rates of depression and anxiety compared to other age groups (Gomes et al., 2019). Moreover, approximately one in three university students are reported to meet the DSM-IVs diagnostic criteria for a mental health disorder (Auerbach et al., 2018). Among those who reported having a mental illness, only about half of the students were receiving treatments. These findings are of concern but not uncommon, as low levels of help seeking behaviours among university student cohorts is frequently reported (Eisenberg et al., 2009; Laidlaw et al., 2016; Rafal et al., 2018; Shahwan et al., 2020), and has been attributed to barriers in help seeking such as stigma (Eisenberg et al., 2009; Laidlaw et al., 2016) as well as poor mental health literacy (Rafal et al., 2018; Shahwan et al., 2020).

Approximately forty five percent of the undergraduate students in the current study reported experiencing early experiences of abuse or neglect. These data are in line with earlier reports comprising university student cohorts, wherein 30% - 64.7% of students reported experiencing at least one trauma in the form of abuse or neglect (Chen et al., 2017; Colburn et al., 2021; Fu et al., 2018). When examining trends in the experiences of trauma based on gender, the present findings were in line with current evidence (Pruessner et al., 2021; Vila-Badia et al., 2021), such that females reported higher instances of sexual abuse compared to males, whereas males reported higher instances of physical abuse compared to females. Regardless of gender or the specific subtypes, the impacts of trauma can have widespread physical and psychological implications, substantially influencing vulnerability to mental health disturbances. Indeed

trauma, is one of the strongest predictors of poor well-being, as well as prognosis, and response to treatments (Noteboom et al., 2021).

**Trauma and Multilocus Genetic Profile Scores**

In the current study we observed interactions between the MGPS score with trauma experiences in relation to stress, anxiety and depression symptoms. Specifically, when exposed to high levels of trauma, individuals with lower MGPS, appeared most affected, reporting higher stress, depressive, and anxiety symptoms compared to those with higher MGPS scores. While initially this was perplexing, others have similarly found an increase in depression symptoms among those with lower multilocus polygenic scores in the context of high trauma experiences, an effect that was not observed among individuals with higher genetic risk (Mullins et al., 2016). However, the few reports that have examined this particular MGPS, in the context of trauma, show it is those with the highest MGPS that display increased levels of interpersonal dependant stress (Starr & Huang, 2020) and depressive symptoms (Starr & Huang, 2019). Importantly, there are several factors that need to be considered when trying to account for the discrepancies in findings, as differences in the assessment of phenotypic traits, as well as the sample composition, sample size and age have all been suggested as possible contributing factors (Bogdan et al., 2018). In fact, it has been cautioned that the MGPS associations may change across development, as twin studies indicate that the importance of environmental factors in the development of depressive symptoms shifts with age (Starr et all., 2019). Expanding on this idea, emerging evidence suggests that age-associated patterns of responding highlight that early-adolescence (between 10-15 years) may be a period when symptoms linked to genetic liability for depression are most commonly observed (Lussier et al., 2020; Rice et al., 2019). These data suggest that fluctuations in the reporting of depressive symptoms beyond these times points may

reflect learned coping mechanisms rather than genetic vulnerability or susceptibility (Lussier et al., 2020). Notably, all MGPS studies that utilized the Pagliaccio 10 SNP MGPS were conducted only in younger children and youth (ages 3-17). Taken together, the later timing of assessment in the current study (18-29 years) could potentially reflect a learned coping or compensatory effect to help explain the divergent findings.

We observed very consistent interactive effects between the MGPS with all forms of trauma (i.e., emotional abuse, physical abuse, sexual abuse, and emotional neglect) to explain depressive symptoms. Specifically, individuals with lower MGPS consistently reported higher depressive symptoms than individuals with higher MGPS scores in the context of high trauma exposure. Interestingly, when examining stress and anxiety symptoms, it was only emotional neglect that interacted with MGPS scores. Emotional maltreatment does have particularly large associations with the development of anxiety (González-Díez et al., 2017), depression (Humphreys et al., 2020) and physiological dysregulation (Müller et al., 2019). Perhaps explaining our findings, emotional neglect, in particular, has been associated with poor social functioning, impaired attachment, increases in fear and avoidance behaviour, and anxiety (Carr et al., 2013; Humphreyes et al., 2020; Müller et al., 2019; Nanda et al., 2016).

### *Genetic Vulnerability Versus Susceptibility*

In childhood-trauma associated disorders such as depression (Coleman et al., 2020) and anxiety (Purves et al., 2017), the relative heritability is suggested to be low to moderate with studies reporting a range anywhere from 18% - 50% (Kendall et al., 2021; Morneau-Vaillancourt et al., 2021). These heritability percentages highlight that other mechanisms, such as environmental factors, may be largely influential in determining psychological outcomes. Indeed, in the context of traumatic events, genetic heritability to mental health outcomes is a

complex and poorly understood relationship (Coleman et al., 2020; Kalin, 2021; Reynolds, 2021). The current findings, revealing that lower genetic scores were associated with higher symptomology in the context of higher trauma, highlight the importance of questions regarding risk versus susceptibility and the large role the environment plays in determining mental health trajectories. Indeed, it is suggested that trauma may be particularly important to the development of depression for those with lower genetic susceptibility compared to those with higher genetic susceptibility, as it causes this individual to cross the liability threshold of disease that otherwise they would not have crossed over in the absence of trauma (Mullins et al., 2016).

Emerging evidence in support of a differential susceptibility model, have demonstrated that the genes included in the Pagliaccio MGPS comprise variants that are malleable to environmental context and influences. Specifically, FKBP5 has been characterized for its role in healthy as well as pathological development depending on the surrounding environmental circumstances (Pérez-Pérez et al.,2018; Zheng & Gan, 2018). Likewise, CRHR1 has been examined from a differential susceptibility perspective, highlighting that genotypic variation can predict positive outcomes in the context of a more supportive environment (Allegrini et al., 2017; Leighton et al., 2017). Other genes included in the MGPS score including NR3C1and NR3C2, have been identified as candidate plasticity genes (Leighton et al.,2017; Zheng et al., 2018). Overall, these findings underscore the importance of taking into consideration the role of the environment and contextual factors when assessing gene variants.

In the current study, individuals with the highest MGPS scores did not report an increase in symptoms of depression, stress and anxiety in the context of high levels of trauma. This begs the questions as to whether being more sensitive to our environments can encourage the development of tools to enhance coping. Indeed, evidence suggests that individuals with high

genetic susceptibility benefit from preventative interventions aimed at developing coping, and in turn are able to successfully mitigate negative outcomes (Choi et al., 2019). Expanding on this idea, emerging evidence has suggested that psychological resilience enhances several protective factors that have been associated with reductions in depressive symptoms (Tang et al., 2020), anxiety symptoms (Amendola et al., 2021) and stress levels (Cabanach et al., 2021) among adolescents. Of course, it is also entirely possible that the experience of trauma may be such a strong environmental risk factor that it renders the influence of genetics negligible (Mullins et al., 2016). Indeed it is possible that environmental influence may "set boundaries" on the impact of genes with higher stressful environmental circumstances over-riding any predisposition to genetic influence (Pagliaccio et al., 2014).

**Compensatory Mechanisms**

When a stressor becomes chronic, such as abuse and neglect in the home, the adversity can disrupt the body's ability to regulate its responses to stress and can lead to compensation or an increase in compensatory mechanisms. As such, individuals with the highest vulnerability perhaps should display the highest levels of stress hormones such as cortisol. In the current study, we did not observe this, as individuals with high MGPS did not show elevated cortisol levels. However, this finding is not unique and is in-fact in line with evidence showing that among individuals who have experienced high levels of trauma, cortisol levels may become blunted as a form of compensation to deal with chronically high levels. Losing the adaptability (rise and fall) of cortisol may, in fact, be protective and help encourage physiological resilience as well as coping (Agorastos et al., 2018; Young et al., 2021). This finding has been replicated throughout several studies conducted within both adult survivors (Bunea et al., 2017; O'Conner et al.,2018; Young et al., 2021) as well as adolescent survivors (Peckins et al., 2020; Zhang et al.,

2021) of traumatic events. Moreover, this effect has been attributed to altered receptor expression and in turn a compensatory down regulation of glucocorticoid receptors (Agorastos et al., 2018; Young et al., 2021) Taken together, in the context of trauma perhaps those with increased genetic susceptibility are more likely to experience a loss of cortisol adaptability or an increase in physiological compensatory mechanisms in response to their chronically adverse environment.

**Limitations**

The current study had several limitations. In particular, the sample size is relatively small in terms of gene candidate studies. However, the strict regulations regarding large sample sizes in genetic work were developed for single polymorphism candidate gene research, that account for smaller amounts of variance in outcomes assessed compared to MGPS studies (Starr & Haung, 2019). In part, the sample was small due to the population stratification effects, resulting in reducing the sample size to only the largest homogenous ethnic group. As such, the current study lacks generalizability to diverse ethnic groups. For genomic data to be representative, scientists must adopt strategies that target diversity and inclusion, which will in turn eliminate issues surrounding population stratification. Unfortunately, and as shown in Appendix H, genotypes significantly varied according to ethnicity. However, in the future our lab plans to pool genetic data across studies to have large enough sample sizes within various ethnic groups to assess gene x environment interactions according to ethnicity in a meaningful way that is working towards bridging the genomic divide. Another limitation included the missing genotypes, which were highlighted in Table 5. However, it is worth mentioning we did follow previously developed protocols that allowed for up to 20% missing genetic information per participant when creating MGPS scores (Pagliaccio et al., 2014; Starr & Haung, 2020). The

present study comprised self-reported data, which has been attributed to limitations surrounding both biases in memory recall as well as influences in current affective state. Moreover, recruitment for this study was through an undergraduate sample of mostly psychology students, thus, this study includes many more females than males. Finally, replication studies should include a measure of coping and resilience to better understand the findings from the current study as they pertain to genetic susceptibility.

**Conclusion**

Taken together, the MGPS approach can be used to help explore the individual variability in trauma responses as it pertains to mental health symptomologies including, stress, anxiety, and depression. In particular, these data highlight the role of genetic variants on genes that regulate the HPA-axis in conferring susceptibility to trauma experiences. However, and perhaps most important, this study emphasizes the importance of environmental factors when examining genetic risk or susceptibility to mental illnesses (Coleman et al., 2020; Kalin, 2021; Reynolds, 2021). Ultimately, the data suggest that experiences of trauma might “set boundaries” on the impact of genes, overriding genetic predisposition to depression or comorbid conditions.

## References

Afifi, T. O., MacMillan, H. L., Boyle, M., Taillieu, T., Cheung, K., & Sareen, J. (2014). Child abuse and mental disorders in Canada. *CMAJ*. https://doi.org/10.1503/cmaj.131792

Agorastos, A., Pervanidou, P., Chrousos, G.P. *(2018)* Early life stress and trauma: developmental neuroendocrine aspects of prolonged stress system dysregulation. *Hormones* **17,** 507–520. https://doi-org.proxy.library.carleton.ca/10.1007/s42000-018-0065-x

Agorastos A, Pervanidou P, Chrousos GP and Baker DG (2019) Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects Beyond Stress System Dysregulation. *Front. Psychiatry* 10:118. doi: 10.3389/fpsyt.2019.00118

Allegrini, A. G., Evans, B. E., de Rooij, S., Greaves-Lord, K., & Huizink, A. C. (2019). Gene× Environment contributions to autonomic stress reactivity in youth. *Development and psychopathology*, *31*(1), 293-307. https://doi.org/10.1017/S095457941700181X

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.

Amendola, S., von Wyl, A., Volken, T., Zysset, A., Huber, M., & Dratva, J. (2021). A longitudinal study on generalized anxiety among university students during the first wave of the COVID-19 pandemic in Switzerland. *Frontiers in Psychology*, *12*.

Anisman, H., & Merali, Z. (1999). Understanding stress: characteristics and caveats. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, *23*(4), 241–249. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760382/

Arroll, B., Macgillivray, S., Ogston, S., Reid, I., Sullivan, F., Williams, B., & Crombie, I. (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *The Annals of Family Medicine*, *3*(5), 449-456. DOI: https://doi.org/10.1370/afm.349

Arteaga-Henríquez, G., Simon, M. S., Burger, B., Weidinger, E., Wijkhuijs, A., Arolt, V., ... & Drexhage, H. A. (2019). Low-grade inflammation as a predictor of antidepressant and anti-inflammatory therapy response in MDD patients: a systematic review of the literature in combination with an analysis of experimental data collected in the EU-Moodinflame Consortium. *Frontiers in psychiatry*, *10*. https://dx-doi-org.proxy.library.carleton.ca/10.3389%2Ffpsyt.2019.00458

Artime, T. M., Buchholz, K. R., & Jakupcak, M. (2019). Mental health symptoms and treatment utilization among trauma-exposed college students. *Psychological trauma: theory, research, practice, and policy*, *11*(3), 274. https://psycnet.apa.org/doi/10.1037/tra0000376

Assary E, Vincent JP, Keers R, Pluess M (2018) Gene–environment interaction and psychiatric disorders: review and future directions. Semin Cell Dev Biol 77:133–143. https://doi.org/10.1016/j.semcdb.2017.10.016

Auerbach, R. P., Alonso, J., Axinn, W. G., Cuijpers, P., Ebert, D. D., Green, J. G., Hwang, I., Kessler, R. C., Liu, H., Mortier, P., Nock, M. K., Pinder-Amaker, S., Sampson, N. A., Aguilar-Gaxiola, S., Al-Hamzawi, A., Andrade, L. H., Benjet, C., Caldas-De-Almeida, J. M., Demyttenaere, K., ... Bruffaerts, R. (2016). Mental disorders among college students in the World Health Organization World Mental Health Surveys. In *Psychological Medicine*. https://doi.org/10.1017/S0033291716001665

Auerbach, R. P., Mortier, P., Bruffaerts, R., Alonso, J., Benjet, C., Cuijpers, P., ... & Murray, E. (2018). WHO World Mental Health Surveys International College Student Project: Prevalence and distribution of mental disorders. *Journal of abnormal psychology*, *127*(7), 623.

Auerbach, R. P., Mortier, P., Bruffaerts, R., Alonso, J., Benjet, C., Cuijpers, P., Demyttenaere, K., Ebert, D. D., Green, J. G., Hasking, P., Lee, S., Lochner, C., McLafferty, M., Nock, M. K., Petukhova, M. V., Pinder-Amaker, S., Rosellini, A. J., Sampson, N. A., Vilagut, G., Zaslavsky, A. M., … WHO WMH-ICS Collaborators (2019). Mental disorder comorbidity and suicidal thoughts and behaviors in the World Health Organization World Mental Health Surveys International College Student initiative. *International journal of methods in psychiatric research*, *28*(2), e1752. https://doi.org/10.1002/mpr.1752

Bakermans-Kranenburg, M. J., & Van Ijzendoorn, M. H. (2015). The hidden efficacy of interventions: Gene× environment experiments from a differential susceptibility perspective. *Annual review of psychology*, *66*, 381-409. https://doi.org/10.1146/annurev-psych-010814-015407

Bandoli, G., Campbell-Sills, L., Kessler, R. C., Heeringa, S. G., Nock, M. K., Rosellini, A. J., Sampson, N. A., Schoenbaum, M., Ursano, R. J., & Stein, M. B. (2017). Childhood adversity, adult stress, and the risk of major depression or generalized anxiety disorder in

US soldiers: a test of the stress sensitization hypothesis. *Psychological medicine*, *47*(13), 2379–2392. https://doi.org/10.1017/S0033291717001064

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological bulletin*, *135*(6), 885. https://psycnet.apa.org/doi/10.1037/a0017376

Belsky, J., & van IJzendoorn, M. H. (2017). Genetic differential susceptibility to the effects of parenting. *Current opinion in psychology*, *15*, 125-130. https://doi.org/10.1016/j.copsyc.2017.02.021

Benson, S., Engler, H., Wegner, A., Rebernik, L., Spreitzer, I., Schedlowski, M., & Elsenbruch, S. (2017). What makes you feel sick after inflammation? Predictors of acute and persisting physical sickness symptoms induced by experimental endotoxemia. *Clinical Pharmacology & Therapeutics*, *102*(1), 141-151. https://doi.org/10.1002/cpt.618

Beiter, R., Nash, R., McCrady, M., Rhoades, D., Linscomb, M., Clarahan, M., & Sammut, S. (2015). The prevalence and correlates of depression, anxiety, and stress in a sample of college students. *Journal of affective disorders*, *173*, 90-96. https://doi.org/10.1016/j.jad.2014.10.054

Binder, E. B. (2009). The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety

Bogdan, R., Baranger, D. A., & Agrawal, A. (2018). Polygenic risk scores in clinical psychology: bridging genomic risk to individual differences. *Annual review of clinical psychology*, *14*, 119-157.

disorders. *Psychoneuroendocrinology*, *34*, S186-S195. https://doi.org/10.1016/j.psyneuen.2009.05.021

Boku, S., Nakagawa, S., Toda, H., & Hishimoto, A. (2018). Neural basis of major depressive disorder: beyond monoamine hypothesis. *Psychiatry and clinical neurosciences*, *72*(1), 3-12. https://doi.org/10.1111/pcn.12604

Border, R., Johnson, E. C., Evans, L. M., Smolen, A., Berley, N., Sullivan, P. F., & Keller, M. C. (2019). No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *American Journal of Psychiatry*, *176*(5), 376-387. https://doi.org/10.1176/appi.ajp.2018.18070881

Border, R., & Keller, M. C. (2017). Commentary: Fundamental problems with candidate gene-by-environment interaction studies–reflections on Moore and Thoemmes (2016). *Journal of Child Psychology and Psychiatry*, *58*(3), 328-330. https://doi.org/10.1111/jcpp.12669

Broerman, R. (2020). Diathesis-Stress Model. *Encyclopedia of Personality and Individual Differences*, 1107-1109. https://doi.org/10.1007/978-3-319-24612-3_891

Buchmann, A. F., Holz, N., Boecker, R., Blomeyer, D., Rietschel, M., Witt, S. H., ... & Zimmermann, U. S. (2014). Moderating role of FKBP5 genotype in the impact of childhood adversity on cortisol stress response during adulthood. *European Neuropsychopharmacology*, *24*(6), 837-845. https://doi.org/10.1016/j.euroneuro.2013.12.001

Bunea, I., Szentágotai-Tătar, A. & Miu, A.C. Early-life adversity and cortisol response to social stress: a meta-analysis. *Transl Psychiatry***7,** 1274 (2017). https://doi-org.proxy.library.carleton.ca/10.1038/s41398-017-0032-3

Butler, K., Klaus, K., Edwards, L., & Pennington, K. (2017). Elevated cortisol awakening response associated with early life stress and impaired executive function in healthy adult males. *Hormones and Behavior*, *95*, 13-21. https://doi.org/10.1016/j.yhbeh.2017.07.013

Cabanach, R. G., Valle, A., Rodríguez, S., Piñeiro, I., & González, P. (2021). Motivational beliefs as protective factors against stress in university students. https://repositorio.uautonoma.cl/handle/20.500.12728/8300

Carr, Clara Passmann MSc[*†]; Martins, Camilla Maria Severi MPhil[*]; Stingel, Ana Maria PhD[‡]; Lemgruber, Vera Braga MD[†]; Juruena, Mario Francisco MD, PhD[*] The Role of Early Life Stress in Adult Psychiatric Disorders, The Journal of Nervous and Mental Disease: December 2013 - Volume 201 - Issue 12 - p 1007-1020.

Capuron, L., Neurauter, G., Musselman, D. L., Lawson, D. H., Nemeroff, C. B., Fuchs, D., & Miller, A. H. (2003). Interferon-alpha–induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. *Biological psychiatry*, *54*(9), 906-914. https://doi-org.proxy.library.carleton.ca/10.1016/S0006-3223(03)00173-2

Cassidy, E. M., Manning, D., Byrne, S., Bolger, E., Murray, F., Sharifi, N., ... & O'Keane, V. (2002). Acute effects of low-dose interferon-α on serum cortisol and plasma interleukin-6. *Journal of Psychopharmacology*, *16*(3), 230-234. https://doi.org/10.1177%2F026988110201600307

Carpenter, L. L., Shattuck, T. T., Tyrka, A. R., Geracioti, T. D., & Price, L. H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology*, *214*(1), 367–375. https://doi.org/10.1007/s00213-010-2007-4

Cattaneo, A., & Riva, M. A. (2016). Stress-induced mechanisms in mental illness: a role for glucocorticoid signalling. *The Journal of steroid biochemistry and molecular biology*, *160*, 169-174. https://doi-org.proxy.library.carleton.ca/10.1016/j.jsbmb.2015.07.021

Chen, L. C., Chen, Y. H., Bai, Y. M., Chen, T. J., Chen, M. H., & Su, T. P. (2020). Antidepressant resistance in adolescents with major depressive disorder: A nationwide longitudinal study. *Journal of Affective Disorders*, *262*, 293-297. https://doi.org/10.1016/j.jad.2019.11.038

Chen, Y. L., Liu, X., Huang, Y., Yu, H. J., Yuan, S., Ye, Y. L., ... & He, Q. Q. (2017). Association between child abuse and health risk behaviors among Chinese college students. *Journal of child and family studies*, *26*(5), 1380-1387.

Cheung, A. H., & Dewa, C. S. (2006). Canadian community health survey: major depressive disorder and suicidality in adolescents. *Healthcare policy = Politiques de sante*, *2*(2), 76–89. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2585433/

Chrousos, G. Stress and disorders of the stress system. *Nat Rev Endocrinol* **5,** 374–381 (2009). https://doi-org.proxy.library.carleton.ca/10.1038/nrendo.2009.106

Choi, K.W., Stein, M.B., Dunn, E.C. *et al.* Genomics and psychological resilience: a research agenda. *Mol Psychiatry* **24,** 1770–1778 (2019). https://doi.org/10.1038/s41380-019-0457-6

Cohen, S., Janicki-Deverts, D., Doyle, W. J., Miller, G. E., Frank, E., Rabin, B. S., & Turner, R. B. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences*, *109*(16), 5995-5999. https://doi.org/10.1073/pnas.1118355109

Copeland, W. E., Keeler, G., Angold, A., & Costello, E. J. (2007). Traumatic events and posttraumatic stress in childhood. *Archives of general psychiatry*, *64*(5), 577–584. https://doi.org/10.1001/archpsyc.64.5.577

Colburn, A. R., Kremer, K. P., & Jackson, D. B. (2021). Early trauma and psychosocial outcomes among college students. *Children and youth services review*, *126*, 106052. https://doi.org/10.1016/j.childyouth.2021.106052

Coleman, J. R., Peyrot, W. J., Purves, K. L., Davis, K. A., Rayner, C., Choi, S. W., ... & Breen, G. (2020). Genome-wide gene-environment analyses of major depressive disorder and reported lifetime traumatic experiences in UK Biobank. *Molecular psychiatry*, *25*(7), 1430-1446. https://doi.org/10.1038/s41380-019-0546-6

Collip, D., Myin-Germeys, I., Wichers, M., Jacobs, N., Derom, C., Thiery, E., ... & van Os, J. (2013). FKBP5 as a possible moderator of the psychosis-inducing effects of childhood trauma. *The British Journal of Psychiatry*, *202*(4), 261-268. https://doi.org/10.1192/bjp.bp.112.115972

Colodro-Conde, L., Couvy-Duchesne, B., Zhu, G., Coventry, W. L., Byrne, E. M., Gordon, S., ... & Eaves, L. J. (2018). A direct test of the diathesis–stress model for depression. *Molecular psychiatry*, *23*(7), 1590-1596. https://doi.org/10.1038/mp.2017.130

Comasco, E., Gustafsson, P. A., Sydsjö, G., Agnafors, S., Aho, N., & Svedin, C. G. (2015). Psychiatric symptoms in adolescents: FKBP5 genotype—early life adversity interaction effects. *European child & adolescent psychiatry*, *24*(12), 1473-1483. https://doi.org/10.1007/s00787-015-0768-3

Culverhouse, R. C., Saccone, N. L., Horton, A. C., Ma, Y., Anstey, K. J., Banaschewski, T., ... & Goldman, N. (2018). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Molecular psychiatry*, *23*(1), 133-142. https://doi.org/10.1038/mp.2017.44

Danner, M., Kasl, S. V., Abramson, J. L., & Vaccarino, V. (2003). Association between depression and elevated C-reactive protein. *Psychosomatic medicine*, *65*(3), 347-356. doi:10.1097/01.PSY.0000041542.29808.01

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., and Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews neuroscience, 9(1), 46.

Davis, E. G., Keller, J., Hallmayer, J., Pankow, H. R., Murphy, G. M., Gotlib, I. H., & Schatzberg, A. F. (2018). Corticotropin-releasing factor 1 receptor haplotype and

cognitive features of major depression. *Translational psychiatry*, *8*(1), 1-9. https://doi-org.proxy.library.carleton.ca/10.1038/s41398-017-0051-0

De Bellis M. D. (2001). Developmental traumatology: the psychobiological development of maltreated children and its implications for research, treatment, and policy. *Development and psychopathology*, *13*(3), 539–564. https://doi.org/10.1017/s0954579401003078

De Berardis, D., Fornaro, M., Orsolini, L., Ventriglio, A., Vellante, F., & Di Giannantonio, M. (2020). Emotional Dysregulation in Adolescents: Implications for the Development of Severe Psychiatric Disorders, Substance Abuse, and Suicidal Ideation and Behaviors.

de Castro-Catala, M., Peña, E., Kwapil, T. R., Papiol, S., Sheinbaum, T., Cristóbal-Narváez, P., ... & Rosa, A. (2017). Interaction between FKBP5 gene and childhood trauma on psychosis, depression and anxiety symptoms in a non-clinical sample. *Psychoneuroendocrinology*, *85*, 200-209. https://doi.org/10.1016/j.psyneuen.2017.08.024

De la Cruz-Cano, E. (2017). Association between FKBP5 and CRHR1 genes with suicidal behavior: a systematic review. *Behavioural brain research*, *317*, 46-61. https://doi.org/10.1016/j.bbr.2016.09.032

DeRijk, R. H., Wüst, S., Meijer, O. C., Zennaro, M. C., Federenko, I. S., Hellhammer, D. H., ... & de Kloet, E. R. (2006). A common polymorphism in the mineralocorticoid receptor modulates stress responsiveness. *The Journal of Clinical Endocrinology & Metabolism*, *91*(12), 5083-5089. https://doi.org/10.1210/jc.2006-0915

DeYoung, C. G., Cicchetti, D., & Rogosch, F. A. (2011). Moderation of the association between childhood maltreatment and neuroticism by the corticotropin-releasing hormone receptor 1 gene. *Journal of child psychology and psychiatry, and allied disciplines*, *52*(8), 898–906. https://doi.org/10.1111/j.1469-7610.2011.02404.x

Delahanty DL, Nugent NR, Christopher NC, Walsh M. Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. *Psychoneuroendocrinology*. 2005;30(2):121-128. doi:10.1016/j.psyneuen.2004.06.004

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., ... & Sher, K. J. (2015). Candidate gene–environment interaction research: Reflections and

recommendations. *Perspectives on Psychological Science*, *10*(1), 37-59. https://doi.org/10.1177%2F1745691614556682

Di Iorio, C. R., Carey, C. E., Michalski, L. J., Corral-Frias, N. S., Conley, E. D., Hariri, A. R., & Bogdan, R. (2017). Hypothalamic-pituitary-adrenal axis genetic variation and early stress moderates amygdala function. *Psychoneuroendocrinology*, *80*, 170-178. https://doi-org.proxy.library.carleton.ca/10.1016/j.psyneuen.2017.03.016

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry*, *168*(10), 1041-1049. https://doi.org/10.1176/appi.ajp.2011.11020191

Duncko, R., Fischer, S., Hatch, S. L., Frissa, S., Goodwin, L., Papadopoulos, A., ... & Hotopf, M. (2019). Recurrence of Depression in Relation to History of Childhood Trauma and Hair Cortisol Concentration in a Community-Based Sample. *Neuropsychobiology*, *78*(1), 48-57. https://doi.org/10.1159/000498920

Dunn, E. C., Brown, R. C., Dai, Y., Rosand, J., Nugent, N. R., Amstadter, A. B., & Smoller, J. W. (2015). Genetic determinants of depression: recent findings and future directions. *Harvard review of psychiatry*, *23*(1), 1–18. https://doi.org/10.1097/HRP.0000000000000054

Eisenberg, D., Gollust, S. E., Golberstein, E., & Hefner, J. L. (2007). Prevalence and correlates of depression, anxiety, and suicidality among university students. *American journal of orthopsychiatry*, *77*(4), 534-542. https://doi.org/10.1037/0002-9432.77.4.534

Eisenberg, D., Downs, M. F., Golberstein, E., & Zivin, K. (2009). Stigma and help seeking for mental health among college students. *Medical Care Research and Review*, *66*(5), 522-541.

Elzinga, B. M., Roelofs, K., Tollenaar, M. S., Bakvis, P., van Pelt, J., & Spinhoven, P. (2008). Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: a study among healthy young subjects. *Psychoneuroendocrinology*, *33*(2), 227-237. https://doi.org/10.1016/j.psyneuen.2007.11.004

Endedijk, H. M., Nelemans, S. A., Schür, R. R., Boks, M. P., Lier, P. V., Meeus, W., ... & Vinkers, C. H. (2020). The Role of Stress and Mineralocorticoid Receptor Haplotypes in the Development of Symptoms of Depression and Anxiety During Adolescence. *Frontiers in Psychiatry*, *11*, 367. https://doi.org/10.3389/fpsyt.2020.00367

Engler, H., Brendt, P., Wischermann, J. *et al.* Selective increase of cerebrospinal fluid IL-6 during experimental systemic inflammation in humans: association with depressive symptoms. *Mol Psychiatry* **22,** 1448–1454 (2017). https://doi-org.proxy.library.carleton.ca/10.1038/mp.2016.264

Farmer, E A., (1996) The genetics of depressive disorders, International Review of Psychiatry, 8:4, 369-372,DOI: 10.3109/09540269609051551

Feurer, C., McGeary, J. E., Knopik, V. S., Brick, L. A., Palmer, R. H., & Gibb, B. E. (2017). HPA axis multilocus genetic profile score moderates the impact of interpersonal stress on prospective increases in depressive symptoms for offspring of depressed mothers. *Journal of Abnormal Psychology, 126*(8), 1017–1028. https://doi-org.proxy.library.carleton.ca/10.1037/abn0000316

Findlay, L. (2017). Depression and suicidal ideation among Canadians aged 15 to 24. Statistics Canada, Catalogue no. 82-003-X. Health Reports, Vol. 28, no. 1, pp. 3-11.

Fischer, S., Gardini, E. S., Haas, F., & Cleare, A. J. (2019). Polymorphisms in genes related to the hypothalamic-pituitary-adrenal axis and antidepressant response–systematic review. *Neuroscience & Biobehavioral Reviews*, *96*, 182-196. https://doi.org/10.1016/j.neubiorev.2018.11.009

Ford, J. D., Stockton, P., Kaltman, S., & Green, B. L. (2006). Disorders of extreme stress (DESNOS) symptoms are associated with type and severity of interpersonal trauma exposure in a sample of healthy young women. *Journal of Interpersonal Violence*, *21*(11), 1399-1416. https://doi.org/10.1177%2F0886260506292992

Ford, J. L., Boch, S. J., & Browning, C. R. (2019). Hair cortisol and depressive symptoms in youth: An investigation of curvilinear relationships. *Psychoneuroendocrinology*, *109*, 104376. https://doi.org/10.1016/j.psyneuen.2019.104376

Flett, G. L., Hewitt, P. L., Blankstein, K. R., & Mosher, S. W. (1995). Perfectionism, life events, and depressive symptoms: A test of a diathesis-stress model. *Current Psychology*, *14*(2),112-137. https://doi.org/10.1007/BF02686885

Flux, M. C., & Lowry, C. A. (2020). Finding intestinal fortitude: Integrating the microbiome into a holistic view of depression mechanisms, treatment, and resilience. *Neurobiology of disease*, *135*, 104578. https://doi.org/10.1016/j.nbd.2019.104578

Fourrier, C., Sampson, E., Mills, N. T., & Baune, B. T. (2018). Anti-inflammatory treatment of depression: study protocol for a randomised controlled trial of vortioxetine augmented with celecoxib or placebo. *Trials*, *19*(1), 447. https://doi-org.proxy.library.carleton.ca/10.1186/s13063-018-2829-7

Fu, H., Feng, T., Qin, J., Wang, T., Wu, X., Cai, Y., ... & Yang, T. (2018). Reported prevalence of childhood maltreatment among Chinese college students: A systematic review and meta-analysis. *PLoS one*, *13*(10), e0205808.https://doi.org/10.1371/journal.pone.0205808

Gao, G., Allison, D. B., & Hoeschele, I. (2009). Haplotyping methods for pedigrees. *Human heredity*, *67*(4), 248–266. https://doi.org/10.1159/000194978

Gerritsen, L., Geerlings, M. I., Beekman, A. T., Deeg, D. J., Penninx, B. W., & Comijs, H. C. (2009). 2.2 Early and late life events and salivary cortisol in older persons. *Stress, the brain and cognition*, 33.

Gialluisi, A., Di Castelnuovo, A., Bracone, F., De Curtis, A., Cerletti, C., Donati, M. B., ... & Iacoviello, L. (2020). Associations between systemic inflammation and somatic depressive symptoms: Findings from the Moli-sani study. *Depression and anxiety*. https://doi.org/10.1002/da.23070

Gomes, A. P., Soares, A. L. G., Kieling, C., Rohde, L. A., & Gonçalves, H. (2019). Mental disorders and suicide risk in emerging adulthood: the 1993 Pelotas birth cohort. *Revista de Saude Publica*, *53*, 96. doi:10.11606/s1518-8787.20190530012356

González-Díez, Z., Orue, I., & Calvete, E. (2017). The role of emotional maltreatment and looming cognitive style in the development of social anxiety symptoms in late adolescents. *Anxiety, Stress, & Coping*, *30*(1), 26-38. https://doi.org/10.1080/10615806.2016.1188920

Green, B. L., Krupnick, J. L., Stockton, P., Goodman, L., Corcoran, C., & Petty, R. (2005). Effects of adolescent trauma exposure on risky behavior in college women. *Psychiatry: Interpersonal and Biological Processes*, *68*(4), 363-378.

Guerry, J. D., & Hastings, P. D. (2011). In search of HPA axis dysregulation in child and adolescent depression. *Clinical child and family psychology review*, *14*(2), 135-160. https://doi.org/10.1007/s10567-011-0084-5

Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2015). Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain, behavior, and immunity*, *49*, 206-215. https://doi-org.proxy.library.carleton.ca/10.1016/j.bbi.2015.06.001

Haroon, E., Daguanno, A. W., Woolwine, B. J., Goldsmith, D. R., Baer, W. M., Wommack, E. C., ... & Miller, A. H. (2018). Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology*, *95*, 43-49. https://doi-org.proxy.library.carleton.ca/10.1016/j.psyneuen.2018.05.026

Hatcher, A. M., Gibbs, A., Jewkes, R., McBride, R. S., Peacock, D., & Christofides, N. (2019). Effect of childhood poverty and trauma on adult depressive symptoms among young men in peri-urban South African settlements. *Journal of Adolescent Health*, *64*(1), 79-85. https://www-sciencedirect-com.proxy.library.carleton.ca/science/article/pii/S1054139X18303392

Hayes, A. F. (2012). PROCESS: A versatile computational tool for observed variable mediation, mod- eration, and conditional process modeling [White paper]. Retrieved from http://www.afhayes.com/ public/process2012.pdf

Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental neurology*, *233*(1), 102-111. https://doi-org.proxy.library.carleton.ca/10.1016/j.expneurol.2011.10.032

Himmerich, H., Patsalos, O., Lichtblau, N., Ibrahim, M. A., & Dalton, B. (2019). Cytokine research in depression: principles, challenges, and open questions. *Frontiers in Psychiatry*, *10*, 30. https://doi.org/10.3389/fpsyt.2019.00030

Hirschfeld R. M. (2000). History and evolution of the monoamine hypothesis of depression. *The Journal of clinical psychiatry*, *61 Suppl 6*, 4–6 https://pubmed.ncbi.nlm.nih.gov/10775017/

Huang, M., & Starr, L. R. (2020). Interpersonal childhood adversity and stress generation in adolescence: Moderation by HPA axis multilocus genetic variation. *Development and psychopathology*, *32*(3), 865-878. https://doi.org/10.1017/S0954579419001123

Huh, H. J., Kim, K. H., Lee, H. K., & Chae, J. H. (2017). The relationship between childhood trauma and the severity of adulthood depression and anxiety symptoms in a clinical sample: The mediating role of cognitive emotion regulation strategies. *Journal of affective disorders*, *213*, 44–50. https://doi-org.proxy.library.carleton.ca/10.1016/j.jad.2017.02.009

Humphreys et al. "Child Maltreatment and Depression: A Meta-Analysis of Studies Using the Childhood Trauma Questionnaire." *Child abuse & neglect* 102 (2020): 104361–20. Web. https://doi-org.proxy.library.carleton.ca/10.1016/j.chiabu.2020.104361

Isaksson, J., Comasco, E., Åslund, C., Rehn, M., Tuvblad, C., Andershed, H., & Nilsson, K. W. (2016). Associations between the FKBP5 haplotype, exposure to violence and anxiety in females. *Psychoneuroendocrinology*, *72*, 196-204. https://doi.org/10.1016/j.psyneuen.2016.07.206

Jaworska-Andryszewska, P., & Rybakowski, J. K. (2019). Childhood trauma in mood disorders: Neurobiological mechanisms and implications for treatment. *Pharmacological reports : PR*, *71*(1), 112–120. https://doi-org.proxy.library.carleton.ca/10.1016/j.pharep.2018.10.004

Jenkins, P. E., Ducker, I., Gooding, R., James, M., & Rutter-Eley, E. (2020). Anxiety and depression in a sample of UK college students: a study of prevalence, comorbidity, and quality of life. *Journal of American college health*, 1-7.

Jokinen, J., & Nordström, P. (2009). HPA axis hyperactivity and attempted suicide in young adult mood disorder inpatients. *Journal of affective disorders*, *116*(1-2), 117-120. https://doi.org/10.1016/j.jad.2008.10.015

Juruena, M. F. (2014). Early-life stress and HPA axis trigger recurrent adulthood depression. *Epilepsy & Behavior*, *38*, 148-159. https://www.sciencedirect.com/science/article/abs/pii/S1525505013005532

Juruena, M. F., Eror, F., Cleare, A. J., & Young, A. H. (2020). The role of early life stress in HPA axis and anxiety. In *Anxiety Disorders* (pp. 141-153). Springer, Singapore. https://doi.org/10.1007/978-981-32-9705-0_9

Kalin, N. H. (2020). The critical relationship between anxiety and depression. *The American Journal of Psychiatry*, *177*(5), 365–367. doi:10.1176/appi.ajp.2020.20030305

Kalin, N. H. (2021). Anxiety, depression, and suicide in youth. https://doi.org/10.1176/appi.ajp.2020.21020186

Kang, C., Shi, J., Gong, Y., Wei, J., Zhang, M., Ding, H., ... & Han, J. (2020). Interaction between FKBP5 polymorphisms and childhood trauma on depressive symptoms in Chinese adolescents: The moderating role of resilience. *Journal of Affective Disorders*, *266*, 143-150. https://doi.org/10.1016/j.jad.2020.01.051

Kappelmann, N., Lewis, G., Dantzer, R., Jones, P. B., & Khandaker, G. M. (2018). Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Molecular psychiatry*, *23*(2), 335-343. https://doi-org.proxy.library.carleton.ca/10.1038/mp.2016.167

Kendall, K. M., Van Assche, E., Andlauer, T. F. M., Choi, K. W., Luykx, J. J., Schulte, E. C., & Lu, Y. (2021). The genetic basis of major depression. *Psychological Medicine*, 1-14.

Khan, M. S., Wu, G. W., Reus, V. I., Hough, C. M., Lindqvist, D., Westrin, Å., ... & Mellon, S. H. (2019). Low serum brain-derived neurotrophic factor is associated with suicidal ideation in major depressive disorder. *Psychiatry research*, *273*, 108-113. https://doi.org/10.1016/j.psychres.2019.01.013

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA psychiatry*, *71*(10), 1121-1128. doi:10.1001/jamapsychiatry.2014.1332

Kim, Y. K., Ham, B. J., & Han, K. M. (2019). Interactive effects of genetic polymorphisms and childhood adversity on brain morphologic changes in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *91*, 4-13. https://doi.org/10.1016/j.pnpbp.2018.03.009

Kim, A. W., Adam, E. K., Bechayda, S. A., & Kuzawa, C. W. (2020). Early life stress and HPA axis function independently predict adult depressive symptoms in metropolitan Cebu, Philippines. *American Journal of Physical Anthropology*, *173*(3), 448-462. https://doi.org/10.1002/ajpa.24105

Kishi, T., Yoshimura, R., Ikuta, T., & Iwata, N. (2018). Brain-derived neurotrophic factor and major depressive disorder: evidence from meta-analyses. *Frontiers in psychiatry*, *8*, 308. https://doi.org/10.3389/fpsyt.2017.00308

Klok, M. D., Giltay, E. J., Van der Does, A. J. W., Geleijnse, J. M., Antypa, N., Penninx, B. W. J. H., ... & Zitman, F. G. (2011). A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females. *Translational Psychiatry*, *1*(12), e62-e62. https://doi.org/10.1038/tp.2011.59

Kohrt, B. A., Worthman, C. M., Ressler, K. J., Mercer, K. B., Upadhaya, N., Koirala, S., ... & Binder, E. B. (2015). Cross-cultural gene− environment interactions in depression, post-traumatic stress disorder, and the cortisol awakening response: FKBP5 polymorphisms and childhood trauma in South Asia: GxE interactions in South Asia. *International review of psychiatry*, *27*(3), 180-196. https://doi.org/10.3109/09540261.2015.1020052

Kranzler, H. R., Feinn, R., Nelson, E. C., Covault, J., Anton, R. F., Farrer, L., & Gelernter, J. (2011). A CRHR1 haplotype moderates the effect of adverse childhood experiences on lifetime risk of major depressive episode in African-American women. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *156*(8), 960-968. https://doi.org/10.1002/ajmg.b.31243

Kuhlman, K. R., Chiang, J. J., Bower, J. E., Irwin, M. R., Seeman, T. E., McCreath, H. E., ... & Fuligni, A. J. (2020). Sleep problems in adolescence are prospectively linked to later depressive symptoms via the cortisol awakening response. *Development and psychopathology*, *32*(3), 997-1006. https://doi.org/10.1017/S0954579419000762

Lahti, J., Räikkönen, K., Bruce, S., Heinonen, K., Pesonen, A. K., Rautanen, A., ... & Eriksson, J. G. (2011). Glucocorticoid receptor gene haplotype predicts increased risk of hospital admission for depressive disorders in the Helsinki birth cohort study. *Journal of psychiatric research*, *45*(9), 1160-1164. https://doi.org/10.1016/j.jpsychires.2011.03.008

Laidlaw, A., McLellan, J., & Ozakinci, G. (2016). Understanding undergraduate student perceptions of mental health, mental well-being and help-seeking behaviour. *Studies in Higher Education*, *41*(12), 2156-2168.

Landry, L. G., Ali, N., Williams, D. R., Rehm, H. L., & Bonham, V. L. (2018). Lack of diversity in genomic databases is a barrier to translating precision medicine research into practice. *Health Affairs*, *37*(5), 780-785. https://doi.org/10.1377/hlthaff.2017.1595

Leighton, C., Botto, A., Silva, J. R., Jiménez, J. P., & Luyten, P. (2017). Vulnerability or sensitivity to the environment? Methodological issues, trends, and recommendations in

gene–environment interactions research in human behavior. *Frontiers in psychiatry*, *8*, 106. https://doi.org/10.3389/fpsyt.2017.00106

LeMoult, J., Humphreys, K. L., Tracy, A., Hoffmeister, J. A., Ip, E., & Gotlib, I. H. (2019). Meta-analysis: Exposure to early life stress and risk for depression in childhood and adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2019.10.011

Levine, J., Barak, Y., Chengappa, K. N. R., Rapoport, A., Rebey, M., & Barak, V. (1999). Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology*, *40*(4), 171-176. https://doi.org/10.1159/000026615

Levy, M. J., Boulle, F., Steinbusch, H. W., van den Hove, D. L., Kenis, G., & Lanfumey, L. (2018). Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. *Psychopharmacology*, *235*(8), 2195-2220. https://doi.org/10.1007/s00213-018-4950-4

Liang, S., Wu, X., Hu, X., Wang, T., & Jin, F. (2018). Recognizing depression from the microbiota–gut–brain axis. *International journal of molecular sciences*, *19*(6), 1592. https://doi.org/10.3390/ijms19061592

Linares, L. O., Shrout, P. E., Nucci-Sack, A., & Diaz, A. (2013). Child maltreatment, dating perpetration of physical assault, and cortisol reactivity among disadvantaged female adolescents. *Neuroendocrinology*, *97*(3), 252-259. https://doi.org/10.1159/000342958

Liu, Z., Zhu, F., Wang, G., Xiao, Z., Wang, H., Tang, J., ... & Li, W. (2006). Association of corticotropin-releasing hormone receptor1 gene SNP and haplotype with major depression. *Neuroscience letters*, *404*(3), 358-362. https://doi.org/10.1016/j.neulet.2006.06.016

Liu, C., Zhang, G., Li, B. *et al.* Role of inflammation in depression relapse. *J Neuroinflammation* **16,** 90 (2019). https://doi.org/10.1186/s12974-019-1475-7

Lopez-Duran, N. L., Kovacs, M., & George, C. J. (2009). Hypothalamic–pituitary–adrenal axis dysregulation in depressed children and adolescents: A meta-analysis. *Psychoneuroendocrinology*, *34*(9), 1272-1283. https://doi.org/10.1016/j.psyneuen.2009.03.016

Lu, L., Jian, S., Dong, M., Gao, J., Zhang, T., Chen, X., ... & Liu, S. (2020). Childhood trauma and suicidal ideation among Chinese university students: the mediating effect of Internet

addiction and school bullying victimisation. *Epidemiology and psychiatric sciences*, *29*. https://doi.org/10.1017/S2045796020000682

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature reviews neuroscience*, *10*(6), 434-445.

https://doi.org/10.1038/nrn2639

Lussier, A. A., Hawrilenko, M., Wang, M. J., Choi, K. W., Cerutti, J., Zhu, Y., ... & Dunn, E. C. (2020). Genetic susceptibility for major depressive disorder associates with trajectories of depressive symptoms across childhood and adolescence. *Journal of Child Psychology and Psychiatry*.

Mahon, P. B., Zandi, P. P., Potash, J. B., Nestadt, G., & Wand, G. S. (2013). Genetic association of FKBP5 and CRHR1 with cortisol response to acute psychosocial stress in healthy adults. *Psychopharmacology*, *227*(2), 231-241. https://doi.org/10.1007/s00213-012-2956-x

Mac Giollabhui, N., Ng, T. H., Ellman, L. M., & Alloy, L. B. (2020). The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. *Molecular Psychiatry*, 1-13. https://doi-org.proxy.library.carleton.ca/10.1038/s41380-020-00867-4

Macedo, D., Chaves Filho, A. J. M., de Sousa, C. N. S., Quevedo, J., Barichello, T., Júnior, H. V. N., & de Lucena, D. F. (2017). Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. *Journal of affective disorders*, *208*, 22-32. https://doi.org/10.1016/j.jad.2016.09.012

McEwen, B. S. (2002). The neurobiology and neuroendocrinology of stress: implications for post-traumatic stress disorder from a basic science perspective. *Psychiatric Clinics of North America*.

McEwen, B. S. (2017). Neurobiological and systemic effects of chronic stress. *Chronic stress*, *1*, 2470547017692328. https://doi.org/10.1177%2F2470547017692328

McQuaid, R.J., McInnis, O.A., Matheson, K., & Anisman, H. (2015). Distress of ostracism: Oxytocin receptor gene polymorphism confers sensitivity to social exclusion. *Social Cognitive and Affective Neuroscience,* 10, 1153-1159.

McQuaid, R. J., Gabrys, R. L., McInnis, O. A., Anisman, H., & Matheson, K. (2019). Understanding the relation between early-life adversity and depression symptoms: The moderating role of sex and an interleukin-1β gene variant. *Frontiers in Psychiatry*, *10*, 151. https://doi.org/10.3389/fpsyt.2019.00151

Morris, M. C., Kouros, C. D., Mielock, A. S., & Rao, U. (2017). Depressive symptom composites associated with cortisol stress reactivity in adolescents. *Journal of affective disorders*, *210*, 181-188. https://doi.org/10.1016/j.jad.2016.12.023

Mondal, A. C., & Fatima, M. (2019). Direct and indirect evidences of BDNF and NGF as key modulators in depression: role of antidepressants treatment. *International Journal of Neuroscience*, *129*(3), 283-296. https://doi-org.proxy.library.carleton.ca/10.1080/00207454.2018.1527328

Morneau-Vaillancourt, G., Coleman, J. R., Purves, K. L., Cheesman, R., Rayner, C., Breen, G., & Eley, T. C. (2020). The genetic and environmental hierarchical structure of anxiety and depression in the UK Biobank. *Depression and anxiety*, *37*(6), 512-520 https://doi.org/10.1002/da.22991

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychological bulletin*, *110*(3), 406. https://psycnet.apa.org/doi/10.1037/0033-2909.110.3.406

Makhubela, M. (2020). Comorbid anxiety and depression psychopathology in university students: a network approach. *South African Journal of Psychology*, 0081246320973839.

Munafò, M. R., Zammit, S., & Flint, J. (2014). Practitioner review: A critical perspective on gene-environment interaction models--what impact should they have on clinical perceptions and practice?. *Journal of child psychology and psychiatry, and allied disciplines*, *55*(10), 1092–1101. https://doi.org/10.1111/jcpp.12261

Müller, L. E., Bertsch, K., Bülau, K., Herpertz, S. C., & Buchheim, A. (2019). Emotional neglect in childhood shapes social dysfunctioning in adults by influencing the oxytocin and the attachment system: Results from a population-based study. *International Journal of Psychophysiology*, *136*, 73-80. https://doi.org/10.1016/j.ijpsycho.2018.05.011

Mullins, N., Power, R. A., Fisher, H. L., Hanscombe, K. B., Euesden, J., Iniesta, R., ... & Lewis, C. M. (2016). Polygenic interactions with environmental adversity in the aetiology of

major depressive disorder. *Psychological medicine*, *46*(4), 759-770. https://doi.org/10.1017/s0033291715002172

Nanda, M.M., Reichert, E., Jones, U.J. *et al.* Childhood Maltreatment and Symptoms of Social Anxiety: Exploring the Role of Emotional Abuse, Neglect, and Cumulative Trauma.*Journ Child Adol Trauma* **9,** 201–207 (2016). https://doi.org/10.1007/s40653-015-0070-z

Nemeroff, C. B. (2007). Prevalence and management of treatment-resistant depression. *Journal of Clinical Psychiatry*, *68*(8), 17.

Nikolova, Y., Ferrell, R., Manuck, S. *et al.* Multilocus Genetic Profile for Dopamine Signaling Predicts Ventral Striatum Reactivity. *Neuropsychopharmacol* **36,** 1940–1947 (2011). https://doi-org.proxy.library.carleton.ca/10.1038/npp.2011.82

Normann, C., & Buttenschøn, H. N. (2020). Gene–environment interactions between HPA-axis genes and childhood maltreatment in depression: a systematic review. *Acta neuropsychiatrica*, *32*(3), 111-121. https://doi.org/10.1017/neu.2020.1

Noteboom, A., Have, M. T., de Graaf, R., Beekman, A., Penninx, B., & Lamers, F. (2021). The long-lasting impact of childhood trauma on adult chronic physical disorders. *Journal of psychiatric research*, *136*, 87–94. https://doi.org/10.1016/j.jpsychires.2021.01.031

Nilsson, K. W., & Åslund, C. (2017). Differential susceptibility properties of the 5HTTLPR gene in relation to depressive symptoms and delinquency. *European Psychiatry*, *41*(S1), S102-S102. https://doi.org/10.1016/j.eurpsy.2017.01.315

O'Connor, D. B., Green, J. A., Ferguson, E., O'Carroll, R. E., & O'Connor, R. C. (2018). Effects of childhood trauma on cortisol levels in suicide attempters and ideators. *Psychoneuroendocrinology*, *88*, 9-16. https://doi.org/10.1016/j.psyneuen.2017.11.004

Olofsdotter, S., Åslund, C., Furmark, T., Comasco, E., & Nilsson, K. W. (2018). Differential susceptibility effects of oxytocin gene (OXT) polymorphisms and perceived parenting on social anxiety among adolescents. *Development and psychopathology*, *30*(2), 449-459. doi:10.1017/S0954579417000967

Othman, N., Ahmad, F., El Morr, C., & Ritvo, P. (2019). Perceived impact of contextual determinants on depression, anxiety and stress: a survey with university

students. *International journal of mental health systems*, *13*(1), 1-9. https://doi.org/10.1186/s13033-019-0275-x

Pace, T. W., Hu, F., & Miller, A. H. (2007). Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, behavior, and immunity*, *21*(1), 9-19. https://doi-org.proxy.library.carleton.ca/10.1016/j.bbi.2006.08.009

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., Botteron, K. N., Harms, M. P., & Barch, D. M. (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *39*(5), 1245–1253. https://doi.org/10.1038/npp.2013.327

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., Botteron, K. N., Harms, M. P., & Barch, D. M. (2015). Amygdala functional connectivity, HPA axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. *Journal of abnormal psychology*, *124*(4), 817–833. https://doi.org/10.1037/abn0000094

Palumbo, M. L., Prochnik, A., Wald, M. R., & Genaro, A. M. (2020). Chronic stress and glucocorticoid receptor resistance in asthma. *Clinical Therapeutics*. https://doi.org/10.1016/j.clinthera.2020.03.002

Parsaik, A. K., Abdelgawad, N., Chotalia, J. K., Lane, S. D., & Pigott, T. A. (2017). Early-Life Trauma in Hospitalized Patients With Mood Disorders and Its Association With Clinical Outcomes. *Journal of psychiatric practice*, *23*(1), 36–43. https://doi-org.proxy.library.carleton.ca/10.1097/PRA.0000000000000202

Patten SB. Age of Onset of Mental Disorders. *Can J Psychiatry*. 2017;62(4):235-236. doi:10.1177/0706743716685043

Paterniti, S., Sterner, I., Caldwell, C., & Bisserbe, J. C. (2017). Childhood neglect predicts the course of major depression in a tertiary care sample: a follow-up study. *BMC psychiatry*, *17*(1), 113. https://link-springer-com.proxy.library.carleton.ca/article/10.1186/s12888-017-1270-x

Peckins, M. K., Roberts, A. G., Hein, T. C., Hyde, L. W., Mitchell, C., Brooks-Gunn, J., ... & Lopez-Duran, N. L. (2020). Violence exposure and social deprivation is associated with cortisol reactivity in urban adolescents. *Psychoneuroendocrinology*, *111*, 104426.

Peng, Q., Yan, H., Wen, Y., Lai, C., & Shi, L. (2018). Association between NR3C1 rs41423247 polymorphism and depression: A PRISMA-compliant meta-analysis. *Medicine*, *97*(39), e12541. https://doi.org/10.1097/MD.0000000000012541

Petralia, M. C., Mazzon, E., Fagone, P., Basile, M. S., Lenzo, V., Quattropani, M. C., ... & Nicoletti, F. (2020). The cytokine network in the pathogenesis of major depressive disorder. Close to translation?. *Autoimmunity reviews*, 102504. https://doi-org.proxy.library.carleton.ca/10.1016/j.autrev.2020.102504

Pérez-Pérez, B., Cristóbal-Narváez, P., Sheinbaum, T., Kwapil, T. R., Ballespí, S., Peña, E., de Castro-Catala, M., Riba, M. D., Rosa, A., & Barrantes-Vidal, N. (2018). Interaction between FKBP5 variability and recent life events in the anxiety spectrum: Evidence for the differential susceptibility model. *PloS one*, *13*(2), e0193044. https://doi.org/10.1371/journal.pone.0193044

Peyrot, W. J., Van der Auwera, S., Milaneschi, Y., Dolan, C. V., Madden, P., Sullivan, P. F., Strohmaier, J., Ripke, S., Rietschel, M., Nivard, M. G., Mullins, N., Montgomery, G. W., Henders, A. K., Heat, A. C., Fisher, H. L., Dunn, E. C., Byrne, E. M., Air, T. A., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Baune, B. T., … Penninx, B. (2018). Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-analysis of 5765 Subjects From the Psychiatric Genomics Consortium. *Biological psychiatry*, *84*(2), 138–147. https://doi.org/10.1016/j.biopsych.2017.09.009

Plieger, T., Felten, A., Splittgerber, H., Duke, É., & Reuter, M. (2018). The role of genetic variation in the glucocorticoid receptor (NR3C1) and mineralocorticoid receptor (NR3C2) in the association between cortisol response and cognition under acute stress. *Psychoneuroendocrinology*, *87*, 173-180. https://doi.org/10.1016/j.psyneuen.2017.10.020

Popejoy, A. B., & Fullerton, S. M. (2016). Genomics is failing on diversity. *Nature News*, *538*(7624), 161.

Polanczyk, G., Caspi, A., Williams, B., Price, T. S., Danese, A., Sugden, K., ... & Moffitt, T. E. (2009). Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: replication and extension. *Archives of general psychiatry*, *66*(9), 978-985. doi:10.1001/archgenpsychiatry.2009.114

Power, C., Thomas, C., Li, L., & Hertzman, C. (2012). Childhood psychosocial adversity and adult cortisol patterns. *The British Journal of Psychiatry*, *201*(3), 199-206. https://doi.org/10.1192/bjp.bp.111.096032

Pruessner M, King S, Vracotas N, Abadi S, Iyer S, Malla AK, Shah J, Joober R. Gender differences in childhood trauma in first episode psychosis: Association with symptom severity over two years. Schizophr Res. 2019 Mar;205:30-37. doi: 10.1016/j.schres.2018.06.043. Epub 2018 Jun 21. PMID: 29935881.

Purves, K. L., Coleman, J. R., Rayner, C., Hettema, J. M., Deckert, J., McIntosh, A. M., ... & Eley, T. C. (2017). The common genetic architecture of anxiety disorders. *BioRxiv*, 203844.

Rafal, G., Gatto, A., & DeBate, R. (2018). Mental health literacy, stigma, and help-seeking behaviors among male college students. *Journal of American college health*, *66*(4), 284-291.

Raison, C. L., Borisov, A. S., Majer, M., Drake, D. F., Pagnoni, G., Woolwine, B. J., ... & Miller, A. H. (2009). Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. *Biological psychiatry*, *65*(4), 296-303. https://doi.org/10.1016/j.biopsych.2008.08.010

Réus, G. Z., Jansen, K., Titus, S., Carvalho, A. F., Gabbay, V., & Quevedo, J. (2015). Kynurenine pathway dysfunction in the pathophysiology and treatment of depression: Evidences from animal and human studies. *Journal of psychiatric research*, *68*, 316-328. https://doi.org/10.1016/j.jpsychires.2015.05.007

Reynolds, G. P. (2021). Early life trauma, DNA methylation and mental illness. https://doi.org/10.2217/epi-2021-0128

Rice, F., Riglin, L., Thapar, A. K., Heron, J., Anney, R., O'Donovan, M. C., & Thapar, A. (2019). Characterizing developmental trajectories and the role of neuropsychiatric genetic risk variants in early-onset depression. *JAMA psychiatry*, *76*(3), 306-313.

Sanabrais-Jiménez, M. A., Sotelo-Ramirez, C. E., Ordoñez-Martinez, B., Jiménez-Pavón, J., Ahumada-Curiel, G., Piana-Diaz, S., ... & Camarena, B. (2019). Effect of CRHR1 and CRHR2 gene polymorphisms and childhood trauma in suicide attempt. *Journal of Neural Transmission*, *126*(5), 637-644. https://doi.org/10.1007/s00702-019-01991-4

Sanz-Martin, A., Preciado-Mercado, S., & Olga-Inozemtseva, G. L. I. (2019). Prefrontal Dysfunction in Girls with Post-Traumatic Stress Disorder Secondary to Child Sexual Abuse, and its Relation to Basal Cortisol Levels. *J Trauma Stress Disor Treat 7*, *3*, 2. DOI: 10.4172/2324-8947.1000193

Schmidt, F. M., Lichtblau, N., Minkwitz, J., Chittka, T., Thormann, J., Kirkby, K. C., ... & Holdt, L. M. (2014). Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity. *Journal of psychiatric research*, *55*, 29-34. https://doi.org/10.1016/j.jpsychires.2014.04.021

Shadrina, M., Bondarenko, E. A., & Slominsky, P. A. (2018). Genetics factors in major depression disease. *Frontiers in psychiatry*, *9*, 334. https://doi.org/10.3389/fpsyt.2018.00334

Shahwan, S., Lau, J. H., Goh, C. M. J., Ong, W. J., Tan, G. T. H., Kwok, K. W., ... & Subramaniam, M. (2020). The potential impact of an anti-stigma intervention on mental health help-seeking attitudes among university students. *BMC psychiatry*, *20*(1), 1-14.

Shapero, B. G., Curley, E. E., Black, C. L., & Alloy, L. B. (2019). The interactive association of proximal life stress and cumulative HPA axis functioning with depressive symptoms. *Depression and anxiety*, *36*(11), 1089-1101. https://doi.org/10.1002/da.22957

Sharma, B., Sood, M., Ahuja, S., & Sharma, U. (2021). Development of New Tool to Measure Depression among Professional Undergraduate University Students. *Psychology and Education Journal*, *58*(4), 23-30. https://doi.org/10.17762/pae.v58i4.4427

Sheerin, C. M., Lind, M. J., Bountress, K. E., Nugent, N. R., & Amstadter, A. B. (2017). The genetics and epigenetics of PTSD: overview, recent advances, and future directions. *Current opinion in psychology*, *14*, 5-11. https://doi.org/10.1016/j.copsyc.2016.09.003

Sheikh, H. I., Kryski, K. R., Smith, H. J., Hayden, E. P., & Singh, S. M. (2013). Corticotropin-releasing hormone system polymorphisms are associated with children's cortisol reactivity. *Neuroscience*, *229*, 1-11. https://doi.org/10.1016/j.neuroscience.2012.10.056

Slavicfh, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin*, *140*(3), 774. https://psycnet.apa.org/doi/10.1037/a0035302

Spence, R., Kagan, L., Nunn, S., Bailey-Rodriguez, D., Fisher, H. L., Hosang, G. M., & Bifulco, A. (2020). Life events, depression and supportive relationships affect academic achievement in university students. *Journal of American college health*, 1-5. https://doi.org/10.1080/07448481.2020.1841776

Starr, L. R., Stroud, C. B., Shaw, Z. A., & Vrshek-Schallhorn, S. (2020). Stress sensitization to depression following childhood adversity: Moderation by HPA axis and serotonergic multilocus profile scores. *Development and Psychopathology*, 1-15. https://doi.org/10.1017/S0954579420000474

Starr, L. R., & Huang, M. (2019). HPA-axis multilocus genetic variation moderates associations between environmental stress and depressive symptoms among adolescents. *Development and psychopathology*, *31*(4), 1339-1352. https://doi.org/10.1017/S0954579418000779

Statistics Canada. Table 105-1101 Mental health profile, Canadian Community Health Survey - Mental Health (CCHS), by age group and sex, Canada and provinces. CANSIM (database). Last updated September 17, 2013

Tang, X., Tang, S., Ren, Z., & Wong, D. F. K. (2020). Psychological risk and protective factors associated with depressive symptoms among adolescents in secondary schools in China: A systematic review and meta-analysis. *Children and Youth Services Review*, *108*, 104680.https://doi.org/10.1016/j.childyouth.2019.104680

Tam, V., Patel, N., Turcotte, M., Bossé, Y., Paré, G., & Meyre, D. (2019). Benefits and limitations of genome-wide association studies. *Nature Reviews Genetics*, *20*(8), 467-484. https://doi.org/10.1038/s41576-019-0127-1

Vila-Badia R, Butjosa A, Del Cacho N, Serra-Arumí C, Esteban-Sanjusto M, Ochoa S, Usall J. Types, prevalence and gender differences of childhood trauma in first-episode psychosis. What is the evidence that childhood trauma is related to symptoms and functional outcomes in first episode psychosis? A systematic review. Schizophr Res. 2021 Feb;228:159-179. doi: 10.1016/j.schres.2020.11.047. Epub 2021 Jan 10. PMID: 33434728.

Vinkers, C. H., Joëls, M., Milaneschi, Y., Gerritsen, L., Kahn, R. S., Penninx, B. W., & Boks, M. P. (2015). Mineralocorticoid receptor haplotypes sex-dependently moderate depression susceptibility following childhood maltreatment. *Psychoneuroendocrinology*, *54*, 90-102. https://doi.org/10.1016/j.psyneuen.2015.01.018

Voth Schrag, R. J., & Edmond, T. E. (2018). Intimate partner violence, trauma, and mental health need among female community college students. *Journal of American college health*, *66*(7), 702-711. https://doi.org/10.1080/07448481.2018.1456443

Wang, Q., Shelton, R. C., & Dwivedi, Y. (2018). Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: A systematic review and meta-analysis. *Journal of affective disorders*, *225*, 422-428. https://doi.org/10.1016/j.jad.2017.08.066

Wasserman, D., Wasserman, J., Rozanov, V., & Sokolowski, M. (2009). Depression in suicidal males: genetic risk variants in the CRHR1 gene. *Genes, Brain and Behavior*, *8*(1), 72-79. https://doi.org/10.1111/j.1601-183X.2008.00446.x

Weeger, J., Ising, M., Müller-Myhsok, B., Uhr, M., Schmidt, U., & Steiger, A. (2020). Salivary cortisol response to psychosocial stress in the late evening depends on CRHR1 genotype. *Psychoneuroendocrinology*, 104685. https://doi.org/10.1016/j.psyneuen.2020.104685

Wesarg, C., Van Den Akker, A. L., Oei, N. Y., Hoeve, M., & Wiers, R. W. (2020). Identifying pathways from early adversity to psychopathology: A review on dysregulated HPA axis functioning and impaired self-regulation in early childhood. *European Journal of Developmental Psychology*, 1-20.

Widom, C. S., DuMont, K., & Czaja, S. J. (2007). A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. *Archives of general psychiatry*, *64*(1), 49–56. https://doi.org/10.1001/archpsyc.64.1.49

Wiens, K., Gillis, J., Nicolau, I., & Wade, T. J. (2020). Capturing risk associated with childhood adversity: independent, cumulative, and multiplicative effects of physical abuse, sexual abuse, and family violence on mental disorders and suicidality. *The Permanente Journal*, *24*. https://dx-doi-org.proxy.library.carleton.ca/10.7812%2FTPP%2F19.079

Wilkinson, P. O., & Goodyer, I. M. (2011). Childhood adversity and allostatic overload of the hypothalamic–pituitary–adrenal axis: a vulnerability model for depressive disorders. *Development and psychopathology*, *23*(4), 1017.

World Health Organization. (2011). Community genetics services: report of a WHO consultation on community genetics in low-and middle-income countries.

Yaylaci, F. T., Cicchetti, D., Rogosch, F. A., Bulut, O., & Hetzel, S. R. (2017). The interactive effects of child maltreatment and the FK506 binding protein 5 gene (FKBP5) on dissociative symptoms in adolescence. *Development and psychopathology*, *29*(3), 1105-1117. https://doi.org/10.1017/S095457941600105X

Yang, L., Hu, Y., Silventoinen, K., & Martikainen, P. (2020). Childhood adversity and depressive symptoms among middle-aged and older Chinese: Results from China health and retirement longitudinal study. *Aging & mental health*, *24*(6), 923-931.https://doi-org.proxy.library.carleton.ca/10.1080/13607863.2019.1569589

Yang, T., Nie, Z., Shu, H., Kuang, Y., Chen, X., Cheng, J., ... & Liu, H. (2020). The Role of BDNF on Neural Plasticity in Depression. *Frontiers in Cellular Neuroscience*, *14*, 82. https://doi.org/10.3389/fncel.2020.00082

Yaribeygi, H., Panahi, Y., Sahraei, H., Johnston, T. P., & Sahebkar, A. (2017). The impact of stress on body function: A review. *EXCLI journal*, *16*, 1057–1072. https://doi.org/10.17179/excli2017-480

Young, E. S., Doom, J. R., Farrell, A. K., Carlson, E. A., Englund, M. M., Miller, G. E., ... & Simpson, J. A. (2021). Life stress and cortisol reactivity: An exploratory analysis of the effects of stress exposure across life on HPA-axis functioning. *Development and psychopathology*, *33*(1), 301-312.

Zhang, L., Hu, X. Z., Yu, T., Chen, Z., Dohl, J., Li, X., ... & Li, M. (2020). Genetic association of FKBP5 with PTSD in US service members deployed to Iraq and Afghanistan. *Journal of psychiatric research*, *122*, 48-53. https://doi.org/10.1016/j.jpsychires.2019.12.014

Zhang, W., Cao, C., Wang, M. *et al.* Monoamine Oxidase A (*MAOA*) and Catechol-O-Methyltransferase (*COMT*) Gene Polymorphisms Interact with Maternal Parenting in Association with Adolescent Reactive Aggression but not Proactive Aggression: Evidence of Differential Susceptibility. *J Youth Adolescence* **45,** 812–829 (2016). https://doi.org/10.1007/s10964-016-0442-1

Zhang, L., Li, Z., Chen, J., Li, X., Zhang, J., & Belsky, J. (2016). The BDNF Val66Met polymorphism interacts with maternal parenting influencing adolescent depressive symptoms: Evidence of differential susceptibility model. *Journal of youth and adolescence*, *45*(3), 471-483. https://doi.org/10.1007/s10964-015-0378-x

Zhang, D. D., Fang, J., Zhang, L., Yuan, J. Y., Wan, Y. H., Su, P. Y., ... & Sun, Y. (2021). Pubertal recalibration of cortisol reactivity following early life parent-child separation. *Journal of Affective Disorders*, *278*, 320-326.

Zheng, Y., Albert, D., McMahon, R. J., Dodge, K., & Dick, D. (2018). Glucocorticoid receptor (NR3C1) gene polymorphism moderate intervention effects on the developmental trajectory of African-American adolescent alcohol abuse. *Prevention Science*, *19*(1), 79-89.

Zheng, L., & Gan, Y. (2018). Influence of early family cohesion on future orientation. *Journal of Individual Differences*. https://doi.org/10.1027/1614-0001/a000260

Zou, W., Feng, R., & Yang, Y. (2018). Changes in the serum levels of inflammatory cytokines in antidepressant drug-naïve patients with major depression. *PloS one*, *13*(6), e0197267. https://doi.org/10.1371/journal.pone.0197267

# Appendices

## Appendix A. Ethics Clearance Certificate


Office of Research Ethics 5110 Human Computer Interaction Bldg | 1125 Colonel By Drive | Ottawa, Ontario K1S 5B6 613-520-2600 Ext: 4085 ethics@carleton.ca

**CERTIFICATION OF INSTITUTIONAL ETHICS CLEARANCE**

The Carleton University Research Ethics Board-B (CUREB-B) has granted ethics clearance for the research project described below and research may now proceed. CUREB-B is constituted and operates in compliance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS2).

**Ethics Protocol Clearance ID:** Project # 109133

**Research Team: Robyn McQuaid (Primary Investigator)**

Kelly Moreland (Co-Investigator) Sabina Franklyn (Co-Investigator (External)) Zachary Kaminsky (Other) Dr. Kimberly Matheson (Research Supervisor) Jennifer Kemp (Research Assistant) Dr. Hymie Anisman (Collaborator)

**Project Title:** Full Board: A Biological and Psychosocial Characterization of Mental Health Symptoms [Sabina Franklyn and Kelly Moreland]

**Funding Source** (If applicable): Effective: **July 31, 2018** Expires: **July 31, 2019**. **Please ensure the study clearance number is prominently placed in all recruitment**

**and consent materials: CUREB-B Clearance # 109133.**

***Restrictions:***

This certification is subject to the following conditions:
Clearance is granted only for the research and purposes described in the application.

Any modification to the approved research must be submitted to CUREB-B via a Change to Protocol Form. All changes must be cleared prior to the continuance of the research.

3. An Annual Status Report for the renewal of ethics clearance must be submitted and cleared by the renewal date listed above. Failure to submit the Annual Status Report will result in the closure of the file. If funding is associated, funds will be frozen.

4. A closure request must be sent to CUREB-B when the research is complete or terminated.

5. Should any participant suffer adversely from their participation in the project you are required to report the matter to CUREB-B.

Failure to conduct the research in accordance with the principles of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2ndedition* and the *Carleton University Policies and Procedures for the Ethical Conduct of Research* may result in the suspension or termination of the research project.

Upon reasonable request, it is the policy of CUREB, for cleared protocols, to release the name of the PI, the title of the project, and the date of clearance and any renewal(s).

Please contact the Research Compliance Coordinators, at ethics@carleton.ca, if you have any questions.

**CLEARED BY: Date: July 31, 2018**

Bernadette Campbell, PhD, Chair, CUREB-B Andy Adler, PhD, Vice-Chair, CUREB-B

## Appendix B. Informed Consent


Informed Consent

**Study Title:** A Biological and Psychosocial Characterization of Mental Health Symptoms
**Study Personnel:** Sabina Franklyn, Carleton University (Graduate Researcher), Kelly Moreland, Carleton University (Graduate Researcher), Jennifer Kemp, Carleton University (Undergraduate Researcher), Dr. Kim Matheson, Carleton University (Faculty Supervisor) Dr. Robyn McQuaid, The Royal's Institute of Mental Health Research (IMHR; Co-Supervisor), Dr. Hymie Anisman, Carleton University (Collaborator) and Dr. Zach Kaminsky, The Royal's IMHR (External Collaborator).

**Purpose and task requirements:** The purpose of this study is to assess how factors such as social resources (e.g. support from friends, and social connections) are used to cope with negative life events or stressors, and the impact of these events on mental health. We are also interested in examining how certain genetic and hormonal/immune factors relate to well-being and mental health symptoms.
In this session, we will be asking everyone to fill out a number of questionnaires regarding information related to your background (e.g., demographic, family and medical history), early life experiences (e.g., trauma, parental bonding), mood (e.g., have they recently been feeling sad or anxious), substance use, and the quality of your interpersonal relationships (e.g., social support, group identities). We are also asking all participants to provide a DNA sample through the simple act of spitting into a tube however, due to the relatively large volume of saliva required (~1 ml) this can take up to 5 minutes. We will use the saliva sample (that you will provide today) to determine the presence or absence of particular genes.

We are also interested in examining differences in stress hormones and immune system functioning among participants. To measure these hormones, we will be asking certain participants to provide a single blood sample at the end of this session. We will have everyone complete an eligibility screening questionnaire to assess whether you would be a good candidate to provide a blood sample, but also if this is something you are comfortable providing. If you are willing and eligible to provide a blood sample, you will go a separate room and a Registered Nurse/Phlebotomist will draw a blood sample (just as they do when you have a blood test at your doctor's office or clinic). A very small amount (approximately 8mL) will be taken. All instruments used for blood withdrawal will be sterile and one-time use only. The blood samples will be analyzed for levels of related hormones (cortisol), cytokines (CRP, IL-6, IL-10, TNF-α, etc.) and epigenetic factors (i.e. tags on your DNA that show how environmental experiences shape the way our genes express). Some of this work will be conducted at the Institute of Mental Health Research by Dr. Robyn McQuaid and Dr. Zachary Kaminsky.
By understanding the biological and psychosocial factors that lead to different mood outcomes, we will gain a better understanding of how mood changes develop. This research will therefore help to develop improved approaches to both treat, and prevent mood disorders in the future.

**Who can participant**: University undergraduate students between the ages of 17-30 who have fluent English comprehension.

You will receive 2% course credit. This session will take 1 hour and 45 minutes.
Potential risks or causes of discomfort for participants
Some individuals might feel discomfort when asked to provide personal, sensitive information. Furthermore, responding to some of the questions in this study or thinking about various stressors or difficulties in your life can be anxiety provoking or make you unhappy. If this is the case, the Debriefing form at the end of the study contains contact information for people who are available to help. You can also choose to withdraw from the study at any point. Inserting the needle usually gives a small pin-prick (as it does when you get blood tests at the doctor's office or clinic). The blood draw is very quick, however, if at any time you wish to stop, please let us know and the nurse will take out the needle. We are looking to collect about a teaspoon of saliva. Some participants may therefore feel discomfort or embarrassment about spitting into a tube in the presence of the researcher, in which case he/she will be happy to leave the room to give you privacy. You will be asked to not drink, eat, smoke or chew gum for 30 minutes before providing this sample.
Anonymity and confidentiality
All information and samples collected from you for this study will be identified with a code number, as opposed to any personal identifiers such as your name or address. We ensure that all information you share with us, such as personal information (i.e. adverse life experiences) and information regarding illegal activities (i.e. substance use) will remain strictly confidential. We will maintain a separate record that matches your personal identification details with this code number. This is necessary in order for us to re-contact you in the future (with your express permission to do so), and so that we can respect your right to withdraw from the study at a later date (to be described below). However, this record that allows your identity to be linked to your information will kept in a separate and secured location, and will only be accessible to the primary researchers, in order to maintain anonymity and confidentiality of your information. All personal identifying information will be destroyed within 5 years of study completion. Furthermore, the saliva and blood samples will be stored in a secured storage area that is only accessible by the researcher and research assistants.

Genetic testing: Common questions and concerns
What is DNA?
DNA is a large molecule that contains information necessary for our bodies to build all the components needed for our development, growth and survival. This information is commonly referred to as the genetic code or the DNA sequence. Some rare diseases can be attributed entirely to simple errors in our DNA sequence. However, the majority of common diseases (including depression) are caused by a combination of many different genetic factors, together with environmental factors (how we grew up, life events, etc).
What will my DNA be used for?
If you compare any two people, their DNA will be about 99% identical. We are interested in the 1% of DNA that is different between people. Our current plan is to investigate these differences, focusing on just a small proportion of your genes (we are targeting less than 100 of the ~30,000 genes that humans have), which we anticipate may be involved in risk of either anxiety or

depression. With your express permission, we will conduct future follow-up studies on your DNA, which will extend the analysis to substantially more genes – potentially all genes. These future studies will be limited to analyses that examine polymorphisms, mutations and epigenetic modifications to DNA molecule, and will not involve any other use or manipulation of your DNA sample. However, in no case will your samples be kept for more than 5 years from study completion, at which time the samples and the sample container will be incinerated. Thus, the data derived from the sample will be kept (stripped of any information that could identify you), but the sample or remnants of the sample, including DNA, will be destroyed (incinerated). At the end of this form, you have the option to opt-out of any such future uses of your DNA sample.

How long will my DNA be stored, and potentially used in research?

By providing a DNA sample and signing this form, you are indicating that you are willing for us to preserve and analyze your DNA sample for an extended period of time (5 years or less). During this period, use of the sample is guaranteed to be limited to studies that examine polymorphisms, mutations and epigenetic modifications to DNA molecule. As indicated above, your saliva and any DNA samples will be destroyed, by incineration, no later than 5 years after study completion.

Will I be told the results of my own genetic analysis?

No. Your DNA sample and genetic information will be identified by a code number, and not your name. This preserves confidentiality of this information. Returning your personal genetic information to you would require that confidentiality to be compromised, so will be avoided. Furthermore, as described above, genetic data collected in this study will not allow accurate prediction of whether or not you will develop any disease. Although in the future we hope to be able to use genetic materials to examine disease susceptibility, our research is in a preliminary phase and we are not currently able to provide this kind of information on an individual basis.

What if something unexpected and potentially dangerous is discovered in my DNA

None of the DNA sites that we plan to analyze are currently known to be predictive of disease with any real accuracy. However, future advances in genetic research could allow disease predictions to be possible based on information from these, or other genetic sites. In exceptional circumstances, if genetic research reveals information about a serious or life-threatening condition that can be prevented or treated through intervention, then we have an obligation to inform you of this information, and potentially also inform your biological relatives who may share similar risk of disease. This would therefore represent a potential breach of confidentiality. In this instance, only information directly relating to disease diagnosis, and participant identity, would be shared. We wish to make clear, however, that it is not our intent to systematically go through the samples after our initial analyses, and so even if it was subsequently discovered that certain genes might carry relevant information for you, it is unlikely that we would actually spot any vulnerabilities you might have.

Can my DNA ever be used to identify me?

This is a complicated question to answer. Unless you have an identical twin (whose DNA will be identical to yours), your DNA is absolutely unique to you. It is this unique nature of genetic material that allows individuals to be identified based entirely on their DNA, through techniques such as DNA fingerprinting. It is therefore theoretically possible that in the future, your identity could be determined from simply analyzing your DNA sample. It is extremely unlikely, however, that you could be identified based on your DNA sample. In order to identify you based purely on your DNA sample, it would be necessary to compare your DNA sample that you provide today, with another DNA sample from you in a DNA database, which is linked to your

identity. DNA databases do exist in countries including Canada, Australia, USA and UK, but are limited to samples from criminal offenders. Access to these databases is strictly limited to law enforcement agencies thus cannot be accessed by researchers. Access to DNA samples taken for this study will similarly be limited to the researchers, and will not be provided to any law enforcement agency unless we become legally obliged to do so (to our knowledge, this has never happened to any research group). Furthermore, these government DNA databases typically contain information about only 13 regions of human DNA, none of which are to be analyzed in the present study.

Right to withdraw from this study

Participation in this study is entirely voluntary. At any point during the study you have the right to not complete certain questions or to withdraw with no penalty whatsoever and will still receive course credit. Furthermore, if at a later date you wish to withdraw from the study, you can contact the principal investigators and we will destroy all of your records (questionnaire answers, responses from the interview, plus DNA sample) from this study. The only exceptions are where data has already been published, in this instance, unpublished data plus your DNA sample will be destroyed, or if 5 years have passed, in which case, all personal identifying information will have been destroyed and there will be no way to re-identify participants.

If you have any additional questions or concerns, please ask the researcher today, or contact any of the graduate researchers or supervisors at a later date.

Sabina Franklyn, Department of Neuroscience, Carleton University
Email: sfran047@uottawa.ca

Kelly Moreland, Department of Neuroscience, Carleton University
Email: KellyMoreland@cmail.carleton.ca

Dr. Robyn McQuaid, The Royal's Institute of Mental Health Research
Phone: 613 722-6521 ext. 6490, Email: Robyn.McQuaid@theroyal.ca

Dr. Kim Matheson, Department of Neuroscience, Carleton University
Phone: 613 520-2600 ext. 2652, Email: kim.matheson@carleton.ca

If you have any ethical concerns with the study, please contact Dr. Bernadette Campbell, Chair, Carleton University Research Ethics Board-B (by phone: 613-520-2600 ext. 4085 or by email: ethics@carleton.ca).

Signatures

Participant's Full Name: _____ Participant's Signature: _____

Researcher's Name: _____ Researcher's Signature: _____

Date_____

How can we use your DNA?:

While we would ideally obtain consent to use your DNA for any future research studies that are aimed at analyzing DNA sequence (Option 1 below), please indicate below how you would like

your DNA sample to be treated in the future. There are no penalties for you associated with your selection.

☐ Option 1: I grant the researcher permission to use my DNA for any future research studies that involve analyses of polymorphisms, mutations and epigenetic modifications to the DNA molecule, within a 5 year period of study completion.

☐ Option 2: I grant the researcher permission to re-contact me to seek consent to use my DNA in future research studies, within a 5 year period of study completion.
Email:_____ Phone Number:_____

☐ Option 3: I grant use of my DNA, but this use will be strictly limited to the analysis of <100 genes, as described in the current research plan. This can only be done within a 5 year period of study completion.

This study has been cleared by the Carleton University Research Ethics Committee (CUREB-B Clearance #109133) and is funded by the Royal's Institute of Mental Health Research.

## Appendix C. Measures

Carleton UNIVERSITY
Canada's Capital University

Demographic and Medical History

The purpose of the following set of questions is to collect demographic information about various aspects of your life. Although some of the questions may seem unrelated to the present study (e.g. weight, height, religion, etc…) these factors may be important determinants of your health and well-being.

1. Gender: ___Female ___Male ___Transgender ___Gender non-Conforming ___Not listed (please specify) _____

2. Age:_____

3. What is your citizenship status?

_____ Canadian citizen

_____ Landed immigrant Since what year?_____ Country of origin _____

_____ Student visa Since what year?_____ Country of origin _____

_____ Temporary visa Since what year?_____ Country of origin _____

_____ Refugee Since what year?_____ Country of origin _____

_____ Permanent Resident Since what year?_____ Country of origin_____

_____ Other (please specify): _____

4. What is your first language? _____

If your first language is not English, how long have you been **fluent** in reading, writing and comprehension of the English language? _____

5. What is your ethnic/racial background? *Please select the one that best applies to you.*

____Asian (e.g., Chinese, Japanese, Korean)
____South Asian (e.g., East Indian, Pakistani, Punjabi, Sri Lankan)
____South East Asian (e.g., Cambodian, Indonesian, Laotian)
____Arab/West Asian (e.g., Armenian, Egyptian, Iranian, Lebanese, Moroccan)
____Black (e.g., African, Haitian, Jamaican, Somali)
____Latin American/Hispanic
____Aboriginal
____White/Euro-Caucasian
____Other (please specify): _____

6. What is your religious affiliation? *Please select the one that best applies to you*

____None—Atheist (e.g., belief that there is NO God)
____None—Agnostic (e.g., belief that the existence of God cannot be known)
____Protestant (e.g., United, Anglican, Baptist, Presbyterian, Lutheran, Pentecostal, Mennonite,"Christian")
____Catholic (e.g., Roman Catholic, Ukrainian Catholic)
____Jewish
____Muslim
____Buddhist
____Hindu
____Sikh
____Bahá'í
____Other (please specify):_____
____Prefer not to answer:_____

7. What is your current living arrangement? *Please select the one that best applies to you.*

_____Living alone in residence (at Carleton University)
_____ Living alone off-campus
_____ Living with friends in residence (at Carleton University)
_____ Living with friends off-campus
_____ Living with roommates in residence (at Carleton University)
_____ Living with roommates off-campus
_____ Living with parents
_____ Living with spouse/significant other
_____ Living with spouse/significant other and young children (13 years and younger)
_____ Living with spouse/significant other and older children (13 years and older)
_____ Living alone with young children (13 years and younger)
_____ Living alone with older children (13 years and older)
_____ Other (please specify) _____

8. What is your current relationship status? *Please select the one that best applies to you.*

_____ Single, and not seeing anyone
_____ Going out with someone
_____ In a serious dating relationship
_____ Have recently broken up. Please specify how many weeks ago you broke up____
_____ Living with an intimate other
_____ Engaged
_____ Married
_____Separated/Divorced. Please specify how many months ago you separated_____
_____ Widowed

9. Is your current (or most recent) partner: Male _____, Female _____, Other_____?

10. Have you had or do you currently have any health related (i.e., medical) illnesses or physical conditions? *Please select the one that best applies to you.*

_____ No, I don't

_____ Yes, I did but I no longer do

_____ Yes, I do

If YES, please specify illness/condition you had/have _____

If YES, please specify treatment received or currently receiving_____

11. Are you currently sick with a cold? No_____ Yes_____

Flu? No_____ Yes_____

12. Do you currently have a mental health condition (e.g. depression, anxiety, etc.)?

No_____

Yes_____

If YES, please specify disorder/condition _____

If YES, are you currently being treated for these symptoms?

No_____

Yes_____ (if yes please specify)_____

13. Have you ever in the past had a psychological disorder/condition (e.g. depression, anxiety, etc.) but no longer do?

NO, I haven't ____ YES, I have_____

If YES, please specify the disorder/condition you had_____

14. Have you ever had thoughts of suicide in your lifetime? No_____ Yes_____

15. Have you had thoughts of suicide in the past 12 months? No_____ Yes_____

16. Have you ever attempted suicide in your lifetime? No_____ Yes_____

17. Have you attempted suicide in the past 12 months? No_____ Yes_____

18. In your opinion, how would you describe your health?

_____Poor

_____Fair

_____Good

_____Very good

_____Excellent

19. Are you on any of the following medications (please check all that apply)?

_____ Anti-inflammatories (please specify) _____

_____ Anti-depressants (please specify) _____

_____ Anti-anxieties (please specify) _____

_____ Allergy medication (please specify) _____

_____ Other prescription drugs (please specify) _____

20. Have you taken any of these medications in the past 24 hours? _____NO _____YES

If yes:

a) Which medication(s)? _____

b) What time did you take it/them? _____

c) How much did you take? _____

21. Are you taking any form of hormonal based contraception (birth control)?

_____NO _____YES

If yes, which one?

____Standard birth control pill

____Evra Patch

____NuvaRing

____Depo-Provera Shot

____Mini (progestin-only) birth control pill

____Other: _____

22. Are you currently on your period? _____NO _____YES

When did your last period begin (how many days ago)? _____

And end (how many days ago)? _____

23. How often do you exercise/week? _____

24. Have you exercised in the last 24hrs? _____NO _____YES

What form of exercise was it? _____

25.Do you currently smoke? _____NO _____YES

If YES, how many/day? _____

26.Do you drink alcohol? _____NO _____YES

If YES, How much alcohol do you drink on average?
_____ drinks per day _____ drinks per week

27.Do you take or use any drugs? _____NO _____YES

If YES, which drugs have you used in the past month? (check as many as apply)
____Cannabis/hash; How many times in the past month? _____
____Ecstasy; How many times in the past month? _____
____Cocaine; How many times in the past month? _____
____Opioids (non-prescription); How many times in the past month? _____
____Other; Please specify _____; How many times in the past month?_____

28.What is your estimate of your family's gross income per year? *Please select the one that best applies to you.*

____ under $15,000
____ $15,000 - $29,999
____ $30,000 - $44,999
____ $45,000 - $59,999
____$60,000 - $74,999
____ $75,000 - $89,999
____ $90,000 - $104,999
____$105,000 or more
____ Not sure

29. What is your employment status (aside from being a student)?
_____ Employed Part-time
_____ Employed Full-time
_____ Unemployed
_____ Retired
_____ Other (please specify_____

30. What time did you wake up this morning? _____

31. When was the last time you ate today? _____

32. What did you have to eat and drink today? _____

33. How many pets do you have?
_____ None
_____ One
_____ Two
_____ Three
_____ 4+

34. If you have pets, what kinds of pets do you own (check all that apply)? ____Cat ____Dog

_____ Other (specify) : _____

35. Are you currently a primary (daily) caregiver of your pet(s)? _____Yes _____ No

Carleton UNIVERSITY
Canada's Capital University

***Beck Anxiety Inventory (BAI)***

Please rate how much you have been bothered by each of the following symptoms over the past week.

| | *Not at All* | *Mildly but it didn't bother me much* | *Moderately- it wasn't pleasant at times* | *Severely- it bothered me a lot* |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| 1. Numbness or tingling | 0 | 1 | 2 | 3 |
| 2. Feeling hot | 0 | 1 | 2 | 3 |
| 3. Wobbliness in legs | 0 | 1 | 2 | 3 |
| 4. Unable to relax | 0 | 1 | 2 | 3 |
| 5. Fear of the worst happening | 0 | 1 | 2 | 3 |
| 6. Dizzy or light-headed | 0 | 1 | 2 | 3 |
| 7. Heart pounding or racing | 0 | 1 | 2 | 3 |
| 8. Unsteady | 0 | 1 | 2 | 3 |
| 9. Terrified | 0 | 1 | 2 | 3 |
| 10. Nervous | 0 | 1 | 2 | 3 |
| 11. Feelings of choking | 0 | 1 | 2 | 3 |
| 12. Hands trembling | 0 | 1 | 2 | 3 |
| 13. Shaky | 0 | 1 | 2 | 3 |
| 14. Fear of losing control | 0 | 1 | 2 | 3 |
| 15. Difficulty breathing | 0 | 1 | 2 | 3 |
| 16. Fear of dying | 0 | 1 | 2 | 3 |
| 17. Scared | 0 | 1 | 2 | 3 |
| 18. Indigestion or discomfort in abdomen | 0 | 1 | 2 | 3 |
| 19. Faint | 0 | 1 | 2 | 3 |
| 20. Face flushed | 0 | 1 | 2 | 3 |
| 21. Sweating (not due to heat) | 0 | 1 | 2 | 3 |

Source: Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology*, *56*(6), 893.

Carleton UNIVERSITY
Canada's Capital University

***Beck Depression Inventory (BDI)***

On this questionnaire are groups of statements. Please read the entire group of statements in each category. Then pick out **ONE** statement in that group which best describes the way you feel. Check off the number beside the statement you have chosen.

---

1. ___ 0 = I do not feel sad
   ___ 1 = I feel sad or blue
   ___ 2a = I am blue or sad all of the time and I can't snap out of it
   ___ 2b = I am so sad or unhappy that it is very painful
   ___ 3 = I am so sad or unhappy that I can't stand it

2. ___ 0 = I am not particularly pessimistic or discouraged about the future
   ___ 1 = I feel discouraged about the future
   ___ 2a = I feel I have nothing to look forward to
   ___ 2b = I feel I won't every get over my troubles
   ___ 3 = I feel that the future is hopeless and things cannot improve

3. ___ 0 = I do not feel like a failure
   ___ 1 = I feel I have failed more than the average person
   ___ 2a = I feel I have accomplished very little that is worthwhile or that means anything
   ___ 2b = As I look back on my life, all I can see is a lot of failures
   ___ 3 = I feel I am a complete failure as a person

4. ___ 0 = I am not particularly dissatisfied
   ___ 1a = I feel bored most of the time
   ___ 1b = I don't enjoy things the way I used to
   ___ 2 = I don't get satisfaction out of anything anymore
   ___ 3 = I am dissatisfied with everything

5. ___ 0 = I don't feel particularly guilty
   ___ 1 = I feel bad or unworthy a good part of the time
   ___ 2a = I feel quite guilty
   ___ 2b = I feel bad or unworthy practically of the time now
   ___ 3 = I feel as though I am very bad or worthless

6. ___ 0 = I don't feel I am being punished
   ___ 1 = I have a feeling that something bad may happen to me
   ___ 2 = I feel I am being punished or will be punished
   ___ 3a = I feel I deserve to be punished
   ___ 3b = I want to be punished

7. ___ 0 = I don't feel disappointed in myself
   ___ 1a = I am disappointed in myself

___ 1b = I don't like myself
___ 2 = I am disgusted with myself
___ 3 = I hate myself

8. ___ 0 = I do not feel I am any worse than anybody else
___ 1 = I am very critical of myself for my weaknesses or mistakes
___ 2a = I blame myself for everything that goes wrong
___ 2b = I feel I have many bad faults

9. ___ 0 = I don't have thoughts of harming myself
___ 1 = I have thoughts of harming myself but I would not carry them out
___ 2a = I feel I would be better off dead
___ 2b = I have definite plans about committing suicide
___ 2c = I feel my family would be better off if I were dead
___ 3 = I would kill myself if I could

10. ___ 0 = I don't cry anymore than usual
___ 1 = I cry more now than I used to
___ 2 = I cry all the time now. I can't stop it
___ 3 = I used to be able to cry but now I can't cry at all even though I want to

11. ___ 0 = I am no more irritable than usual
___ 1 = I am more irritable than usual
___ 2 = I am much more irritable than usual
___ 3 = I am irritable all the time

12. ___ 0 = I have not lost interest in other people
___ 1 = I am less interested in other people than I used to be
___ 2 = I have lost most of my interest in other people and I have little feeling for them
___ 3 = I have lost all my interest in other people and don't care about them at all

13. ___ 0 = I make decisions about as well as ever
___ 1 = I am less sure of myself now and try to put off making decisions
___ 2 = I can't make decisions anymore without help
___ 3 = I can't make decisions at all anymore

14. ___ 0 = I don't feel I look any worse than I used to
___ 1 = I am worried that I am looking old or unattractive
___ 2 = I feel that there are permanent changes in my appearance and they make me look unattractive
___ 3 = I feel that I am ugly or repulsive looking

15. ___ 0 = I can work about as well as before
___ 1a = It takes extra effort to get started at doing something
___ 1b = I don't work as well as I used to
___ 2 = I have to push myself very hard to do anything
___ 3 = I can't do any work at all

16. ___ 0 = I can sleep as well as usual

___ 1 = I wake up more tired in the morning than I used to
___ 2 = I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
___ 3 = I wake up early every day and can't get more than 5 hours sleep

17. ___ 0 = I don't get any more tired than usual
___ 1 = I get tired more easily than I used to
___ 2 = I get tired from doing anything
___ 3 = I get too tired to do anything

18a. ___ 0 = My appetite is no worse than usual
___ 1 = My appetite is not as good as it used to be
___ 2 = My appetite is much worse now
___ 3 = I have no appetite at all any more

18b. ___ 0 = I am not eating more than usual
___ 1 = I am eating a little more than usual
___ 2 = I am eating somewhat more than usual
___ 3 = I am eating a lot more than usual

18c. ___ 0 = I have had no change in food preferences lately
___ 1 = I have been craving more carbohydrates (starches or sweets lately)
___ 2 = I have had irresistible craving for sweets and starches lately

19a. ___ 0 = I haven't lost much weight, if any, lately
___ 1 = I have lost more than 5 pounds
___ 2 = I have lost more than 10 pounds
___ 3 = I have lost more than 15 pounds

19b. ___ 0 = I have not gained any weight lately
___ 1 = I have gained more than 5 pounds
___ 2 = I have gained more than 10 pounds
___ 3 = I have gained more than 15 pounds

20. ___ 0 = I am no more concerned about my health than usual
___ 1 = I am concerned about aches and pains or upset stomach or constipation or other unpleasant feelings in my body
___ 2 = I am so concerned with how I feel or what I feel that it's hard to think of much else
___ 3 = I am completely absorbed in what I feel

21. ___ 0 = I have not noticed any recent change in my interest in sex
___ 1 = I am less interested in sex than I used to be
___ 2 = I am much less interested in sex now
___ 3 = I have lost interest in sex completely

22. ___ 0 = I have not had any increase in nightly sleep length lately
___ 1 = I have had at least 1-hour increase in sleep length
___ 2 = I have had at least 2-hour increase in sleep length
___ 3 = I have had at least 3-hour increase in sleep length

My average nightly sleep length in the past week is: _____ hours

23. ___ 0 = I am not feeling more fatigued than usual
___ 1 = I feel more fatigued than usual lately, but it does not interfere with my daily functioning
___ 2 = I feel more fatigued than usual lately, and it interferes somewhat with my daily functioning
___ 3 = I feel more fatigued than usual lately, and it significantly interferes with my daily functioning

24. ___ 0 = I have not had any mood swings or slumps lately
___ 1 = I have had some mood swings or slumps lately but very minor
___ 2 = I have had more mood swings or slumps than usual
___ 3 = I have had severe mood swings or slumps lately

25. ___0 = I have not been more sensitive in social situations lately
___ 1 = I have been feeling slightly more sensitive in social situations lately
___ 2 = I have been feeling much more sensitive in social situations lately
___ 3 = I have been feeling extremely sensitive in social situations lately

Source: Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory of measuring depression. *Archives of General Psychiatry, 4*, 561-571.
In addition we have added 7 items regarding sleep, eating and sensitivity that reflect a-typical depression, as our lab has done in the past.

Carleton UNIVERSITY
Canada's Capital University

***Depression Anxiety and Stress Scale (DASS – 21)***

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

*The rating scale is as follows:*

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

| | | | | | |
|---|---|---|---|---|---|
| 1 | I found it hard to wind down | 0 | 1 | 2 | 3 |
| 2 | I was aware of dryness of my mouth | 0 | 1 | 2 | 3 |
| 3 | I couldn't seem to experience any positive feeling at all | 0 | 1 | 2 | 3 |

| | | | | | |
|---|---|---|---|---|---|
| 4 | I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion) | 0 | 1 | 2 | 3 |
| 5 | I found it difficult to work up the initiative to do things | 0 | 1 | 2 | 3 |
| 6 | I tended to over-react to situations | 0 | 1 | 2 | 3 |
| 7 | I experienced trembling (eg, in the hands) | 0 | 1 | 2 | 3 |
| 8 | I felt that I was using a lot of nervous energy | 0 | 1 | 2 | 3 |
| 9 | I was worried about situations in which I might panic and make a fool of myself | 0 | 1 | 2 | 3 |
| 10 | I felt that I had nothing to look forward to | 0 | 1 | 2 | 3 |
| 11 | I found myself getting agitated | 0 | 1 | 2 | 3 |
| 12 | I found it difficult to relax | 0 | 1 | 2 | 3 |
| 13 | I felt down-hearted and blue | 0 | 1 | 2 | 3 |
| 14 | I was intolerant of anything that kept me from getting on with what I was doing | 0 | 1 | 2 | 3 |
| 15 | I felt I was close to panic | 0 | 1 | 2 | 3 |
| 16 | I was unable to become enthusiastic about anything | 0 | 1 | 2 | 3 |
| 17 | I felt I wasn't worth much as a person | 0 | 1 | 2 | 3 |
| 18 | I felt that I was rather touchy | 0 | 1 | 2 | 3 |
| 19 | I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat) | 0 | 1 | 2 | 3 |
| 20 | I felt scared without any good reason | 0 | 1 | 2 | 3 |
| 21 | I felt that life was meaningless | 0 | 1 | 2 | 3 |

Source: Lovibond. L. Manual for the Depression Anxiety and Stress Scales. Sydney, Australia; Psychology Foundation of Australia; 1995.

Carleton UNIVERSITY
Canada's Capital University

**Child Trauma Questionnaire (CTQ) – Short Form**

These questions ask about some of your experiences growing up as a child and a teenager. For each question, circle the number that best describes how you feel. Although some of these questions are of a personal nature, please try to answer as honestly as you can. Your answers will be kept confidential.

| *Never true* | *Rarely true* | *Sometimes true* | *Often true* | *Very Often true* |
|---|---|---|---|---|

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| **When I was growing up, . . .** | | | | | |
| 1. I didn't have enough to eat. | 1 | 2 | 3 | 4 | 5 |
| 2. I knew that there was someone to take care of me and protect me. | 1 | 2 | 3 | 4 | 5 |
| 3. People in my family called me things like "stupid", "lazy", or "ugly". | 1 | 2 | 3 | 4 | 5 |
| 4. My parents were too drunk or high to take care of the family. | 1 | 2 | 3 | 4 | 5 |
| 5. There was someone in my family who helped me feel important or special. | 1 | 2 | 3 | 4 | 5 |
| **When I was growing up, . . .** | | | | | |
| 6. I had to wear dirty clothes. | 1 | 2 | 3 | 4 | 5 |
| 7. I felt loved. | 1 | 2 | 3 | 4 | 5 |
| 8. I thought that my parents wished I had never been born. | 1 | 2 | 3 | 4 | 5 |
| 9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital. | 1 | 2 | 3 | 4 | 5 |
| 10. There was nothing I wanted to change about my family. | 1 | 2 | 3 | 4 | 5 |
| **When I was growing up, . . .** | | | | | |
| 11. People in my family hit me so hard that it left me with bruises or marks. | 1 | 2 | 3 | 4 | 5 |
| 12. I was punished with a belt, a board, a cord (or some other hard object). | 1 | 2 | 3 | 4 | 5 |
| 13. People in my family looked out for each other. | 1 | 2 | 3 | 4 | 5 |
| 14. People in my family said hurtful or insulting things to me. | 1 | 2 | 3 | 4 | 5 |
| 15. I believe that I was physically abused. | 1 | 2 | 3 | 4 | 5 |
| **When I was growing up, . . .** | | | | | |
| 16. I had the perfect childhood. | | 1 | 2 | 3 | 4 5 |
| 17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor. | 1 | 2 | 3 | 4 | 5 |
| 18. Someone in my family hated me. | | 1 | 2 | 3 | 4 5 |
| 19. People in my family felt close to each other. | 1 | 2 | 3 | 4 | 5 |
| 20. Someone tried to touch me in a sexual way or tried to make me touch them. | 1 | 2 | 3 | 4 | 5 |
| **When I was growing up, . . .** | | | | | |
| 21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them. | 1 | 2 | 3 | 4 | 5 |
| 22. I had the best family in the world. | | 1 | 2 | 3 | 4 5 |
| 23. Someone tried to make me do sexual things or watch sexual things. | 1 | 2 | 3 | 4 | 5 |
| 24. Someone molested me (took advantage of me sexually). | 1 | 2 | 3 | 4 | 5 |
| 25. I believe that I was emotionally abused. | 1 | 2 | 3 | 4 | 5 |

**When I was growing up, . . .**

| | | | | | |
|---|---|---|---|---|---|
| 26. There was someone to take me to the doctor if I needed it. | 1 | 2 | 3 | 4 | 5 |
| 27. I believe that I was sexually abused. | 1 | 2 | 3 | 4 | 5 |
| 28. My family was a source of strength and support. | 1 | 2 | 3 | 4 | 5 |

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., ... & Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child abuse & neglect*, *27*(2), 169-190.

## Appendix D. Blood Eligibility Questionnaire

Carleton UNIVERSITY
Canada's Capital University

Screening Questionnaire

In order to examine certain hormones and immune factors for this study, we require a blood sample. We would like to collect a blood sample from any participants who meet our criteria on the below questionnaire and are comfortable doing so. This would be done by a registered nurse or registered phlebotomist (exactly as when one gives a sample of blood at a clinic/doctor's office). Please answer the following questions as honestly and accurately as possible by selecting the appropriate statement.

1) Have you been diagnosed with any of the following conditions? (Please select all that apply)

____ Diabetes
____ Heart condition
____ Autoimmune disorder
____ None of the above

2) Are you currently being treated for any physical illness or injury?

____ Yes
____ No

3) If you answered "yes" to the previous question, please specify the illness or injury you are being treated for

_____
_____
_____

4) Are you currently taking any of the following medications? (please check all that apply)

____ Anti-inflammatories
____ Anti-depressants
____ Anti-anxieties
____ Allergy medication
____ Other prescription drugs

5) If you answered "yes" to the previous question, please indicate the name of all medications you are currently taking

_____
_____
_____

_____
_____
_____

6) Have you given blood before?

____ Yes, I have donated blood at Canadian Blood Services/Red Cross
____ Yes, I have had blood tests (e.g., at a doctor's office)
____ No, I have never given blood before

7) Have you had any issues during blood tests at a clinic or doctor's office before?

____Yes
____ No

If yes please specify:

_____
_____
_____

8) When you think about needles and blood tests, how anxious/nervous do you feel?

____Not anxious at all
____ Slightly anxious/nervous
____ Moderately anxious/nervous
____ Extremely anxious or nervous

9) If you were to meet all the above criteria are you willing to provide a quick blood sample (will take roughly 5 minutes).

____ Yes
____ No

***Eligibility scoring:***
*In order for participants to pass eligibility criteria, they first must not have been diagnosed with diabetes, heart disease/condition or an autoimmune disorder and they must not be taking anti-inflammatory medications. If they have any of the above conditions/medications, they will not be asked to provide blood. If participant meet these criteria and have given blood/had blood tests before, had no issues and are not 'extremely anxious/nervous', they will be considered eligible. If participants have not given blood or had blood test before, but report they are 'not at all anxious' they will also be considered eligible. Additionally, anyone who says they are not willing will be automatically ineligible.*

## Appendix E. Blood Consent Form

Carleton UNIVERSITY
Canada's Capital University

**Study Title:** A Biological and Psychosocial Characterization of Mental Health Symptoms

In order to understand the biological basis of mental health symptoms, we require a blood sample, which allows us examine stress hormones, immune factors, and epigenetic factors that we cannot assess with the saliva sample you provided. Understanding how these biological factors are linked to mental health is very important to our research questions and to help inform the causes and treatments of mental health disorders in the future. However, providing a blood sample is completely optional.

Blood collection is done by a registered nurse or registered phlebotomist (exactly as when one gives a sample of blood at a clinic/doctor's office).

Your responses to the screening questionnaire met our criteria for providing a blood sample. Are you willing to provide a blood sample (will take roughly 5 minutes).

____ Yes ____ No

Participant Name _____

Participant Signature Date _____

Researcher Name _____

Researcher Signature Date _____

## Appendix F. Debriefing

Carleton UNIVERSITY
Canada's Capital University

**Study Title:** A Biological and Psychosocial Characterization of Mental Health Symptoms

**What are we trying to learn in this research?**
In this study we are evaluating the effects of one's early life experiences (e.g., stressors, trauma) and the quality of our social relationships/connections with others on mental health outcomes (e.g., depression, anxiety symptoms and problematic substance use). Recently, there have been efforts made to better understand the association between our social connections and depressive and anxiety symptoms. We asked you to provide blood samples in order to assess how these variables influence cortisol, cytokines (proteins related to immune system functioning) and epigenetic factors (i.e. tags on your DNA that show how environmental experiences shape the way our genes express). These biological factors have been linked to depression, however, not all individuals who have depression exhibit these markers and it is thought that this might be due to the heterogeneity of those with depression and the high comorbidity with other disorders such as anxiety. Therefore, by linking different biological and psychosocial factors to distinct depressive and anxiety symptoms, we can gain a better understanding of theses disorders.

Moreover, not all individuals respond to stressful life events in the same way. Some people react strongly, whereas others do not. Research has focused on important genetic factors, which may underlie increased risk to develop depression and anxiety related symptoms. These genetic factors include small deviations of certain genes that control the functioning of neurochemical systems in the brain. The slight deviations are called polymorphisms, and are fairly common. We are assessing whether adverse life experiences affect people differently depending on the presence of different polymorphisms. You were asked to provide a saliva sample, genetic material (e.g., DNA) can be extracted from this saliva sample. Therefore we were interested in examining the relationships between your responses on some of the questionnaires (e.g., experiences of trauma, depressive and anxiety symptoms) with certain genes. These polymorphisms are different from the epigenetic 'tags' on your DNA, but both are important factors when understanding stress responses and mental health.

**Why is this research important?** By understanding the genetic, hormonal and psychosocial factors that lead to different mood outcomes, we will gain a better understanding of how mood changes develop. This research will help to develop improved approaches to both treat, and prevent mental health concerns in the future.

We hope that being a participant in this research has proven to be a worthwhile learning experience, and that you find some benefit in being a participant in this study. Thank you very much for your willingness to participate.

**Where can I learn more?**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3721019/
https://www.ncbi.nlm.nih.gov/pubmed/28235397
https://www.ncbi.nlm.nih.gov/pubmed/29684053

*What if I have questions later?*
**Please contact:**

Sabina Franklyn, Department of Psychology, Carleton University
Email: sfran047@uottawa.ca

Kelly Moreland, Department of Neuroscience, Carleton University
Email: KellyMoreland@cmail.carleton.ca

Dr. Robyn McQuaid, The Royal's Institute of Mental Health Research
Phone: 613 722-6521 ext. 6490, Email: Robyn.McQuaid@theroyal.ca

Dr. Kim Matheson, Department of Neuroscience, Carleton University
Phone: 613 520-2600 ext. 2652, Email: kim.matheson@carleton.ca

This ethics protocol for this project has been cleared by Carleton University Research Ethics Board-B (CUREB-B Clearance #109133).

If you have any ethical concerns with the study, please contact Dr. Bernadette Campbell, Chair, Carleton University Research Ethics Board-B (by phone: 613-520-2600 ext. 4085 or by email: ethics@carleton.ca).

***Is there anything that I can do if I found this experiment to be emotionally draining?***
Thank you very much for your participation in this study. If you have experienced any distress while completing these measures, please consult the resources below:

**Carleton University Health and Counseling Services**: 613-520-6674
**Distress Centre Ottawa and Region**: (613) 238-3311, Web Site: www.dcottawa.on.ca/.
**Mental Health Crisis Line:** within Ottawa (613) 722-6914, Web Site: http://www.crisisline.ca/

Thank you for participating in this research!

## Appendix G. Blood Collection Sampling Information

Carleton UNIVERSITY
Canada's Capital University

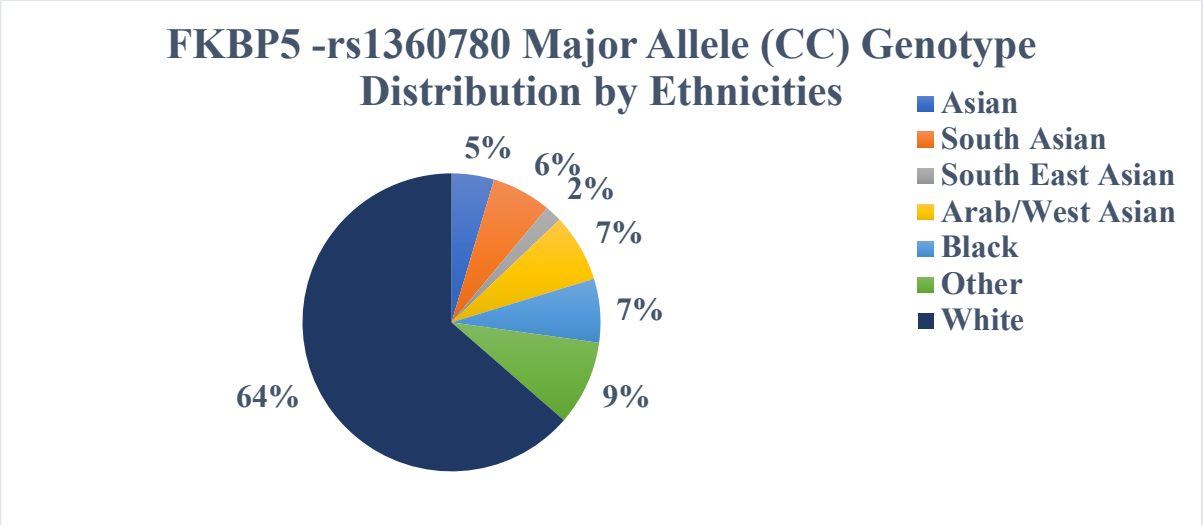
The participant blood samples will be collected into chilled EDTA coated Vacutainer tubes. Samples will be taken at one time point at the end of the session. Once in the lab, 2mL of whole blood will be immediately aliquoted into an Eppendorf tube and frozen at -80°C until needed for later epigenetic analyses. Remaining blood samples will be centrifuged for 15 minutes at 4°C and 2100g. Plasma will then be aliquoted into Eppendorf tubes and frozen at -80°C until needed for assays. See Below for complete Blood Sampling Information, including amounts of blood collected.

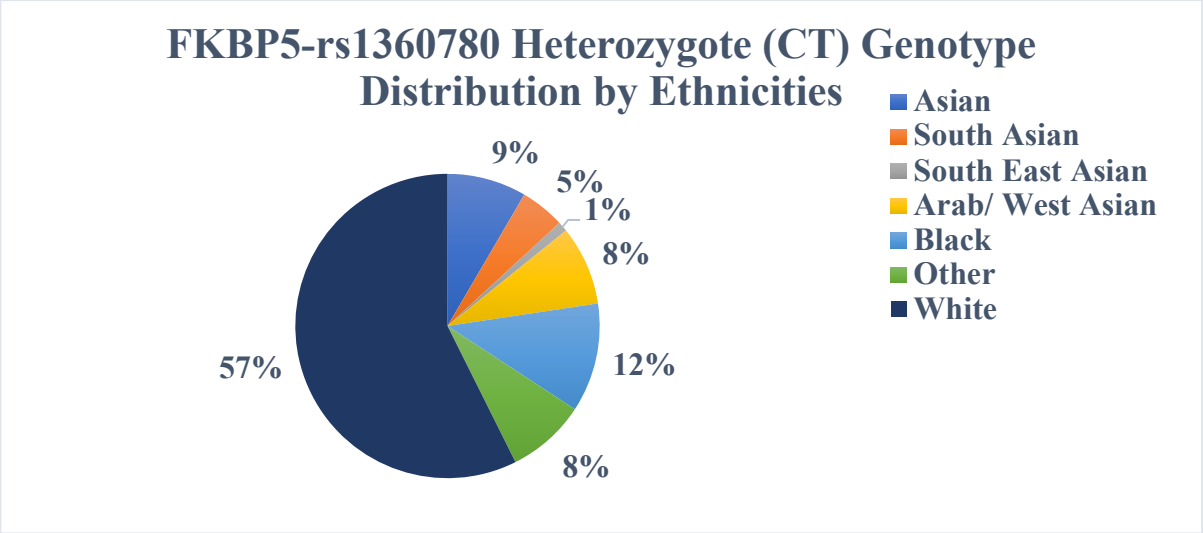
*Amount of blood needed for each assay/time-point:*

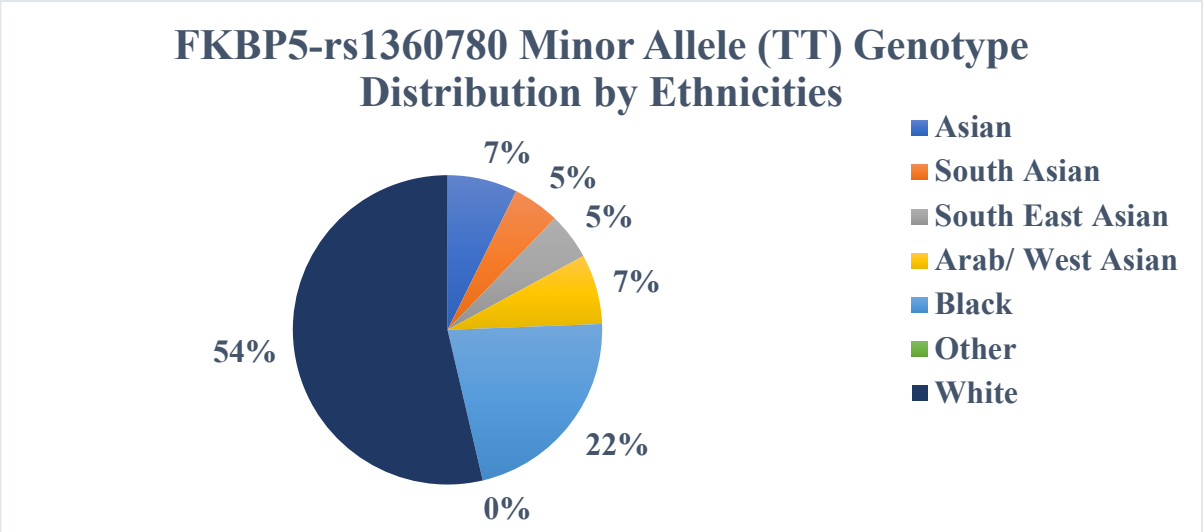
| **Hormone/Peptide** | **Plasma/Serum needed** | **blood needed** |
|---|---|---|
| Cortisol | 80 µl | 173µl |
| CRP | 250 µl | 540µl |
| TNF-α | 250 µl | 540µl |
| IL-6 | 250 µl | 540µl |
| IL-1B | 250 µl | 540µl |
| IL-10 | 250 µl | 540µl |
| Il-4 | 250 µl | 540µl |
| IL-13 | 250 µl | 540µl |
| Extra | 600µl | 1300µl |
| Epigenetic Assay | 0 µl | 2mL |
| | **TOTAL** | 7.253mL |

## Appendix H. Genotype Distribution on HPA-Axis SNPs by Ethnicities

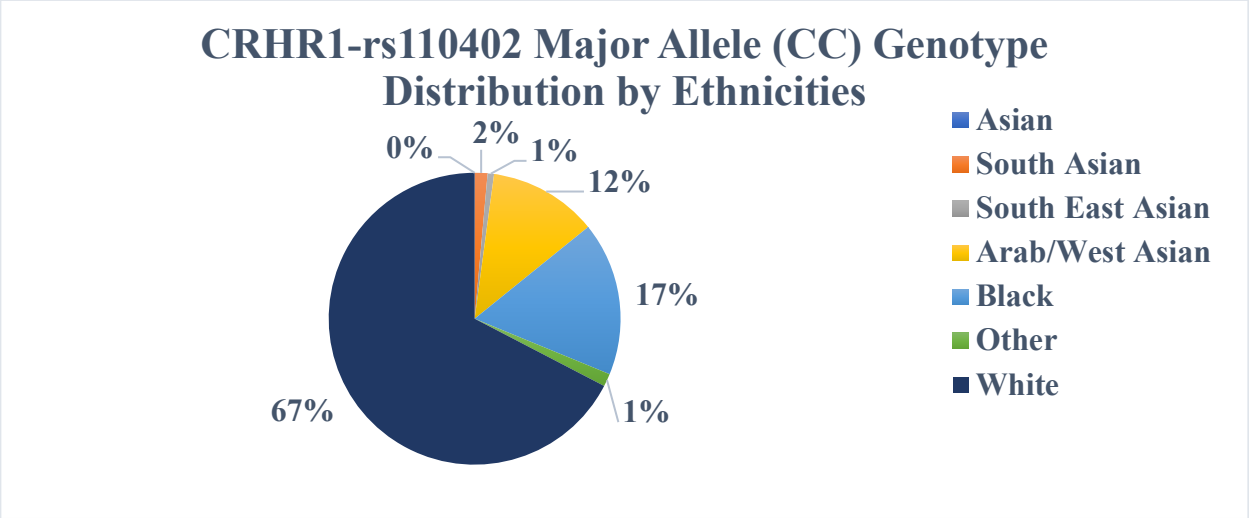
**FKBP5-rs1360780**

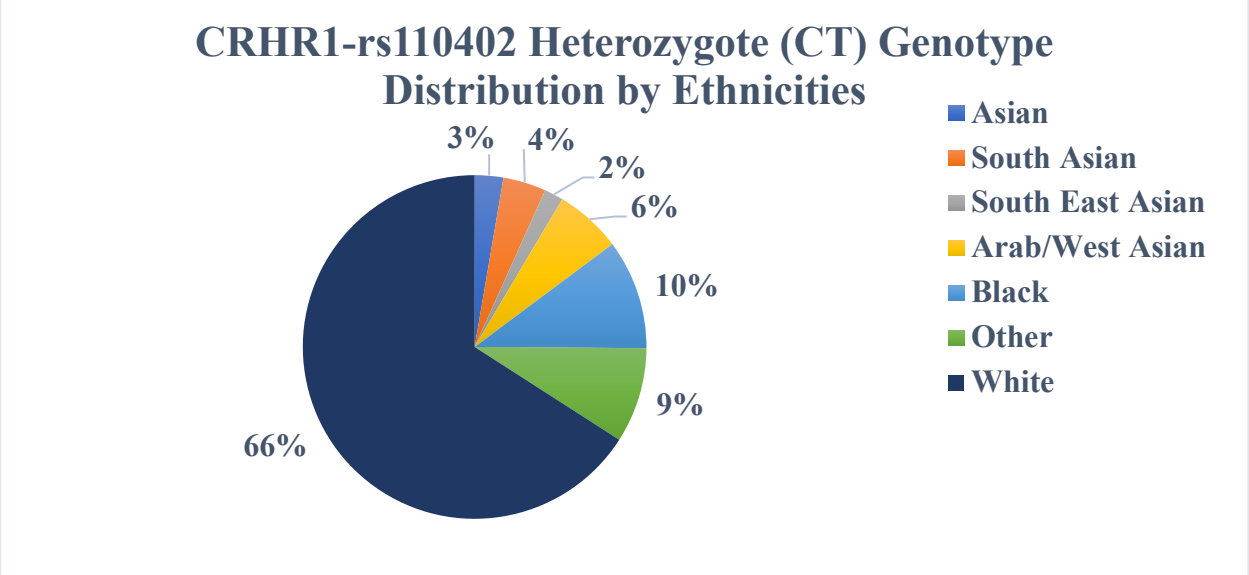


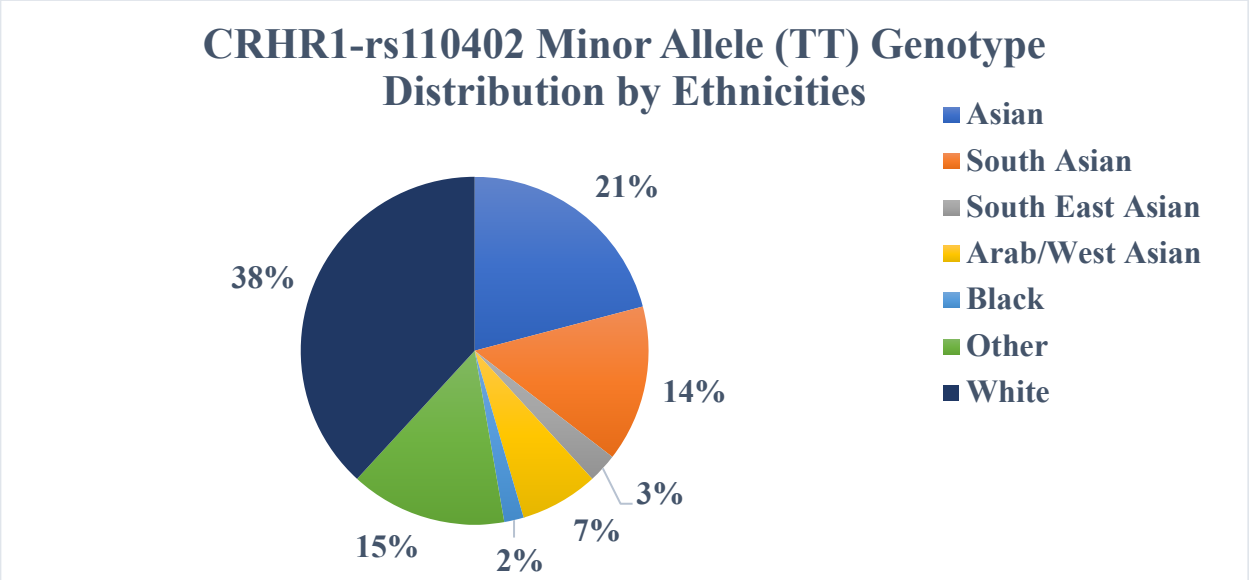



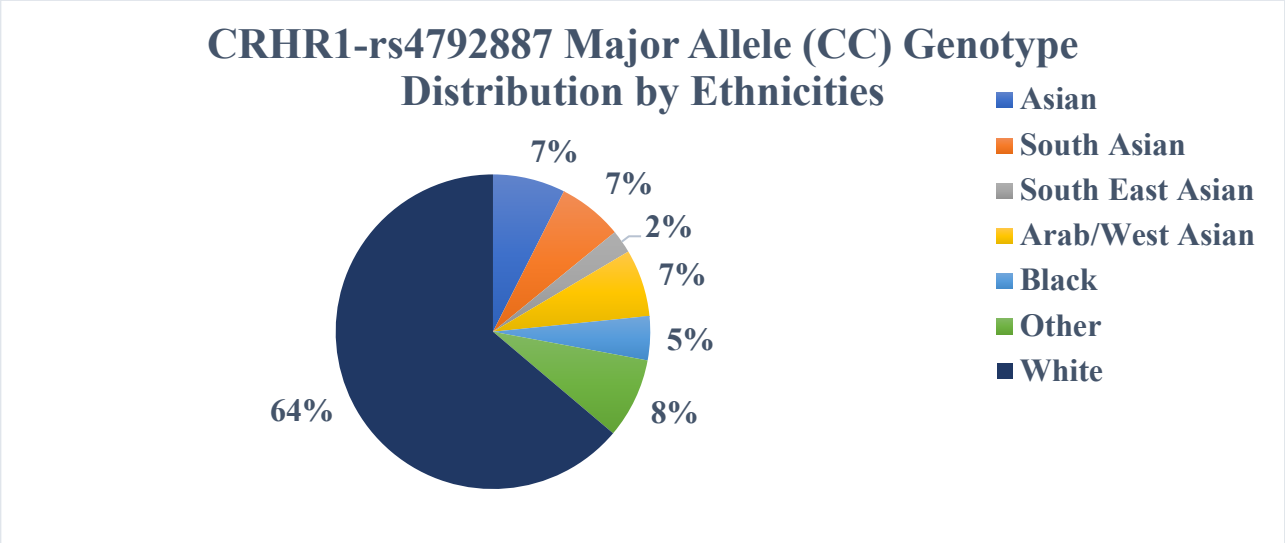
**CRHR1-rs110402**

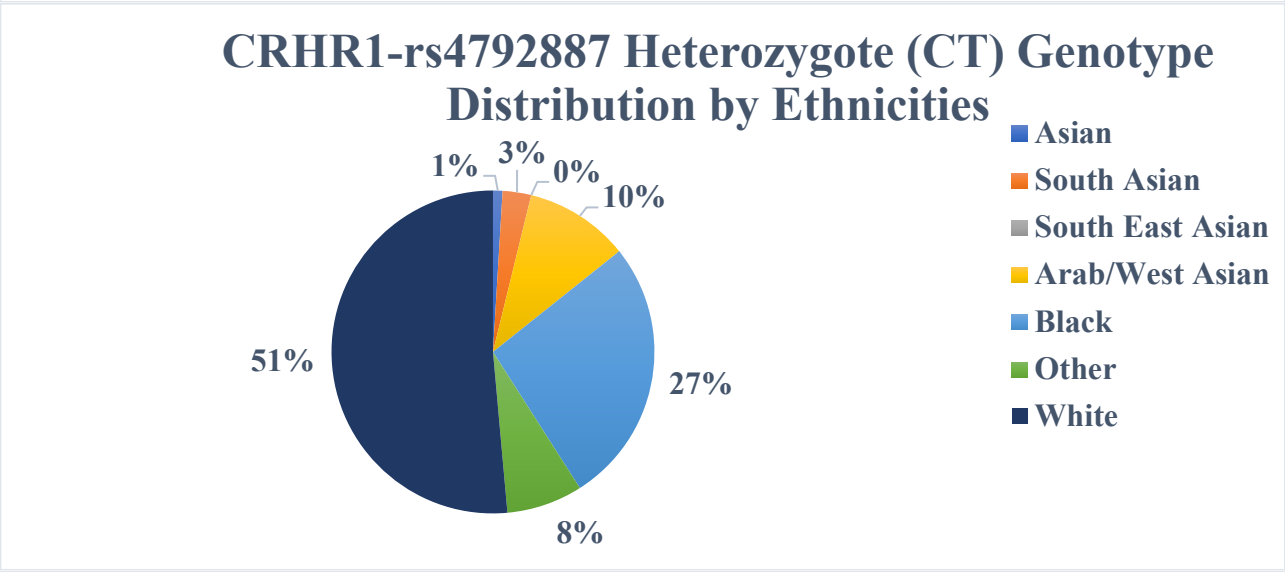


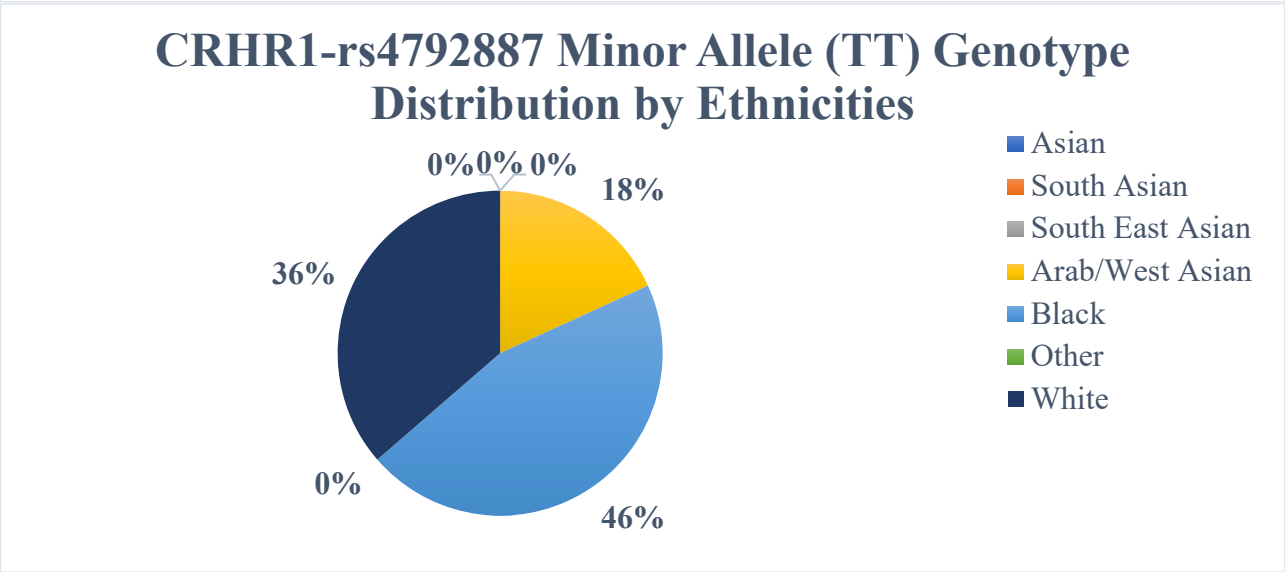



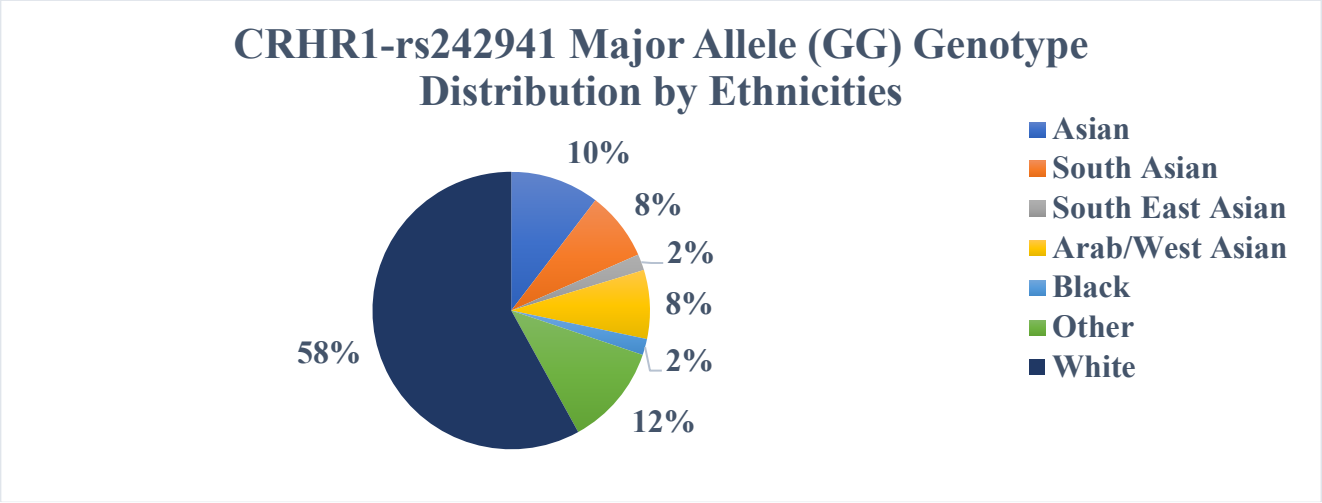
**CRHR1-rs4792887**

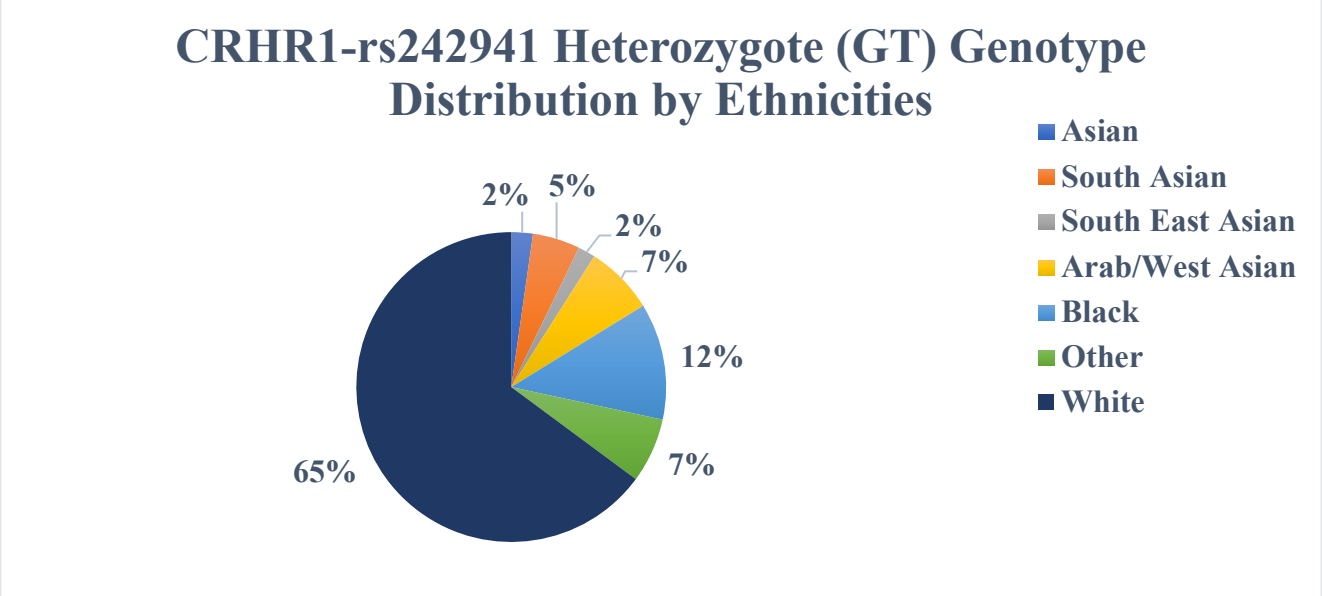


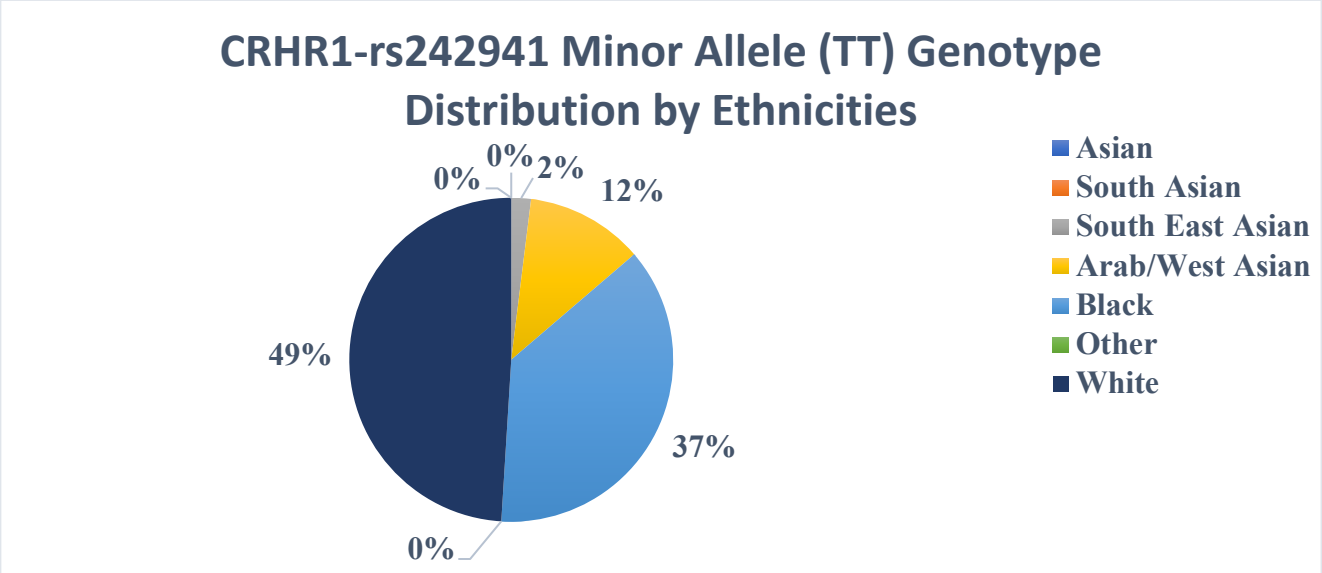



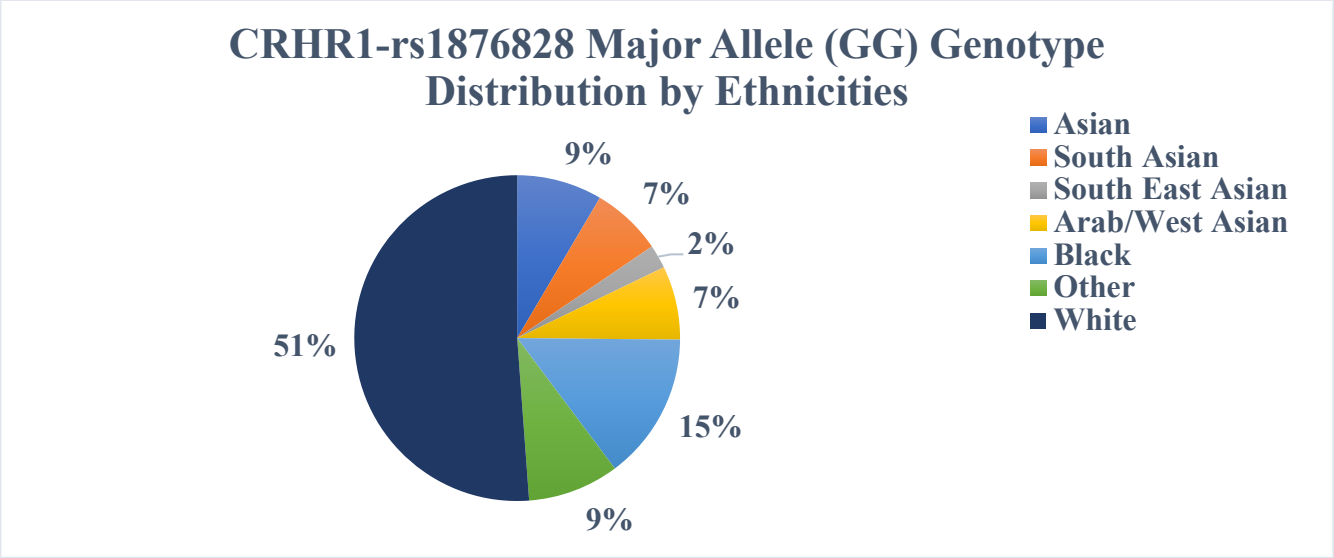
**CRHR1-rs242941**

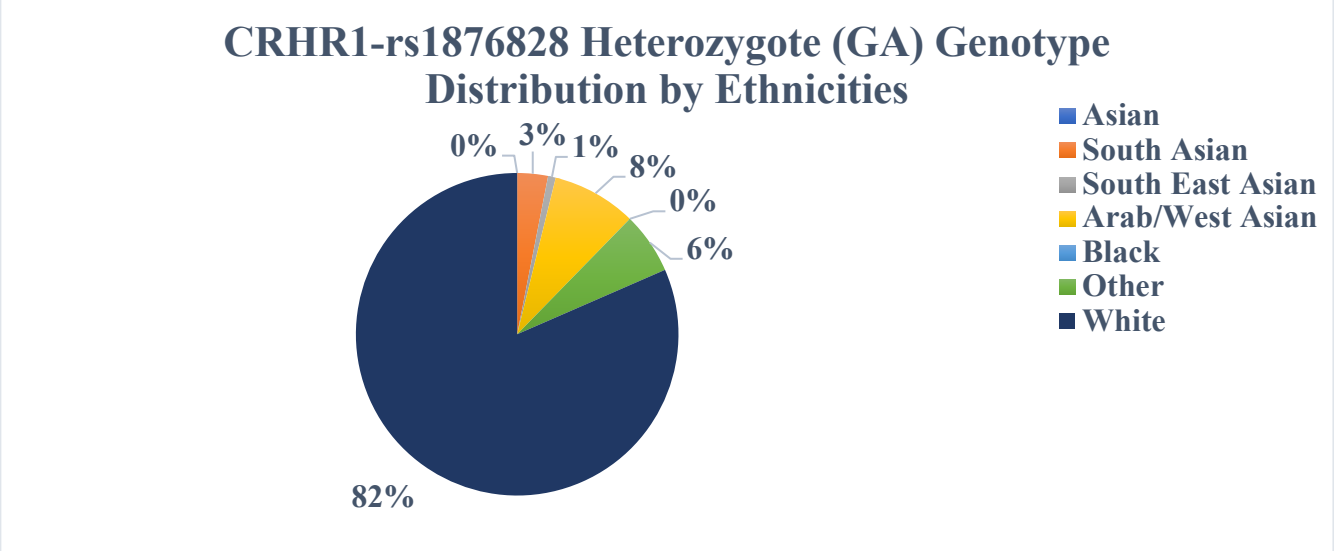


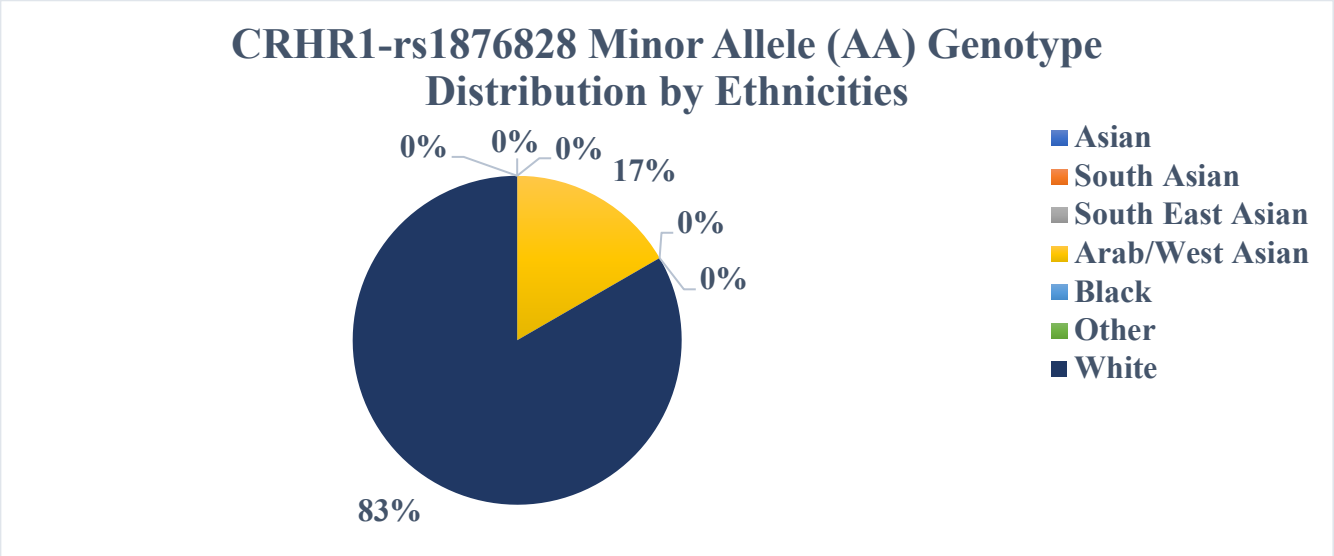



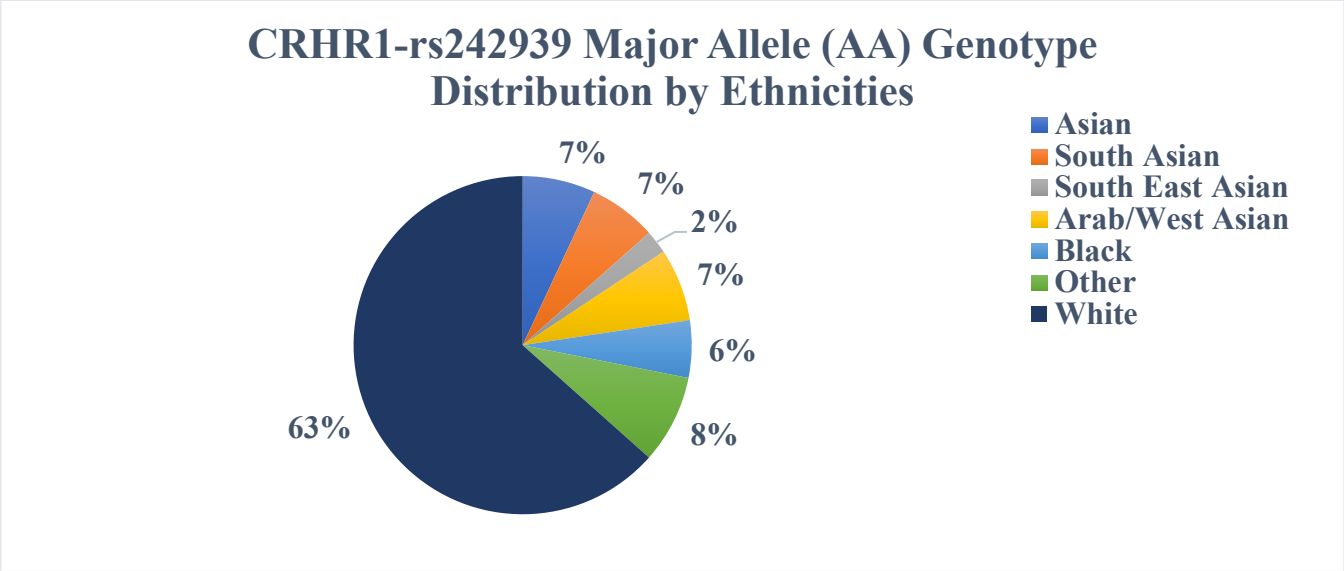
**CRHR1-rs1876828**

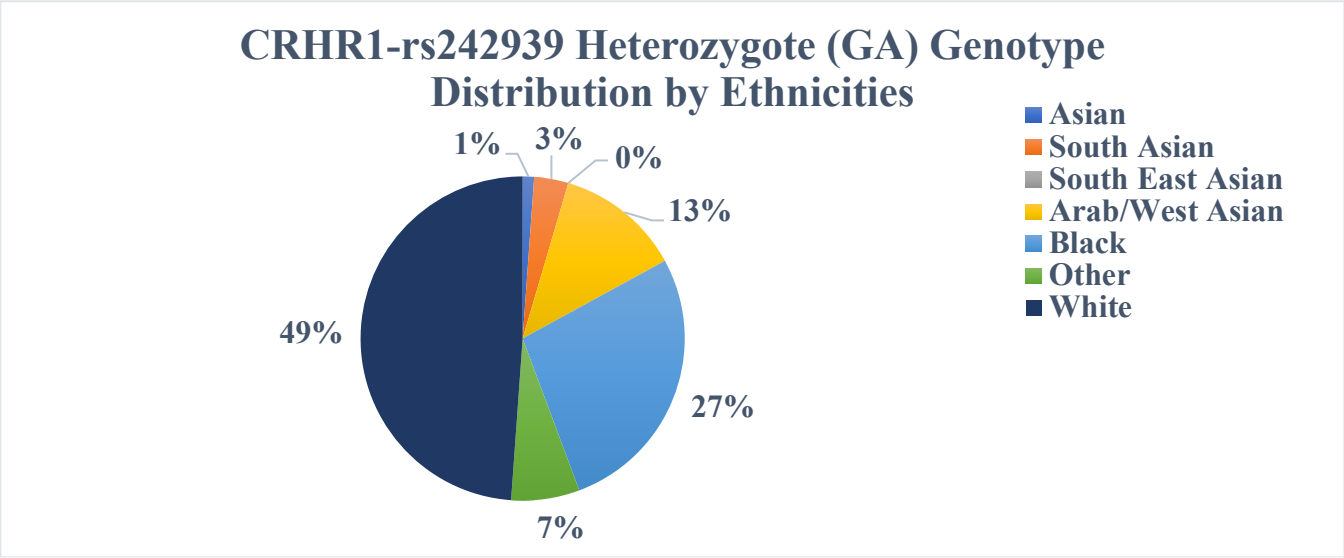


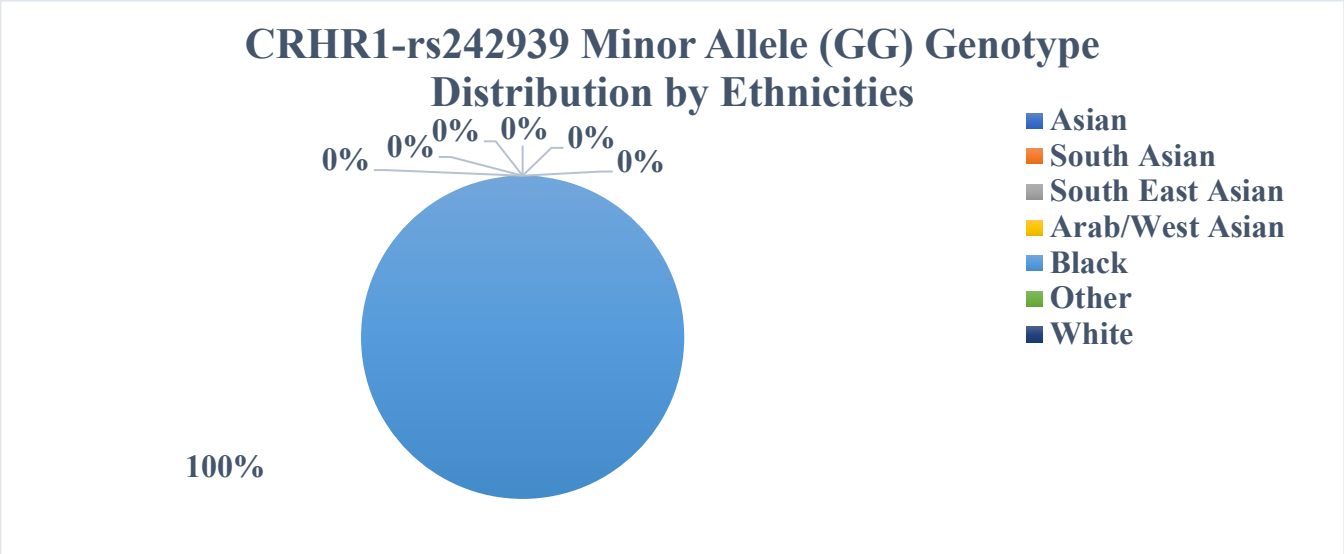



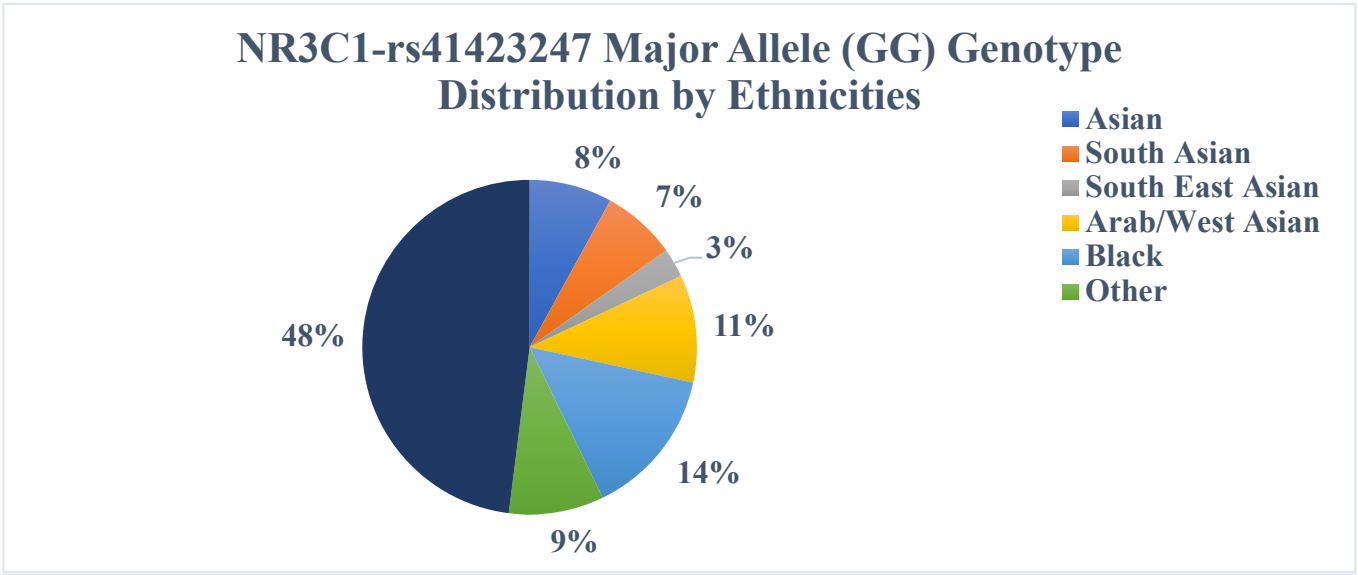
**CRHR1-rs242939**

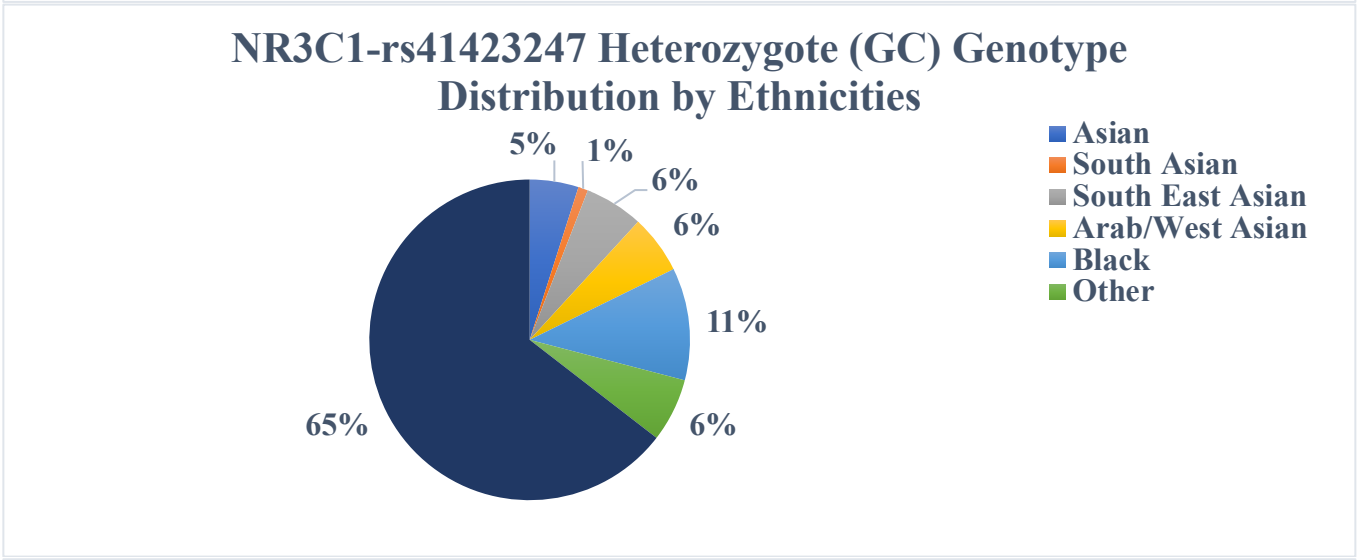


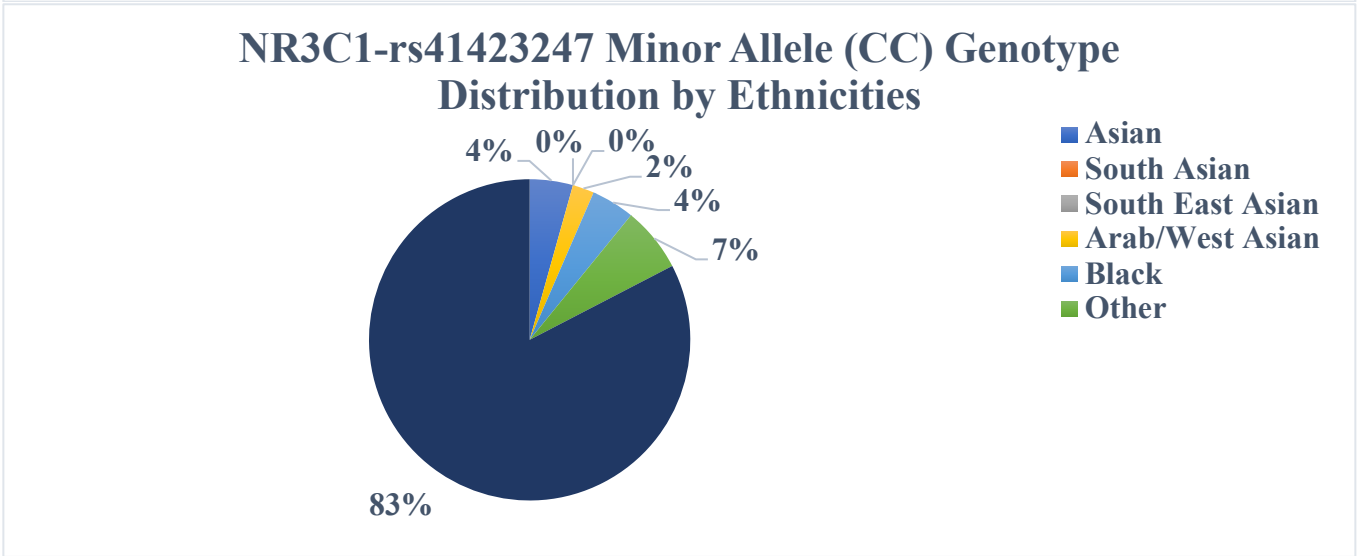



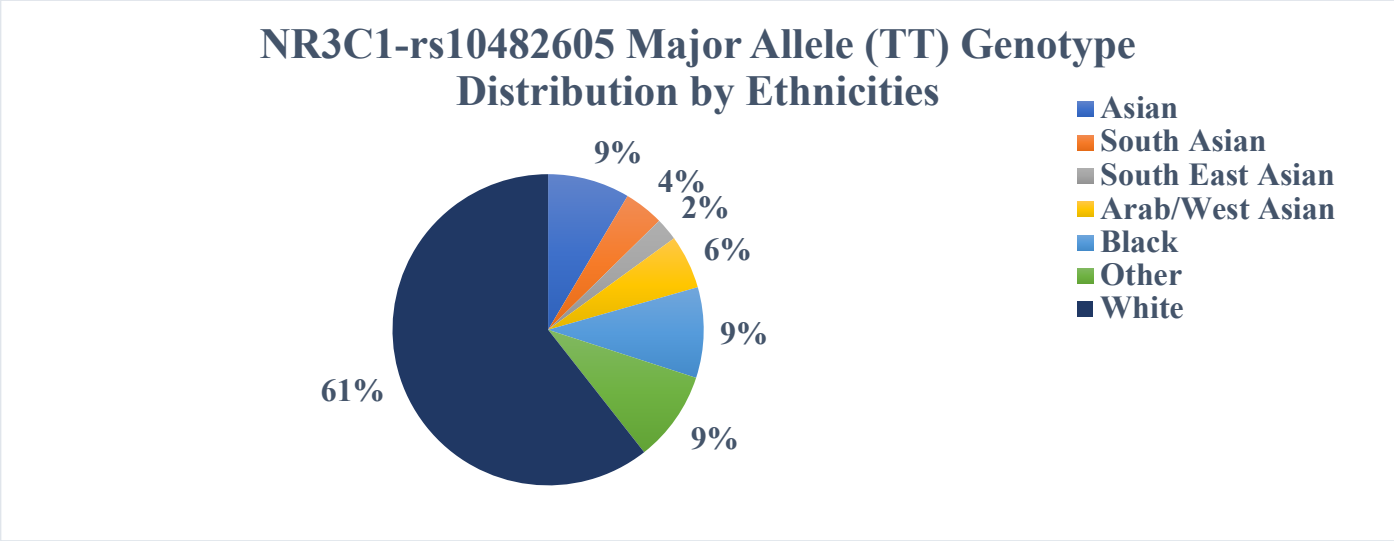
**NR3C1-rs41423247**

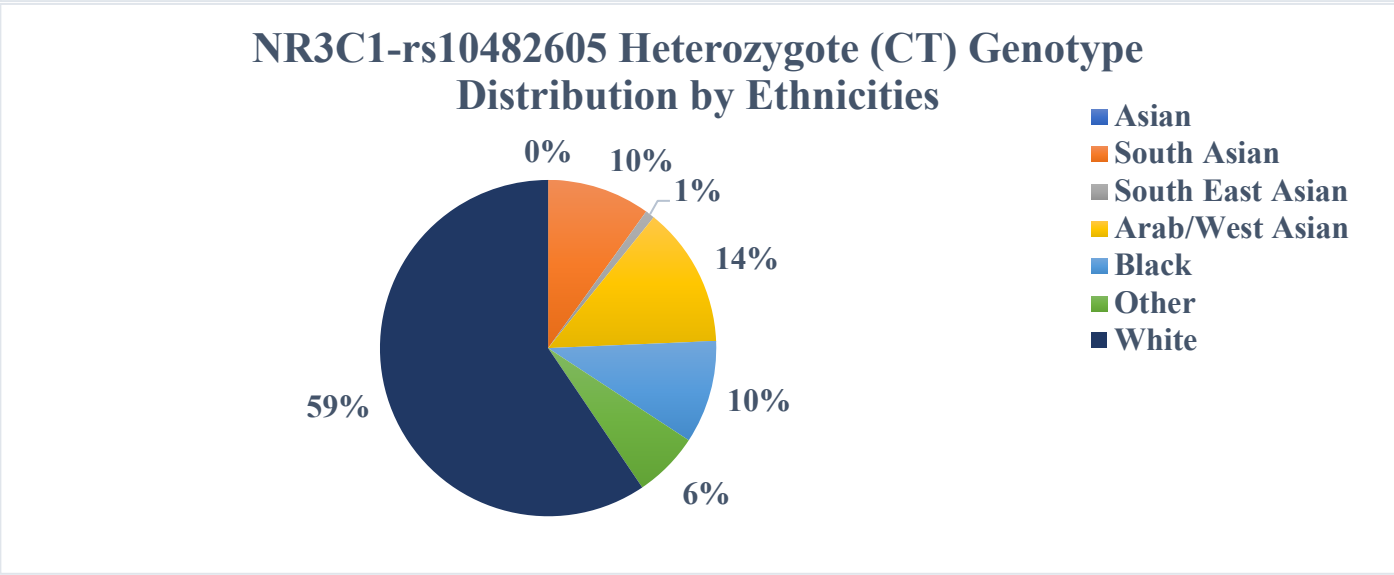


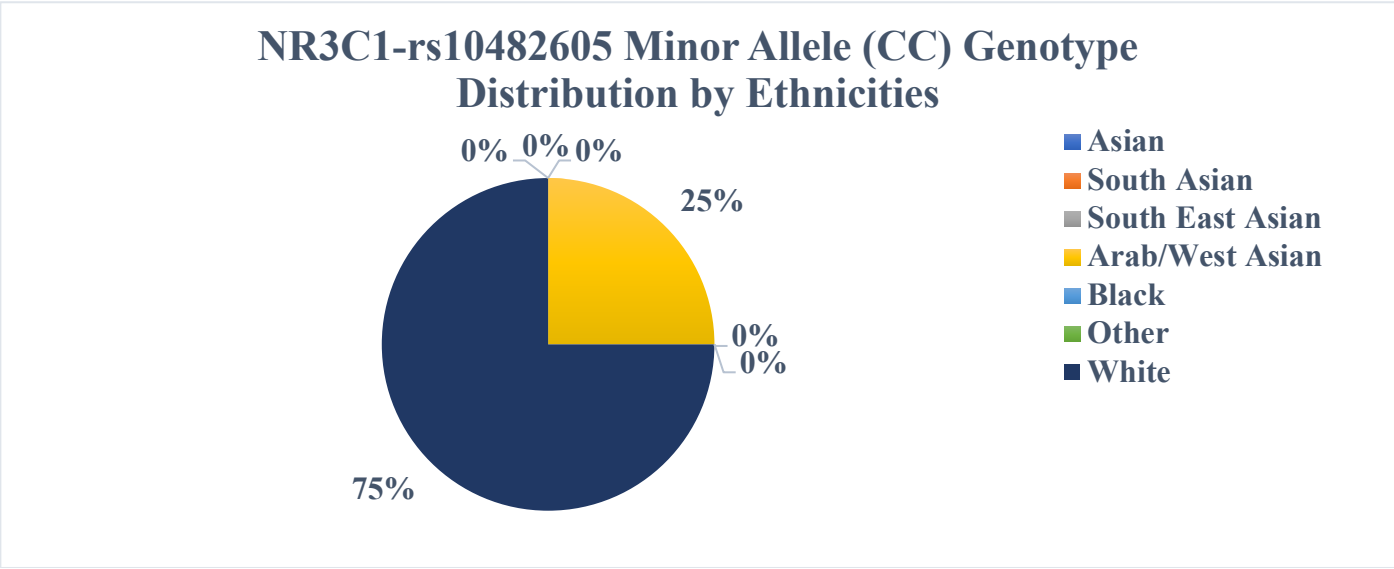



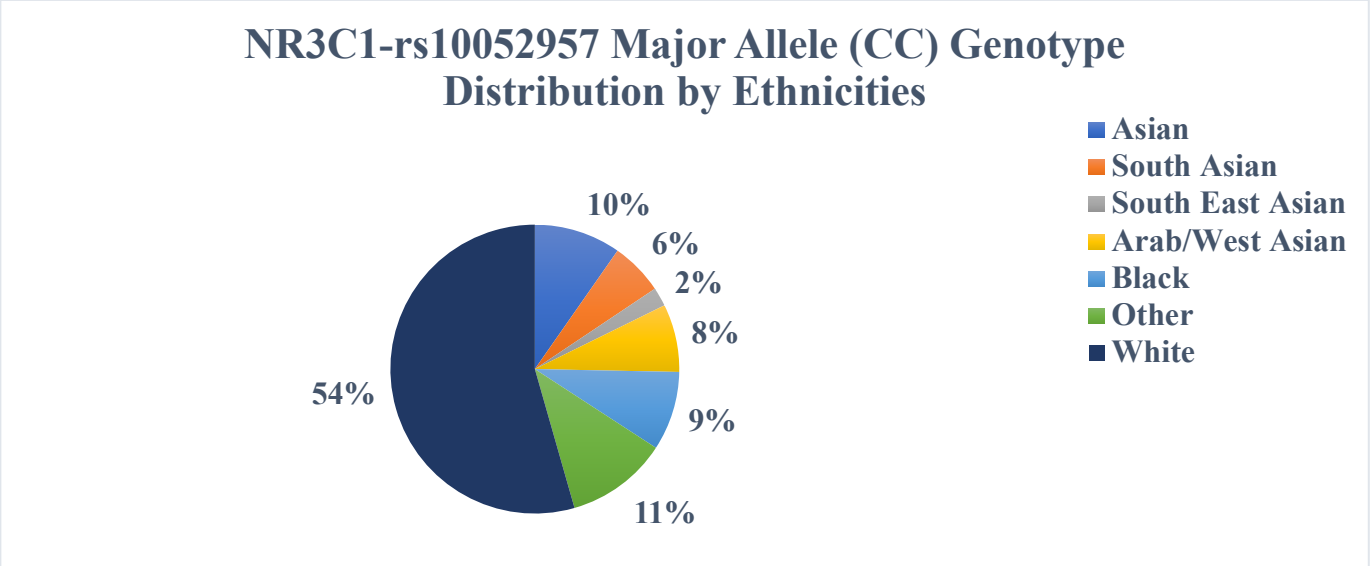
NR3C1-rs10482605

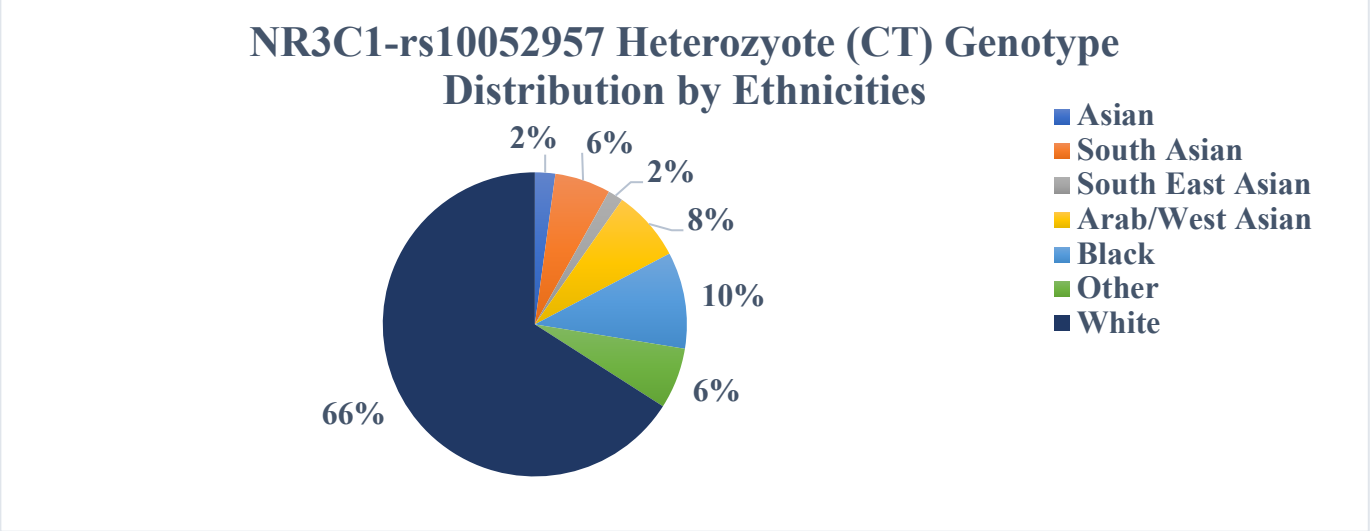


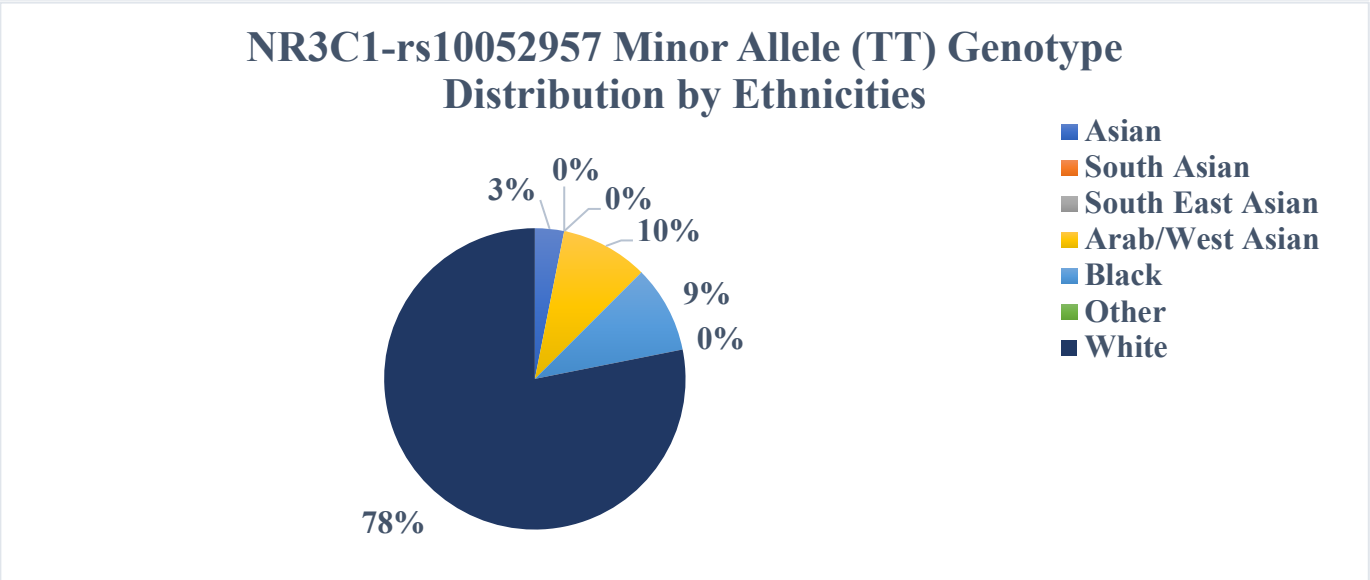



NR3C1-rs10052957



NR3C2-rs5522