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Association of Interpersonal Trauma and Polygenic Risk Scores with Depressive Symptoms in College Students

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Abstract

ASSOCIATION OF INTERPERSONAL TRAUMA AND POLYGENIC RISK SCORES WITH DEPRESSIVE SYMPTOMS IN COLLEGE STUDENTS

By Rowan K. O'Hara, B.S.

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Bioinformatics at Virginia Commonwealth University.

Virginia Commonwealth University, 2023.

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Major depression is considered a complex trait influenced by both polygenic risk factors and environmental exposures, such as childhood trauma. This study applied statistical genetic methods to calculate aggregate genetic risk for major depression to predict depressive symptoms scores in a college student sample. Data were from the Spit for Science (S4S) study in which college students from a large urban university self-reported interpersonal trauma (IPT) exposure prior to college and depressive symptoms from the past month (N = 7502; ancestry group: 20% African [AFR], 12% Admixed Americas [AMR], 10% East Asian [EAS], 49% European [EUR], 8% South Asian [SAS]). Major depression-PRS were created using PRS-CSx with summary statistics from large-scale genome-wide association studies (GWAS) of major depression in EUR, AFR, and EAS ancestry cohorts. Mean depressive symptoms scores and rates of IPT exposure were statistically significantly higher in female participants (μ_{score} = 9.50, $prop._{IPT}$ = 0.42) than in males (μ_{score} = 8.21, $prop._{IPT}$ = 0.32, all $p < 0.001$). In the phenotypic-only model, symptoms of depression were associated with IPT exposure ($\beta = 1.48$, $p = 8.21\times10^{-22}$) and sex ($\beta = 1.05$, $p = 4.38\times10^{-21}$), but there was no evidence of statistical interaction between them ($p = 0.218$). In the fixed effects meta-analysis across ancestry groups, major depression-PRS were significantly associated with depressive symptoms ($\beta = 0.209$, $p = 1.14\times10^{-4}$), accounting for a small proportion of the variance (R^2 range: 0.0003 - 0.004). Sex ($\beta = 1.091$, $p = 1.59\times10^{-22}$) and IPT exposure ($\beta = 1.320$, $p = 4.59\times10^{-5}$) were strongly associated with depressive symptoms, but statistical interactions between major depression-PRS and IPT exposure were not found ($p = 0.251$). When inspecting results by ancestry groups, major depression-PRS were only statistically significant with depressive symptoms scores in the European ($\beta = 0.277$, $p = 3.91\times10^{-4}$) and Admixed Americas ($\beta = 0.454$, $p = 6.10\times10^{-3}$) ancestry groups. In every model, biological sex and IPT exposure had significant main effects on depressive symptoms scores. Further study is needed as more large-scale GWAS become available to increase the predictive ability of PRS across the ancestry spectrum in the pursuit of health equity in precision psychiatry.

Keywords: major depression, depression symptoms, polygenic risk scores (PRS), interpersonal trauma (IPT), cross-ancestry, gene by environment interaction, statistical genetics, college students, college behavioral health

Introduction

Major Depression

In the United States, major depressive disorder (MD) is a common psychiatric disorder, affecting 8.4% of the adult population in 2020 (*Major Depression*, n.d.). The lifetime prevalence of MD in the United States is much higher at 19.2%-20.6% (Hasin et al., 2018; Kessler & Bromet, 2013). MD is comorbid with many other psychiatric disorders, including substance use, anxiety, and personality disorders (Hasin et al., 2018). A clinical diagnosis requires endorsing at least one of the two cardinal symptoms: feeling sad, blue, or depressed, referred to as *depressed mood*, or loss of interest in, or could not enjoy, the usual activities that would typically give them pleasure, referred to as *anhedonia* (American Psychiatric Association, 2013, p. 161). Additionally, the Diagnostic and Statistical Manual of Mental Disorders (DSM, 5th edition) criteria for clinical depression also requires patients to positively endorse at least five out of nine symptoms lasting for two or more weeks (Goldberg, 2011; Malhi & Mann, 2018). Other symptoms include decreased ability to concentrate, feelings of worthlessness or guilt, suicidal ideation, fatigue, and changes in sleep or weight (e.g., body weight changing >5% in a month) (American Psychiatric Association, 2013, p. 161). Depressive symptoms and their frequency can also be quantified using psychometric self-report measures, such as the Symptom Checklist-90 (SCL-90), to assess current depressive symptoms (Derogatis et al., 1973). While clinical diagnosis from the DSM requires experiencing the symptoms causing dysfunction and lasting for at least two weeks, the SCL-90 or other depressive symptoms measures typically assess symptoms experienced within the last 30 days (American Psychiatric Association, 2013, p. 160; Derogatis et al., 1973).

Evidence has shown sex differences in the prevalence and presentation of MD and its symptoms. The lifetime occurrence rate of depression is two times higher in females than in males (Altemus et al., 2014; Maier et al., 1999). Some research has reported that females tend to have more internalizing symptoms, such as depressed mood, anhedonia, appetite or weight disturbance, and sleep disturbance. In contrast, males have reported more comorbid substance abuse and externalizing symptoms, like risk-taking behaviors (Cavanagh et al., 2017). For example, Cavanagh et al. (2017) conducted a systematic review and meta-analysis of 32 studies

(N = 108,260) and found that half of the DSM-5 depressive symptoms' frequency and intensity were significantly higher for women than men.

Prevalence and risk for MD have also been shown to differ between age groups (*Major Depression*, n.d.). Emerging adulthood is a critical developmental epoch to study depressive symptoms because of its transitional nature as changes occur in responsibilities, finances, and social support during this time. During the transition from high school to college, a decrease in family cohesion has also been associated with an increase in depressive symptoms ($p < 0.01$) (Guassi Moreira & Telzer, 2015). In the United States, the median age of onset for MD is 22.7 years (Kessler & Bromet, 2013).

MD is important to study because of its many negative outcomes, including suicidal ideation or attempts, comorbid disorders, and/or functional impairment. Some research supports that college students experience higher MD rates than the general population (Ibrahim et al., 2013). Suicidal behavior has also been shown to be elevated among those with MD (H. Cai et al., 2021). Suicide was the third leading cause of death in the US in 2020 for the 15-24-year-old age group, indicating interventions for MD and suicidal ideation may be necessary for this age group (*WISQARS Details of Leading Causes of Death*, n.d.). Impairment is another risk of MD, and reduced function can range from mild to severe (American Psychiatric Association, 2013, p. 167). Severe impairment can include the inability to care for oneself, muteness, or catatonia (American Psychiatric Association, 2013, p. 167).

Genetic Architecture of Major Depression

The combination of genetic factors for disease liability, including the number and effect size of risk variants and their allele frequencies, is referred to as a trait's 'genetic architecture' (Smoller, 2016). Some standard study designs used to ascertain these risk factors for MD are twin and family studies, linkage studies, candidate gene studies, and genome-wide association studies.

Twin studies often examine the differences in phenotypes between twins who share a familial environment to determine how much genetics contribute to disease outcomes (Smoller, 2016). Monozygotic (MZ) twins are genetically identical, while dizygotic (DZ) twins only share half of their genetic material like other siblings. Heritability can be estimated by comparing MZ

and DZ twins' disorder concordance rates (Smoller, 2016). The heritability of MD is estimated to be ~37% from twin studies, meaning both genetic and environmental factors are at play (Kendler et al., 2006; Sullivan et al., 2000). Furthermore, evidence has shown that the heritability of MD for women may be higher than for men (0.57 versus 0.43, respectively) (Kendler et al., 2001a, 2006, 2018). Although the genetic variance shared between the sexes is approximately 90%, some variants could have sex-specific effects (Flint & Kendler, 2014; Kendler et al., 2018).

Historically, linkage studies were proposed to identify genetic risk factors for complex traits given their success for some Mendelian traits. Linkage studies map disease-related genes to their chromosomal location (Smoller, 2016). Logarithm of the odds (LOD) scores are used to estimate the probability of two loci being inherited together or "linked" (Flint & Kendler, 2014). In family studies that evaluate two siblings with MD, "affected sibling design," a score of 2.2 suggests linkage of a trait to a genomic region, a score of 3.6 is statistically significant, and a score of 5.4 is highly significant (Flint & Kendler, 2014). The maximum LOD score found by Middeldorp et al. (2009) for MD, which had an affected sibling design, was 2.1 in an Australian and Dutch sample (chr17:19,426,481-19,426,503) (N = 278). Schol-Gelok et al. (2010) found a maximum LOD score of 2.66 in a Dutch affected sibling study (chr19:3029918) (N = 115), suggesting linkage but failed to be statistically significant. In sum, linkage studies have not been successful for identifying genomic regions for common complex diseases like psychiatric disorders (Smoller, 2016).

Candidate gene studies select genes of interest based on neurobiological factors, typically neurotransmitters, that are hypothesized to have a possible causative effect (Duncan et al., 2014; Smoller, 2016). For example, a meta-analysis of 46 studies found a gene that encodes a serotonin transporter, *5-HTTLPR*, to have a small but statistically significant association with depression (OR = 1.08) (Clarke et al., 2010). Historically, these studies have failed to replicate results for complex diseases and are more likely to present false positives (Duncan et al., 2014; Smoller, 2016; Sullivan, 2007). Candidate gene study results have also largely failed to be replicated in large-scale genome-wide association studies (GWAS), which were powered for replication (Flint & Kendler, 2014). After multiple testing corrections, Wray et al. (2012) found no candidate genes significantly associated with MD out of the 180 tested (N = 6,104, 40% cases).

Technological advancements in genotyping arrays have allowed thousands to millions of single nucleotide polymorphisms (SNPs), which are variants in one base-pair, to be genotyped. GWAS, which use thousands of individual genomes to associate SNPs with a phenotype across a population, are a method of identifying these variants (Duncan et al., 2014; Tam et al., 2019). In contrast to candidate gene studies, GWAS are considered to be agnostic because they are not hypothesis based and can test hundreds of thousands to millions of SNPs across the entire genome (Duncan et al., 2014).

MD is considered a highly polygenic disorder as there are many risk variants that contribute to genetic susceptibility for disease onset that have small effect sizes (Demirkan et al., 2011; Flint & Kendler, 2014). GWAS have identified over 100 risk variants for MD (Howard et al., 2019; Levey et al., 2021). For example, several large-scale GWAS have implicated SNP rs12624433 located in the *SLC12A5* gene to be associated with MD and depressive symptoms (OR = 1.008 - 1.033) (Baselmans et al., 2019; Howard et al., 2019; Mitchell et al., 2022; Yao et al., 2021).

Results from GWAS can be used in aggregate to estimate SNP-based heritability (h^2_{SNP}), which uses all measured SNPs to explain phenotypic variance (Flint & Kendler, 2014; Lee et al., 2013). The h^2_{SNP} of MD is estimated to be between 8.7-30% depending on the population and depression assessment (Lee et al., 2013; Lubke et al., 2012; Peterson, Cai, et al., 2017; Wray et al., 2018). This is lower than the estimated heritability from twin studies of 37% (Sullivan et al., 2000). SNP-based heritability represents the lower bound of heritability due to other types of variants not being included, such as copy number variants or rare variants (Flint & Kendler, 2014). The co-heritability, also known as genetic correlation, of MD diagnosis from structured clinical interviews and depressive symptoms as assessed by the SCL-90 is positive and largely overlapping (r_g = 0.35 - 0.45) (Kendler et al., 2019).

Polygenic risk scores (PRS), a common method of determining aggregate genetic risk, are calculated by summing the number of risk variants an individual has for a phenotype of interest and then weighing them by their effect size based on GWAS summary statistics (Choi et al., 2020; Smoller, 2016; Wray et al., 2021). Including other SNPs than just the variants that reached genome-wide significance tends to increase the predictive ability of PRS (Choi et al., 2020; Demirkan et al., 2011). However, PRS is unable to perfectly predict phenotypes of

complex disorders due in part to excluding other genetic risk variants or environmental risk factors and interactions between them (Wray et al., 2021). Wray et al. (2018) found that MD-associated PRS only explained 1.9% of the variance in MD liability in an independent sample (N = 480,359, 28% cases). The variance explained by PRS may be increased by including a broader definition of depression to increase sample size (Howard et al., 2019). Nevertheless, this is complicated by reduced specificity for clinically defined MD, which has been shown to decrease the h^2_{SNP} of MD (N. Cai et al., 2020). Heritability for broad definitions of MD, such as self-report (h^2_{SNP} = 11%) or symptoms (h^2_{SNP} = 13 - 14%), were lower than strict definitions of MD, such as meeting DSM or Composite International Diagnostic Interview (CIDI) criteria (h^2_{SNP} = 26%) (N. Cai et al., 2020).

Current Limitations

The genetic architecture of MD is not completely understood due in part to several limitations of the research. Self-identified race and ethnicity can be indicators of social and environmental exposures but are not appropriate metrics on which to base genetic analyses. GWAS historically have focused primarily on participants of European genetic ancestry (Peterson et al., 2019). This lack of diverse sampling reduces the generalizability of findings across populations, and if not addressed, it will limit precision medicine. There are many benefits to including participants of diverse ancestries. Doing so can increase sample size, improve fine-mapping, prevent further disparities in healthcare, and expand the repertoire of genetic risk variants studied, improving the power to identify significantly associated SNPs (Peterson, 2021; Peterson et al., 2019). However, this can also increase heterogeneity in genetic architecture, and if not appropriately addressed, could lead to false positive associations due to population stratification (Y. R. Li & Keating, 2014; Morris, 2011). Population stratification refers to systematic differences in genotypes between ancestral groups observed when conducting population genetics studies, possibly confounding associations (Hellwege et al., 2017). Allele frequencies, and therefore genetic risk variants for disease outcomes, along with linkage disequilibrium (LD) patterns can differ between ancestry groups (Marchini et al., 2004; Peterson et al., 2019; Webb et al., 2017). Cross-population GWAS have found that while ancestral groups share many risk variants, some variants may have ancestry-specific effects (Levey et al., 2021). A study using the Million Veteran Program dataset found 223 independently significant SNPs associated with MD in a GWAS of European ancestry sample (N = 250,215); however, no risk

variants were statistically significant in a GWAS of individuals of African ancestry (N = 59,600) (Levey et al., 2021). Two-hundred and six of the 223 variants identified by the European ancestry GWAS were available for analysis in the African ancestry sample, and 125 (61%) of these SNPs had the same direction of effect in both samples. However, after multiple testing corrections, only one SNP was statistically significantly associated with MD in the African ancestry sample (Levey et al., 2021).

Sex differences in genetic architecture are another vital consideration for GWAS to gain a greater understanding of MD. Evidence suggests that the genetic risk factors for the sexes are not identical (Kendler et al., 2001b). Kang et al. (2020) found that there may be variants with sex-specific effects for MD, such as the SNPs in the *PDE4A*, *FDX1L*, and *MYO15B* genes. Furthermore, the X-chromosome is often excluded from GWAS due to limitations in study analyses (Khramtsova et al., 2019). The last 3+ large-scale GWAS from Psychiatric Genomics Consortium have not assessed sex differences despite epidemiological and twin studies suggesting sex differences. Differences in genetic architecture could contribute to the higher prevalence and risk of MD for women than for men (Altemus et al., 2014; Hasin et al., 2018; Weissman et al., 1996).

Although environmental factors are known to contribute to disease risk, environmental exposures have not usually been included in large-scale GWAS (Peterson, 2021). Interpersonal trauma (IPT) exposure, which refers to someone experiencing physical or sexual assault, during childhood is an environmental risk factor significantly affecting MD liability (Peterson et al., 2018). Childhood sexual assault was more prevalent in those with MD than controls (10.3% versus 2.5%, respectively) (Peterson et al., 2018). Children experiencing IPT is not uncommon in the United States as the National Survey of Children's Exposure to Violence found that 37.3% of youth surveyed reported experiencing physical abuse (Finkelhor et al., 2015). Research supports that experiencing childhood IPT strongly predicts developing depression later in life (Cisler et al., 2012; Hovens et al., 2010; Peterson et al., 2018). In a college sample, depressive symptoms and suicidal ideation have also been associated with IPT exposure (M. Li et al., 2022). The severity of depressive symptoms also significantly correlates with IPT exposure; however, the strength of this correlation (r = 0.14, p < 0.01) suggests there are other contributing risk factors (Fowler et al., 2013).

Sex differences in IPT exposure could also contribute to the sex differences in the prevalence of MD. In the United States, women have a higher prevalence of experiencing IPT than men (37.4% vs 30.9%) (Smith et al., 2017). Childhood maltreatment is also higher among women than men ($p < 1\times10^{-80}$) (Dalvie et al., 2020). Females report higher rates of IPT, specifically sexual assault, while males report higher physical assault (Overstreet et al., 2017; Schleider et al., 2021). However, experiencing sexual assault does seem to have a more significant effect on males than females in later developing depression (Kendler & Gardner, 2014).

Gene by Environment Interaction

Gene-environment interaction studies investigate the relationship between environmental factors on genetic effects (Smoller, 2016). In the context of IPT exposure, the effect on disease outcome from the presence, type, or severity of exposure can be moderated by genotype. There is some evidence that there is a gene-environment interaction between PRS and childhood IPT that can predict MD risk (Dalvie et al., 2020; Mitchell et al., 2021; Peterson et al., 2018; Peyrot et al., 2014); however, other studies found conflicting evidence that suggests there is no significant gene-environment interaction between PRS and childhood IPT (Peyrot et al., 2018). Peterson et al. (2018) found that classifying samples based on adversity exposure identified three genetic loci with heterogeneous effects. Individuals with a higher genetic load of risk variants may still develop MD regardless of IPT exposure, and individuals who experience trauma may develop MD regardless of genetic load (Peterson et al., 2018). The time period in which IPT exposure occurs can have different effects. Childhood trauma has been shown to have a significant interaction with MD-PRS, while adult trauma has not (Shen et al., 2020).

To better understand genetic and environmental risk factors for depression symptoms, this master's thesis: 1) examined if exposure to pre-college IPT is associated with depression symptoms and if these associations vary by sex and 2) assessed if pre-college IPT moderates the association of aggregate genetic risk (PRS) with depressive symptoms. It was hypothesized that IPT exposure would be positively associated with depressive symptoms scores and that IPT exposure would moderate the association of MD-PRS with depressive symptoms scores.

Methods

Participants

The data was collected as part of a larger ongoing cohort study called Spit 4 Science (S4S), which follows students throughout their time at a large urban college starting their first year (Dick et al., 2014). Data consists of self-report measures and genotypes from saliva DNA samples. Five cohorts have completed data collection (N = 12,358). Surveys asked questions about demographics, personality and behavior, family, friends, and experiences growing up. Data collected at the baseline assessment also asked about experiences before starting college. Data collected at subsequent follow-up assessments asked about their experiences since the prior assessment (i.e., past year). For the present study analyses, the following data from this existing study was used: demographic information, questions regarding exposure to physical or sexual assault and depressive symptoms, and genotypes. All surveys were completed online using the RedCap system (Research Electronic Data Capture; Harris et al., 2019). The total sample size for the present analyses was N = 7,502 participants.

Table 1: Distribution of IPT Exposure and Depression Symptom Scores by Sex and Genetic Ancestry

	N	IPT Exposure*	Depression Score*
Sex			
Female	4829 (64%)	2018 (42%)	9.50 (3.86)
Male	2673 (36%)	857 (32%)	8.21 (3.64)
Ancestry			
African	1525 (20%)	584 (38%)	8.68 (3.75)
Admixed Americas	921 (12%)	375 (41%)	9.28 (4.02)
East Asian	734 (10%)	218 (30%)	9.37 (3.88)
European	3700 (49%)	1501 (41%)	9.12 (3.79)
South Asian	622 (8%)	197 (32%)	8.76 (3.90)
Total	7502 (100%)	2875 (38%)	9.04 (3.83)

* prior to starting college

Sex and genetic ancestry are shown by sample size and percentage of the total sample size. Interpersonal trauma (IPT) exposure prior to starting college is shown by sample size and percentage of participants who endorsed ever experiencing IPT by demographic group. Depressive symptoms scores are shown by mean and standard deviation for each demographic group. For example, females made up 64% of the total sample and had a mean depressive symptoms score of 9.50. Forty-two percent of females were IPT-exposed.

Measures

Trauma exposure was measured by a 5-item abbreviated version of the Life Events Checklist (LEC; Gray et al., 2004) that assesses exposure to a range of potentially traumatic events (i.e., natural disaster, sexual assault, physical assault, other unwanted sexual experience,

motor vehicle accident) experienced, with a "yes" or "no" response. To capture pre-college exposure, the baseline time-point (i.e., year 1 fall) was used, wherein individuals reported on lifetime trauma exposure types experienced before attending college. The present study used sexual assault, physical assault, and other unwanted sexual experience items to create a composite IPT exposure variable. Yes/no endorsement on these three questions was used to create a binary exposure variable for 'any' type experienced. Missingness for the IPT variables could result from participants skipping individual items, selecting "I choose not to answer," or as a result of incompatible responses. An incompatible response was due to participants being able to check more than one option for the IPT exposure questions, as it was possible to check both "yes" and "never happened to me" to an IPT exposure. All incompatible responses were marked as missing. Participants who did not endorse any IPT exposure but had any missingness were excluded due to the uncertainty that they would have responded "yes" to the missing items. Participants with any missingness that endorsed at least one item were included because it is known that they had an IPT exposure. Participants were excluded from analyses if all three answered IPT questions were incompatible or missing.

Depressive symptoms scores were calculated based on participants' answers to an abbreviated SCL-90 comprising four questions (Derogatis et al., 1973). Each question assessed how much discomfort each symptom had caused the participant in the last 30 days. Those symptoms were "feeling blue," "worrying too much about things," "feeling no interest in things," and "feeling hopeless about the future." Participants were asked to answer using a Likert scale with the options being 1– Not at all, 2 – A little bit, 3 – Moderately, 4 – Quite a bit, or 5 – Extremely. Missingness for the depressive symptoms scores were addressed by using a prorated sum score calculated by averaging the answers to the questions the participant did answer and then multiplying by four, which was the total number of questions for that scale. Participants had to have answered at least half of the questions to be included in the analysis. The range for depressive symptom scores was from 4 to 20.

Ancestry Assignment & Quality Control

Ancestry assignment for S4S has been previously described by Peterson et al. (2017), and this current study's ancestry sample sizes are shown in **Table 1**. Ancestry principal component analysis (PCA) was used as a method for empirically assigning ancestral subgroups to achieve

more homogeneous samples for analysis (Peterson, Edwards, et al., 2017), thereby reducing potential spurious effects due to population stratification. Participants were empirically assigned to genetic ancestry populations using the 1000 Genome Project (1KGP) phase 3 reference panel's 26 populations, which were collapsed into five super-populations (1000 Genomes Project Consortium, 2015). The five ancestry super-populations include African descent (AFR), admixed from the Americas (AMR), East Asian descent (EAS), European descent (EUR), and South Asian descent (SAS). This was done by calculating the median and variance for each 1KGP population using all 10 ancestry principal components (PCs) and the Mahalanobis distance between each sample and all 26 populations. New samples can be assigned by calculating the minimum Mahalanobis distance between each participant and the 26 1KGP populations, then assigning the participant to the corresponding closest super-population. Using this method allows researchers to retain participants for GWAS that would otherwise have to be excluded due to missing their self-reported census data or recent genetic admixture.

Samples were genotyped using three different arrays (cohorts 1-3: Affymetrix BioBank array, cohort 4: Smokescreen array, cohort 5: Infinium Global Screening Array-24 v3.0 BeadChip) and harmonized. Initial quality control (QC) was previously done as described by Webb et al. (2017). Briefly, pre-imputation QC excluded low-quality SNPs identified by SNPolisher. Other missingness thresholds for SNPs and samples exclusion included SNPs missing >0.05 of genotypes, samples missing >0.02 of genotypes, and SNPs missing >0.02 of genotypes after sample filtering (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Webb et al., 2017). Software SHAPEIT2 (Delaneau et al., 2013) and IMPUTE2 (Howie et al., 2009) were used to perform the imputation with the 1KGP phase 3 reference panel.

Analyses

R (Version 4.3.1) was used for descriptive statistics and all regression analyses (R Core Team, 2023). The *lm* function from the stats package was used for all linear regression models. The significance of each risk factor in the models were inspected by marginal p-values ($p < 0.05$) and R^2 metrics. A phenotypic-only linear regression model included: sex, any IPT exposure, and sex by any IPT exposure interaction terms (**Model 1**).

Model 1.

$$Depressive\ symptoms\ scores \sim sex\ +\ IPT\ exposure\ +\ sex\ *\ IPT\ Exposure$$

To assess whether genetic liability varies by IPT exposure, MD-PRS developed in well-powered samples using PRS-CSx was applied in S4S. PRS-CSx is a method that increases the predictability of PRS when using an ancestrally diverse population (Ruan et al., 2022). Coupled continuous shrinkage is used in the PRS-CSx method to adjust SNP effect sizes for local LD patterns across populations (Ruan et al., 2022). The GWAS summary statistics from the Psychiatric Genomics Consortium (PGC; EUR *n* = 500,199 and EAS *n* = 98,502) and the Million Veterans Project (MVP; EUR *n* = 807,029 and AFR *n* = 59,600) were combined to create a MD-PRS (Giannakopoulou et al., 2021; Howard et al., 2019; Levey et al., 2021). Using the summary statistics from diverse ancestry populations to create weights in PRS-CSx has been shown to improve the transferability and predictability of PRS in diverse ancestry cohorts compared to PRS created from a single ancestry (Ruan et al., 2022). Prior to using PRS-CSx, the European summary statistics from PGC and MVP were meta-analyzed in METAL using inverse variance weighting (Willer et al., 2010). PRS were centered and scaled prior to regression analyses to improve interpretation across groups.

A linear regression model applied in each ancestry group using PRS to predict depressive symptoms scores in the S4S cohort (**Model 2**). Covariates included sex and 10 ancestry PCs to control for sex and ancestry stratification and IPT exposure and sex by IPT exposure. Ancestry PCs were centered and scaled within ancestry prior to regression analyses to improve interpretation across groups. These analyses determined if PRS are associated with depressive symptoms in each of the S4S ancestral groups.

Model 2.

$$Depressive\ symptoms\ scores \sim PCs\ +\ sex\ +\ IPT\ +\ PRS\ +\ sex\ *\ IPT$$

To determine if there is a significant interaction between PRS and IPT, within-ancestry linear regression models were used to predict depressive symptoms scores by using a MD-PRS by IPT exposure interaction term (**Model 3**). Covariates included sex and 10 ancestry PCs to control for sex and ancestry stratification and IPT exposure. Interactions between covariates were also accounted for by including an IPT exposure and sex interaction term to ensure

significance is not a result of confounded effects (Duncan et al., 2014). These models were applied for each ancestral group, and cross-population effects were estimated by both fixed and random effects meta-analysis using METASOFT (Han & Eskin, 2011). By meta-analyzing the ancestry-stratified **Model 3**, statistical power and precision are increased, allowing these results to be generalized across ancestry populations.

Model 3.

$$Depressive\ symptoms\ scores \sim PCs + sex + IPT + PRS + sex * IPT + PRS * IPT$$

Because this is the first study using MD-PRS to predict depression symptoms scores in a cross-ancestry meta-analysis, it was unknown if heterogeneity would be present across ancestry groups. Heterogeneity statistics were inspected by conducting Cochran's Q and I^2 tests to aggregate evidence for heterogeneity in effect size across groups. Cochran's Q test is the squared, weighted, and summed differences between each study's effect-size estimates and the overall effect (Zeggini & Ioannidis, 2009). If Cochran's Q is $p < 0.10$, it is possible that heterogeneity is present (Zeggini & Ioannidis, 2009). I^2 index quantifies heterogeneity by estimating the percentage of the variance between studies not due to sampling error, meaning the variance is due to differences in effect sizes (Zeggini & Ioannidis, 2009). However, the number of studies included in the meta-analysis was small ($N = 5$) and heterogeneity tests may not be adequately powered (Zeggini & Ioannidis, 2009).

Results

Phenotypic Associations

Table 2: Two-Sample t-test and Two-Proportions z-test Results

	Female		Male			
	M	**SD**	**M**	**SD**	t	p-value
Depression Symptoms	9.50	3.86	8.21	3.64	14.35	3.22×10^{-46} *
	N	**%**	**N**	**%**	X^2	p-value
Any IPT Exposure	2018	42%	857	32%	68.5	6.43×10^{-17} *

* $p < .001$

The two-sample *t*-test and two-proportion *z*-test results showed that there was a significant difference in the mean depressive symptoms scores and the proportion of those who were IPT exposed between the sexes. Females had a higher average depressive symptoms score and experienced higher rates of IPT exposure than males.

Participants had a mean depressive symptoms score of 9.04 (σ = 3.83), and approximately 38% of the sample experienced IPT prior to starting college (**Table 1**). The Welch Two-Sample *t*-test testing the difference between female (μ = 9.50) and male (μ = 8.21) mean depressive symptoms scores indicated the difference was statistically significant ($t(5796.37) = 14.35$, $p = 3.22 \times 10^{-46}$; **Table 2**). However, the effect of sex was small (Cohen's $d = 0.34$). The Two-Proportions *z*-test comparing the difference in the proportion of females (prop. = 0.42) and males (prop. = 0.32) who had experienced any IPT prior to college showed that the difference was statistically significant ($\chi 2 = 68.5$, $p = 6.43 \times 10^{-17}$; **Table 2**). On average, participants exposed to IPT had depressive symptoms scores 1.73 points higher than those who were not exposed. The Welch Two-Sample *t*-test testing the difference between IPT-exposed (μ = 10.11) and IPT-unexposed (μ = 8.38) mean depressive symptoms scores indicated the difference was statistically significant ($t(5675.22) = 19.04$, $p = 1.15 \times 10^{-78}$). Both female and male IPT-exposed groups had a higher mean depressive symptoms score than their unexposed counterparts (**Figure 1**). The average female depressive symptoms score was higher than the male average in both the exposed and unexposed groups (**Figure 1**).

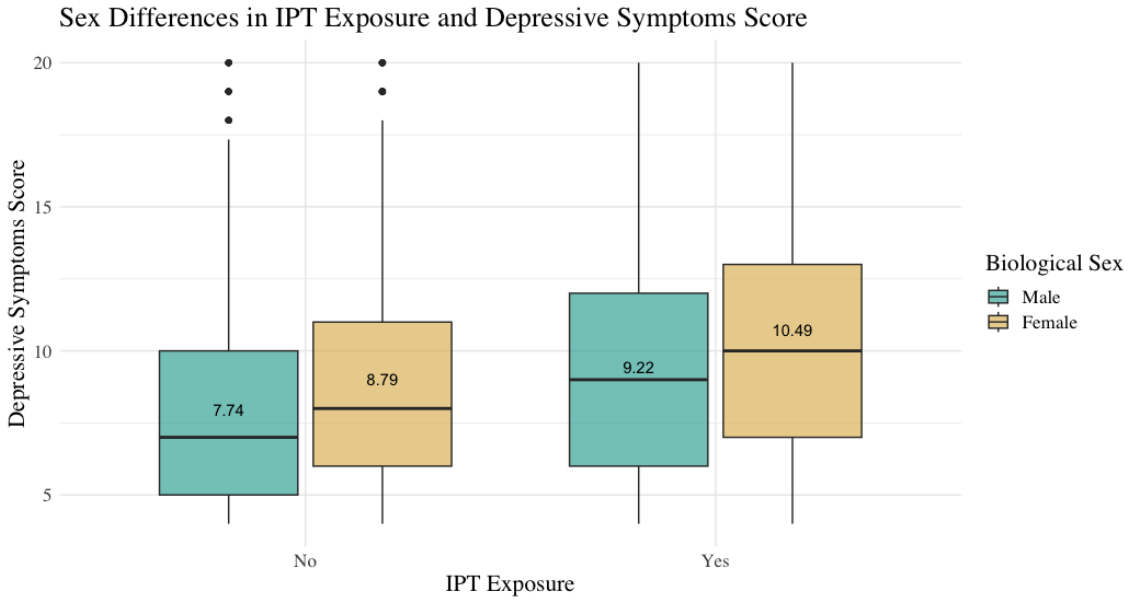

Figure 1. These boxplots illustrate sex differences in interpersonal trauma (IPT) and depressive symptoms scores. The mean depressive symptoms scores for females (μ = 10.49) and males (μ = 9.22) exposed to IPT were higher than the female (μ = 8.79) and male (μ = 7.74) unexposed groups.

Model 1 was fit and estimated using ordinary least squares to predict depressive symptoms scores with sex, IPT exposure, and sex by IPT exposure. The model explained a statistically significant proportion of variance (R^2 = 7%, F(3, 7498) = 181.99, $p < .001$, adj. R^2 = 7%; **Table 3**). For predicting depressive symptoms scores, sex, and IPT exposure were significant predictors, but there was no statistical evidence of an interaction. Inspecting sex and IPT exposure, IPT exposure (β = 1.48, R^2 = 1.22%, OR = 4.83, $p = 8.21 \times 10^{-22}$) had a greater impact on predicting depressive symptoms scores than sex (β = 1.05, R^2 = 1.18%, OR = 2.87, $p = 4.38 \times 10^{-21}$; **Table 3**).

Table 3: Association between Sex and IPT with Depression Symptom Scores Results

Predictors	β	**Standard Error**	**Partial R^2**	**Odds Ratio [95% CI]**	***p*-value**
Sex	1.05	0.111	1.18%	2.87 [2.30, 3.57]	4.38×10^{-21} *
IPT Exposure	1.48	0.153	1.22%	4.38 [3.24, 5.92]	8.21×10^{-22} *
Sex × IPT Exposure	0.21	0.19	0.02%	1.23 [0.86, 1.79]	0.251

* $p < .001$

Biological sex and IPT exposure were significantly associated with depressive symptoms scores.

Genetic Associations

Within-ancestry linear regression models included 10 ancestry PCs covariates, biological sex, IPT exposure, and MD-PRS to predict depressive symptoms scores (**Model 2**). MD-PRS was only statistically significant in European ($\beta = 0.216$, $p = 3.12\times10^{-4}$) and Admixed Americas ($\beta = 0.342$, $p = 7.34\times10^{-3}$) ancestries, and was nominally associated in the South Asian ancestry group ($\beta = 0.248$, $p = 0.097$). Biological sex and IPT exposure were significant in each of the five ancestry groups ($p < 0.01$).

The meta-analysis of **Model 3** (across ancestry groups) found that IPT exposure, biological sex, and MD-PRS were all associated with depressive symptoms scores in both the fixed effects and random effects models ($p < 0.05$; **Table 4**). IPT exposure had the largest effect sizes in both models ($\beta_{fixed} = 1.32$, $p_{fixed} = 4.52\times10^{-5}$; $\beta_{random} = 1.32$, $p_{random} = 4.52\times10^{-5}$), followed by sex ($\beta_{fixed} = 1.091$, $p_{fixed} = 1.20\times10^{-22}$; $\beta_{random} = 1.105$, $p_{random} = 4.67\times10^{-17}$), and then MD-PRS ($\beta_{fixed} = 0.209$, $p_{fixed} = 1.14\times10^{-4}$; $\beta_{random} = 0.202$, $p_{random} = 0.016$; **Table 4**). However, inspecting the heterogeneity statistics suggested there may be significant heterogeneity in MD-PRS effect sizes across ancestry ($I^2 = 49.44$, Cochran's Q $p = 0.095$; **Table 4**). Nevertheless, MD-PRS was also significant in a random effects model ($\beta_{random} = 0.202$, $p_{random} = 0.016$). There was no statistical evidence of interaction between any of the predictors.

Looking at within-ancestry results of **Model 3**, IPT exposure ($p < 0.01$) and biological sex ($p < 0.01$) were significant in all ancestry groups. However, MD-PRS were only significant in European ($\beta = 0.277$, $p = 3.91\times10^{-4}$) and Admixed Americas ($\beta = 0.454$, $p = 6.10\times10^{-3}$) ancestry groups (**Table 5**). IPT exposure had larger effect sizes (β range: 1.17- 2.19) and R^2 (R^2 range: 0.033 - 0.063) values than sex (β range: 0.72 - 1.57; R^2 range: 0.011 - 0.038) and MD-PRS (β range: -0.025 - 0.454; R^2 range: 0.0003 - 0.004; **Figure 2**; **Table 5**). As shown in **Figure 2**, the confidence intervals of the effect sizes all overlap, suggesting they were not statistically different from each other. Effect sizes are more precisely estimated in the European ancestry group and the meta-analysis, most likely due to sample size. The smaller sample sizes had limited power to detect effects.

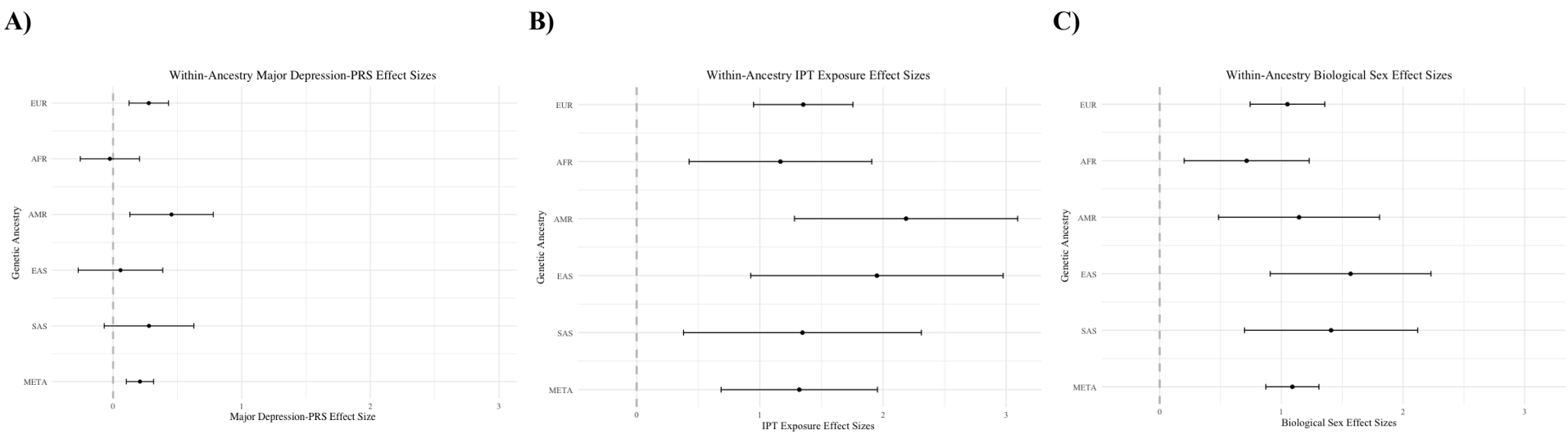

Figure 2. Forest plots of Model 3 effect sizes for A) MD-PRS, B) IPT exposure, and C) biological sex by ancestry compared to the fixed effects model meta-analysis estimates.

Table 4: PRS × IPT Interaction Meta-Analysis Results

	Fixed Effects Model			Random Effects Model				
Predictors	β	**S.E.**	***p*-value**	β	**S.E.**	***p*-value**	I^2	**Cochran's Q *p*-value**
Sex	1.091	0.111	1.20×10^{-22} ***	1.105	0.132	4.67×10^{-17} ***	19.10	0.293
IPT Exposure	1.32	0.324	4.52×10^{-5} ***	1.32	0.324	4.52×10^{-5} ***	<0.0001	0.721
PRS	0.209	0.054	1.14×10^{-4} **	0.202	0.08	0.016 **	49.44	0.095 *
Sex × IPT Exposure	0.146	0.187	0.437	0.146	0.187	0.437	<0.0001	0.920
PRS × IPT Exposure	-0.108	0.088	0.218	-0.108	0.088	0.218	<0.0001	0.69

* $p < .1$ ** $p < .05$ *** $p < .001$

Predictors' estimate, standard error (S.E.), *p*-value for fixed effects and random effects meta-analysis and heterogeneity statistics are shown here.

Table 5: Within-Ancestry Results Compared to the Fixed Effect Model Meta-Analysis

Predictors	**EUR** N = 3700	**AFR** N = 1525	**AMR** N = 921	**EAS** N = 734	**SAS** N = 622	**META** N = 7502
Sex						
β	1.050	0.715	1.145	1.569	1.409	1.091
Standard Error	0.157	0.262	0.337	0.337	0.362	0.111
p-value	$2.25 \times 10^{-11*}$	$6.43 \times 10^{-3*}$	$7.11 \times 10^{-4*}$	$3.73 \times 10^{-6*}$	$1.12 \times 10^{-4*}$	$1.20 \times 10^{-22*}$
R^2	0.019	0.011	0.016	0.038	0.037	
IPT Exposure						
β	1.352	1.167	2.187	1.950	1.346	1.320
Standard Error	0.206	0.378	0.462	0.522	0.492	0.324
p-value	$5.57 \times 10^{-11*}$	$2.05 \times 10^{-3*}$	$2.5 \times 10^{-6*}$	$2.00 \times 10^{-4*}$	$6.35 \times 10^{-3*}$	$4.52 \times 10^{-5*}$
R^2	0.033	0.038	0.063	0.056	0.034	
Sex × IPT Exposure						
β	0.094	0.437	-0.175	0.060	0.350	0.146
Standard Error	0.257	0.437	0.559	0.640	0.646	0.187
p-value	0.713	0.318	0.754	0.926	0.588	0.437
R^2	0.00003	0.0006	0.0001	0.00001	0.0004	
PRS						
β	0.277	-0.025	0.454	0.057	0.279	0.209
Standard Error	0.078	0.117	0.165	0.168	0.177	0.054
p-value	$3.91 \times 10^{-4*}$	0.832	$6.10 \times 10^{-3*}$	0.732	0.116	$1.14 \times 10^{-4*}$
R^2	0.004	0.0003	0.0082	0.0025	0.0041	
PRS × IPT Exposure						
β	-0.148	-0.074	-0.275	0.282	-0.108	-0.108
Standard Error	0.122	0.190	0.258	0.302	0.330	0.088
p-value	0.224	0.697	0.287	0.350	0.744	0.218
R^2	0.0004	0.00009	0.0011	0.0011	0.0002	

* $p < .001$

The within-ancestry Model 3 effect sizes, standard errors, *p*-values, and partial R^2 are shown here in comparison to the fixed effects model meta-analysis.

Discussion

Phenotypic Associations

The purpose of the first aim of this thesis was to examine if exposure to pre-college IPT is associated with depression symptoms and if these associations vary by sex. It was hypothesized that IPT exposure would be positively associated with depressive symptoms scores. IPT exposure was a significant predictor for depressive symptoms scores, and those who were exposed to IPT had a mean depressive symptoms score 1.73 points higher than those unexposed. The difference between the mean depressive symptoms scores of IPT-exposed and IPT-unexposed was statistically significant ($p = 8.21 \times 10^{-22}$), supporting the hypothesis. These results are in concordance with the previous literature. Peterson et al. (2018) found that adversity exposure was significantly associated with major depression ($p = 2.6 \times 10^{-19}$). Peterson et al. (2018) found that adversity exposure explained 11.6% of the variance in the major depression phenotype. In the current study, IPT exposure accounted for 1.22% of the phenotypic variance of depressive symptoms scores. This difference may be due to how depression and trauma were defined. While clinical depression and SCL-90 symptom scores are genetically correlated (r_g = 0.35 - 0.45), using PRS built from MD diagnoses to predict non-clinical depression symptoms in S4S may explain the lower R^2 (Kendler et al., 2019). Peterson et al. (2018) also defined adversity as an aggregate risk across a range of stressful life events, while this study focused on physical and sexual assault.

Mean depressive symptoms scores were statistically significantly higher in female participants than in males. Female participants also had statistically significantly higher exposure rates to IPT than males. Female participants also reported higher depressive symptoms scores than males when they were split into IPT-exposed and -unexposed (**Figure 1**). These differences show that biological sex and IPT exposure have main effects on depressive symptoms scores. However, there was no evidence of an interaction between sex and IPT exposure. The absence of a statistically significant sex by IPT exposure interaction is most likely not due to a lack of power as these analyses were well-powered to discover these types of phenotypic interactions. Hovens et al. (2010) found that for all types of childhood abuse studied, including emotional neglect, psychological, physical, and sexual abuse, the interaction of gender and trauma exposure

was also not statistically significant. These results show that biological sex and IPT exposure are important predictors of depressive symptoms scores, but there is no evidence of an interaction.

Genetic Associations

The second aim of this thesis was to assess if pre-college IPT moderates the association of aggregate genetic risk (PRS) with depressive symptoms. It was hypothesized that IPT exposure would moderate the association of MD-PRS with depressive symptoms scores, meaning the additive interaction of having both main effects confers greater risk. **Model 2** results found that MD-PRS was a significant predictor of depressive symptoms scores for those of European and Admixed Americas ancestries and nominally predictive in South Asian ancestry. IPT exposure and biological sex were significant predictors in every ancestry model.

In the meta-analysis of **Model 3** across ancestries, sex and IPT exposure were statistically significant using both the fixed effects and random effects models. MD-PRS were also significant in the meta-analysis, but with some evidence of heterogeneity present (Cochran's Q $p < 0.1$). There was no evidence of an interaction between MD-PRS and IPT exposure or sex by IPT exposure, failing to support the stated hypothesis. The within-ancestry results of **Model 3** show similar patterns. Biological sex and IPT exposure had statistical significant main effects on the prediction of depressive symptoms scores in every ancestry group. In contrast, MD-PRS was significant in only the European and Admixed Americas ancestries. No interactions were found in any ancestry group. Peyrot et al. (2018) also found no interaction between MD-PRS and childhood trauma in a European sample.

Limitations & Future Research

The limited availability of large-scale GWAS summary statistics for non-European ancestry groups could have contributed to the limited performance of MD-PRS across ancestry groups. Three cohorts were included in PRS-CSx to generate the meta-PRS for each ancestry, including PGC (EUR n = 500,199 and EAS n = 98,502) and MVP (EUR n = 807,029 and AFR n = 59,600). The largest sample by over ten-fold was of European ancestry from two different cohorts. The smallest sample size was African ancestry from the MVP, which differs from this project's demographic as this veteran population skews older and is > 90% male. This could have impeded the ability of the MD-PRS to predict depression symptoms in a much younger college-age sample that slightly skews female. Going forward, large-scale GWAS should

prioritize collecting samples of non-European ancestry (e.g., Admixed Americas, South Asian, Oceanic, and Middle Eastern ancestry), to facilitate transferability of results across the ancestry spectrum.

MD-PRS could have also been affected by the sample sizes available in the S4S dataset. The smallest sample sizes were Admixed Americas (12%), East Asian (10%), and South Asian (8%) ancestry groups. There was less precision in the estimation of effect sizes of predictors for these cohorts as shown by the confidence intervals in **Figure 2**. Another limitation may be the reference panels and genotyping arrays. Since genetic research has primarily focused on individuals of European ancestry, there are limited ancestries represented in the reference panels and genotyping arrays better capture EUR genetic variants (Peterson et al., 2019). These limitations most likely contributed to the limited MD-PRS performance and the lack of significance in the MD by IPT exposure interaction, as the power issue with the PRS effect reduces the power to discover an interaction.

Future research should also investigate types of trauma and other factors, such as age of exposure, duration, and frequency of trauma. As previously mentioned, Hovens et al. (2010) studied many more types of trauma as predictors of depression and anxiety. The number of trauma types and frequency created childhood trauma indices. Depressive disorder was associated with childhood trauma scores ($p < 0.001$), with odds ratios increasing with childhood trauma scores (Hovens et al., 2010). Those who experienced regular physical abuse (OR = 3.06 [1.43, 6.56]) had a higher odds ratio than those who experienced more infrequent physical abuse (OR = 2.03 [1.07, 3.86]). The severity and types of exposure impact the development of psychopathology later in life. Future research should determine if the type and severity of trauma are associated with PRS of MD and/or other related phenotypes (e.g., depression symptoms, suicide, or anxiety) and if they moderate these phenotypes.

Previous studies have only been conducted using a single ancestry population, and this is the first study to our knowledge that investigates depression-PRS and IPT exposure using cross-ancestry methods. The cross-ancestry methodology of this thesis increases the generalizability of these results. The publicly available methods pipeline produced by this project will hopefully encourage others in the field to incorporate participants of non-European ancestry and conduct cross-ancestry meta-analyses to produce more robust results with greater power.

Furthermore, the results of this thesis show that sex and IPT exposure prior to college are important predictors of depression symptoms in a college-age sample. This information can be used as a preventative measure to identify students who may be more at risk of developing depression symptoms during their transition into young adulthood and higher education.

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