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A Person-Centered Data Analytic Approach to Dopaminergic Polygenic Moderation of Child Maltreatment Exposure

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Abstract

The present study illustrates the utility of latent class analysis, a person-centered data analytic approach, as an innovative method for identifying naturally occurring patterns of polygenic risk, specifically within the dopaminergic system. Moreover, this study tests whether latent classes of polygenic variation moderate the effect of child maltreatment exposure on internalizing symptoms among African-ancestry youth. African-ancestry youth were selected for this study because youth of color are overrepresented in the child welfare system (Dettlaff & Boyd, 2020) and because African-ancestry individuals are significantly underrepresented in genomics research (Fatumo et al., 2022). Results identified three latent classes of dopaminergic gene variation. Class 1 was marked predominately by homozygous minor alleles, Class 2 was characterized by homozygous major and heterozygous presentations, and Class 3 was marked by heterozygous alleles on the DAT-1 SNPs and a combination of homozygous major and minor alleles on the other SNPs. Results indicated that a greater number of maltreatment subtypes experienced was associated with higher internalizing symptoms only for children with the latent polygenic *Class 2* pattern. This latent class was distinctly characterized by more homozygous major or heterozygous allelic presentations along all three DAT-1 single nucleotide polymorphisms. This significant latent polygenic class by environment interaction was replicated in an independent replication sample. Together, findings suggest that African-ancestry children with a pattern of dopaminergic variation characterized by this specific combination of polygenic variation are more vulnerable to developing internalizing symptoms following maltreatment exposure, relative to their peers with other dopamine-related polygenic patterns.

Keywords

maltreatment; polygenic; person-centered; depression; dopamine

Child maltreatment is a major public health concern, with approximately 37% of youth investigated for possible maltreatment in the United States before the age of 18 (Kim et al., 2017). National estimates indicate that anywhere from 618,000 to 1,256,000 children

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are exposed to abuse or neglect annually (USDHHS, 2020; Sedlak et al., 2010). Child maltreatment deprives children of the species-expected nurturant family environments needed for adaptive development, thereby compromising children's psychological health (Cicchetti & Toth, 2015). Moreover, stress associated with exposure to maltreatment can become embedded in children's self-regulatory capacities and progressively impair physical and mental health across the life course (e.g., Shenk et al., 2022). The sequelae of child maltreatment can be far reaching and cover a wide spectrum of physical and mental health disturbances that occur across the life course (Widom, 2014). A multiple-levels-of-analysis approach is integral to more fully articulating the diverse ways that child maltreatment compromises health (Cicchetti & Dawson, 2002). Regarding mental health, approximately 50% of internalizing disorders (i.e., depression, anxiety) are attributable to childhood maltreatment (Green et al., 2010; Zeanah & Humphreys, 2018) and exposure to maltreatment predicts internalizing symptoms that emerge early in development and are persistent across the life course (Nanni et al., 2012; Winter et al., 2022). Notably, not all individuals who experience child maltreatment go on to development internalizing symptoms (Cicchetti & Toth, 2015). Identifying individual factors that modify risk for the development of internalizing symptoms is critical to prevention and intervention efforts.

Child Maltreatment and Genetic Influences.

Genetic influences on adjustment and development in children with exposures to abuse and/or neglect have focused primarily on gene by environment (maltreatment) interactions (GxE). GxE interactions are often conceptualized within a diathesis-stress framework with the environment serving as a moderator that evokes latent main effect genetic influences on the development of psychopathology (Moffitt et al., 2005). However, in the case of child maltreatment, the environmental exposure is severe and toxic, with its own robust main effects on a variety of outcomes that have been shown to persist across the life course (e.g., Cicchetti & Toth, 2015; Danese & Tan, 2014; Li, Zhao, & Yu, 2019; Nelson et al., 2017; Noll, 2021).

Genetic variation has been found to moderate the environmental effects of maltreatment, providing insight into which children exposed to maltreatment are more vulnerable to multiple adverse outcomes. A recent systematic review of this literature indicated empirical support for polymorphisms of the following genes as moderators of the impact of maltreatment exposure on the development of depression and internalizing symptoms: the serotonin transporter gene (5HTTLPR), the dopamine transporter gene DAT1, the brain derived neurotrophic factor (BDNF), monoamine oxidase-A (MAOA), the corticotropin releasing hormone receptor 1 (CRHR1), FK506 binding dopamine (FKBP5), and the C-reactive protein (CRP) (see Maglione et al., 2018 for review). This perspective is consistent with a differential susceptibility conceptualization (Belsky & Pleuss, 2009). However, research on child maltreatment typically does not include contrasts with exceptionally enriched and supportive environments; rather, demographically comparable families also facing similar environmental adversities (e.g., poverty, exposure to community violence) allow for greater specificity of unique maltreatment effects. As GxE research in maltreatment has advanced, methods to incorporate polygenic models have gained importance.

The majority of GxE literature has utilized a candidate gene approach in which a single gene, or single nucleotide polymorphism (SNP) is tested in interaction with an environmental factor to predict an outcome. As noted by Salvatore and Dick (2015), this work has become controversial due to a number of challenges including the selection of the gene variant, replication failures and inconsistent findings, small sample sizes, population heterogeneity, lack of appropriate handling of covariates as well as other statistical limitations (e.g., Duncan & Keller, 2011; Keller, 2014). A variety of recommendations have been proffered to address these limitations and controversies and to guide the next generation of research in this area (see Assary et al., 2018; Dick et al., 2015; Duncan & Keller, 2011; Eaves, 2006; Johnston et al., 2013; Keller, 2014; Moffitt et al., 2005; Salvatore & Dick, 2015).

First, researchers have been called upon to engage in a critical evaluation of the biological plausibility of the genes, outcomes, and theorized mechanisms under investigation. Second, the importance of assessing environmental exposure and outcomes with separate informants, and reliable and valid assessments has been underscored. Third, population heterogeneity can contribute to variation in allele frequencies across ancestral subpopulations (i.e., population stratification, Cardon & Palmer, 2003) and careful attention to this issue is required. Fourth, statistical guidelines have been advanced including the need for appropriate statistical controls and consideration of gene-environment correlation. Fifth, replication of GxE findings across independent samples has been identified as a critical path forward for this work. Additionally, because the majority of GxE studies have been conducted using samples of European ancestry, there is a critical need for greater representation of diverse individuals in GxE research (Peterson et al., 2019). Finally, polygenic scores that consider multiple genes simultaneously have become increasingly widespread given the increased awareness of limitations described above and the recognition that most outcomes are highly polygenic (Belsky & Domingue, 2023; Boyle & Pritchard, 2017; Visscher, Hill, & Wray, 2008).

Polygenic risk scores (PRS) are values representing an estimate of an individual’s genetic liability to a specific disease or outcome of interest. PRS are traditionally calculated by computing the sum of risk alleles for an individual, weighted by the risk allele effect size estimated by a large GWAS on the specific outcome (Choi, Mak, O’Reilly, 2020; Wray et al., 2021). With this method, investigators must first identify a large prior GWAS conducted on the outcome of interest. This is often referred to as the Discovery sample. Next, investigators ascertain the GWAS summary statistics from the prior GWAS study of the Discovery sample and determine the list of SNPs in common between the Discovery and their independent sample (e.g., Target sample). Various methods are currently available to choose the DNA variants and weights from the prior GWAS to apply to the current study (see Wray et al., 2014 for review).

Although this approach offers many advances and has become relatively cost-effective (Tam et al., 2019), most GWAS were conducted on participants of European ancestry (e.g., Coleman et al., 2020; Direk et al., 2017; Armstrong-Carter et al., 2021; Martin et al., 2019). Indeed, recent research indicates that the vast majority (86%) of genomics studies were conducted in individuals of European ancestry (Fatumo et al., 2022; Hindorff et al., 2018;

Peterson et al., 2019; Popejoy & Fullerton, 2016). A few notable exceptions include recent work that calculated separate polygenic scores for African ancestry individuals based on ancestry-aligned prior GWAS (e.g., Elam et al., 2021; Elam et al., 2022; Kuo et al., 2021).

Because European ancestry GWAS are not equally predictive when applied to non-European populations, GWAS-derived PRS perform sub-optimally in non-European populations (Belsky & Domingue, 2023; Martin et al., 2019; Peterson et al., 2019; Wray et al., 2021). This presents a significant challenge in conducting research with individuals of non-European ancestral backgrounds and is contributing to the perpetuation of underrepresentation of non-White individuals in research (Popejoy et al., 2019). Therefore, although GWAS-derived PRS present a number of important advantages for the field, the current limitations in applying these scores to non-European ancestry individuals make it a less optimal option for research with other populations. Given the disproportionate representation of Black youth and families in the child welfare system (Dettlaff & Boyd, 2020), application of European-ancestry based GWAS are especially problematic within the study of child maltreatment exposure.

Additionally, child maltreatment is an adversity known to set in motion a host of varied probabilistic risk mechanisms resulting in a span of physical and mental health outcomes (e.g., Cicchetti & Toth, 2016). Genetic variation is theorized to moderate the influence of child maltreatment exposure, rather than exert a main effect influence on the development of psychopathology and negative health outcomes. Because of this theoretical framework, understanding which GWAS to apply as a moderator is less obvious than in studies in which genetic variation is theorized to exert a main effect on a discrete disorder or outcome (i.e., schizophrenia). Indeed, Bogdan and colleagues (2018) asserted that “the genetic architecture supporting the development of psychopathology (e.g., depression) in the context of stress may be distinct from the genetic architecture conferring general disorder risk as assessed in the original GWAS from which these PRS were derived.”

Recently, genome-wide gene-environment interaction studies have been conducted that address this gap in understanding the moderating role of polygenic variation in the etiology of depression (e.g., Arnau-Soler et al., 2019; Mullins et al., 2016; Peyrot et al., 2017; Van der Auwera et al., 2017). Although critical advances for the field, these studies have relied on a variety of retrospective measures of stressful life events, as well as varied definitions and assessments of childhood adversity and trauma exposure that prohibit generalizability and replicability of findings. Additionally, this recent work has relied almost exclusively on samples of European-ancestry, further perpetuating the underrepresentation of individuals of other backgrounds in research. A notable exception is a study by Dunn and colleagues (2016) which tested GWEIS (genome-wide by environment interaction study) among Black and Latina women. Among the Black women, a genome-wide significant interaction was identified between a variant of CEP350 and self-reported stressful life events in the prediction of depression; however, this effect was not replicated in the replication sample.

Dopaminergic system

Dopamine is a catecholamine neurotransmitter that plays a critical role in a wide range of physiological functions (Klein, Battagello, Cardoso, et al., 2018). The dopaminergic

system has been implicated in the reward seeking behaviors, decision making, pleasure, and motivation (Kanarik, Grimm, Mota, et al., 2022) and has been implicated in anhedonia specifically, and depression more broadly (Belujon & Grace, 2017; Der-Avakian & Markou, 2012; Wise, 2008; Yadid & Friedman, 2008). Furthermore, prior candidate gene (Guo & Tillman, 2009; Mandelli & Serretti, 2013) and GWAS (Howard, Adams, Shirali et al., 2018; Wray, Ripke, Mattheisen et al., 2018) studies support the role of genetic variants in the dopaminergic system in depression. For instance, GWAS studies have identified that the dopamine receptor D2 (DRD2) gene differentiates depressed and non-depressed individuals (Howard et al., 2018; Liu et al., 2020; Wray et al., 2018). Moreover, Pearson-Fuhrhop and colleagues (2014) utilized an additive literature-based genetic risk score and found a significant main effect association between the dopamine risk score and depressive symptoms. Prior candidate GxE studies also support the role of genetic variation in the dopamine system as moderating the impact of adversity on the development of internalizing symptoms (Cao et al., 2018; Haeffel et al., 2008; Mandelli & Serretti; Vaske et al., 2009), which lend support to the notion that dopamine-related polymorphisms may enhance environmental sensitivity to the development of internalizing symptoms. It is worth noting that results have been mixed (e.g., Guo et al., 2009) and the limitations described above apply to these studies.

Current Study

Person-centered data analytic methods aim to identify discrete subgroups of individuals within a sample that share a similar pattern on a set of observed variables. In this way, person-centered methods offer an important data-driven method for capturing heterogeneity within a sample (Collins & Lanza, 2010). Although growing in popularity, person-centered methods have scarcely been applied to the problem of capturing the complexity of multiple genetic influences when GWAS are unavailable. Latent class analysis (LCA; Collins & Lanza, 2010) presents an innovative method for identifying naturally occurring patterns of multiple genetic polymorphisms. For example, Dean and Raftery (2010) showed the utility of latent class analysis for identifying patterns of genetic variation across a large number of SNPs. Additionally, Musci and colleagues (2014) used this approach to examine naturally occurring patterns of BDNF gene variation and to determine whether the efficacy of a preventive intervention varied depending on patterns of BDNF gene variation.

Herein we proffer that LCA provides an alternative to GWAS derived PRS, which have been conducted overwhelmingly with European-ancestry populations, and are therefore, suboptimal for other populations (Peterson et al., 2019; Martin et al., 2019; Wray et al., 2021). We aim to identify data-driven patterns of polygenic risk, specifically within the dopaminergic system, among a sample of youth of African ancestry. In doing so, we will advance our understanding of polygenic moderation of maltreatment exposure on the development of internalizing symptoms among youth of African ancestry. We advance prior literature not only by identifying naturally-occurring patterns of polygenic variation of the dopamine system among African-ancestry youth, but also by employing a sample of youth with child protective service (CPS) documented maltreatment exposures and demographically matched comparison youth.

Method

Participants and Procedures

The present study included 1,002 children aged 6–13 (50.7% male; M_{age} = 10.08, SD = 1.59). The high-risk sample (98.2% had histories of receiving public assistance) included children with documented histories of exposure to maltreatment (n = 491; 49.0%) and non-maltreated children (n = 511; 51.0%), who participated in a research-based summer camp (see Cicchetti & Manly, 1990 for more information about the research camp setting). The participants for this investigation were Black as indexed by the Add Health system for coding race and ethnicity (http://www.cpc.unc.edu/projects/addhealth/data/code/race; DeYoung et al., 2011). To verify an accurate degree of homogeneous ancestry, a SNP panel of 106 ancestral informative genetic markers (AIMS) was utilized to classify individuals into African, European, and Native American descent (Lai et al., 2009; Yaeger et al., 2008). The current sample had a mean proportion of African ancestry of .93, validating genetic homogeneity with self-reported race.

Participants were initially recruited based on documented records of child abuse and neglect through the Department of Human Services (DHS). A DHS liaison reviewed Child Protective Services (CPS) records and identified children who had been maltreated. Children in foster care were not recruited. The DHS liaison then contacted a random sample of eligible families and explained the study to parents who were free to either agree to participate or to decline to have their information released to project staff. Interested parents provided project staff with informed consent for both their and their child's participation in the summer camp research program and for full access to any DHS records pertaining to the family.

Children exposed to maltreatment are disproportionately from low-income, single-parent families (USDHHS, 2021). Therefore, the DHS liaison identified demographically comparable families (i.e., families receiving Temporary Assistance for Needy Families) without histories of CPS or preventive services involvement to recruit into the non-maltreated comparison group. As with the group exposed to maltreatment, the DHS liaison contacted a random sample of eligible non-maltreated participants to discuss study details. If participants expressed interest, then their information was passed to project staff who were provided consent to search family DHS records and further verify the absence of maltreatment for all children in the family. Further, trained research staff conducted the Maternal Child Maltreatment Interview (Cicchetti et al., 2003) with all mothers to confirm the lack of maltreatment. If any conflicting information was provided that suggested the non-maltreated participants may have experienced maltreatment, then they were excluded from the comparison group.

Children enrolled in the study participated in week-long research summer camps and provided assent for research activities. Trained camp counselors, unaware of maltreatment status, worked with the same group of eight children (four with maltreatment exposure and four without) for the duration of the week (~35 hours of contact). Counselors were upper-class undergraduate and graduate students recruited through local universities. Once hired, they completed an extensive two-week training on conducting behavioral assessments

and were approved by an established trainer for validity and reliability via pilot sessions ensuring high quality behavioral assessments. After providing assent, children completed study procedures, including ratings of their own experiences, sociometric ratings of their camp peers, and provided DNA salivary samples. At the end of each week, counselors completed measures of emotional and behavioral functioning for each child based on their observation and interactions.

Measures

Genetic variants and genotyping

Genetic Variants.: Based on previous polygenic analysis with the current sample (Thibodeau et al., 2019) which relied on an extensive literature review to identify genetic variants thought to confer environmental sensitivity and demonstrated moderation effects on child maltreatment outcomes, a set of dopaminergic genes and alleles was selected for inclusion in the polygenic mixture modeling (see Thibodeau et al., 2019 for basis of selecting these variants). These genes and alleles include the following (a) the 7-repeat allele of DRD4-VNTR, (b) the 'C' allele of DRD4 C-521- rs1800955, (c) the 'A' allele of DRD2-rs1800497, (d) the 10-repeat allele of DAT1-VNTR, (e) the 'T' allele of DAT1-rs40184, (f) the 'T' allele of DAT1-rs27072. Because the extant G x E literature is unclear as the most appropriate coding model for each variant with an all-African ancestry sample, and because mixture modeling is a data-driven approach, we elected to code each variant with three levels: homozygous minor (2), heterozygous (1), homozygous major (0)[1]. This avoids making assumptions about the function of minor alleles. Notably, the DRD4-VNTR gene was dichotomously coded as presence (1) or absence (0) of the 7-repeate allele because there are several possible genotypes that would not map onto a three-level variable.

Genotyping Procedures.: Trained research assistants obtained DNA samples from participants by collecting buccal cells using the Epicentre Catch-All Collection Swabs or by collecting saliva using the Oragene DNA Self-Collection kits. For buccal cells, DNA was extracted and prepared for polymerase chain reaction (PCR) amplification using the Epicentre BuccalAmp DNA Extraction Kit (Epicentre, Cat. No. BQ090155C). For saliva samples, DNA was purified from 0.5 ml of Oragene-DNA solution using the DNAgenotek protocol for manual sample purification using prepIT-L2P. Sample concentrations were determined using the Quant-iT PicoGreen dsDNA Assay Kit (P7589, Invitrogen). Genotyping was preformed following previously published protocols. First, DNA was whole-genome amplified using the Repli-g kit (Qiagen, Catalogue No. 150043) per the kit instructions to preserve the availability of data over the long-term for this valuable sample. Then, amplified samples were diluted to a working concentration. The *DRD4* exon 3 VNTR length was determined by PCR amplifying DNA with primers DRD4 F3 (5'CGGCCTGCAGCGCTGGGA3') and DRD4 R2 D4 (5'CCTGCGGGTCTGCGGTGGAGT3') on a MasterCycler Gradient (Eppendorf, Inc). Using a CEQ8000 (Beckman Coulter, Inc.), the resulting products were analyzed

[1]Major and minor alleles were determined based on allele frequency for each SNP in African samples, as catalogued by the National Center for Biotechnology Information (NCBI) dbSNP database. The dbSNP frequencies for each SNP were consistent with the SNP allele distributions in our sample.

for length. The DAT1 VNTR was genotyped using the previously reported primers TGTGGTGTAGGGAACGGCCTGAG and CTTCCTGGAGGTCACGGCTCAAGG (Barr et al., 2001; Vandenbergh et al., 1992); the fragments were then analyzed on a 3130xl Genetic Analyzer (Applied Biosystems). The DRD4 C-521rs1800955 polymorphism is located in the promoter region of *DRD4* gene. This polymorphism was genotyped using a Taq Man SNP assay from Applied Biosystems, Inc. Allelic determinations were made using Taq Man Genotyping Master Mix (Applied Biosystems, Catalog No. 4371357) with amplification on an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200 with JMP 8.0 (SAS, Inc., Cary, NC). The call rate was 99.5%. The genotyping procedures for DAT1 rs40184, DAT1-rs27072, and DRD2 rs1800497 were similar to those of rs1800955. For any genotype that could not be determined after the first run, the assay was repeated up to four times and if the null result endured, then a genotype was not assigned to that individual and was treated as missing. DNA samples were genotyped in duplicate for quality control; furthermore, human DNA from cell lines was purchased from Coriell Cell Repositories for all representative genotypes in duplicate and genotypes confirmed by sequencing using DTC& chemistry on an ABI 3130×1. These, and a negative template control, were run alongside study samples representing 9% of the total data output. Any samples that were not able to be genotyped to a 95% or greater confidence level were repeated under the same condition. Frequencies of SNP distributions did not deviate from Hardy-Weinberg equilibrium (HWE) with the exception of DRD4-VNTR ($\chi 2$ (1, N = 993) = 17.46, p <.05). As reported in DeYoung et al. (2011), and consistent with Thibodeau et al. (2019), deviation from HWE is not unusual for the DRD4-VNTR, and in situations of strict quality control, is not likely to impact the results. See Supplemental Table 1 for information on linkage disequilibrium.

Maltreatment—The Maltreatment Classification System (MCS; Barnett et al., 1993) was used to code CPS records from birth until age 10–12. Exposure to the following subtypes were coded: neglect, physical abuse, sexual abuse, emotional abuse. Given that multi-type maltreatment exposure is frequently the norm (Vachon et al., 2015; Warmingham et al., 2019), we elected to operationalize maltreatment exposure as a continuous variable representing the number of subtypes a child experienced (ranging from 0 = non-maltreated to 4 = exposure to four subtypes). Among children exposed to maltreatment (N = 491), 212 (43.2%) were exposed to one form of maltreatment, 193 (39.3%) were exposed to two forms, 76 (15.5%) were exposed to three forms, and 10 (2.0%) were exposed to four types.

Internalizing Psychopathology Outcomes

Depressive Symptoms.: The Child Depression Inventory (CDI; Kovacs, 1982) is a widely used, reliable, and well-validated 27-item self-report questionnaire to assess depressive symptomatology in school-age children (Saylor et al., 1984). Children chose from three options (scored 0 to 2) for each item in order characterize their experiences and symptoms in the past two weeks, with higher scores representing more depressive symptomology. The 27-items were summed and used as an indicator of an *internalizing symptom* latent factor.

Anxiety Symptoms.: The Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds & Richmond, 1997) is a 37-item self-report measure completed by children to assess

symptoms of anxiety. Children responded “yes” or “no” to each item to indicate presence of each anxiety symptom. The RCMAS is a well-validated measure with good psychometric properties in samples of school-aged children (Muris et al., 2002; Reynolds & Richmond, 1997). The following subscales were included as indicators of an *internalizing symptom* latent factor: social anxiety, physical anxiety, and worry).

Data Analytic Approach

Latent Class Analysis—Analyses were conducted using Mplus version 8 (Muthén & Muthén, 2017). We used a latent class analysis (LCA) approach to find the best fitting polygenic class solution. Models with differing class solutions were evaluated by considering entropy values, information criteria statistics (i.e., Akaike information criterion [AIC], Bayesian information criterion [BIC], sample-size adjusted BIC [ssBIC], and the log likelihood [LL]), and the Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-LRT). We also considered theoretical interpretability, as recommended by Wickrama and colleagues (2016). Full-information maximum likelihood (FIML) methods were used to estimate missing data for parameter estimation in LCA models (all individual SNPs were missing < 1%). Once the best fitting class solution was chosen, we used a common approach to examine GxE associations (Lanza et al., 2013) within a larger structural equation modeling (SEM) framework. After the best-fitting class solution was selected, a new categorical variable for the most likely class membership based on posterior probabilities for each latent class was created. Note that the average latent class probabilities for most likely latent class membership ranged from .93 to 1.0 in our final LCA model. In the final step, the LCA class assignment variable was embedded within the SEM as a predictor variable.

Polygenic Moderation—Using the restrictive standards designed to reduce false-positive findings and enhance replicability of gene-environment interactions (e.g., Hewitt, 2012; Johnston, Lahey, & Matthys, 2013), we elected to generate random 50% splits of the sample and test GxE interactions within each randomly-split sample to ensure replication. Compared to replication within independent samples (e.g., Caspi et al., 2008), randomly splitting large samples minimizes the risk of false findings due to differences in methods and samples (Johnston et al., 2013). The random 50% split was generated with the 50% sample function in SPSS, based on participants that would be included in the final SEM GxE model, which resulted in Sample 1 (N=503) and Replication Sample 2 (N= 499). The two random samples did not significantly differ on sex, history of child maltreatment, or allele frequency distributions of included SNPs. Identical statistical analyses were then conducted first with Sample 1 and repeated with Replication Sample 2.

To test for main and interactive effects of maltreatment and dopaminergic polygenic latent class membership on internalizing symptoms, we estimated structural equation models (SEM) with a maximum likelihood estimation method separately in each sample. First, confirmatory factor analysis (CFA) was used to determine the factor structure of the latent factor, *internalizing symptoms*, which was indicated by the following manifest variables: 1) CDI sum score, 2) RCMAS social anxiety subscale, 3) RCMAS physical anxiety subscale, 4) RCMAS worry subscales. Next, the SEM was specified with the following exogenous variables predicting the latent internalizing factor: child maltreatment (cumulative number

of subtypes experienced), dummy codes for genetic class solution (see below for details), and the following covariates: sex, age, African ancestry marker, and all two-way interaction terms between sex, age, African ancestry, maltreatment, and genetic class dummy codes. Missing data for endogenous variables were estimated as a function of exogenous variables based on the missing at random assumption (Schafer & Graham, 2002). The amount of missing data from study variables was 8.9% for CDI and 31.5% for RCMAS scales. Full information maximum likelihood estimation (FIML; Muthén & Muthén, 2019) was used to obtain parameter estimates for all participants with necessary data on outcome variables. Global model fit for the CFA and SEM were evaluated with guidelines presented by Hu and Bentler (1999).

Results

Latent Class Solutions

To determine the best class solution, we tested the latent model by increasing the number of classes until non-identification of the estimated model solution was found. Non-identification occurred at the four-class solution. The class solutions and fit indices are presented in Table 1. As is common with mixture models, the available fit indices did not converge on a clearly superior class solution. However, the three-class solution was determined to be the optimal model based on several statistical and theoretical factors. First, this solution presented the lowest AIC and highest Entropy of the solutions, and the LMR-LRT indicated that the 3-class model was a statistically significant fit to the data compared to the two-class solution. Thus, we proceeded with our analysis using the three-class solution.

Latent Class Characteristics

See Figure 1 for characteristics of the three-class solution. The largest class (N = 756; 74.9%; *Class 2*) was distinctly characterized by more homozygous major or heterozygous allelic presentations along all three DAT-1 SNPs. The second largest class (N = 227; 22.5% of the sample; *Class 3*) was characterized by heterozygous minor allelic presentations on the DAT-1 SNPs. Last, the smallest class was characterized by predominantly homozygous minor alleles on all three DAT-1 SNPs (N = 27; 2.7% of the sample; *Class 1*). See Table 2 for frequencies of individuals SNPs across the 3 classes.

Polygenic Moderation

Prior to testing GxE interactions on internalizing psychopathology outcomes, the polygenic latent classes were tested for evidence of confounding gene-environment correlations (rGE). Maltreatment status (non-maltreated = 0, maltreated = 1) did not differ across latent class membership ($\chi 2$ (2, $N = 1002$) = 2.61 $p = .27$). Moreover, polygenic latent classes did not significantly differ on the number maltreatment subtypes experienced ($F(2, N = 1002) = 1.35$, $p = .54$) or on any psychopathology indicators: CDI sum score ($F(2, 912) = 1.20$, $p = .30$); RMCAS social anxiety ($F(2, 685) = 1.80$, $p = .17$); RCMAS physical anxiety ($F(2, 685) = 1.81$, $p = .17$); RCMAS worry ($F(2, 685) = 0.82$, $p = .44$). Polygenic classes also did not significantly differ on study covariates, including sex ($\chi 2$ (2, $N = 1002$) = .07 $p = .97$; age ($F(2, 1002) = 0.63$, $p = .53$); or African ancestral makers ($F(2, 985) = 0.33$, $p =$

.72); Confirmatory factor analysis (CFA) was conducted in Sample 1 (N=467) and Sample 2 (N = 458) to determine the factor structure of the latent variable: internalizing symptoms. Bivariate correlations for each Sample are presented in Table 3. Results from Sample 1 suggested adequate model fit χ^2 (2) = 3.21 p = .20, CFI = .99, RMSEA = .04 (90% CI: 0.00–0.11), SRMR = .01 and standardized factor loadings were statistically significant for internalizing indicators: CDI sum (λ = .71, p < .001), RCMAS scales physical (λ = .80, p < .001), social (λ = .77, p < .001), and worry (λ = .81, p < .001).

Results from Replication Sample 2 suggested similarly adequate model fit χ^2 (2) = 5.62 p = .06, CFI = .99, RMSEA = .06 (90% CI: 0.00–.13), SRMR = .01 and standardized factor loadings were statistically significant for internalizing indicators: CDI sum (λ = .70, p <.001), RCMAS scales physical (λ = .77, p < .001), social (λ = .82, p < .001), and worry (λ = .81, p < .001).

Structural Model

Sample 1.: The SEM showed good model fit in Sample 1 (N = 458), χ^2 (62) = 79.45 p = .07, CFI = .97, RMSEA = .03 (90% CI: 0.00–.04), SRMR = .04. An examination of the standardized path coefficients (see Table 4 for all coefficients) revealed that the only significant main or interactive effect on internalizing symptoms was the interaction between Class 2 (vs. Class 3) and maltreatment (β = .33, p = .006). The reference class for the dummy-coded genetic LCA was rotated so as to make all relevant comparisons between classes 1, 2, and 3, with no additional significant effects emerging (all coefficients for Samples 1 and 2 are included in Table 4).

We probed the interaction of child maltreatment and genetic Class 2 (vs. genetic Class 3). Among members of Class 2, childhood internalizing symptoms increased as a function of the cumulative number of maltreatment types experienced (β = .23, p = .008). In contrast, maltreatment did not significantly predict childhood internalizing symptoms for members of Class 3 (β = - .12, p = .36).

Replication Sample 2.: The SEM showed good model fit in Sample 2 (N=456), χ^2 (62) = 58.84 p = .60, CFI = 1.00, RMSEA = .00(90% CI: 0.00–.03), SRMR = .05). An examination of the standardized path coefficients revealed that the only significant effect (main or interactive) on childhood internalizing symptoms was that of the interaction between child maltreatment and genetic Class 2 (vs. Class 3; β = .27, p = .04). Mirroring results of the SEM with Sample 1, probing the interaction revealed that, among members of genetic Class 2, childhood internalizing symptoms increased as a function of the cumulative number of maltreatment types experienced (β = .15, p = .06). In contrast, maltreatment did not significantly predict childhood internalizing symptoms for members of Class 3 (β = - .13, p = .30).

Sensitivity analysis: Two-class solution.: Given the small class membership size of Class 1 (2.7% of the sample), comparisons with this group may be underpowered, and the class itself may not be a trustworthy or replicable unique mixture. Thus, we repeated GxE analysis using a 2-class solution for sensitivity testing. The 2-class solution yielded two respective classes: Class 1 (N=241)—similar in size to the original Class 3 (N=224); and Class 2

(N=761)—similar in size to the original Class 2 (N=751). We then estimated the GxE SEM as described in our Data Analytic Plan, but with one dummy code (and interaction terms), rather than two. Given the similar results (detailed below), and the inability to make an absolute determination on the superiority of the 2- and 3-class solutions, we have presented this analysis as a secondary set. See Table 5 for the 2-class GxE model results.

GxE with 2-class solution: Sample 1.: The SEM showed good model fit in Sample 1 (N = 458), χ^2 (47) = 63.82 p = .05, CFI = .97, RMSEA = .03 (90% CI: 0.00–.04), SRMR = .05. In line with the 3-class solution, an examination of the standardized path coefficients revealed that the only significant main or interactive effect on internalizing symptoms was the interaction between Polygenic Class and maltreatment (β = .26, p = .03). We probed the interaction of child maltreatment and Polygenic Class. Among members of Class 1, childhood internalizing symptoms did not significantly increase as a function of the cumulative number of maltreatment types experienced (β = −.08, p = .54). In contrast, maltreatment significantly predicted greater childhood internalizing symptoms for members of Class 2 (β = .19, p = .03).

GxE with 2-class solution: Sample 2.: The SEM showed good model fit in Sample 2 (N=456), χ^2 (47) = 63.40 p = .60, CFI = .97, RMSEA = .03 (90% CI: 0.00–.04), SRMR = .04). In line with the 3-class GxE models, an examination of the standardized path coefficients revealed that the only significant effect (main or interactive) on childhood internalizing symptoms was that of the interaction between child maltreatment and Polygenic Class (β = .31, p = .02). Mirroring results of the SEM with Sample 1, probing the interaction revealed that, among members of genetic Class 2, childhood internalizing symptoms increased as a function of the cumulative number of maltreatment types experienced (β = .16, p = .06). In contrast, maltreatment did not predict increased childhood internalizing symptoms for members of Class 1 (β = - .16, p = .20).

Discussion

Using person-centered methods, the present study demonstrates an alternative approach to the dilemma of testing polygenic moderation within the area of child maltreatment research with youth of color. The majority of prior work in this area has relied on a data-driven method based on results of prior genome-wide association studies (GWAS) to derive a polygenic risk score (PRS). However, the GWAS data-driven method does not currently represent the most appropriate approach for testing genetic moderation of exposure to maltreatment because the majority of prior GWAS studies are based on European-ancestry samples and PRS derived from European-ancestry samples do not perform as well with non-European ancestry populations (Fatumo et al., 2022; Hindorff, et al., 2018; Peterson et al., 2019; Popejoy & Fullerton, 2016). Given the well-documented disproportionate representation of Black youth in the child welfare system (Dettlaff & Boyd, 2020), alternative approaches are required. Additionally, the GWAS data-driven method typically assumes a genetic main effect on the development of psychopathology. Because child maltreatment exposure exerts a robust main effect influence on a broad array of negative outcomes, genetic influences are routinely conceptualized as moderating this effect. Thus, to employ the GWAS data-driven approach, prior research examining GWAS as a moderator

would be required (i.e., genome-wide by environment interaction studies; GWEIS). To date, no studies have examined child maltreatment exposure specifically within the context of GWEIS, and given excessive cost associated with these types of studies, alternative solutions are required. Thus, the field is currently left with suboptimal approaches for examining polygenic influences within research examining the impact of child maltreatment on the development of psychopathology.

Results of the present study demonstrate the utility of using latent class analysis for determining polygenic moderation of maltreatment exposure on internalizing symptoms among youth. Specifically, this study focused on moderation of maltreatment exposure by genes associated with the dopaminergic system. The dopaminergic system plays a critical role in the reward system, pleasure, and motivation, and has been implicated in anhedonia specifically, and depression more broadly (Belujon & Grace, 2017; Der-Avakian & Markou, 2012; Wise, 2008; Yadid & Friedman, 2008). Results of person-centered analyses identified three naturally occurring patterns of variation among genes associated with the dopaminergic system among a sample of children of African ancestry. The largest class (*Class 2*; representing 74.9% of the sample) was marked by homozygous major or heterozygous presentations on the majority of SNPs. The second largest class (*Class 3*; representing 22.5% of the sample) was characterized by heterozygous alleles on the DAT-1 SNPs and a combination of homozygous major and homozygous minor on other SNPs. The smallest class (*Class 1*; representing 2.7% of the sample) was marked predominately by homozygous minor alleles on all three DAT-1 SNPs. Importantly, the three latent classes differed significantly on four out of six genes associated with the dopamine system. These findings are noteworthy because they show significant variability across genes within this system and suggest that the latent polygenic classes were not derived based on one or two gene variants. Rather, results underscore the need for a holistic approach to capturing variability across variants and suggest that a single candidate gene approach is not sufficient to capture this naturally occurring variation.

In the context of child maltreatment research, the purpose of employing latent class analysis to examine patterns of polygenic variation is to determine whether risk associated with maltreatment exposure impacts symptomatology differently depending on naturally occurring patterns of variation among dopamine genes. Given concerns regarding replication failures within the gene by environment (GxE) literature (e.g. Salvatore & Dick, 2015), calls have been made for researchers to utilize replication samples to test the GxE effect (e.g., Johnston et al., 2013). To this end, we generated two random independent samples from our entire sample of African-ancestry children resulting in Sample 1 (N=503) and Replication Sample 2 (N=499). Results of analyses conducted with *both* samples support polygenic moderation of maltreatment in the development of internalizing symptoms. In other words, we found a significant latent polygenic class by maltreatment interaction in Sample 1 that was replicated in Replication Sample 2. Results indicated that a greater number of maltreatment subtypes experienced was associated with higher internalizing symptoms for individuals with the *Class 2* latent polygenic class only. These findings suggest that individuals of African ancestry with a pattern of dopaminergic variation characterized by this specific combination of homozygous major and heterozygous alleles are more vulnerable to developing internalizing symptoms following maltreatment exposure,

than their peers with other polygenic patterns. Individuals with a *Class 2* pattern may be more susceptible to internalizing symptoms than those with a *Class 3* pattern because of differences in dopaminergic variants and the resultant downstream effects on functioning following maltreatment exposure. These findings have implications for prevention and intervention efforts for children exposed to maltreatment. Specifically, early intervention may be especially critical for children with the *Class 2* pattern, given evidence of their vulnerability to the development of internalizing symptoms following maltreatment. For example, Child-Parent Psychotherapy (CPP; Lieberman, et al., 2015) is an efficacious intervention for young children and families following child maltreatment (e.g., Cicchetti et al., 2011; Toth et al., 2002). Although CPP may be beneficial for all children with maltreatment exposure, given their unique vulnerability for the development of internalizing symptoms, it may be especially useful for interrupting the development of internalizing symptoms among children with *Class 2* patterns.

Prior GxE research on genetic variation within the dopamine system and exposure to adversity has been mixed (e.g., Guo et al., 2009; Haeffel et al., 2008; Vaske et al., 2009) and none have applied a person-centered approach to handling genetic variation within the dopaminergic system. Haeffel and colleagues (2008) examined DAT1 rs40184 polymorphisms (a single candidate gene approach) and found evidence that those with TT genotype who reported higher maternal rejection evidenced greater depression. Our findings are consistent and expand on these by showing that individuals with the *Class 2* polygenic pattern, which includes TT genotype on DAT1 rs4084 among other polymorphisms, exhibit greater internalizing symptoms following more maltreatment exposures. Thus, the current study points to a novel approach for examining polygenic variation and shows evidence that this latent polygenic class moderates risk associated with maltreatment exposure within two independent samples.

Our person-centered method to examining polygenic risk is not only an alternative to GWAS derived scores, but also an alternative to a candidate gene approach. The candidate gene method for calculating PRS is a theory-driven and literature-based method that uses existing scientific studies to select SNPs associated with a behavior or biological process of interest (e.g., Belsky & Israel, 2014; Elam et al., 2016). Common approaches to candidate PRS calculation include an additive coding method in which minor alleles across multiple SNPs are summed to index a PRS. Limitations of this approach include the implicit assumption that minor alleles across various SNPs uniformly represent either risk alleles or plasticity alleles (Thibodeau et al., 2019). This is an especially tenuous assumption among non-European ancestry samples in which much less is known about the frequency and function of various genetic polymorphisms (Fatumo et al., 2022; Hindorff et al., 2018; Popejoy & Fullerton, 2016).

The current study presents an alternative approach to considering patterns of multiple gene variants that is especially useful in the context of child maltreatment. Strengths include 1) the person-centered empirically-derived approach to conceptualizing polygenic variation, 2) CPS record ascertainment of maltreatment exposure coded with the Maltreatment Classification System (MCS; Barnett et al., 1993), 3) replication of GxE results in an independent sample, 4) a focus exclusively on Black youth, who are overrepresented in

the child welfare system and underrepresented in genomics research, 5) comprehensive inclusion of covariates, covariate by gene, and covariate by environment interaction terms as recommended by Keller (2014). In spite of these strengths, there are limitations worth noting. To our knowledge, this is one of the first studies to apply a latent class analysis approach to examine polygenic variation with an African ancestry sample, which means much work remains to test this method with other gene variants, other forms of adversity exposures, and other ancestry groups. Additionally, there are limitations regarding our selected gene variants. First, we included only six variants, all associated specifically with the dopaminergic system, which represents an extremely small aspect of the genome. Second, two of the six gene variants did not vary across the three classes, suggesting that they may be less influential to the findings. Third, we relied on a systematic review (Thibodeau et al., 2019) that included a study from the same sample as the current study to select our gene variants, which introduces one layer of non-independence. Further, because of the overrepresentation of European-ancestry populations in prior studies, the studies from the Thibodeau et al (2019) review of genes related to environmental sensitivity included mostly European ancestry samples. Although we recognize that this is a limitation, it is somewhat offset by the scarce literature with African ancestry samples identifying similar genetic variants as sensitive to environmental exposures (e.g., Beach et al., 2010; Brody et al., 2013; Brody et al., 2014; Cho & Kogan, 2016; Mitchell et al. 2014; Simons et al., 2014). Additional research to apply person-centered methods to a greater number of gene variants representing multiple systems simultaneously will advance our understanding of the complex interplay of genes and environment in the development of psychopathology. It is important to emphasize that person-centered methods, such as latent class analysis used in the current study, are data-driven approaches and although they represent an innovative method for capturing naturally occurring patterns of gene variation, findings may not generalize to other samples, even from similar populations. Our relatively large sample size helps with this issue but replication is necessary. Lastly, our approach for applying auxiliary variables into latent class models to test moderation may introduce bias and more parameter shifts than alternative approaches, such as the ML three-step approach (Asparouhov & Muthen, 2014). However, the number of interaction terms in our models precludes our use of this approach at this time. This decision is consistent with Arch (2021), given the assertion in that paper that mixture regression is still a relatively new technique, and the field lacks pedagogical examples for conducting such analysis with complex models including several auxiliary variables and several interaction terms.

In conclusion, the striking under-representation of African ancestry individuals in genomics research (Fatumo et al., 2022; Hindorff et al., 2018; Popejoy & Fullerton, 2016) has resulted in a body of research in which the generation of PRS is challenging for research with African-ancestry cohorts. This dilemma is especially problematic for research in child maltreatment given the disproportionate over-representation of Black children and families in the child welfare system (Dettlaff & Boyd, 2020). Given that not all children exposed to maltreatment develop internalizing symptoms, this investigation offers an alternative approach to studying polygenic moderation of maltreatment exposure among Black youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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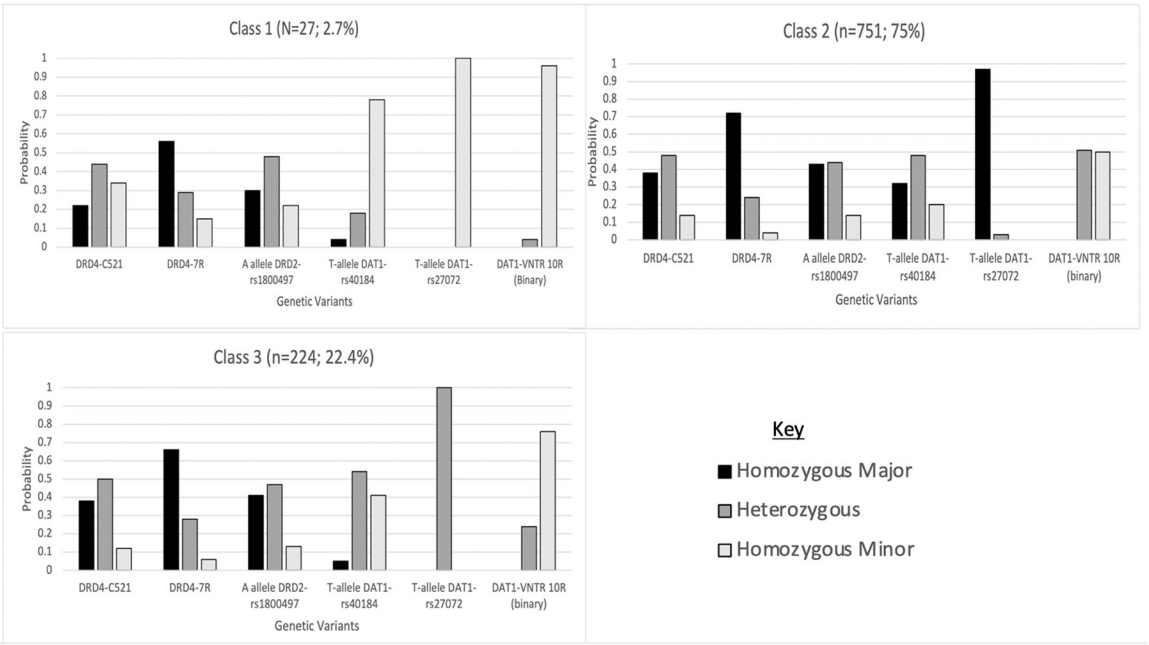

Figure 1.
Dopaminergic Latent Classes

Table 1.

Class enumeration (N = 1,002)

	1 Class	2 Classes	3 Classes*	4 Classes
AIC	10242.62	10100.14	**10091.95**	*No convergence
BIC	10296.63	**10213.06**	10263.78	
ssBIC	10261.70	**10140.02**	10152.63	
LL	−5119.31	−5027.07	−5010.97	
Entropy		0.87	**0.95**	
Group size (%)				
C1	1002, 100%	241, 24.05%	27, 2.7%	
C2		761, 75.95%	751, 74.95%	
C3			224, 22.4%	
C4				
LMR-LRT (*p*)		<.001	**.01**	

Note.

*Indicates class solution chosen as the best fitting model.

AIC= Akaike information criterion; BIC = Bayesian information criterion; ssBIC= sample size-adjusted BIC; LMR-LRT = Lo-Mendell-Rubin adjusted likelihood ratio test.

Table 2.

Class x SNP contingency table.

	Class 1 N (%)	Class 2 N (%)	Class 3 N (%)	Class 1 v 2 v 3 χ^2	Class 2 vs. 3 χ^2
DRD4–7R				**10.14***	**3.34**
No 7R present	15(55.6%)	540 (72.3%)	145 (66.2%)		
7R w/ other VNTR	8 (29.6%)	176 (23.6%)	61 (27.9%)		
7R or 7R/7R	4 (14.8%)	31 (4.1%)	13 (5.9%)		
DAT-1rs40184				**119.50*****	**81.41*****
Homozygous Major	1 (3.7%)	242 (32.4%)	11 (4.9%)		
Heterozygous	5 (18.5%)	355 (47.6%)	122 (54.5%)		
Homozygous Minor	21 (77.8%)	149 (20.0%)	91 (40.6%)		
DAT-1rs27072				**1960.20*****	**937.10*****
Homozygous Major	0 (0.0%)	740 (99.2%)	0 (74.2%)		
Heterozygous	0 (0.0%)	6 (0.8%)	224 (23.1%)		
Homozygous Minor	27 (100%)	0 (0.0%)	0 (2.7%)		
DAT1-VNTR10R				**70.0*****	**51.73*****
No 10R present	1 (3.7%)	379 (51.1%)	53 (23.8%)		
10R present	26 (96.3%)	363 (48.9%)	170 (76.2%)		
DRD4 C-521rs1800955				**9.50**	**0.91**
Homozygous Major	6 (1.6%)	282 (28.2%)	87(23.2%)		
Heterozygous	12 (2.5%)	357 (74.5%)	110 (23.0%)		
Homozygous Minor	9 (6.2%)	109 (75.2%)	27 (18.6%)		
DRD2rs1800497				**3.20**	**0.74**
Homozygous Major	8 (29.6%)	319 (42.7%)	89 (41.7%)		
Heterozygous	13 (48.1%)	327 (43.8%)	105 (46.9%)		
Homozygous Minor	6 (22.2%)	101 (13.5%)	30 (13.4%)		

Table 3.

Bivariate correlations among SEM variables

	1	2	3	4	5	6	7	8
1. Maltreatment	-	.02	−.02	.05	**.13**	.11	.06	−.05
2. Sex	**.12**	-	.01	**.10**	**.11**	.05	.09	−.04
3. Age	.03	−.06	-	**−.12**	.09	**.13**	−.01	−.001
4. CDI	**.13**	.08	−.06	-	**.57**	**.55**	**.54**	.05
5. RCMAS-Social	.09	**.20**	.06	**.52**	-	**.61**	**.67**	.01
6. RCMAS-Physical	.03	.09	**.18**	**.56**	**.60**	-	**.61**	−.07
7. RCMAS-Worry	.04	.07	.03	**.54**	**.64**	**.65**	-	−.03
8. African Ancestry	−.01	.04	−.07	−.01	.06	.06	.09	-

Note. Sample 1 correlations are presented below the diagonal and Sample 2 correlations are presented above the diagonal. Sex is coded = female, 1 = male. Maltreatment = cumulative number of maltreatment subtypes experienced, CDI = Child Depression Inventory sum score, RCMAS-Social = social anxiety subscale, RCMAS-Physical = physical anxiety subscale, RCMAS-Worry = worry subscale. Significant ($p < .05$) correlations are bolded.

Table 4.

Polygenic Moderation of Child Maltreatment with 3-class Solution

	Sample 1 (N=458)		Replication Sample 2 (N=456)	
	β	*p*	β	*p*
Child Maltreatment	−.115	.358	−.133	.303
Polygenic Class 1 (C1)	.042	.675	−.090	.366
Polygenic Class 2 (C2)	−.065	.466	−.091	.327
Sex	.151	.201	−.059	.628
Age	−.097	.467	−.031	.822
African Ancestry (AF)	.081	.471	.062	.678
C1*maltreatment	.007	.939	.008	.909
C2*maltreatment	**.326**	**.006****	**.270**	**.036***
C1*sex	−.094	.291	.121	.176
C2*Sex	−.013	.911	.113	359
C1*Age	.034	.580	.091	.222
C2*Age	.125	.283	.029	.802
C1*AF	−.047	.503	−.138	.057
C2*AF	.018	.870	−.116	.255
Sex*maltreatment	−.114	.234	.040	.651
Age*maltreatment	.025	.732	−.082	.255
AF*maltreatment	.064	.470	.007	.923
AF*Sex	−.149	.107	.032	.701
Age*Sex	−.148	.055	−.146	.052
Age*AF	−.029	.668	−.038	.490

Note: Standardized beta coefficients are reported. Polygenic Class 1 (C1) and Class 2 (C2) represent dummy codes (Class 3 is reference group). Sex is coded 0 = female, 1 = male. AF = African ancestry.

* $p < .05$,

** $p < .01$,

*** $p < .001$.

Table 5.

Polygenic Moderation of Child Maltreatment with 2-class Solution

	Sample 1 (N=458)		Replication Sample 2 (N=456)	
	β	*p*	β	*p*
Child Maltreatment	−.077	.748	−.164	.198
Polygenic Class	−.088	.539	−.094	.297
Sex	.038	.748	−.016	.890
Age	−.048	.717	−.033	.807
African Ancestry (AF)	−.001	.990	.021	.885
Class*maltreatment	**.257**	**.029** *	**.307**	**.015** *
Class*Sex	.114	.336	.072	.554
Class*Age	.081	.480	.036	.751
Class*AF	.096	.377	−.096	.344
Sex*maltreatment	−.100	.295	.033	.710
Age*maltreatment	.023	.747	−.088	.217
AF*maltreatment	.064	.471	.014	.854
AF*Sex	−.136	.135	.052	.533
Age*Sex	−.151	.051	−.144	.055
Age*AF	−.057	.378	−.042	.453

Note: Standardized beta coefficients are reported. Polygenic Class is coded (Class 1 =0, Class 2=1), AF = African ancestry. Sex is coded 0 = female, 1 = male.

* $p < .05$,

** $p < .01$,

*** $p < .001$.