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ORIGINAL RESEARCH

Genetic Moderation of the Association Between Early Family Instability and Trajectories of Aggressive Behaviors from Middle Childhood to Adolescence

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Abstract

The present study tested models of polygenic by environment interaction between early childhood family instability and polygenic risk for aggression predicting developmental trajectories of aggression from middle childhood to adolescence. With a longitudinal sample of 515 racially and ethnically diverse children from low-income families, primary caregivers reported on multiple components of family instability annually from child ages 2–5 years. A conservative polygenic risk score ($p = 0.05$) was generated based on a prior meta-genome wide association study. Trajectories of aggression were identified using a curve of factors model based on a composite of primary caregiver, alternate caregiver, and teacher reports at five ages from 7.5 to 14 years. The family instability by polygenic interaction predicted growth in children's aggression such that children with lower levels of family instability and lower polygenic risk exhibited a steeper decline in aggression from 7.5 to 14. Findings support the need to model gene-environment interplay to elucidate the role of genetics in the development of aggressive behaviors.

Keywords Gene by environment · Polygenic risk · Aggression

Introduction

A central challenge to survival and development for any organism is preparing for and adapting to unpredictable environments. From an evolutionary perspective, genetic polymorphisms exist to maximize adaptability across varying environmental contexts (Ellis and Del Giudice 2019). Genotypic variability allows humans to maximize biological fitness by making phenotypic adjustments to meet the demands of both optimal and suboptimal environments (West-Eberhard 2003). Harsh, stressful, or unpredictable environments may reinforce a phenotype that is maladaptive in optimal environments, but serve an adaptive function in highly stressful environments. Environmental stress occurring at early developmental stages when organisms are highly plastic may be especially impactful (Ellis and Del Giudice 2014).

One environmental stressor in modern society that many children face is family instability, referred to as instability throughout the manuscript, which can be defined broadly as events contributing to the disruption of the day-to-day structure and routines of a child's life (Ackerman et al. 1999). Instability may encompass residential mobility, family structure instability, parental incarcerations, household chaos, and other destabilizing events (Ackerman et al. 1999; Forman and Davies 2003). Building from an evolutionary-developmental perspective, this study examines associations between early childhood instability and developmental trajectories of aggressive behaviors from middle childhood to adolescence conditional on genetic predisposition to behave aggressively, as measured by a polygenic risk score (PRS) generated from a meta-Genome Wide Association Study (GWAS) (Pappa et al. 2016).

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Instability and Aggressive Behavior Development

Theoretically, exposure to instability may lead to aggression by reinforcing a pattern of behaviors that increases short-term biological fitness in response to environmental stress and uncertainty (Belsky et al. 2012). The adaptive calibration model (Del Giudice et al. 2011) suggests that physiological responses to stress (and resulting behavioral sequalae) function as adaptive responses to highly unpredictable or dangerous environments. Accordingly, high early childhood stress may reinforce hypervigilance or an unemotional responsivity pattern (Ellis and Del Giudice 2019). Highly hypervigilant children may be prone to reactive aggression (Bubier and Drabick 2009) and children with an unemotional pattern may exhibit low empathy and high reactive and proactive aggression (Fanti et al. 2009). While hypervigilance or unemotionality may be maladaptive in many settings, such as school (Campbell and Stauffenberg 2008), such traits may be adaptive in the context of high instability. For example, in highly unpredictable environments, hypervigilance may be adaptive in alerting a child to changes in the environment. Similarly, any benefits of proactive aggression (e.g., hitting another child to take their toy) may not be coupled with the negative social reinforcements that would dissuade such behaviors (e.g., rejection by the victim) if a child's social environments are highly transient.

Externalizing problems, defined as a broad aggregation of aggressive, oppositional, and defiant behaviors (Achenbach and Rescorla 2001), are a widely replicated developmental outcome associated with instability (Milan et al. 2006; Fowler et al. 2014; Womack et al. 2019), empirically supporting theoretical links between instability and children's emerging aggressive behavior. In particular, early childhood has been identified as a developmentally sensitive period for relations with instability (Cavanagh and Huston 2008; Womack et al. 2019; Zilanawala et al. 2019). For example, experiencing multiple family structure transitions before age 3 predicted a pattern of elevated externalizing behaviors from ages 5 to 11, accounting for family structure transitions between 5 and 11 (Zilanawala et al. 2019). Using data from the current sample, Womack et al. (2019) found residential mobility and family structure instability in the first five years of life to predict externalizing behaviors at age 10.5, accounting for residential and family structure transitions between 5 and 10.5 as well as externalizing behaviors at age 5.

Models for Gene by Environment Interaction

While high instability has been associated with externalizing problems (Fowler et al. 2014; Milan et al. 2006; Womack et al. 2019), not all children who experience instability develop externalizing problems, and some children who experience low instability display high levels of externalizing behaviors. Behavior genetics research has provided evidence of genetic influence on children's externalizing problems, especially aggressive behavior (Gelhorn et al. 2006; Rhee and Waldman 2002), and interactions with the environment (e.g., maltreatment) to influence phenotypic development (Musci et al. 2019; Salvatore et al. 2015). Several proposed models provide a framework for understanding why children could experience the same level of instability and exhibit different levels of externalizing behaviors.

The diathesis-stress model posits that an individual's diathesis, such as a genetic predisposition for psychopathology, interacts with environmental stressors to lead to psychopathology (Monroe and Simons 1991). Two recent studies demonstrated evidence of a PRS by environment interaction predicting externalizing problems (Bares et al. 2020; Ruisch et al. 2020). For example, in a sample of African American adolescents living in urban poverty, Bares et al. (2020) found that among lifetime alcohol users, the association between polygenic risk for alcohol use and adolescent-reported conduct problems was stronger among children who reported greater family and neighborhood stressors (e.g., residential mobility, family structure instability, exposure to violence). In the present study, a diathesis-stress model would be supported if children exposed to high levels of instability and high PRS showed increasing trajectories of aggression relative to peers with high levels of only instability or only polygenic risk (see Fig. 1a).

Several recent twin studies have provided evidence counter to the diathesis-stress model, suggesting that the heritability of externalizing behaviors *declines* as environmental stress increases (Burt and Klump 2014; Button et al. 2005; Middeldorp et al. 2014; Tuvblad et al. 2006). For example, in a sample of 500 6–10 year old twin pairs, Burt and Klump (2014) found the proportion of variance in conduct problems attributable to additive genetics to decline as parent–child conflict increased. Similarly, in a large sample of Dutch twins, genetics accounted for an additional 20% of the variance in age 7 externalizing behaviors for children in high SES homes compared to low SES homes (Middeldorp et al. 2014). Such findings are consistent with the vulnerable-stable model (Luthar et al. 2000), which proposes that individuals genetically predisposed to aggression would display high levels of aggressive behaviors at all levels of instability, while individuals less genetically predisposed to aggression would display high levels of aggressive behaviors only at greater levels of instability (see Fig. 1b).

Other gene by environment interaction models, such as the differential susceptibility (Belsky and Pluess 2009) or vantage sensitivity (Pluess and Belsky 2013) models focus

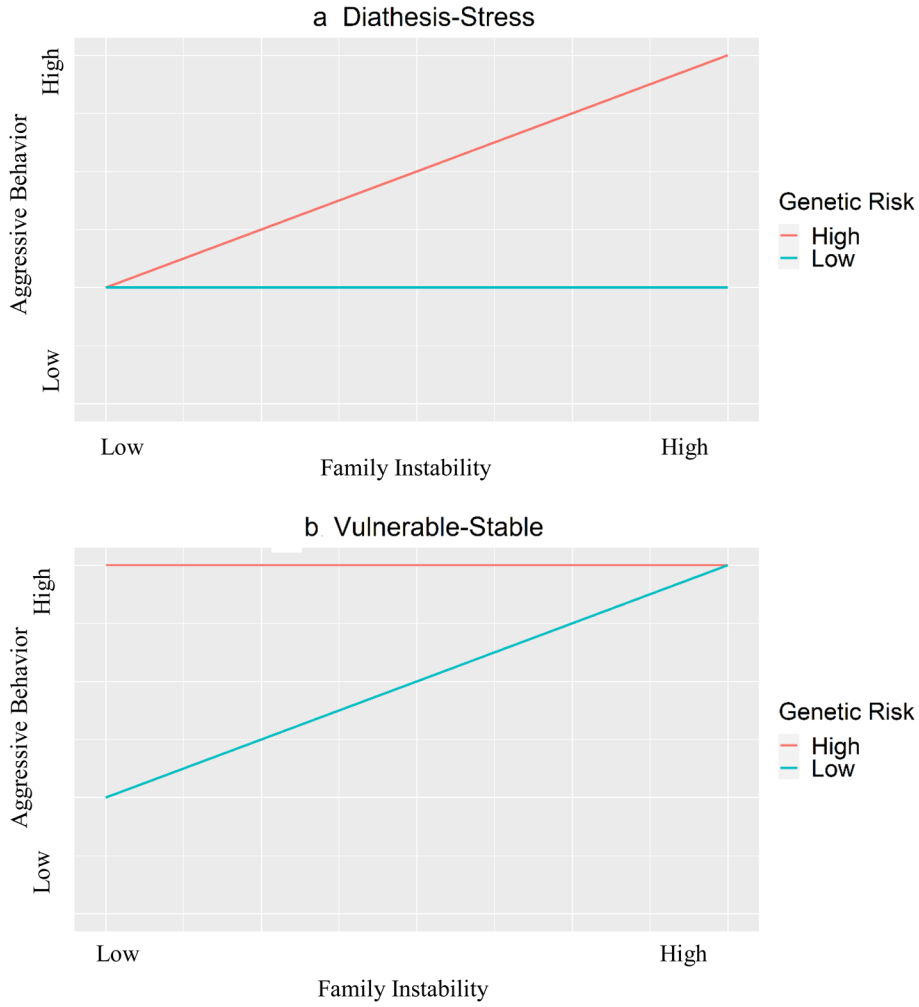

Fig. 1 Plots of example gene by environment interactions between family instability and polygenic risk for aggression

on genetic variation in sensitivity to the environment and require assessment of highly supportive and highly stressful environments to test them.

Previous GWASs of Aggressive Behaviors

Until recently, the largest GWAS of aggressive behavior in childhood and adolescence was a meta-GWAS of parent-reported aggression across nine cohorts of Northern European ancestry between the ages of 3 and 15 years, analyzed together ($N = 18{,}988$) and in separate early childhood ($N = 15{,}668$; age range of 3–7 years) and middle childhood to adolescent ($N = 16{,}311$; age range of 8–15 years) subsamples (Pappa et al. 2016). Pappa et al. (2016) report significant single nucleotide polymorphism (SNP)-based heritability ranging from 10 to 54% across cohort and suggestive evidence of genetic associations, particularly on chromosome 2, but no significant SNPs at the genome-wide level. More recently, a new and larger meta-GWAS published as a bioRxiv preprint (Ip et al. 2021) examined child and adolescent aggression across 29 cohorts of Northern European ancestry between the ages of 1.5 and 18 years ($N = 87{,}485$), and similarly found no SNPs that met the genome-wide significance criterion and much lower SNP heritability (3.31%). However, 11 of 16 PRSs formed based on these findings were associated with mother-report of age 7 aggressive behavior within an independent sample, although the variance explained was small (0.036–0.44%). Importantly, although both Ip et al. (2021) and Pappa et al. (2016) identified significant regions in gene-based analyses, neither the significant regions nor the top SNP-level associations overlapped across the two studies. However, in addition to their somewhat narrower age range, Pappa et al. (2016) predicted a more narrowly-defined phenotype (parent-report of aggressive behavior), whereas Ip et al. (2021) included parent-, self-, and teacher-reports in their analyses.

On the whole, findings from GWAS in both child-to-adolescent and adult samples indicate that the effects of individual SNPs on aggressive phenotypes are small and heterogeneous across reporter and age, with few associations at genome-wide significance to date and none replicated (Ip et al. 2021; Odintsova et al. 2019). However, PRSs

aggregating across multiple small associations from GWAS that fail to reach genome-wide significance may nevertheless capture meaningful variance in complex psychological phenotypes (Murray et al. 2020). For instance, based on a GWAS of nearly 1.5 million adults of European ancestry, Karlsson Linnér et al. (2020) created a polygenic score for broadly-defined externalizing behaviors (including ADHD, substance use, risky sexual behavior, and risky behavior), and found this score to be associated with symptom counts of conduct disorder, oppositional defiant disorder, and substance use, but not aggressive behaviors. Similarly, Tielbeek et al. (2017) created a polygenic score for antisocial behaviors based on a GWAS of 16,400 children and adults of European ancestry, which was associated with mother-reported conduct problems in female, but not male children. As such, despite prediction of relevant phenotypes in independent samples, these studies still find inconsistencies that exist across individual characteristics and traits.

Generally, improved prediction within GWAS and using PRSs has been achieved by increasing the sample size of discovery datasets, allowing researchers to capture the effects of SNPs across the genome with increasing power and precision (e.g., Lee et al. 2018, for educational attainment). However, one trade-off is that collapsing across phenotypically and genetically heterogeneous traits may result in failure to detect genetic influences specific to more narrowly-defined phenotypes For aggression, twin studies show strong stability of genetic influences across age, but also some evidence of age-specificity, with novel genetic influences emerging in middle childhood and middle and late adolescence (Van Beijsterveldt et al. 2003; Veroude et al. 2016; Vierikko et al. 2006). As such, we elected to base our analyses on the middle childhood-to-adolescent subsample of the discovery GWAS by Pappa et al. (2016), which corresponded most closely to our sample in age range and measurement of aggressive behavior, rather than larger GWASs that included adult participants or traits such as substance use and risky sexual behavior (e.g., Karlsson Linnér et al. 2020; Tielbeek et al. 2017).

Current Study

At present, there is a dearth of literature examining interactions between children's genetic architecture and environmental features in early childhood using a contemporary polygenic risk approach. Previous studies have observed interactions between environmental stressors and genetics predicting externalizing behaviors in general and aggression in particular at a single age (Bares et al. 2020; Burt and Klump 2014). However, genes and the environment may also interact to predict the direction and rate of change in aggression across development, but we are aware of no gene by environment studies examining development of aggressive behavior across childhood. The present study tests a polygenic by environment interaction between early childhood instability and polygenic risk for aggression in middle childhood predicting trajectories of aggression from middle childhood to adolescence. We hypothesize an instability by PRS interaction predicting both the level and growth of aggression, with no specific hypotheses about the shape of the interaction given the dearth of literature in this area.

Methods

Participants

Participants were 731 families recruited as a part of the Early Steps Multisite Study, a randomized controlled trial of the Family Check-Up parenting intervention (see Dishion et al. 2008). Families were recruited from Women, Infant, and Children Nutritional Supplement (WIC) programs around the metropolitan areas of Pittsburgh, PA, Eugene, OR, and Charlottesville, VA. To be eligible for the study, families needed to have a child between the ages of 2 years 0 months and 2 years 11 months, and meet two out of the three following criteria: child behavior problems 1 SD above the mean, family problems (e.g., maternal depression), and sociodemographic risk (e.g., low educational attainment). Of the 731 families recruited, 272 (37%) were recruited in Pittsburgh, 271 (37%) in Eugene, and 188 (26%) in Charlottesville. Across sites, target children (49% female) belonged to the following racial groups: 27.9% African American, 50.1% European American, 13.0% biracial, and 8.9% other races (e.g., American Indian). Thirteen percent of participants identified as Hispanic. Following the baseline assessment at age 2, half of the families were randomly assigned to receive the Family Check-Up parenting intervention.

Procedures

Data were collected during in-home assessments at child ages 2, 3, 4, 5, 7.5, 8.5, 9.5, 10.5, and 14 with primary caregivers, target children, and, when available, alternate caregivers (e.g., father, grandparent). The present study utilized survey data collected from primary and alternate caregivers during the in-home assessments. Following each in-home assessment between 7.5 and 14 years, a packet of questionnaires was sent to target child's primary teacher. All participants were financially compensated following each assessment. Custodial parent's written consent was obtained prior to administration of any measures at each assessment. A Certificate of Confidentiality was obtained from the National Institute of Health to offer protection of participants' confidentiality and encourage

honest reporting. Institutional review board approval was obtained for all screening and assessment procedures.

Retention

Analyses were limited to the 515 children (86.7% of the initial sample) for whom there are genetic data collected at age 14. Attrition analyses revealed no statistically significant differences for instability, baseline primary caregiver education, baseline family income, baseline child externalizing behaviors, intervention status, child gender, or child race between the 515 children included in the present study and the 216 children for whom there were no genetic data. Additionally, among children who participated at age 14, there were no significant difference in any of the aforementioned variables between children who provided a sample for genotyping and children who participated in the age 14 assessment but did not provide genetic data.

Measures

Instability

An instability composite score was calculated for assessments at child ages 2, 3, 4, 5, guided by items from the Family Instability Questionnaire (Ackerman et al. 1999). Specifically, instability was measured at each wave by the presence or absence (coded 1, or 0, respectively) of instability across eight domains over the previous year: residential moves, transitions in a child's primary caregiver, primary caregiver cohabitating relationship transitions, primary caregiver-reported work stress (coded yes = 1, no = 0), death or serious illness of a close family member, household chaos, household overcrowding, and incarcerations of adults living in the home.

Primary caregiver relationship transitions were coded separately for separations and new cohabitating relationships. Household chaos was assessed using the Confusion, Hubbub, and Order Scale (CHAOS), a 15-item scale completed by primary caregivers that assesses the level of disorganization, noise, and disorder in the home (Matheny et al. 1995). CHAOS scores that fell at or above one SD above the sample mean at each age were coded as a 1, and scores less than one SD above the mean were coded as a 0. Household overcrowding was assessed as a person to room ratio greater than 1, in line with Census Bureau guidelines for overcrowding (United States Census Bureau 2020). To capture instability across early childhood, scores from ages 2 through 5 were averaged.

Aggressive Behaviors

Primary and alternate caregivers completed the Child Behavior Checklist (CBCL 6–18) and teachers completed the Teacher Report Form (TRF) at child ages 7.5, 8.5, 9.5, 10.5, and 14. The CBCL 6–18 and TRF yield an 18-item (17 on the TRF) aggressive behavior factor that encompasses physical aggression ("Physically attacks people") and verbal aggression ("Threatens people") (Achenbach and Rescorla, 2001). The frequency of child behaviors is assessed on a three-point Likert scale: 0 (*not true*), 1 (*somewhat or sometimes true*), and 2 (*very true or often true*). Cronbach alphas from age 7.5 to 14 ranged from 0.86 to 0.92 for primary caregivers, 0.84–0.91 for alternate caregivers, and 0.92–0.94 for teachers, indicating acceptable internal reliability. Latent aggressive behavior factors based on primary caregiver, alternate caregiver, and teacher reports at each age were estimated within the curve of factors model with primary caregiver factor loadings set to 1.

Aggression PRSs

Genotyping was performed at Rutgers University Cell and DNA Repository (RUCDR) using the Affymetrix Biobank1 Array. Genotyping was conducted in 2016 for 280 individuals (278 passed initial quality control thresholds; mean call rate = 99.3%, SD = 0.504%) and in 2017 for 239 individuals (237 passed; mean call rate = 29.98%, SD = 0.499%), with allele calls performed using the apt-genotype-axiom program in the Affymetrix Power Tools v-1.16 software package (Thermofisher Scientific 2020). Data were imputed to the 1000 Genomes Phase three reference panel using the Michigan Imputation Server (Das et al. 2016), and we retained only SNPs above the imputation quality criterion of $r^2 = 0.80$ (the squared correlation between imputed allele dosages and masked genotypes; Das et al. 2016). Both before and after imputation, we screened out data according to the following criteria: missing SNP or individual data ≥ 5% (43,239 SNPs out of 550,214 in the non-imputed data; no SNPs in post-imputation data cleaning and no individuals), minor allele frequency ≤ 1% (181,136 SNPs pre-imputation; 65 SNPs post-imputation), and deviations from Hardy Weinberg Equilibrium at $p \leq 10^{-6}$ (4187 SNPs pre-imputation; 7776 SNPs post-imputation). After quality control screening, data were available for 515 individuals on 4,048,277 imputed SNPs. To account for population admixture, we conducted principal components analysis of all autosomal SNPs in Plink v1.9 after removing regions of long range linkage disequilibrium (LD) and pruning local LD using PLINK's sliding window procedure (LD $r^2 = 0.20$, window size = 200 SNPs, step size = 100 SNPs). The first 20 components were extracted.

The aggression PRS was formed based on summary statistics from the middle childhood sample in an aggression meta-GWAS (Pappa et al. 2016), selected for its similarity to our own sample in age range and measurement of aggression. PRS were formed using the R program PRSice v2 (Euesden et al. 2015) and PLINK v1.9 (Purcell et al. 2007). Beginning with the 1,506,214 SNPs present in both the GWAS findings and our imputed data, we first screened out a total of 221,705 strand-ambiguous SNPs (A/T and C/G), we accounted for LD using Plink's clumping procedure ($r^2 = 0.3$, 250 kb window), which forms clumps of related SNPs within the sliding window and retains the SNP with the lowest GWAS p value from each. Using the 165,969 SNPs that remained after clumping, we formed PRS as the unit-weighted sum of risk alleles divided by total alleles falling below a series of GWAS p thresholds from 0.00001 to 0.10. Although it is common for studies of PRS to test scores including SNPs at p thresholds up to 0.50 or 1.0, we wished to include only SNPs with relatively large effects, especially as alleles were unit-weighted. For analyses, we selected the score at a threshold of $p = 0.05$ representing the largest score at or below the traditional alpha level, which included a total of 14,834 SNPs. No tests were run using scores other than the PRS $p = 0.05$. Prior to analyses, we z-scored the Aggression PRS, then regressed it onto the first 20 principal components and saved the residual to use as a predictor in the study models.

Covariates

Sociodemographic covariates assessed using a structured interview at the baseline age 2 assessment included family income, target child gender (coded 1 for male, 0 for female), target child race (coded 1 for nonwhite, 0 for White), and primary caregiver's education. Family income was coded on a 13-point scale from $4999 or less (1) to $90,000 or more (13). Primary caregiver education was coded on a 9-point scale ranging from "No Formal Schooling" (1) to "Graduate Degree" (9). Additionally, intervention status and site location (with Oregon coded as the reference group) were accounted for as covariates in analyses.

Primary caregiver criminal behavior was also included as a study covariate to account for caregiver behaviors or attitudes that may contribute to family instability or the development of child aggressive behaviors. At the age 4 assessment, primary caregivers completed a 17-item abbreviated version of the Elliott Self-Report of Delinquency scale (Elliott et al. 1985). To encompass current and past criminal behaviors, questions were adapted to ask how frequently the primary caregiver engaged in criminal activities since they were 12. The Self-Report of Delinquency Scale assesses aggressive behaviors (e.g., attacked someone with a weapon, hit someone with the idea of hurting them) and other criminal behaviors (e.g., theft, destruction of property). Cronbach alphas indicate that the adapted Self-Report of Delinquency scale demonstrated acceptable internal consistency ($\alpha = 0.87$).

Data Analysis

Descriptive statistics and intercorrelations were calculated using the base package in R (R Core Team 2020). Structural equation models were fit using the 'lavaan' package version 0.6–8.1587 (Rosseel 2012). Parameters were estimated using maximum likelihood with robust standard errors and missing data were handled using full-information maximum likelihood estimation. A curve of factors model (McArdle 1988) was fit to primary caregiver, alternate caregiver, and teacher reports of externalizing behaviors from ages 7.5 to 14. Curve of factors models allow confirmation of factor invariance and measure change at the factor-level, which reduces measurement error (McArdle 1988). A quadratic growth model fit the growth of aggressive behaviors better than a linear growth model ($X^2_{df=4} = 28.88$, $p < 0.001$).

To test the study hypotheses, the intercept, slope, and quadratic growth terms were regressed onto early childhood instability, aggression PRS, a product (interaction) term of instability and aggression PRS, and sociodemographic covariates. To account for potential interactive effects between covariates and genes or covariates and environmental predictors (Keller 2014), covariate by aggression PRS and covariate by instability interaction effects on the growth parameters were estimated. Non-significant covariate by aggression PRS and covariate by instability paths were dropped from the final model (see Supplementary Table 1 for model results with all interactions). Early childhood instability, the aggression PRS, and continuous study covariates were standardized before creating the product terms. Significant interactions were probed at the mean, one SD below the mean, and one SD above the mean using the 'probe2WayMC' function in the 'semTools' package version 0.5–3 (Jorgensen et al. 2020).

Results

Descriptive Statistics and Intercorrelations

Descriptive statistics for instability, aggression PRS, and reports of externalizing behaviors can be found in Table 1. The mean instability score from 2 to 5 years was 1.74 ($SD = 0.87$), indicating that the average child experienced 1.74 events each year. Only 5 children (1.0% of the study sample) had instability scores of 0, indicating that they did not experience any of the instability indicators between ages 2 and 5. Fifty children (9.7% of the study sample) had

Table 1 Descriptive statistics of independent and dependent variables

Construct	Full sample ($n=515$)		White subsample ($n=247$)		Black subsample ($n=161$)	
	n	Mean (*SD*)	*n*	Mean (*SD*)	*n*	Mean (*SD*)
Instability	515	1.74 (0.87)	247	1.68 (0.88)*	161	1.88 (0.85)*
Aggression PRS	515	0.02 (0.00)	247	0.02 (0.00)	161	0.00 (0.00)
PC aggressive behavior 7.5	453	9.29 (7.03)	225	9.33 (6.99)	132	9.89 (7.27)
PC aggressive behavior 8.5	448	8.06 (6.99)	213	8.10 (7.02)	133	7.33 (6.40)
PC aggressive behavior 9.5	475	7.74 (6.77)	226	7.62 (6.57)	147	8.53 (7.10)
PC aggressive behavior 10.5	463	7.59 (6.90)	223	7.67 (6.80)	143	8.35 (7.36)
PC aggressive behavior 14.5	495	7.56 (7.32)	244	7.30 (6.95)	154	7.77 (7.97)
AC aggressive behavior 7.5	345	7.44 (6.45)	181	7.69 (6.62)	92	7.33 (6.40)
AC aggressive behavior 8.5	338	7.13 (6.01)	172	7.15 (5.60)	88	7.49 (6.70)
AC aggressive behavior 9.5	361	6.76 (6.11)	185	6.72 (5.75)	104	6.53 (6.32)
AC aggressive behavior 10.5	337	5.94 (6.13)	170	6.21 (6.12)	101	5.78 (6.48)
AC aggressive behavior 14	345	6.49 (6.27)	181	6.45 (6.06)	99	6.10 (6.44)
Teacher aggressive behavior 7.5	257	5.46 (7.55)	135	5.05 (7.18)	54	7.37 (8.88)
Teacher aggressive behavior 8.5	316	5.37 (7.53)	160	4.39 (6.29)*	82	7.91 (9.40)*
Teacher aggressive behavior 9.5	314	5.32 (7.53)	156	4.28 (5.99)*	93	7.98 (9.25)*
Teacher aggressive behavior 10.5	301	5.37 (7.36)	144	4.23 (6.57)*	91	7.64 (8.12)*
Teacher aggressive behavior 14	457	4.70 (7.39)	226	3.46 (6.02)*	138	7.23 (8.81)*

PC primary caregiver, *AC* alternate caregiver, *PRS* polygenic risk score

*Indicates a significant mean difference between White and Black youth

instability scores of three or higher, indicating that they experienced three or more of the instability indicators *each year* between ages 2 and 5.

Descriptive statistics are presented separately for White and Black children in addition to the full sample. Black children experienced significantly higher levels of instability than White children ($t_{df=350.42}=2.20$, $p=0.028$, Cohen's d = 0.22). Teachers (but not primary or alternate caregivers) reported significantly higher levels of aggressive behavior for Black children relative to White children at ages 8.5–14. Effect sizes of these differences were medium (Cohen's d's = 0.47–0.53).

Instability was modestly, albeit significantly associated with primary caregiver, alternate caregiver, and teacher reports of aggressive behavior at every age with the exception of the teacher report at age 9.5 (r's = 0.12-0.23, $p<0.05$). Univariate correlations between the aggression PRS and aggressive behaviors were nonsignificant across reporters and ages. Correlations of aggressive behavior ratings within and between rater were generally positive and significant across time. Intercorrelations between study variables for the full sample are presented in Table 2. Intercorrelations for primary study variables calculated separately for White and Black children were similar in magnitude and direction to intercorrelations for the full sample (see Table 3).

Aggression PRS by Instability Interaction

The curve of factors model including main effects, the interaction term, and covariates had an acceptable fit to the data ($X^2_{df=357}=456.06$, $p<0.001$, RMSEA = 0.02, CFI = 0.97, TLI = 0.97). Full results are reported in Table 4. Plots of all interactions are depicted in Fig. 2. There was a significant main effect of instability on the intercept of aggressive behaviors, but not a main effect of aggression PRS or interaction. For the slope of aggression, there was a significant negative effect of the interaction term. Probing the simple slopes indicated that children experiencing *lower* instability (1 SD below the mean) demonstrated a shallower initial decline in aggression at higher aggression PRS ($B=0.35$, $SE=0.216$, $p=0.028$). Simple slopes for moderate (at the mean) and high levels (1 SD above the mean) of instability were nonsignificant. Finally, there was a significant positive effect of the interaction term on the quadratic growth of aggression. Probing the simple slopes revealed that at *low* levels of instability (1 SD below the mean), children with higher aggression PRSs demonstrated steeper negative quadratic growth ($B=-0.05$, $SE=0.02$, $p=0.011$). Simple slopes were nonsignificant for children at mean levels of instability or instability 1 SD above the mean.

To aid in interpretation of the curve of factors model, predicted trajectories of aggression were plotted for children

Table 2 Intercorrelations between instability, polygenic risk, and aggression variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Instability	1																
2. Aggression PRS	0.01	1															
3. PC AGG 7.5	0.19*	− 0.02	1														
4. PC AGG 8.5	0.19*	0.01	0.75*	1													
5. PC AGG 9.5	0.20*	0.03	0.74*	0.77*	1												
6. PC AGG 10.5	0.16*	0.02	0.66*	0.73*	0.75*	1											
7. PC AGG 14	0.14*	0.02	0.57*	0.62*	0.66*	0.67*	1										
8. AC AGG 7.5	0.18*	0.08	0.50*	0.43*	0.42*	0.46*	0.32*	1									
9. AC AGG 8.5	0.19*	0.04	0.53*	0.56*	0.58*	0.55*	0.46*	0.69*	1								
10. AC AGG 9.5	0.21*	0.07	0.50*	0.56*	0.62*	0.57*	0.45*	0.55*	0.70*	1							
11. AC AGG 10.5	0.20*	0.01	0.42*	0.48*	0.52*	0.57*	0.40*	0.46*	0.64*	0.70*	1						
12. AC AGG 14	0.13*	0.07	0.38*	0.42*	0.42*	0.43*	0.63*	0.45*	0.52*	0.55*	0.53*	1					
13. TEA AGG 7.5	0.15*	0.07	0.34*	0.24*	0.25*	0.19*	0.21*	0.36*	0.22*	0.30*	0.14	0.22*	1				
14. TEA AGG 8.5	0.12*	0.03	0.13*	0.18*	0.13*	0.20*	0.17*	0.24*	0.19*	0.16*	0.12	0.14*	0.60*	1			
15. TEA AGG 9.5	0.08	0.03	0.27*	0.20*	0.28*	0.23*	0.18*	0.19*	0.15*	0.22*	0.18*	0.09	0.69*	0.59*	1		
16. TEA AGG 10.5	0.23*	0.07	0.21*	0.24*	0.28	0.25*	0.25*	0.21*	0.33*	0.33*	0.23*	0.16*	0.56*	0.55*	0.61*	1	
17. TEA AGG 14	0.13*	0.00	0.25*	0.29*	0.34	0.32*	0.41*	0.17*	0.28*	0.28*	0.25*	0.27*	0.46*	0.35*	0.46*	0.46*	1

PC primary caregiver, *AC* alternate caregiver, *TEA* teacher, *PRS* Polygenic Risk Score, *AGG* aggressive behavior subscale on the Child Behavior Checklist and TRF

*Indicates $p < 0.05$

Table 3 Intercorrelations between instability, polygenic risk, and aggression variables by race

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Instability	–	0.02	0.22*	0.18*	0.23*	0.22*	0.16*	0.13	0.15*	0.21*	0.22*	0.13	0.15	0.13	0.11	0.16	0.06
2. Aggression PRS	0.04	–	0.01	0.02	0.01	0.02	0.05	0.16	0.14	0.17	0.06	0.11	0.12	0.02	− 0.08	0.10	− 0.02
3. PC AGG 7.5	0.10	− 0.04	–	0.71*	0.73*	0.60*	0.51*	0.54*	0.47*	0.44*	0.39*	0.42*	0.33*	0.20*	0.30*	0.16	0.19*
4. PC AGG 8.5	0.25*	0.07	0.78*	–	0.79*	0.68*	0.58*	0.45*	0.59*	0.51*	0.50*	0.49*	0.20*	0.23*	0.14	0.20*	0.25*
5. PC AGG 9.5	0.17*	0.08	0.74*	0.76*	–	0.72*	0.61*	0.40*	0.53*	0.57*	0.54*	0.46*	0.30*	0.13	0.22*	0.26*	0.30*
6. PC AGG 10.5	0.12	0.06	0.75*	0.79*	0.81*	–	0.63*	0.47*	0.47*	0.50*	0.59*	0.44*	0.22*	0.19*	0.18*	0.30*	0.30*
7. PC AGG 14	0.12	0.06	0.65*	0.71*	0.72*	0.71*	–	0.27*	0.36*	0.31*	0.32*	0.68*	0.23*	0.19*	0.13	0.20*	0.42*
8. AC AGG 7.5	0.26*	0.07	0.31*	0.41*	0.44*	0.42*	0.31*	–	0.67*	0.51*	0.52*	0.43*	0.34*	0.22*	0.13	0.19	0.02
9. AC AGG 8.5	0.31*	− 0.04	0.48*	0.55*	0.62*	0.59*	0.53*	0.67*	–	0.59*	0.64*	0.44*	0.23*	0.14	0.11	0.29*	0.09
10. AC AGG 9.5	0.22*	0.03	0.42*	0.53*	0.63*	0.59*	0.49*	0.53*	0.80*	–	0.78*	0.57*	0.28*	0.04	0.15	0.33*	0.17*
11. AC AGG 10.5	0.20*	− 0.01	0.44*	0.50*	0.53*	0.58*	0.45*	0.29*	0.64*	0.56*	–	0.52*	0.29*	0.20*	0.31*	0.38*	0.26*
12. AC AGG 14	0.22*	0.09	0.32*	0.42*	0.41*	0.46*	0.56*	0.41*	0.60*	0.49*	.51*	–	0.28*	0.13	0.11	0.16	0.22*
13. TEA AGG 7.5	0.11	0.20	0.32*	0.25	0.21	0.23	0.20	0.47*	0.09	0.42*	− 0.15	0.07	–	0.59*	0.64*	0.64*	0.37*
14. TEA AGG 8.5	0.03	0.13	0.10	0.23*	0.20	0.31*	0.17	0.48*	0.33*	0.34*	0.16	0.20	0.61*	–	0.55*	0.50*	0.31*
15. TEA AGG 9.5	− 0.08	0.16	0.24*	0.23*	0.34*	0.31*	0.22*	0.35*	0.15	0.32*	0.17	0.06	0.69*	0.56*	–	0.62*	0.38*
16. TEA AGG 10.5	0.26*	0.16	0.26*	0.34*	0.35*	0.31*	0.30*	0.36*	0.51*	0.42*	0.24	0.31*	0.33	0.50*	0.49*	–	0.44*
17. TEA AGG 14	0.13	0.07	0.24*	0.30*	0.42*	0.37*	0.39*	0.29*	0.39*	0.45*	0.31*	0.32*	0.35*	0.28*	0.37*	0.43*	–

Correlation coefficients for Black children are presented below the diagonal and coefficients for White children are presented above the diagonal

PC primary caregiver, *AC* alternate caregiver, *TEA* teacher, *AGG* aggressive behavior subscale on the Child Behavior Checklist and TRF

*Indicates $p < 0.05$

Table 4 Predictors of aggression development

Predictor	Intercept (age 7.5)		Slope		Quadratic	
	Beta (*SE*)	*p* value	Beta (*SE*)	*p* value	Beta (*SE*)	*p* value
Early childhood family instability	1.26 (0.30)	< 0.001	− 0.02 (0.14)	0.899	− 0.01 (0.02)	0.765
Aggression PRS	0.26 (0.28)	0.352	0.09 (0.12)	0.503	− 0.01 (0.02)	0.470
Instability × PRS	0.50 (0.29)	0.081	− 0.26 (0.13)	0.035	0.04 (0.02)	0.011
Intervention status	− 0.25 (0.56)	0.682	− 0.05 (0.24)	0.840	0.00 (0.03)	0.996
TC gender (males as reference group)	− 1.59 (0.55)	0.004	− 0.11 (0.24)	0.657	0.02 (0.03)	0.479
TC race (white as reference group)	− 1.31 (0.62)	0.035	0.34 (0.26)	0.191	− 0.03 (0.03)	0.445
Pittsburgh site	2.50 (0.71)	< 0.001	− 0.54 (0.29)	0.068	0.05 (0.04)	0.195
Virginia site	− 0.18 (0.65)	0.786	− 0.25 (0.30)	0.408	0.05 (0.04)	0.198
Household income	− 0.28 (0.28)	0.320	0.21 (0.13)	0.116	− 0.03 (0.02)	0.087
PC education (age 2)	− 0.24 (0.27)	0.374	− 0.03 (0.11)	0.794	− 0.00 (0.01)	0.890
PC criminal behavior	0.37 (0.32)	0.254	0.09 (0.13)	0.484	− 0.01 (0.02)	0.754
Group × instability	1.27 (0.52)	0.015				
Pittsburgh × instability	1.20 (0.60)	0.045				
Virginia × instability	1.74 (0.57)	0.002				

For site location, Eugene, Oregon was coded as the reference group

Model fit: $X^2_{df=200} = 324.99$, $X^2/df = 1.62$, RMSEA = 0.04, CFI = 0.96, TLI = 0.95

TC target child, *PC* primary caregiver

with aggression PRSs 1 SD below and above the mean experiencing low, moderate, and high instability (Fig. 3). While the average predicted trajectory of aggression is declining from age 7.5 to 14 for children at low, medium, and high levels of instability and genetic risk, children experiencing low instability display a flatter trajectory of aggression when they were at high relative to low genetic risk. Put differently, among children experiencing low instability, children with a high aggression PRS did not display the decline in aggression across late-childhood observed in children with low aggression PRSs.

Study covariates were only significantly associated with the intercept of aggressive behaviors. Specifically, males exhibited a higher intercept relative to females, and nonwhite youth displayed a lower intercept. Significant instability by treatment status and instability by site location interactions were observed on the intercept (see Supplementary Figs. 1 and 2, respectively). Simple slope analyses revealed that children in both the intervention and control groups, and children at each site location exhibited increasing levels of aggressive behaviors as instability increased. There was a significant main effect of the Pittsburgh site, indicating that children in Pittsburgh were rated as displaying higher levels of aggressive behaviors relative to children in Eugene.

Sensitivity Analyses

We conducted sensitivity analyses by fitting a multigroup curve of factors model to a subset of 247 White and 161 Black children. The PRS by instability interactions failed to reach significance for Black or White children in predicting the intercept ($B = 0.76, 0.09$; $SE = 0.42, 0.69$ for White and Black youth, respectively, $p's > 0.05$), slope ($B = -0.32, -0.07$; $SE = 0.17, 0.22$ for White and Black youth, respectively, $p's > 0.05$), or quadratic ($B = 0.04, 0.03$; $SE = 0.02, 0.03$ for White and Black youth, respectively, $p's > 0.05$) coefficients. However, the directions of the associations were consistent with those in the full model. Constraining the associations between the interaction term and the intercept, slope, and quadratic coefficients to be equal for Black and White children did not result in a significant reduction in model fit ($X^2_{df=3} = 1.84$, $p = 0.607$), providing support for our approach of testing PRS by instability interactions across race.

Power Analysis

Monte Carlo simulations were conducted in Mplus version 8.4 (Muthén and Muthén 2017) to determine the statistical power to reject the null hypothesis that there is no main effect of instability or aggression PRS or an interaction between the two in predicting the growth of aggressive behaviors. Post-hoc power analyses were conducted based on the full sample growth curve model, which included the main effects of instability, aggression PRS, and study covariates, the interaction between instability and aggression PRS, and significant covariate by aggression PRS and covariate by instability interactions. Power analyses were based on 1,000 simulated samples and a sample size of 515. Power to detect the observed main effect of instability

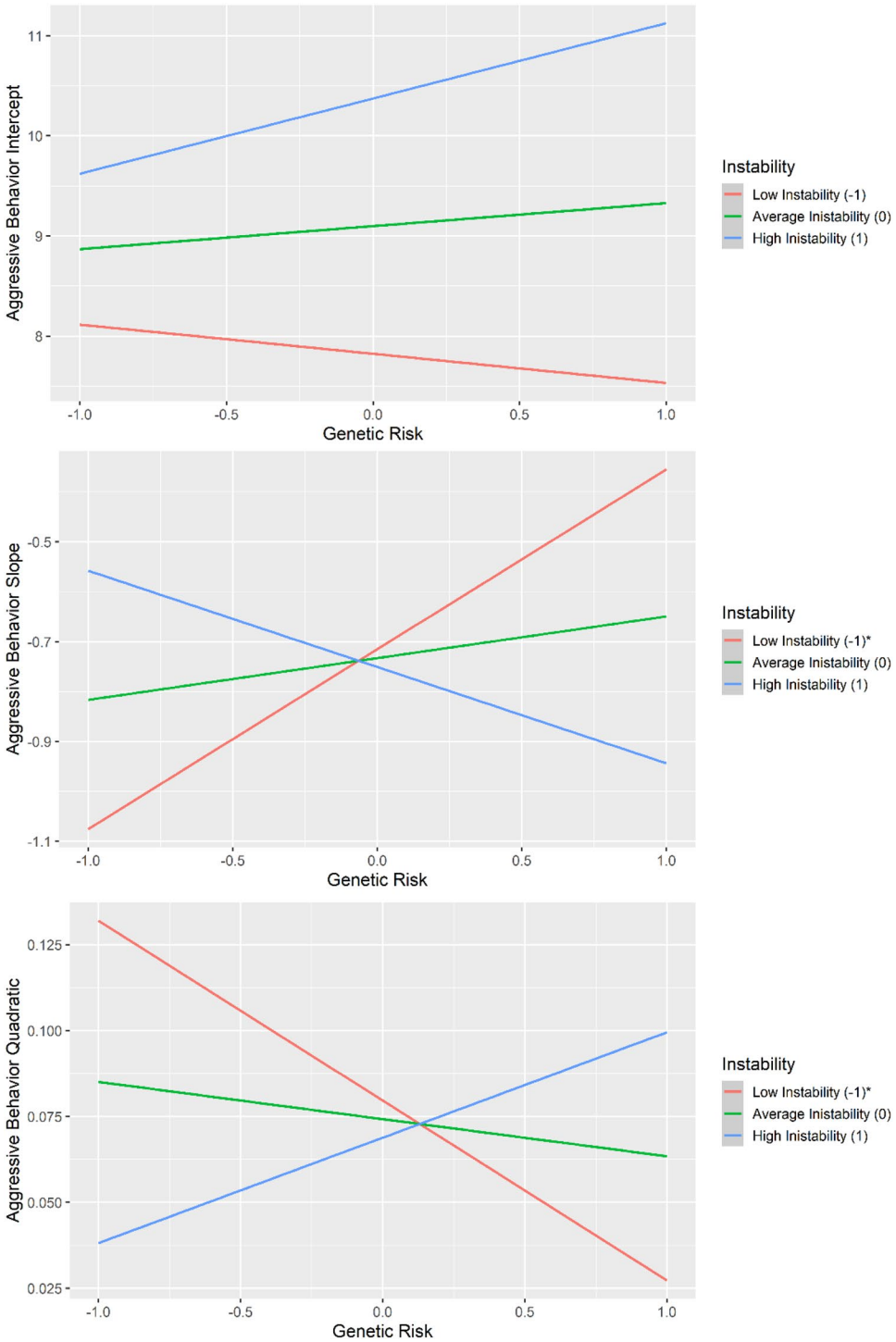

Fig. 2 Family instability by aggression PRS interactions predicting the intercept, slope, and quadratic growth of aggression. *Indicates that the simple slope is significantly different than 0 at the $p < 0.05$ level

on the intercept of aggressive behaviors was 0.998. Power to detect the observed effects of the instability by aggression PRS interaction on the slope and quadratic growth of aggressive behavior were 0.647 and 0.748, respectively, indicating that the present study was slightly underpowered to detect the interactions.

Discussion

Results from the present study partially support the hypothesis of an early childhood instability by aggression PRS interaction predicting the developmental trajectory of

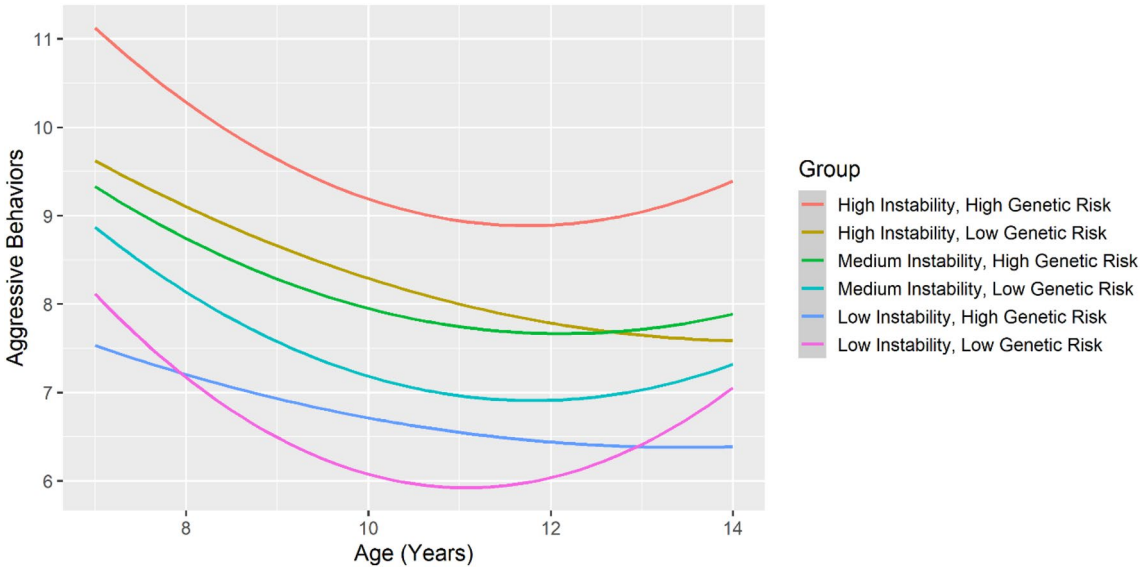

Fig. 3 Predicted trajectories of aggression. Low instability refers to an instability score 1 SD below the mean, medium instability refers to an instability score at the mean, and high instability refers to an instability score 1 SD above the mean. Low genetic risk refers to having a PRS 1 SD below the mean and high genetic risk refers to having a PRS 1 SD above the mean

aggression from age 7.5 to 14 years. Consistent with a vulnerable-stable framework (Luthar et al. 2000; see Fig. 1b), there was a significant main effect of instability on initial levels of aggressive behaviors such that youth in higher instability homes displayed higher levels of aggressive behaviors regardless of aggression PRS. However, at lower levels of instability, higher aggression PRSs predicted a slower rate of decline in aggression across late childhood. This resulted in a flatter trajectory of aggression across late childhood for children with higher aggression PRS scores that diverged from children with lower PRS scores experiencing low levels of instability, who demonstrated a steeper decrease in aggression across late childhood.

This interaction, in conjunction with the main effect of instability on the intercept, add genetically-informed evidence to the existing literature (Milan et al. 2006; Womack et al. 2019) highlighting the salience of early childhood instability as an adverse environmental feature. High instability may reinforce a fast life history strategy, which emphasizes behaviors related to maximizing short-term biological fitness including impulsive and aggressive behaviors (Ellis and Del Giudice 2019). From a bioecological perspective (Bronfenbrenner and Ceci 1994), exposure to environmental stress (e.g., instability), may overwhelm an individual's genetic predispositions and "socially push" an aggressive phenotype (Raine 2002).

In the context of low instability, children at high genetic risk for aggression displayed a trajectory characterized by greater aggressive behavior across late childhood relative to children with low genetic propensity for aggression. While aggression may serve an adaptive function in more unpredictable environments, polygenic risk for aggression may predispose children to phenotypes that are maladaptive in predictable environments with the resources to meet their needs. It should be noted that the effect size of the aggression PRS score was small (i.e., about 0.13 standard deviation difference between the age 10 aggression scores between children at 1 SD above and below the instability mean), which is consistent with other polygenic research (Salvatore et al. 2015).

In the present study, instability and child genetic propensity for aggression were operationalized as aggregate constructs of related environmental or genetic factors. The use of a PRS consisting of thousands of SNPs is limited in its ability to test interactions between single genetic polymorphisms and environmental features relative to candidate gene studies, which examine interactions between the environment and a single genetic polymorphism. However, candidate gene studies also have important weaknesses relative to PRS-based studies. For example, candidate gene studies are known to have an inflated Type 1 error rate and accordingly, are often substantially underpowered to detect very small gene by environment effects. Consequently, significant findings using candidate gene approaches are overrepresented in the published literature (Duncan and Keller 2011). The use of a conservative PRS leverages the additive power of aggregating across multiple SNPs, while retaining specificity by utilizing only SNPs observed to have a relatively large effect size in the GWAS.

Similarly, operationalizing instability as a broad construct limits the ability to examine genetic interactions with specific features of instability (e.g., residential mobility). However, instability in one domain often co-occurs with instability in another domain (Tasca et al. 2011; Womack et al. 2019), and children who experience multiple types of family transition tend to be at higher risk for externalizing behaviors compared to children who experience only one type of instability (Simmons et al. 1987; Tasca et al. 2011). Thus, examining interactions between polygenic risk and specific domains of instability may overlook potential additive effects of cross-domain instability (e.g., a separation accompanied by a move creating more stress than a separation without a move). Through the use of a conservative PRS and the instability index, the present study sought to balance increasing statistical power by using broader measurements while maintaining measurement specificity over broader genetic (e.g., genome wide PRS) and environmental experiences (e.g., the adverse childhood experiences scale; Hardt and Rutter 2004).

Limitations and Directions for Future Research

Findings must be considered in the context of the sociodemographic risk and extremely high rates of instability of the present sample. For context, rates of residential mobility within a given year for this sample (ranging from 34.3 to 58.7%) were 3.0–5.2 times higher than national averages (estimated to be 11.3% between 2019 and 2020; United States Census Bureau 2020). Likewise, the likelihood of a parental separation between two and five years of age in this sample (65.3%) was higher than that among unmarried cohabiting parents in the Fragile Families and Child Wellbeing study between birth and five (51.0%), a sample recruited to be at high risk for caregiver separation (McClain 2011).

In addition, the study sample was recruited to be at risk to develop conduct problems (see Dishion et al. 2008). Thus, findings likely have limited generalizability to more affluent community populations. The direction of the observed PRS by instability interaction was consistent with a social push model, which suggests that genotypic influences on an individual's development would be more commonly evident in the context of lower stress environments, whereas environmental influence would be expected to contribute greater variance in contexts of higher stress (Raine 2002). However, the ubiquitous sociodemographic risk of the study sample limited our ability to formally test a social push model, which typically requires a greater range of environmental adversity than is available in this sample (Raine 2002). Based on the homogenous sociodemographic risk of the study sample, the present results may reflect an underestimate of polygenic by environment interaction commensurate with a social push model as all children in the present study experienced some sociodemographic adversity in early childhood based on recruitment criteria, and even children 1 SD below the instability mean experienced nearly one instability event each year. It is possible that in a sample with a greater proportion of families experiencing lower mean levels of instability and sociodemographic risk, aggression polygenic risk may have a greater influence on the development of aggressive behaviors in more stable families.

Another limitation was that the aggression factor was based in part on primary caregiver-report, and the majority of primary caregivers in this sample (94.7% biological parents) contributed half the child's genes as well as the environment. Therefore, passive gene by environment correlation and potential interactive effects between a child's genotype and nonshared parental genotype may both have contributed to children's environments (Kong et al. 2018). By measuring aggression longitudinally as a latent factor that also included alternative caregiver and teacher reports, we attempted to reduce the reliance on primary caregiver reports, while maximizing the sample size. Adoption studies provide an opportunity for future research to replicate findings in an environment provided by a non-biological caregiver.

The application of a PRS score generated from an entirely Northern European GWAS to a racially diverse sample represents a limitation of the present study and a limitation of the field more broadly. To date, the major GWASs of aggressive behaviors and related phenotypes have been conducted exclusively on discovery samples of European ancestry (Ip et al. 2021; Pappa et al. 2016; Karlsson Linnér et al. 2020; Tielbeek et al. 2017). In a literature review of studies primarily with physical health outcomes, Duncan et al. (2019) found evidence that PRSs generated from European ancestry discovery samples underperformed when applied to samples of African ancestry. However, a recent study by Brick et al. (2019) found that 59.3% of the additive genetic variance in alcohol use disorders is attributable to genome-wide SNPs shared across individuals of European and African ancestry. Expanding GWASs to include individuals of African, Latinx, and Asian ancestries is critical to improving the predictive power of polygenic scores (Peterson et al. 2019). In the meantime, substantial overlap in the genetic structure of externalizing-related pathology between individuals of European and African ancestry (Brick et al. 2019) may permit the application of PRSs to individuals of non-European ancestries.

The present study was underpowered to test the stability of gene by environment interactions across racial or ethnic background, limiting our ability to conclude that the polygenic by environment interaction holds for both Black and White youth. However, the direction of the interaction coefficient for both Black and White youth in our sensitivity analysis is commensurate with the direction

of the interaction coefficient in the full sample. Moreover, zero-order correlations between aggression polygenic risk, instability, and all reports of aggressive behaviors were similar in direction and magnitude for White and Black children, providing evidence that genetic risk for aggression has a similar association with phenotypic aggression across reporters for White and Black children. In the present study, Black children were rated by teachers (but not primary or alternate caregivers) as behaving more aggressively, identifying teacher perceptions of Black and White students as a potential source of heterogeneity in ratings of aggressive behaviors.

Additionally, our sample did not permit us to examine the polygenic by environment interaction for other racial groups (e.g., Asian, Latinx). As this study is the first to examine a polygenic by early instability interaction, replication of the findings is warranted, particularly in larger samples with greater sociodemographic variability.

Conclusions

The present study identified an interaction between early childhood instability and polygenic risk for aggression predicting growth in aggressive behaviors from middle childhood to adolescence. At lower instability, children with a low aggression PRS evinced a steeper decline in aggressive behaviors than children at high polygenic risk for aggression. At high instability, children exhibited comparably high levels of aggression at both high and low genetic risk for aggression, perhaps with aggression being reinforced as an adaptive response to meet basic needs. In the context of low instability, children at an elevated genetic risk for aggressive behaviors may benefit from behavioral interventions targeted at reducing aggression.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10519-021-10069-5.

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Author Contributions All authors contributed to the study conception and design. Data aggregation and analysis were performed by SW. The first draft of the manuscript was written by SW with substantial input from all authors. All authors commented on previous versions of the manuscript and have read and approved the final manuscript.

Data Availability The data that support the findings of this study are available from the principal investigators, [DS, MW, and KL], upon reasonable request.

Code Availability The R code that supports the findings of this study is available from the corresponding author [SW], upon reasonable request.

Declarations

Conflicts of interest Sean Womack, Sierra Clifford, Melvin Wilson, Daniel Shaw, and Kathryn Lemery-Chalfant declare that they have no conflicts of interest.

Ethical Approval All procedures performed in the current study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the University of Virginia Institutional Review Board (IRB# PRO19090045).

Consent to Participate Written informed consent from primary caregivers at each wave, and verbal assent from youth beginning at age 14.

Consent for Publication Not applicable.

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