Childhood Maltreatment and Adolescent Non-Suicidal Self-Injury: The Roles of Hypothalamic-Pituitary-Adrenal Axis Polygenic Factors and Depression

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Abstract

Childhood maltreatment is closely associated with adolescent self-injurious behavior; however, research examining the underlying mechanisms from the "gene × environment - endophenotype - behavioral phenotype" theoretical perspective remains limited. Based on the polygenic risk score research paradigm, this study utilized questionnaire methods and DNA genotyping technology to investigate the relationship between childhood maltreatment and adolescent self-injurious behavior in two independent samples (the main sample comprised 407 adolescents, Mage = 12.77 ± 0.74 years; the validation sample comprised 109 adolescents, Mage = 12.54 ± 0.60 years), while examining the moderating effect of hypothalamic-pituitary-adrenal (HPA) axis polygenic risk scores and the mediating role of depression. The results indicated that: (1) childhood maltreatment was positively associated with adolescent self-injurious behavior; (2) the interaction between HPA axis polygenic risk scores and childhood maltreatment did not directly influence adolescent self-injurious behavior, but exerted indirect effects through depression. Specifically, adolescents with higher HPA axis polygenic risk scores exhibited elevated depression levels following childhood maltreatment compared to those with lower scores, consequently increasing their risk for self-injurious behavior. These findings were replicated in another independent sample. The results contribute to elucidating the formation mechanisms of adolescent self-injurious behavior from multiple perspectives of early environment, genetic factors, and individual endophenotypes, and provide directions for intervention strategies.

Full Text

Childhood Abuse and Adolescent Non-Suicidal Self-Injury: The Effects of Hypothalamic–Pituitary–Adrenal Axis Multilocus Genetic Variation and Depression

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Abstract

Childhood abuse is closely associated with adolescent non-suicidal self-injury (NSSI), yet research examining the underlying mechanisms from a "gene × environment–endophenotype–behavioral phenotype" theoretical perspective remains limited. Drawing on the multilocus genetic profile score paradigm, this study employed questionnaire methods and DNA genotyping to investigate the relationship between childhood abuse and adolescent NSSI in two independent samples (the main sample comprised 407 adolescents, Mage = 12.77 ± 0.74 years; the validation sample comprised 109 adolescents, Mage = 12.54 ± 0.60 years). We examined the moderating role of hypothalamic–pituitary–adrenal (HPA) axis multilocus genetic profile score (MGPS) and the mediating role of depression. Results revealed that: (1) childhood abuse was positively associated with adolescent NSSI; (2) the interaction between HPA axis MGPS and childhood abuse did not directly affect NSSI but exerted an indirect effect through depression. Specifically, adolescents with higher HPA axis MGPS exhibited elevated depression levels following childhood abuse, which in turn increased their risk for NSSI compared to those with lower MGPS. These findings were replicated in the independent validation sample. The results advance our understanding of NSSI etiology by integrating early environmental, genetic, and endophenotypic factors, and provide directions for intervention efforts targeting adolescent self-injury.

Keywords: childhood abuse, non-suicidal self-injury, depression, hypothalamic–pituitary–adrenal axis, multilocus genetic profile score

1. Introduction

Non-suicidal self-injury (NSSI) refers to the direct, deliberate destruction of one's own body tissue without suicidal intent, including behaviors such as cutting, burning, and hitting oneself—acts that are not socially or culturally sanctioned (Nock, 2009; Yu et al., 2013). NSSI typically emerges during early adolescence (Nock, 2009) and tends to decline from mid-adolescence through young adulthood (Brown & Plener, 2017; Moran et al., 2012). Adolescent NSSI shows high prevalence rates and has attracted considerable research attention. Meta-analytic findings indicate an international prevalence rate of 17.2% among

adolescents (Swannell et al., 2014), while Chinese adolescent samples report a higher rate of 27.2% (Fan et al., 2021). Adolescent NSSI predicts a range of future psychopathological problems, including substance abuse and suicide risk (Mars et al., 2014; Wilkinson et al., 2011). Investigating risk factors and mechanisms underlying adolescent NSSI is therefore crucial for promoting mental health.

Childhood abuse represents a significant risk factor for NSSI (e.g., Baiden et al., 2017), and emerging evidence suggests that hypothalamic–pituitary–adrenal (HPA) axis genes and depression—a potential endophenotype for NSSI—play important roles (Bai et al., 2023; Valencia-Agudo et al., 2018). However, how childhood abuse, HPA axis genetic variation, and depression jointly influence NSSI remains unresolved. Grounded in the "gene × environment–endophenotype–behavioral phenotype" framework, this study examines the mechanisms underlying adolescent NSSI to inform prevention and intervention efforts.

1.1 Childhood Abuse and NSSI

Early environmental experiences profoundly influence mental and physical health across development, with adverse effects potentially persisting from childhood through adolescence and adulthood (Iob et al., 2023; Miller et al., 2018; Paul & Ortin, 2019). Childhood abuse, encompassing emotional, physical, and sexual abuse (Bernstein et al., 2003), represents a common form of early adversity. The developmental psychopathology model of NSSI posits that childhood trauma impairs adaptive functioning in motivation, emotion, and relationships, leading individuals to adopt self-injury as a maladaptive coping strategy (Yates, 2004). Similarly, the integrated model of NSSI suggests that distal factors such as childhood abuse create interpersonal vulnerabilities—including poor communication skills—that increase NSSI risk (Nock, 2009).

Empirical research consistently demonstrates this link across community and clinical samples, with childhood abuse predicting NSSI both concurrently and prospectively. Cross-sectional studies reveal that maltreated youth show higher NSSI rates (Baiden et al., 2017; Gu et al., 2020; Wan et al., 2015), while longitudinal research shows childhood abuse predicts NSSI 3–8 months (Garisch & Wilson, 2015) and 2 years later (Bai et al., 2023). A meta-analysis reported moderate effect sizes for all three abuse subtypes (odds ratios = 2.31–3.03) (Liu et al., 2018). Notably, childhood abuse appears to exert more stable effects on NSSI than neglect, with abuse (particularly emotional abuse) remaining a significant predictor even when both are entered simultaneously (Zhang et al., 2022), underscoring its independent contribution.

1.2 The Moderating Role of HPA Axis Polygenic Variation

Although childhood abuse increases NSSI risk, not all maltreated individuals develop psychopathology, suggesting genetic polymorphisms moderate this rela-

tionship (Iob et al., 2023). The diathesis-stress model proposes that individuals carrying specific risk alleles show heightened vulnerability to negative environments (Monroe & Simons, 1991), whereas the differential susceptibility model posits that certain genes confer heightened sensitivity to both positive and negative environments, yielding better outcomes in supportive contexts but greater psychopathology risk under adversity (Belsky & Pluess, 2009). Both frameworks emphasize gene–environment (G×E) interactions.

The HPA axis regulates cortisol secretion and stress responsivity, with dysregulation implicated in depression, anxiety, and NSSI (Koss & Gunnar, 2018; Reichl et al., 2016). Key HPA axis genes—including corticotropin-releasing hormone type 1 receptor (*CRHR1*), FK506 binding protein 5 (*FKBP5*), glucocorticoid receptor (*NR3C1*), and catechol-O-methyltransferase (*COMT*)—modulate axis function (Oswald et al., 2004; Polanczyk et al., 2009; Stramecki et al., 2020; Tyrka et al., 2016) and have garnered extensive research attention. For instance, following early adversity, *FKBP5* rs1360780 T allele carriers show greater depression and PTSD risk than CC homozygotes (Binder et al., 2008; Piechaczek et al., 2019), and *FKBP5* rs3800373 AA carriers with high childhood trauma exhibit elevated suicide risk (Roy et al., 2012). Recent work has begun examining G×E effects on NSSI, finding that *FKBP5* rs3800373 moderates the impact of distal and proximal stress on adolescent NSSI (Bai et al., 2023).

Traditional single-locus studies often yield inconsistent results. For example, reviews of HPA axis gene–environment interactions in depression show mixed findings for *FKBP5* rs1360780 (Normann & Buttenschøn, 2019, 2020). Recent research demonstrates that HPA axis genes can have cumulative, additive effects in G×E interactions (McKenna et al., 2021). The multilocus genetic profile score (MGPS) approach provides greater genetic information, enhanced explanatory power, and increased statistical power compared to single-locus analyses (Cao & Rijlaarsdam, 2023; McKenna et al., 2021). Starr and Huang (2019) found that HPA axis MGPS interacted with stress to predict adolescent depression, whereas single-locus analyses revealed only sporadic effects. Preliminary evidence also suggests HPA axis MGPS moderates the effect of childhood trauma (including abuse, family conflict, and violence) on NSSI (Zeng et al., 2024).

1.3 The Mediating Role of Depression

According to the "gene × environment–endophenotype–behavioral phenotype" model (Caspi & Moffitt, 2006; Zhang et al., 2021), HPA axis genes may influence NSSI indirectly through endophenotypes. In psychiatric genetics, endophenotypes are quantifiable traits associated with disease manifestation that reflect underlying genetic liability (Leboyer et al., 1998). Depression encompasses symptoms such as depressed mood, anhedonia, cognitive impairment, and sleep/appetite disturbances (Otte et al., 2016). Previous research has used anhedonia—a core depressive symptom characterized by markedly diminished interest or pleasure in activities (Watson et al., 2020)—as an endophenotype for disorders such as OCD and schizophrenia (Umesh et al., 2018; Xu et al., 2020).

Theoretical work also proposes that depressive features like hopelessness, anhedonia, and cognitive deficits represent potential endophenotypes for suicide and NSSI (Hu et al., 2021; Lamontagne et al., 2022). Brodsky (2016) similarly suggested that early adversity interacts with genetic factors to promote vulnerability traits (e.g., chronic pessimism, emotional dysregulation) that increase NSSI risk. Thus, depression—as both a potential NSSI endophenotype and a common emotional vulnerability in adolescence—may mediate the interactive effect of childhood abuse and genetic factors on NSSI.

Although direct empirical tests of this mediation are scarce, research shows that HPA axis MGPS interacts with early adversity (e.g., interpersonal stress, prenatal maternal stress) to predict depression, with high-MGPS individuals showing elevated depression risk under negative conditions (McKenna et al., 2021; Starr & Huang, 2019). Meta-analyses and longitudinal studies demonstrate that depression prospectively predicts NSSI (Fox et al., 2015; Valencia-Agudo et al., 2018), with higher depressive symptoms associated with increased NSSI one year later (Wu et al., 2019). Depression also mediates the link between early adversity and NSSI (Hu et al., 2023). Recent work found that *FKBP5* MGPS interacted with maladaptive parenting to predict internalizing problems, which in turn increased NSSI risk (Zhou & Gong, 2023). However, whether childhood abuse interacts with HPA axis MGPS to influence depression and subsequent NSSI remains unexplored.

In summary, this study adopts a "gene × environment–endophenotype–behavioral phenotype" framework and the MGPS approach to examine: (a) the association between childhood abuse and adolescent NSSI, (b) the moderating role of HPA axis MGPS, and (c) the mediating role of depression (see hypothesized model in [Figure 1: see original paper]). When G×E interactions are significant, we will test whether the pattern conforms to diathesis-stress or differential susceptibility models (Widaman et al., 2012).

[Figure 1: see original paper] Hypothesized model. Note: HPA axis MGPS = hypothalamic–pituitary–adrenal axis multilocus genetic profile score.

2. Method

2.1 Participants

Participants were recruited from two middle schools in Shaanxi Province. Based on prior HPA axis polygenic research, G×E interaction effect sizes range from 0.02 to 0.08 (McKenna et al., 2021; Starr & Huang, 2019). Power analysis using G*Power 3.1.9.7 indicated that 101–395 participants were needed to achieve 80% statistical power ($\alpha = 0.05$). A total of 421 middle school students participated. Inclusion criteria were: no reading disability, no alcohol or substance abuse in the past 6 months, and no serious physical illness. Five participants who refused to provide genetic samples and nine with invalid questionnaires were excluded, yielding a final sample of 407 adolescents (*M*age = 12.77 ± 0.74 years; 195 boys, 212 girls). Maternal education: 85.5% junior high school or below, 11.1% high

school, 3.4% college or above. Paternal education: 78.6% junior high school or below, 14.0% high school, 7.4% college or above. Monthly family income: below ¥3,000 (22.0%), ¥3,000–6,000 (53.8%), ¥6,000–10,000 (16.8%), above ¥10,000 (7.4%).

2.2 Measures and Procedures

2.2.1 Childhood Abuse The Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003) assessed adolescents' retrospective reports of childhood abuse. This 28-item measure (25 clinical items, 3 validity items) demonstrates strong psychometric properties (Wang et al., 2022). Five-item subscales assessed emotional abuse (e.g., "Someone in my family said hurtful or insulting things to me"), physical abuse (e.g., "Someone in my family hit me so hard it left bruises or marks"), and sexual abuse (e.g., "Someone tried to touch me in a sexual way or make me touch them"). Emotional neglect (e.g., "Someone in my family made me feel important or special") and physical neglect (e.g., "I had to wear dirty clothes") subscales were also included. Items were rated on a 5-point scale (1 = never, 5 = always), with higher scores indicating greater abuse/neglect. Cronbach's α was 0.85 for abuse and 0.80 for neglect.

2.2.2 Depression The Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) measured depressive symptoms via adolescent self-report. The 20-item scale (e.g., "I was bothered by things that usually don't bother me") uses a 4-point response format (0 = rarely or none of the time, 3 = most or all of the time). Total scores reflect depression severity. The CES-D shows good reliability and validity in Chinese adolescents (Chen et al., 2009). Cronbach's α was 0.91.

2.2.3 Non-Suicidal Self-Injury NSSI was assessed using a scale derived from the Revised Diagnostic Interview for Borderlines (DIB-R; Zanarini et al., 1989) and validated in Chinese youth (Wang et al., 2015; You et al., 2012). The 10-item measure evaluates NSSI behaviors (e.g., cutting, burning, severe scratching) occurring in the past 12 months using a binary response format (0 = no, 1 = yes). Total scores indicate NSSI frequency. Cronbach's α was 0.88.

2.2.4 HPA Axis Genotyping and MGPS Calculation Saliva samples (3 ml) were collected for DNA extraction using a universal DNA purification kit. Genotyping of *CRHR1* rs110402, *FKBP5* rs1360780 and rs4713902, *NR3C1* rs41423247, and *COMT* rs4680 was performed using Sequenom matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (San Diego, CA, USA). Genotyping efficiency exceeded 99%. All polymorphisms showed minor allele frequencies (MAF) >5% and were in Hardy–Weinberg equilibrium (ps $>$ 0.05) (see). These loci are associated with depression and NSSI risk (see), with acceptable linkage disequilibrium (r2 $\leq$ 0.10) (Pagliaccio et al., 2014).

Following established methods (Pagliaccio et al., 2014), MGPS was calculated by coding each single nucleotide polymorphism (SNP) as 1 if the participant carried the risk/susceptibility genotype and 0 otherwise, then summing across loci. Higher scores indicate greater genetic risk/susceptibility (see). Five participants with missing genetic data were excluded from genetic analyses (Coley et al., 2017).

Genotype distribution (main sample)

SNP characteristics and risk genotype coding

2.2.5 Procedure The study was approved by Shaanxi Normal University's ethics committee. Schools, guardians, and adolescents received detailed information about questionnaire administration, saliva collection, and DNA extraction before providing informed consent. Questionnaires assessing childhood abuse, depression, NSSI, and demographics were administered first, followed by saliva collection (participants were instructed to avoid eating, drinking, chewing gum, or smoking for 30 minutes prior). Samples were shipped to a biotechnology company for DNA extraction and genotyping. All procedures were conducted by trained psychology graduate students.

2.3 Data Analysis

Data were analyzed using SPSS 25.0, the PROCESS macro, and R. First, Harman's single-factor test assessed common method bias. Second, Pearson correlations examined variable interrelationships. Third, PROCESS Model 8 tested the hypothesized model, examining: (a) the interaction between childhood abuse and HPA axis MGPS in predicting NSSI, and (b) depression as a mediator. Sex, age, and childhood neglect were controlled, along with their interactions with study variables to avoid confounding G×E effects (Keller, 2014). Bootstrap resampling (5,000 iterations) was used. Missing data were handled via expectation-maximization imputation. Continuous variables were standardized. False discovery rate (FDR) was controlled using Benjamini–Hochberg correction ($q < 0.05$) (Benjamini & Yekutieli, 2001). Significant interactions were probed via simple slopes analysis, and re-parameterized regression tested theoretical models (Widaman et al., 2012).

Sensitivity analyses included: (1) testing each SNP separately, and (2) evaluating the equal-effects model to assess whether any single locus dominated or whether effects canceled out. The decomposition model (including five main effects and five interaction terms) was compared to the equal-effects model (constraining these effects to equality). Nonsignificant $\Delta R2$ would support the equal-effects assumption and justify polygenic scoring (Cao & Rijlaarsdam, 2023).

2.4 Results

2.4.1 Common Method Bias Harman's single-factor test on childhood abuse, depression, and NSSI items revealed 12 factors with eigenvalues >1

in the main sample, with the first factor explaining 22.21% of variance—well below the 40% threshold, indicating no severe common method bias.

2.4.2 Descriptive Statistics and Correlations Means, standard deviations, and correlations are presented in . HPA axis MGPS did not correlate significantly with childhood abuse or neglect (ps > 0.05), nor with depression or NSSI (ps > 0.05). Childhood abuse correlated positively with depression (r = 0.47, $p < 0.001$) and NSSI (r = 0.27, $p < 0.001$), and depression correlated with NSSI (r = 0.43, $p < 0.001$).

Correlations among study variables (main sample)

2.4.3 Main Effects: Childhood Abuse, HPA Axis MGPS, and Depression PROCESS Model 8 results showed a significant childhood abuse × HPA axis MGPS interaction on depression (β = 0.17, t = 2.58, p = 0.010, q = 0.041, 95% CI [0.04, 0.29]). Depression significantly predicted NSSI (β = 0.36, t = 6.84, $p < 0.001$, $q < 0.001$, 95% CI [0.26, 0.47]), while the interaction did not directly predict NSSI (β = –0.05, t = –0.67, p = 0.504, q = 0.723, 95% CI [–0.18, 0.09]) (see). Thus, the interaction indirectly affected NSSI through depression.

Simple slopes analysis revealed that the association between childhood abuse and depression strengthened with higher MGPS. For low-MGPS adolescents (M – 1 SD), childhood abuse positively predicted depression (β = 0.29, t = 3.53, $p < 0.001$, 95% CI [0.13, 0.45]). For high-MGPS adolescents (M + 1 SD), this association was stronger (β = 0.59, t = 5.37, $p < 0.001$, 95% CI [0.38, 0.81]) (see [Figure 2: see original paper]). The interaction accounted for ΔR2 = 0.02.

Hypothesized model tests (main sample)

[Figure 2: see original paper] Interaction between HPA axis MGPS and childhood abuse on adolescent depression (main sample)

2.4.4 Gene–Environment Interaction Pattern As shown in [Figure 2: see original paper], at low childhood abuse levels, depression did not differ by MGPS (β = –0.06, t = –1.03, p = 0.306, 95% CI [–0.18, 0.06]). At high abuse levels, high-MGPS adolescents showed higher depression than low-MGPS adolescents (β = 0.20, t = 2.68, p = 0.008, 95% CI [0.05, 0.34]). Re-parameterized regression analysis yielded a crossover point estimate (C = –0.30, 95% CI [–0.90, 0.31]) outside the observed range of childhood abuse scores (–0.70 to 5.43). The F-test indicated that the differential susceptibility model did not explain significantly more variance than the diathesis-stress model (ΔR2 = 0.002, $F(1, 389) = 1.05$, p = 0.306), supporting a diathesis-stress pattern (Widaman et al., 2012). Thus, high HPA axis MGPS confers increased depression risk specifically under adverse (high abuse) conditions.

2.4.5 Sensitivity Analyses Single-locus analyses revealed a significant G×E effect only for *CRHR1* rs110402 (β = 0.14, t = 2.69, p = 0.007, q = 0.015); all

other SNPs showed nonsignificant effects (ps > 0.05, qs > 0.05), demonstrating MGPS's superior explanatory power. The equal-effects model test showed no significant difference from the decomposition model (ΔR2 = 0.02, $F(8, 387) = 1.30$, $p = 0.240$), indicating no single-locus dominance or canceling effects, thus supporting polygenic scoring.

3. Validation Sample

3.1 Participants

We sought to replicate key findings in an independent sample. Power analysis indicated that 101 participants were needed to detect effect sizes of 0.02–0.08 with 80% power ($\alpha = 0.05$). An additional 114 middle school students were recruited. Inclusion criteria matched the main sample. Two participants who refused saliva collection and three with invalid questionnaires were excluded, yielding a final sample of 109 adolescents ($M = 12.54$ years, $SD = 0.60$; 67 girls). Maternal education: 84.3% junior high or below, 14.8% high school, 0.9% college or above. Paternal education: 77.8% junior high or below, 14.8% high school, 7.4% college or above. Family income: below ¥3,000 (13.1%), ¥3,000–6,000 (65.4%), ¥6,000–10,000 (17.8%), above ¥10,000 (3.7%). Independent samples t-tests showed no significant differences between validation and main samples on childhood abuse, NSSI, HPA axis MGPS, sex, parental education, or family income (ps > 0.05). However, the validation sample was slightly younger, $t(514) = 2.97$, $p = 0.003$, and reported higher depression, $t(514) = -5.28$, $p < 0.001$.

3.2 Measures and Procedures

3.2.1 Measures Identical measures were used. Cronbach's α coefficients were 0.83 for childhood abuse, 0.91 for depression, and 0.84 for NSSI.

3.2.2 Genotyping and MGPS Calculation Genotyping procedures matched the main sample, with efficiency >98%. All SNPs showed MAF >5%; all except rs110402 were in Hardy–Weinberg equilibrium (ps > 0.05) (see). Excluding rs110402 did not alter results. MGPS calculation followed the main sample procedure. Two participants with missing genetic data were excluded.

Genotype distribution (validation sample)

3.2.3 Procedure Procedures were identical to the main sample, conducted one year later.

3.3 Data Analysis

Analyses paralleled the main sample. Following molecular genetics conventions, replication was defined as $p < 0.05$ (Kuan et al., 2022).

3.4 Results

3.4.1 Common Method Bias Harman's test revealed 17 factors with eigenvalues >1, with the first factor explaining 19.59% of variance, indicating no severe common method bias.

3.4.2 Descriptive Statistics and Correlations Correlations are shown in . HPA axis MGPS did not correlate with childhood abuse, neglect, depression, or NSSI (ps > 0.05). Childhood abuse correlated with depression ($r = 0.32$, $p = 0.001$) and NSSI ($r = 0.29$, $p = 0.002$), and depression correlated with NSSI ($r = 0.56$, $p < 0.001$).

Correlations among study variables (validation sample)

3.4.3 Main Effects: Childhood Abuse, HPA Axis MGPS, and Depression PROCESS Model 8 revealed a significant childhood abuse × HPA axis MGPS interaction on depression ($\beta = 0.31$, $t = 2.18$, $p = 0.032$, $q = 0.191$, 95% CI [0.03, 0.59]). Depression significantly predicted NSSI ($\beta = 0.50$, $t = 5.36$, $p < 0.001$, $q < 0.001$, 95% CI [0.32, 0.69]), while the direct interaction effect on NSSI was nonsignificant ($\beta = 0.14$, $t = 1.05$, $p = 0.297$, $q = 0.776$, 95% CI [–0.12, 0.40]) (see). Simple slopes showed that the abuse–depression association strengthened with higher MGPS: nonsignificant for low-MGPS adolescents ($\beta = 0.12$, $t = 0.70$, $p = 0.488$, 95% CI [–0.23, 0.47]) but significant for high-MGPS adolescents ($\beta = 0.74$, $t = 3.12$, $p = 0.002$, 95% CI [0.27, 1.21]) (see [Figure 3: see original paper]). The interaction accounted for $\Delta R2 = 0.04$.

Hypothesized model tests (validation sample)

[Figure 3: see original paper] Interaction between HPA axis MGPS and childhood abuse on adolescent depression (validation sample)

3.4.4 Gene–Environment Interaction Pattern At low abuse levels, depression did not differ by MGPS ($\beta = –0.08$, $t = –0.61$, $p = 0.544$, 95% CI [–0.33, 0.18]). At high abuse levels, high-MGPS adolescents showed higher depression ($\beta = 0.45$, $t = 2.36$, $p = 0.020$, 95% CI [0.07, 0.82]). The crossover point estimate (C = –0.45, 95% CI [–1.17, 0.24]) fell outside the abuse score range (–0.72 to 4.78), and the differential susceptibility model did not outperform the diathesis-stress model ($\Delta R2 = 0.003$, $F(1, 94) = 0.370$, $p = 0.544$), supporting diathesis-stress (Widaman et al., 2012).

3.4.5 Sensitivity Analyses Single-locus analyses revealed no significant G×E effects on depression for any SNP (ps > 0.05, qs > 0.05), again demonstrating MGPS's superior sensitivity. The equal-effects model was not significantly different from the decomposition model ($\Delta R2 = 0.04$, $F(8, 92) = 0.60$, $p = 0.776$), supporting polygenic scoring.

4. Discussion

Consistent with hypotheses, childhood abuse was positively associated with adolescent NSSI. Extensive research identifies early adversity as a critical risk factor for psychopathology (Iob et al., 2023; Miller et al., 2018), and childhood abuse specifically predicts NSSI across cultures (Baiden et al., 2017; Gu et al., 2020; Wan et al., 2015). The effect remained significant after controlling for sex, age, and neglect, indicating independent predictive utility. Adolescence involves multiple stressors (Starr & Huang, 2019), and childhood abuse impairs adaptive capacities, increasing reliance on maladaptive coping like NSSI (Yates, 2004).

Although we found no direct G×E effect on NSSI, the childhood abuse × HPA axis MGPS interaction indirectly affected NSSI through depression. Adolescents with high MGPS exhibited stronger abuse–depression associations, elevating NSSI risk. This supports the "gene × environment–endophenotype–behavioral phenotype" model (Caspi & Moffitt, 2006; Zhang et al., 2021), suggesting G×E effects operate through endophenotypes to influence behavioral outcomes. It also aligns with Brodsky's (2016) theory that early adversity and genetic factors interact to shape emotional vulnerability traits that promote NSSI. Previous work shows HPA axis MGPS interacts with stress to predict depression (Starr & Huang, 2019), which prospectively predicts NSSI (Valencia-Agudo et al., 2018) and mediates adversity–NSSI links (Hu et al., 2023). Our findings extend this literature by elucidating how early adversity, polygenic risk, and depression jointly influence NSSI, offering psychobiological insights and suggesting that depression intervention may be an effective prevention strategy for high-risk youth.

The G×E pattern supported diathesis-stress: high MGPS conferred depression risk only under high abuse conditions. This aligns with prior research on HPA axis G×E effects on internalizing problems (Cao & Zhang, 2019; Keijser et al., 2021). Potential mechanisms include HPA axis gene–environment interactions influencing epigenetic modifications (Klengel et al., 2013; Ramo-Fernández et al., 2019) and limbic system structure/function (Di Iorio et al., 2017; Pagliaccio et al., 2014), which may underlie depression and NSSI (Quevedo et al., 2016; Zhang et al., 2016). Future research should investigate these pathways.

This study is the first to apply the "gene × environment–endophenotype–behavioral phenotype" framework to NSSI, demonstrating that adolescent self-injury results from the interplay of childhood abuse, HPA axis polygenic risk, and depression. Results were replicated in an independent sample. The study also highlights the advantages of MGPS over single-locus approaches (McKenna et al., 2021; Starr & Huang, 2019). However, limitations exist. First, our early adolescent sample limits generalizability across developmental stages, when emotion regulation and NSSI patterns vary (Brown & Plener, 2017; Zimmermann & Iwanski, 2014) and G×E patterns may differ (Cao et al., 2023). Second, although MGPS improves genetic coverage, it does not

capture all relevant variants; future studies should include additional loci (e.g., *FKBP5* rs3800373; Bai et al., 2023) and employ genome-wide by environment interaction (GWEIS) approaches (Jia et al., 2023). Third, retrospective self-report of childhood abuse may involve recall bias, and cross-sectional design precludes causal inferences. Future research should use multi-informant measures and longitudinal designs. Fourth, the validation sample was relatively small; larger samples are needed to confirm these patterns.

In conclusion, childhood abuse positively predicted adolescent NSSI, and this association was moderated by HPA axis MGPS via depression. High polygenic risk amplified the abuse–depression link, increasing NSSI vulnerability. These findings support a diathesis-stress model and underscore the value of targeting depression in prevention efforts for maltreated youth with high HPA axis genetic risk.

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