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Polygenic Scores for Depression are Associated with Indices of Neighborhood Adversity

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Abstract

Genome-wide association studies have allowed for the creation of polygenic scores (PGSs) reflecting genetic liability for depression, yet recent work suggests that these PGSs may also reflect greater genetic propensity towards higher levels of stress exposure. The current study sought to extend prior findings to examine whether an established depression PGS (DEP-PGS) is associated with greater stress exposure at the neighborhood level in a sample of preadolescent children. This study included 278 children of European ancestry between the ages of 7 and 11 (45.3% female) and their parent. Parents and children completed clinical interviews and questionnaires and children provided genetic samples. Children's neighborhoods were defined based on their current home address and geocoded indices of neighborhood adversity (i.e., area socioeconomic disadvantage, crime, opportunity) were matched to zip codes. As hypothesized, children with greater genetic liability for depression as reflected by DEP-PGSs were more likely to live in neighborhoods characterized by greater adversity. Findings were maintained when statistically controlling for family socioeconomic status and parent's and children's histories of depression and anxiety. The current findings build upon prior research highlighting depression-relevant gene-environment correlations and extend this work to provide evidence that DEP-PGSs may capture genetic liability for exposure to stressful contexts at the neighborhood level. Future research is needed to replicate findings in diverse samples and to examine whether neighborhood-level adversity mediates the relation between DEP-PGSs and future depression risk in youth.

General Scientific Summary

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GWAS-derived polygenic scores for depression (DEP-PGS) have been previously linked to individual-level stress exposure in youth, but it remains unclear if DEP-PGSs are also associated with neighborhood-level adversity in preadolescent youth. Findings indicated that youth with greater DEP-PGSs were more likely to live in neighborhoods marked by greater adversity (i.e., encompassing higher socioeconomic disadvantage and crime and lower opportunities/ resource availability).

Keywords

genetic risk; polygenic scores; depression; neighborhood adversity; stress exposure

Major depressive disorder (MDD) is a highly prevalent disorder with a lifetime prevalence of approximately 21% (Kessler et al., 2012) and is among the leading contributors to the global burden of disease (Vos et al., 2016), thereby highlighting the critical need to understand the factors contributing to its risk. There are clear genetic influences, with heritability estimates suggesting that approximately 40% of liability to MDD is due to genetic factors (Sullivan et al., 2000). Given this, much research over the past few decades has attempted to identify genes contributing to depression risk. Although initial studies focused on a few single candidate genes, as this area of research has grown it has become increasingly clear that genetic risk for MDD is not due to the impact of a few isolated genes (Bosker et al., 2011; Duncan et al., 2019). Rather, genetic risk for depression arises from the cumulative impact of numerous genetic variants dispersed across the genome that each contribute a small amount of risk variance (Duncan et al., 2019).

Therefore, in recent years there has been increasing focus on utilizing large genome wide association studies (GWASs). These GWASs have successfully derived polygenic scores (PGSs) that reflect genetic liability for depression (i.e., DEP-PGSs) (Als et al., 2023; Howard et al., 2018; Hyde et al., 2016; Wray et al., 2018), though these DEP-PGSs explain notably less variance in depression risk than behavioral genetic studies. Importantly, even though these DEP-PGSs have thus far been established based on adult samples with diagnoses or elevated levels of depression, they also appear to generalize to early risk in youth. For example, one meta-analytic GWAS derived a DEP-PGS that is not only associated with depression risk in adults (Howard et al., 2019), but also predicts the emergence of depression symptoms in youth (Kwong et al., 2021; Perret et al., 2023). Similarly, another DEP-PGS derived from the largest depression GWAS to-date (Als et al., 2023) was also associated with depression symptom trajectories in two independent samples of youth (Grimes et al., 2024), despite the fact that it was originally derived using adult samples. Thus, DEP-PGSs may effectively capture risk for depression across development, including during late childhood when this risk first begins to increase. However, questions remain regarding whether the genetic variants in these DEP-PGSs contribute directly to depression risk or whether they contribute to depression risk via indirect pathways.

It has been suggested that GWAS-derived PGSs may not simply convey risk for specific disorders directly, but rather, may also indirectly confer risk via environmental exposure (i.e., environmentally mediated pleiotropy; Avinun, 2020). In other words, DEP-PGSs may

capture genetic variants directly associated with risk of exposure to stressful environments that subsequently increase depression risk rather than solely capturing genetic risk for depression itself. Associations between genotype and environmental exposures are called gene-environment correlations (rGEs; Plomin et al., 1977). There are three types of rGEs that characterize the nature of these associations. Passive rGE refers to the association between the genes inherited from and the environment provided by one's parents. Active rGE refers to the process by which one's genotype influences their behavior and traits, which leads them to self-select their environment. Evocative rGE refers to process by which one's genotype influences their behavior and traits, which then impacts their environment by evoking a response from others. In support of the proposition that PGSs may convey risk for psychopathology via the environment, the existence of rGEs have been well-documented (Jaffee & Price, 2007; Kendler & Baker, 2007; Knafo & Jaffee, 2013).

Furthermore, increasing evidence suggests that GWAS-derived PGSs ostensibly derived to assess genetic risk for depression may inadvertently capture genetic liability associated with stressful environments. One study found that higher scores on a DEP-PGS (Wray et al., 2018) among youth was associated with lower family socioeconomic status across two independent samples (Machlitt-Northen et al., 2022). Another recent study using a large depression GWAS meta-analysis (Howard et al., 2019) found that higher scores on a DEP-PGS were associated with greater peer victimization among youth (Perret et al., 2023). Finally, our research group has also shown that this same DEP-PGS is associated with increased exposure to stressful life events in youth (Feurer et al., 2022), which was partially replicated in an independent sample (Harrison et al., 2023). We also found that this DEP-PGS explained more variance in youth's exposure to stressful life events (3.2–4.0%) than their own depression symptoms (0.52%; Feurer et al., 2022). This is not altogether surprising, as the heritability of depression symptoms is non-significant in children whereas the heritability of MDD in adolescents and adults is approximately 40% (Rice, 2010). However, this DEP-PGS notably also explained more variance in youth stress exposure than the amount of variance in depression risk accounted for by the DEP-PGS in the original adult GWAS discovery sample (1.5–3.2%; Howard et al., 2019). This highlights the possibility that this DEP-PGS may be a stronger predictor of stressful environments (which themselves robustly contribute to depression risk; Hammen, 2005; Kessler, 1997) than direct liability for depression itself, though it is also possible that findings may have resulted from the application of PGS based on a GWAS in adults to a child sample. Nevertheless, together these findings provide evidence that DEP-PGSs are associated with risk of exposure to stressful environments. However, further research is needed to confirm whether these rGEs are also observed across independent samples and whether DEP-PGSs are also associated with other forms of stressful environments.

Although these prior studies have observed links between DEP-PGS and individual-level stress exposure, it is important to note that environmental contexts outside this microsystem level also play an important role in youth development and risk (Bronfenbrenner, 1977). One environmental context that may be of particular importance is neighborhood-level adversity. Consistent with research showing that individual-level stress exposure robustly increases risk for depression (Ge et al., 1994; Hammen, 2005; Kessler, 1997), meta-analytic work shows that neighborhood-level adversity (e.g., neighborhood socioeconomic disadvantage,

crime) is also positively associated with depression risk (Baranyi et al., 2021; Richardson et al., 2015; Stirling et al., 2015; Sui et al., 2022). Although precise mechanisms of risk are not clear, neighborhood-level adversity is associated with core processes known to impact depression risk in youth including sleep disruption (Chung et al., 2024) and reward processing (Granros et al., 2024; Hyde et al., 2022; Israel et al., 2025). Notably, neighborhood socioeconomic disadvantage (Richardson et al., 2015; Sui et al., 2022) is also linked with exposure to more specific forms of adversity (e.g., higher crime, lower access to resources) that may also help to explain how neighborhood-level disadvantage confers risk for depression (Hyde et al., 2022; Leventhal & Brooks-Gunn, 2000). Finally, living in a neighborhood characterized by high levels of disadvantage may increase the salience and impact of other forms of stress on depression risk, with some evidence that the link between non-interpersonal chronic stressors (e.g., neighborhood conditions) and risk for depression onset is stronger among individuals with lower, compared to higher socioeconomic status (Vrshek-Schallhorn et al., 2015).

Recent research has found evidence of rGEs when considering neighborhood-level environmental characteristics. For example, behavioral genetics research has suggested not only is neighborhood socioeconomic disadvantage heritable (~16%), but that genetic variance associated with depression risk is also correlated with neighborhood disadvantage (Strachan et al., 2017). Further highlighting a potential genetic influence on exposure to neighborhood-level adversity, another study examining rGEs in adolescents observed an association between an education-relevant PGS and neighborhood socioeconomic status (Krapohl et al., 2017). Finally, another study in adults observed an association between a DEP-PGS and neighborhood deprivation (Hill et al., 2016). However, it remains unknown whether DEP-PGSs also capture genetic variance associated with neighborhood-level adversity in children.

The goal of the current study was to extend prior rGE findings linking youth DEP-PGSs and individual-level stress exposure (Feurer et al., 2022; Harrison et al., 2023; Machlitt-Northen et al., 2022; Perret et al., 2023) to examine whether youth's genetic liability for depression is also associated with neighborhood-level adversity. Using the largest GWAS of depression to-date (Als et al., 2023), we hypothesized that children with greater genetic risk for depression would live in neighborhoods characterized by higher levels of adversity (i.e., greater neighborhood socioeconomic disadvantage, greater neighborhood crime, and lower opportunity/ resource access). As neighborhood socioeconomic disadvantage uniquely predicts variance in depression risk independently of individual-level socioeconomic factors (Galea et al., 2007), we also hypothesized that associations between children's DEP-PGS and neighborhood-level adversity would be maintained after statistically controlling for the influence of individual-level socioeconomic status. Finally, consistent with our hypothesis that DEP-PGSs may inadvertently reflect rGEs, rather than direct risk specifically for depression or other internalizing psychopathologies, we hypothesized that this relation would be at least partially independent of parent and child diagnoses of depression and anxiety.

Method

Participants

Participants were 278 children of European ancestry recruited from upstate New York between 2013 and 2016 as part of a larger study on attentional biases for affective stimuli in children. The area from which participants were recruited encompasses urban, suburban, and rural areas. As the larger study was designed to recruit a representative community sample, the only inclusion criterion was that the child be between 7 and 11 years old and the only exclusion criteria was the presence of a learning or developmental disorder, per parent report, that would make it difficult for them to complete the study. The average age of the children was 9.46 years (SD = 1.45) and 45.3% were girls. Participants were limited to European ancestry for two reasons. First, this was done to match the ancestry of the original sample from which the DEP-PGS was derived (Als et al., 2023) as PGS's from European samples perform poorly when applied to non-European samples (Duncan et al., 2019). Second, this was the largest homogenous group available for genetic imputation, as described below, and the remaining homogenous ancestral groups were too small to allow for meaningful comparison across groups. Family income, as assessed using an ordinal scale in $5,000 increments, ranged from $0-$5,000 to more than $115,000 with a median of $40,000-$45,000 per year.

Procedure

Potential participants were recruited from the community through a variety of means designed to recruit a representative sample (e.g., television and Facebook ads, billboards in the community). Upon arrival at the laboratory, parents provided consent and children provided assent to participate in the study. After this, parents and children completed diagnostic clinical interviews. Children also provided blood or saliva samples for analysis. Parents provided address information for geocoding and reported their annual family income for the previous year. All procedures were approved by the university's institutional review board.

Measures

Genotyping, Quality Control, and Genetic Imputation: Youth DNA was collected and isolated from either buccal cells or blood using established methods (Carskadon et al., 2019; Freeman et al., 1997; Lench et al., 1988). Participants were genotyped using OmniExpressExome arrays (Illumina, Inc.) that were run on an Illumina HiScan system following the manufacturer's protocols and were genetically imputed using the Michigan Imputation Server. To prepare data for imputation, we first conducted principal components analysis (PCA) using the 1000 Genomes Project (1KG) Phase III (Version 5) reference panel (Auton et al., 2015) to determine genetic ancestry. Data was screened for well genotyped markers (> 90%) with MAF > 10% and data was strand aligned to the 1000 Genomes reference data. PCA was conducted with FlashPCA version 2 (Abraham et al., 2017) and samples consistent with European Ancestry (the largest homogenous population) were identified and selected for imputation. After individuals with European Ancestry were identified, the original data was screened to prepare for imputation. Markers with genotyping rate > 95% and MAF > 10% and samples with < 90% missingness were

selected (i.e., strand alignment and allele frequencies compared to European Ancestry 1KG reference panel) using a Perl script developed by Rayner et al. (2016). Next, data were genetically imputed using the 1KG reference panel and ShapeIT phasing with Minimac3 via the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!pages/home).

Following imputation, markers that were not bi-allelic, were not autosomal, or had poor imputation quality score ($r^2 < 0.7$) were removed. Single nucleotide polymorphisms (SNPs) that had <95% genotyping rate, <1% minor allele frequency, or < .0001 Hardy Weinberg equilibrium rate and people who had a missingness by individual rate of <90% were removed. Following analytic quality control, imputed data from youth were selected and a genetic relationship matrix (GRM) was computed using the GCTA software tool [version 1.25.3](Yang et al., 2011) to remove genetically related individuals (>.05). A total of 278 unrelated youth of European Ancestry were retained for analysis. Data management and analysis were performed using PLINK version 1.9 (Purcell et al., 2007) and R version 3.4.3.

Genome-wide association study (GWAS) summary statistics were obtained for 7,547,115 markers from the most recent GWAS of depression (Als et al., 2023), excluding the 23andMe sample. Weights were then adjusted using continuous shrinkage priors in a Bayesian framework from the PRS-CS-auto methodology with the default settings selected (Ge et al., 2019). The 1000 Genomes Project's European reference panel provided by the PRS-CS developers was used to adjust for LD (https://github.com/getian107/PRScs). Individual levels scores were created using Plink v1.90b6.18 (www.cog-genomics.org/plink/1.9/) (Chang et al., 2015). When overlapping markers from the adjusted summary statistics with the cleaned and imputed sample data that passed QC, 1,064,766 variants were included in the polygenic scores.

Neighborhood Indices

Neighborhood Definition. Participants' neighborhoods were determined based on the zip code of their current address at the time of study enrollment.

Area Deprivation Index. Neighborhood socioeconomic disadvantage indices were obtained from the 2015 Area Deprivation Index (Kind & Buckingham, 2018). The Area Deprivation Index is a factor score calculated from 5-year census data from the American Community Survey on 17 socioeconomic factors including income, education, employment, and housing quality. The Area Deprivation Index provides a nationally-ranked index score ranging from 1 to 100, such that a score of 1 indexes the lowest levels of area disadvantage compared to the national average and a score of 100 indicates the highest levels of disadvantage.

The Area Deprivation Index defines neighborhoods as census block groups, which is consistent with prior literature in large urban areas. However, examinations of area socioeconomic deprivation in rural and suburban areas remain sparse, and there is a lack of consensus regarding the extent to which census block groups appropriately capture neighborhoods outside of urban areas (de Marco & de Marco, 2010). Furthermore, as census block groups are defined based on population size, their geospatial size tends to be much larger in rural areas compared to suburban and urban areas, thereby making comparison

of neighborhoods difficult when considering studies encompassing both rural and non-rural areas, like in the current study. Therefore, to be consistent with prior research using the current sample (Feurer et al., 2020), neighborhoods were defined by participants' zip codes. Consistent with prior studies that examined the Area Deprivation Index at the zip code level (Chan et al., 2021; Liu et al., 2023), all Area Deprivation Indices within participant zip codes were averaged.

Neighborhood Crime. Neighborhood crime indices were obtained from the 2015 CrimeRisk database (Applied Geographic Solutions, 2015), which is a database containing geocoded information about crime risk indices for multiple types of crime including property (i.e., burglary, larceny, motor vehicle theft) and personal (i.e., murder, rape, robbery, assault) crime rates for each zip code within the target county. Total crime risk indices, reflecting the relative risk of a crime occurring in an area compared to the national average, were calculated from a thorough analysis of crime reports in the target county across a 7-year period. A score of "100" reflects the national average for total crime risk.

Child Opportunity Index. Indices of neighborhood opportunity were obtained from the 2015 Childhood Opportunity Index 2.0 (Acevedo-Garcia et al., 2014). The Childhood Opportunity Index is calculated using publicly available data from a variety of sources (e.g., the American Community Survey, the Department of Education, the Environmental Protection Agency) aggregated at the zip code level to provide nationally-normed indices of the quality of education, health and environment, and social and economic resource availability and opportunities within one's neighborhood. The Childhood Opportunity Index reflects overall neighborhood opportunity and scores range from 1 to 100, where a score of 1 reflects the lowest levels of opportunity and a score of 100 reflects the highest levels of opportunity.

Psychopathology: To determine whether any observed relations were at least partially independent of parent or child history of psychopathology, we assessed parents' and children's histories of major depressive disorder (MDD) and anxiety disorders with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Kaufman et al., 1997), respectively. Of the parents, 142 had a lifetime history of MDD (n=14 current) and 91 had a lifetime history of at least one DSM-IV anxiety disorder (n=58 current). Of the children, 14 had a lifetime history of MDD (n=4 current) and 28 had a lifetime history of at least one anxiety disorder (n=23 current). Of the parents with a lifetime history of a DSM-IV anxiety disorder, 31 had a lifetime history of posttraumatic stress disorder (n=8 current), 34 had lifetime social anxiety disorder (n=21 current), 24 had lifetime panic disorder (n=16 current), 16 had lifetime generalized anxiety disorder (n=13 current), 10 had lifetime agoraphobia (n=9 current), and 7 had lifetime obsessive-compulsive disorder (n=5 current). Of the children with a lifetime history of an anxiety disorder, 2 had a lifetime history of posttraumatic stress disorder (n=0 current), 8 had lifetime social anxiety disorder (n=8 current), 2 had lifetime panic disorder (n=2 current), 6 had lifetime generalized anxiety disorder (n=6 current), 1 had lifetime agoraphobia (n=1 current), and 3 had lifetime obsessive-compulsive disorder (n=2 current). The lifetime prevalence of MDD

and anxiety disorders in children and the lifetime prevalence of anxiety in parents was comparable to national rates (Costello et al., 2003; Kessler et al., 2012). However, the lifetime prevalence of MDD for parents in this sample was notably higher than national prevalence rates (51% versus 21%; Kessler et al., 2012), perhaps due to the relatively low income of families in this sample (Galea et al., 2007; Ridley et al., 2020). A subset of 20 SCID-I and 20 K-SADS-PL interviews from this project were coded by a second interviewer, and kappa coefficients for lifetime diagnoses of MDD in parents (κ=1.00) and children (κ=1.00) as well as lifetime diagnoses of anxiety disorder in parents (κ=0.86) and children (κ=1.00) were good.

Transparency and Openness

This study was not preregistered. Data from this project is available from the first author upon reasonable request. Data from this project is not able to be posted to an online repository as not all participants gave consent for their data to be shared. All syntax and raw output for statistical analyses are presented in the Supplementary Materials. We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study.

Analytic Plan

A principal component analysis was conducted to index overall neighborhood adversity and reduce the number of primary analyses conducted. The principal component analysis resulted in a single factor reflecting neighborhood adversity with an eigenvalue greater than 1 (λ = 2.56) that explained 85.29% of the variance. The factor loadings for the neighborhood measures were – Neighborhood Area Deprivation Index: 0.97, Crime: 0.86, and Child Opportunity Index: −0.94.

A multiple regression was conducted in SPSS to examine the relation between children's DEP-PGS and neighborhood adversity. In these analyses, children's DEP-PGS was the predictor variable and the extracted factor for neighborhood adversity was tested as the outcome variable. The first 10 principal components of ancestry were entered as covariates to control for population stratification. Child age and sex were also included as covariates.

Next, sensitivity analyses were conducted to examine whether findings were maintained when statistically controlling for a series of covariates. Specifically, regression analyses were re-conducted as described above while also individually statistically controlling for the influence of individual-level indices of socioeconomic status (i.e., family income, family-to-neighborhood income ratio, parent education [college degree: yes versus no]), parental history of MDD, parental history of anxiety, child history of MDD, and child history of anxiety. Family-to-neighborhood income ratio was calculated as family income divided by the average income of all households within one's neighborhood (i.e., Zip Code) as indexed by the 2015 5-Year Estimate from the American Community Survey. A family-neighborhood income ratio lower than 1 reflected lower income compared to one's neighbors.

Finally, given evidence that some specific forms of neighborhood adversity are more robustly linked to youth depression risk than others (Stirling et al., 2015), we also examined

whether children's DEP-PGS uniquely predicted variance in each form of neighborhood adversity. First, mimicking the primary analyses, we examined whether children's DEP-PGS was associated with each individual form of neighborhood adversity (i.e., Area Deprivation Index, Crime, Child Opportunity Index). Next, we reconducted these analyses to see if the relation between children's DEP-PGS and each form of adversity was maintained while simultaneously adjusting for the other forms of adversity as covariates (e.g., in the model predicting Area Deprivation Index, Crime and Childhood Opportunity Index were included as covariates).

Results

Table 1 presents descriptive statistics and correlations among child sociodemographic variables and all neighborhood level indices.

Regression analyses were conducted to examine whether children's DEP-PGSs were associated with overall neighborhood-level adversity. As presented in Table 2, results indicated that the main effect of children's DEP-PGS was significant ($\beta = .22$, $p < .001$), such that higher DEP-PGSs were associated with higher neighborhood adversity factor scores (see Figure 1).

Next, we examined whether these findings were maintained when statistically controlling for the influence of family income, family-to-neighborhood income ratio, and parental education as well as parental and child lifetime history of MDD and anxiety disorders. Of note, children's DEP-PGS was positively correlated with parental history of MDD (r=.20, p=.001), parental history of anxiety (r=.13, p=.033), and child history of MDD (r=.12, p=.044). The significant main effect of DEP-PGS on neighborhood adversity was maintained even after individually statistically controlling for the influence of each of these covariates (all ps≤.001), indicating that the relations were at least partially independent of these variables. See Supplementary Table 1 for full details.

Finally, we examined whether children's DEP-PGS was uniquely associated with any specific form of neighborhood adversity. Looking first at the relations between child DEP-PGS and individual indices of neighborhood adversity, regression analyses showed that children with greater DEP-PGSs lived in neighborhoods characterized by a higher Area Deprivation Index ($\beta = .25$, $p < .001$), higher Crime Index ($\beta = .15$, $p = .013$), and lower Child Opportunity Index ($\beta = -.22$, $p < .001$) (see Supplementary Table 2 and Supplementary Figure 1). Follow-up tests examining unique relations between DEP-PGS and forms of neighborhood adversity indicated that children's DEP-PGS was uniquely associated with neighborhood Area Deprivation Index when statistically controlling for Crime and Childhood Opportunity Index ($\beta = .05$, $p = .026$). However, children's DEP-PGS was not associated with Crime or Childhood Opportunity Index when statistically adjusting for other indices of neighborhood adversity (lowest $p = .360$). See Supplementary Table 3 for full details, including variance inflation factors.

Discussion

The goal of the current study was to extend prior depression-relevant rGE research by examining whether an established GWAS-derived DEP-PGS (Als et al., 2023) is associated with elevated levels of adversity at the neighborhood-level. Consistent with our hypotheses, we found that children with a higher DEP-PGS, reflecting a greater number of genetic variants associated with depression risk, were more likely to live in neighborhoods characterized by higher adversity. These findings were maintained when statistically controlling for the influence of parent's and children's history of MDD and anxiety disorders, suggesting that the relation between youth genetic risk for depression and neighborhood-level adversity is, at least in part, independent of youth and parent internalizing psychopathology.

These findings are consistent with prior research highlighting associations between genes and environmental exposures (Jaffee & Price, 2007; Kendler & Baker, 2007; Knafo & Jaffee, 2013). Specifically, building from prior research showing that GWAS-derived DEP-PGSs are associated with elevated levels of individual-level stress exposure (e.g., peer victimization [Perret et al., 2023), stressful life events (Feurer et al., 2022; Harrison et al., 2023)), the current study extends this prior work to show that a depression-relevant rGE for children is also observed when considering neighborhood-level stress exposure. Importantly, the relation between children's DEP-PGS and neighborhood adversity was maintained when statistically controlling for the influence of multiple indices of family socioeconomic status, suggesting a unique influence of this DEP-PGS on neighborhood-level adversity that is not simply due to family socioeconomic disadvantage. The precise mechanism through which children's DEP-PGS is associated with neighborhood adversity independently of the influence of family-level socioeconomic status remains an area for future investigation (but see discussion below on passive and evocative rGEs for plausible examples). Although no studies to our knowledge have examined the relation between DEP-PGSs and neighborhood adversity in children, results are consistent with prior findings showing that adult genetic liability for depression is associated with overall neighborhood disadvantage (Hill et al., 2016). Furthermore, the observed effect size for the main effect of children's DEP-PGS on neighborhood adversity ($r_{effect\ size}$ = .22) is comparable to the observed effect in adults (r = .31).

The extension of this prior work to youth depression-relevant rGEs for neighborhood-level adversity provides further evidence that youth's DEP-PGSs may capture genetic variance associated with exposure to a wide range of stressful environments, rather than being linked to any specific form of environmental exposure. Not only were youth DEP-PGSs associated with neighborhood-level adversity, which is categorically different than individual-level stress exposures (e.g., peer victimization, stressful life events), but sensitivity analyses showed that children's DEP-PGS was associated with multiple forms of neighborhood adversity that have previously been linked with depression risk (e.g., socioeconomic disadvantage, personal crime/community safety; (Baranyi et al., 2021; Richardson et al., 2015; Stirling et al., 2015; Sui et al., 2022). Neighborhood socioeconomic disadvantage is a commonly examined form of neighborhood-level adversity, yet this multifaceted form of environmental hardship captures multiple distinct aspects of adversity including both threat

(e.g., crime) and deprivation (e.g., low resource/opportunity access; (L. W. Hyde et al., 2022). By examining multiple types of neighborhood adversity and not just socioeconomic disadvantage, the current study sought to provide a more comprehensive and nuanced understanding of how neighborhood adversity may be linked to youth depression-relevant genetic risk.

Importantly, findings from sensitivity analyses indicated that children's DEP-PGS was uniquely associated with neighborhood socioeconomic disadvantage when statistically controlling for the influence of neighborhood crime and opportunity/ resource access. In other words, results indicated that the depression-relevant rGE for neighborhood socioeconomic disadvantage was not driven by neighborhood threat or deprivation. However, given that some specific forms of neighborhood adversity are more strongly linked to youth depression risk than others (e.g., crime versus socioeconomic status; (Stirling et al., 2015), future longitudinal research should examine whether specific forms of neighborhood adversity (e.g., threat versus deprivation) uniquely mediate the relation between youth DEP-PGSs and prospective risk for depression onset in youth.

Although findings highlight an association between youth DEP-PGSs and exposure to neighborhood adversity, it is unlikely that the youth themselves actively chose the neighborhoods in which their families lived (i.e., active rGE). Rather, it is more likely that the depression-relevant rGE observed in the current study reflects either a passive or evocative rGE. Consistent with a passive rGE (Jaffee & Price, 2007; Plomin et al., 1977), children's genotypes were inherited from their parents, who also determined where the children lived. Therefore, parents' own genetic liability for depression may have contributed to them moving into (or remaining in) neighborhoods marked by higher levels of adversity, either by choice or necessity. This would have resulted in a correlation between the child's genotype (i.e., increased genetic risk for depression inherited from their parent) and their neighborhood environment (in which their parent is raising them). Alternatively, consistent with an evocative rGE (Jaffee & Price, 2007; Plomin et al., 1977), genetically-mediated traits of the child (e.g., chronic health conditions, conduct issues) may have influenced the parent's decision to live in certain neighborhoods. As illustrated, either a passive or an evocative rGE for the child would be driven by the decisions or circumstances of their parent, from whom they inherited part of their genotype, highlighting the presence of a parallel, potentially active, rGE in the parents. Future research should examine whether the form of the observed rGE for children changes over development as they obtain increasing control over their environments. For example, if children's DEP-PGSs continue to be associated with neighborhood adversity after their transition to adulthood, when they have more direct control over their environment, this could also provide evidence for a potential shift from a passive and/or evocative rGE in childhood to an active rGE in adulthood.

As hypothesized, findings from the current study provide further evidence that GWAS-derived DEP-PGSs may confer risk via environmental pathways (Avinun, 2020). Similar to prior work examining depression-relevant rGEs in youth samples (Feurer et al., 2022), children's DEP-PGS was associated with more variance in neighborhood-level adversity (up to 6.3%) than variance in their own or their parent's history of MDD (up to 4.0%). Furthermore, the relation between children's DEP-PGS and neighborhood adversity was

maintained when statistically controlling for the influence of MDD and anxiety histories in children and their parent. Altogether, findings are consistent with prior suggestions that GWASs for depression may inadvertently capture genetic variance related to a variety of stressful environments (Feurer et al., 2022). This said, the current study did not examine change in depression over time and only focused on preadolescent children, for whom the heritability of depression is low (Rice, 2010). It remains unknown whether children's DEP-PGSs continue to be more strongly associated with neighborhood adversity than direct depression risk as youth transition to adolescence and the heritability of depression (Rice, 2010) and risk of depression onset (Hankin et al., 1998) significantly increase. Furthermore, the application of adult-derived GWAS weights to generate DEP-PGSs in children may have introduced biases in our data. Therefore, replication of the current findings in older adolescent and adult samples is needed before strong conclusions can be drawn.

Though interpretations of results remain speculative pending replication (including replication in older samples), the current findings raise important questions regarding the extent to which DEP-PGS reflect risk for depression that is independent of environmental factors. If youth DEP-PGSs better capture genetic liability for exposure to adverse environments (e.g., neighborhood adversity) than direct biological risk for depression, it may be that DEP-PGSs may reflect liability for stress-relevant psychopathologies, more generally. This also calls into question whether "hypothesis-free" GWAS-derived PGSs for other stress-related forms of psychopathology (e.g., posttraumatic stress disorder [PTSD], anxiety disorders) may similarly capture genetic variance related to stress exposure, rather than, or in addition to, genetic variance that directly contributes to the disorders. Preliminary research in adults shows that anxiety PGSs are associated with stressful life events (Crouse et al., 2024), but this relation has not been observed in youth samples (Baldwin et al., 2023; Harrison et al., 2023). However, it remains unknown if rGEs for anxiety PGSs may be observed when considering broader forms of environmental exposure (e.g., neighborhood adversity, overall exposome). Future research with very large samples and multiple in-depth assessments of environment is also needed to effectively parcel out genetic liability for environmental exposures from DEP-PGSs to differentiate genetic pathways that confer risk for adversity exposure versus more environment-free risk for depression.

Although replication is needed in older samples, the existence of this replicated rGE is not altogether surprising when considering that environmental risk factors play a large role in the etiology of depression for many, as stress exposure is one of the most robust predictors of depression onset (Hammen, 2005; Kessler, 1997). Indeed, although recent, well-powered GWASs have derived PGSs associated with depression risk (Als et al., 2023; Howard et al., 2019), early attempts to derive DEP-PGSs were not successful, ostensibly due to the disorder's etiological heterogeneity and the fact that MDD is only moderately heritable (Levinson et al., 2014). As GWASs for depression have improved in recent years with increasing sample sizes, it is possible that the improved performance of these DEP-PGSs may be, at least in part, due to increased power to capture genetic liability for a variety of stressful environments, rather than just biological predisposition for depression. To confirm whether different forms of environmental stress mediate the impact of GWAS-derived DEP-PGSs on depression risk, multi-wave longitudinal research is needed in which stress exposure is assessed across multiple levels (e.g., individual and neighborhood). Again,

noting the lower heritability of depression in childhood (Rice, 2010), studies are also needed to determine whether the potential mediating role of environment may change across development from childhood into adulthood.

It is important to frame these results within the context of strengths and limitations of the current study. One of the major strengths of the current study is the utilization of a validated and established DEP-PGS that is associated with depression risk across development (Als et al., 2023; Grimes et al., 2024). Other strengths include the utilization of objective, geocoded indices of neighborhood adversity and the examination of multiple indices of neighborhood adversity and opportunity. However, there are also some limitations that are important to acknowledge. First, the current sample was restricted to children of European ancestry to match the sample of the original GWAS. Therefore, the findings cannot be generalized to youth of other ancestries. This is a particularly significant limitation, as individuals belonging to marginalized racial and ethnic groups are disproportionately exposed to higher levels of neighborhood adversity (Riley, 2018), and the relation between indices of neighborhood adversity and depression risk may differ across racial/ethnic groups (Alegría et al., 2014). As GWASs continue to expand to include participants of multiple ancestries, research will be needed to examine if the current findings replicate in diverse samples. Second, it is important to note that children's neighborhoods were defined based on their current address at the time of study enrollment, but it is unknown how long children had lived at these addresses, if their current neighborhoods were similar to other neighborhoods they may have lived in earlier in childhood, or how much time they spend within their neighborhoods. Third, there is a lack of consensus regarding the geospatial demarcation of neighborhoods, particularly outside of urban settings (de Marco & de Marco, 2010), and it is possible that census-derived geospatial boundaries may serve as better neighborhood boundaries for participants living in suburban settings, whereas zip codes may better define neighborhoods for participants living in more rural settings where the population is more sparse and spread out. Although this topic requires further evaluation, this was outside the scope of the current study. Fourth, the sample was relatively limited in size by genetic research standards, particularly when considering that observed effect sizes for the relation between DEP-PGS and depression in both adult and youth samples are small (Grimes et al., 2024; Howard et al., 2019; Kwong et al., 2021; Perret et al., 2023). However, if DEP-PGS has a larger effect on environmental adversity than on depression phenotypes, this may explain why we were able to detect a robust rGE, despite the modest sample size. Findings should be replicated in larger samples that span larger geographic areas to capture greater variability in neighborhood characteristics (e.g., the Adolescent Brain and Cognitive Development Study; Barch et al., 2018). Fifth, future studies should include genetic information from parents and siblings to permit disentanglement of direct and indirect genetic effects on neighborhood environment. Finally, the lifetime prevalence of parental MDD was notably high in the current sample. However, this is not altogether unexpected, given that participants were recruited from a relatively low-income area (i.e., median family income=$40,000-$45,000, average neighborhood ADI=70.20). However, results should remain tentative pending replication in other samples that may be more representative in terms of MDD prevalence and income distribution.

In summary, the current study extends prior research by showing that a GWAS-derived DEP-PGS is associated with neighborhood-level adversity. These findings contribute to a burgeoning body of research highlighting associations between genes and environmental exposures and provide further evidence that DEP-PGSs may inadvertently capture genetic variance associated with stress exposure and adversity, rather than direct risk for depression itself. Finally, as the current findings suggest that previously observed rGEs for DEP-PGSs also extend to neighborhood-level adversity, it is important for future longitudinal studies to formally evaluate whether stress exposure at the individual- and neighborhood-level mediates the impact of DEP-PGSs on prospective risk for depression onset in youth. Furthermore, given evidence that DEP-PGSs also interact with stress exposure to predict depression (Fang et al., 2020), these future studies should also test if stress exposure simultaneously moderates the relation between children's DEP-PGS and future depression risk within a three-variable system (Goldstein et al., 2023). If future studies show that neighborhood-level adversity both mediates and moderates the relation between children's DEP-PGS and prospective risk for depression, findings have critical implications for the development of preventative interventions that can be widely implemented at the community-level to mitigate risk for depression onset in youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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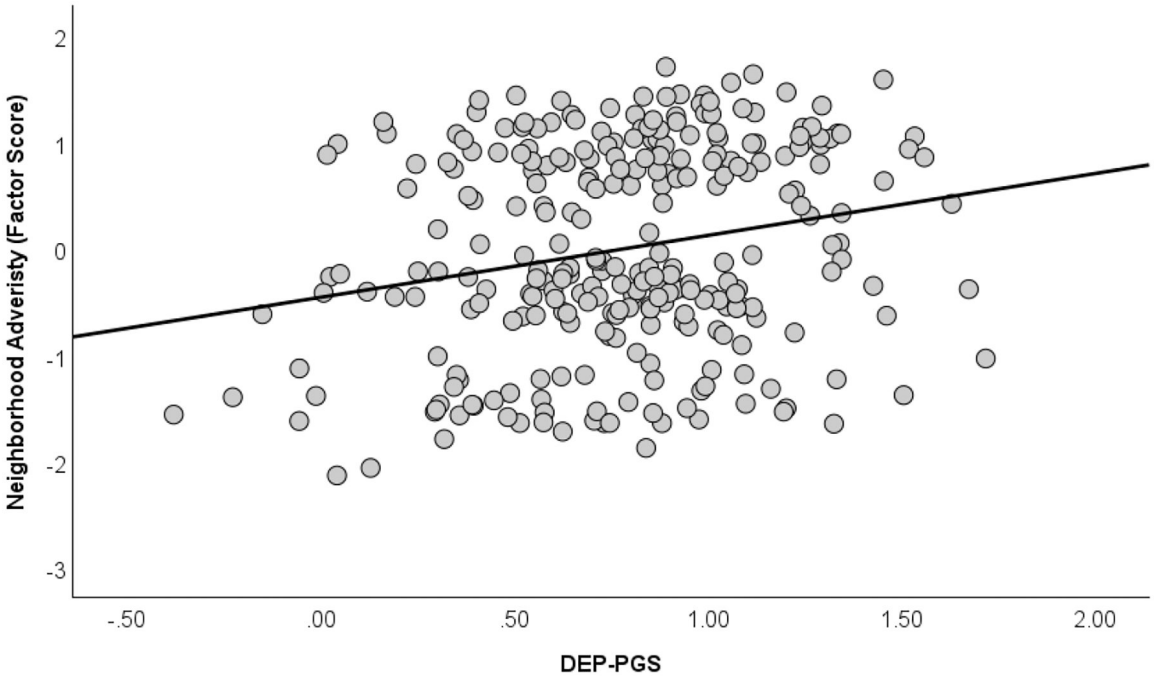

Figure 1.

Scatterplot of regression analyses depicting the main effect of children's depression-relevant polygenic score (DEP-PGS) on neighborhood adversity (factor score), statistically adjusting for the first 10 principal components of ancestry, child age, and child sex.

Table 1

Descriptive Statistics and Correlations for Sociodemographic and Neighborhood Variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Child Age	-								
2. Child Sex (% Female)	−.04 [−.16, .08] *p*=.510	-							
3. Family Income (median)	.002 [−.12, .12] *p*=.975	.071 [−.05, .19] *p*=.236	-						
4. Family-to-Neighborhood Income Ratio	.011 [−.11, .13] *p*=.859	.049 [−.07, .17] *p*=.419	.972 [.97, .98] *p*<.001	-					
5. Parent Education (% College Degree)	−.120 [−.23, −.002] *p*=.046	.031 [−.09, .15] *p*=.608	.481 [.39, 57] *p*<.001	.461 [.36, .55] *p*<.001	-				
6. Area Deprivation Index	.062 [−.06, .18] *p*=.302	−.121 [−.24, −.003] *p*=.044	−.145 [−.26, −.03] *p*=.016	.05 [−.07, .17] *p*=.407	−.115 [−.23, .002] *p*=.055	-			
7. Crime Index	.052 [−.07, .17] *p*=.392	−.082 [−.20, .04] *p*=.174	−.104 [−.22, .01] *p*=.084	.065 [−.05, .18] *p*=.278	−.047 [−.16, .07] *p*=.434	.754 [.70, .80] *p* < .001	-		
8. Child Opportunity Index	−.026 [−.14, .09] *p*=.670	.084 [−.03, .20] *p*=.164	.097 [−.02, .21] *p*=.106	−.095 [−.21, .02] *p*=.115	.101 [−.02, .22] *p*=.093	−.916 [−.93, −.90] *p* < .001	−.660 [−.72, −.59] *p* < .001	-	
9. Neighborhood Adversity Factor	.050 [−.07, .17] *p*=.403	−.104 [−.22, .01] *p*=.084	−.125 [−.24, −.01] *p*=.037	.076 [−.04, .19] *p*=.210	−.096 [−.21, .02] *p*=.109	.968 [.96, .98] *p* < .001	.864 [.83, .89] *p* < .001	−.935 [−.95, −.92] *p* < .001	-
Mean (*SD*) or Median	9.46 (1.45)	45.3%	$40,000-$45,000	0.85 (0.54)	34.9%	70.20 (10.14)	69.89 (33.28)	47.29 (23.83)	0.00 (1.00)
Range	7.05 – 11.99	-	≤$5,000 to >$115,000	0.06 – 2.40	-	53.34 – 83.66	13 – 143	17 – 88	−1.56 – 1.31

Note. 95% confidence intervals are indicated in brackets.

Table 2

Primary Regression Analysis Examining the Main Effect of Child DEP-PGS on Neighborhood Adversity (Factor Score)

	B	SE	95% CI		*p*
			LL	UL	
PC 1	13.04	13.63	−13.78	39.87	.339
PC 2	−9.13	12.30	−33.34	15.09	.459
PC 3	6.36	11.95	−17.17	29.89	.595
PC 4	−7.60	12.76	−32.73	17.52	.552
PC 5	23.19	13.28	−2.95	49.33	.082
PC 6	9.08	5.52	−1.79	19.96	.101
PC 7	−40.42	16.79	−73.49	−7.36	.017
PC 8	−1.98	15.85	−33.19	29.22	.901
PC 9	−1.11	12.42	−25.56	23.34	.929
PC 10	2.16	2.56	−2.89	7.20	.401
Child Age	0.05	0.04	−0.03	0.13	.190
Child Sex	−0.19	0.12	−0.43	0.05	.113
Child DEP-PGS	0.61	0.16	0.29	0.94	<.001

Note. PC = principal components for ancestry. DEP-PGS = depression-relevant polygenic score.