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Genotypic and Socioeconomic Risks for Depressive Symptoms in Two U.S. Cohorts Spanning Early to Older Adulthood

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The developmental pathways linking genetic risk for depression and depressive symptoms in adulthood remain poorly understood. Using data from the National Longitudinal Study of Adolescent Health ($N = 5,690$), we found that the association between genetic risk for depressive symptoms and increases in depressive symptoms from early adolescence to adulthood was partially mediated by four socioeconomic resource variables assessed in adulthood: educational attainment, total assets, debt, and access to health insurance. In a preregistered and confirmatory replication using data from the Wisconsin Longitudinal Study ($N = 8,964$), the genetic risk for depression symptoms change across late midlife was again partially mediated by the four socioeconomic resource variables. Using within-family, sibling-difference analyses, however, we found no evidence in support of direct genetic effects on the putative environmental mediators. The results highlight the need to explore between- and within-family model specifications for a more complete understanding of gene-environment pathways to psychiatric disease.

General Scientific Summary

This study found that genetic differences linked to depression may influence how people experience social and economic challenges, like debt or educational opportunities, which in turn may affect changes in their mental health over time. By comparing siblings, the research also tested whether these genetic effects are likely to cause changes in people's environments or are instead shaped by broader family or social patterns.

Keywords: depressive symptoms, genetics, polygenic risk, social determinants of health, sibling-difference models

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submission (<https://osf.io/m479x/>; Sbarra, 2025). Access to Add Health genetic data operates under a restricted use contract and is not available for public sharing (<https://addhealth.cpc.unc.edu/data/#restricted-use>). Interested parties who have access to the data can reproduce the Add Health analyses reported here. The Wisconsin Longitudinal Study data are publicly available, and the data used in this analysis are included as the additional online materials on the Open Science Framework with our statistical code.

David A. Sbarra served as lead for conceptualization, data curation, formal analysis, software, visualization, writing—original draft, and writing—review and editing. Sam Trejo served in a supporting role for conceptualization, formal analysis, writing—original draft, and writing—review and editing. K. Paige Harden served in a supporting role for conceptualization, formal analysis, methodology, writing—original draft, and writing—review and editing. Jeffrey C. Oliver served in a supporting role for conceptualization, formal analysis, methodology, and writing—review and editing. Yann C. Klimentidis served in a supporting role for conceptualization, formal analysis, methodology, writing—original draft, and writing—review and editing.

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What doesn't kill you can leave you limping for the rest of your days. What doesn't kill you can make you scared to leave your house, or even your bedroom, and have you trembling, or mumbling incoherently, or leaning with your head on a window pane, wishing you could return to the time before the thing that didn't kill you. (Haig, 2016, p. 125)

In his searing portrait of depression, the writer Haig (2016) details years of living with the pernicious illness and its total grip on his persona. When you are depressed, it can be impossible to work or even to think clearly, and these experiences often foreclose important social and economic opportunities; loss of these opportunities, in turn, can be depressogenic. Depression and high levels of depressive symptoms are unfortunately common and associated with considerable emotional suffering (Lim et al., 2018). Globally, the past-year prevalence of depressive disorders stands at roughly 280 million people (GBD 2019 Mental Disorders Collaborators, 2022), and depressive illness is the leading cause of years lost to disability, which is an international marker of disease burden that characterizes the number of years people live with a physical or mental disability (Ferrari et al., 2013). Depression is highly comorbid with other psychiatric conditions, especially anxiety and substance use disorders (Groen et al., 2020), and is associated with elevated risk for a range of negative physical health outcomes (Moussavi et al., 2007). High levels of symptoms are also burdensome and serve as an independent mark of risk for subsequent major depressive disorder (Horwath et al., 1994; Musliner et al., 2016).

In terms of etiology, the genetic contribution to risk for depression and depressive symptoms has been studied extensively (Flint, 2023). The heritability of depression is roughly 30% (Kendler et al., 2006), and the advent of molecular genetic techniques is yielding an increasing list of genome-wide association studies (GWAS) of depression (Flint, 2023; Mitchell et al., 2021). For many health-related and behavioral phenotypes, including depression and depressive symptoms, GWAS have led to the emergence of polygenic risk scores, otherwise known as polygenic indices (PGIs), which are composite scores representing the overall level of genetic risk of a given individual for a given phenotype (Lewis & Vassos, 2020).¹ The promise of PGIs rests in their ability to summarize the contributions of multiple genetic variants in a single index that captures the greatest detectable portion of genetic influences on the trait (Belsky & Harden, 2019; Chabris et al., 2015; Harden & Koellinger, 2020). While PGIs may more accurately characterize the genetic basis of complex traits than previous methods that relied on studying the actions of single candidate gene variants, their effect sizes remain modest (Owen & Williams, 2021). The PGIs for depression, for example, account for roughly 2% of variation in the observable phenotypes (Mistry et al., 2018), despite the fact that the heritability of depression as estimated from twin and family studies is much higher.

Depression From a Bioecological Perspective: The Important Role of Gene–Environment Correlation (*r*GE)

Although replicable genetic associations with depression are now well established (Mitchell et al., 2021), the pathways from measured genetic risk to later symptomology are poorly understood. In the current report, we use a PGI for depressive symptoms in two large data sets to predict change in depressive symptoms over 10 years. Our primary goal is to explore the ways in which the genetic risk for depression may operate in tandem with four measures of socioeconomic resources—wealth, debt, educational attainment, and the

availability of health insurance—to predict symptom changes across adulthood.

To study this issue, we draw on the bioecological model of human development (Bronfenbrenner & Ceci, 1994), which holds that the genetic propensity for specific developmental outcomes is shaped through interactions with a person's social environment. The study of *r*GE—the degree to which genotypes shape the types of environments people create or to which they are exposed (Plomin et al., 1977)—fits within this model and presents a conceptual means of studying how genetic risk for depression may be conveyed over time (Jaffee & Price, 2007; Scarr & McCartney, 1983). From this perspective, genetic risk can influence environmental exposures via behavior in one of three ways (Jaffee & Price, 2007): (a) passively, whereby aspects of a person's genotype and environment are both shaped by parents' genotypes (e.g., highly intelligent parents have intelligent children and more books in the home); (b) evocatively, in which aspects of a person's genetically influenced traits pull for specific responses from others (e.g., people with more hostile temperaments evoke angry responses from others); and (c) actively, in which genetically influenced traits shape the selection of specific environments (e.g., people who are depressed may seek to avoid social situations).

A key element of bioecological thinking and *r*GE analyses is that person–environment transactions have consequences for phenotypic development, including mental illness symptom presentation. For example, genetically influenced risk for depression may shape the extent to which people advance in their educational attainment; in turn, diminished educational attainment may foreclose employment, economic, and social opportunities that protect against depressed mood. In this article, we attempt to study the ways in which genetic risk may be associated with socioeconomic resources.² We first examine whether the socioeconomic resource variables mediate the association between genetic risk and change in symptom outcomes. We then test, in a set of preregistered and confirmatory analyses using within-family, sibling-difference models, whether the associations between the genetic risk and socioeconomic resource variables are consistent with a causal influence.

Socioeconomic Resources and Depressive Symptoms

Bioecological thinking recognizes the need to consider the ways individual experiences are shaped by the social contexts in which people live (Bronfenbrenner & Ceci, 1994; Huggard et al., 2023; Patel et al., 2018; Remes et al., 2021), including opportunities for educational and career advancement, meaningful work, the

¹ Polygenic risk score and PGI are interchangeable terms in the literature, both referring to genetic composite variables derived from GWAS. In this report, we use the term PGI throughout to be consistent with language used by the Polygenic Index Repository of the Social Science Genetic Association Consortium (SSGAC) in calculating the PGI scores used in this report (see Becker et al., 2021).

² As noted by Jaffee and Price (2007), the ability to represent or study *r*GE depends in large part on measurement. We do not typically measure specific environmental exposures but can more often (and perhaps easily) assess the outcomes of specific exposures. For example, if the genetic risk for depression forecloses educational opportunities, the variable we often have access to is not the environment of “diminished educational opportunities” but instead the outcome of those experiences, which is educational attainment. In essence, we are often in the situation of studying proxies for the environmental exposures of interest.

accumulation of financial assets, and the availability of social safety systems (e.g., health insurance). Accordingly, the *rGE* framework guiding our analyses holds that people at high genetic risk for depression may have social opportunities foreclosed (e.g., by missing school or being forced to drop out of college; having difficulty with consistent work, which affects future earnings) or experience particular social/financial hardships by virtue of these foreclosures (e.g., accumulated debt and loss of health insurance), which in turn, may be depressogenic.

Ample research suggests these socioeconomic resource variables are associated with depressive symptoms (Remes et al., 2021). For example, in a detailed study of British undergraduate students, increased financial strain predicted worsening of depression over time, and depression and financial strain both predicted diminished exam performance across 2 years in school (Andrews & Wilding, 2004; Huggard et al., 2023). Financial debt and loss of financial resources are especially depressogenic (Gathergood, 2012), and some data suggest that psychological health improves as indebtedness lifts (Hojman et al., 2016). In many ways, debt is embedded under the larger construct of the absence of wealth, which refers to nonincome assets and resources a person owns or has access to, including money in savings, stocks, and home ownership (Ettman et al., 2022). Wealth is negatively correlated with depression, and several mechanisms are posited to explain the association, including the idea that a lack of wealth accumulation and depression are both associated with lower perceived social status and rank (Ettman et al., 2022). Educational attainment is also negatively associated with depressive symptoms (von dem Knesebeck et al., 2011), and cotwin analyses suggest that a college degree (relative to completing high school alone) may be protective in reducing risk for depressive symptoms (McFarland & Wagner, 2015). Finally, there is growing evidence that the availability of health insurance, especially mental health insurance brought about by parity legislation, is associated with improved psychological functioning (Sipe et al., 2015; Tian et al., 2012). County-level data in the United States from 1999 to 2016 indicates that the availability of health insurance is a significant and unique predictor of suicide rates (Steelesmith et al., 2019), and time-varying analyses of the state-level enactment of mental health insurance is associated with a significant reduction in suicide rates, suggesting a causal role for improved mental health coverage on improved psychological well-being (Lang, 2013).

Between- Versus Within-Family Analyses: Adding Sibling Difference Analyses to *rGE* Studies

A key challenge for *rGE* studies is to determine whether genetic risk is associated with environmental exposures in a manner that is consistent with a causal effect (Jaffee & Price, 2007). With the advent of PGI indices, a common means of studying *rGE* processes is via statistical mediation in which the genetic risk is associated with outcomes of interest via the putative environmental exposures of interest. For example, a recent study showed that genetic risk for elevated body mass index is associated with increases in depressive symptoms via early life stress (Avinun & Hariri, 2019). Other research in this area suggests the PGI for educational attainment is associated with depressive symptoms via socioeconomic status (Avinun, 2019). In addition, recent work suggests that a PGI for depression is associated with socioeconomic indicators of adversity across two community samples (Machlitt-Northen et al., 2022).

These findings are compelling, but rely entirely on between-family correlational research designs, which makes inferring causation along the $X \rightarrow M$ path of a mediational model impossible. In many respects, between-family analyses represent a business-as-usual model for psychological science.

In contrast, because genetic differences between siblings are random, within-family, sibling-difference models that specify an association between a genetic PGI index and an outcome of interest can be understood as a form of causal analysis (Belsky et al., 2018; D'Onofrio et al., 2013; Madole & Harden, 2023; Selzam et al., 2019; Trejo & Domingue, 2018; Veller et al., 2024). As a result of the process of biological recombination, a child inherits a quasirandom half of each parent's genome. Because they share the same biological parents, all DNA differences between full siblings are the result of recombination and segregation at meiosis, and are therefore unconfounded by the social and environmental factors that have become correlated with parental genetic characteristics (Brumpton et al., 2020). In the present study, we complement our preregistered between-family analyses by also conducting within-family, sibling-difference analyses. This approach allows us to investigate whether the mediators in between-family analyses do, in fact, emerge as a result of a causal process set in motion by genetic variation in risk for depression.

The Present Study

Using data from two large cohort studies—the National Longitudinal Study of Adolescent Health (Add Health) and the Wisconsin Longitudinal Study (WLS)—this article examines whether genetic risk for depressive symptoms predicts changes in depressive symptoms via four socioeconomic resource processes: educational attainment, wealth, debt, and the availability of health insurance. In a series of exploratory analyses, we established our models of interest in the Add Health data, then conducted a preregistered conceptual replication (<https://osf.io/vzshx>) of the work in the WLS. The WLS is an ideal sample for the replication effort, largely because the WLS (a) includes genetic information that can be used to score the depressive symptoms PGI developed by the Social Science Genetic Association Consortium (SSGAC; Becker et al., 2021) and (b) includes a sample of roughly 1,800 sibling pairs with data on the PGI and at least one of our outcomes of interest. At the same time, the WLS differs from Add Health in a number of important ways, especially in the timing of the assessments. In Add Health, the primary outcome of depressive symptoms was measured in early adulthood, when the participants were 24–32 years of age, and our between-family models assessed change over 12 years from adolescence into early adulthood. In the WLS, we study depressive symptom outcomes on two occasions: 1992–1993 and 2003–2004, when the participants were roughly 54 and 64 years old, respectively. The WLS replication, therefore, assesses change across a decade in midlife. The studies also differ as a function of when and how the social determinant variables were assessed. Overall, the goals of our WLS analyses were not to conduct a direct replication, but instead to (a) examine whether the broad pattern of (between-family) mediation holds in confirmatory analyses and (b) examine whether evidence exists that would be consistent with causal effects from genetic risk for depressive symptoms to the social and environmental mediator variables.

We preregistered two sets of between-family confirmatory analyses. Having established evidence for a mediational process in the

Add Health data, we hypothesized, for the WLS data, that (a) the association between the depressive symptoms PGI and changes in self-reported depressive symptoms between the 1992–1993 and the 2003–2004 assessments would be significantly different from zero, and (b) this total effect will be significantly reduced by a set of four mediating variables: educational attainment, total assets, having struggled with significant debt, and health care and health insurance difficulties. We then examined whether these effects would be consistent with a causal influence in the within-family, sibling-difference models. As outlined in the preregistration, we expected to observe evidence consistent with causal effects along the a paths in the mediational model, and that siblings with higher (within-family) genetic loading for depressive symptoms would evidence not only greater depressive symptoms, but also report lower educational attainment, lower net worth, greater experiences with significant financial loss and debt, and more health care challenges due to insurance difficulties.

Finally, in an exploratory sensitivity analysis that was not part of the preregistered plan, we examined whether associations between the genetic risk for depressive symptoms and the social determinant mediators remained significant after accounting for the educational attainment PGI. This analysis helps contextualize the findings by examining whether the associations of interest are specific to genetic risk for depressive symptoms or are better explained by the PGI for educational attainment.

Transparency and Openness

All analytic code is included with this submission (<https://osf.io/m479x/>). Access to Add Health genetic data operates under a restricted use contract and is not available for public sharing (<https://addhealth.cpc.unc.edu/data/#restricted-use>). Interested parties who have access to the data can reproduce the Add Health analyses reported here. The WLS data are publicly available, and the data used in this analysis are included as the additional online materials on the Open Science Framework (OSF) with our statistical code. We preregistered a set of confirmatory hypotheses for the conceptual replication analyses in the WLS (see <https://osf.io/vzshx>).

Method

Participants and Procedure

The National Longitudinal Study of Adolescent Health (Add Health)

The Add Health study is a longitudinal investigation of over 20,000 adolescents in the United States who were in Grades 7–12 during the 1994–1995 school year. The present study includes 5,690 participants ($n = 3,007$ female) who provided genetic material for DNA genotyping. At the first assessment, participants were an average of 16.01 years old ($SD = 1.74$ years) with a roughly equivalent distribution of about 15%–18% of the sample in each of the six grades between seventh and 12th. Although the complete Add Health sample is diverse and nationally representative, the genetic subsample is 99% White and of European-Caucasian ancestry. Add Health Wave 4 self-report data were collected between 2007 and 2009 (with 97% collected in 2008) when participants were an average of 29.02 years old ($SD = 1.74$). Thus, in the Add Health sample, we tracked symptom change across the 12 years of late

adolescence and early adulthood when participants were an average of 16–29 years of age.

The WLS

The WLS began in 1957 as a study of 10,371 high school graduates in Wisconsin, United States, and data were collected on the original respondents in 1957, 1964, 1975, 1992, 2004, and 2011. The sample is broadly representative of white, non-Hispanic, American men and women who completed at least a high school education. Data were collected from a select group of siblings, empaneled randomly, on several occasions, including 1994 and 2005. The analyses reported in this study are limited to the 1992/1994 and 2004/2005 graduate and sibling assessments, and we merged the extant phenotypic data with the available genetic data. In 2007–2008, saliva samples were collected via mail for genetic analyses, and PGI data were available for 8,964 participants ($n = 4,663$ female). At the 1992/1994 assessment, the graduates were an average of 53.25 years old ($SD = 0.65$); siblings were roughly the same age, but with a greater spread in the distribution ($M = 53.52$ years, $SD = 7.40$). At the 2004/2005 assessment, the graduates were an average of 64.6 years old ($SD = 0.71$); as with the earlier assessment, siblings were roughly the same age with a greater spread in the distribution ($M = 63.93$ years, $SD = 7.12$). The analyses in the WLS thus track depressive symptom change across slightly more than a decade in late midlife. Because the sibling-difference models rely on the family-level average for the PGI variable and the computation of within-family deviations from the family-level PGI score for each sibling, we report sibling pair analyses that include complete data from both members of a sibling dyad for a given construct; for these analyses, the total sample sizes ranged from 3,130 to 3,882.

Measures

Table 1 provides an overview and side-by-side comparisons of the measures in each of the two data sets.

Depressive Symptoms

In both samples, we assessed depressive symptoms using items from the Center for Epidemiological Studies of Depression (CESD) scale (Andresen et al., 1994; Radloff, 1977), which is widely used to assess depressive symptoms. The CESD question stems ask participants about experiencing specific depressive symptoms over the last 7 days on a 4-point (0–3) scale from *never or rarely to most of the time or all of the time*.

In the Add Health data, the use of specific CESD items varied across time. To address inconsistencies in measurement, we adopted a higher order confirmatory factor analytic approach that models depressive symptomatology as a multidimensional construct (see Widaman et al., 2013). We began by mapping all the available CESD items at Wave 1 (19 items) and Wave 4 (10 items), and we used all these items in the confirmatory factor analysis. Specifically, we specified a two-factor model at each wave: one factor reflecting negative affect/somatic complaints (e.g., “felt depressed” and “felt tired”) and the other reflecting positive affect (reverse-coded; e.g., “enjoyed life” and “felt happy”). These first-order factors were specified to load onto a second-order latent depression factor at each wave. We then computed the higher order depression composites

Table 1
Side-by-Side Comparison of Measures in the Add Health and WLS Studies

Construct	National Longitudinal Survey of Adolescent Health (Add Health)	WLS
Primary outcome		
Depressive symptoms	CESD scale.	CESD scale.
PGI	Multitrait PGI for depressive symptoms, developed by the SSGAC.	Multitrait PGI for depressive symptoms, developed by the SSGAC.
Net worth	Single item: “What is your best estimate of the total value of your assets and the assets of everyone who lives in your household and contributes to the household budget? Include all assets, such as bank accounts, retirement plans and stocks. Do not include equity in your home.”	Net worth composite as a summary of participants’ home equity, business equity, other real estate equity, vehicle equity, total value of participants’ and spouses’ total retirement balances, total value of participants’ and spouses’ checking and saving accounts, total value of participants’ and spouses’ CDs and Government Saving Bonds, and total value of participants’ and spouses’ other stocks and assets.
Educational attainment	Single item self-reported as the highest level of education achieved to date at the 2004 assessment.	Educational attainment was assessed on an ordinal scale in which participants high school graduates (all WLS participants) indicated if they had additional educational experiences, including the number of years in college as well as graduate study (if applicable).
Debt	Regression-based weighted composite of two items assessing total debt burden: “Now, think about your debts besides any mortgage on your home. How much do you and others in your household owe altogether? Include all debts, including all types of loans, credit card debt, medical or legal bills, etc.” and “Suppose you and others in your household were to sell all of your major possessions (including your home), turn all of your investments and other assets into cash, and pay off all of your debts. Would you have something left over, break even, or be in debt?”	Single item: “Have you ever gone deeply into debt or suffered substantial financial loss?” The response choice was binary (yes/no).
Insurance and health care difficulties	Single item evaluated health insurance availability asking participants how many months they have had health insurance over the last year. The variable is operationalized as the number of months of health insurance in the past 12 months.	Total score summary composite of nine binary items assessing health care and insurance difficulties over the past 12 months—for example, “In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because your insurance company wouldn’t approve, cover or pay for care?”; “In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because your insurance required a referral but you couldn’t get one?”

Note. WL = Wisconsin Longitudinal; WLS = Wisconsin Longitudinal Study; CESD = Center for Epidemiological Studies of Depression; PGI = Polygenic Risk Inventory; SSGAC = Social Science Genetic Association Consortium; CD = certificate of deposit.

at Waves 1 and 4, and we used these composites in the analyses.³ In the WLS, depressive symptoms were assessed using the full 20-item CESD scale at both the 1992 and 2004 assessments, and the scales demonstrated strong internal consistency (α at 1992 assessment = .71 and α at 2004 assessment = .88).

Polygenic Risk Inventory (PGI)

We used a multitrait PGI for depressive symptoms, developed by the SSGAC, and the details of the PGI calculations are detailed in a recent report by Becker and colleagues (Becker et al., 2021; Turley et al., 2018). This PGI was derived using multitrait analysis of GWAS, a method that improves detection of trait-specific genetic signals by leveraging genetic correlations across multiple related phenotypes. Unlike univariate GWAS, multitrait analysis of GWAS integrates association information from traits such as neuroticism, subjective well-being, and educational attainment to augment the power and precision of the depressive symptoms PGI. While this PGI is not a “pure” biological indicator of depression risk, it reflects

the broad polygenic liability underlying depressive symptoms, including pleiotropic effects across traits such as neuroticism, subjective well-being, and educational attainment (as well as potential confounding by population stratification, assortative mating, and indirect genetic effects). This broader polygenic architecture is conceptually aligned with our *r*GE framework, which posits that genetic risk may influence depression indirectly via genetically correlated environmental exposures. Furthermore, this PGI has demonstrated higher predictive validity than univariate scores and is widely recommended for maximizing statistical power in population-based analyses (Belsky & Harden, 2019). Thus, its use enhances our ability to detect polygenic associations relevant to both direct and indirect pathways of risk. Higher values on the depressive symptoms PGI reflect greater genetic risk for depressive symptoms. The same weights and variant inclusion criteria were applied to both the Add Health and WLS

³ The full details of the CESD factor analysis are available as the additional online materials on the OSF materials (<https://osf.io/m479x/>).

samples. Although minor discrepancies in single nucleotide polymorphism overlap may result from differences in genotyping or imputation quality, the PGIs are functionally equivalent and represent the same polygenic signal across both data sets. For ease of data interpretation, we standardize the PGI variable based on the Add Health and WLS distributions (i.e., completed a within-sample standardization). To account for population stratification (i.e., allele frequency differences between exposed and unexposed populations due to ancestry differences), we also controlled for the full set of 20 principal components (PC) derived by the SSGAC when computing the PGIs in both Add Health and the WLS (Price et al., 2006). In both samples, the PCs were created by estimating single nucleotide polymorphism loadings from unrelated individuals, and then PC scores were computed for all individuals in each sample. Finally, in a sensitivity analysis, we also used the educational attainment PGI in the WLS, which characterizes the genetic basis of greater educational attainment (for a detailed description of this PGI, see Belsky et al., 2018).

Net Worth

In Add Health, we used a single item to assess participants' net worth, which asked, "What is your best estimate of the total value of your assets and the assets of everyone who lives in your household and contributes to the household budget? Include all assets, such as bank accounts, retirement plans and stocks. Do not include equity in your home." Participants responded to this item on a 9-point scale in bins ranging from 1 = *less than \$5,000* to 9 = *\$1,000,000 or more*. The average score on this net worth variable was 3.78 ($SD = 1.93$), which is slightly below \$25,000 or more total net worth. In the WLS, we created a net worth composite as a summary of participants' home equity, business equity, other real estate equity, vehicle equity, total value of participants' and spouses' total retirement balances, total value of participants' and spouses' checking and saving accounts, total value of participants' and spouses' certificate of deposits and Government Saving Bonds, and total value of participants' and spouses' other stocks and assets. The mean net worth for participants in the WLS at the 2004 assessment was \$827,192 ($SD = \$1,339,296$, $Mdn = 445,000$). We log-transformed the WLS net worth variable for the analyses.

Educational Attainment

In the Add Health study, we used a single item to assess participants' educational attainment, which was self-reported as the highest level of education achieved to date at the 2004 assessment (ranging from "8th grade or less" to "completed post baccalaureate professional education (e.g., law school, med school, and nurse).") Seventeen percent of the sample reported completing high school, 34% reported completing "some college" and an additional 20% reported completing a bachelor's or equivalent degree. Since the WLS recruited high school graduates, these target participants completed at least high school; some sibling participants did not. In the WLS sample, educational attainment was assessed on an ordinal scale, with the majority of participants (52%) completing at least 1 year of college and 14.5% completing a bachelor's degree.

Debt

In the Add Health Study, we quantified total debt using a regression-based weighting that combined two debt-related questions assessed at

Wave 4, including the items, "Now, think about your debts besides any mortgage on your home. How much do you and others in your household owe altogether? Include all debts, including all types of loans, credit card debt, medical or legal bills, etc." and, "Suppose you and others in your household were to sell all of your major possessions (including your home), turn all of your investments and other assets into cash, and pay off all of your debts. Would you have something left over, break even, or be in debt?" In the regression-based weighting of the ordinal variable, the total debt variable was regressed on the "left over/break even/still debt" variable. Using the unstandardized parameters in this model, we computed a weighted ordinal variable, then combined this weighted composite with a standardized variable of the total debt score. Twenty percent of the Add Health sample reported that they would be in debt if they sold their major possessions. On the composite variable, higher scores reflect higher debt load. We assessed the extent to which respondents in the WLS experienced debt using a single item assessed at 2004/2005: "Have you ever gone deeply into debt or suffered substantial financial loss?" The response choice was binary (yes/no). Sixteen percent of the full WLS sample reported that they had experienced substantial financial loss.

Insurance and Health Care Difficulties

In the Add Health study, we evaluated health insurance availability with a single item, asking participants how many months they have had health insurance over the last year. Sixty-nine percent of participants had health insurance for all of the prior 12 months, 15% reported 0 months of health insurance in the past year ($M = 9.25$, $SD = 4.62$). The 2004/2005 WLS assessment included a series of items asking about difficulties obtaining health care or not being able to afford health care. From this assessment, we created a nine-item "Insurance and Healthcare Difficulties" summary score, including the following items, all of which were assessed on a yes/no (1/0) binary scale: (a) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because you could not afford medical care?"; (b) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because your insurance company would not approve, cover, or pay for care?"; (c) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because your insurance required a referral but you could not get one?"; (d) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because your doctor refused to accept your insurance plan?"; (e) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because medical care was too far away?"; (f) "Did your insurance company not approve, cover, or pay for care because of a change in your health insurance?"; (g) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because you could not get there when the doctor's office was open?"; (h) "In the past 12 months, did you experience difficulty or delay in obtaining any type of health care, or not receive health care you thought you needed because you did not know where to go to get care?"; and (i) "In the past 12 months, did you experience difficulty or delay

in obtaining any type of health care, or not receive health care you thought you needed because it took too long to get an appointment?”. We evaluated the scale reliability using a latent variable modeling approach for binary data (Raykov et al., 2010), based on a fitted two-parameter logistic item response model. The resulting composite reliability coefficient was 0.84, indicating strong internal consistency among the nine dichotomous indicators. The resulting summary score suggested these difficulties were relatively uncommon in the WLS sample (family level $M = 0.19$, $SD = 0.62$, range = 0–8).

Covariates

Given established gender differences in depressive symptomology (Parker & Brotchie, 2010), we included gender as a covariate in all analyses of depressive symptom change. Given the strong genetic correlation between depressive symptoms and measures of personality and other indicators of well-being (Baselmans et al., 2019), we have concerns about overcontrolling our statistical models. Thus, we included individual difference variables in a series of sensitivity analyses. In the Add Health sample, we included a set of six trait-level covariates, including optimism (assessed via agreement with four items, including feeling optimistic about the future, expecting “things to go my way,” expecting more good things to happen than bad things, and counting on good things to happen), and five dimensions of personality (neuroticism, extraversion, openness, conscientiousness, and agreeableness), which were assessed using the 20-item short form of the International Personality Item Pool (IPIP) five-factor model. The Mini-IPIP has a strong five-factor structure and demonstrates acceptable reliability in the Add Health Sample (Baldasaro et al., 2013). In the WLS, personality was assessed using the 29-item version of the Big-Five Inventory (John et al., 1991), and participants were asked the extent to which they agreed about descriptive statements on a 6-point scale from strongly disagree to agree strongly. We used the composite scales of neuroticism, conscientiousness, extraversion, openness, and agreeableness. The internal consistencies of these scales are reported in the literature as ranging from Cronbach $\alpha = .61$ –.77 (Stephan et al., 2018). Purpose in life was assessed using a six-item version of Ryff’s Purpose in Life Scale (Ryff, 1989), which uses descriptive statements on a 7-point scale from *strongly disagree* to *strongly agree*. Higher scores reflect greater self-reported purpose in life. Self-report optimism was assessed with the six-item Revised Life Orientation Test (Scheier et al., 1994), which is a widely used measure of optimism. In the WLS, Revised Life Orientation Test items were assessed on a 4-point scale from *strongly agree* to *strongly disagree*. Higher scores reflect greater self-reported optimism.

Finally, in our analyses with the Add Health data, we were able to account for geographical cost-of-living differences, which may confound the association between our mediators and depressive symptoms. In particular, we created a composite score for each participant based on the U.S. Census Bureau’s American Community Survey tract-level information by standardizing four variables: (a) median household income in the past 12 months within the tract, (b) median family income in the past 12 months within the tract, (c) median value for specified owner-occupied units, and (d) median contract rent for renter-occupied units paying cash rent. This composite was highly internally consistent ($\alpha = .97$).

Data Analysis

The data were analyzed using R for statistical computing (R Core Team, 2013). Our analyses using the Add Health data were largely exploratory, but we preregistered a set of confirmatory hypotheses for the WLS analysis (see <https://osf.io/vzshx>). We conducted the between-family analyses by specifying a series of multiple mediator path models using the lavaan package (Rosseel, 2012). In all of the analyses, the primary outcome was depressive symptoms measured at the final assessment, accounting for depressive symptoms at an earlier assessment in both Add Health and the WLS. We used the depressive symptom PGI as the primary predictor variable, then assessed the indirect effects of PGI scores on depressive symptom change via the four social determinant mediators: educational attainment, net worth, debt, and health insurance difficulties. A basic schematic of the mediational path model is outlined in Figure 1. Because the Add Health data included genetically identical monozygotic twins, we limited the analyses to full siblings and dizygotic pairs; given the large sample size, we randomly selected one participant from each family, then bootstrapped the standard errors on the indirect effects using the lavaan package. In the WLS analyses, debt was operationalized as a bivariate variable, which precluded bootstrapping the standard errors of the indirect effect; instead, we conducted a resampling strategy by randomly selecting one sibling pair from each WLS family, running the mediational analyses, then outputting the standard errors. We completed this analysis 1,000 times and used the average standard effort to calculate the confidence intervals (CIs) on the indirect effects. All code from our analyses is included as the additional online materials on the OSF (<https://osf.io/m479x/>).

The within-family, sibling-difference models can be specified in multiple ways. We followed the approach outlined in Trejo and Domingue (2018). For all outcomes and the key depressive symptoms PGI predictor, we created family-level average scores, then calculated each participant’s and sibling’s deviation from the family-level average score. Given the mirrored nature of the sibling differences, a standard error correction is needed that applies a within transformation. In R, the fixed effect package (Berge, 2018) applies this correction, and the final mixed model predicted sibling differences in the outcomes of interest as a function of sibling differences in the depressive symptoms PGI.

Results

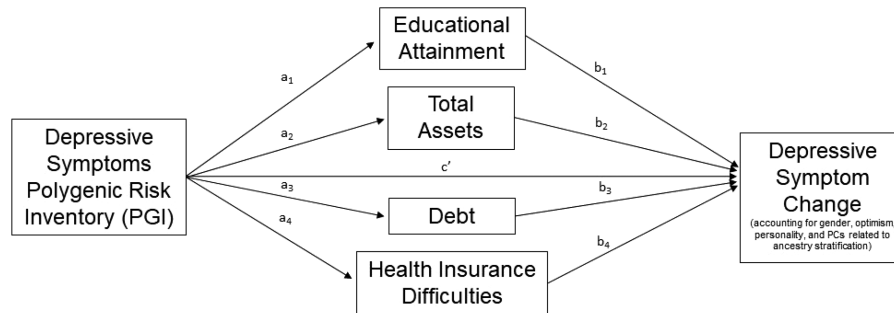
Table 2 illustrates the zero-order correlations among the key study variables in the Add Health and WLS data. Given the large sample sizes, almost all of the correlations were significantly different from zero. In both studies, the depressive symptoms PGI was modestly positively correlated with self-report depressive symptoms at both assessments, and in the expected direction with the socioeconomic variables (e.g., greater genetic risk for depressive symptoms associated with lower educational attainment in both samples).

Exploratory Analyses in Add Health

We followed a series of model-building steps to examine changes in depressive symptoms across early adulthood. As illustrated in Table 3, Model 1 examined the total effect of the depressive symptoms PGI on depressive symptoms at Wave 4. (For all analyses with Add Health data, we used the bootstrap option in lavaan to estimate the standard errors via 1,000 resamples.) This model included the

Figure 1

Path Model Representation of the Multiple Mediator Model Guiding the Between-Family Analyses



Note. In both Add Health and the WLS samples, we conducted residualized regression analyses to examine the extent to which the PGI for depressive symptoms was associated with changes in self-reported depressive symptom over the follow-up period. Our change models also accounted for gender and the genetic PCs. PGI = Polygenic Risk Inventory; a paths = associations from the PGI to the socioeconomic mediators; b paths = associations from the mediators to depressive symptom change; c' = direct effect, the association between the PGI and change in depressive symptoms with the mediators in the model; WLS = Wisconsin Longitudinal Study; PC = principal component.

social determinant mediator variables and explained 9.3% of the variance in Wave 4 (W4) depressive symptoms. In Model 1, all four of the indirect effects were significantly different from zero. Together, the four indirect effects accounted for 32.6% of the total effect (of the PGI on depressive symptom change). Model 1 is fully saturated; therefore, we do not report model fit statistics. In Model 2 (Table 1), we added gender and depressive symptoms at Wave 1, as well as the 20 genetic PC variables. Model 2 accounts for gender, depressive symptoms at Wave 1, the cost of living composite, and the genetic PCs; this full symptom change model explained 22.6% of the variance in W4 depressive symptoms. As with Model 1, all indirect effects were significant and in the expected direction; the indirect effects explained 32.4% of the total effect.

In Model 2, controlling for gender, depressive symptoms at Wave 1, the cost of living composite, and the 20 genetic PCs, genetic risk for depressive symptoms was significantly associated with less total assets, greater debt, lower educational attainment, and fewer months of health insurance, and these variables, in turn, were associated with greater increases in depressive symptoms across the 14-year assessment period. We note that although the total and indirect effects were significant, the effects were small (standardized estimates for the total and indirect effect, $\beta = .12$ and $\beta = .039$, respectively). In a final sensitivity analysis, we examined whether the indirect effects would remain different from zero when accounting for trait optimism and personality variables.

The goal of this analysis was to evaluate whether the social determinant variables, which we have argued represent indicators of

Table 2

Descriptive Statistics and Bivariate Correlations Among Study Variables

Construct	$M \pm SD$	1	2	3	4	5	6	7	8
Add health study ($N = 5,689$)									
1. Depression PGI	0.001 \pm 1.00	—							
2. W1 depressive symptoms	0.012 \pm .31	.12	—						
3. W4 depressive symptoms	-0.016 \pm .31	.16	.45	—					
4. Gender	53% female	.02	.14	.09	—				
5. Educational attainment	5.69 \pm 2.16	-.17	-.12	-.17	.12	—			
6. Total assets	3.80 \pm 1.92	-.11	-.12	-.18	-.06	.20	—		
7. Debt	0.975 \pm 0.50	.09	.12	.20	.03	-.02	-.41	—	
8. Health insurance in past year	9.25 \pm 4.63	-.09	-.09	-.15	.10	.30	.19	-.14	—
Wisconsin Longitudinal Study ($N = 8,964$)									
1. Depression PGI	0.00 \pm 1.00	—							
2. W1 depressive symptoms	16.84 \pm 15.83	.10	—						
3. W4 depressive symptoms	14.65 \pm 14.79	.10	.50	—					
4. Gender	47% female	.00	.07	.08	—				
5. Educational attainment	13.76 \pm 2.41	-.09	-.08	-.09	-.15	—			
6. Total assets	827,192 \pm 1,339,297.20	-.05	-.10	-.10	-.07	.24	—		
7. Debt	0.16 \pm 0.36	.04	.07	.08	-.09	.03	-.05	—	
8. Insurance and health care difficulties	0.19 \pm 0.70	.04	.09	.15	.03	-.00	-.03	.10	—

Note. In both samples, the gender variable is coded as follows: 0 = male, 1 = female. For binary variables, point-biserial correlations are reported. PGI = Polygenic Risk Inventory; W1 = Wave 1; W4 = Wave 4.

Table 3
Path Model Regression Estimates From Multiple Mediator Models in the Add Health Study

Parameter	Model 1			Model 2			Model 3		
	β	SE	95% CI	β	SE	95% CI	β	SE	95% CI
Depression PGI → W4 depressive symptoms (direct effect)	.033	0.004	[0.026, 0.042]	.025	0.004	[0.017, 0.033]	.016	0.004	[0.008, 0.024]
W1 depressive symptoms				.395	0.017	[0.361, 0.492]	.312	0.015	[0.283, 0.342]
Gender				.024	0.008	[0.040, 0.008]	.034	0.008	[0.005, 0.001]
Cost of living composite				.073	0.027	[0.022, 0.129]	.099	0.025	[0.050, 0.148]
a paths									
PGI → assets (a1)	-.206	0.027	[-0.260, -0.156]	-.213	0.029	[-0.268, -0.156]	-.212	0.029	[-0.267, -0.157]
PGI → education (a2)	-.385	0.029	[-0.443, -0.327]	-.428	0.031	[-0.488, -0.362]	-.428	0.034	[-0.498, -0.364]
PGI → debt (a3)	.051	0.007	[0.036, 0.064]	.047	0.007	[0.032, 0.062]	.034	0.012	[0.010, 0.059]
PGI → health insurance (a4)	-.395	0.065	[-0.522, -0.274]	-.451	0.067	[-0.591, -0.323]	-.442	0.070	[-0.577, -0.299]
b paths									
Assets → W4 depression (b1)	-.011	0.003	[-0.016, -0.006]	-.007	0.003	[-0.012, -0.002]	-.005	0.002	[-0.011, -0.001]
Education → W4 depression (b2)	-.018	0.002	[-0.022, -0.014]	-.013	0.002	[-0.017, -0.009]	-.005	0.002	[-0.009, -0.001]
Debt → W4 depression (b3)	.090	0.010	[0.070, 0.109]	.066	0.010	[0.046, 0.086]	.017	0.015	[-0.011, 0.046]
Health insurance → W4 depression (b4)	-.004	0.001	[-0.006, -0.002]	-.004	0.001	[-0.006, -0.002]	-.006	0.002	[-0.010, -0.003]
Indirect (ab) and total effects									
Indirect effect via assets (ab1)	.002	0.001	[0.001, 0.004]	.002	0.001	[0.001, 0.003]	.001	0.001	[0.000, 0.002]
Indirect effect via education (ab2)	.007	0.001	[0.005, 0.009]	.005	0.001	[0.004, 0.008]	.002	0.001	[0.001, 0.004]
Indirect effect via debt (ab3)	.005	0.001	[0.003, 0.006]	.003	0.001	[0.002, 0.005]	.001	0.001	[-0.000, 0.002]
Indirect effect via health insurance (ab4)	.002	0.001	[0.001, 0.003]	.002	0.001	[0.001, 0.003]	.002	0.001	[0.001, 0.003]
Total indirect effect	.016	0.001	[0.013, 0.018]	.012	0.001	[0.010, 0.015]	.005	0.001	[0.003, 0.008]
Total effect	.049	0.004	[0.041, 0.058]	.037	0.004	[0.028, 0.045]	.021	0.004	[0.012, 0.030]

Note. Model 1 = four indirect effects only; Model 2 = W1 depressive symptoms, gender cost of living composite, and four indirect effects; Model 3 = added personality variables of extraversion, openness to experiences, conscientiousness, and agreeableness, and trait-level optimism. Models 2 and 3 also contain all 20 PCs as covariates in the path model predicting Wave 4 depressive symptoms. Gender coded as 0 = *male*, 1 = *female*. CI = confidence interval; PGI = Polygenic Risk Inventory; W1 = Wave 1; W4 = Wave 4; PC = principal component.

socioenvironmental context and risk, continue to operate indirectly when we account for person-level characteristics that are correlated with depressive symptoms. At the same time, we recognize that including neuroticism in the model may be a form of overcorrection, given the high correlation between neuroticism and depressive symptoms (Kendler et al., 2019). Therefore, we account for extraversion, conscientiousness, openness to experience, agreeableness, and trait optimism, but do not include neuroticism in the model. As shown in Table 2, Model 3 explained 31.40% of the variance in Wave 4 depressive symptoms. The four indirect effects explained 50% of the total effect, but only three of the four remained significantly different from zero. In the full model, the indirect effect for total assets was no longer significant ($p = .10$).

Overall, our exploratory analyses with the Add Health data provided clear evidence for indirect effects from the depressive symptoms PGI to changes in depressive symptoms (from ages 17 to 29 years) via the four social determinant variables. In the most conservative model, the indirect effect from debt was not reliably different from zero, but the effects through low total assets, low educational attainment, and fewer months with health insurance remained significant. These effects are potentially consistent with an rGE process in which genetic risk may foreclose important opportunities that, when diminished, become depressogenic. Given these findings in the Add Health data, we conducted a preregistered conceptual replication and extension of this work. Importantly, to the extent that the same pattern of significant indirect effects emerges, we sought to examine whether these findings are consistent with a causal effect from genetic risk to any one of the putative mediator variables. We approached this causal question using a series of within-family, sibling-difference analyses.

Confirmatory Analyses: Conceptual Replication and Sibling-Differences Analyses in the WLS

Between-Family Analyses in the WLS

Using the WLS data, our preregistered analytic plan followed the same model-building strategy we used for the Add Health analyses.⁴ As shown in Table 3 (Model 1), when predicting depressive symptoms at the 2004 WLS assessment, all four of the indirect effects were significantly different from zero. This model explained 4.4% of the variance in depressive symptom outcomes, and the indirect effects accounted for 15.5% of the total effect. When including gender in the model, examining symptom change from 1994 to 2004 (Model 2), all four of the indirect effects remained significantly different from zero. Overall, this model accounted for 27% of the variance in depressive symptoms at the 2004 assessment, and the indirect effects accounted for 17% of the total effect. WLS participants evidencing greater genetic risk for depressive symptoms showed significantly greater increases in depressive symptoms across the WLS follow-up period, and a portion of this increase was attributable to reports of having gone deeply into debt (or suffering substantial financial loss), having lower net worth, having

⁴ Because we use a binary variable as a mediator, lavaan defaults to diagonally weighted least squares estimation algorithm. Therefore, we completed a bootstrapping procedure by resampling our random selection of sibling participants (one participant from each family) and running the analyses using DWLS estimation procedures. We completed this analysis 1,000 times to create distributional estimates of the model parameters. The details of this resampling procedure are included in our statistical code as the additional online materials on the OSF (<https://osf.io/m479x/>).

lower educational attainment, and having experienced health care difficulties due to health insurance.

As noted in our preregistered plan, we considered Model 3 a sensitivity analysis, largely because of the genetic overlap between depression, optimism, purpose in life, and other dimensions of personality. Table 4 (Model 3) displays the results from the analysis with these intrapsychic covariates. Overall, this model explained 38% of the variance in depression symptoms at the 2004 WLS assessment. The indirect effects through debt and insurance difficulties remained significant, but the indirect effects through educational attainment and total assets were not different from zero. In this model, indirect effects explained 8.65% of the total effect, but overall, the total indirect effect was not reliably different from zero.

Within-Family, Sibling-Difference Analyses in the WLS

In the WLS (between-family) analyses, we have robust evidence that the depression PGI is associated with changes in depressive symptoms, and, in our most conservative model, that a portion of this association is accounted for by the experiences of debt and health insurance difficulties. The next set of analyses examined a series of within-family, sibling-difference models. The results are presented in Table 5. To ease interpretation, we break down the analyses in a series of questions.

Are Sibling Differences in Genetic Risk for Depressive Symptoms Associated With (a) Self-Reported Depressive Symptoms and (b) Changes in Self-Report Depressive Symptoms in the WLS? As shown in Table 4, sibling differences in genetic risk for depressive symptoms were significantly positively associated with greater depressive symptoms in 1994 and 2004, but not with symptom change across the study period. At each time point, however, the association between genetic risk and self-reported symptoms is consistent with a causal association from genetic risk.

Are Sibling Differences in Genetic Risk for Depressive Symptoms Associated With Differences in the Socioeconomic Resource Variables? Sibling differences in genetic risk depressive symptoms were significantly associated with lower levels of both total assets and educational attainment; these effects are consistent with a causal association from genetic risk for depression and lower levels of both variables.

In a Series of Sensitivity Analyses, Are Sibling Differences in Genetic Risk for Depressive Symptoms Associated With Total Assets and Educational Attainment After Accounting for Sibling Differences in the Genetics of Educational Attainment? We conducted sensitivity analyses to determine if the genetic risk effect would persist if we also accounted for sibling differences in the genetics of educational attainment. Effectively, this analysis examines whether the associations between genetic risk for depression and both assets and educational attainments are confounded by the association of these variables with the genetics of educational attainment. For both educational attainment and total assets, accounting for the PGI for educational attainment reduced the depression genetic risk effect to zero. In both models, sibling differences in the genetics of educational attainment were reliably different from zero and in the expected direction: independent of genetic risk for depression, siblings who evidenced higher scores on the educational attainment PGI also evidenced greater educational attainment in the

WLS ($B = 0.56, SE = 0.07, 95\% CI = [0.43, 69]$)⁵ and total assets ($B = 102,967.7, SE = 41,455.5, 95\% CI [21,655.41, 184,269.90]$). The sibling-difference association between the genetic risk for depression and debt was not reliably different from zero, nor was the association between sibling differences in genetic risk for depression and health insurance difficulties.

Discussion

Across two large cohort studies, this article examined whether the genetic risk for depressive symptoms was associated with prospective changes in self-reported depressive symptoms over a decade, and whether these associations were statistically mediated by four socioeconomic resource variables: educational attainment, net worth, debt, and the availability of health insurance or health care-related insurance difficulties. In both the Add Health study (tracking depressive symptom change across a decade in early adulthood) and in the WLS (tracking depressive symptom change across a decade into early older adulthood), our between-family analyses revealed strong evidence for (a) increases in self-reported depressive symptoms across the follow-up periods as a function of genetic risk for depressive symptoms, and (b) partial mediation through the socioeconomic resource variables in all but the most conservative analyses.

Confidence in these results is bolstered by the relatively large sample sizes in Add Health and the WLS, as well as the exploratory-confirmatory sequence of our analyses; after conducting a series of exploratory analyses with the Add Health data, we preregistered a conceptual replication in the WLS. The between-family analyses, however, only reveal part of the story, and our *r*GE analyses were premised on establishing evidence for a causal influence from the genetic risk variable to any of the four putative mediator variables. To address this issue, we also preregistered a set of within-family, sibling-difference analyses, which allow for the examination of causation along the a-path of our mediational model (Selzam et al., 2019; Trejo & Domingue, 2018). These analyses revealed that the genetic risk for depressive symptoms was indeed associated with self-reported depressive symptom levels in the WLS in a manner consistent with a causal process, but we found little support that genetic risk for depression has an independent causal impact on any of the mediator variables, especially when conducting a sensitivity analysis that accounted for sibling differences in the genetics of educational attainment.

We organized our between-family hypotheses based largely on the bioecological model of human development and a growing literature suggesting that—above and beyond intrapsychic risk factors alone—socioeconomic resources may play a causal role in conveying genetic risk for depression into self-reported experiences (Huggard et al., 2023). It is easy to imagine plausible pathways for these processes to unfold. Genetic risk for depressive symptoms may shape the ability to attend school or to participate actively,

⁵ The basic educational attainment PGI to reported educational attainment effect using the WLS data was reported in Belsky et al. (2018). The model reported here accounts for sibling differences in genetic risk for depression as well, which was not part of the Belsky et al. (2018) report. We also tested whether the association between sibling differences in genetic risk for depression and self-reported depression held after accounting for the educational achievement PGI. For both assessments of depressive symptoms, accounting for PGI for educational achievement did not reduce the sibling-difference associations with the PGI for depressive symptoms to zero.

Table 4
Path Model Regression Estimates From Multiple Mediator Models in the Wisconsin Longitudinal Study

Parameter	Model 1			Model 2			Model 3		
	β	SE	95% CI	β	SE	95% CI	β	SE	95% CI
PGI → W4 depressive symptoms (direct effect)	.077	0.003	[0.056, 0.096]	.039	0.000	[0.019, 0.058]	.021	0.002	[0.004, 0.041]
W1 depressive symptoms				.395	0.017	[0.361, 0.492]	.312	0.015	[0.283, 0.342]
Gender				.024	0.008	[0.040, 0.008]	.034	0.008	[0.005, 0.001]
a paths									
PGI → assets (a1)	-.050	0.003	[-0.071, -0.030]	-.046	0.003	[-0.069, -0.024]	-.046	0.003	[-0.68, -0.025]
PGI → education (a2)	-.091	0.003	[-0.102, -0.055]	-.077	0.004	[-0.110, -0.051]	-.079	0.004	[-0.104, -0.053]
PGI → debt (a3)	.015	0.001	[0.006, 0.0237]	.016	0.001	[0.007, 0.025]	.016	0.001	[0.006, 0.026]
PGI → insurance difficulties (a4)	.034	0.003	[0.012, 0.057]	.032	0.004	[0.006, 0.057]	.028	0.003	[0.003, 0.053]
b paths									
Assets → W4 depressive symptoms (b1)	-.066	0.003	[-0.085, -0.046]	-.024	0.000	[-0.043, 0.007]	.009	0.002	[-0.007, 0.027]
Education → W4 depressive symptoms (b2)	-.066	0.003	[-0.087, -0.046]	-.045	0.000	[-0.064, -0.027]	.003	0.003	[-0.016, 0.027]
Debt → W4 depressive symptoms (b3)	.166	0.010	[0.102, 0.230]	.090	0.000	[0.036, 0.154]	.009	0.008	[0.038, 0.145]
Insurance difficulties → W4 depressive symptoms (b4)	.100	0.000	[0.070, 0.132]	.060	0.000	[0.034, 0.088]	.042	0.0003	[0.018, 0.067]
Indirect effects									
Indirect effect via assets (ab1)	.003	0.001	[0.001, 0.006]	.001	0.000	[0.000, 0.002]	-.000	0.0001	[-0.001, 0.0003]
Indirect effect via education (ab2)	.007	0.002	[0.003, 0.010]	.003	0.000	[0.001, 0.005]	-.000	0.0002	[-0.001, 0.001]
Indirect effect via debt (ab3)	.002	0.001	[-0.000, 0.0034]	.001	0.000	[0.000, 0.003]	.001	0.0002	[0.000, 0.002]
Indirect effect via insurance difficulties (ab4)	.005	0.002	[0.002, 0.009]	.003	0.000	[0.000, 0.004]	.001	0.0002	[0.000, 0.002]
Total indirect effect	.014	0.000	[0.011, 0.023]	.008	0.000	[0.005, 0.011]	.002	0.000	[-0.000, 0.004]
Total effect	.090	0.015	[0.010, 0.018]	.047	0.000	[0.027, 0.066]	.023	0.000	[.006, 0.043]

Note. Model 1 = four indirect effects only; Model 2 = W1 depressive symptoms, gender cost of living composite, and four indirect effects; Model 3 = added personality variables of extraversion, openness to experiences, conscientiousness, and agreeableness, and trait-level optimism and purpose in life. Models 2 and 3 also contain all 20 PCs as covariates in the path model predicting Wave 4 depressive symptoms. Gender coded as: 0 = male, 1 = female. CI = confidence interval; PGI = Polygenic Risk Inventory; W1 = Wave 1; W4 = Wave 4; PC = principal component.

which may foreclose other social, work, and financial opportunities in a manner that is ultimately depressogenic. One problem with this analysis rests in potential confounding (Rohrer, 2018); the genetics of depressive symptoms are highly correlated with other traits (Baselmans et al., 2019), and between-family analyses cannot circumvent this limitation. All DNA differences between full siblings are the result of random genetic recombination and are therefore unconfounded by the social and environmental factors that have become correlated with parental genetic characteristics. Thus, any analysis in which genetic risk variables are alleged to give rise to a dependent variable of interest cannot be assumed to be a causal process unless the tools of causal inference are applied, including but not limited to within-family designs, Mendelian randomization, behavior genetic methods, propensity scores, or instrumental variable analyses (cf. Whisman et al., 2021). To the best of our knowledge, much of the current research on the rGE process related to

adult mental health has not yet used these methods of causal inference (Avinun, 2020), and in this respect, what we think may be active rGE may not be so (see Jaffee & Price, 2007).

The null findings for the sibling-difference models underscore the importance of distinguishing between population stratification and environmental confounding in genetic association studies. Population stratification refers to allele frequency differences due to systematic ancestry differences across subpopulations, which can lead to spurious associations if not properly controlled (Price et al., 2006). In contrast, environmental confounding can occur even within ancestrally homogeneous samples when genetic variation correlates with environmental exposures influencing the outcome. This distinction is crucial, as conflating the two can mislead interpretations of genetic associations. These issues are particularly salient in the context of GWAS, where the social experiences that shape depressive symptoms—such as lower income or reduced

Table 5
Results of Sibling-Difference Models Including the WLS Depressive Symptom PGI as Key Predictor

Outcome	B	SE	95% CI	Total sample size
Depression (2004)	1.34	0.46	[0.44, 2.22]	3,490
Depression (1994)	1.64	0.51	[0.62, 2.66]	3,130
Depression change (1994 → 2004)	0.63	0.39	[-0.14, 1.40]	3,455
Assets	-75,658.10	38,112.6	[-150,404.4, -911.91]	3,837
Debt	0.02	0.01	[-0.0066, 0.04]	3,386
Educational attainment	-0.17	0.07	[-0.30, -0.04]	3,882
Health insurance difficulties	-0.01	0.03	[-0.06, 0.04]	3,382

Note. WLS = Wisconsin Longitudinal Study; PGI = Polygenic Risk Inventory; CI = confidence interval.

access to education—may themselves be genetically correlated due to population structure or pleiotropy. As a result, GWAS summary statistics, and by extension PGIs, may incorporate gene frequencies associated with both depression and its environmental correlates (Haworth et al., 2019; Turkheimer, 2011). From this perspective, the PGI is not a pure index of genetic risk for depressive symptoms, but a composite measure that reflects complex gene—environment interdependencies. This limitation complicates attempts to test causal pathways—particularly along the a-paths in mediation models—because associations between PGIs and environmental variables may partly reflect confounding embedded in the GWAS discovery sample. Our use of within-family, sibling-difference models was motivated by this concern: these models help control for such confounding by holding constant shared familial and ancestral background, thereby providing a more rigorous test of causality.

Our within-family analyses, which inherently control for shared familial environment and ancestry, provide a more stringent test of causal hypotheses. Although we did not find evidence supporting a causal impact of genetic risk on the socioeconomic mediators, these models are valuable for mitigating biases arising from both population stratification and environmental confounding. This aligns with findings from Selzam et al. (2019) and Brumpton et al. (2020), who emphasize that within-family designs reduce confounding from both population stratification and indirect genetic effects—factors that can bias estimates in Mendelian randomization and standard PGI analyses. Furthermore, Young (2024) underscores that family-based GWAS approaches are critical for clarifying direct genetic effects by eliminating environmental confounding and controlling for shared familial structure. Together, these findings underscore the importance of applying family-based models in psychiatric genetic research, particularly when examining environmentally mediated pathways.

The exploratory analyses incorporating the PGI for educational attainment revealed an important nuance in interpreting associations between the depression PGI and the socioeconomic variables. Specifically, we found that the associations of the depression PGI with both educational attainment and total assets were substantially attenuated—or even eliminated—after controlling for genetic propensity toward higher educational achievement. This pattern suggests that some of the observed associations in between-family models may not reflect environmental mediation, but rather shared genetic underpinnings across related traits. That is, the depression PGI may capture genetic influences that are pleiotropically related to both depression and cognitive or academic functioning, which in turn shape socioeconomic trajectories. These findings underscore the value of including multiple, theoretically relevant PGIs in future mediation studies to disentangle causal pathways from genetic correlation. Doing so may improve specificity in identifying which environmental factors plausibly mediate genetic risk, and which are better understood as co-occurring outcomes defined in part by a broader, polygenic architecture.

Although we failed to find evidence that genetic risk for depression is causally associated with the specific socioeconomic resource variables, the analyses presented here certainly do not close the case on a bioecological model of depression. In many ways, the measurement of the constructs of interest in both Add Health and the WLS was relatively limited. This is always a key trade-off in genetic epidemiology—large sample sizes are needed, but data collection with many people often comes at a cost to measurement quality.

In particular, we wish to call attention to two of the variables that we believe are not studied well enough in social genomics: debt and health insurance difficulties. Debt is a highly burdensome psychological experience (Achtziger, 2022), as is a lack of health insurance, and in the United States, medical debt is increasingly common (Kluender et al., 2021). To the extent that these experiences cause psychological entrapment or humiliation, there are many plausible pathways in which they may be depressogenic (Kendler et al., 2003). The sibling-difference models reported here can only speak to causation along the a-path of our mediational model. It is quite possible that social experiences can be depressogenic without first arising from genetic risk for depressive symptoms.

Related to this issue is emerging evidence that GWAS results from unrelated individuals can introduce indirect genetic effects that make causal inference (from genetic risk to a phenotype of interest) challenging. Within-family GWAS methods find smaller estimates for depressive symptoms than derived from population estimates (Howe et al., 2022), suggesting indirect effects may be operating, although the extent to which these processes are impacting causal inferences is not yet clear. The difference in estimates between the population-level and within-family GWAS for depressive symptoms provides additional evidence that the assumption of a genetic PGI (for depressive symptoms) unconfounded by environmental influences should be questioned.

Although the work reported here has a number of strengths, the results of this study should be viewed in light of several limitations. First, our analyses are limited to participants of European ancestry. The Add Health genotyping was completed in a European ancestry subsample of the larger study, which is more diverse and representative; the WLS is largely limited to people of White non-Hispanic backgrounds. The lack of genetic diversity in the sample limits the overall generalizability of the findings. Second, although our conceptual model was designed with the intention of studying developmental pathways from genetic risk to later depressive symptomatology, doing so mechanistically presented challenges in both data sets. For example, in Add Health and in the WLS, the mediator variables were measured on the same occasion as depressive symptoms. By definition, the socioeconomic resource variables are assessed in a manner that would allow those experiences to follow from participants' genetic risk for depressive symptoms, but a more complete study of rGE would also have the outcomes in question following a change in the intermediate processes. Third, although we managed to organize a conceptual replication from the Add Health study in the WLS, the measurement of the four variables was different in each study, and neither of the studies have excellent measurement of all four of the variables. For example, we created the health care/health insurance difficulties composite in the WLS based on the extant questionnaires, but doing so presents a number of psychometric challenges for interpreting the data (Flake & Fried, 2020). Indeed, the correlations between health insurance availability and educational attainment in Add Health ($r = .30$) and between health care-related insurance difficulties and educational attainment in the WLS ($r = -.001$) were quite different, underscoring large differences between the samples that may reflect differences in measurement or differences in patterns of associations at different historical and developmental periods. Despite these limitations, both studies use the same GWAS and methodology (Becker et al., 2021) to create the PGI scores, which provides an excellent means for attempting to replicate research across two relatively large and independent samples. Related to this point, our

operationalization of the social determinant risk variable was limited to the extant data collected in the Add Health and WLS samples. For example, the single assessment of debt in the WLS was not exclusive to debt and included mention of “significant financial losses,” which may not imply a long-term experience of debt obligations. In addition, we were not able to correct for cost of living in our operationalizations of wealth, which would be ideal given rural/urban cost of living differences. Finally, we were unable to account for all potential confounders in the existing samples that may explain long-term changes in depressive symptomology. For example, it would be ideal to account for trauma exposure when considering depressive symptoms. The extent to which the social determinant mediators may operate in combination with life event exposures would be an interesting area for further study.

Conclusion

Using data from two large longitudinal studies, this article examines genetic risk for depressive symptoms and the potential developmental pathways that may convey this risk over time. Conceptually, this work was organized under a r GE framework and sought to understand the extent to which genetic risk for depression may be associated with—and perhaps shape—later socioeconomic resources. In a series of exploratory analyses using the Add Health data (tracking depressive symptom change across a decade in early adulthood), we found evidence for (a) increases in self-reported depressive symptoms across the follow-up period as a function of genetic risk for depressive symptoms, and (b) partial mediation through four socioeconomic resource variables: education attainment, debt, total assets, and the availability of health insurance. After conducting a series of exploratory analyses with the Add Health data, we preregistered a conceptual replication in the WLS (tracking symptom change over a decade in midlife and early older adulthood) and again found support for potential mediating processes through these social determinant variables. Thus, in two relatively large-scale studies, we replicated effects that may be consistent with a r GE framework. To examine the robustness of these effects, we also preregistered a confirmatory set of sibling-difference analyses, which provide a critical test of causal inference from the PGI for depressive symptoms to the socioeconomic resource variables. These analyses revealed that the genetic risk for depressive symptoms was indeed associated with self-reported depressive symptom levels in the WLS in a manner consistent with a causal process, but we found little support that genetic risk for depression has an independent causal impact on any of the mediator variables. We discuss the implications of these findings for understanding developmental pathways toward depressive symptoms and the need to consider confounding processes when searching for the environmental mechanisms that may convey genetic risk.

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