Challenges in studying the interplay of genes and environment. A study of childhood financial distress moderating genetic predisposition for peak smoking

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Abstract

Smoking is one of the leading causes of preventable disease and death in the U.S., and it is strongly influenced both by genetic predisposition and childhood adversity. Using polygenic indices (PGIs) of predisposition to smoking, we evaluate whether childhood financial distress (CFD; a composite measure of financial adversity) moderates genetic risk in explaining peak-cigarette consumption in adulthood. Using the Health and Retirement Study (HRS), we find a substantial reduction in the relationship between genetic risk and peak smoking for those who did not suffer financial adversity in childhood. Among adult smokers who grew up in high-CFD households, a one standard deviation higher PGI is associated with 2.9 more cigarettes smoked per day at peak. By contrast, among smokers who grew up in low-CFD households, this gradient is reduced by 37 percent (or 1.1 fewer). These results are robust to controlling for a host of prime confounders. By contrast, we find no evidence of interactions between the PGI and typical measures of childhood SES such as parental education - a null result that we replicate in the Wisconsin Longitudinal Study (WLS) and the English Longitudinal Study of Aging (ELSA). This suggests the role of childhood financial distress in the relationship with peak smoking is distinct from that of low childhood SES, with high CFD potentially reflecting more acute distress than do measures of low childhood SES. Our evidence also suggests low childhood SES is a weaker proxy for acute distress, providing an alternative explanation for the childhood SES null result. **keywords:** Smoking | G×E | Polygenic Index | Health Inequality

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1 Introduction

Smoking is one of the leading causes of preventable disease and death in the U.S. (Mokdad et al., 2004; United States Department of Health and Human Services, 2014). Each year tobacco use kills over 400,000 Americans – who die up to 15 years earlier than nonsmokers – and costs more than $193 billion in annual health-related economic losses (Mokdad et al., 2004; DHHS, 2010; Kaplan et al., 1995). Smoking is more prevalent among low socioeconomic status (SES) groups (Cutler and Lleras-Muney, 2010) and a significant source of the substantial disparities in health between them (Chaloupka and Warner, 2000; Contoyannis et al., 2004; Mackenbach et al., 2004; Khang et al., 2009; Cutler et al., 2011). Such disparities are formed early in life and become more pronounced as individuals age (Case et al., 2002, 2005; Currie and Stabile, 2003; Shonkoff et al., 2009). Indeed, an extensive literature has shown the importance of early-life circumstances in explaining adult health outcomes (Currie and Rossin-Slater, 2015; Caspi et al., 2016; Doyle et al., 2009; Institute of Medicine, 2015; Osler et al., 2003; Almond and Currie, 2011; Condliffe and Link, 2008; Fernald et al., 2012; Gluckman and Hanson, 2006b,a; Bateson and Gluckman, 2011). Adverse childhood experiences in particular are associated with a range of smoking behaviors: early smoking initiation, initiation as an adult, ever smoking, current smoking, and heavy smoking (Anda et al., 1999; Ford et al., 2011). Such experiences can have negative effects on socio-emotional development and may influence smoking outcomes through preferences for risk-taking (e.g., Resnick et al., 1997). These relationships are stronger for those that have experienced several distinct types of adverse experiences (Anda et al., 1999),[1] i.e., it increases in the degree of adversity.

Genetic makeup matters too. Twin studies (comparing the correlation in traits between identical and fraternal twins) suggest that some 35% to 86% of the variance in heaviness of smoking is related to genetic differences between individuals, with the remainder attributed to environmental influences (Kaprio et al., 1981; Swan et al., 1990; Hettema et al., 1999; Koopmans et al., 1999; Lessov et al., 2004; Broms et al., 2006; Boardman et al., 2010).

While genes may predispose individuals to certain unhealthy behaviors and to certain health conditions, the influence of genetic factors may depend substantially on environmental exposures, so called gene-by-environment (G×E) interplay (Haldane, 1946; Plomin et al., 1977; Rutter, 2006; McAllister et al., 2017). Theory suggests disparities emerge by an interaction of cumulative disadvantage and genes, pointing at the importance of the early-life environment (Kuh and Shlomo, 2004; Caspi, 2004; Meaney and Szyf, 2005; Meaney, 2010; Cole, 2009; Rutter, 2012; Mitchell et al., 2013; Reiss et al., 2013). Therefore, G×E interplay may be cumulative in nature, and stronger for early- vs. late-life environments.

Thus far, however, studies have focused largely on G×E interplay between contemporaneous environments and smoking (Boardman et al., 2010, 2011; Fletcher, 2012; Domingue et al., 2015; Meyers et al., 2013; Schmitz and Conley, 2016; Treur et al., 2017). For example, one study

[1] Emotional, physical, and sexual abuse; a battered mother; parental separation or divorce; and growing up with substance-abusing, mentally ill, or incarcerated household members.

(Meyers et al., 2013) suggests that an individual's *current* social environment in adulthood moderates genetic vulnerability to smoking.[2]

Here, we test the hypothesis that a protective environment during childhood, as measured by the absence of financial distress, moderates the genetic risk for smoking in adulthood. Two developments make our analysis possible. The study of G×E interplay has traditionally been hampered by a lack of credible gene-behavior associations and by a lack of data sets with both genetic and precisely measured data on the environment. Studies attempting to discover genetic main effects or G×E interaction were severely underpowered to detect true associations (Benjamin et al., 2012; Duncan and Keller, 2011; Hewitt, 2012; McGue, 2013). Recent advances in molecular genetics, however, have established robust associations between specific genetic variants and smoking behavior (Liu et al., 2010; Thorgeirsson et al., 2008, 2010; The Tobacco and Genetics Consortium et al., 2010; Liu et al., 2019). These studies have used significantly larger samples, applied stringent standards for statistical significance, and demonstrated out-of-sample replication to robustly identify genetic associations.

A second critical development has been the recent collection of genetic samples in large, representative data sets containing extensive measures of environment, health, and health behavior, at different points in the life cycle. Such variables are typically not found in the medical samples used for gene discovery, and social science data sets have lacked genetic information. We here use rich information from one such study, the Health and Retirement Survey (HRS) (Sonnega et al., 2014).

We find that the relation between a proxy for genetic predisposition and peak life-cycle levels of smoking is substantially reduced for those who did not suffer financial distress in childhood. These results remain when controlling for a rich set of potential confounding factors, such as educational attainment and age of smoking initiation. Yet, we do not find such moderation when considering interactions between genetic predisposition and broader measures of childhood socio-economic circumstances such as parental education.

We also explore interactions between childhood conditions and genetic predisposition for smoking intensity in two other data sets: the English Longitudinal Study of Aging (ELSA) and the Wisconsin Longitudinal Study (WLS). Unfortunately, neither of these data sets has measures of childhood financial distress that are comparable to those in the HRS. A measure of general childhood SES based on parental education and father's occupation can be constructed across all three data sets, but we fail to find evidence of interactions between the PGI and this SES measure in any of these data sets. The fact that we also find a null-result in the HRS, the same dataset in which we established our main result, suggests that childhood financial

[2]They find the association between genetic risk and cigarettes smoked per day to be larger for those experiencing traumatic events and smaller for those who live in neighborhoods with greater social cohesion, using a small ($\sim$ 1,500) sample of African Americans. Other studies evaluate the existence of G×E interplay for another health outcome, obesity. These find that unfavorable SES conditions amplify the genetic influence of 32 obesity-related genetic variants on body mass index (BMI), especially for recent birth cohorts (Liu and Guo, 2015); that years of schooling protect for genetic risk in type-2 diabetes (Liu et al., 2015); and that the social environment moderates the genetic influence of a variant near the FTO gene on the development of obesity in children (Foraita et al., 2015).

distress (CFD) and childhood socioeconomic status (childhood SES) operate in distinct ways. This is perhaps not surprising, as a measure of childhood SES based on parental education and occupational class arguably does not sufficiently capture the more acute distress aspects of our CFD measures. Further, our analyses suggest low childhood SES is a weak proxy for acute distress, with only 33.50 percent of households in the bottom quartile of parental education meeting the conditions of a High CFD upbringing. If indeed it is the distress aspects of low childhood CFD that matter, this provides a potential explanation for why we consistently fail to find evidence of interactions between genetic predisposition and childhood SES when predicting smoking behavior.

The results in the HRS on childhood financial distress provide evidence that more acute financial distress can exacerbate genetic propensities for heavy smoking. A task for future work is to better harmonize measures of childhood distress across data sets to enable more informative replication exercises. This work highlights the challenges of studying the interplay of genes and environments.

2 Data and Descriptive Statistics

Single nucleotide polymorphisms (SNPs) differ across individuals, thereby providing a measure of genetic variation. Following strict statistical procedure for multiple hypotheses testing and controlling for population stratification, previous genome-wide association studies (GWAS) have identified genome-wide significant relationships between specific SNPs and smoking quantity (Liu et al., 2010; Thorgeirsson et al., 2010; The Tobacco and Genetics Consortium et al., 2010; Liu et al., 2019). We focus here on a measure of smoking intensity that is highly correlated with nicotine use disorder: the maximum number of cigarettes smoked per day at peak consumption (max CPD). We measure genetic predisposition to heavy smoking through a polygenic index that aggregates all measured SNPs using the LDpred method (Vilhjálmsson et al., 2015) to correct for SNP-level correlations (linkage disequilibrium). The GWAS coefficients from Liu et al. (2019) are used as weights in this score, which was constructed for the HRS as part of the SSGAC's PGI Repository (Becker et al., 2021). We winsorize the LDpred PGI at the 1st and 99th percentiles.

Our main analysis sample consists of 6,301 individuals from the HRS who are current or former smokers, born between 1920 and 1960, with non-missing genetic and demographic data, and who are genetically of European descent, following the accepted practice of restricting the genetic diversity to match as closely as possible that of the discovery sample. In the HRS, max CPD is constructed as a combination of two survey items. First, former smokers who quit by the time of the survey are asked retrospectively: "When you were smoking the most, about how many cigarettes or packs did you usually smoke in a day?" Second, for those who are still actively smoking when surveyed, we take the maximum value (across waves) of their

contemporaneously reported smoking quantities.[3]

We measure childhood financial distress (CFD) by aggregating a series of retrospective questions about conditions from birth until age 16. Specifically, HRS survey items permit the construction of binary indicators for the following adverse events or conditions: (1) Family Poor: whether respondent indicated growing up in poverty (as opposed to average or well-off conditions), (2) Move or Help: indicates if the family ever had to move or ask relatives for help for financial reasons during childhood, and (3) Father Unemployed: indicates if the individual ever endured an extended period with an unemployed or absent father (see the Appendix for more details). Although there are many ways to aggregate these survey responses, we take a simple and transparent approach and construct a measure of CFD that assigns respondents to a Low CFD group if they experienced no more than one of these adverse conditions growing up. Individuals assigned to the High CFD group experienced more than one of these conditions. In robustness exercises (section 4), we show that results are robust to using a sum score that sums up all three binaries.

Table 1 presents summary statistics for some of the main variables in our sample. Approximately 76 percent of our sample is classified as belonging to the Low CFD group (4,788 out of 6,301 individuals). Our main outcome variable of interest is maximum cigarettes smoked per day at peak consumption (max CPD). The average value of max CPD is 24.66 in our sample (over a pack a day). Figure 1 presents histograms of max CPD for both the High and Low CFD groups. For both CFD groups, the distribution peaks in the 20-29 cigarette range. However, the distribution of max CPD is shifted rightward for the High CFD group. In particular, a lower fraction of High CFD individuals exhibit max CPD in the 1-9 cigarette range (0.11 v.s. 0.16), but a higher fraction in the 60+ category (0.10 v.s. 0.07), consistent with a shift in the distribution towards higher levels of max CPD for the High v.s. the Low CFD group. The average max CPD among High CFD individuals is 3.22 higher than the Low CPD average (p-val < 0.001).

Figure 2 graphically depicts the interplay between CFD and the PGI in our sample. For each CFD group, we plot a non-parametric local polynomial estimate of the unconditional relationship between the PGI and max CPD. Max CPD is rising with higher levels of the PGI (expressed in std. dev. from mean zero) regardless of the level of CFD. However, the gap between the average max CPD for the two groups appears to widen with greater levels of the PGI. As indicated by the conditional means reported in Table 1, the difference in average max CPD between the High and Low CFD groups with below the mean levels of the PGI is approximately 2.5 cigarettes (24.87 v.s. 22.42), while this difference grows to 3.78 cigarettes (29.17 v.s. 25.39) among those with above the mean levels of the PGI.

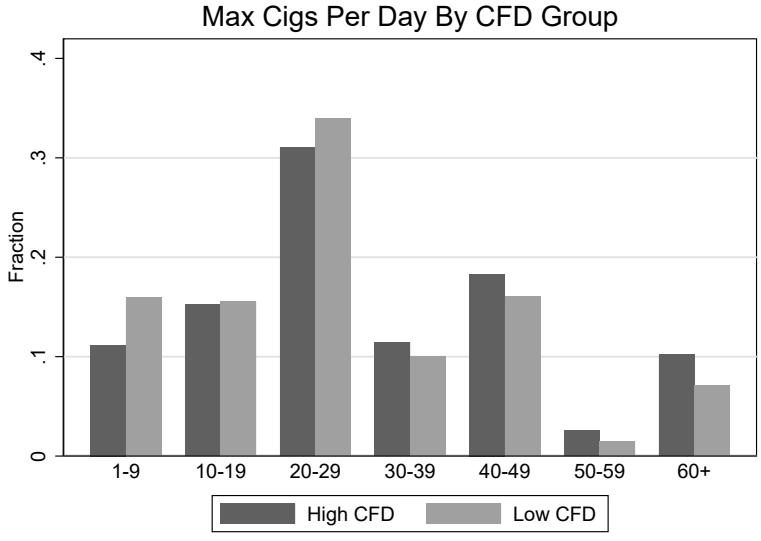
[3]If there are non-missing values of both quantities - as might be the case for a former smoker who starts smoking again while in the panel - we take the maximum of the retrospective and contemporaneous measures.

Table 1: Summary Statistics

Variable	Mean	Std. Dev.	N
Max Cigs. Per Day :			
All	24.661	17.145	6,301
High CFD and Low PGI	24.873	16.425	723
High CFD and High PGI	29.167	19.154	790
Low CFD and Low PGI	22.42	16.217	2,425
Low CFD and High PGI	25.391	17.223	2,363
CFD Measures:			
Family Well Off / Not Poor	0.726	0.446	6,301
Father Nev. Unemp.	0.733	0.442	6,301
Family Never Moved / Asked Help	0.742	0.437	6,301
CFD	0.76	0.427	6,301
Genetic Measure :			
max CPD PGI	0	1	6,301
Demographics:			
Male	0.504	0.5	6,301
Birth Year	1941.035	10.424	6,301

"Low PGI" refers to negative PGI (below the mean); "High PGI" refers to positive PGI (above the mean). "CFD" takes the value 1 for individuals who experienced at most one of the three CFD conditions (low CFD), and 0 otherwise (High CFD). The max CPD PGI refers to a polygenic index of maximum cigarettes per day formed from the summary statistics of the Liu et al. (2019) GWAS using LDpred and all SNPs, constructed for the HRS as part of the SSGAC's PGI Repository (Becker et al., 2021).

Figure 1: **Distribution of Max CPD by High and Low CFD**



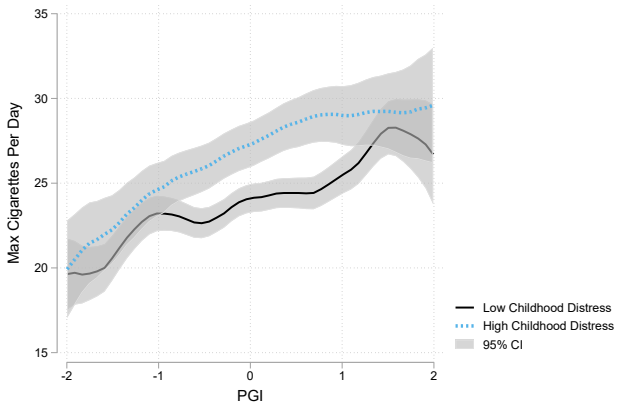


Figure 2: Max cigarettes per day (max CPD) as a function of the polygenic index (PGI) for High CFD (dotted blue) and Low CFD (solid black). The shaded area indicates the 99 percent confidence interval. In constructing the Figure, we used kernel-weighted local polynomial smoothing. All estimations were performed in STATA using the command *lpoly*. To reduce the influence of outliers, the sample was winsorized below the 1^{st} and above the 99^{th} percentile of max CPD and of the PGI. PGI refers to a polygenic index of maximum cigarettes per day formed from the summary statistics of the Liu et al. (2019) GWAS using LDpred and all SNPs, constructed for the HRS as part of the SSGAC's PGI Repository (Becker et al., 2021).

3 Results

To formally test for the presence of a GxE interaction, we estimate linear regression models of the following form:

$$Y_i = \alpha + \beta g_i + \gamma CFD_i + \rho\left[CFD_i \times g_i\right] + Z_i^{'}\theta + \varepsilon_i \tag{1}$$

where Y_i is max CPD for individual i; g_i is the polygenic index; CFD_i is our dichotomous measure of Low CFD, and Z_i is a vector of individual characteristics. Our baseline results includes the following controls in Z_i: the first 20 principal components of the full matrix of SNP data to adjust for population stratification (Price et al., 2006; Rietveld et al., 2014), a male indicator, a complete set of dummies for birth year, a complete set of indicators for region of birth (New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, Pacific, and Missing), and interactions between the male indicator and all other controls. As Keller (2014) points out, when genetic and environmental variables are correlated with controls, one can detect spurious GxE interactions that might actually reflect interactions with the controls. For this reason, Z_i also includes a complete set of interactions between g_i and the previously mentioned controls, along with a full set of interactions between CFD_i and the controls. We refer to this collection of Z_i variables as our baseline demographic controls.

Table 2 reports the OLS estimations of equation (1) using our binary indicator for Low CFD

Table 2: Interplay between the PGI and Childhood Financial Distress in Max CPD

	Max cigarettes per day			
	(1)	(2)	(3)	(4)
PGI x Low CFD	-0.693	-0.947	-1.025*	-1.075*
	(0.513)	(0.518)	(0.517)	(0.521)
PGI	2.772**	2.896**	2.921**	2.909**
	(0.453)	(0.456)	(0.454)	(0.457)
Low CFD	-2.658**	-2.114**	-2.004**	-1.887**
	(0.510)	(0.512)	(0.515)	(0.519)
Controls:				
Demographic	✓	✓	✓	✓
Education		✓	✓	✓
Parental Smoking			✓	✓
Age of Initiation				✓
Obs.	6,301	6,301	6,301	6,212
R^2	0.163	0.175	0.182	0.191

Coefficients estimated from OLS regression of max CPD on Low CFD (indicator for recalling at most one of three adverse conditions), the PGI, the interaction between the PGI and Low CFD, and various controls. *Demographic* refers to the baseline control vector Z_i; *Education* includes a set of indicators for highest degree of education completed, along with interactions with the PGI and CFD; *Parental Smoking* includes dummy variables for categorical variables related to parental smoking (none smoked, one smoked, both smoked, missing), along with interactions with the PGI and CFD; *Age of initiation* includes self-reported age (in years) when started smoking, along with interactions with the PGI and CFD; PGI refers to a polygenic index of maximum cigarettes per day formed from the summary statistics of the Liu et al. (2019) GWAS using LDpred and all SNPs, constructed for the HRS as part of the SSGAC's PGI Repository (Becker et al., 2021). Robust standard errors clustered at the household level shown in parenthesis. ** P-value < 0.01 * P-value < 0.05.

and different sets of controls. Across the columns of Table 2, we progressively add important confounding variables such as educational attainment, parental smoking, and age of smoking initiation. We find that both Low CFD and low genetic predisposition (low PGI) are associated with reduced peak smoking. Further, the coefficient on the interaction term, ρ, is consistently negative, and is statistically significant in specifications that control for parental smoking. After controlling for educational attainment (Column 2), the difference in coefficients across subsequent columns is quite small, even when including very predictive controls (Oster, 2016). For instance, age of smoking initiation was significantly correlated with Low CFD and is a strong predictor of genetic vulnerability to smoking (Hartz et al., 2012). Yet, even controlling for the respondent's age of smoking initiation does not reduce the estimate of the interaction. Column (4) presents our baseline "full control" specification results. The coefficient estimates suggest that, on average, an individual from a High-CFD background with low genetic risk (PGI 1 std. dev. below mean) smoked 5.8 (2×2.909) fewer cigarettes per day at peak than an individual from a High-CFD background with high genetic risk (PGI 1 std. dev. above mean).[4] However, this genetic gradient is significantly smaller for those from Low-CFD backgrounds: a high genetic risk individual smoked on average only 3.668 more cigarettes per day at peak than a low genetic risk individual.[5]

Now contrast the results with the gradient in education. College graduates smoke, on average, -2.59 (s.e. 0.52) fewer max CPD than those without a college degree. The interaction between High CFD and high genetic risk ($2 \times 1.075 = 2.15$ max CPD) is over 80% of the difference in max CPD between a college graduate and someone without a college degree. Thus, the observed G×E interaction is not only statistically significant but also economically meaningful.

4 Robustness, Threats to Identification, and Replication

4.1 Parental Education

A natural concern is whether the interactions we find between the PGI and financial distress might actually reflect interactions between the PGI and more general dimensions of SES - like parental education - that could be correlated with distress.[6] To explore this, we augment our full-control specification from Column (4) of Table 2 to include average parental years of schooling (averaged across parents), along with its interactions with the PGI and the Low CFD indicator. Before doing so, we first point out an important limitation: parental education is missing for a non-trivial number of individuals in the HRS. In Column (1) of Table 3, we replicate our main full-control specification (without any controls for parental education), but restrict the sample

[4] As a useful benchmark, the 2019 Liu et al. (2019) GWAS reports an effect of 2.96 extra CPD per SD-unit PGI in HRS data using the all SNPs LDpred PGI, which is nearly identical to our estimate of 2.909.

[5] $2 \times (\hat{\beta}_{PGI} - \hat{\beta}_{PGI \times LowCFD}) = 2 \times (2.909 - 1.075) = 3.668$.

[6] In analyzing childhood financial distress, we avoid using parental education as a proxy for household conditions. In part, this is due to our focus on measuring acute distress. Households may have less educated parents, or experience consistently below average incomes, but these conditions do not necessarily generate the kinds of adversity that may trigger nicotine dependence.

Table 3: Robustness Exercises

	Max cigarettes per day				
	(1)	(2)	(3)	(4)	(5)
PGI x Low CFD	-1.045	-1.047	-1.141*	-0.468*	0.078
	(0.581)	(0.586)	(0.544)	(0.224)	(0.094)
PGI	2.886**	2.864**	3.054**	3.107**	1.317
	(0.510)	(0.514)	(0.480)	(0.542)	(1.018)
Low CFD	-1.808**	-1.845**	-1.284*	-0.981**	-0.325**
	(0.571)	(0.584)	(0.567)	(0.221)	(0.117)
Sample	Par Educ.	Par Educ.	Geno. < 80	Baseline	Par Educ.
Parental Educ		✓			✓
CFD Measure	Low CFD	Low CFD	Low CFD	CFD Index	Avg. Par. Educ.
Obs.	5,378	5,378	5,609	6,212	5,378
R^2	0.207	0.209	0.192	0.194	0.201

Coefficients estimated from OLS regression of max CPD on Low CFD (indicator for recalling at most one of three adverse financial distresses), the PGI, the interaction between PGI and Low CFD, and various controls. PGI refers to a polygenic index of maximum cigarettes per day formed from the summary statistics of the Liu et al. (2019) GWAS using LDpred and all SNPs, constructed for the HRS as part of the SSGAC's PGI Repository (Becker et al., 2021). Robust standard errors clustered at the household level shown in parenthesis. ** P-value < 0.01 * P-value < 0.05.

to those with non-missing parental education information. The sample size is reduced to 5,378 (from 6,301). In this smaller sample, we continue to find a substantial negative interaction between the PGI and Low CFD (-1.045) that is comparable in size to our baseline estimate (-1.075). The reduction in sample size reduces the precision of this estimate, and this estimate is not statistically significant at conventional levels (p-val = 0.068). In Column (2) of Table 3, we add average parental education as a regressor (including interactions with the PGI and CFD), and this barely changes the coefficient on our key interaction of interest (-1.047 v.s. -1.045). The nearly identical results across Columns (1) and (2) suggests little role for confounding on this dimension.

4.2 Mortality Bias

A common concern in studies of genetic measures and health outcomes is possible selection bias arising from differential mortality. Individuals had to survive long enough to be genotyped (at least until 2006) in order to make it into our sample. We expect both higher levels of the PGI, and higher levels of childhood financial distress to be positively associated with mortality. This raises the possibility that the high PGI, high CFD individuals who make it into our sample could be positively selected on unobservable factors, potentially biasing our estimates of GxE interactions. We do not believe this is a concern here for two reasons. First, this would bias our estimates against finding a substantial interaction. We find a larger increase in smoking intensity in high CFD households compared to low CFD households. Mortality bias here would likely mean that the high CFD, high PGI individuals in our sample smoke less than those who died before being genotyped. If we could include deceased individuals in our sample, we would

expect our estimated interaction to increase in magnitude as we incorporate high CDF, high PGI individuals with even more intense smoking behavior.

Second, we note that if mortality bias is driving our results, it would likely arise from patterns among particularly old individuals. Christopoulou et al. (2011) find that differential mortality only generates biased estimates of smoking prevalence for American men over age 80. Guided by this as a benchmark, we re-estimate our baseline full-control specification in Column (3) of Table 3 restricting the sample to individuals aged no more than 80. Although this procedure reduces the sample size to 5,609, we estimate a negative and significant interaction between PGI and Low CFD (-1.141) which is larger in magnitude than our baseline estimate. This suggests that mortality bias is unlikely to significantly drive our results. If anything, our results may be understating the extent of GxE interaction.

4.3 Alternate Measures of Childhood Conditions

We have focused on a simple binary measure of childhood financial distress that we think reasonably captures acute conditions that is transparent and easy to understand. However, it is reasonable to ask whether our coding of CFD is somewhat arbitrary and whether one could more efficiently use the information contained in the underlying survey items. In particular, a reasonable alternative may be to simply add up our three binary measures of disadvantage into a sum score taking values between 0 and 3, coded so that 0 indicates that the individual has experienced all three sources of financial distress, and 3 indicates that the individual has not experienced any source of financial distress. Thus, higher values of our environmental measure always correspond to more protective childhood conditions. Column (4) of Table 3 presents estimates of our baseline full-control specification using this index as our measure of CFD. The coefficient on the interaction between the PGI and the CFD index (-0.468) is negative and statistically significant. Holding all else equal, being raised in a childhood environment with one fewer indicator for financial distress is associated with a PGI - max CPD gradient that is 0.468 cigarettes smaller per standard deviation of the PGI. This interaction is similar to the degree of moderation we obtain when moving from the High CFD to the Low CFD category based on our binary measure.

In Column (5) of Table 3, we re-estimate our baseline full control specification but now use average parental education as a measure of childhood conditions. This comparison is useful because parental education is a commonly used measure of childhood socioeconomic status (SES). We find no evidence of an interaction between the PGI and average parental education. The estimated interaction coefficient is small in magnitude (0.078) and statistically insignificant. In Section 4.6, as part of a replication exercise using a measure of SES across three data sets based on a factor analysis of several components of SES, we likewise fail to find evidence of an interaction between the PGI and a more continuous SES variable that incorporates information on parental education and father's occupation.

How to reconcile this finding with the evidence of GxE interactions in CFD? If we believe

that our CFD and parental education variables are measuring the same underlying basket of childhood conditions, then the lack of an interaction between the PGI and parental education raises questions about the robustness of our results. However, there are some important conceptual differences between the childhood conditions captured by parental education and those captured by our CFD measures. Differences in parental education arguably map into more continuous differences in income, wealth, neighborhoods, etc. By contrast, the events and conditions captured by our CFD variables capture more acute and potentially traumatic financial distress. A plausible explanation is that acute financial distress in childhood may create conditions that promote smoking intensity particularly strongly among those with high PGIs for max CPD. Childhood financial distress is not captured well by using lower childhood SES as a proxy. Lower SES in childhood is certainly correlated with the likelihood of distress, but the continuous variation in a measure like average parental education is unlikely to cleanly indicate conditions of acute adversity. Indeed, even among households with low levels of parental education, episodes of acute distress are not typical. Among the observations in the bottom quartile of parental education (average less than or equal to 8 years of schooling), only 33.50 percent meet the conditions of a High CFD upbringing. This suggests that childhood financial distress (CFD) and childhood socioeconomic status (childhood SES) are distinct in how they influence the interaction between the PGI for max CPD and smoking intensity.

4.4 Alternate Polygenic Indices

Another issue that may affect the robustness of our results is our choice of polygenic index. Our main estimates use a PGI that aggregates all SNPs and corrects for SNP-level correlation using the LDpred method. Of course, alternate choices could be made. To assess the robustness of our results to alternate PGIs, we re-estimate our baseline full-control specification using 23 different PGIs that correspond to different p-value thresholds using estimated relationships from the Liu et al. (2019) GWAS. Each row in Figure 3 plots the estimated coefficient on the interaction between the PGI and Low CFD, along with associated confidence intervals. Estimates at the top of the Figure use PGIs that focus on fewer SNPs with more stringent p-value thresholds, starting with a "score" that only uses allele counts of the absolute top hit SNP, rs10519203. The second row includes SNPs with estimated relationships from the Liu et al. (2019) GWAS that have p-values of less than $p = 10^{-30}$. This is a rather stringent cutoff that focuses on SNPs with large and precisely estimated associations. There are 475 SNPs studied in the Liu et al. (2019) GWAS with associations that meet this p-value threshold. The interaction uncovered for this score is of a comparable, even slightly larger, size and statistical significance as found for the LDpred score used in our main analyses that uses all SNPs (shown at the very bottom of the Figure).

Moving further down in the graph, subsequent PGIs include more and more SNPs as the p-value thresholds become less and less stringent. A striking pattern emerges: including more and more SNPs into the PGI reduces the magnitude of the estimated $G \times E$ interaction, with

the interaction becoming statistically insignificant for thresholds less stringent than $p = 10^{-15}$. The LDpred PGI, which is our baseline PGI, includes all SNPs but also corrects for correlation between SNPs. This is important because as more SNPs are included in a PGI, the index can start to "double count" SNPs, introducing a source of measurement error into the PGI. When the all SNP LDpred index is used, we find a statistically significant interaction between the PGI and CFD that is larger in magnitude than the uncorrected all SNPs index. This suggests that the lack of significant interactions found when using other indexes with thresholds looser than $p = 10^{-15}$ may arise from a failure to correct for linkage disequilibrium.

The pattern of GxE estimates contained in Figure 3 raises questions about which PGI one should prefer when conducting a GxE analysis. From one perspective, it might be preferable to use a "top hit" index since we know more about the biological pathways associated with these SNPs, and can therefore more clearly interpret main associations and interactions. For max CPD, there are clear biological channels that link the top hit SNPs to smoking behavior. The p-value threshold of $p = 10^{-30}$ corresponds to the three top loci associated with the Cholinergic Receptor Nicotinic Beta 3 Subunit (CHRNB3), the Cholinergic Receptor Nicotinic Alpha 3 Subunit (CHRNA3), and the Cytochrome P450 Family 2 Subfamily A Member (6CYP2A6) genes (Liu et al., 2019). The α5-α3-β4-nicotinic receptor subunit genes on chromosome 15 and the α6-β3 nicotinic receptor subunit genes on chromosome 8 are involved in the pharmacodynamic effects of nicotine. The CYP2a6 gene on chromosome 19 codes the primary enyzme that metabolizes nicotine. Variants in these regions are also associated with an increase in a smokers risk for nicotine dependence, influence the development of lung cancer and chronic obstructive pulmonary disease, and are associated with an earlier age of diagnosis of lung cancer (Bierut et al., 2007; Bierut, 2010; Chen et al., 2015; Saccone et al., 2007, 2010).

However, focusing only on PGIs using "top hit" SNPs may be undesirable if this limits statistical power to detect GxE interactions. Including all SNPs can generate an index that is more predictive of the underlying phenotype and could therefore provide a more precise estimate of any GxE interaction. In Figure 4, we plot the correlation coefficients (and associated 95 percent confidence intervals) between observed max CPD and smoking intensity PGIs constructed with different p-value thresholds. As seen by the blue markers, the correlation between the PGI and max CPD substantially rises as more and more SNPs are included in the index.

While PGIs that incorporate more SNPs are more predictive of max CPD, it is not automatically clear that this makes them preferable for the purposes of GxE analyses. Adding more SNPs not only increases the predictive power of the PGI, but it may also alter the mix of biological mechanisms captured by the index, as well as patterns of correlation with rearing environments. Indeed, the square markers in Figure 4 show the pattern of correlations between the max CPD PGI for different p-value thresholds and a PGI for educational attainment (EA) from the SSGAC Polygenic Index Repository (Becker et al., 2021) for the HRS that includes all SNPs and based on LDpred to account for linkage equilibrium. For stringent p-value thresholds, the max CPD PGI has nearly zero correlation with the (all SNPs) EA PGI. However, as more SNPs are included, a negative and statistically significant correlation with the (all SNPs) EA

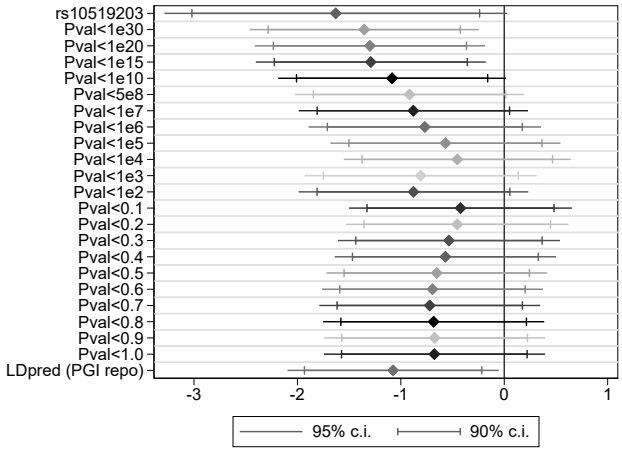


Figure 3: Estimated coefficients (and associated confidence intervals) for the interaction term between the PGI and Low CFD for different p-value thresholds (moving from very stringent [top loci] to including all SNPs [bottom]) of the PGI for max CPD. At the very bottom is the PGI based on LDpred for a p-value of 1 (Vilhjálmsson et al., 2015).

PGI emerges. This pattern could arise simply as a result of the max CPD PGI becoming a more precise estimate of a latent genetic factor. Adding more SNPs in the construction of a PGI can reduce the measurement error associated with a PGI as a proxy for this factor.

The pattern in Figure 4 is also consistent with a more structural rather than statistical interpretation. While we know that more stringent max CPD PGIs are heavily weighting mechanisms like nicotine metabolism that are uncorrelated with education, less stringent max CPD PGIs could be more heavily weighting less biologically proximate channels that may operate, possibly, through fundamental decision-making and behavioral channels that may also influence educational attainment. As the PGI for max CPD includes more and more SNPs (that are more distal to the biology of smoking, potentially reflecting behavior) the PGI for max CPD increasingly resembles the highly polygenic nature of the (all SNPs) PGI for educational attainment (Okbay et al., 2016). There is no reason to believe that a particular environmental factor (like CFD) should necessarily interact with these more distal polygenic mechanisms in the same way (they could interact either more or less strongly). From this perspective, the loss of statistical significance observed moving down the rows of Figure 3 could reflect a shift towards PGIs that more heavily weight mechanisms that truly do not interact with CFD.

Overall, we find it reassuring that we find evidence of our main GxE interaction both when using PGIs based on the "top hit" SNPs, and when using an index with all SNPs that corrects for linkage disequilibrium. We leave it as a task for future work to provide a more complete explanation of the pattern of GxE interactions found in Figure 3.

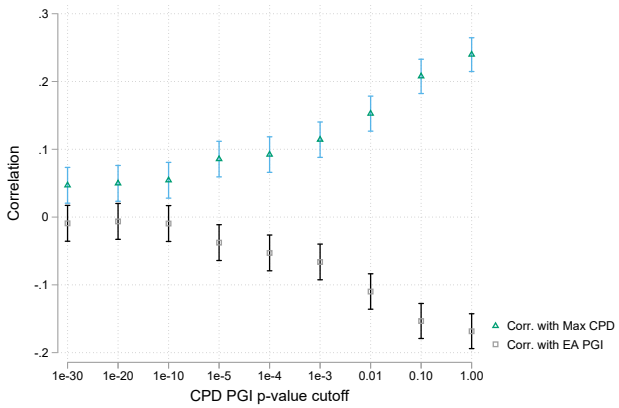


Figure 4: Raw unconditional correlations between PGIs for max CPD with different p-value cutoffs and (1) Max CPD (triangles) and with (2) the LDpred PGI (all SNPs) for Educational Attainment (squares).

4.5 Genetic Correlations with CFD

A causal interpretation of our results would suggest that some aspects of a low childhood financial distress environment (Low CFD) reduced the influence of genetic factors. However, correlation is not causation: CFD is not randomly assigned, and may be correlated with unobserved characteristics of the individual and her family (Plomin, 1990, 2014). Indeed, we do find evidence of correlation between the LDpred PGI and our measures of CFD, with higher levels of the PGI being associated with higher rates of CFD (see Appendix Table 5). This may suggest that the GxE we uncovered is due to gene-environment correlation (rGE). However, we consider this unlikely for several reasons. First, although statistically significant, the differences in CFD across high and low levels of the PGI appears to be modest. In a simple bivariate regression, a one standard deviation higher PGI is associated with a 1.7 percentage point increase in the incidence of high CFD status. By contrast, a one standard deviation higher level of average parental education is associated with a much larger 7.6 percentage increase in high CFD status. Further, as detailed in Section 4.1, controlling for parental education does not affect our main GxE estimate.

A second argument against the importance of rGE in this context comes from results using other PGIs. In Section 4.4, we estimate a statistically strong interaction between CFD and a PGI based on the stringent p-value threshold $p < 10^{-30}$. In Appendix Table 6, we fail to find any evidence that this PGI is correlated with our CFD measures. These null correlations are also fairly precisely estimated. For example, in a bivariate regression, we find that a one standard deviation increase in this "top hits" PGI is associated with a 0.3 *percentage point* difference in the incidence of high CFD, with a 95 percent confidence interval that allows us to rule out associations larger in magnitude than 1.4 percentage points. The absence of a correlation between genetic risk and CFD suggests the observed $G \times E$ interaction did not reflect a spurious

gene-environment correlation (rGE) or a non-linear effect of genetic risk G that resulted from correlation between G and E. Finally, we note that rGE is unlikely to affect our main results because we include a rich set of interactions between the PGI, our CFD measure, and other controls including own education, parental smoking, and (in robustness checks) average parental education.

Other interpretations are still possible. For example, if genetic risk G is correlated with an unobserved environment E^* (e.g., "family social and cultural norms") and E^* in turn is correlated with the observed environment E (e.g., "family well off"), then the effect of the observed environment E may not be causal, but rather proxy for the existence of an interaction between G and the unobserved environment E^*. Since E is correlated with E^*, our analyses still provide evidence for a true causal $G \times E$ interaction between max CPD and some environment that is correlated with childhood financial distress. However, in this example, improving the financial health of high CFD households with children may not improve later-life outcomes, since it might be something else, say family social and cultural norms, rather than the absence of childhood financial distress, that matters.[7]

4.6 Replication

The availability of genomic data in several major social science data sets provides an opportunity to replicate our analyses. In this section, we attempt to replicate our estimates in the English Longitudinal Study of Aging (ELSA) and the Wisconsin Longitudinal Study (WLS). Unfortunately, we were not able to test the same hypothesis in these data sets, since the HRS measures of childhood CFD, which capture aspects of childhood financial distress, are not available in these data sets.

The English Longitudinal Study of Aging (ELSA) is similar to the HRS and has some measures of early childhood that are somewhat comparable to those in the HRS. Specifically, we used two questions in wave 6, "Have you ever experienced severe financial hardship?," and "If yes, at what age?," to create an indicator equal to 1 if the respondent experienced severe financial hardship before the age of 16. We obtained a smaller and imprecisely estimated coefficient for the interaction term in ELSA that can potentially be explained in several ways. First, in the HRS we were able to combine multiple measures of financial hardship (versus one in ELSA) and

[7] A more significant threat to a causal interpretation of our result occurs in a situation where genetic risk G is correlated with an unobserved environment E^*, and the true relation contains interactions between E and E^*. Consider the situation where the true data generating process is the following:

$$Y = \beta_0 + \beta_1 E + \beta_2 E^* + \beta_3 E\, E^* + \beta_4 G + \epsilon \tag{2}$$

We observe G, but $E^* = \alpha G + \nu$. The data generating process can be expressed as:

$$\begin{aligned} Y &= \beta_0 + \beta_1 E + \beta_2[\alpha G + \nu] + \beta_3 E[\alpha G + \nu] + \beta_4 G + \epsilon \\ &= \beta_0 + \beta_1 E + [\beta_2 \alpha + \beta_4] G + \beta_3 \alpha E\, G + [\beta_2 \nu + \beta_3 E\, \nu + \epsilon] \\ &= \gamma_0 + \gamma_1 E + \gamma_2 G + \gamma_3 E\, G + e \end{aligned}$$

where the expectation of γ_3 equals $\beta_3 \alpha$, which is the strength of the E and E^* interaction and not the E and G interaction.

Table 4: Meta analysis based on childhood SES

	HRS	WLS	ELSA	Meta-analysis
PGI x Childhood SES factor	0.006	0.010	-0.016	-0.002
	(0.013)	(0.020)	(0.013)	(0.008)
N	5,533	2,712	5,999	

the sample size in the HRS is about the same as that of ELSA. In other words, we may have greater precision in measuring SES and its interaction with the PGI in the HRS. Second, the context (UK) is quite different from that of the US. For example, while smoking is much more prevalent in the UK, the reported max cigarettes smoked per day is smaller (15 on average in ELSA vs 25 in the HRS).

The Wisconsin Longitudinal Study (WLS) does not contain measures of CFD that are comparable to those in the HRS. However, the HRS, ELSA, and WLS all contain information on parental education and father's occupation - variables that are often used to measure different aspects of childhood SES. We thus conducted a meta-analysis that combined the HRS, ELSA and WLS, focusing on ages 50^{+}. By combining datasets we aimed to improve statistical power. We constructed an alternative measure of childhood SES, as a latent factor of parental SES constructed by combining father's education, mother's education and the fathers (former) occupational status (grouped into six categories shared between the three datasets). These were the only childhood SES-related measures consistently available in all three datasets. By also combining measures of childhood SES, we aimed to reduce measurement error and thereby further increase statistical power. Appendix A.4 provides details on the construction of the childhood SES measure.

We then regressed max CPD on the Liu et al. (2019) PGI (including all SNPs) and the childhood SES factor as in equation 1, meta-analyzing the three datasets. We find no evidence for an interaction effect: the coefficient of the interaction in the HRS, WLS, ELSA and the meta-analysis of max CPD is statistically insignificant in all cases (see Table 4).

These null results are quite consistent with earlier results from the HRS in which we consistently failed to find interactions between the PGI and more continuous measures of childhood conditions (e.g., parental education). Financial distress in childhood, as measured by recall questions that ask explicitly for such stressors, is very different from parental socioeconomic status, as measured by parental education and father's occupational prestige. Low levels of parental education and occupational prestige may be a poor proxy for financial distress (see also our earlier discussion). Another potential explanation for the lack of replication in these data sets is inadequate statistical power. In Appendix section A.3, we conduct power calculations to assess power under different assumptions about the true $G \times E$ effect size. In particular, these power calculations apply to detecting effects consistent with our baseline results on CFD (not the harmonized measure of childhood SES). While the ELSA sample is adequately powered to detect effects consistent with our baseline estimate (or the slightly larger estimate we find

using the $p < 10^{-30}$ PGI), we would be underpowered to detect effects in the ELSA that are smaller (e.g., 35 percent smaller than our baseline). The WLS sample, which is substantially smaller than the HRS or ELSA samples, is not large enough to offer a well-powered test unless one assumes larger effect sizes than those found in the HRS.

The inability to replicate our main GxE specification highlights a challenge in conducting replicable gene-by-environment interactions. The results in Table 4 are not at odds with our main findings and conclusions (since childhood SES here is conceptually distinct from CFD). However, because of the specificity of the CFD environment that we study, we are not able to provide evidence from another data set due to the lack of comparable measures of CFD. This raises the possibility that our estimated interaction between the PGI and CFD is an anomaly that may not replicate across contexts (or across data sets in the American context). We cannot provide evidence to rule this out and believe it is more responsible to interpret our results as suggestive. Future work should attempt to better measure CFD in other genotyped data sets with smoking data, but this is beyond the scope of this paper.

5 Discussion

We have provided empirical evidence that low financial distress in childhood, or correlates of low childhood financial distress, may substantially offset the genetic risk of heaviness of smoking. If this result holds, policies targeting childhood financial distress may have the potential to reduce genetic risk for peak smoking. From a public perspective, naturally we should beware of government policies targeting groups based on genetic information. But policymakers do not need to know the genetic makeup of individuals to develop policy (Belsky and Israel, 2014). For example, if social-science genetic studies, such as ours, find that smokers are solely genetically at-risk individuals, one might be limited to pharmacotherapy or to pharmacogenetic interventions (Hall et al., 2005; Nutt, 2007). But, if these are the genetically at-risk individuals who have experienced adverse (childhood) environments, prevention efforts targeting modifiable characteristics of such environments may reduce later-life dependence.

At the same time we want to be cautious about our results. First, our results are specific to acute levels of financial distress in childhood. More continuous measures of variation across the entire distribution of childhood conditions - like parental education - show no interaction with the PGI. We believe that there are good reasons for why this pattern could arise. It is plausible that severe conditions during childhood could accentuate genetic risk for smoking in a substantially different way than having a middle class rather than upper middle class childhood. Nevertheless, the specificity of the moderating environment studied here demands more validation before we can be confident in these results.

A second note of caution arises from the fact that we were not able to replicate the findings across datasets. Comparable measures of childhood financial distress were not available in the ELSA and WLS, which necessitated examining a measure of childhood SES (a factor score

of parental education and father's occupation) that could be constructed across all data sets. Within the same dataset (the HRS) we uncover a strong interaction between childhood financial distress and the PGI but find no interaction with this common measure of SES. The null results in the ELSA and WLS are thus consistent with our main results, but do not provide validation of our main conclusion about the moderating role of childhood distress. A key task for future work is to better measure childhood distress in genotyped data sets to more adequately test the findings here.

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A Appendix

A.1 Data

The Health and Retirement Study (HRS) is a longitudinal household survey providing rich data on about 26,000 individuals, representative of the U.S. population over the age of 50. Up to 12 waves, over 24 years, of data per respondent are available. We use the publicly available HRS core survey and linked genetic data for the years 2006, 2008, and 2010. HRS core surveys are conducted biennially using a combination of face-to-face and telephone interviewing. A random subset of the about 26,000 total participants was selected to participate in enhanced face-to-face interviews and saliva specimen collection (for DNA) in 2006, 2008, 2010, and 2012. Genotyping was conducted from 2011-2014, using the Illumina Human Omni-2.5 Quad beadchip (HumanOmni2.5-4v1 array), with coverage of approximately 2.5 million SNPs. To increase SNPs coverage, we used the best-guess genotypic data which was imputed using approximately 21 million DNA variants from the 1000 Genomes Project, phase I (The 1000 Genomes Project Consortium et al., 2012).

A.2 Childhood Financial Distress (CFD)

A set of retrospective questions about an individual's household financial circumstances during childhood were collected in the HRS. We dichotomized all CFD variables, assigning a value of 1 for low CFD and 0 otherwise. The four variables we construct are:

- *Family Well Off*: Low CFD indicates respondents who reported that their family was "pretty well off financially" or "average" from birth to age 16. High CFD indicates respondents who reported that their family was "poor."
- *Never Move or Ask for Help*: The HRS asks separate questions about whether a respondent's family ever had to move residences or ask relatives for help due to financial reasons. Both measures capture extraordinary financial hardship, and therefore we combine them into a single variable to improve overall frequency.[8] Low CFD indicates respondents whose family never had to move or ask relatives for help for financial reasons. High CFD indicates respondents whose families did either move or asked relatives for help.
- *Father Employed*: Low CFD indicates respondents whose father never experienced a significant unemployment spell of "several months or more." High CFD indicates respondents whose father did experience a significant unemployment spell, or those whose fathers were dead or never lived with them.[9]

[8] About 18 percent of respondent families had to move, and about 13 percent had to ask for help. When combined, about 25 percent had to take at least one of these actions.

[9] This variable incorporates information on family structure since it takes the value 0 if the child is raised without a father.

- *Low CFD Index*: We construct a simple index by summing all three measures, taking values $\{0, 1, 2, 3\}$. We then divide the sample into low CFD (index values of $\{0, 1\}$) and high CFD (index values of $\{2, 3\}$). The latter dichotomous measure is the main SES index used in the analyses.

A.3 Power Calculations

Here we calculate the statistical power associated with our test of an interaction between the PGI and low CFD status. For the purpose of these power calculations, we consider the following data generating process:

$$Y_i = \beta_0 + \beta_g PGI_i + \beta_e E_i + \beta_{gxe} G_i \times E_i + \varepsilon_i \tag{3}$$

Matching features of our data and the main estimates from Column (4) of Table 2, we assume that the PGI is distributed $N(0, 1)$, and that E_i is a binary, taking a value 1 with probability 0.75 and 0 otherwise. We set $\beta_g = 2.9$, $\beta_e = -1.6$. We consider three possible values of β_{gxe}: -1.35, -1.00, and -0.65. The assumed β_{gxe} value of -1.00 matches our baseline estimates in Table 2. The larger (in magnitude) coefficient of -1.35 corresponds to our estimate when using the PGI based on the $p < 10^{-30}$ PGI instead of the all SNPs LDpred PGI. Given a particular assumption about β_{gxe}, for each sample size, we simulate 2,000 independent samples from the data generating process and estimate our basic specification. The power calculated for this sample size is the fraction of these samples in which we reject the null hypothesis of β_{gxe} at the 0.05 level of significance.

Figure 5 displays power calculations for the three assumed levels of β_{gxe}. Recall, that our main HRS analysis sample has a sample size of 6,313 while the ELSA replication sample has a sample size of 5,999 and the WLS replication sample has a sample size of 2,712. Figure 5 reveals that sample sizes of 6,000 (comparable to the HRS and ELSA) are well-powered to detect an effect of $\beta_{gxe} = -1.35$ (power = 0.86), less well-powered to detect an effect of $\beta_{gxe} = -1.00$ (power = 0.62), and definitely underpowered to detect an effect of $\beta_{gxe} = -0.65$ (0.31). By contrast, a sample of the size of WLS is not large enough to be well-powered to detect any of the effect sizes considered here.

Our basic conclusion from the power calculations in Figure 5 is that we are reasonably powered in the ELSA to replicate effects similar to those found in the HRS, though we are underpowered to detect effects that are much smaller than our baseline HRS estimate. The WLS sample is too small to provide a well-powered test, unless one assumes that the true β_{gxe} is slightly larger than our baseline HRS estimate. Taken together, these calculations suggest that inadequate statistical power could contribute to our inability to replicate results in the ELSA and WLS, especially if one believes that effect sizes in these contexts are smaller than those suggest by our baseline estimates.

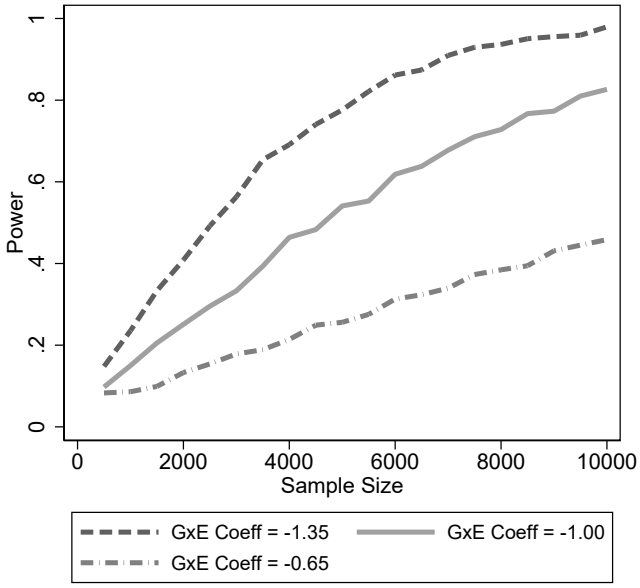


Figure 5: Power calculations for the test of the null hypothesis of no $G \times E$ interaction. For each sample size, we simulute 2,000 independent samples from a data generating process that approximates features of our baseline estimates. Our estimate of power is the fraction of samples for which we reject the null hypothesis at the 0.05 level of significance.

A.4 Childhood SES

In an attempt to replicate our results we constructed a measure of childhood SES through an estimate of parental SES using variables that are consistently measured in the Health and Retirement Study (HRS), the Wisconsin Longitudinal Study (WLS), and the English Longitudinal Study of Aging (ELSA). We estimate a general structural equation model, with observed and latent variables. For the observed variables we used:

- Mother's years of education
- Father's years of education
- Father's occupation

These variables existed in HRS, WLS, and ELSA studies with some minor differences. Father's occupations variables were assigned 0 to "Other", 1 to "Farmers", 2 to "Services + Operators + Admin/Clerical , 3 to "Sales", 4 to "Management", and 5 to "Professional". These categories were ranked based on an analysis of income and education levels in the 3 studies. However, ELSA does not include the category of "Farmer" as an occupation, and therefore it was excluded for ELSA. The years of education reported by the father and mother also vary between surveys. In the HRS and ELSA the minimum years of parental education reported is 0 and the maximum

is 14 for ELSA and 17 or more for HRS. In the WLS, the minimum years of schooling is 7 years and the maximum 18. From the general structural equation model we calculate a standardized childhood SES latent factor.

The distribution of the childhood SES factor for ELSA is bigger than that of HRS and WLS due to the presence of a higher rate of respondents that reported 0 years of education on maternal and paternal education. Since these are likely coding errors as the oldest ELSA cohorts were exposed to at least 7 years of compulsory education, we imputed 7 years of education for those respondents and included dummy variables identifying these individuals in the structural model, resulting in a smaller and more comparable distribution of the SES factor across the three studies.

A.5 Polygenic Index

The polygenic index PGI_i is constructed using the software Plink (Purcell et al., 2007) as the weighted sum of g_{ij}, the genotype of individual i for SNP $j = 1, ..., J$.

$$PGS_i = \sum_{j=1}^{J} \hat{\beta}_j g_{ij} \tag{4}$$

where $\hat{\beta}_j$ are the GWAS-estimated additive effect sizes of the alleles of SNP j, coded as having 0, 1, or 2 instances of the allele which is positively correlated with the phenotype (Dudbridge, 2013). In our main analyses we measure genetic predisposition to heavy smoking through a polygenic index that aggregates all SNPs (p-value = 1) using the LDpred method (Vilhjálmsson et al., 2015) to correct for SNP-level correlations (linkage disequilibrium). The GWAS coefficients from Liu et al. (2019) are used as weights in this score, which was constructed for the HRS as part of the SSGAC's PGI Repository (Becker et al., 2021). Since all-SNP scores are prone to large positive and negative outliers, we winsorize the LDpred PGI at the 1st and 99th percentiles.

We also construct a set of alternate PGIs at different p-value thresholds. No clumping or pruning was performed. We calculate the simple weighted sum of all SNPs present in the imputed HRS data set for which we have GWAS estimated additive effect sizes $\hat{\beta}_j$ and that have a GWAS P-value of less than 10^{-30} (chosen to focus on SNPs associated with the top three GWAS loci). We also use PGIs with varying p-values in our analyses of how the results change as a larger number of SNPs is included in the PGI.

A.6 Correlation Between Measures of CFD and the PGI

Table 5 shows the correlation coefficients among our three measures of childhood financial distress, our low CFD indicator that combines these measures, the outcome variable (max CPD), and the LDpred PGI. Standard errors for these correlation coefficients are presented in parentheses. The correlation between the measures of (a lack of) childhood financial distress and the PGI are negative and significant, with the exception of the "Never Moved or Asked for Help"

measure (see Table 5). Figure 6 plots the distributions of the LDpred PGI for high and low CFD backgrounds. We do this separately for our aggregated "High CFD" measure, as well as for the three separate CFD conditions, used to define this aggregated measure. A Kolmogorov-Smirnov test for differences between the distribution of the PGI among high and low CFD individuals provides evidence of significant differences. For our aggregated measure of CFD, we can reject the null hypothesis of equal distributions with P-value=0.018.

Table 6 shows the correlation coefficients among our three measures of childhood financial distress, our low CFD indicator that combines these measures, the outcome variable (max CPD), and the PGI constructed with "top hit" SNPs with associations having $p < 10^{-30}$). Here we find no evidence of any significant correlations between this PGI and any of the CFD measures. Figure 7 plots the distributions of this $p < 10^{-30}$) PGI for high and low CFD backgrounds. Across all of the measures of CFD, we fail to reject the null hypothesis that the distribution of the PGI is equal across CFD groups.

Table 5: Correlations Between CFD Measures and the LDpred all SNPs PGI

Variables	Max CPD	PGI	Fam. Not Poor	Nev. Mov. / Asked Help	Fath. Nev. Unemp.	Low CFD
Max Cigs. Per Day	1.000					
PGI (LDpred)	0.124**	1.000				
	(0.013)					
Fam. Not Poor	-0.086**	-0.032*	1.000			
	(0.013)	(0.013)				
Nev. Moved / Asked	-0.067**	-0.025	0.375**	1.000		
	(0.013)	(0.013)	(0.012)			
Father Nev. Unemp.	-0.062**	-0.042**	0.340**	0.359**	1.000	
	(0.013)	(0.013)	(0.012)	(0.012)		
Low CFD	-0.080**	-0.037**	0.667**	0.691**	0.652**	1.000
	(0.013)	(0.013)	(0.009)	(0.009)	(0.010)	

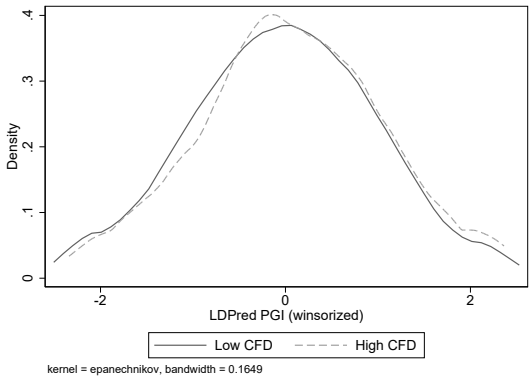
Pairwise correlations among the main variables of interest. Standard errors for pairwise correlations listed in parentheses.

Table 6: Correlations Between CFD Measures and the top SNPs PGI ($p < 10^{-30}$)

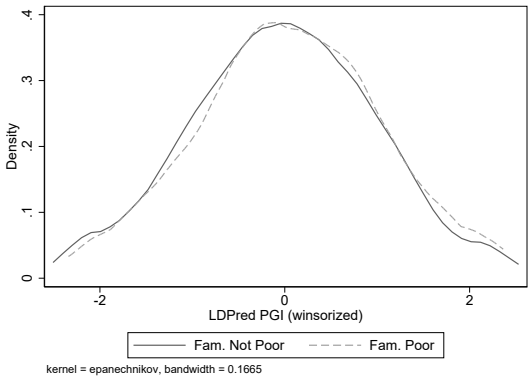
Variables	Max CPD	PGI	Fam. Not Poor	Nev. Mov. / Asked Help	Fath. Nev. Unemp.	Low CFD
Max Cigs. Per Day	1.000					
PGI	0.047**	1.000				
	(0.014)					
Fam. Not Poor	-0.086**	0.006	1.000			
	(0.013)	(0.013)				
Nev. Moved / Asked	-0.067**	0.012	0.375**	1.000		
	(0.013)	(0.013)	(0.012)			
Father Nev. Unemp.	-0.062**	0.018	0.340**	0.359**	1.000	
	(0.013)	(0.013)	(0.012)	(0.012)		
Low CFD	-0.080**	0.007	0.667**	0.690**	0.669**	1.000
	(0.013)	(0.013)	(0.009)	(0.009)	(0.010)	

Pairwise correlations among the main variables of interest. Standard errors for pairwise correlations listed in parentheses.

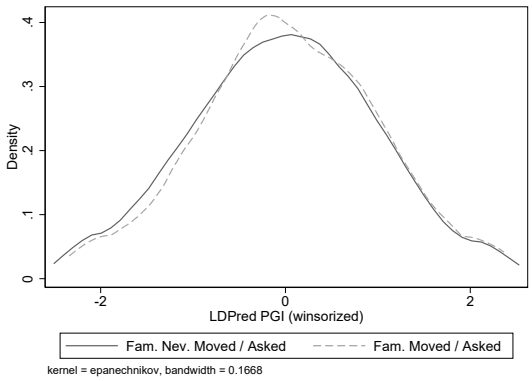
Figure 6: **Epanechnikov kernel density distributions of the PGI by CFD**
Kolmogorov-Smirnov test for equality of distributions (KS) P-value shown.



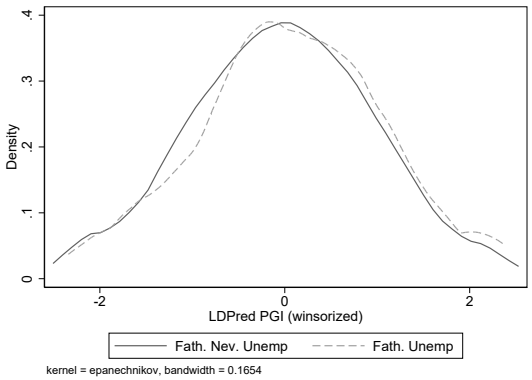
(a) High (1) versus Low (0) CFD. KS P-value=0.018



(b) Fam. Well Off. KS P-value=0.148

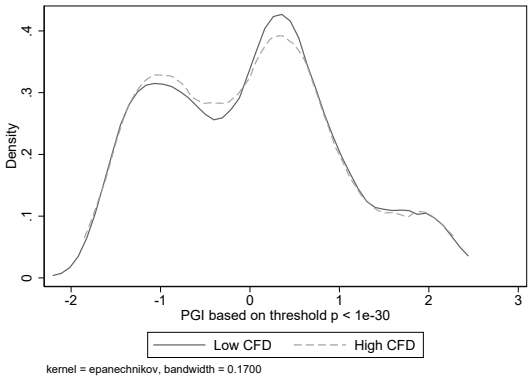


(c) Nev. Mov/Help. KS P-value=0.064

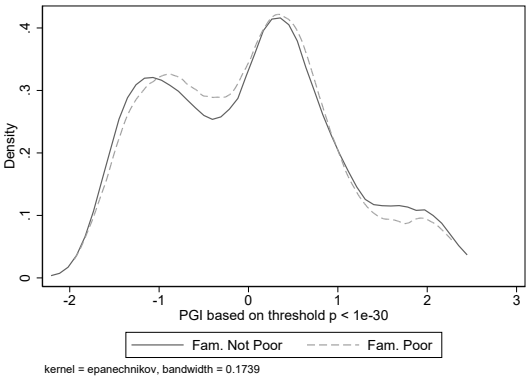


(d) Father Emp. KS P-value=0.010

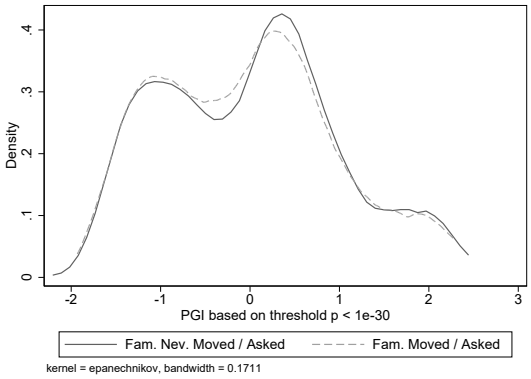
Figure 7: **Epanechnikov kernel density distributions of the PGI by CFD**
Kolmogorov-Smirnov test for equality of distributions (KS) P-value shown.



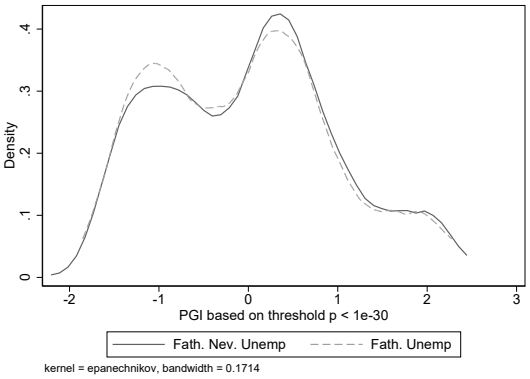
(a) High (1) versus Low (0) CFD. KS P-value=0.688



(b) Fam. Well Off. KS P-value=0.422



(c) Nev. Mov/Help. KS P-value=0.341



(d) Father Emp. KS P-value=0.299