

Gene-Environment Pathways to Cognitive Intelligence and Psychotic-Like Experiences in Children

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25

Abstract

26 **Background**

27 In children, psychotic-like experiences (PLEs) are related to risk of psychosis,
28 schizophrenia, and other mental disorders. Maladaptive cognitive functioning is a well-
29 known risk factor and early marker for psychosis, schizophrenia, and other mental
30 disorders. Since cognitive functioning is linked to various genetic and environmental
31 factors during development, we hypothesize that it mediates the effects of those factors on
32 childhood PLEs. Using large longitudinal data, we tested the relationships of genetic and
33 environmental factors (such as familial and neighborhood environment) with cognitive
34 intelligence and their relationships with current and future PLEs in children.

35

36 **Methods**

37 To estimate associations against potential confounding bias, we leveraged large-scale
38 multimodal data of 6,602 children (aged 9-10 years old; 47.15% females; 5,211 European-
39 ancestry) from the Adolescent Brain and Cognitive Development Study. Linear mixed
40 model and a novel structural equation modeling (SEM) method that allows estimation of
41 both components and factors were used to estimate the joint effects of cognitive
42 phenotypes polygenic scores (PGSs), familial and neighborhood socioeconomic status
43 (SES), and supportive environment on NIH Toolbox cognitive intelligence and PLEs. We
44 adjusted for ethnicity (genetically defined), schizophrenia PGS, and additionally
45 unobserved confounders (using computational confound modeling).

46

47 **Results**

48 We identified that lower cognitive intelligence and higher PLEs correlated significantly
49 with several genetic and environmental variables: i.e., lower PGSs for cognitive
50 phenotypes, lower familial SES, lower neighborhood SES, lower supportive parenting
51 behavior, and lower positive school environment. In SEM, lower cognitive intelligence
52 significantly mediated the genetic and environmental influences on higher PLEs (Indirect
53 effects of PGS: β range=-0.0355~ -0.0274; Family SES: β range=-0.0429~ -0.0331;
54 Neighborhood SES: β range=0.0126~ 0.0164; Positive Environment: β range=-0.0039~ -

55 0.003). Supportive parenting and a positive school environment had the largest total impact
56 on PLEs (β range=-0.152~ -0.1316) than any other genetic or environmental factors.

57

58 **Conclusions**

59 Our results reveal the role of genetic and environmental factors on children's PLEs via its
60 negative impact on cognitive intelligence. Our findings have policy implications in that
61 improving the school and family environment and promoting local economic development
62 might be a way to enhance cognitive and mental health in children.

63

64 **Keywords**

65 Cognitive intelligence; psychotic-like experiences; genetic-environmental pathway;
66 structural equation modeling; confounding adjustments

67

68

69 **Key Points**

- 70 ● While existing research shows the association between cognitive decline and
71 PLEs, the genetic and environmental pathways to cognitive intelligence and
72 psychotic risk in children remain unclear.
- 73 ● We identified the significant role of genetic and environmental factors (family,
74 neighborhood, and school) on children's PLEs via a negative impact on cognitive
75 intelligence.
- 76 ● Leveraging large samples with multimodal longitudinal data and advanced
77 computational modeling for adjustment of observed/unobserved confounding bias,
78 our results underscore the importance of incorporating socioeconomic policies into
79 children's cognitive and mental health programs.

80

81

Introduction

82 Childhood is the critical developmental period in human life. Cognitive intelligence
83 and mental health in this period significantly impact key life outcomes at later ages, including
84 academic performance, economic productivity, physical health, intelligence, and
85 psychopathology (Shonkoff, 2012; Walker et al., 2021). Literature shows the significant
86 impact of social adversities on cognitive ability and mental health in early childhood. Lower
87 family socioeconomic status (SES), particularly household income, is linked to lower
88 neurocognitive ability and higher risk of psychopathology in childhood (Hair et al., 2015;
89 Noble et al., 2015; Peverill et al., 2021; Tomasi & Volkow, 2021; Weissman et al., 2018).

90 Additional to family SES, the importance of neighborhood social environment on
91 children's neurocognitive ability has been also emphasized (Gard et al., 2021; Tooley et al.,
92 2020). Adverse neighborhood environment, such as the percent of families below poverty
93 line, low education levels, and exposure to violence, is associated with lower cognitive
94 performance and a greater risk for psychosis in children (Butler et al., 2018; Karcher,
95 Schiffman, et al., 2021; Rakesh et al., 2021; Taylor et al., 2020). Conversely, as protective
96 factors against familial and neighborhood socioeconomic challenges, supportive parenting
97 (Brody et al., 2017; Brody et al., 2019; Holmes et al., 2018; Luby et al., 2012; Luby et al.,
98 2016) and positive school environment (Gard et al., 2021; Piccolo et al., 2019; Rakesh et al.,
99 2021) have been highlighted to improve child cognition and mental health.

100 Psychotic-like experiences (PLEs), which are prevalent in childhood, indicate the
101 risk of psychosis (van der Steen et al., 2019; Van Os & Reininghaus, 2016). Although they
102 are not a direct precursor of schizophrenia, children reporting PLEs in ages of 9-11 years are
103 at higher risk of psychotic disorders in adulthood (Kelleher & Cannon, 2011; Poulton et al.,
104 2000). PLEs also point towards the potential for other psychopathologies including mood,
105 anxiety, and substance disorders (van der Steen et al., 2019), are linked to deficits in
106 cognitive intelligence (Cannon et al., 2002; Kelleher & Cannon, 2011) and show a stronger
107 association with environmental risk factors during childhood than other
108 internalizing/externalizing symptoms (Karcher, Schiffman, et al., 2021).

109 Maladaptive cognitive intelligence may act as a mediator for the effects of genetic
110 and environmental risks on the manifestation of psychotic symptoms (Cannon et al., 2000;
111 Keefe et al., 2006; Reichenberg et al., 2005). Abnormal neurodevelopment, influenced by
112 genetic factors, combined with disrupted cognitive processes resulting from
113 socioenvironmental adversity, may eventually give rise to the positive symptoms of

114 schizophrenia, relevant to PLEs (Garety et al., 2001; Howes & Murray, 2014). Family studies
115 show a decline in cognitive intelligence preceding psychotic symptoms is related to genetic
116 risk (Cosway et al., 2000; Curtis et al., 2001). In more recent studies these associations have
117 led to the model positing that cognitive intelligence mediates the genetic risk for
118 psychopathology and PLEs (Karcher, Paul, et al., 2021; Pat et al., 2021).

119 To minimize potential bias in the estimates of environmental effects, it is crucial to
120 adjust for genetic confounding (Sariasan et al., 2016), given the substantial genetic influence
121 on intelligence (Bouchard & McGue, 1981; Deary et al., 2006; Plomin & Spinath, 2004) and
122 PLEs (Bentall & Fernyhough, 2008; Maxwell et al., 2023). Recent advances in genetics have
123 led to the development of the polygenic score (PGS) approach: a computational method to
124 estimate the genetic loading for a complex trait using statistical associations of each single-
125 nucleotide polymorphism (SNP) identified by genome-wide association studies (GWAS)
126 (Choi et al., 2020). Particularly, PGS for two related but distinct phenotypes—cognitive
127 performance and educational attainment—holds significant importance. As the two most
128 frequently used proxies of cognitive intelligence in genetic studies, PGSs for cognitive
129 performance and educational attainment are positively correlated with intelligence,
130 educational attainment, income, self-rated health, and height (Judd et al., 2020; Lee et al.,
131 2018; Okbay et al., 2022; Selzam et al., 2019). Furthermore, the PGS for educational
132 attainment is associated with a wide range of biological and social outcomes, including brain
133 morphometry (Judd et al., 2020; Karcher, Paul, et al., 2021), psychopathologies such as
134 PLEs, autism, depression, Alzheimer’s disease, neuroticism (Karcher, Paul, et al., 2021;
135 Okbay et al., 2022), cognitive decline (Joo et al., 2022; Karcher, Paul, et al., 2021; Ritchie et
136 al., 2020), BMI, time spent watching television, geographic residence (Abdellaoui et al.,
137 2022), and wealth inequality (Barth et al., 2020). Similar to the terms used in prior research,
138 we will collectively refer to these two PGSs of focus as ‘cognitive phenotypes PGSs’
139 throughout this paper (Joo et al., 2022; Okbay et al., 2022; Selzam et al., 2019). An important
140 gap in the literature is the lack of integrated assessment of the effects of genetic and
141 environmental factors at multiple levels (e.g., familial vs neighborhood) to dissect the genetic
142 and environmental effects underlying abnormal cognitive intelligence and the PLEs.
143 Addressing this with large multimodal data will allow for a more complete understanding of
144 the factors related to the development of PLEs.

145 In this study, we systematically explore the longitudinal trajectories of genetic and
146 environmental influences on PLEs, mediated through cognitive intelligence. Toward this
147 goal, we firstly assess the associations of cognitive phenotype PGSs, family and

148 neighborhood SES, and supportive environment with children's cognitive intelligence and
149 longitudinally measured PLEs. To maintain robustness of our assessment, we employed
150 statistical and computational approaches to carefully consider potential confounding. We then
151 test the mediating effect of cognitive intelligence on the relationship between genetic and
152 environmental factors and PLEs. Our investigation traces these effects from the baseline and
153 through the 1-year and 2-year follow-ups, providing a nuanced understanding on the role of
154 cognitive phenotype polygenic scores, family socioeconomic status, neighborhood
155 socioeconomic status, and positive family and school environments in shaping PLEs in
156 children aged 9-10 years.

157

Materials and Methods

158 **Study Participants**

159 We used the multi-modal genetic and environmental data of 11,878 preadolescent
160 children aged 9-10 years old collected from 21 research sites of the Adolescent Brain
161 Cognitive Development (ABCD) Study, one of the largest longitudinal studies for children's
162 neurodevelopment in the United States. We analyzed the baseline, first year, and second year
163 follow-up datasets included in ABCD Release 4.0, downloaded on January 25, 2022. After k-
164 nearest neighbor imputation of missing values of covariates (categorical variables: sex,
165 genetic ancestry, marital status of the caregiver, ABCD research sites; continuous variables:
166 age, BMI, family history of psychiatric disorders; 4.67% of total observations imputed) using
167 the R package VIM (Kowarik & Templ, 2016), we removed participants with missing data on
168 study variables (missing genotype: N=3,260; follow-up observations: N=1,180;
169 neighborhood information: N=694; cognitive intelligence tests: N=126; PLEs: N=5; positive
170 environment: N=11). The final samples included 6,602 multiethnic children, which
171 comprised 890 of African ancestry (13.48%), 91 of East Asian ancestry (1.38%), 5,211 of
172 European ancestry (78.93%), 229 of Native American ancestry (3.47%), and 181 not
173 specified (2.74%).

174

175 **Data**

176 **NIH Toolbox Cognitive Performance**

177 Children's neurocognitive abilities were assessed using the NIH Toolbox Cognitive
178 Battery, which has seven cognitive instruments for examining executive function, episodic
179 memory, language abilities, processing speed, working memory, and attention (Thompson et
180 al., 2019). We utilized baseline observations of uncorrected composite scores of fluid
181 intelligence (Dimensional Change Card Sort Task, Flanker Test, Picture Sequence Memory
182 Test, List Sorting Working Memory Test), crystallized intelligence (Picture Vocabulary Task
183 and Oral Reading Recognition Test), and total intelligence (all seven instruments) provided in
184 the ABCD Study dataset.

185

186 **Psychotic-Like Experiences (PLEs)**

187 Baseline and 1- and 2-year follow-up of PLEs were measured using the children's
188 responses to the Prodromal Questionnaire-Brief Child Version. In line with previous research
189 (Karcher et al., 2018; Karcher et al., 2020; Karcher, Schiffman, et al., 2021), we computed
190 *Total Score* and *Distress Score*, each indicating the number of psychotic symptoms and levels
191 of total distress. Considering self-reports and parent-reports of psychopathology may differ
192 (Achenbach, 2006), we additionally used parent-rated PLEs derived from four items of the
193 Child Behavior Checklist according to previous studies (Karcher et al., 2018; Karcher et al.,
194 2020; Karcher, Schiffman, et al., 2021). Self-reported PLEs and parent-reported PLEs had
195 significant positive correlation (Pearson's correlation of baseline year: $r = 0.095\sim0.0989$,
196 $p<0.0001$; 1-year follow-up: $r = 0.1322\sim0.1327$, $p<0.0001$; 2-year follow-up: $r =$
197 $0.1569\sim0.1632$, $p<0.0001$).

198

199 **Polygenic Scores (PGS)**

200 To investigate the aggregated effect of genetic components, we estimated PGS of two
201 representative cognitive phenotypes for each participant: educational attainment (EA) and
202 cognitive performance (CP) (Choi et al., 2020). We used the summary statistics released from
203 a GWAS (Lee et al., 2018) of European-descent individuals for EA ($n=1,131,881$) and CP
204 ($n=257,841$). EA was measured as the years of schooling; CP, measured as the respondent's
205 score on cognitive ability assessments of general cognitive function and verbal-numerical
206 reasoning, was assessed in participants from the COGENT consortium and the UK Biobank.
207 To construct PGS of schizophrenia for sensitivity analyses, we used the summary statistics
208 from the multiple GWAS of European sample ($n=65,967$; Ruderfer et al. (2018)) and East
209 Asian sample ($n=58,140$; Lam et al. (2019)). We applied PRS-CSx, a high-dimensional
210 Bayesian regression framework that improves cross-population prediction via continuous
211 shrinkage prior to SNP effect sizes (Ge et al., 2019) (For details, see **Appendix S1**). The two
212 PGSs for cognitive phenotypes had a positive significant correlation (Pearson's correlation: r
213 $=0.4331$, $p<0.0001$).

214

215 **Family-, Neighborhood-, and School-level Environment**

216 We assessed children's family-level SES with family income, parental education, and
217 family's financial adversity based on parent self-reporting (Karcher et al., 2020; Taylor et al.,

218 2020; Tomasi & Volkow, 2021). Higher family income and parental education and lower
219 family's financial adversity denote a higher family SES.

220 Neighborhood-level SES was assessed using the *Area Deprivation Index* (ADI), the
221 percentage of individuals below -125% of the poverty level (henceforth "*poverty*"), and *years*
222 *of residence*, which were associated with PLEs in prior research (Karcher, Schiffman, et al.,
223 2021). Higher values of ADI and *poverty* and fewer *years of residence* indicate a lower
224 neighborhood SES.

225 Based on existing literature (Karcher, Schiffman, et al., 2021; Rakesh et al., 2021),
226 we measured the level of positive parenting behavior and positive school environment to
227 assess the effect of positive family and school environment on each individual.

228

229 **Statistical Modeling**

230 In this study, we employ linear mixed models and a novel structural equation
231 modelling (SEM) method to examine the longitudinal trajectories of genetic and
232 environmental influences on PLEs mediated by cognitive intelligence. We specifically
233 investigate the mediating role of cognitive intelligence within the impacts of cognitive
234 phenotype polygenic scores (PGSs), high family socioeconomic status (SES), low
235 neighborhood SES, and positive family and school environments on PLEs. These influences
236 are examined across three periods of PLEs observations: baseline, 1-year follow-up, and 2-
237 year follow-up (**Figure 1**).

238

239 **Linear Mixed Models**

240 Using linear mixed models to minimize potential population stratification from
241 different household environments and geographical locations (Choi et al., 2020), we analyzed
242 the genetic and environmental effects on cognitive intelligence and PLEs. Key variables of
243 interest were PGS, family SES, neighborhood SES, and positive environment. To avoid
244 multicollinearity, CP and EA PGSs were used separately in two other models. As a random
245 factor, the variable indicating ABCD research sites was used. Variables within each model
246 had no signs of multicollinearity (Fox & Monette, 1992) (generalized variance inflation
247 factor < 2.0 for every variable in all models). The child's sex, age, genetic ancestry, BMI,
248 marital status of the caregiver, and family history of psychiatric disorders were included as

249 covariates in the model (Karcher, Schiffman, et al., 2021). All continuous variables were
250 standardized (z-scaled) beforehand to get standardized estimates, and the analyses were
251 conducted with the *lme4* package in R version 4.1.2. Throughout this paper, threshold for
252 statistical significance was set at $p < 0.05$, with correction for multiple comparisons using the
253 false discovery rate. 95% bootstrapped confidence intervals were obtained with 5,000
254 iterations.

255

256 **Path Modeling**

257 To test the plausibility of whether cognitive intelligence may mediate the association
258 between genetic and environmental factors and PLEs, we used an up-to-date SEM method,
259 integrated generalized structured component analysis (IGSCA) (Hwang, Cho, Jung, et al.,
260 2021). This approach is suited to our study using the multi-modal genetic and environmental
261 variables in that it estimates models with both factors and components as statistical proxies
262 for the constructs.

263 Standard SEM using latent factors (i.e., indirectly measured indicators that explain
264 the covariance among observed variables) to represent indicators such as PGS or family SES
265 relies on the assumption that observed variables within each construct share a common
266 underlying factor. If this assumption is violated, standard SEM cannot effectively control for
267 estimation biases. The IGSCA method addresses this limitation by allowing for the use of
268 composite indicators (i.e., components)—defined as a weighted sum of observed variables—
269 as constructs in the model, more effectively controlling bias in estimation compared to the
270 standard SEM. During estimation, the IGSCA determines weights of each observed variable
271 in such a way as to maximize the variances of all endogenous indicators and components.

272 We assessed path-analytic relationships among the six key constructs: cognitive
273 phenotypes PGSs, family SES, neighborhood SES, positive family and school environment,
274 general intelligence, and PLEs. Considering that the observed variables of the PGSs, family
275 SES, neighborhood SES, positive family and school environment, and PLEs are evaluated as
276 a composite index by prior research, the IGSCA method can mitigate bias more effectively by
277 representing these constructs as components. Notably, investigations carried out by Judd et al.
278 (2020) and Martin et al. (2015) utilized composite indicators to examine the genetic influence
279 on educational attainment and ADHD. Moreover, socioenvironmental influences are often
280 treated as composite indicators as highlighted in Judd et al. (2020). When considering the

281 psychosis continuum, studies like that of van Os et al. (2009) postulate that psychotic
282 disorders are likely underpinned by a multiplicity of background factors rather than a single
283 common factor. This perspective is substantiated by a multitude of prior research that deploys
284 composite indices for the measurement of psychotic symptoms. For these reasons, we
285 statistically represented these constructs as the weighted sums of their observed variables or
286 components (Cho et al., 2021). On the other hand, we represented general intelligence as a
287 common factor that determines the underlying covariance pattern of fluid and crystallized
288 intelligence, based on the classical *g* theory of intelligence (Jensen, 1998; Spearman, 1904).

289 The IGSCA model included the same covariates used in the linear mixed model as
290 well as the ABCD research site as an additional covariate. We applied GSCA Pro 1.1
291 (Hwang, Cho, & Choo, 2021) to fit the IGSCA model to the data and checked the model's
292 goodness-of-fit index (GFI) (Jöreskog & Sörbom, 1986), standardized root mean square
293 residual (SRMR), and total variance of all indicators and components explained (FIT) to
294 assess its overall goodness-of-fit. Ranging from 0 to 1, a larger FIT value indicates more
295 variance of all variables is explained by the specified model (e.g., FIT=0.50 denotes that the
296 model explains 50% of the total variance of all variables) (Hwang, Cho, & Choo, 2021). The
297 rules-of-thumb cutoff criteria in IGSCA is $GFI \geq 0.93$ and $SRMR \leq 0.08$ for an acceptable fit
298 (Cho et al., 2020). Finally, we conducted conditional process analyses to investigate further
299 the indirect and total effects of the constructs in the model. As a trade-off for obtaining robust
300 nonparametric estimates without distributional assumptions for normality, the IGSCA method
301 does not return exact p-values (Hwang, Cho, Jung, et al., 2021). As a reasonable alternative,
302 we obtained 95% confidence intervals based on 5,000 bootstrap samples to test the statistical
303 significance of parameter estimates.

304

305 **Sensitivity Analyses**

306 To ensure robustness of the main analyses results, we conducted multiple sensitivity
307 analyses. As the European-descent-based GWAS was used for constructing PGS, we reran the
308 main analyses using participants of European ancestry (n=5,211) to adjust for ethnic
309 confounding. Next, we tested effects of gene x environment interactions on cognitive
310 intelligence and PLEs, respectively. We also tested the effects of cognitive phenotypes PGS
311 adjusting for schizophrenia PGS, given the association of schizophrenia PGS and cognitive
312 deficit in psychosis patients (Shafee et al., 2018) and individuals at-risk of psychosis (He et

313 al., 2021). Lastly, we adjusted for unobserved confounding bias in the linear mixed model,
314 using a recently developed framework for causal inference based on null treatments approach
315 (Miao et al., 2022). Designed to discern causal effects from multiple treatment variables
316 within non-randomized, observational data, the null treatments approach hinges on the
317 assumption that no fewer than half of the confounded treatments exert no causal influence on
318 the outcome. It circumvents the need for prior knowledge regarding which treatments are null
319 and eliminates the necessity for independence among treatments. Given our model's inclusion
320 of numerous treatment variables with shared variances due to the presence of unobserved
321 confounders (Abdellaoui et al., 2022; Okbay et al., 2022)—including cognitive phenotypes
322 PGS, family and neighborhood SES, positive family and school environments—we opted to
323 employ this method.

324

325

326

Results

327 **Demographics**

328 **Table 1** presents the demographic characteristics of the final samples. For multiethnic
329 subjects (main analyses, n=6,602), 47.15% were female, and the parents of 70.21% were
330 married. In European ancestry samples (sensitivity analyses, n=5,211), 46.71% were female,
331 and the parents of 77.47% were married. Children of European ancestry showed significantly
332 different marital status ($p<0.0001$), lower BMI ($p<0.0001$) and family history of psychiatric
333 disorders ($p<0.0001$) compared to children of other genetic ancestries. Our linear mixed
334 model and IGSCA analyses were adjusted using sex, age, marital status, BMI, family history
335 of psychiatric disorders, and ABCD research sites as covariates.

336

337 **Genetic influence on cognitive phenotypes correlates positively with intelligence and
338 negatively with PLEs**

339 As shown in **Figure 2**, higher PGSs of cognitive capacity phenotypes correlated
340 significantly with higher intelligence (CP PGS: $\beta=0.1113\sim0.1793$; EA PGS:
341 $\beta=0.0699\sim0.1567$). While CP PGS was associated only with lower baseline year *Distress*
342 *Score* PLEs ($\beta=-0.0323$), EA PGS was associated with lower baseline year and follow-up

343 PLEs of all measures (baseline: $\beta=-0.0518\sim-0.0519$; 1-year: $\beta=-0.0423\sim-0.043$; 2-year: $\beta=-$
344 $0.036\sim-0.0463$). No significant correlations were found between CP PGS and follow-up
345 PLEs ($p>0.05$). The effects of EA PGS were larger on baseline year PLEs than follow-up
346 PLEs. The effect sizes of EA PGS on children's PLEs were larger than those of CP PGS (EA
347 PGS: $\beta=-0.036\sim-0.0519$; CP PGS: $\beta=-0.0323$). (Table S1).

348

349 **Family and neighborhood SES correlates positively with intelligence and negatively with**
350 **PLEs**

351 Parental education associated positively with all types of intelligence
352 ($\beta=0.0699\sim0.1745$) and negatively with baseline year *Total* and *Distress Score* PLEs ($\beta=-$
353 $0.0528\sim-0.043$), 1-year follow-up PLEs ($\beta=-0.0538\sim-0.0449$), and 2-year follow-up PLEs
354 ($\beta=-0.0459\sim-0.0389$). Family income correlated positively with intelligence
355 ($\beta=0.0723\sim0.1365$) and negatively with 2-year follow-up parent-rated PLEs ($\beta=-0.0503\sim-$
356 0.0502). Family's financial disadvantage correlated negatively with baseline year parent-
357 rated PLEs ($\beta=0.0726\sim0.0728$), 1-year follow-up PLEs of all types ($\beta=0.0307\sim0.0577$), and
358 2-year follow-up PLEs of all types ($\beta=0.0461\sim0.0581$).

359 The ADI correlated significantly negatively with all types of intelligence ($\beta=-$
360 $0.0684\sim-0.054$). Additionally, a higher ADI correlated significantly with higher baseline year
361 PLEs ($\beta=0.0587\sim0.0914$), 1-year follow-up PLEs ($\beta=0.0523\sim0.0613$), and 2-year follow-up
362 PLEs ($\beta=0.0397\sim0.0449$).

363 We found no significant associations of *poverty* with any of the target variables ($p>$
364 0.05). *Years of residence* correlated significantly with crystallized intelligence
365 ($\beta=0.035\sim0.0372$) and baseline year *Total Score* PLEs ($\beta=-0.029\sim-0.0273$). (Table S1).

366

367 **Positive family and school environments correlate positively with intelligence and**
368 **negatively with the influence of PLEs**

369 Positive parenting behaviors showed significant negative correlations with baseline
370 year PLEs ($\beta=-0.0702\sim-0.0419$), 1-year follow-up PLEs ($\beta=-0.0588\sim-0.0397$), and 2-year
371 follow-up PLEs ($\beta=-0.0623\sim-0.0356$) (Figure 2). Positive school environment was associated

372 positively with total intelligence ($\beta=0.0353\sim0.0397$) and fluid intelligence
373 ($\beta=0.0514\sim0.0545$) and negatively with all three measures of baseline year PLEs ($\beta=-$
374 $0.1193\sim-0.0468$), 1-year follow-up PLEs ($\beta=-0.1078\sim-0.04$), and 2-year follow-up PLEs ($\beta=-$
375 $0.1068\sim-0.0586$) (**Table S1**).

376

377 **Structural Equation Modeling-Integrated Generalized Structured Component Analysis**

378 The IGSCA model showed that intelligence mediated the effects of genes and
379 environments on the risk for psychosis (PLEs) (**Figure 3** and **Table 2**). Estimated factor
380 loadings of latent factor variable and weights of component variables are presented in **Table**
381 **S2**. The model showed a good model fit with a GFI of 0.9735, SRMR of 0.0359, and FIT
382 value of 0.4912 (Cho et al., 2020). Intelligence was under significant direct influences of the
383 cognitive phenotypes PGS ($\beta=0.2427$), family SES ($\beta=0.2932$), neighborhood SES ($\beta=-$
384 0.1121), and positive environment ($\beta=0.0268$). Family SES and positive environment had
385 significant negative direct effects on PLEs of all years. Cognitive phenotypes PGS and
386 neighborhood SES showed no significant direct effects on any of the PLEs ($p>0.05$).
387 Intelligence significantly mediated the effects of the PGS, family and neighborhood SES, and
388 positive environment on PLEs of all years: the PGS (baseline year: $\beta=-0.035$; 1-year: $\beta=-$
389 0.0355 ; 2-year: $\beta=-0.0274$), family SES (baseline year: $\beta=-0.0423$; 1-year: $\beta=-0.0429$; 2-
390 year: $\beta=-0.0331$), neighborhood SES (baseline year: $\beta=0.0162$; 1-year: $\beta=0.0164$; 2-year:
391 $\beta=0.0126$), and positive environment (baseline year: $\beta=-0.0039$; 1-year: $\beta=-0.0039$; 2-year:
392 $\beta=-0.003$).

393 For all observed years, positive environment had largest total effects on PLEs
394 (baseline year: $\beta=-0.152$; 1-year: $\beta=-0.1316$; 2-year: $\beta=-0.1364$), followed by family SES
395 (baseline year: $\beta=-0.1216$; 1-year: $\beta=-0.1119$; 2-year: $\beta=-0.1164$), neighborhood SES
396 (baseline year: $\beta=0.0504$; 1-year: $\beta=0.0329$; 2-year: $\beta=0.0192$), and PGS (baseline year: $\beta=-$
397 0.0498 ; 1-year: $\beta=-0.036$; 2-year: $\beta=-0.0365$). The total effects of each indicator on PLEs
398 were significant except for those of neighborhood SES ($p>0.05$).

399

400 **Sensitivity Analyses**

401 As sensitivity analyses, we reran our main analyses with adjustment for ethnic

402 confounding, schizophrenia PGS, and unobserved confounding, respectively. Results of
403 linear mixed model and IGSCA analyses were consistent (**Table S3-S7**). See **Appendix S2**
404 for detailed results.

405

406 Discussion

407 This study investigated the relationships of the genetic and environmental influences
408 on the development of intelligence and the PLEs in youth, leveraging genetic data from the
409 large epidemiological samples and a multi-level environmental (socioeconomic) data. Our
410 results support the model that genetic factors (PGS for cognitive phenotypes), socioeconomic
411 conditions, and family and school environments may influence cognitive intelligence in
412 children, and this impact may lead to the individual variability of the current and future PLEs
413 in children. Our analysis with integrated data shows the contributions of genetic and
414 environmental factors, respectively, to cognitive and mental wellness in children, and further
415 provides policy implications to improve them.

416 Our SEM shows that cognitive intelligence mediates the environmental and genetic
417 influence on the current and future PLEs. The environmental factors (family SES,
418 neighborhood SES, and positive parenting and schooling) and PGS of cognitive phenotypes
419 exhibit significant indirect effects via cognitive intelligence on PLEs. Prior research
420 identifying the mediation of cognitive intelligence focused on either genetic (Karcher, Paul,
421 et al., 2021) or environmental factors (Lewis et al., 2020) alone. Studies with older clinical
422 samples have shown that cognitive deficit may be a precursor for the onset of psychotic
423 disorders (Eastvold et al., 2007; Fett et al., 2020; Vorstman et al., 2015). Our study advances
424 this by demonstrating the integrated effects of genetic and environmental factors on PLEs
425 through the cognitive intelligence in 9-11 years old children. Such comprehensive analysis
426 contributes to assessing the relative importance of various factors influencing children's
427 cognition and mental health, and it can aid future studies designed for identifying health
428 policy implications. Considering the directions and magnitudes of the effects, though the
429 effects of PGS remain significant, aggregated effects of environmental factors account for
430 much greater degrees on PLEs.

431 Our results of cognitive intelligence mediating the genetic and environmental effects
432 on PLEs may be related to several potential mechanisms. Children raised in higher family
433 SES may have sufficient nutrition and cognitive stimulants, whereas children living in

434 deprived neighborhoods may be exposed to higher rates of crime, air pollution, and substance
435 abuse (Lewis et al., 2020; Marshall et al., 2020; Taylor et al., 2020; Tomasi & Volkow, 2021).
436 Environmental enrichment may be associated with longer periods of neural plasticity (e.g.
437 myelination, maturation of brain circuitry), leading to higher cognitive ability and lower risk
438 of mental disorders like PLEs ([Tooley et al., 2021](#)). This may be further linked to the
439 cognitive reserve theory. The theory suggests that genetic influence for cognitive phenotypes
440 and environmental enrichment promotes more efficient, flexible brain networks, which may
441 lead to greater resilience against psychopathology (Stern, 2009). Indeed, prior clinical studies
442 show the linkage between cognitive reserve and psychosis (Amoretti et al., 2018; Leeson et
443 al., 2011).

444 Our results indicate that genetic influences on cognitive phenotypes are significantly
445 linked to PLEs. PGSs for CP and EA were strongly correlated with PLEs (baseline year, 1-
446 year follow-up, and 2-year follow-up). These associations were robust after adjustment for
447 schizophrenia PGS, ethnic confounding and unobserved confounders. Cognitive phenotypes
448 PGS generally show higher predictive performance than PGS of any other traits (Lee et al.,
449 2018; Okbay et al., 2022; Plomin & von Stumm, 2018). Genetic variants associated with CP
450 and EA are related to complex traits across the life span, including neuroticism, depressive
451 symptoms, smoking in adulthood, cognitive decline at a later age ([Joo et al., 2022](#)), risk for
452 Alzheimer's disease ([Lee et al., 2018; Okbay et al., 2022](#)), brain volume, area, and thickness,
453 as well as psychotic disorders (Karcher, Paul, et al., 2021). Prior gene expression studies
454 suggest that polygenic signals for schizophrenia, bipolar disorder, and EA are significantly
455 enriched in the central nervous system, particularly the cerebellum (Finucane et al., 2018).
456 Our findings emphasize the importance of cognitive phenotypes PGS as a biomarker which
457 not only implicates cognitive traits but also exhibits genetic overlap with the PLEs.

458 The differing magnitudes of the PGS impact between EA and CP warrant attention.
459 The effects of the EA PGS on the PLEs of all years were 160.68%~371.67% larger than those
460 of CP PGS. This discrepancy may result from that the larger sample size of EA GWAS than
461 that of CP GWAS. Alternatively, the discrepancies in effect sizes may suggest different
462 genetic compositions between EA and CP. Recent literature documents that more than half of
463 the polygenic signal for EA is related to noncognitive and social skills required for successful
464 educational attainment (Demange et al., 2021), whereas CP may rather be linked to cognitive
465 skills. This observation also supports the well-established relationships of the EA PGS with
466 socioeconomic and life-course outcomes (e.g., social mobility (Belsky et al., 2018), voter
467 turnout (Aarøe et al., 2020), BMI, income, time spent watching television, geographic

468 residence (Abdellaoui et al., 2022), and wealth inequality (Barth et al., 2020), which may be
469 influenced by unobserved environmental factors (Young et al., 2019). In our analysis, the
470 utilization of two PGSs a more comprehensive evaluation, contributing to an estimation of
471 the genetic and environmental factors that attempted to minimize confounding bias.

472 Furthermore, the significant effects of cognitive phenotypes PGS on cognitive
473 intelligence ($\beta=0.0699\sim0.1793$) remained robust and similar in magnitude after adjusting for
474 genetic ancestry ($\beta=0.0754\sim0.1866$) and other (unobserved) confounding ($\beta=0.0546\sim0.1776$).
475 As we controlled for family-, neighborhood-, and school-level environmental factors and
476 unobserved confounders, our results may be interpreted as significant genetic influences on
477 individual's cognitive intelligence. This interpretation is supported by a recent study (Isungset
478 et al., 2022): Despite of the socioeconomic differences in Norway (a typical social democratic
479 welfare state) and the US (a typical liberal welfare state), the magnitudes of genetic influence
480 on cognitive intelligence were similar (Norway: $\beta=0.18$; US: $\beta=0.17$). Cognitive phenotypes
481 PGS is an important genetic factor across the nations and societies. Therefore, analyses
482 omitting the genetic influence may be subject to overestimation of the socioeconomic impact
483 (Plomin & von Stumm, 2018; Sariasan et al., 2016).

484 This study shows that a high SES and positive environment, particularly positive
485 parenting behavior and school environment, is associated with higher intelligence and a lower
486 risk for PLEs in children. While prior research has emphasized the dominant role of family
487 SES (e.g. family income) (Tomasi & Volkow, 2021), our SEM analyses (IGSCA) showed
488 that positive environmental factors such as supportive parenting and schooling have a greater
489 impact on children's PLEs. Specifically, the effect sizes were the highest in supportive family
490 and school environment, followed by family and neighborhood SES. Even after adjusting for
491 genetic ancestry and unobserved confounders, the strong associations of positive parenting
492 and schooling with higher intelligence and fewer PLEs remained significant. These findings
493 suggest that interventions that target positive family and school environments may be
494 particularly effective. Recent research supports this notion, showing that interventions that
495 promote supportive parenting and inclusive school environments can improve neurocognitive
496 ability, academic performance, and decrease risk behaviors such as drinking and emotional
497 eating (Brody et al., 2017; Brody et al., 2019; Holmes et al., 2018).

498 Moreover, our results showed that positive parenting and schooling in baseline year
499 were associated not only with baseline year PLEs but also with PLEs 1-2 years later. This is
500 in line with prior research showing that intervention focused on parenting behavior and

501 school environment have long-lasting positive effects that extend into adulthood and even
502 across generations (Cunha & Heckman, 2007; Hill et al., 2020).

503 While policy implications in observational studies like ours might be limited, our
504 findings show the importance of comprehensive approaches considering the entire ecosystem
505 of children's lives—including residential, family, and school environment—for future
506 research aimed to enhance children's intelligence and mental health. When we combine the
507 total effect sizes of neighborhood and family SES, as well as positive school environment and
508 parenting behavior ($\sum |\beta| = 0.2718\sim0.3242$), they considerably surpass the total effect
509 sizes of cognitive phenotypes PGSSs ($|\beta| = 0.0359\sim0.0502$). It has been suggested that a
510 holistic and quantitative approach that takes into account the comprehensive ecosystem of
511 family, school, and residential environments may ensure policy effects and efficient use of
512 resources (Cree et al., 2018; Garner & Yogman, 2021; Shonkoff, 2012). For example, the
513 Health Impact in 5 Years Initiative of the US Centers for Disease Control and Prevention
514 (CDC, 2018) includes 14 evidence-based interventions, such as providing school-based
515 prevention programs, public transportation, home improvement loans, and earned income tax
516 credits, to tackle the social determinants of public health. Our study strengthens the idea that
517 an interdisciplinary science-driven, coordinated approach to intervening in the select
518 environmental factors may allow practical improvements in child development, particularly
519 in those who are at a disadvantage.

520 Our study has some limitations. First, due to data availability constraints in the
521 ABCD study, we only utilized baseline observations for NIH Toolbox cognitive
522 intelligence, and we could not test whether PLEs might be a mediator of intelligence.
523 Second, the generalizability of our findings may be limited since most of the participants
524 included in our analysis are from European ancestry. Although the ABCD Study aimed to
525 achieve its representativeness by recruiting from an array of school systems located around
526 each of the 21 research sites, chosen for their diversity in geography, demographics, and
527 socioeconomic status, it is not fully representative of the US population (Compton et al.,
528 2019). Third, the duration of the follow-up period utilized in this study is relatively short
529 (1-year and 2-year follow-up), which may limit the interpretability of our findings for
530 understanding cognitive and psychiatric development during later childhood. Future
531 research could potentially benefit from employing longer follow-up periods, as more
532 follow-up observations are being collected in the ABCD Study. Fourth, while we used a
533 wide range of statistical methods to adjust for confounding bias from observed and
534 unobserved variables (e.g., genetic ancestry), we did not account for other types of

535 potential bias such as sample selection bias. Fifth, despite a number of causal inference
536 methods used in this study, the ABCD Study is a non-randomized dataset. Given the
537 observational nature of the ABCD Study, interpreting our results as actual causality
538 requires more caution. Finally, we did not include all important environmental variables,
539 such as air pollution (Marshall et al., 2020) and social capital (Krabbendam, 2005), which
540 are not collected in the ABCD study.

541 In conclusion, our study provides potential pathways of genetic factors of
542 cognitive phenotypes and environmental factors of family, school, and neighborhood to
543 cognitive and mental wellness in children. Our findings underscore the importance of a
544 comprehensive approach that considers both biological and socioeconomic features in
545 promoting young children's cognitive ability and mental health. Given the importance of
546 child development, it requires joint efforts from multiple disciplines.

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561

562 **Author Contributions**

563 JP, EL, and GC conducted the main analyses. HH, YYJ, and JC supervised the study.
564 JP, EL preprocessed data. JP, EL, GC, HH performed statistical analyses. EL, BK, GK, and

565 YYJ constructed PGS. JP, EL, GC, YYJ, and JC drafted and critically reviewed the
566 manuscript. All authors read and approved the final draft.

567

568 **Data Availability**

569 All codes used in this study can be found at
570 https://github.com/Transconnectome/Intell_PLE_Pathway. Due to ABCD Study's policy in
571 data sharing, we provide a synthetic dataset instead of real observations. This synthetic
572 dataset was generated with conditional GAN (Xu et al., 2019) to imitate the data structure of
573 our final study samples. After automatic hyperparameter optimization with Optuna (Akiba et
574 al., 2019), the synthetic dataset showed overall quality score of 84.15%. Note that analyses
575 results from the synthetic data may not be 100% identical to the results presented in this
576 paper, due to the differences between synthetic vs original dataset.

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919 **Figures**

920

921 **Figure 1: Study diagram for longitudinal trajectories of genetic and environmental**
922 **influences on PLEs through cognitive intelligence.** This study examines the mediating role
923 of cognitive intelligence within the effects of cognitive phenotype PGSs, high family SES,
924 low neighborhood SES, and positive family and school environments on PLEs observed at
925 baseline, 1-year follow-up, and 2-year follow-up in children aged 9-10 years. Both direct and
926 indirect effects, as well as total effects, were evaluated for statistical significance.

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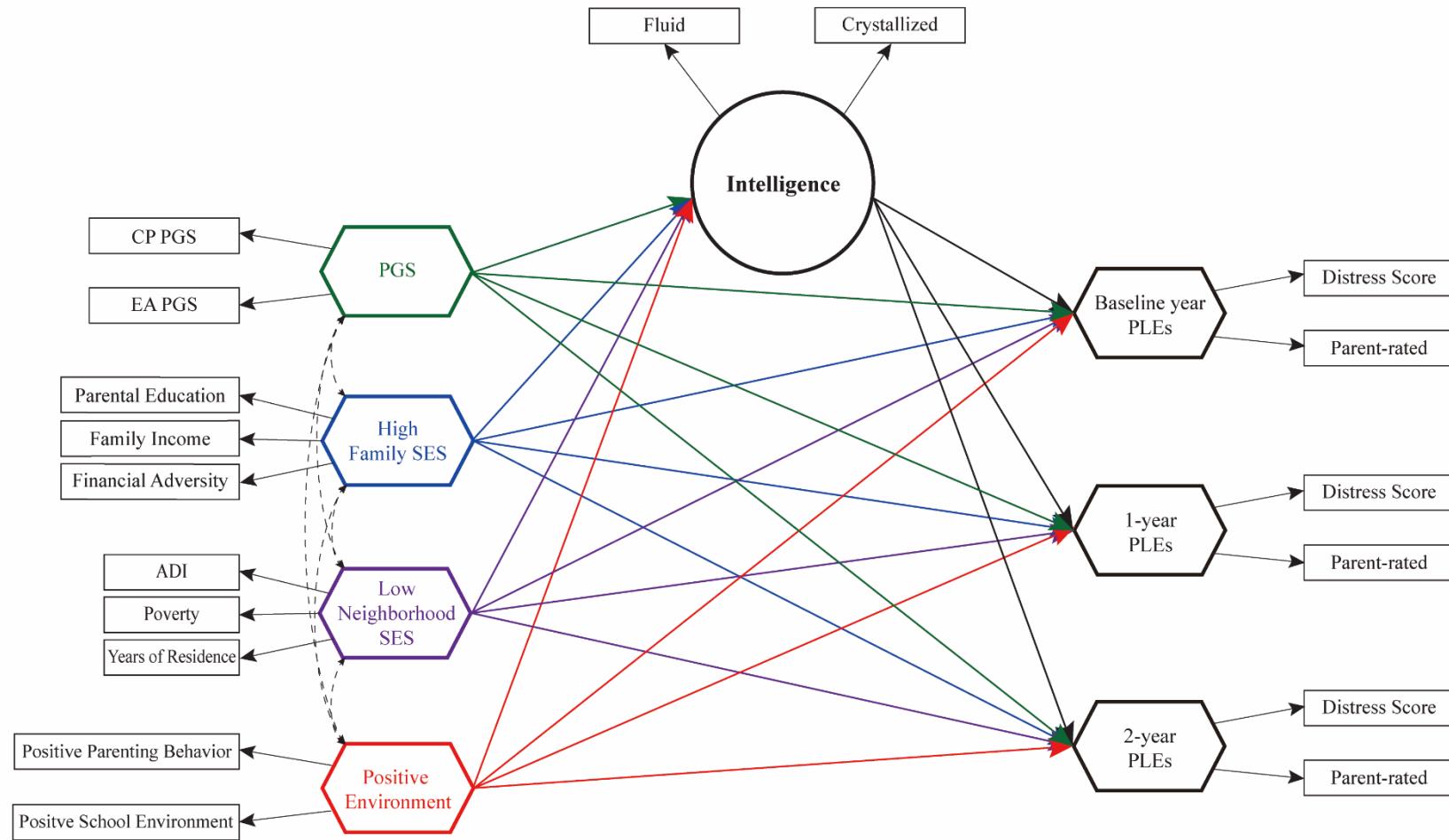
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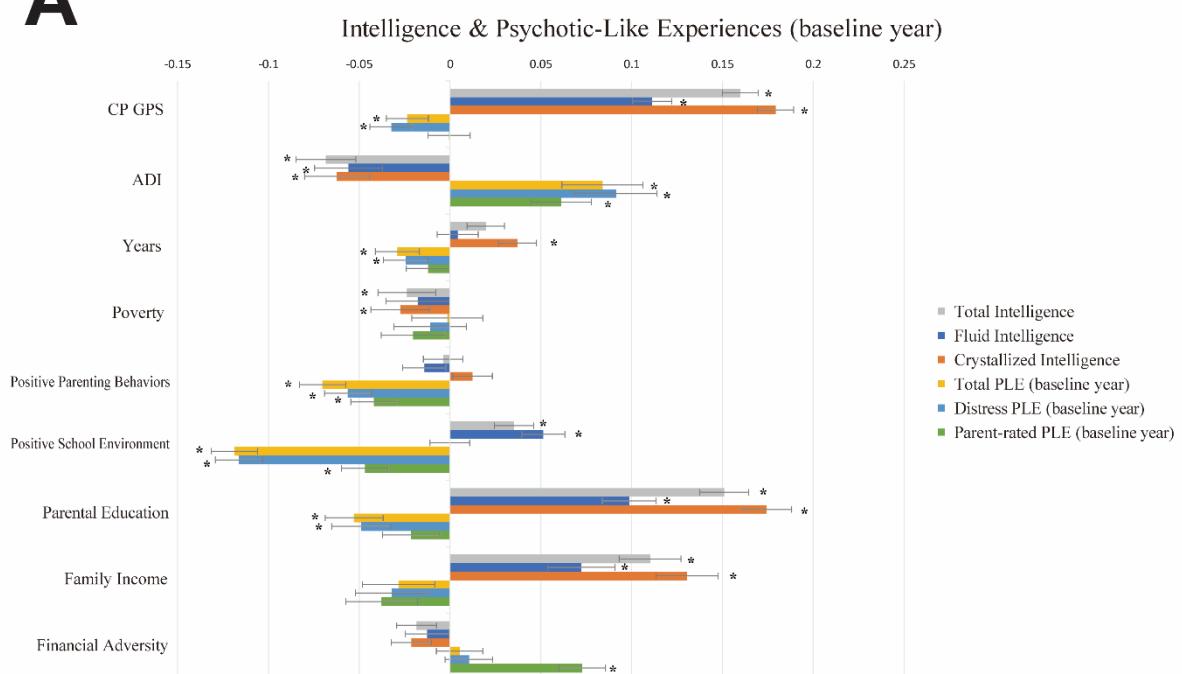


947 **Figure 2: Linear models testing genetic, socioeconomic, and environmental factors**
948 **associated with cognitive intelligence and PLEs.** Standardized coefficients of a linear
949 mixed model with CP PGS (A, B) and EA PGS (C, D). The analyses included 6,602 samples
950 of multiethnicity. Cognitive intelligence and PLEs correlated with the PGSs, residential
951 disadvantage, positive environment, and family SES in the opposite directions. Error bars
952 indicate 95% bootstrapped confidence intervals with 5,000 iterations. CP and EA denote
953 cognitive performance and education attainment, respectively; PGS, polygenic scores; SES,
954 socioeconomic status; PLEs, psychotic-like experiences; ADI, Area Deprivation Index;
955 Poverty, percentage of individuals below -125% of the poverty level; Years, years of
956 residence. (*p-FDR<0.05)

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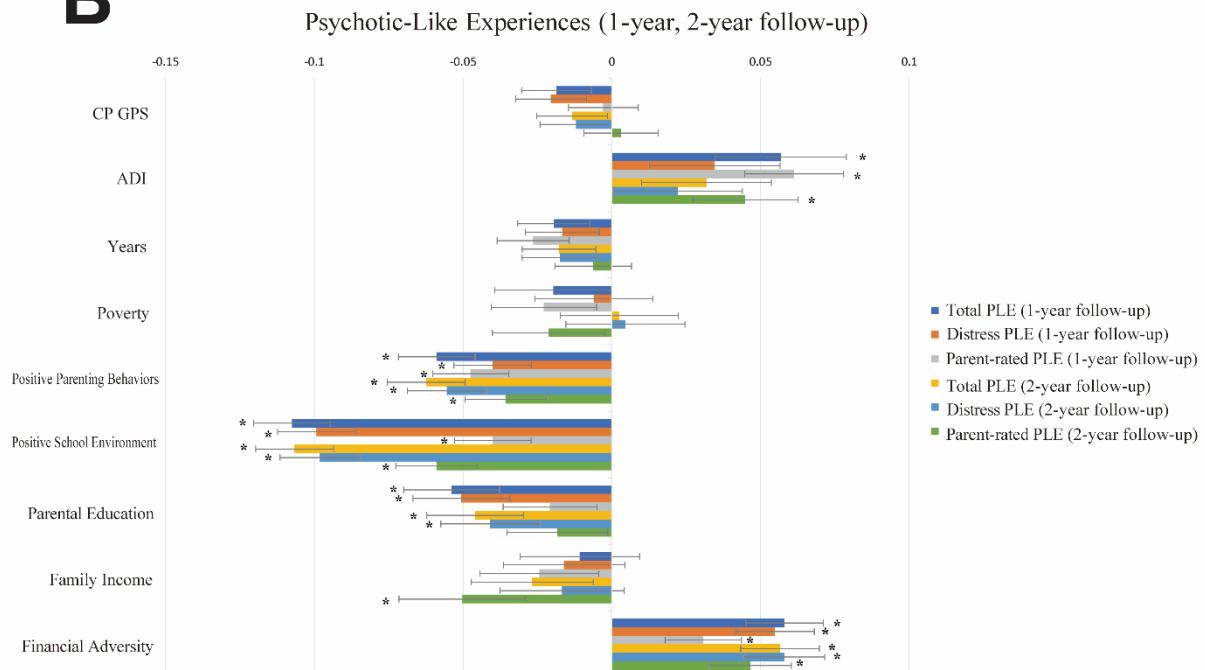
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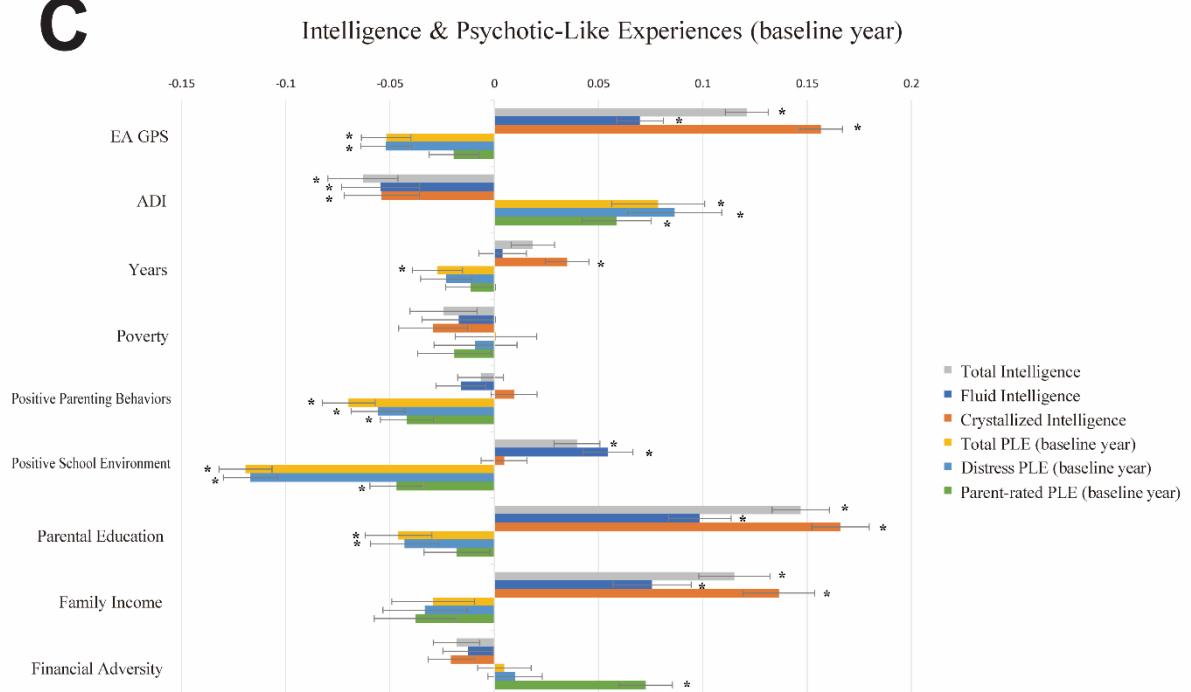
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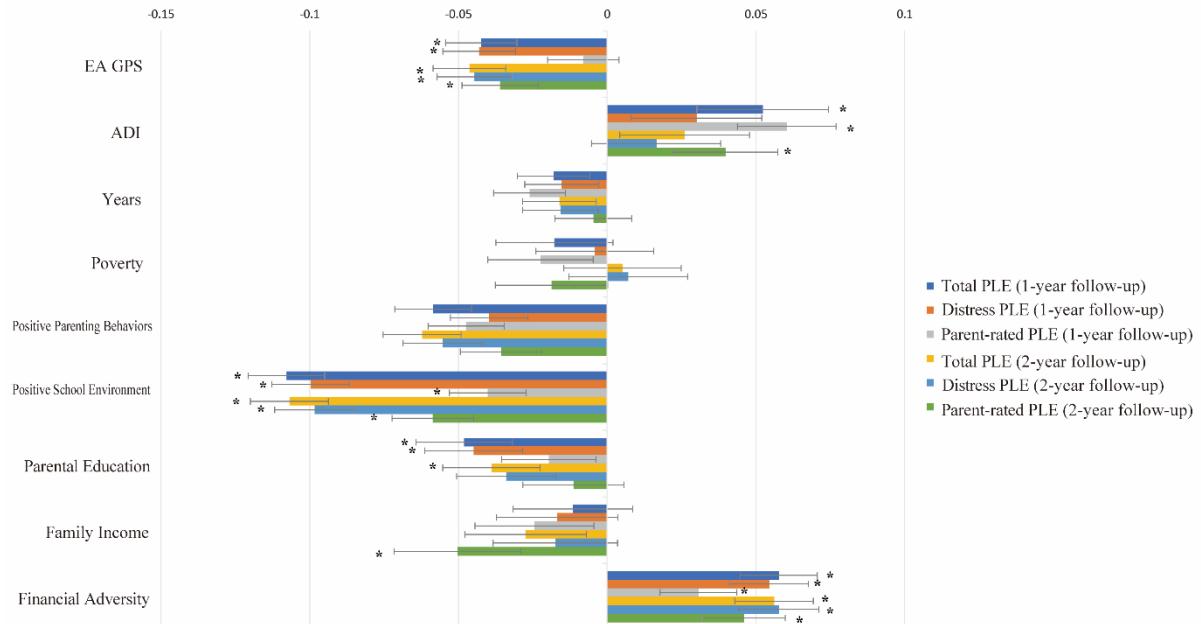
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D

Psychotic-Like Experiences (1-year, 2-year follow-up)



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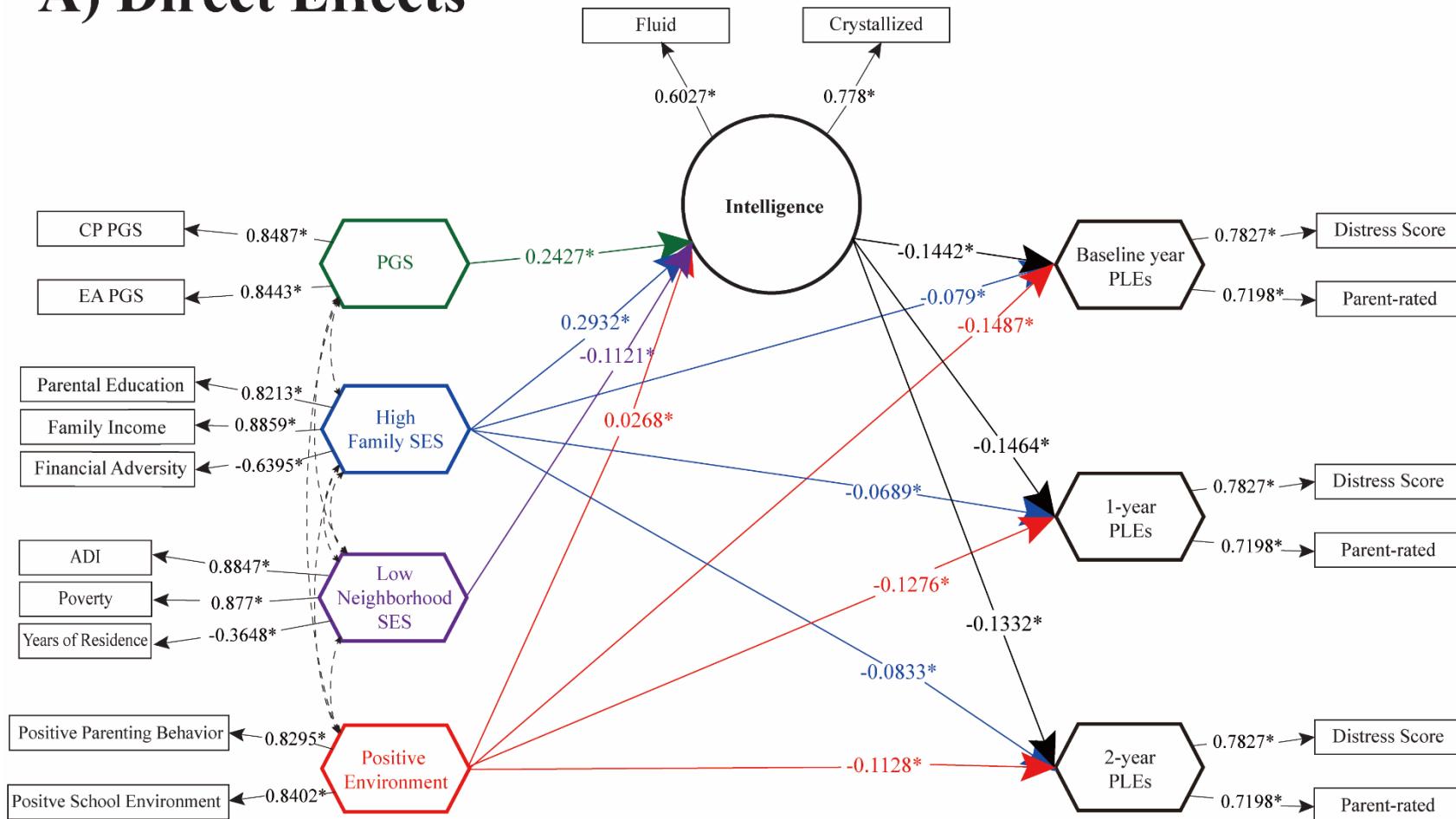
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966 **Figure 3: Direct/Indirect effects of gene-environment factors to cognitive and PLEs**
967 **outcomes**

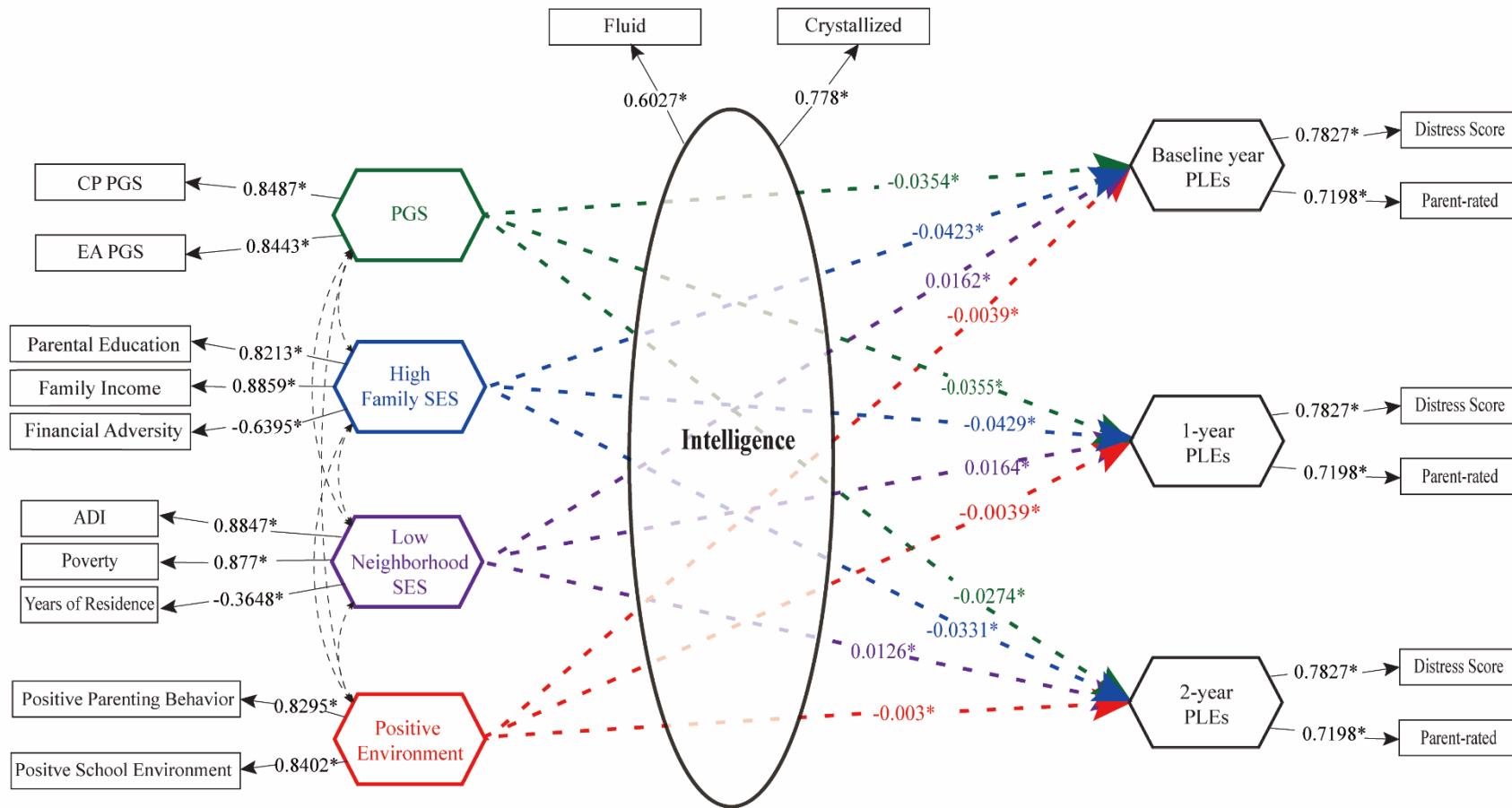
968 A. Direct pathways from PGS, high family SES, low neighborhood SES, and positive
969 environment to cognitive intelligence and PLEs. Standardized path coefficients are indicated
970 on each path as direct effect estimates (significance level * $p<0.05$). **B.** Indirect pathways to
971 PLEs via intelligence were significant for polygenic scores, high family SES, low
972 neighborhood SES, and positive environment, indicating the significant mediating role of
973 intelligence. **C.** Relative effect sizes of direct and indirect pathways within the total effects on
974 PLEs. The standardized effect sizes of direct pathways are colored within each bar. In **A-B**,
975 child sex, genetic ancestry, BMI, marital status, family history of psychiatric disorders, and
976 ABCD research sites were included as covariates. CP PGS and EA PGS denote polygenic
977 scores of cognitive performance and education attainment, respectively; SES, socioeconomic
978 status; PLEs, psychotic-like experiences; Crystallized and Fluid, crystallized and fluid
979 intelligence; ADI, Area Deprivation Index; Poverty, percentage of individuals below -125%
980 of the poverty level; Years, years of residence.

981 Note: * indicates a statistically significant parameter estimate at $\alpha=0.05$.

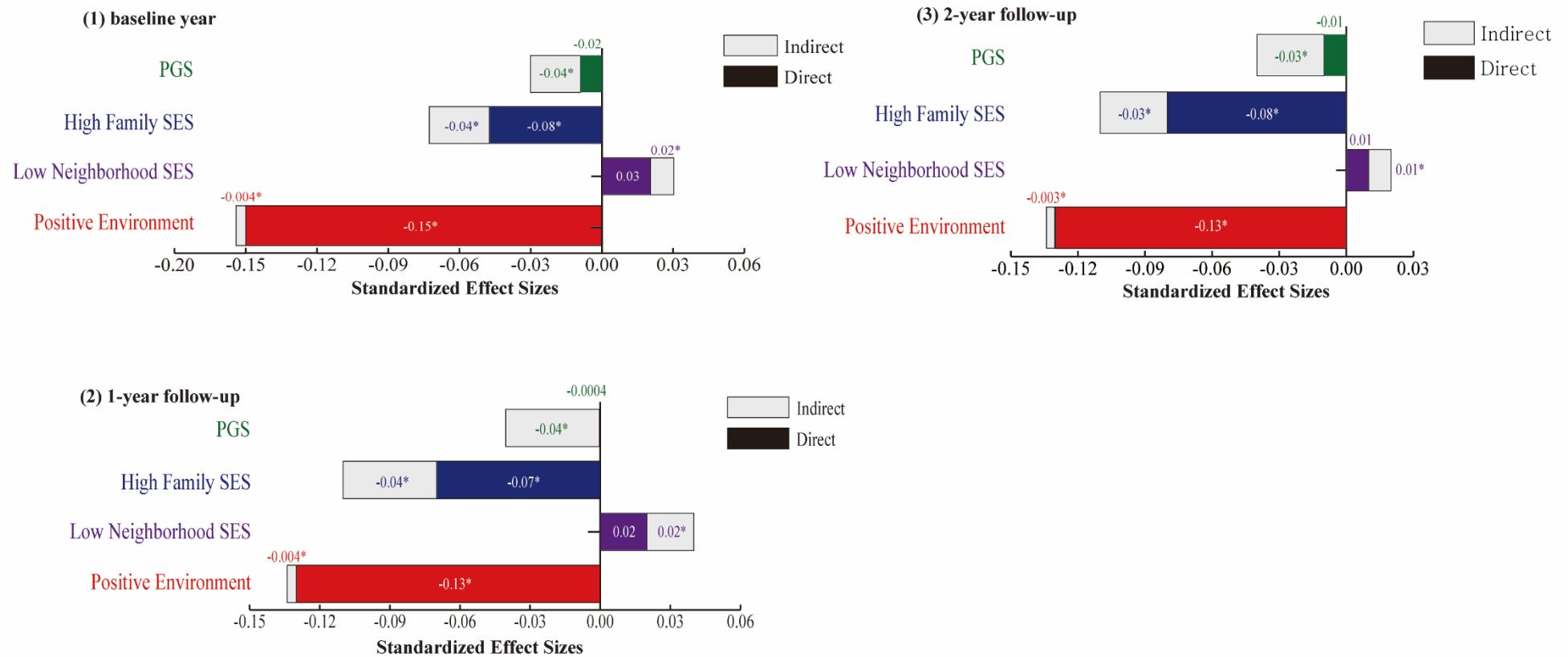
A) Direct Effects



B) Indirect Effects



C) Relative Effect Sizes



Tables

Table 1. Demographic characteristics of the study participants.

Of the initial 11,878 ABCD samples, we obtained data for the variables of interest for 6,602 multiethnic children. For multiethnic subjects (main analyses, n=6,602), 47.15% were female, and the parents of 70.21% were married. In European ancestry samples (sensitivity analyses, n=5,211), 46.71% were female, and the parents of 77.47% were married. Children of European ancestry had significantly different marital status ($p<0.0001$), lower BMI ($p<0.0001$) and higher family history of psychiatric disorders ($p<0.0001$) than children of multiethnic ancestries. There were no significant differences in other characteristics between the two ancestry groups.

The 6,602 multiethnic participants consisted of 890 African-ancestry (13.48%), 229 Native American ancestry (3.47%), 91 East Asian ancestry (1.38%), 181 not specified (2.74%), and 5,211 European ancestry (78.93%) children. Differences between genetic ancestry groups were calculated using χ^2 tests for categorical variables and t tests for continuous variables.

Demographic Characteristics		European Ancestry (n=5,211)			Multiethnic (n=6,602)			Test Statistics	
		N	Ratio (%)	Mean (SD)	N	Ratio (%)	Mean (SD)	t(df)/ χ^2 (df)	p value
Sex	Male	2,777	53.29%		3,489	52.85%		-0.4795 (11811)	0.6316
	Female	2,434	46.71%		3,113	47.15%			
Marital Status of the Caregiver	Married	4,037	77.47%		4,635	70.21%		-10.2326 (11811)	<0.0001
	Widowed	38	0.73%		50	0.76%			
	Divorced	485	9.31%		610	9.24%			
	Separated	155	2.97%		232	3.51%			
	Never Married	275	5.28%		718	10.88%			
	Living with Partner	221	4.24%		357	5.41%			
Age (rounded to chronological month)	5,211			118.99 (7.46)	6,602		118.94 (7.41)	0.3652 (11811)	0.715
BMI				18.29 (3.67)			18.72 (4.12)	-5.8889 (11811)	<0.0001
Family History of Psychiatric Disorders (proportion of first-				0.10 (0.11)			0.09 (0.11)	4.4296 (11811)	<0.0001

degree relatives who experienced mental illness)									
Genetic Ancestry	African	-			890	13.48%			
	Native American	-			229	3.47%			
	East Asian	-			91	1.38%			
	European	5,211	100%		5,211	78.93%			
	Not Specified	-			181	2.74%			

Table 2. IGSCA analysis of multiethnic samples. Sex, age, genetic ancestry, BMI, parental education, marital status of the caregiver, household income, and family's financial adversity based on parents' self-report, family history of psychiatric disorders, and ABCD research sites were included as covariates. Family socioeconomic status was included to confirm that the associations of PGS, neighborhood disadvantage, and positive environment are meaningful. SE and CI represent standard error and confidence intervals, respectively. Significant effects are marked with a star (*).

Analysis of Total/Direct/Indirect Effects						
Effect Type	Paths	Estimate	SE	95% CI		Significance
1. Effects from PGS to Intelligence (baseline year)						

Direct Effect	PGS→Intelligence	0.242736	0.01277	0.218202	0.267954	*
2. Effects from High Family SES to Intelligence (baseline year)						
Direct Effect	High Family SES →Intelligence	0.293171	0.016737	0.260337	0.326413	*
3. Effects from Low Neighborhood SES to Intelligence (baseline year)						
Direct Effect	Low Neighborhood SES →Intelligence	-0.1121	0.016768	-0.14568	-0.08118	*
4. Effects from Positive Environment to Intelligence (baseline year)						
Direct Effect	Positive Environment→Intelligence	0.026793	0.012552	0.003984	0.052633	*
5. Effects from Intelligence to Psychotic-like Experiences (all years)						
Direct Effect	Intelligence→ Psychotic-like Experiences (baseline year)	-0.14421	0.027683	-0.20344	-0.09516	*
Direct Effect	Intelligence→ Psychotic-like Experiences (1-year follow-up)	-0.14638	0.027507	-0.20834	-0.09983	*
Direct Effect	Intelligence→ Psychotic-like Experiences (2-year follow-up)	-0.11276	0.028708	-0.17428	-0.063	*
6. Effects from PGS to Psychotic-like Experiences (baseline year)						
Total Effect	PGS→ Psychotic-like Experiences	-0.05017	0.011354	-0.07292	-0.02853	*
Indirect Effect	PGS→ Intelligence→ Psychotic-like Experiences	-0.035	0.007126	-0.0508	-0.02273	*
Direct Effect	PGS→ Psychotic-like Experiences	-0.01516	0.01347	-0.04085	0.012389	

7 Effects from High Family SES to Psychotic-like Experiences (baseline year)						
Total Effect	High Family SES→ Psychotic-like Experiences	-0.12126	0.019087	-0.15851	-0.08313	*
Indirect Effect	High Family SES→ Intelligence→ Psychotic-like Experiences	-0.04228	0.008652	-0.06139	-0.02707	*
Direct Effect	High Family SES→ Psychotic-like Experiences	-0.07898	0.020747	-0.11856	-0.03698	*
8. Effects from Low Neighborhood SES to Psychotic-like Experiences (baseline year)						
Total Effect	Low Neighborhood SES→ Psychotic-like Experiences	0.050374	0.018277	0.013545	0.085934	*
Indirect Effect	Low Neighborhood SES→ Intelligence→ Psychotic-like Experiences	0.016166	0.003944	0.009843	0.025298	*
Direct Effect	Low Neighborhood SES→ Psychotic-like Experiences	0.034209	0.0184	-0.00268	0.069813	
9. Effects from Positive Environment to Psychotic-like Experiences (baseline year)						
Total Effect	Positive Environment→ Psychotic-like Experiences	-0.15256	0.013871	-0.17965	-0.1252	*
Indirect Effect	Positive Environment→ Intelligence→ Psychotic-like Experiences	-0.00386	0.002065	-0.00859	-0.00058	*
Direct Effect	Positive Environment→ Psychotic-like Experiences	-0.14869	0.014025	-0.17573	-0.12073	*
10. Effects from PGS to Psychotic-like Experiences (1-year follow up)						
Total Effect	PGS→ Psychotic-like Experiences	-0.035895	0.011646	-0.058499	-0.013458	*

Indirect Effect	PGS→ Intelligence→ Psychotic-like Experiences	-0.03553	0.007062	-0.05176	-0.02376	*
Direct Effect	PGS→ Psychotic-like Experiences	-0.00036	0.013579	-0.02566	0.028107	
11. Effects from High Family SES to Psychotic-like Experiences (1-year follow up)						
Total Effect	High Family SES→ Psychotic-like Experiences	-0.11184	0.018291	-0.1478	-0.07584	*
Indirect Effect	High Family SES→ Intelligence→ Psychotic-like Experiences	-0.04291	0.008569	-0.06242	-0.0288	*
Direct Effect	High Family SES→ Psychotic-like Experiences	-0.06892	0.019586	-0.10522	-0.02866	*
12. Effects from Low Neighborhood SES to Psychotic-like Experiences (1-year follow up)						
Total Effect	Low Neighborhood SES→ Psychotic-like Experiences	0.032947	0.018055	-0.00264	0.068773	
Indirect Effect	Low Neighborhood SES→ Intelligence→ Psychotic-like Experiences	0.016409	0.004003	0.010133	0.025893	*
Direct Effect	Low Neighborhood SES→ Psychotic-like Experiences	0.016538	0.018503	-0.02066	0.051855	
13. Effects from Positive Environment to Psychotic-like Experiences (1-year follow up)						
Total Effect	Positive Environment→ Psychotic-like Experiences	-0.13149	0.013154	-0.15756	-0.10589	*
Indirect Effect	Positive Environment→ Intelligence→ Psychotic-like Experiences	-0.00392	0.00208	-0.0087	-0.00059	*
Direct Effect	Positive Environment→ Psychotic-like Experiences	-0.12757	0.013237	-0.15343	-0.10137	*

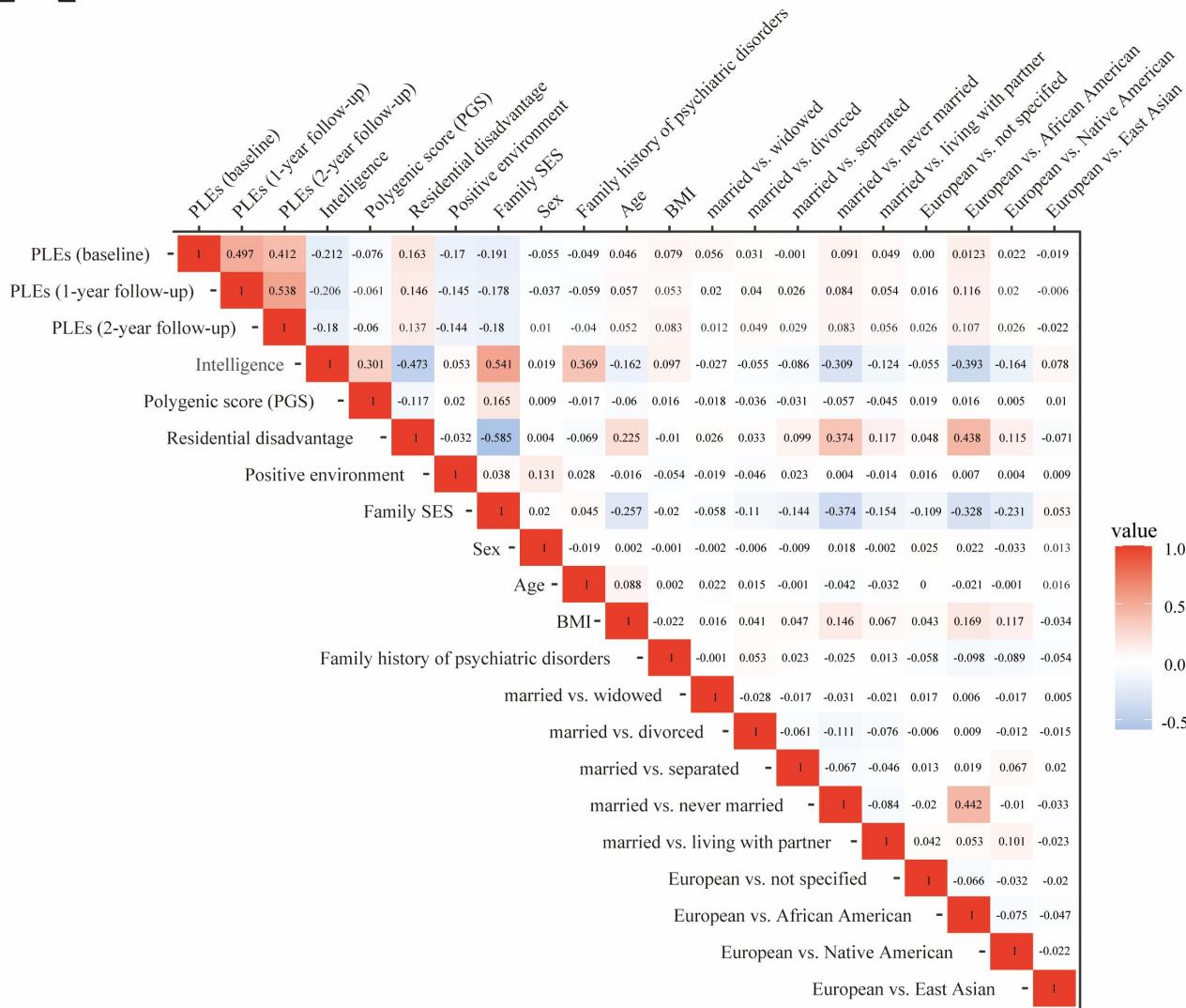
14. Effects from PGS to Psychotic-like Experiences (2-year follow up)						
Total Effect	PGS→ Psychotic-like Experiences	-0.03643	0.012196	-0.06027	-0.01272	*
Indirect Effect	PGS→ Intelligence→ Psychotic-like Experiences	-0.02737	0.007142	-0.04307	-0.01508	*
Direct Effect	PGS→ Psychotic-like Experiences	-0.00906	0.014737	-0.03696	0.021152	
15. Effects from High Family SES to Psychotic-like Experiences (2-year follow up)						
Total Effect	High Family SES→ Psychotic-like Experiences	-0.11632	0.018067	-0.15258	-0.08174	*
Indirect Effect	High Family SES→ Intelligence→ Psychotic-like Experiences	-0.03306	0.008796	-0.05228	-0.01807	*
Direct Effect	High Family SES→ Psychotic-like Experiences	-0.08326	0.019462	-0.12066	-0.04392	*
16. Effects from Low Neighborhood SES to Psychotic-like Experiences (2-year follow up)						
Total Effect	Low Neighborhood SES→ Psychotic-like Experiences	0.01921	0.018684	-0.01767	0.055261	
Indirect Effect	Low Neighborhood SES→ Intelligence→ Psychotic-like Experiences	0.012641	0.003814	0.006533	0.0215	*
Direct Effect	Low Neighborhood SES→ Psychotic-like Experiences	0.006569	0.019176	-0.03173	0.042823	
17. Effects from Positive Environment to Psychotic-like Experiences (2-year follow up)						
Total Effect	Positive Environment→ Psychotic-like Experiences	-0.13627	0.013881	-0.1635	-0.10926	*

Indirect Effect	Positive Environment → Intelligence → Psychotic-like Experiences	-0.00302	0.001703	-0.0069	-0.00043	*
Direct Effect	Positive Environment → Psychotic-like Experiences	-0.13325	0.014009	-0.16069	-0.10565	*

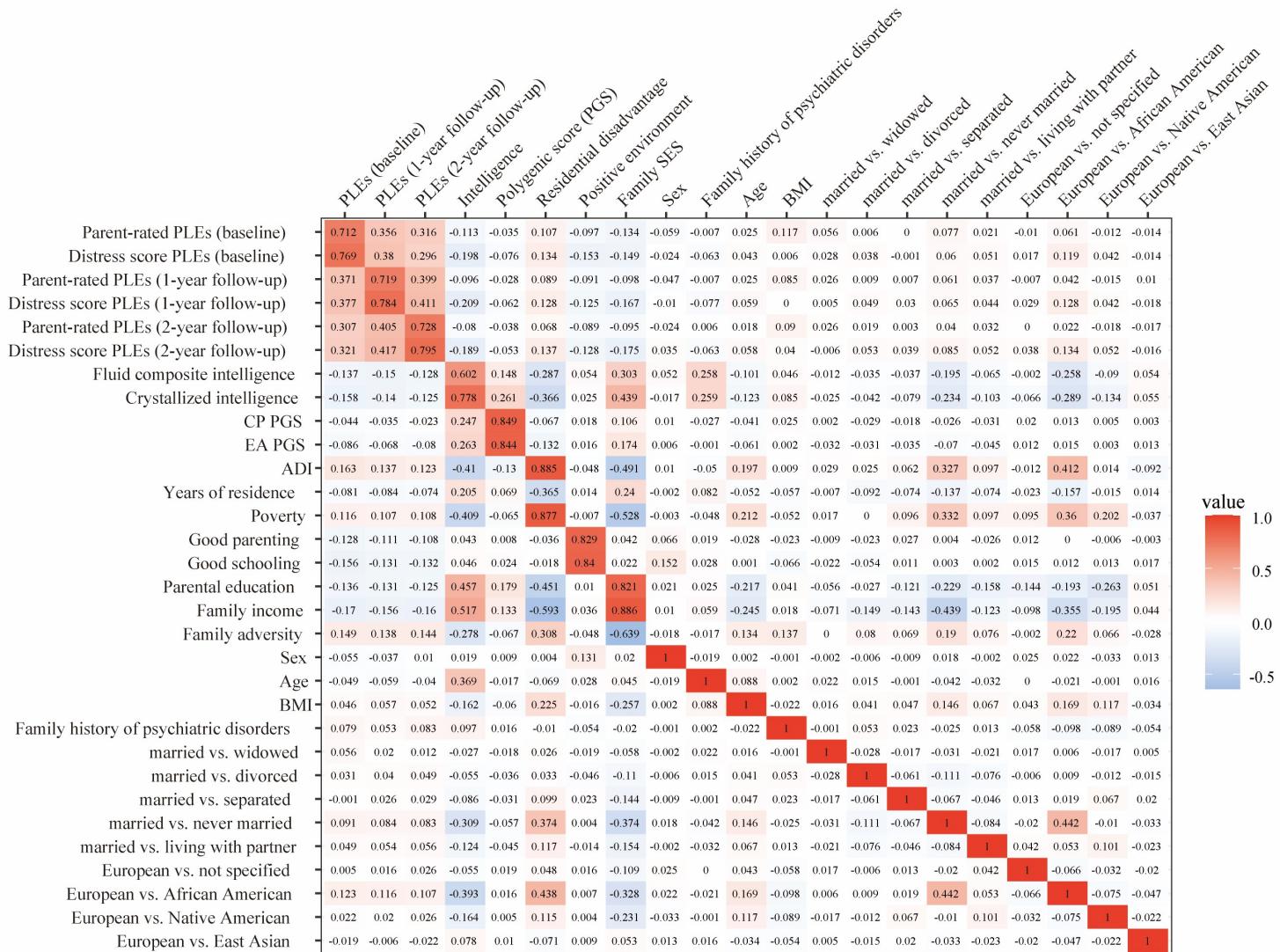
Supporting Information

Figure S1. Component correlation matrix of IGSCA analysis. **A.** Correlation between all component / factor variables of the IGSCA model. **B.** Correlation between all observed variables used to construct the relevant component / factor variables in the IGSCA model. CP PGS and EA PGS denote polygenic scores of cognitive performance and education attainment, respectively; PLEs, psychotic-like experiences; Crystallized and Fluid, crystallized and fluid intelligence; ADI, Area Deprivation Index; Poverty, percentage of individuals below -125% of the poverty level; Years, years of residence.

A



B



Appendix S1. Supplementary Methods

Genotype data

The ABCD study collected saliva samples of study participants at the baseline visit and shipped the samples from the collection site to the Rutgers University Cell and DNA Repository. Genomic DNA was extracted and genotyped using the Affymetrix NIDA Smokescreen array (733,293 SNPs). We removed any inferior SNPs with (i) genotype call rate<95%, (ii) sample call rate<95%, and (iii) rare variants with minor allele frequency (MAF)<0.01. Variant imputation was performed with the Michigan Imputation Server (Das et al., 2016) using the 1000 Genome phase 3 version 5 multiethnic Grch37/hg19 reference panel with Eagle ver2.4 phased output (Loh et al., 2016). For the imputed 12,046,090 SNPs, we only retained data from any individuals with <5% missing genotypes; without extreme heterozygosity (F coefficient < 3 standard deviations from the population mean); and SNPs with >0.4 imputation quality INFO score, <5% missingness rate, >0.01 MAF and Hardy-Weinberg equilibrium ($p>10^{-6}$). The genetic ancestry of each participant was determined with the fastSTRUCTURE algorithm (Raj, Stephens, & Pritchard, 2014), available from ABCD Release 4.0. Considering the diverse ethnic and racial backgrounds of the study participants, we estimated both kinship coefficients (K.C.s) and ancestrally informative principal components (P.C.s) to additionally control familial relatedness and ancestry admixture using PC-Air (M. P. Conomos, Miller, & Thornton, 2015) and PC-Relate (Matthew P. Conomos, Reiner, Weir, & Thornton, 2016). We selected unrelated participants that were inferred to be more distant than 4th-degree relatives (K.C.>0.022) and removed any outliers that fell significantly outside (>6 S.D. limits) the center in P.C. space. In the rest of this paper, we used final genotype data (11,301,999 variants) of 10,199 unrelated multiethnic samples, including 7,893 European-ancestry participants, after Q.C.

Polygenic Scores (PGS)

Hyperparameters of PGSs were optimized in the held-out validation set of 1,579 unrelated participants, consisting of 88 of African ancestry (5.57%), 25 of East Asian ancestry (1.58%), 1,365 of European ancestry (86.45%), 88 of Native American ancestry (2.91%), and 55 not specified (3.48%). The

validation set was created during the quality control process of the study genotype data when we selected unrelated study participants of the original ABCD samples with pairwise kinship coefficients of less than 0.022 among them. To select the optimal hyperparameter, we fitted linear regression models for intelligence composite scores within the validation set and evaluated the model performance in terms of the highest R^2 and effect size (beta). The models were adjusted for age, sex, and the first ten principal components of genotype data. For the PGS of multiethnic participants, genetic ancestry determined by ADMIXTURE (Alexander et al., 2009) was additionally included as a covariate. The validation samples were only used for hyperparameter tuning for PGS optimization and were excluded from any further analyses. The PGSs were residualized against the first ten ancestrally informative P.C.s to adjust for population stratification.

Parent-rated Psychotic-like Experiences

As self-reports and parent-reports of psychopathology often differ, parent-rated PLEs derived from four items of the Child Behavior Checklist:

- 1) "Hears sounds or voices that other people think aren't there."
- 2) "Sees things that other people think aren't there."
- 3) "Does things that other people think are strange."
- 4) "Has thoughts that other people would think are strange."

Each question was scored from 0=not true, 1=somewhat or sometimes true, and 2=very true or often true.

Family and Neighborhood Socioeconomic Status (SES)

We assessed children's family SES based on family Income, parental Education, and family's financial adversity. All three variables were based on self-reported responses of children's primary caregiver. For family income, the caregivers were asked "*What is your TOTAL COMBINED FAMILY INCOME for the past 12 months? This should include income (before taxes and deductions) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment*

benefits, workman's compensation, help from relative (include child payments and alimony), and so on. If Separated/Divorced, please average the two household incomes." Answer choices are shown below:

- 1) Less than \$5,000
- 2) \$5,000 through \$11,999
- 3) \$12,000 through \$15,999
- 4) \$16,000 through \$24,999
- 5) \$25,000 through \$34,999
- 6) \$35,000 through \$49,999
- 7) \$50,000 through \$74,999
- 8) \$75,000 through \$99,999
- 9) \$100,000 through \$199,999
- 10) \$200,000 and greater

Parental education was measured as the highest grade or level of school completed or highest degree received by the primary caregiver. ("What is the highest grade or level of school you have completed or the highest degree you have received?"). Answer choices were:

- 0) Never attended/Kindergarten only
- 1) 1st grade
- 2) 2nd grade
- 3) 3rd grade
- 4) 4th grade
- 5) 5th grade
- 6) 6th grade
- 7) 7th grade
- 8) 8th grade

- 9) 9th grade
- 10) 10th grade
- 11) 11th grade
- 12) 12th grade
- 13) High school graduate
- 14) GED or equivalent Diploma
- 15) Some college
- 16) Associate degree: Occupational
- 17) Associate degree: Academic Program
- 18) Bachelor's degree (ex. BA)
- 19) Master's degree (ex. MA)
- 20) Professional School degree (ex. MD)
- 21) Doctoral degree (ex. PhD)

Family's financial adversity is measured with Parent-Reported Financial Adversity Questionnaire, reflecting family's financial ability to pay for basic life expenses (Diemer et al., 2013). The questionnaire asked whether the child's caregiver and family experienced any of the following difficulties within the past 12 months:

- 1) "Needed food but couldn't afford to buy it or couldn't afford to go out to get it?"
- 2) "Were without telephone service because you could not afford it?"
- 3) "Didn't pay the full amount of the rent or mortgage because you could not afford it?"
- 4) "Were evicted from your home for not paying the rent or mortgage?"
- 5) "Had services turned off by the gas or electric company, or the oil company wouldn't deliver oil because payments were not made?"
- 6) "Had someone who needed to see a doctor or go to the hospital but didn't go because you could not afford it?"

7) “Had someone who needed a dentist but couldn’t go because you could not afford it?”

Each of the seven items was scored with 0=no or 1=yes.

Neighborhood SES was measured by Residential History Derived Scores based on the census tracts of each respondent’s primary address. The national percentile score of Area Deprivation Index (ADI) (Karcher, Schiffman, et al., 2021; Rakesh et al., 2021) was calculated from the 2011–2015 American Community Survey 5-year summary. Components used for deriving ADI includes:

- 1) Percentage of population aged ≥ 25 y with <9 y of education
- 2) Percentage of population aged ≥ 25 y with at least a high school diploma
- 3) Percentage of employed persons aged ≥ 16 y in white collar occupations
- 4) Median family income
- 5) Income disparity defined by Singh as the log of 100 x ratio of the number of households with <10000 annual income to the number of households with >50000 annual income.
- 6) Median home value
- 7) Median gross rent
- 8) Median monthly mortgage
- 9) Percentage of owner
- 10) Percentage of occupied housing units with >1 person per room (crowding)
- 11) Percentage of civilian labor force population aged ≥ 16 y unemployed (unemployment rate)
- 12) Percentage of families below the poverty level
- 13) Percentage of population below 138% of the poverty threshold
- 14) Percentage of single
- 15) Percentage of occupied housing units without a motor vehicle
- 16) Percentage of occupied housing units without a telephone

17) Percentage of occupied housing units without complete plumbing (log)

Positive Family and School Environment

Positive parenting behavior was assessed using the ABCD Children's Report of Parental Behavioral Inventory. We used the average values of mean summary scores of five questionnaire items about first and second caregivers. Single values were used for respondents lacking a second caregiver. Positive school environment was assessed as the sum of children's responses to twelve items in the ABCD School Risk and Protective Factors Survey.

Prior work used response items about the first caregiver for positive parenting behavior and the first six items about the school environment for positive school environment (Rakesh et al., 2021). However, to obtain a comprehensive and accurate assessment, we also included items about the second caregiver and six additional questions about the school environment.

Children were asked to choose between 1=Not like him/her, 2=Slightly like him/her, or 3=A lot like him/her about the five questions regarding the first and second caregiver:

- 1) Smiles at me very often.
- 2) Is able to make me feel better when I am upset.
- 3) Believes in showing his/her love for me.
- 4) Is easy to talk to.
- 5) Makes me feel better after talking over my worries with him/her

The following questions were asked to assess positive school environment:

- 1) In my school, students have lots of chances to help decide things like class activities and rules.
- 2) I get along with my teachers.
- 3) My teacher(s) notices when I am doing a good job and lets me know about it.
- 4) There are lots of chances for students in my school to get involved in sports, clubs, or other school activities outside of class.

- 5) I feel safe at my school.
- 6) The school lets my parents know when I have done something well.
- 7) I like school because I do well in class.
- 8) I feel I'm just as smart as other kids my age.
- 9) There are lots of chances to be part of class discussions or activities.
- 10) In general, I like school a lot.
- 11) Usually, school bores me.
- 12) Getting good grades is not so important to me.

Each of the 12 items was scored with 1=NO!, 2=no, 3=yes, 4=YES!. Item 11 and 12 were reverse coded when obtaining summary scores.

Appendix S2. Supplementary Results

Results of linear mixed models with European samples

As the European-descent-based GWAS was used for constructing PGS, we reran the main analyses using participants of European ancestry (n=5,211) to adjust for ethnic confounding (females 46.71%, mean age 118.99 [SD 7.46]).

The results of linear mixed models were similar to those of main analyses (**Table S3**). Higher intelligence was significantly associated with higher CP and EA PGS (β s > 0.0754, p <0.0001), lower ADI (β s < -0.0503, p =0.0253), more *years of residence* (β s > 0.0268, p =0.0311), positive school environment (β s > 0.0365, p =0.004), higher parental education (β s > 0.1067, p <0.0001), more family income (β s > 0.0561, p =0.0166), and less family's financial disadvantages (β s < -0.0427, p =0.011). No significant association of *poverty* and supportive parenting behavior with intelligence was found (p >0.05).

More Total and Distress Score PLEs were significantly associated with lower CP and EA PGS (baseline: β s < -0.0316, p =0.0212; 1-year: β s < -0.0422, p =0.0016; 2-year: β s < -0.0489, p =0.0002), higher ADI (baseline: β s > 0.0554, p =0.0421), less supportive parenting (baseline: β s < -0.0722, p <0.0001; 1-year: β s < -0.0473, p =0.0013; 2-year: β s < -0.0693, p <0.0001), less positive school environment (baseline: β s <

0.1076, $p<0.0001$; 1-year: $\beta s<-0.0896$, $p=0.0013$; 2-year: $\beta s<-0.0847$, $p<0.0001$), lower parental education (baseline: $\beta s<-0.0632$, $p=0.0011$; 1-year: $\beta s<-0.0567$, $p=0.004$; 2-year: $\beta s<-0.0463$, $p=0.0198$), more family's financial disadvantage (1-year: $\beta s>0.0605$, $p=0.005$; 2-year: $\beta s>0.0646$, $p<0.0001$). No significant association of *years of residence, poverty*, and family income with Total and Distress Score PLEs was found ($p>0.05$). Parent-rated PLEs was positively associated with ADI (baseline: $\beta=0.0486$, $p=0.0378$; 1-year: $\beta s>0.0527$, $p=0.0225$) and negatively with positive school environment (baseline: $\beta s<-0.0522$, $p=0.0018$; 2-year: $\beta s<-0.0601$, $p=0.0009$) and family's financial disadvantage (2-year: $\beta s>0.0501$, $p=0.0216$).

Results of IGSCA with European samples

The results of IGSCA in European ancestry samples were similar to those in multiethnic participants (**Table S4**). It showed a good model fit with a GFI of 0.9695, SRMR of 0.0397, and FIT value of 0.4854.

Intelligence was under a significant direct influence of the cognitive phenotypes PGS ($\beta=0.2987$ [95% CI=0.2673~0.3281]), neighborhood SES ($\beta=-0.0931$ [95% CI=-0.1303~-0.0586]), family SES ($\beta=0.3034$ [95% CI=0.2683~0.3413]), and positive environment ($\beta=0.0396$ [95% CI=0.0104~0.0698]). Neighborhood SES ($\beta=0.0411$ [95% CI=0.0037~0.0784]), family SES ($\beta=-0.0531$ [95% CI=-0.0956~-0.0101]), and positive environment ($\beta=-0.1473$ [95% CI=-0.1779~-0.1163]) showed significant direct influence on baseline year PLEs, but cognitive phenotypes PGS did not. Constructs that had significant direct effects on PLEs of 1-year and 2-year follow-up were family SES ($\beta s<-0.0850$) and positive environment ($\beta s<-0.1222$).

Intelligence had a significant mediating effect on the pathways of the PGS ($\beta=-0.0555$ [95% CI=-0.0754~-0.0392]), family SES ($\beta=-0.0563$ [95% CI=-0.07749~-0.0392]), neighborhood SES ($\beta=0.0173$ [95% CI=0.0098~0.0271]), and positive environment ($\beta=-0.0074$ [95% CI=-0.0142~-0.0019]) to baseline year PLEs. For PLEs of 1-year and 2-year follow-up, the mediation effects of intelligence were also significant with all four constructs: PGS (1-year: $\beta=-0.0397$ [95% CI=-0.0586~-0.0235]; 2-year: $\beta=-0.0204$ [95% CI=-0.0389~-0.0036]), family SES (1-year: $\beta=-0.0404$ [95% CI=-0.0601~-0.0238]; 2-year: $\beta=-0.0207$ [95% CI=-0.0399~-0.0036]), neighborhood SES (1-year: $\beta=0.0124$ [95% CI=0.0064~0.0208]; 2-year: $\beta=0.0064$ [95% CI=0.0011~0.0132]), and positive environment (1-year: $\beta=-0.0053$ [95% CI=-0.0142~-0.0019]; 2-year: $\beta=0.0064$ [95% CI=0.0011~0.0132]).

0.0108~0.0012]; 2-year: $\beta=-0.0027$ [95% CI=-0.0067~-0.0002]). Positive environment had the largest total effects on PLEs among the constructs (baseline year: $\beta=-0.1547$; 1-year: $\beta=-0.1274$; 2-year: $\beta=-0.1386$).

Results of linear mixed models adjusted for schizophrenia PGS with multiethnic samples

We also assessed whether the effects of cognitive phenotypes PGS in the linear mixed model are significant including schizophrenia PGS. The results showed that inclusion of schizophrenia PGS in the models did not change much of the main results (Table S5). Schizophrenia PGS was negatively associated with total and fluid intelligence in EA PGS model (Total intelligence $\beta=-0.0293$, 95% CI=-0.0488~-0.01, $p=0.0048$; Fluid intelligence $\beta=-0.0317$, 95% CI=-0.0522~-0.0097, $p=0.0062$). No significant association was found between schizophrenia PGS and PLEs of all three time points ($p>0.05$).

Results of linear mixed models adjusted for unobserved confounders with multiethnic samples

Unobserved confounding variables may bias linear regression estimates. In particular, linear estimates may be subject to collider bias when those unobserved confounders and genetic factors are jointly associated with environmental factors and target traits (Akimova et al., 2021). Thus, bias from unobserved confounding variables were adjusted using the null treatments approach (Miao et al., 2022). This approach can identify the causal effects of multiple treatment variables in presence of unobserved confounders. Assuming that fewer than half of the treatments have causal effects on the outcome, it first estimates the joint distribution of treatments-confounders to obtain asymptotic bias using a factor model. Second, it estimates the relationship between treatments, confounders, and outcome using standard density estimation methods (e.g., least squares regression). Finally, by eliminating the asymptotic bias from the estimated treatments-confounders-outcome relationship, it can adjust for unobserved confounding even without specifying which treatments are null.

The significance of effects of PGSs was mostly preserved after adjusting for unobserved confounders (Table S6). Higher cognitive phenotypes PGSs correlated significantly with higher intelligence (CP PGS: $\beta>0.1111$, $p<0.0001$; EA PGS: $\beta>0.0546$, $p=0.0002$). CP PGS was associated

with lower baseline year Distress Score PLEs ($\beta = -0.0348$, $p=0.021$) and EA PGS was associated with lower Total and Distress Score PLEs of baseline year and follow-up years (baseline: $\beta_s < -0.0534$, $p=0.0002$; 1-year: $\beta = -0.0375$, $p=0.0149$; 2-year: $\beta_s < -0.0391$, $p=0.017$). We found no significant associations of neighborhood SES variables with any of the target variables ($p > 0.05$).

While positive parenting behaviors did not have significant association with intelligence, positive school environment was significantly associated with higher total and fluid intelligence ($\beta_s > 0.0328$, $p=0.0242$). Positive parenting behaviors had significant negative correlations with all types of PLEs of baseline year and follow-up years (baseline: $\beta_s < -0.0412$, $p=0.036$; 1-year: $\beta_s < -0.0435$, $p=0.0316$; 2-year: $\beta_s < -0.0558$, $p=0.0017$). Positive school environment was also negatively associated with all types of PLEs of baseline year and follow-up years (baseline: $\beta_s < -0.0464$, $p=0.036$; 1-year: $\beta_s < -0.0952$, $p < 0.0001$; 2-year: $\beta_s < -0.0583$, $p=0.0095$).

Parental education and family income were not significantly associated with all types of intelligence and PLEs of all three time points. Family's financial disadvantage did not show significant association with intelligence and baseline year PLEs, but it had positive associations with 1-year follow-up Total Score ($\beta = 0.0604$, $p=0.0113$) and Distress Score PLEs ($\beta = 0.0532$, $p=0.0197$) and 2-year follow up Total Score ($\beta > 0.0544$, $p=0.0284$) and Distress Score PLEs ($\beta = 0.0584$, $p=0.0224$).

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