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The Positive End of the Polygenic Score Distribution for ADHD: A Risk, Protective or Resilience Factor?

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Key Points

Question: Does having a low polygenic score (PGS) for ADHD reduce one's risk for ADHD relative to the incidence rate in the population; are individuals with low PGS more resilient to childhood maltreatment?

Findings: In this longitudinal study of 7,190 adolescents followed into adulthood, individuals with low PGS had a two-fold risk reduction for ADHD (4.1%) relative to the observed incidence of ADHD (8.3%) and showed superior functional outcomes relative to those with medium and high PGS. No evidence of resilience was detected.

Meaning: Low PGS may be a protective factor in not only the genesis of ADHD, but also for negative functional outcomes in adulthood.

Abstract

Importance: Polygenic scores (PGS) are widely used to characterize genetic liability for heritable mental disorders, including attention-deficit/hyperactivity disorder (ADHD). However, little is known about the effects of having a low burden of genetic liability for ADHD, including whether this functions as a protective or resilience factor for psychopathology and functional outcomes in later life. Understanding the consequences of being on the "positive" side of the PGS distribution may shed light on mechanisms of risk *and* resilience for ADHD.

Objective: To examine the association of low PGS for ADHD and functional outcomes in adulthood. To also examine whether these associations are moderated by early childhood maltreatment.

Design: Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health), conducted between 2007 and 2008. Data analyses were conducted from March 2019 to April 2019.

Setting: Population-based sample in the United States.

Participants: Add Health adults aged 24 to 32 for whom genotypic and phenotypic data were available (*n*=7,190).

Exposure: PGS for ADHD were used to examine associations for ADHD and across a range of functional outcomes in adulthood.

Main Outcome and Measures: Regression models tested the association of ADHD PGS and adult functional outcomes, including cognition, educational attainment, mental health (e.g., depression) and physical health (e.g., body mass index). Interactions between ADHD PGS and childhood maltreatment were examined for each outcome variable.

Results: Individuals at the lowest end of the ADHD PGS distribution exhibited a two-fold risk reduction (95% CI=2.8-5.3%) of ADHD relative to the observed prevalence in Add Health (8.3%). Individuals with low ADHD PGS (<20th percentile) demonstrated consistently superior adult functional outcomes relative to majority of individuals along the ADHD PGS distribution, including those who were in the medium and high ADHD PGS groups. No interactions between ADHD PGS and childhood maltreatment emerged.

Conclusions and Relevance: Low ADHD PGS may be a robust protective factor in not only the genesis of ADHD, but also of negative functional outcomes that are typically disrupted among adults with ADHD. There was no evidence that low PGS confers resilience to childhood maltreatment, however. Psychiatric PGS may hold crucial information for the purposes of clinical prediction, beyond simply risk and the absence of risk.

The Positive End of the Polygenic Score Distribution for ADHD: A Risk, Protective or Resilience Factor?

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with an estimated worldwide prevalence of 7.2%.[1] It is associated with a range of negative functional outcomes in adulthood, including poor cognitive functioning,[2] low educational attainment,[3] depression and substance misuse[4,5] involvement in the criminal justice system,[6] greater perceived stress[7] and poor physical health.[3,8] ADHD has a highly heritable[9–12] polygenic architecture.[13] As such, studies are increasingly using polygenic scores (PGS)[14] to characterize the aggregate genetic liability for ADHD, which have reliably shown that high PGS is associated with greater risk for ADHD and related negative outcomes.[9,15–19] Yet, little is known about the consequences of having a very low burden of genetic liability for ADHD.[20,21] While low ADHD PGS is expected to convey a reduction in risk for ADHD relative to individuals with higher PGS, does low PGS also convey a reduction in risk for ADHD relative to the general prevalence rate in a given population (i.e., as a protective factor)? Furthermore, are individuals with low PGS more resilient to environmental adversity? Answers to these questions have potentially important implications towards uncovering the mechanisms of risk *and* resilience for ADHD.[20]

PGS are computed as the linear composite of single nucleotide polymorphisms (SNPs) weighted according to genome-wide association study (GWAS) summary statistics.[22] Psychiatric PGS are distributed normally in population-based samples,[21] reflecting the continuum of genetic risk for psychopathology in a population.[20] Whereas individuals on the right-tail (e.g., >20th percentile) are often characterized as "high risk," [23,24] individuals at the left-tail (e.g., <20th percentile) are traditionally considered a "low risk" group.[23] However, the term "low risk" for this subgroup is ambiguous, given that studies examining the consequences of low

psychiatric PGS are exceedingly rare. Krapohl and colleagues (2015)[21] showed that individuals in the lowest septile PGS for educational attainment had greatest amount of parent-reported behavior problems relative to individuals in the highest PGS septile, who had the fewest behavior problems. However, no associations were detected between low (or high) psychiatric PGS, including for ADHD, with various behavioral and socioemotional outcomes. Notably, this study was limited by the severely underpowered GWAS for psychiatric outcomes relative to the educational attainment GWAS. Given that a significantly higher-powered GWAS is now available for ADHD, a re-examination of this association is warranted.

Another open question[20,21] is whether low psychiatric PGS may confer *resilience* to environmental adversity. For example, childhood maltreatment (i.e., physical and sexual abuse, neglect) is an established risk factor for negative physical, mental and cognitive health outcomes in later life.[25] In a sample 1,985 depressed patients and controls from the Netherlands, the odds of having a major depressive disorder (MDD) was highest among those who had the highest MDD PGS and experienced severe childhood maltreatment (relative to individuals experiencing moderate or no/low maltreatment).[26] However, individuals at the lowest end of the MDD PGS distribution showed low odds of MDD regardless of maltreatment severity.[26] It should be noted that this finding was inconsistent with findings from a similar study featuring depressed patients and controls (N=2,669) from the United Kingdom.[27] Thus, it remains unclear whether low psychiatric PGS is a resilience or a risk factor in the face of environmental adversity.

Despite the rapid adoption of PGS in genetic association studies, most studies and recent reviews of this emerging literature[22,28] have ignored the functional implications of having low psychiatric PGS. This study used data from a population-based dataset to rigorously investigate the association of the ADHD PGS distribution as it pertains to ADHD and functional outcomes

that are known to be related to ADHD, including educational attainment, cognition, mental and physical health. Furthermore, this study examined whether associations between ADHD PGS and functional outcomes were moderated by childhood maltreatment. First, individuals with low ADHD PGS were expected to have a reduced risk of ADHD, relative to observed population incidence rate. Second, individuals with low ADHD PGS were expected to have superior functional outcomes in adulthood relative to those with medium and high ADHD PGS. Finally, ADHD PGS was expected to interact with childhood maltreatment, such that individuals with low ADHD PGS will more resilient to adversity relative to individuals with high ADHD PGS.

Methods

Participants

Data were from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a stratified sample of adolescents in grades 7-12 from high schools across the U.S. Data were collected from adolescents, parents, fellow students, school administrators, siblings, friends and romantic partners across four waves: Wave I (1994-1995, grades 7-12, *N*=20,745), Wave II (1995-1996, grades 8-12, *N*=14,738), Wave III (2001-2002, ages 18-26, *N*=15,197), and Wave IV (2007-2008, ages 24-32, *N*=15,701). Wave IV phenotypic data were used given the focus on adult outcomes as a function of childhood ADHD. The current analyses were performed for individuals where both genotypic and phenotypic information were available (*N*=7,190). Within the genotypic subsample, the mean age at Wave IV was 29.03 (*s.d.*=1.75), 46% of this sample was male, and the racial-ethnic composition was 69.5% Caucasian (including Hispanic), 21.2% African American, .4% Native American, 5.2% Asian, and 3.7% “Other.” Demographic information comparing the genetic subsample with the non-genetic subsample is available on the Online Supplement (eTable 1).

Measures

ADHD. Childhood ADHD symptoms were assessed retrospectively using 17 of the 18 items for ADHD, keyed to the *Diagnostic and Statistical Manual of Mental Disorders.*[29] Items were rated on a 4-point Likert scale regarding how often the symptom "best describes your behavior when you were [between 5 and 12]." Each item was dichotomized to indicate the presence (i.e., *often* or *very often* response*)* or absence (i.e., *never* or *sometimes* response) of the symptom. In line with the DSM, diagnostic criteria for ADHD was defined as having 6 or more symptoms of inattention and/or 6 or more symptoms of hyperactivity/impulsivity.

Cognitive Ability. Cognitive ability was assessed via the Add Health Picture Vocabulary Test (AHPVT) at Wave I. The task measures receptive vocabulary, verbal ability and scholastic aptitude. For this test, the interviewer read a word aloud and the participant selected an illustration that best fit its meaning. Each word had four simple, black-and-white illustrations arranged in a multiple-choice format. The standardized score for AHPVT was used.

Educational Attainment. Educational Attainment was assessed at Wave IV through the following question: "What is the highest level of education that you have achieved to date?" The scale ranged from 1 ("8th grade or less") to 10 ("some graduate training beyond a master's degree").

Mental Health and Behavior. All mental health and behavior outcomes were assessed at Wave IV. Depression symptoms were measured using an abbreviated version of the Center for Epidemiologic Studies Depression Scale (CES-D[30]). Lifetime DSM-IV criteria for abuse or dependence for alcohol was assessed as the presence of at least 1 of the 4 items pertaining to alcohol abuse, and/or three of the 7 items pertaining to alcohol dependence occurring together in a 12-month period. Lifetime DSM-IV criteria for "other drug" abuse and dependence were

assessed using the same criteria, but for illicit substances. Ever arrested was measured by whether the participant responded affirmatively to the question: "have you ever been arrested" and/or whether the Wave IV interview was being conducted in prison. Perceived stress was measured via an abbreviated 4-item version of the Cohen's Perceived Stress Scale,[31] which assessed perception of stress across various life contexts. Items were rated on a 5-point Likert scale, where 0="never" and 4="very often."

Physical Health. All physical health outcomes were assessed at Wave IV. BMI classification was measured on a 1-6 scale, where 1=underweight (BMI<18.5), 3=overweight (BMI=20-30), and 6=obese III (BMI>40). Stage 2 Hypertension was present if the participant responded affirmatively to the question: "has a doctor, nurse or other health care provider ever told you that you have or had: high blood pressure or hypertension, systolic blood pressure, and diastolic blood pressure?" High blood cholesterol was present if the participant responded affirmatively to the question: "has a doctor, nurse or other health care provider ever told you that you have or had: high blood cholesterol or triglycerides or lipids?"

Childhood Maltreatment. Maltreatment was assessed retrospectively at Wave IV as the frequency of self-reported neglect, physical abuse, and sexual abuse prior to the age of 12. Following previous Add Health investigations,[32,33] if any item occurred at least once, childhood maltreatment was scored as positive.

Genotyping and Quality Control. Saliva were obtained from participants at Wave IV. Genotyping was done on the Omni1-Quad BeadChip and the Omni2.5-Quad BeadChip. Add Health European genetic samples were imputed on Release 1 of the Human Reference Consortium (HRS r1.1). Non-European samples were imputed using the 1000 Genomes Phase 3 reference panel. Of 606,673 variants, 13,721 were removed with a per-variant missing call rate

filter of 0.02; 245,589 were removed with a Hardy-Weinberg Equilibrium filter of 0.0001, and 609 were removed with a minor allele frequency filter of 0.01, leaving 346,754 SNPs carried through to imputation. Additional details of the quality control are available online (https://www.cpc.unc.edu/projects/addhealth/documentation/guides).

Polygenic Scores (PGS). PGS were computed as the linear composite of SNPs associated with ADHD, weighted by each SNPs effect size according to meta-analytic GWAS,[13] which included 55,374 individuals (20,183 cases and 35,191 controls) from 12 studies of mixed ancestries and a replication sample of 93,916 individuals from two mixed ancestry cohorts. This study used an *a priori* GWAS p-value threshold of p=1 rather than an empirical p-value threshold to minimize potential bias due to overfitting.[34] PGS were then standardized according to genetic ancestry groups in Add Health.[35] Additional controls for the population stratification were done by covarying the first 10 ancestry-specific principal components (PC) of the genetic data in the analyses.[36]

Statistical Analysis

First, a logistic regression was modeled where ADHD PGS (measured continuously) was regressed on ADHD diagnostic status, controlling for age, biological sex and genetic PCs. A margins test was conducted to compute the expected probability of ADHD at each .5 increments of PGS, from the approximate lowest score to the highest. Then, in the multigroup PGS comparisons, low (<20th percentile), medium (21st – 70th percentiles) and high (>80th percentile) PGS groups were defined based on empirical precendents[23] (see eFigure 1). Between PGS group comparisons were conducted in a multivariate analysis of variance (MANOVA), controlling for age, biological sex, and the first 10 principle components of the genetic data. Pairwise contrasts were probed between each PGS group on the dependent variables. Finally, in the gene-

environment interaction models, main effects and the interaction of PGS group and maltreatment exposure were regressed on each functional outcome. The alpha were set to .005 to correct for multiple testing (i.e., 11 dependent variables). Logistic regression was modeled for binary outcomes, negative binomial regressions for zero-inflated positively skewed count outcomes, and linear regression for quantitative outcomes. Bivariate correlations between PGS and ADHD, as well as all other dependent variables are in eTable 2.

Results

PGS and ADHD Diagnostic Status

PGS was positively associated with ADHD diagnostic status, as expected (OR=1.24, 95% CI=1.14-1.35). Figure 1 (and eTable 3) shows the predicted probabilities of ADHD by .50 increments in ADHD PGS, ranging from the approximate lowest end of the PGS distribution (-3.50) to the highest (3.50). Individuals at the mean (PGS=0) had a 8.19% predicted probability of meeting diagnostic criteria for ADHD (*s.e.*=.32%, 95% CI=7.57-8.81%), falling entirely within the observed incidence of ADHD in Add Health (8.3%). However, individuals at the lowest end of the PGS distribution (-3.50) had a 4.1% predicted probability for ADHD (*s.e.*=.60%, 95% CI=2.8-5.3%), a two-fold reduction in risk from the observed incidence of ADHD in Add Health.

PGS Groups and Adult Functional Outcomes

MANOVA was used to compare PGS group differences across cognition, educational attainment, mental health and behavior, and physical health outcomes (Table 1 and Figure 2). Compared to individuals in the high PGS group (>80th percentile), individuals in the low PGS group (<20th percentile) had higher standardized scores on the AHPVT, greater educational attainment, less depression symptoms, less likelihood of illicit drug abuse or dependence, less likelihood of being ever arrested, less perceived stress, and lower BMI (Table 2). Unexpectedly,

individuals in the low PGS group had a greater likelihood of alcohol abuse or dependence relative to individuals in the high PGS group (mean difference=.26, *s.e.*=.04, $p<.01$, 95% CI=.18-.35). No significant group differences emerged for stage 2 hypertension and high blood cholesterol.

Individuals in the low PGS group were also superior across multiple functional outcomes relative to individuals in the medium PGS group (21^{st}-79^{th} percentile). Low PGS individuals had higher standardized scores on the AHPVT, greater educational attainment, less depression symptoms, less likelihood of being ever arrested, less perceived stress, lower BMI, and less likelihood of stage 2 hypertension (Table 2). Individuals with low PGS also had a greater likelihood of alcohol abuse or dependence than individuals in the high PGS group (mean difference=.15, *s.e.*=.04, $p<.01$, 95% CI=.06-.23). No significant differences between groups emerged with respect to the likelihood of illicit drug abuse or dependence and high blood cholesterol.

PGS Groups by Maltreatment on ADHD and Adult Functional Outcomes

Multiple regressions were conducted to test the interactive effect of PGS group and childhood maltreatment on ADHD diagnostic status and each of the functional outcomes (eTables 4-6). None of the interactions for PGS and maltreatment were statistically significant after Bonferroni correction ($p<.005$) for the dependent variables tested. PGS was significantly, albeit weakly correlated with childhood maltreatment ($r=.03$, $p=.02$). The results were entirely consistent when standardized residuals of the regression of PGS group on childhood maltreatment were used in the gene-environment interaction models instead (available upon request).

Discussion

These findings may spur a crucial shift in perspective with regard to the predictive utility of psychiatric PGS, which appears to capture more than just the risk and the absence of risk for a psychiatric outcome. In the case of ADHD PGS, the findings show that where one lies along the distribution may predict diverging functional consequences, for better and for worse. Whereas the majority individuals reside within approximately one standard deviation of the PGS mean, there are also a subset of individuals below this threshold who exhibited a reduction in ADHD risk and superior functional outcomes relative to everyone else in the population. This calls into question whether it is apt characterize low PGS individuals as having "low genetic risk."[23] For instance, recent GWAS show the rising risk profiles for individuals across the PGS distribution for ADHD[13] and MDD,[37] but only relative to those at the lowest PGS percentile. The current findings suggest that prior comparisons of risk profiles by PGS percentile may have been exaggerated because those at the lowest PGS percentiles may be more reflective of "super controls" rather than typical non-clinical controls at the population level.[20] In fact, most individuals in the population have a modest burden of genetic liability for ADHD, which is consistent with dimensional characterizations of externalizing psychopathology more broadly.[38] Future genetic association studies may wish to identify the point along the PGS distribution that best maps on to the prevalence rate of the outcome in question, which should serve as a more useful reference point when examining the relative risk of a given PGS.

Notably, ADHD PGS was inversely associated with alcohol abuse or dependence. Evidence of shared genetic influences between ADHD and alcohol use disorder is mixed, including two studies showing no association between ADHD PGS and adult problematic alcohol use[39] and dependence[40] and other studies showing a robust positive association.[41,42] Experts have speculated that having low genetic liability for one psychiatric disorder may confer

a greater liability for another, perhaps as an evolutionary trade-off against the costs and benefits of being at the extreme end of the PGS distribution.[20] Future studies can explicitly test this hypothesis by examining PGS associations across a wider range psychopathology, including the externalizing and internalizing continuum.[38]

Another key finding is that while low ADHD PGS conferred a protective effect on ADHD and functional outcomes in adulthood, having a low burden of genetic liability for ADHD did not increase one's protection from the detrimental effects of childhood maltreatment. Notably, this study only focused on the interactive effects between ADHD PGS and childhood maltreatment because of its well-known negative effects on functional outcomes in later life.[25] Other environmental factors may be important to examine in the context of gene-environment interplay as well, especially considering that both environmental adversity and enrichment may differentially moderate genetic associations on these outcomes (i.e., "differential susceptibility" hypothesis).[43] One model that has yet to be tested is whether individuals at the low end of the PGS distribution might potentially profit more from environmental enrichment than those at the higher end of the distribution.

The findings should be interpreted in light of some study limitations. First, racial-ethnic differences with regard to the functional outcomes related to PGS could not be entirely ruled out. This limitation is somewhat alleviated by the several methods that were employed to safeguard against the effects of population stratification (i.e., PGS that were standardized by genetic ancestry, PCs covaried in each of the analyses). Second, ADHD PGS effect sizes as they pertained to ADHD and functional outcomes were uniformly small. However, effect sizes are directly linked to the size of the GWAS discovery sample, which will continue to grow.[44] Finally, this investigation did not assess other disorders that are known to covary with ADHD.

More complex phenotypic models that account of the shared genetic underpinnings of co-occurring phenotypes are needed in future studies.

PGS may soon play a role in clinical contexts.[22,28] It is possible that individuals at high genetic risk may benefit more from an intervention relative to those at moderate and even low genetic risk.[45,46] At the same time, it may be useful to consider PGS as part of a broad constellation of both risk and protective factors when determining treatment recommendations for ADHD and other psychiatric disorders. Uncertainty in clinical decision making can be reduced with a comprehensive view of patient care that aggregates our increasing knowledge of polygenic liability along with crucial clinical information (i.e., biomarkers, environmental factors) pertinent to the individual.

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Table 1. Multivariate analysis of variance (MANOVA) comparing PGS status across functional outcomes (continued on next page)

				Between Subjects Effects			**95% Confidence Interval**		
Dependent Variable	**PGS Status**	**Mean**	***s.e.***	***F***	***p***	***df***	**Lower**	**Upper**	**Partial Eta^2**
Cognition									
AHPVT standardized score	Low	104.07	.37	10.20	<.01	14	103.34	104.79	.02
	Medium	101.39	.22				100.96	101.81	
	High	99.26	.38				98.52	100.00	
Educational Attainment									
Highest degree attained	Low	5.91	.05	20.90	<.01	14	5.80	6.01	.04
	Medium	5.53	.03				5.47	5.59	
	High	5.09	.06				4.98	5.20	
Mental Health and Behavior									
CES-D depression symptoms	Low	6.07	.12	10.02	<.01	14	5.83	6.31	.02
	Medium	6.72	.07				6.58	6.86	
	High	7.01	.13				6.77	7.26	
DSM-IV alcohol abuse/dependence	Low	.32	.01	10.19	<.01		.30	.34	.02
	Medium	.29	.01				.28	.30	
	High	.25	.01				.22	.27	
DSM-IV illicit drug abuse/dependence	Low	.08	.01	2.07	.01	14	.06	.09	.00
	Medium	.08	.00				.07	.09	
	High	.10	.01				.09	.12	
Ever arrested	Low	.26	.01	43.34	<.01	14	.23	.28	.08
	Medium	.29	.01				.28	.31	
	High	.35	.01				.32	.37	
Perceived Stress	Low	4.51	.08	7.84	<.01	14	4.35	4.66	.02
	Medium	4.85	.05				4.75	4.94	
	High	5.05	.08				4.89	5.21	

Table 1. Multivariate analysis of variance (MANOVA) comparing PGS status across functional outcomes (Continued)

				Between Subjects Effects			**95% Confidence Interval**		
Dependent Variable	**PGS Status**	**Mean**	***s.e.***	***F***	***p***	***df***	**Lower**	**Upper**	**Partial Eta^2**
Physical Health									
BMI	Low	3.12	.04	5.18	<.01	14	3.05	3.19	.01
	Medium	3.34	.02				3.30	3.38	
	High	3.44	.04				3.37	3.51	
Hypertension stage 2	Low	.11	.01	4.67	<.01	14	.10	.13	.01
	Medium	.14	.01				.13	.15	
	High	.14	.01				.13	.16	
High blood cholesterol	Low	.08	.01	3.70	<.01	14	.07	.10	.01
	Medium	.07	.00				.06	.08	
	High	.09	.01				.08	.11	

Caption. Results show a multivariate analysis of variance controlling for age, biological sex, and the first 10 principle components of the genetic information (i.e., genetic ancestry). "Low" PGS is the lowest quintile (<20th percentile) of the PGS distribution, "Medium" PGS is the combination of the second, third, and fourth quintiles (21st – 79th percentile) of the PGS distribution, "High" PGS is the fifth quintile (>80th percentile) of the PGS distribution.

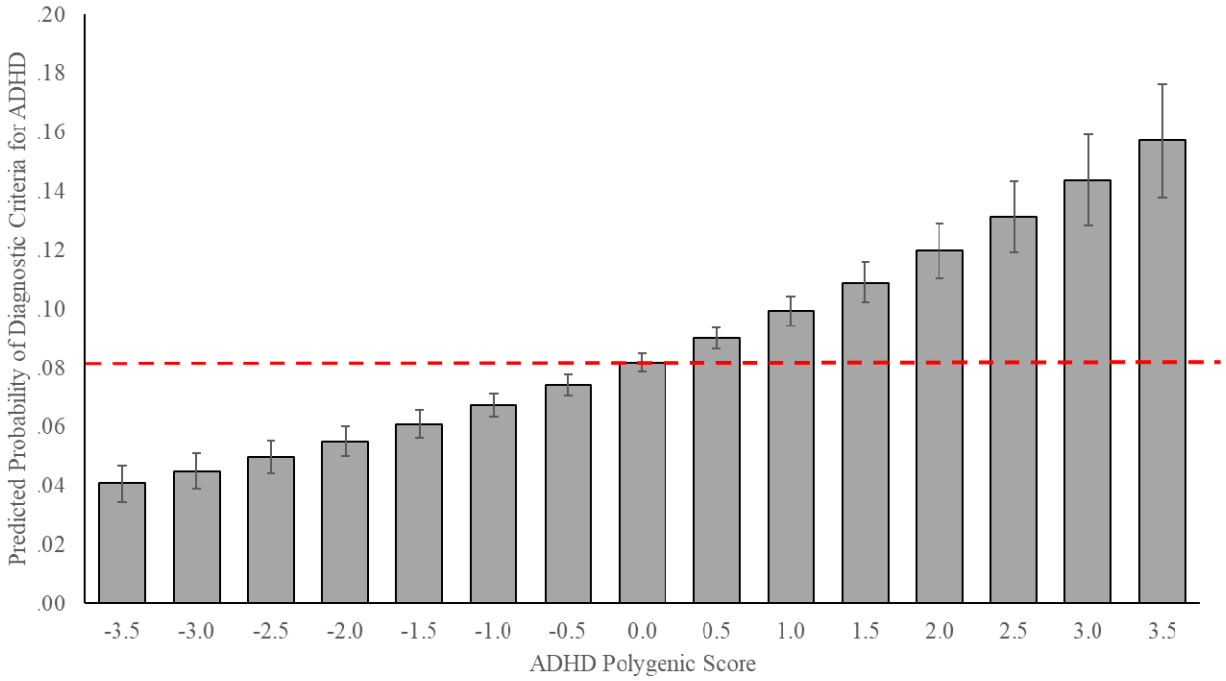
Table 2. Pairwise contrasts of PGS groups on dependent variables (continued on next page)

					95% Confidence Interval	
PGS Group Contrasts	**Dependent Variable**	**Mean Difference**	***s.e.***	***p***	**Lower**	**Upper**
Low versus Medium	Cognition					
	AHPVT standardized score	2.68	.43	<.01	1.84	3.53
	Educational Attainment					
	Highest degree attained	.38	.06	<.01	.26	.82
	Mental Health and Behavior					
	CES-D depression symptoms	-.67	.14	<.01	-.95	-.39
	DSM-IV alcohol abuse/dependence	.03	.01	.03	0	.06
	DSM-IV illicit drug abuse/dependence	.00	.01	.86	-.02	.02
	Ever arrested	-.04	.01	.01	-.01	-.06
	Perceived stress	-.34	.09	<.01	-.52	-.16
	Physical Health					
	BMI	-.22	.04	<.01	-.30	-.14
	Hypertension stage 2	-.02	.01	.02	-.05	0
	High blood cholesterol	.01	.01	.23	-.01	.03
Low versus High	Cognition					
	AHPVT standardized score	4.80	.53	<.01	3.75	5.84
	Educational Attainment					
	Highest degree attained	.82	.08	<.01	.67	.97
	Mental Health and Behavior					
	CES-D depression symptoms	-.92	.18	<.01	-1.27	-.58
	DSM-IV alcohol abuse/dependence	.07	.02	<.01	.04	.11
	DSM-IV illicit drug abuse/dependence	-.02	.01	.04	-.43	0
	Ever arrested	-.09	.02	<.01	-.12	-.06
	Perceived stress	-.55	.12	<.01	-.77	.32

Table 2. Pairwise contrasts of PGS groups on dependent variables (continued from previous page)

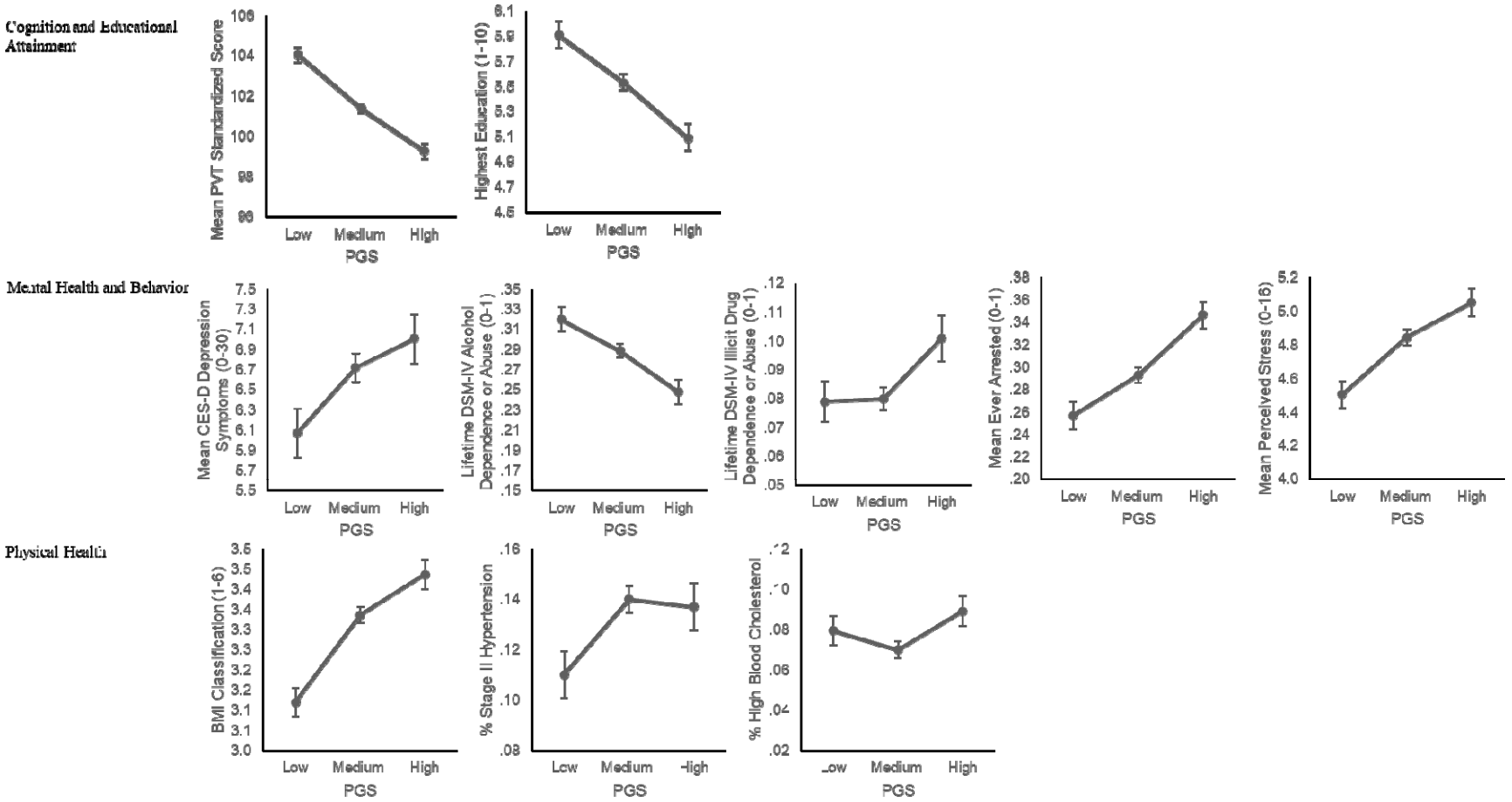
					95% Confidence Interval	
PGS Group Contrasts	**Dependent Variable**	**Mean difference**	***s.e.***	***p***	**Lower**	**Upper**
Low versus High	Physical Health					
	BMI	-.32	.05	.00	-.42	-.22
	Hypertension stage 2	-.03	.01	.06	-.05	.00
	High blood cholesterol	-.01	.01	.39	-.03	.01
Medium versus High	Cognition					
	AHPVT standardized score	2.12	.44	.00	1.26	2.97
	Educational Attainment					
	Highest degree attained	.44	.06	.00	.32	.56
	Mental Health and Behavior					
	CES-D depression symptoms	-.25	.14	.08	-.54	.03
	DSM-IV alcohol abuse/dependence	.04	.01	.00	.01	.07
	DSM-IV illicit drug abuse/dependence	-.02	.01	.02	-.04	.00
	Ever arrested	-.05	.01	.00	-.08	-.03
	Perceived stress	-.21	.09	.03	-.39	-.02
	Physical Health					
	BMI	-.10	.04	.01	-.18	-.02
	Hypertension stage 2	.00	.01	.91	-.02	.02
	High blood cholesterol	-.02	.01	.03	-.04	.00

Figure 1. Predicted probabilities of meeting diagnostic criteria for ADHD in Add Health by ADHD PGS



Caption. Figure shows the predicted probabilities of meeting diagnostic criteria for ADHD in Add Health by .5 increments of ADHD PGS, according to a binary logistic regression that controlled for age, biological sex, and the first 10 principle components of the genetic information (i.e., genetic ancestry). Dotted red line shows the Add Health prevalence rate of ADHD (8.3%). For example, individuals at -3.5 PGS have a 4.1% predicted probability of meeting diagnostic criteria for ADHD, which represents a two-fold reduction in risk of ADHD relative to the Add Health prevalence rate. In contrast, individuals at 3.5 PGS have a 15.7% predicted probability of meeting criteria for ADHD, which is a nearly two-fold increase in risk over the general prevalence rate. Error bars reflect standard errors.

Figure 2. Associations between ADHD PGS levels and functional outcomes.



Caption. Plots of the predicted means for each dependent variable by each ADHD PGS level, obtained from a multivariate analysis of variance controlling for age, biological sex, and the first 10 principle components of the genetic information (i.e., genetic ancestry). "Low" PGS is the lowest quintile (<20th percentile) of the ADHD PGS distribution, "Medium" PGS is the combination of the second, third, and fourth quintiles (21st – 79th percentile) of the ADHD PGS distribution, "High" PGS is the fifth quintile (>80th percentile) of the ADHD PGS distribution. Standard errors are shown on each figure.