The positive end of the polygenic score distribution for ADHD: a low risk or a protective factor?

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Abstract

Background. 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 a low burden of genetic liability for ADHD, including whether this functions as a low risk or protective factor for ADHD and related functional outcomes in later life. The current study examines the association of low ADHD PGS and functional outcomes in adulthood.

Methods. Participants were from Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health) ($N = 7088$; mean age = 29, S.D. = 1.74). ADHD PGS was computed from an existing genome-wide association study, and adult functional outcomes, including cognition, educational attainment, mental health, and physical health were assessed during in-home interviews.

Results. Individuals at the lowest end of the ADHD PGS distribution (i.e. lowest 20th percentile) had the lowest probabilities of ADHD, exhibiting a 17–19% reduction in risk for ADHD relative to the observed 8.3% prevalence rate of ADHD in Add Health. Furthermore, individuals with low ADHD PGS had higher cognitive performance, greater levels of educational attainment, and lower BMI relative to individuals representing the rest of the ADHD PGS distribution, including those who were in the medium and high-PGS groups.

Conclusions. Findings indicate that psychiatric PGS likely capture far more than just the risk and the absence of risk for a psychiatric outcome; where one lies along the PGS distribution may predict diverging functional consequences, for better and for worse.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with an estimated prevalence of 8.9% among children (aged 6 to 11) in the United States (Danielson *et al.*, 2018). It is associated with a range of negative functional outcomes in adulthood, including poor cognitive functioning (Boonstra *et al.*, 2005), low-educational attainment (Kuriyan *et al.*, 2013), depression and substance misuse (Lee *et al.*, 2011; Agnew-Blais *et al.*, 2018), involvement in the criminal justice system (Fletcher and Wolfe, 2009), increased stress (Combs *et al.*, 2015), and poor physical health (Brook *et al.*, 2013; Kuriyan *et al.*, 2013). Etiologically, ADHD is among the most heritable of the psychiatric disorders; twin studies have estimated that between 70–75% of the variance in ADHD dimensions can be accounted for by genetic differences in the population (Nikolas and Burt, 2010; Chang *et al.*, 2013; Faraone and Larsson, 2019). Recently, this heritability has been shown to be highly polygenic, reflecting many genes of individually small effects (Franke *et al.*, 2009; Larsson *et al.*, 2014; Zayats *et al.*, 2015; Demontis *et al.*, 2019). As such, studies are increasing using polygenic scores (PGS) (Dudbridge, 2013) to characterize the aggregate genetic liability for ADHD.

PGS are typically computed as the linear composite of alleles one carries across single nucleotide polymorphisms (SNPs) tested in association with a psychiatric trait, with each SNP weighted according to genome-wide association study (GWAS) summary statistics on the trait in question (Anderson *et al.*, 2019). One consistent observation of psychiatric PGS is that they are distributed normally in population-based samples (Krapohl *et al.*, 2016), reflecting the continuum of genetic risk for psychopathology in a population (Plomin *et al.*, 2009). Whereas individuals on the right-tail (e.g. >20th percentile) are often characterized as 'high risk' (Khera *et al.*, 2018; Torkamani *et al.*, 2018), individuals at the left-tail (e.g. <20th percentile) are traditionally considered a 'low risk' group (Torkamani *et al.*, 2018). However, the term 'low risk' for this subgroup is ambiguous and questionable, especially given that few studies have empirically examined the implications of having low PGS. For instance, low risk could equate to the baseline of risk for the disorder observed in the population. Low risk could also indicate a *reduction* of risk for the disorder relative to the population baseline, perhaps reflecting a biologically protective effect of having few risk alleles. In general, few researchers have been 'thinking positively' (Plomin *et al.*, 2009, 875) about PGS, and thus, may have been neglecting potentially important functional consequences of being in the low end of the PGS distribution.

Studies have reliably shown that high PGS is associated with greater risk for ADHD and related negative outcomes (Hamshere *et al.*, 2013; Groen-Blokhuis *et al.*, 2014; Stergiakouli *et al.*, 2015; Riglin *et al.*, 2016; Du Rietz *et al.*, 2017; Demontis *et al.*, 2019). Conversely, low PGS has also been shown to confer reduced risk for ADHD relative to the higher PGS groups (Wray *et al.*, 2018; Demontis *et al.*, 2019). However, it is questionable whether low PGS also confers a *reduction* in risk for ADHD relative to individuals in the general population, such as those with medium PGS. In a study of 1985 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) (Peyrot *et al.*, 2014). However, individuals at the lowest end of the MDD PGS distribution showed low odds of MDD regardless of maltreatment severity (Peyrot *et al.*, 2014). Notably, this finding was inconsistent with findings from a similar study featuring depressed patients and controls from the United Kingdom (Mullins *et al.*, 2016).

Krapohl *et al.* (2016) showed that individuals in the lowest septile PGS for educational attainment had the greatest amount of parent-reported behavior problems relative to individuals in the highest PGS septile, who had the fewest behavior problems (Krapohl *et al.*, 2016). 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 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.

Despite the ascendancy of PGS in genetic association studies, most studies in this emerging literature have ignored the functional implications of having low-psychiatric PGS (Bogdan *et al.*, 2018; Anderson *et al.*, 2019). This study used data from a population-based dataset to investigate the association of the ADHD PGS distribution as it pertains to ADHD and functional outcomes associated with ADHD, including educational attainment, cognition, and mental and physical health. In line with the hypothesis that low ADHD PGS may confer a protective effect on ADHD and related functional outcomes, individuals with low ADHD PGS were expected to have a reduced risk of ADHD, relative to (1) those at medium and higher ADHD PGS levels and (2) the observed population prevalence rate of ADHD in Add Health. Furthermore, individuals with low ADHD PGS were also expected to have superior functional outcomes in adulthood relative to those with medium and 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 ($N = 7088$). Within the genotypic subsample, the mean age at Wave IV was 29.00 (S.D. = 1.74), 46% of this sample was male, and the racial-ethnic composition was 63.6% Caucasian (including Hispanic), 20.7% African American, 0.2% Native American, 5.1% Asian, and 10.3% 'Other.' Although there were a few statistical differences between the genetic and non-genetic Add Health subsamples across demographic variables (see Online Supplementary eTable 1), these differences were very small in terms of their effect sizes.

Measures

ADHD

Childhood ADHD symptoms were self-reported by the participant retrospectively (when the participants were between ages 5 and 12) at Wave III, keyed to the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013). Seventeen 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 were defined as having six or more symptoms of inattention and/or six 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 (CES-D) Scale (Radloff, 1977). Lifetime DSM-IV criteria for alcohol abuse or dependence were assessed as the presence of at least 1 of the 4 items pertaining to alcohol abuse, and/or 3 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 conducted with the participant while in prison. Perceived stress was measured via an abbreviated 4-item version of the Cohen's Perceived Stress Scale (Cohen *et al.*, 1983), 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.'
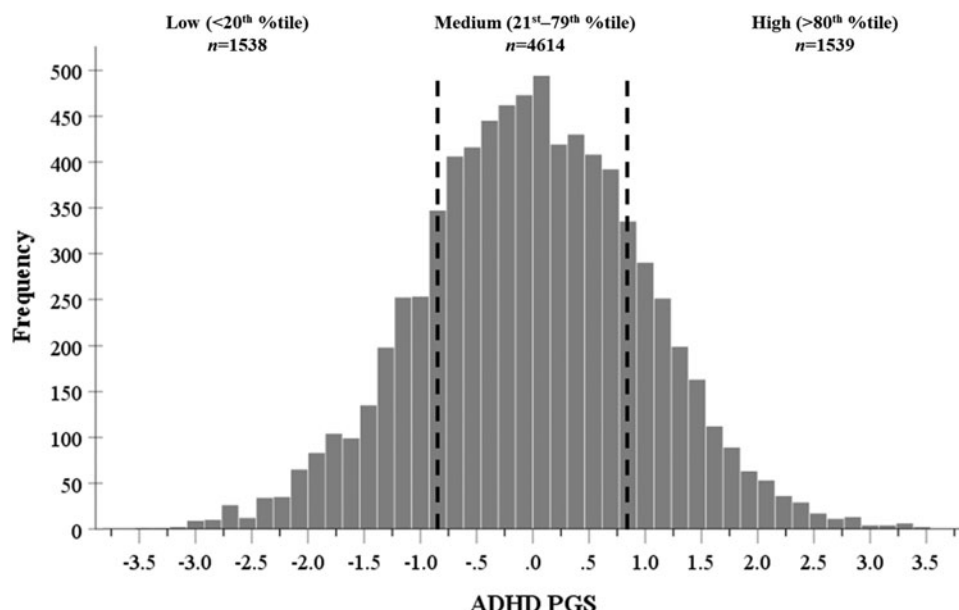
Fig. 1. The ADHD PGS distribution in Add Health. Dotted lines represent thresholds at <20th percentile (ADHD PGS ⩽ −0.83) and >80th percentile (ADHD PGS ⩾ 0.85) of the ADHD PGS distribution, respectively.

Physical health

All physical health outcomes were assessed at Wave IV. Body mass index (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?'

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 SNP effect size according to meta-analytic GWAS (Demontis et al., 2019). This GWAS featured 55 374 individuals (20 183 cases and 35 191 controls) from 12 studies of mixed (but predominantly European) ancestries and a replication sample of 93 916 individuals from two mixed ancestry cohorts. This study used a GWAS p value threshold of $p = 1$ rather than an empirical p value threshold to minimize potential bias due to overfitting (Benjamini et al., 2001). PGS were then standardized according to

genetic ancestry groups in Add Health (Braudt and Harris, 2018). 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 (Price et al., 2006).

Statistical analysis

First, a logistic regression was modeled where ADHD PGS (measured continuously and categorically) was regressed on ADHD diagnostic status, controlling for age, biological sex, and genetic PCs. Predicted and observed probabilities of ADHD were computed for each category of the PGS (i.e. binned into 20th percentiles; see Fig. 1). Then, low (<20th percentile), medium (21st–70th percentiles), and high (>80th percentile) PGS groups were compared across adult functional outcomes. These group comparisons were conducted using parametric and nonparametric tests: a one-way ANOVA was performed to examine differences on the AHPVT standardized scores (a normally distributed quantitative outcome), Kruskal–Wallis H tests were used to test for differences on ordinal or quantitative discrete/non-normal outcomes (i.e. educational attainment, depression symptoms, perceived stress, and BMI) and χ^2 tests were used for binary outcomes (e.g. DSM-IV alcohol abuse/dependence, illicit drug abuse/dependence, ever arrested, hypertension, and high-blood cholesterol). Pairwise contrasts were probed between each PGS group on the outcome variables. The alphas were set to 0.005 to correct for multiple testing (i.e. 0.05 divided by 11 dependent variables). Bivariate correlations between PGS and ADHD as well as all other dependent variables are in online Supplementary eTable 2. Due to the stratified and clustered nature of the sampling performed in Add Health, sampling weights were applied in all analyses.

Results

PGS and ADHD diagnostic status

As expected, ADHD PGS was positively associated with ADHD diagnostic status (OR 1.22, $p < 0.001$, 95% CI 1.10–1.36).

Table 1. Tests comparing PGS status across functional outcomes

| Dependent variable (range)	PGS status	Mean	S.E.	F, χ² or H	p*	df	Lower	Upper
Cognition								
AHPVT standardized score (50–141)	Low	104.13	0.72	F = 24.56	<0.001	2	102.70	105.55
	Medium	101.40	0.55				100.32	102.49
	High	99.06	0.64				97.80	100.32
Educational attainment								
Highest degree attained (1–10)	Low	5.87	0.11	H = 109.30	<0.001	2	5.66	6.08
	Medium	5.54	0.07				5.40	5.70
	High	5.09	0.10				4.89	5.29
Mental health and behavior								
CES-D depression symptoms (0–15)	Low	6.17	0.16	H = 11.71	<0.001	2	5.85	6.49
	Medium	6.73	0.11				6.52	6.93
	High	7.00	0.21				6.59	7.41
DSM-IV alcohol abuse/dependence (0–1)	Low	0.32	0.02	χ² = 2.08	0.350	2	0.29	0.35
	Medium	0.29	0.01				0.27	0.31
	High	0.25	0.02				0.21	0.29
DSM-IV illicit drug abuse/dependence (0–1)	Low	0.08	0.01	χ² = 13.12	<0.001	2	0.06	0.10
	Medium	0.08	0.00				0.07	0.09
	High	0.10	0.01				0.08	0.12
Ever arrested (0–1)	Low	0.26	0.01	χ² = 28.32	<0.001	2	0.24	0.29
	Medium	0.29	0.01				0.27	0.31
	High	0.34	0.02				0.31	0.38
Perceived stress (0–16)	Low	4.56	0.11	H = 13.91	<0.001	2	4.34	4.77
	Medium	4.85	0.08				4.70	5.00
	High	5.02	0.11				4.79	5.24
Physical health								
BMI (1–6)	Low	3.11	0.04	H = 37.70	<0.001	2	3.04	3.18
	Medium	3.33	0.03				3.27	3.39
	High	3.47	0.06				3.36	3.58
Hypertension stage 2 (0–1)	Low	0.12	0.01	χ² = 5.72	0.060	2	0.09	0.14
	Medium	0.14	0.01				0.13	0.16
	High	0.14	0.01				0.12	0.17
High blood cholesterol (0–1)	Low	0.08	0.01	χ² = 2.85	0.240	2	0.06	0.10
	Medium	0.07	0.01				0.06	0.08
	High	0.09	0.01				0.07	0.11

*p values are reported to the thousandths decimal point due to the Bonferroni correction threshold of $p < 0.005$.

Note. Results show parametric and nonparametric tests of PGS group comparisons on functional outcomes. A one-way ANOVA was performed to examine differences on continuous and normally distributed outcomes. Kruskal–Wallis H tests were used to test for differences on ordinal or continuous outcomes, and χ^2 tests were used for binary outcomes. '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, and 'High' PGS is the fifth quintile (>80th percentile) of the PGS distribution.

Figure 1 shows the predicted and observed probabilities of ADHD by the ADHD PGS group, ranging the bottom 20th percentile (PGS ⩽ −0.83) of PGS to the top 20th percentile (PGS ⩾ 0.85). ADHD probabilities significantly differed by the PGS group ($\chi^2(2) = 22.21$, $p < 0.001$). Individuals in the lowest 20th percentile of ADHD PGS (i.e. low PGS) had lower probabilities of ADHD than those in the middle percentiles (i.e. medium PGS; $\chi^2(1) = 6.04$, $p = 0.01$) and those in the highest 20th percentile
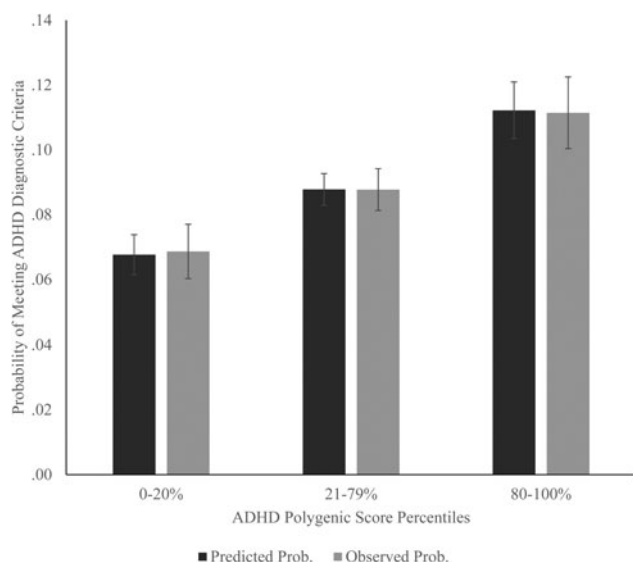
Fig. 2. Predicted and observed probabilities of meeting diagnostic criteria for ADHD in Add Health by ADHD PGS. Figure shows the predicted and observed probabilities of meeting diagnostic criteria for ADHD in Add Health by ADHD PGS groups, according to a binary logistic regression that controlled for age, biological sex and the first 10 principal components of the genetic information (i.e. genetic ancestry). Error bars reflect standard errors.

(i.e. high PGS; $\chi 2(4) = 20.24$, $p < 0.001$), although it should be noted that the pairwise contrast between the low and medium PGS did not reach significance with a Bonferroni correction ($p < 0.005$). Furthermore, those in the medium PGS group had lower probabilities of ADHD than those in the high-PGS group ($\chi^2(1) = 9.69$, $p = 0.002$).

For those in the low-PGS group, the predicted probability of ADHD was 6.77% (s.e. = 0.62, 95% CI 5.54–7.99%) and the observed probability was 6.87% (s.e. = 0.83, 95% CI 5.39–8.71%). Overall, individuals in the low-PGS group had a roughly 17–19% reduction in risk for ADHD relative to the Add Health ADHD prevalence rate of 8.3%.

Individuals in the medium PGS group had a predicted ADHD probability of 8.78% (s.e. = 0.49, 95% CI 7.82–9.75%) and an observed ADHD probability of 8.78% (s.e. = 0.65, 95% CI 7.58–10.14%). As expected, those in the medium PGS group had an ADHD risk profile that was approximately equivalent to the general population as well as the Add Health ADHD prevalence rate.

Individuals in the high-PGS group had the highest probabilities of ADHD; the predicted probability of ADHD was 11.22% (s.e. = 0.87, 95% CI 9.49–12.95%) and the observed probability was 11.14% (s.e. = 1.10, 95% CI 9.14–13.53%). Being in the top 80th percentile of polygenic risk for ADHD conferred a 35% increase in risk for ADHD relative to the Add Health ADHD prevalence rate of 8.3%.

PGS groups and adult functional outcomes

Parametric and nonparametric tests were performed to compare PGS group differences across cognition, educational attainment, mental health and behavior, and physical health outcomes (Table 1 and Fig. 2). There were significant group differences for most of the outcomes examined, with the exception of

DSM-IV alcohol abuse/dependence ($\chi^2(2) = 2.08$, $p = 0.350$), hypertension ($\chi^2(2) = 5.72$, $p = 0.060$), and high-blood cholesterol ($\chi^2(2) = 2.85$, $p = 0.240$).

Pairwise contrasts (Table 2) showed, not surprisingly, that low and high-PGS individuals differed most significantly (after Bonferroni correction) across the functional outcomes, where low-PGS individuals had significantly higher-AHPVT standardized scores and educational attainment, significantly fewer depression symptoms, and significantly lower rates or levels of illicit drug abuse/dependence, being ever arrested, perceived stress, and BMI relative to their high-PGS counterparts. These groups did not differ on their alcohol abuse/dependence rates, hypertension, or on high-blood cholesterol.

Interestingly however, low-PGS individuals also differed significantly from medium PGS individuals on several functional outcomes, suggesting the possibility of a protective effect of low PGS. In particular, low PGS individuals had significantly higher AHPVT standardized scores and greater levels of educational attainment, as well as significantly lower levels of the BMI. Low-PGS individuals did not significantly differ from their medium PGS counterparts on mental health and behavioral outcomes (i.e. depression symptoms, alcohol abuse/dependence, illicit drug abuse/dependence, rates of being ever arrested, perceived stress) and on other indices of physical health (i.e. hypertension and high-blood cholesterol).

Finally, and also notably, medium-PGS individuals differed from high-PGS individuals across all the major functional domains. Medium-PGS individuals had higher AHPVT standardized scores and educational attainment, lower rates of illicit drug abuse/dependence, being ever arrested, and perceived stress, and also lower BMI relative to their high-PGS counterparts (Fig. 3).

Secondary analyses

ADHD PGS may not be generalizable to non-European populations given that the GWAS was performed on predominantly European-ancestry populations (Demontis et al., 2019). Although these analyses include safeguards against population stratification (i.e. controlling for 10 PCs) and standardized PGS by genetic ancestry, parallel analyses were conducted for the European-only subsample of Add Health (n = 4506) to determine whether the results were only specific to European-ancestry individuals in the sample. ADHD PGS was significantly predictive of ADHD in the European-subsample (OR 1.28, $p < 0.001$, 95% CI 1.13–1.46), which was similar to full sample. Furthermore, omnibus parametric and nonparametric tests showed the same pattern of results in the European only subsample as with the full sample (online Supplementary eTable 3). That is, significant PGS group differences emerged across most major indices of functioning with the exception of alcohol abuse/dependence, hypertension, and high-blood cholesterol. The directions of these differences were also consistent with what was reported in the full sample (see online Supplementary eTable 4).

Discussion

Results from this investigation yielded the following discoveries. First, individuals at the lowest end of the ADHD PGS distribution (i.e. lowest 20th percentile) had the lowest probabilities of ADHD, particularly in relation to individuals with high PGS (i.e. the highest 20th percentile). Second, individuals with low ADHD PGS had

Table 2. Pairwise contrasts of PGS groups on dependent variables

PGS group contrasts (dummy code)	Dependent variable	T, χ^2 or H	Test statistic df	p^*
Low (0) v. medium (1)	Cognition			
	AHPVT standardized score	$T = 5.52$	5871	<0.001
	Educational attainment			
	Highest degree attained	$H = 36.14$	1	<0.001
	Mental health and behavior			
	CES-D depression symptoms	$H = 2.56$	1	0.109
	DSM-IV alcohol abuse/dependence	$\chi^2 = 0.81$	1	0.369
	DSM-IV illicit drug abuse/dependence	$\chi^2 = 0.24$	1	0.625
	Ever arrested	$\chi^2 = 2.45$	1	0.118
	Perceived stress	$H = 2.85$	1	0.091
	Physical health			
	BMI	$H = 21.56$	1	<0.001
	Hypertension stage 2	$\chi^2 = 4.14$	1	0.042
	High blood cholesterol	$\chi^2 = 0.48$	1	0.487
Low (0) v. high (2)	Cognition			
	AHPVT standardized score	$T = 6.75$	2934	<0.001
	Educational attainment			
	Highest degree attained	$H = 107.24$	1	<0.001
	Mental health and behavior			
	CES-D depression symptoms	$H = 8.97$	1	0.003
	DSM-IV alcohol abuse/dependence	$\chi^2 = 2.08$	1	0.149
	DSM-IV illicit drug abuse/dependence	$\chi^2 = 9.05$	1	0.003
	Ever arrested	$\chi^2 = 24.13$	1	<0.001
	Perceived stress	$H = 13.61$	1	<0.001
Low (0) v. high (1)	Physical health			
	BMI	$H = 35.72$	1	<0.001
	Hypertension stage 2	$\chi^2 = 5.19$	1	0.023
	High blood cholesterol	$\chi^2 = 0.60$	1	0.438
Medium (1) v. high (2)	Cognition			
	AHPVT standardized score	$T = 2.85$	5873	0.004
	Educational attainment			
	Highest degree attained	$H = 46.82$	1	<0.001
	Mental health and behavior			
	CES-D depression symptoms	$H = 4.23$	1	0.040
	DSM-IV alcohol abuse/dependence	$\chi^2 = 0.75$	1	0.386
	DSM-IV illicit drug abuse/dependence	$\chi^2 = 11.00$	1	0.001
	Ever arrested	$\chi^2 = 20.37$	1	<0.001
	Perceived stress	$H = 7.72$	1	0.005
	Physical health			
	BMI	$H = 7.81$	1	0.005
	Hypertension stage 2	$\chi^2 = 0.53$	1	0.467
	High blood cholesterol	$\chi^2 = 2.79$	1	0.095

$^*p$ values are reported to the thousandths decimal point due to the Bonferroni correction threshold of $p < 0.005$.
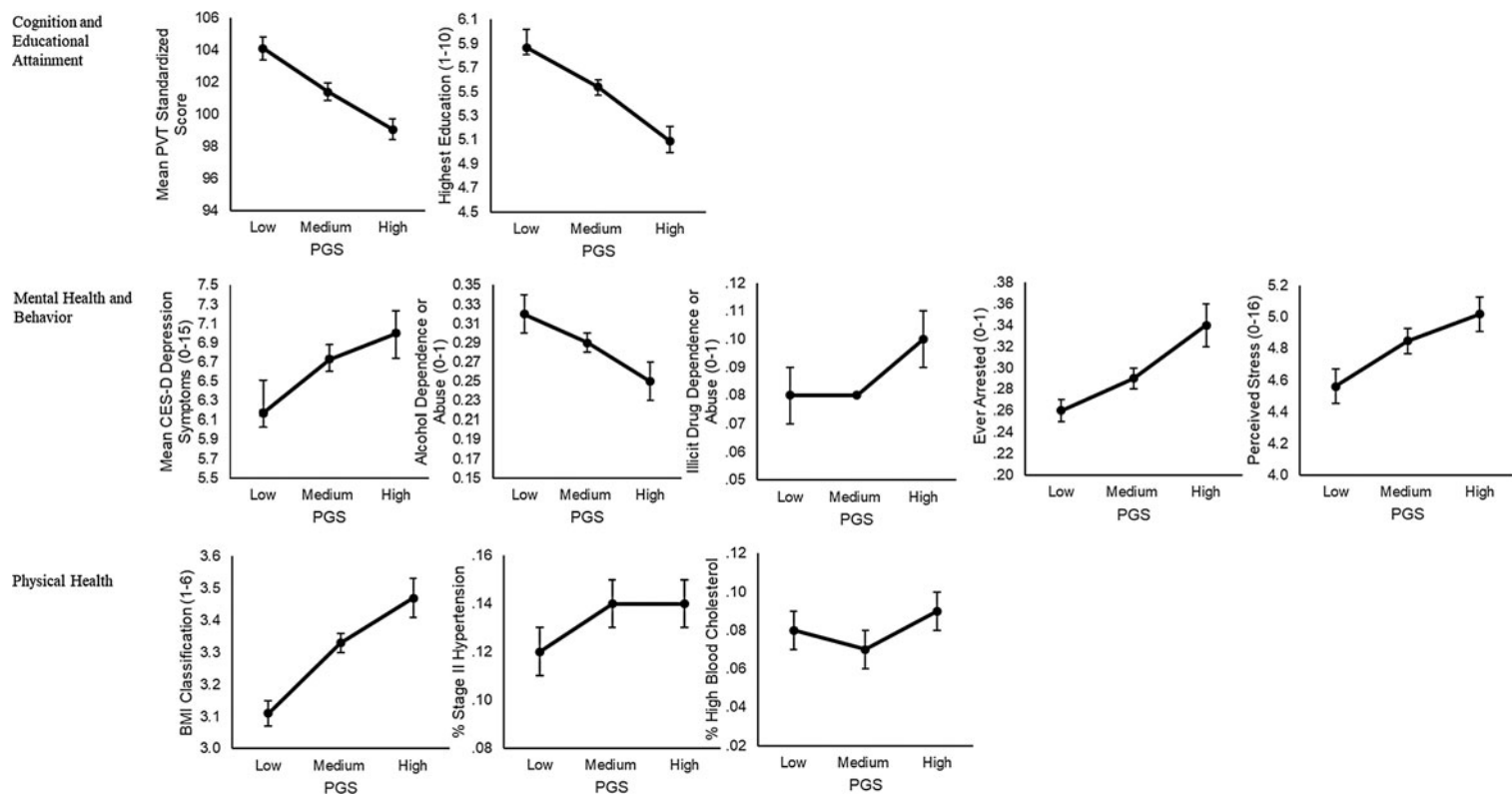
Fig. 3. Associations between ADHD PGS levels and functional outcomes. Plots of the observed means for each dependent variable by each ADHD PGS level, obtained from a multivariate analysis of variance controlling for age, biological sex, and the first 10 principle components of the genetic information (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, and 'High' PGS is the fifth quintile (>80th percentile) of the ADHD PGS distribution. Standard errors are shown on each figure.

a 17–19% reduction in risk for ADHD relative to the observed 8.3% prevalence rate of ADHD in Add Health, which also tracks with the national prevalence rate among children in the U.S. population (Danielson *et al.*, 2018). Third, individuals with low ADHD PGS demonstrated superior functional outcomes (i.e. higher cognitive performance, greater levels of educational attainment, and lower BMI) relative to individuals representing the rest of the ADHD PGS distribution, including those who were in the medium and high-PGS groups. Collectively, these findings indicate that PGS likely capture far more than just the risk and the absence of risk for a psychiatric outcome; where one lies along the PGS distribution may predict diverging functional consequences, for better and for worse.

First, this study provides novel evidence of qualitative differences depending on where one lies on the psychiatric PGS distribution. In the current study, low-PGS individuals were not only distinguishable from their high-PGS counterparts on ADHD and adult functional outcomes (which was expected), but they were also distinguishable from their medium PGS peers by virtue of their superior functioning on their cognitive abilities, higher educational attainment, and lower BMI. These findings call into question whether it is apt characterize low-PGS individuals as having 'low genetic risk' (Torkamani *et al.*, 2018) because it does not sufficiently disambiguate those with fewer susceptibility alleles from the vast majority of individuals in the population who carry a modest burden of genetic liability for psychiatric illness (i.e. the medium PGS group). This issue is magnified in recent findings from GWAS, which have shown that psychiatric risks increase across the PGS distribution for ADHD (Demontis *et al.*, 2019) and MDD (Wray *et al.*, 2018). However, these studies have only shown how the risk for psychiatric illness increases as a function of PGS when the lowest PGS percentile is the reference point. The effect sizes from these comparisons 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 (Plomin *et al.*, 2009). Future genetic association studies should consider using more informative (i.e. less biased) reference points when examining the relative psychiatric risk as a function of one's PGS. For instance, researchers could instead select a point along the PGS distribution that best maps on to the prevalence rate of the outcome in question. The practical utility of this approach was demonstrated in the current investigation.

Another significant discovery from this study is that medium and high-PGS individuals also differed in their risk for ADHD as well as on several indices of adult functional outcomes (i.e. higher cognitive abilities and educational attainment, lower rates of illicit drug abuse/dependence, being ever arrested and perceived stress, and lower BMI). This finding may be crucial because it points to the possibility of a PGS 'clinical threshold,' as theorized in the classic liability threshold model of psychiatric illness (Knopik *et al.*, 2016, 36–37). The liability threshold model states that while genetic risk is distributed normally in the population, the disorder should only occur once a threshold of liability has been met or exceeded. Individuals who meet or exceed this liability threshold may also carry a different set of causal risk factors that differentiate them from those at the extreme ends of the normal range (Rutter *et al.*, 1996; Rutter and Sroufe, 2000). Thus, it is plausible that observed qualitative differences between medium and high-PGS individuals on ADHD risk and adult functional outcomes may reflect not only differences in their genetic risk, but also environmental risks as well. Clearly, future studies aiming

to identify a clinical threshold for PGS that draws the line between disorder and non-disorder (or perhaps more apt for those who subscribe to dimensional characterizations of psychiatric illness, distress *v.* non distress) will be important if PGS is to be useful for clinical practice.

The findings should be interpreted in light of several study limitations. First, the absence of ADHD GWAS featuring well-powered samples of non-European individuals make it challenging to generalize ADHD PGS to populations that are not of predominantly European ancestry, such as Add Health. This limitation was 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). Additionally, the European-only analyses showed that PGS group differences on the risk for ADHD and adult functional outcomes were almost entirely consistent with what was observed from the full sample. Still, future investigations should anticipate the greater prediction error that comes with using a European-based PGS in mixed samples. Second, the data used in this study were limited to retrospective self-reports, which might be confounded via rater bias or potential issues with validity. In the case of ADHD, participants retrospectively reported on their childhood ADHD symptoms as adults (at Wave III). While adults are fairly reliable reporters of their own ADHD when compared to parents and clinicians (Adler *et al.*, 2006; Kooij *et al.*, 2008), they also tend to under-report the severity of their symptoms (Kooij *et al.*, 2008). Still, having ADHD data from multiple raters would have strengthened this study considerably, especially given that heritability estimates of ADHD differ by rater (Larsson *et al.*, 2013, 2014; Merwood *et al.*, 2013). 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.

Findings from this study may spur a crucial shift in perspective with regard to the utility of psychiatric PGS in future investigations. Furthermore, PGS may soon play a role in clinical prediction and decision making (Bogdan *et al.*, 2018; Anderson *et al.*, 2019). For instance, it is possible that individuals at high-genetic risk may benefit more from an interventions relative to those at moderate and even low-genetic risk (Mega *et al.*, 2015; Natarajan Pradeep *et al.*, 2017). 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 genetic risks along with crucial clinical information (i.e. biomarkers, environmental factors) pertinent to the individual.

Information on how to obtain the Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this analysis.

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