How the ADHD polygenic risk score adds to our understanding of ADHD and associated traits: A Systematic review

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Systematic review: How the ADHD polygenic risk score adds to our understanding of ADHD and associated traits

Objective: To investigate, by systematically reviewing the literature, if the ADHD polygenic risk score (PRS) associates with ADHD and related traits in independent clinical and population samples.

Method: Pubmed, Embase and PsychoInfo were systematically searched, alongside study bibliographies. Quality assessments were conducted, and a best-evidence synthesis was applied. Studies were excluded when 1) predictor was not based on the latest ADHD genome-wide association study; 2) PRS was not based on genome-wide results; 3) study was a review. Initially, 197 studies were retrieved [dd. Feb 22nd 2020]; a second search [dd June 3rd 2020] retrieved a further 49 studies; from both searches, 57 studies were eligible and 44 studies met inclusion criteria.

Results: Included studies were published in the last three years. Over 80% of the studies were rated excellent based on a standardized quality assessment. Evidence of associations between ADHD PRS and the following categories was strong: ADHD, ADHD traits brain structure, education, externalizing behaviors, neuropsychological constructs, physical health and socio-economic status. Evidence for associations with addiction, autism and mental health are mixed and were, so far, inconclusive. Odds ratios for PRS associating with ADHD ranged from 1.22-1.76; variance explained in dimensional assessments of ADHD traits was 0.7%-3.3%.

Conclusion: A new wave of high quality research using the ADHD PRS has emerged. Eventually, symptoms may be partly identified based on PRS, but the current ADHD PRS is useful for research purposes only. This review shows the ADHD PRS is robust and reliable, associating not just ADHD but many outcomes and challenges known to be linked to ADHD.

Keywords: Attention Deficit/Hyperactivity Disorder, genetics, neurodevelopment, comorbidity, psychiatry

ADHD is a neurodevelopmental disorder that affects approximately 5% of children and 2.5% of adults[1]. Decades of past research have established the significant twin heritability of ADHD and family studies demonstrate its high familiality[2,3]. More recently, significant SNP heritability estimates for ADHD have been reported[4]. Together this evidence supports the hypothesis that common genetic variants acting additively play a role in the causes of ADHD[3]. In addition, twin, family, and molecular genetic studies suggest that these common variants may to some degree be shared with other conditions and traits, including autism and autistic traits[5,6,7,8,9,10], tobacco and alcohol use[11,12], and depressive and hypomanic symptoms[13,14,15].

A genome-wide association study (GWAS) is the principal tool for identifying common genetic variants across the genome that influence complex traits[16]. Following previous GWAS's using comparatively smaller samples, the latest GWAS on individuals with ADHD (n=20,183) and controls (n=35,191) identified 12 independent loci associated with ADHD[17]. Several characteristics of the study suggested that these findings were robust: for example, significant SNP heritability of 22% was reported, the genome-wide significant loci were replicated, and no marker demonstrated heterogeneity between studies.

GWAS data can be used to create a polygenic score, or, as often referred to in studies of psychopathological traits, a polygenic risk score (PRS). PRS's can estimate an individual's genetic liability for a particular disorder or trait, based on current knowledge of the trait's genetic architecture. Technically, a PRS is calculated as the weighted sum of the risk alleles, carried by an individual, which are associated with a disorder based on a GWAS. Demontis et al[17] reported that the variance in ADHD explained by their ADHD PRS was 5.5% in individuals of European ancestry (note that European ancestry individuals were also used to calculate the score). In their samples, the PRS had an OR of 1.56 between cases and controls and acted in a dose-dependent fashion: the higher the PRS, the higher the OR for having

ADHD. PRS's can be calculated in any genotyped sample and thus the degree to which the ADHD PRS associates both with ADHD as well as other phenotypes can be explored. The latter is interesting given the reported co-occurrence and genetic overlap of ADHD with many other traits like autism and substance use, as described above.

A PRS is thus a major methodological development, not only for the genetic field, but in terms of potential utility in a range of other research fields due to the fact that they can be easily calculated in any genotyped sample. The potential of PRS for clinical utility, screening and personalized health is currently a major topic of debate[18,19].

Here we present a systematic review of all studies using the ADHD PRS based on the largest ADHD GWAS to date[17] and provide a systematic quality assessment of all included studies. In our review, we structured our results by the following outcome domains: diagnosed ADHD and ADHD traits (dimensional assessments of ADHD symptoms or traits), addiction, autism and autistic traits, brain-based (imaging) measures, educational attainment, externalizing behaviors, , mental health, neuropsychological constructs, physical health, socioeconomic variables and other (uncategorized) outcomes. Please see Table S1 for the complete list of outcomes per category. We also note the ancestry of the samples used in the literature to date.

METHODS

Details of the outline of our review and methods applied were preregistered with PROSPERO Framework (https://www.crd.york.ac.uk/PROSPERO) with registration number CRD42020176391 on April 28 2020, and followed as registered except the following: 1) The study by Hayden et al. (2013), on which we based our quality assessments, proposes six quality domains. However, given some overlap in items of domains 1 and 2, we combined these, and thus used five domains instead of six. 2) Given the sheer amount of studies resulting from the latest GWAS (n= 44), and the importance of an adequately powered GWAS to use the PRS reliably, we decided to exclude a systematic overview of studies based on older GWAS's.

Study selection

PubMed, Embase, and PsychInfo were systematically searched for published, peer reviewed studies written in English using the search terms: ("ADHD"[Title/Abstract] OR "Attention Deficit"[Title/Abstract] OR "Attention-Deficit"[Title/Abstract] OR "Hyperactivity"[Title/Abstract] OR "Hyperactive"[Title/Abstract] OR "attention deficit hyperactivity disorder"[Title/Abstract] OR "Attention problems"[Title/Abstract]) AND ("Polygenic risk score"[Title/Abstract] OR "Polygenic score"[Title/Abstract]). Bibliographies of selected studies were also searched (by NB). A first search was conducted February 22nd 2020, and a second search on June 3rd 2020. All abstracts were inspected by two reviewers (TJCP and NB). Studies were excluded when a) the predictor was not an ADHD PRS b) the PRS was not based on genome-wide results (but e.g., on a certain selection of SNPs) c) the ADHD PRS was not based on the latest GWAS results of ADHD[17], or c) the study was a review.

Figure 1 provides a flowchart on the selection and reasons for exclusion of studies.

INSERT FIGURE 1

The ADHD PRS

GWAS results allow the calculation of an individual polygenic risk score (PRS), which is based on the aggregate effect of common genetic variants that are associated with the trait of interest[20,21]. The PRS can be used to test the association between the aggregated common genetic risk for ADHD and other human traits.

Categorization of outcome measures

Categorization of outcomes was loosely based on ICD/ICF[22,23] but not completely for the following reasons. First, these classification systems would have meant losing specificity. Second, these systems are not designed specifically with ADHD in mind. For example, we chose to categorize externalizing behaviors and addiction as two specific categories, due to their relevance to ADHD, rather than putting them under the umbrella category of mental health. Thus, some categories were made more or less specific, based on deliberation and consensus between AR and TP. Outcomes that were only studied once and did not fall readily into categories with other outcomes were placed in an 'Other' category. Table S1 provides an overview of outcome measures in each category.

Quality assessment

In general, scientific studies may encounter various biases resulting in potentially reduced validity and generalization of findings. Based on two studies by Hayden et al.[24,25], we set up a

series of quality assessment criteria, clustered in five domains, to evaluate the quality of studies that we included in the current review.

1. Study participation

A clear description of characteristics of the sample under study is key to evaluate how adequately the sample represents the population of interest, and how potential attrition may lead to selection bias affecting a proper representation.

2. The ADHD PRS

The validity and statistical power of a PRS depends on two crucial conditions. The first one is a powerful GWAS discovery sample, and the second one is proper quality control (QC) of the genetic data of the target sample under study. With the publication of the summary statistics of the largest GWAS on ADHD three years ago[17], for the first time, a reasonably powerful ADHD PRS became possible. Standard QC protocols are available[26] to ensure that genetic data are correctly processed, and that important data checks are applied. Furthermore, when analysing PRS data, a proper correction for population stratification should be applied.

3. Assessment of outcome measures

The current review includes multiple outcome measures that were tested for an association with the ADHD PRS. In the quality assessment, the validity and reliability of these outcome measures, either tested in the study, or as citation to earlier publication, were the focus of evaluation.

4. Confounding factors

Several confounding factors can play a role in the relation between the genetic risk for ADHD and the outcome measures. Given the variety of outcome measures the focus of evaluation was on the following generic confounders: gender, age, socioeconomic status (SES), use of medication and co-occurring disorders.

5. Analysis and data presentation

For a reader to judge the quality of a study, a proper presentation of the statistical analyses and results is required. Of importance is also the target sample size, as sufficient statistical power is required to provide accurate conclusions on the relation between the ADHD PRS and outcome measures. Lastly, multiple testing correction should be applied when more than one outcome measure is tested for an association with the predictor variable (i.e., ADHD PRS).

A checklist consisting of criteria as described above was used to evaluate the quality of the 44 selected studies. Every item was rated positive (+), negative (-), or +/- (i.e., fulfilling part of the criterium) by two independent reviewers (TJCP and NB). In case of any disagreement between the reviewers, consensus was achieved by discussion. Studies were then ranked based on the number of biases. A bias was present when more than 50% of the criteria of one domain had a negative score. The highest quality was attained if at least 50% of the items of each domain were rated as being positive[24,25]. Of note, since item M (treatment and comorbidity) could only be rated for the clinical samples, and not applicable (NA) for the population samples, this item was excluded from the bias count.

Best-evidence synthesis

Within each of the categories, considerable variation was present in outcome measures. Therefore, we performed a best-evidence synthesis, to define the evidence for a true association between the ADHD PRS and respective outcome category. The evidence for each category was determined by taking into account the number of studies evaluating this association, the quality of these studies, and the consistency of findings across studies[27]. Based on this evaluation, four increasing levels of evidence can be defined[28].

RESULTS

The 44 studies that met our inclusion criteria are listed in Table 1, and the results are summarized in Figure S1. Categories of outcome(s) are given in the first column for each study. Samples are described in terms of name (where available), type, nationality, size, sex and age ranges. Choice of SNP p-value threshold (pT) is listed in the 4th column; Outcomes along with covariates are listed in the 5th column. Results (6th column) focus on the statistics, effect sizes and their direction, for direct effects. The Results column describes any mediation analyses in terms of % reduction in direct effect and outlines any sensitivity/replication analyses. Negative findings are reported but statistics for negative findings are omitted for space considerations. The Results column also specifies the author(s)' choice of significance threshold for testing the association between the ADHD PRS and outcome measure(s).

INSERT TABLE 1

Descriptives of outcome measures and samples

Outcome measures were categorized in the following domains (number of studies shown in parenthesis): diagnosed ADHD (n=10), ADHD traits (n=16); substance and non-

substance-based addiction phenotypes (n=8), autism spectrum disorders or autistic traits (n=5), brain-based (imaging) variables (n=8), educational attainment (n=9), externalizing behaviors (n=8), mental health (n=11), neuropsychological constructs (n=6), physical health (n=4), socio-economic variables (n=4) and "other" (uncategorized outcomes) (n=9).

Across the 44 studies, a total of 48 samples were used. Four studies included two samples and note that these 48 samples are not all independent (see below). In terms of sample characteristics, 25 of the 48 samples (52%) were population samples, 16 (33%) were clinical samples and 7 (15%) were community samples enriched for individuals with ADHD or mental illness. Children (under 18's) made up just over half the samples (n=25; 52%), 13 (27%) were adult samples and the remaining (n = 10, 21%) included both children and adults. It was most common for samples to come from Europe (n = 25, 52%) followed by North America (n = 17, 35%), a mix of continents (n= 4, 9%), Asia (n = 1, 2%) and one had missing country of origin (2%). The samples employed in more than one study were ALSPAC (6 studies), IMAGEN (3 studies), National Longitudinal Study of Adolescent to Adult Health (3 studies), Child and Adolescent Twin Study in Sweden (3 studies), Generation R (2 studies), community based sample recruited close to Oregon Health & Science University USA (2 studies), and iPSYCH (2 studies).

Diagnosed ADHD. The ADHD PRS consistently associated with diagnosed ADHD in all 10 studies. The odds ratios ranged from 1.22-1.76. This range omits one study which associated with ADHD within a cohort with bipolar disorder[29] and two studies which did not provide enough information to calculate odds ratios[30,31]. Several studies[17,32] showed, using deciles or groups based on low/medium/high scorers, that the ADHD PRS operated in a dose dependent manner in terms of its influence on ADHD status.

In terms of ADHD and co-occurring conditions, ADHD PRS was associated with having combined ADHD and ASD in a multiplex family design including unaffected relatives

and relatives with either or both conditions[31]. The ADHD PRS did not differentiate bipolar disorder cases with ADHD from bipolar disorder cases without ADHD[29]. In the context of other psychiatric disorders, ADHD PRS was associated with ADHD when controls were individuals with other psychiatric disorders[33];

ADHD Traits. This was the most commonly studied outcome and all studies found positive significant associations with the ADHD PRS (16 studies). Percent variance explained in ADHD traits by the ADHD PRS ranged from 0.7-3.3%. These values were either directly reported, or converted from correlations provided in the studies. Five studies that reported on ADHD traits[29,34,35,36,37] are omitted from this range because their study designs were different (e.g. they only investigated subscales, they investigated familial effects, the sample was bipolar disorder cases).

Four of these studies investigated the ADHD trait subscales separately, namely hyperactivity/impulsivity and inattention. Two (50%) studies found that the ADHD PRS was positively associated with higher scores on both subscales[38,39] whereas two (50%) found that the ADHD PRS was positively associated with the hyperactivity/impulsivity subscale but not significantly associated with inattention[33,36].

Addiction. A range of addiction phenotypes were studied: seven studies on substance related addiction[32,40,33,41,42,43,44] and one study on a non-substance related addiction – gambling[45]. Three studies did not find the ADHD PRS associated with their addiction phenotypes (which focused on gambling behaviors, substance abuse and marijuana use disorders). The other five studies reported all or some significant positive associations, including with cocaine dependence, substance use disorders, alcohol (intake frequency and alcohol-related diagnoses), smoking, cannabis use disorder, use of illicit drugs, and severity of addiction.

Autism spectrum disorders and autistic traits. Five studies investigated diagnosed autism or autistic traits. Only one (on autism) reported a significant positive association with the ADHD PRS, although full effect sizes were not provided[31]. One study on autistic traits reported a significant positive association in males only but the effect was not present for the full sample or in females[46].

Brain-based (imaging) phenotypes. All but one of the eight studies on brain structure or connectivity[47,48,49,50,51,36,52,37] reported significant associations with the ADHD PRS. Five of these also conducted mediation analyses, within which there was a variety evidence that brain structure mediates the association between the ADHD PRS and ADHD. The specific brain-based outcomes are listed in Table S1: 7 of the 8 studies included structural measurements, including both gross indices such as grey matter volume or more detailed measurements such as subcortical structures; two studies included functional parameters.

Educational attainment. Seven of the nine studies reported that the ADHD PRS was associated with lower educational attainment[32,33,35,36,44,53,54] . One nonsignificant finding came from a study which did not test a straightforward association but separated the PRS into transmitted and nontransmitted alleles[34] and thus tested two separate PRS's for their association with educational attainment, which reduces power.

Externalizing behaviors. The ADHD PRS was significantly positively associated with a range of externalizing behaviors across eight studies: cross-sectional assessments of irritability, surgency, impulsivity, aggression, risk taking, and there was evidence that the ADHD PRS was also associated with trajectories of increasing and persistent irritability and with high decreasing trajectories of externalizing behaviors[55,33,56,57,50,44,58].

Mental health. Within this category, there were 11 studies[21,32,54,59,29,60,61,35,44,62] with a broad range of phenotypes but not consistent significant findings. The ADHD PRS was significantly positively associated with the general psychopathology factor in children (also

referred to as 'p' factor)[60]. Higher ADHD PRS was associated with a bipolar disorder subtype combined with ADHD when compared to unaffected controls but did not associate with bipolar disorder when compared to unaffected controls. Four studies explored schizophrenia or subthreshold psychotic experiences, and none reported a significant association with the ADHD PRS. In terms of anxiety, depression and neuroticism, results were mixed. For example, the ADHD PRS was associated with higher neuroticism in one study of older adults[44], and more perceived stress in another study[32] but was not associated with neuroticism in a youth sample . The ADHD PRS positively associated with depression in a study of older adults[44]. In a study of children, the ADHD PRS was positively associated with any anxiety or depressive disorder but there were some nonsigificant associations for specific disorders dependent on the type of diagnostic tool that was used[63]. In terms of trajectories of depression across ages 10-18 years in youth, the higher scores on the ADHD PRS associated with an early-adolescence–onset depression class but not late-onset depression[62]. The ADHD PRS also positively associated with a range of eating disorder traits in youth[61].

Neuropsychological constructs. Of the six studies on neuropsychological constructs[64,33,65,36,52,37] , five included working memory and all reported significant associations between poorer working memory and higher ADHD PRS. Other neuropsychological constructs studied in relation to the ADHD PRS were executive function outcomes (all nonsignificant); vigilance/arousal (significant negative association); output speed, mental clock and response inhibition (all nonsignificant); focused attention and delay discounting (significant). Three studies used the neuropsychological variables such as working memory as mediators in models of the association between the ADHD PRS and ADHD[36,37,65] (see Table 1).

Physical health. Of the four studies exploring physical health[32,50,35,44] , three included BMI and all showed a significant positive association with ADHD PRS (albeit using different

methods, see Table 1). The other physical health phenotypes studied were height[44] (mixed evidence), hypertension and blood cholesterol[32] (no associations for either in PRS group comparisons).

Socio-economic Status (SES). Four studies[35,41,58,66] tested whether the PRS associated with variables related to socioeconomic status. All studies showed a significant association with the ADHD PRS being negatively associated with SES. The study by Selzam et al[35]. showed a significant negative association with SES in both their between and within family design.

Other (uncategorized) outcomes. In terms of the nine uncategorized outcomes[29,35,41,42,49,58,67,68,69], the ADHD PRS was positively associated with being bullied[69], bullying chronicity[69] and a victimization adversity scale[58], a total adversity scale[58], earlier age of onset of bipolar disorder[29], reduced participation in research studies[68], selected methylation probes, reduced parental monitoring, and risk of parental mental disorder or substance use disorder[41]. The ADHD PRS did not associate with infant neuromotor functioning[46], community disadvantage and did not associate with ADHD traits in youth with mild traumatic brain injury[67].

Quality assessments

Table 2 shows the items of the quality assessment (QA), and Table 3 the levels of evidence. The results of the QA for each study are presented in Table 4. Three studies had two biases, and five studies had one bias, leaving 36 studies without any notable bias. Studies that did have one or two biases were randomly distributed across categories. Item K (correction for age, gender, and socio-economic status) was rated most often as -/+ since the majority of studies did not correct for socio-economic status and this criteria was not relevant for the SES outcome category. Furthermore, sample sizes of target samples were in some

studies n< 500 which we considered small, although expected effect sizes may differ between outcome measures.

The criteria from the best-evidence synthesis (Table 2) suggested that the evidence for an association between the ADHD PRS and the following outcome categories was 'strong': diagnosed ADHD, ADHD traits, brain-based imaging phenotypes, education, externalizing behaviors, neuropsychological constructs, physical health and socioeconomic status. The criteria from the best-evidence synthesis (Table 2) suggested that the evidence was 'inconclusive' for the addiction, autism and autistic traits and mental health categories. The 'Other' category was not included in the best-evidence synthesis.

INSERT TABLE 2

INSERT TABLE 3

INSERT TABLE 4

DISCUSSION

Overall, our literature review demonstrates that the ADHD PRS is reliable, robust, and operates in a dose dependent manner. We found strong evidence from our best-evidence synthesis that the common genetic variants underlying ADHD, as captured by the ADHD polygenic risk score, associated with not only diagnosed ADHD but also with more dimensional ADHD traits, more externalizing behaviors, impaired working memory and education attainment, reduced brain volume, higher BMI and reduced SES. These findings illustrate that the well-known phenotypic associations between ADHD and many of these phenotypes, stemming from decades of research in epidemiology and developmental psychology, may partly be explained by shared genetic effects. There is an emerging literature, albeit not with conclusive evidence according to our best-evidence synthesis,

suggesting outcomes beyond childhood, such as addiction and adult mental health, may also associate with the ADHD PRS. Some phenotypic outcomes are less researched than others; this led to quite broad outcome categories in some instances (e.g., physical health) whereas others were able to be more specific because of the larger literature (diagnosed ADHD; ADHD traits, externalizing behaviors and addiction).

The ADHD PRS appears to carry a degree of specificity both in relation to other PRS's, in terms of the wider context of neurodevelopment and mental health, and in its capacity to significantly associate with only ADHD-relevant phenotypes. Illustrating this, some studies used a multi-PRS model and found that the signal from the ADHD PRS remained significant when controlling for other PRS's[60,69 ,62]. In the wider context of neurodevelopment and mental health, the ADHD PRS often did not associate with other conditions such as autism and schizophrenia[73,59,31,44] or family history for mental health conditions[62, 58,] and it only associated with bipolar disorder when it co-occurred with ADHD[29]. When studies included negative control traits they invariably did not, as predicted, associate with the ADHD PRS[33,44]. Yet, there were also some surprising and novel cross-disorder findings: for example, the ADHD PRS was associated with eating disorder traits in adolescents[61]. However, note that the effect sizes of these eating disorder trait associations (.10-.13%) were at least five times lower than the lowest estimated effect size for ADHD PRS associating with ADHD traits (0.7%, the range being 0.7-3.3%). Thus, the literature supports the validity of the ADHD PRS: the most consistent and strongest associations were with diagnosed ADHD and ADHD traits.

As a literature, the use of the ADHD PRS is fast growing (44 studies in under three years), of high quality (as indicated by our QA assessment), with both breadth -- in terms of the wide range of outcome phenotypes --, and depth -- in terms of both replication within and between studies and extensive analytic protocols. Risk of false positives in PRS studies is potentially high from a combination of authors being free to pick multiple significance thresholds on which to test associations and multiple phenotypes. Most studies appeared to have clear measures in place to avoid false positives: as noted in Table 1, the majority employed some form of significance criterion correction and stated their SNP-based significance thresholds (pT), most selected a single pT and provided a justification for their choice, and many included sensitivity analyses to ensure results were robust. Common sensitivity analyses included repeating analyses on other pT, on different ancestral groups within the sample, excluding children on medication and in community samples by excluding diagnosed ADHD children.

Within the studies on non-ADHD disorders, the ADHD PRS appears useful for predicting trajectories. Specifically, the ADHD PRS appears to have transdiagnostic utility in characterizing subgroups of individuals with early onset symptoms in non-ADHD conditions. For example, while ADHD PRS did not associate with schizophrenia, within a schizophrenia sample it associated with cognitive trajectory from adolescence into adulthood, being most strongly associated with the subgroup with (earliest) preadolescent cognitive impairment[54]. The ADHD PRS did not associate with bipolar disorder, but it associated with an earlier age of onset within bipolar disorder cases[29]. Finally, the ADHD PRS associated with an early onset depression trajectory class but not a later-onset depression trajectory class in youth assessed longitudinally at ages 10 to 18 years[62].

The ADHD PRS has been used in several studies to investigate gene-environment correlation, namely, genetic influences on environmental exposure. Direct effects of the ADHD PRS are reported on lower socioeconomic status[35], lower parental education and income[41], worse labor market outcomes[66], adversity[58] and bullying victimization[69,58]. Two studies went beyond direct genetic effects by applying within family analytic designs. De Zeeuw et al (2019) split the ADHD PRS into transmitted and nontransmitted alleles to test for a process termed "genetic nurture"[34,122]. They did not find that the parents' nontransmitted ADHD PRS (the part of the ADHD PRS inherited by parents but not transmitted to their offspring), influenced the offspring's ADHD symptoms. Selzam et al's more elaborate design involved splitting up the covariance within their sample of twin siblings into between-family and within-family effects[35]. They conclude that some of the association between the ADHD PRS and educational attainment might be due to passive gene-environment correlation effects. It is important to note going forwards that part of the signal in a PRS may be correlated with socioeconomic factors.

The reviewed literature included multiple studies investigating PRS-brain-behavior pathways relevant to ADHD. This new literature is worth highlighting in part because most attempts pre-GWAS to link neuroimaging data simultaneously to both genetics and behavior was a noble failure, beset with issues of multiple testing and low power[123,124]. The studies in our review demonstrate that reduced brain volume mediates the association between the ADHD PRS and ADHD. For example, in one recent study, the ADHD PRS was negatively associated with total brain volume and total brain volume accounted for 16% of the association between ADHD PRS and ADHD diagnosis[49]. Mediation was also employed successfully in other categories. For example, in the neuropsychological category [65], the association between the

ADHD PRS and ADHD diagnosis was mediated by working memory and arousal alertness latent variables. In the externalizing category, it was shown that externalizing symptoms mediated the association between the ADHD PRS and adversity[58].

The ADHD PRS can teach us about the core aspects of ADHD and its nosology. Eventually, the ADHD PRS may contribute to the clinical picture for individual patients, but due to the current small effect sizes, the ADHD PRS is useful for research purposes only. Given the presence of the three presentations of ADHD in the DSM-5 (combined, predominantly inattentive, predominantly hyperactive-impulsive), it is perhaps surprising that only four of the 16 studies on ADHD traits investigated associations of the ADHD PRS separately by ADHD symptom domain[38,33,39,36]. Another study that touched on nosology proposed that emotional dysregulation should be considered a core component of ADHD, in light of their finding that an ADHD subgroup with emotional dysregulation had a higher ADHD PRS score compared to other ADHD subgroups[55].

Given the variety of outcome categories, and variety of outcome measures within categories, a meta-analysis was not conducted. Still, we report the current range in effect sizes for ADHD and ADHD traits. Furthermore, to obtain insights into the reliability and strength of the associations, we applied a best-evidence synthesis that was based on a careful and systematic quality assessment of all studies. Other limitations of our systematic review include the fact that it is difficult to estimate the power of studies based on their target sample size without knowing the expected effect size of an association[125]. We restricted our review to studies employing PRS based on the largest and latest GWAS on diagnosed ADHD. This meant excluding studies on PRS derived from ADHD traits or ADHD traits combined with

diagnosed ADHD (e.g., [126]) and studies using older ADHD PRS (e.g. reviewed by [33]) and studies using a cross-disorder PRS that includes the ADHD PRS. Not all of the 44 studies are completely independent due to some partially or completely overlapping samples. For most categories, every study was based on a different sample. However, it should be noted that three of the 10 studies on mental health outcomes used the ALSPAC sample and two used the CATSS sample. However, given that the evidence for the mental health category was mixed and inconclusive, the repeated use of the ALSPAC and CATSS sample in this category does not appear to have inflated the consistency of the evidence for these categories. In terms of the other categories, two of the 16 ADHD trait studies and three of the eight studies on brain-based outcomes employed the IMAGEN sample and two of the eight addiction studies employed the Add Health sample. Lastly, we included studies based on clinical, enriched, and population-based samples. We found no differences between the samples in their associations with the outcome measures: In the outcome measures for which we observed inconclusive results, (i.e., autism, addiction, and mental health) significant associations did not cluster by sample type.

While emphasizing the high quality of most of the reviewed literature and the strong evidence that has emerged for associations of the ADHD PRS with outcomes, a number of limitations and suggestions for improvements in this field of research are noted. Ideally, field standard approaches in terms of the method of analyzing PRS's would be devised and pre-registration is essential. At present, there are multiple approaches and methods which are only beginning to be formally compared[127]. The selected pT and the justifications for selection of pT varied widely across studies: some selected $p<.05$ to avoid over-fitting, some selected the pT that most accurately predicted ADHD in Demontis et al[17], some use pT=1 to capture all variance, and others applied ranges of multiple pT. When studies did not specify their selected p-value

threshold, we had to select one from which to report the results and this may exacerbate false positives. A reference-standardized approach may be needed to compare PRS across different target samples, to avoid factors often specific to the target sample influencing PRS, including the variants considered, LD and allele frequency estimates[127]. It will be exciting to see future work that combines the ADHD PRS with rare variation and copy number variation or that incorporates the sex chromosomes.

As shown in Table 1, the majority of this literature was conducted on European ancestry samples: of the 44 studies, 77% (n =34 studies) had European ancestry, 91% (n = 41) had most or all European ancestry, one study had missing ancestry and 5% (n=2) had non-European ancestry participants (Japanese and African American, respectively). To maximize the value of the data, some studies ran sensitivity analyses on their samples based on different ancestral populations[32,65]. Major initiatives in terms of both sample ascertainment and method development are needed to ensure the genetic architecture of ADHD is understood regardless of ancestry of the population under study[128]. At present, the literature on the ADHD PRS only offers partial insight globally because roughly only one in twenty studies on the current ADHD PRS to date employs non-European ancestry participants.

It is noted that some of the associations identified here are largely supported by studies employing LD score regression as well as from past twin studies. LD score regression provides an estimate of the degree of shared genetic effects in common genetic architecture. PRS studies are distinguishable for several reasons, including that they allow tests for association between ADHD and other phenotypes that currently lack a large GWAS. Furthermore, as seen in this review, PRS can also easily be manipulated within more complex

analytic frameworks to test more complex hypotheses, such as analyses involving trajectory modelling or mediation models.

In terms of individual prediction, the existing literature only goes so far as to compare groups scoring high, medium and low on the ADHD PRS in a small number of our reviewed studies. The ADHD PRS cannot yet accurately predict individual outcomes, and a PRS is only as accurate as the discovery sample from which it is computed. Anyone who has used direct-to-consumer testing can upload their genetic data on a new tool to calculate their own ADHD PRS[129]. Most individuals who score high on the current ADHD PRS will not develop ADHD because the signal is too weak. There is a strong need for public engagement and public debates on the clinical usability of PRS[130]. It is possible that a more predictive ADHD PRS will be used in the future, in combination with other known risk factors and clinical features, to support health services with prediction, diagnosis and intervention[131]. As pointed out elsewhere, there are some similarities between existing successful health screening practices -- such as the newborn APGAR score and neonatal blood spot screening -- with how a PRS would be obtained and could work in practice[19].

In sum, our review identified 44 relevant studies and demonstrates that strong evidence has accumulated that the ADHD PRS associates with not only ADHD and ADHD traits, but also reduced brain volume, lower education attainment, more externalizing behaviors, impaired working memory, higher BMI and lower socioeconomic status. Alongside these direct effects, the ADHD PRS is being used to reveal more complex processes such gene-environment correlation and that the ADHD PRS influences ADHD symptoms via effects on brain structure. Genetic associations that might have been expected based on past literature, such as between the ADHD PRS and addiction, autism and mental health, are so far inconclusive

from the available evidence. In the context of other known risk factors for ADHD, the ADHD PRS does not have the largest effect size. Nevertheless, the ADHD PRS brings advantages in terms of being based on genetic variants, and thus being biologically-based, possessing a degree of causality and being unchanging across the lifespan (unlike most other risk factors). The estimated SNP heritability of ADHD is larger than the percent variance explained by the current ADHD PRS. We can expect, therefore, that with a larger GWAS of ADHD, a more accurate and predictive PRS will emerge going forward.

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Table 1: Description of included studies

Category	Study	Sample	ADHD PRS p-value threshold(s) (pT)	Outcome measures and covariates	Results
ADHDt, BRAIN	*1. Albaugh et al. 2019*[48]	IMAGEN Study, France, UK, Ireland, Germany n=1471-1597 participants, age range: 12-16 years 52% female, 48% male Population sample Western European ancestry	PRS calculation based on pT= 0.05	MRI: neuroanatomic imaging, and imaging of white matter tract microstructure correlates of ADHD symptomatology ADHD traits: composite score of the Development and Well-Being Assessment (DAWBA)[70] and the Strengths and Difficulties Questionnaire[71] (SDQ) Covariates: Age, sex, site, socioeconomic status, pubertal stage, total brain volume, PCs	ADHD PRS was significantly associated with ADHD traits in participants with available cortical thickness data (r = 0.125, p < 0.001), and with available diffusion data (r = 0.137, p < 0.001). ADHD PRS predicted neuroanatomic imaging, and imaging of white matter tract microstructure as it significantly associated with the ADHD dimensional symptom score (b = −0.044, p = 0.045). Sex did not significantly moderate the association between PRS score and mean FA. Repeated analyses with the PRS SNP threshold changed to p < 0.01 and <0.10 showed consistent results, as did repeated analyses controlling for IQ. In voxel-wise analysis within white matter skeleton regions, the neuroanatomic imaging, and imaging of white matter tract microstructure association was significantly associated with ADHD traits. Strongest associations (p < 0.001, uncorrected) were revealed in portions of the left inferior fronto-occipital, superior longitudinal and inferior longitudinal fasciculi. ADHD PRS not associated with cortical thickness in the cortical areas that were significantly associated with ADHD traits

					Statistical thresholds were p<.05 family-wise error corrected and brain data was threshold-free cluster enhancement corrected.
ADHDt, OTHER	*2. Stojanovski et al. 2019*[67]	Philadelphia Neurodevelopmental Cohort, USA 1233 participants with no traumatic brain injury (TBI); 204 with mild TBI; 79 with high risk TBI. Age range: 8-21 years 47% female, 53% male Population sample European ancestry	PRS calculation based on pT= 1	Mild traumatic brain injury (TBI), and ADHD symptoms. Structured interview assessed symptoms and criteria corresponding to ADHD diagnostic criteria ADHD (Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM5)[72]) Covariates: age, sex, parental education, PCs	A significant interaction between ADHD PRS and group (mild TBI versus no TBI) (t_{1427} = -2.1, p = .04). ADHD PRS showed a positive association with ADHD symptom score in youths without TBI (t_{1224} = 3.5, ΔR^2 = .009%, p = .004) and no association with ADHD symptom score in those with mild TBI (t_{196} = 20.4, ΔR^2 = 2.004%, p = .70). Sensitivity analyses were run excluding individuals with ADHD and individuals taking medication for emotions or behavior issues. Both these analyses showed a similar interaction pattern but the interaction did not reach significance. p<.05 significance threshold employed since only one comparison was run.

ADHD, ASD	*3. Jansen et al. 2019*[73]	Inside Out Sample, The Netherlands Clinical sample age range: 2–18 years (mean: 9.06, SD: 2.66) ADHD only sample: 280 participants, 25% female, 75% male; ASD only sample: 295 participants, 27% female, 73% male. Combined sample (ASD only and ADHD only samples above plus 113 participants with both ASD+ADHD), 24% female, 76% male. All European Ancestry Control sample from the Netherlands, n= 943, age range	PRS calculation based on eight pT (0.01 - 1)	DSM-IV[74] ADHD diagnosis, ASD diagnosis, and combined(either ASD, ADHD or both diagnoses) Parent-rated Child Behavior Check- list/6–18 (CBCL)[75]. Covariates: Age, PCs	ADHD PRS predicted both the combined (ADHD and/or ASD) diagnoses (OR 1.28; $p = 1.3 \times 10^{-3}$)and ADHD-only (OR 1.4; $p = 3.6 \times 10^{-4}$), but not ASD-only. At the most optimal p-value threshold, $R^2 = 0.02\%$ for the combined (ADHD and/or ASD) sample and $R^2 = 0.045\%$ for the ADHD-only sample. Planned sensitivity analyses between ADHD symptom severity scales and PRS were not run due to low correlations. Significance threshold was p<.05 Bonferroni corrected for 72 tests.

		17-79 years, 37% male, 63% female.			
ADHD, ADDICTION, EA, MH, PHYSICAL	*4. Li 2019*[32]	National Longitudinal Study of Adolescent to Adult Health (Add Health), USA 7088 participants, mean age: 29.00 years (SD: 1.74) 54% female, 46% male Population sample 63.6% Caucasian (including Hispanic), 20.7% African American, 0.2% Native American, 5.1% Asian, and 10.3% 'Other.'	PRS calculation based on pT= 1. PRS groups defined as low (<20th percentile), medium (21st–70th percentiles), and high (>80th percentile) compared on outcomes	ADHD diagnosis based on retrospectively self-reported ADHD symptoms keyed to the DSM-IV[74]. 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 12-month period. Educational attainment, measured by the question 'what is the highest level of education that you have achieved to date?'. Scale ranged from 1 ('8th grade or less') to 10 ('some graduate training beyond a master's degree'). Cognitive ability, measured by Add Health Picture Vocabulary Test (AHPVT)[76].	ADHD PRS was associated with ADHD diagnosis (OR 1.22, p < 0.001). In terms of probability of ADHD by PRS group, PRS low = PRS medium < PGS high and PRS low<PRS high at p<.005. Overall significant group differences (comparing high, medium, low PRS groups) were reported for all outcomes except alcohol abuse/dependence rates, hypertension, or on high-blood cholesterol (at p<.005). Low and high ADHD PRS groups differed significantly (after Bonferroni correction) on all outcomes with exception of alcohol abuse/dependence rates, hypertension, or on high-blood cholesterol. In some cases, the low PRS group differed significantly from the medium PRS group, suggesting a protective role for low PRS scores. Low PRS group had higher cognition and education attainment and lower BMI than medium PRS group. These same variables significantly distinguished the medium and high PRS groups, as did drug abuse/dependence, ever being arrested and perceived stress. Bonferroni corrected significance threshold of p<.005 applied throughout. Secondary analyses demonstrated consistent results in European-ancestry subsample of total sample.

				Mental health, measured by diagnoses based on the DSM-IV[74], the Center for Epidemiologic Studies Depression (CES-D) Scale[77], and an abbreviated 4-item version of the Cohen's Perceived Stress Scale[78]. Also, it was asked whether participant was 'ever arrested'. Physical health determined based on body mass index (BMI) and patients reported if they had hypertension or high blood cholesterol as reported by a doctor. Covariates: age, sex PCs	
ADHDt	*5. Burton et al. 2019*[38]	Spit for Science sample, USA n =5154 (comprising n= 4426 participants with parent report; n =728 with self report), age range: 6–17 years, (mean: 11.0 years SD: 2.8). Of total sample, n= 379 had community	PRS calculation based on 10 pT (0.00001 - 0.5)	Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) score[79]: Total, inattentive and hyperactive/impulsive subscales. Divided sample into low, medium and high SWAN-scoring groups (low: z-score <-1.11, n = 670; medium: z-score -1.11 to 1.11, n = 3,745, and high: z-score <1.11, n = 739). Also categorized sample using cut-off identified in ROC	ADHD PRS was significantly associated with SWAN total score (b= .005, p = 1.7 x 10-11, R^2 = .009), separately for parent-report (b= .0045, p = 9.0 x 10-9, R^2 = .009) and self-report (b= .042, p = 6 x 10-4, R^2 = .016) and separately for inattentive (b= .004, p = 1.6 x 10-10, R^2 = .008) and hyperactive/impulsive subscales (b= .004, p = 1.3 x 10-9, R^2 = .007). The association with the total score was still significant after excluding individuals with an ADHD community diagnosis. Comparisons of ADHD PRS in the categorized SWAN-scoring groups showed low<high, medium<high but low=medium. ADHD PRS was also significantly higher when comparing groups scoring above versus below the optimal cut-off identified in ROC analyses for parent-reported SWAN and using the Swanson cut-point of z-score >1.65. The self-rated subsample did not show a significant difference between groups. Significance threshold corrected for multiple testing throughout.

		ADHD diagnosis 49% female, 51% male Population sample European Ancestry		analyses and published cut-off of z-score>1.65. Covariates: age, sex, array, PCs	
EA	*6. Gialluisi et al. 2019*[53]	Multiple samples of children with developmental dyslexia and either unrelated controls or siblings. From eight European countries and USA (n = 2562–3468) 41% female, 59% male Clinical sample European Ancestry	PRS calculation based on 12 pT (0.01 - 1)	Diagnoses based on school history of reading problems, word reading tests, or dyslexia diagnosis. Eight outcomes relating to word reading, spelling, rapid naming, and phonology that are considered core deficits in dyslexia: Word reading (WRead), nonword reading (NWRead), and word spelling (WSpell), Phoneme awareness (PA), digit span (DigSpan, a measure of verbal short-term memory), and rapid automatized naming of letters (RANlet), digits (RANdig), and pictures (RANpic). Covariates: PC's	ADHD PRS was negatively associated with WRead, Wspell, and NWRead (R^2 0.004 – 0.007%, p ~ [10^{-5}–10^{-7}]). ADHD PRS was not significantly associated with the other 5 outcomes. A significance threshold of 6.94 x 10−5 .was applied to correct for multiple testing due to multiple other PRS being tested in parallel.
SES	*7. Rietveld*	Longitudinal data from the Health and	No pT applied	Six later-life US labor market outcomes: currently working for pay, individual	ADHD PRS was significantly associated with all six labor market outcomes. One SD increase in ADHD PRS associated with decrease in employment likelihood (10.15% lower odds), lower gross individual

	& Patel 2019[66]	Retirement Study (HRS), USA N=9033 including participants and spouses, age range: 50-65 years 54% female, 46% male Population sample European Ancestry		earnings (gross individual income), total household wealth (net value of total wealth, excluding second home, if applicable), receiving governmental assistance in the form of social security disability insurance, receiving unemployment or workers' compensation, receiving other governmental transfers. Educational attainment included as mediator and measured by years of education. Covariates: sex, age, marital status, number of living children, self-reported health, whether health limits work, tenure in current occupation, log of spousal earnings, PCs	income (15.80%), lower household wealth (12.98%). Higher ADHD PRS associated with increased likelihood of receiving social security disability benefits (20.56% higher odds), receiving unemployment or worker compensation (6.72% higher odds), and receiving governmental transfers (27.38% higher odds). For all six outcomes, some of the association was reduced when educational attainment was added as a mediator. Most results were highly consistent when split by sex and when split by assessments conducted at ages 50-55 and 50-59 years. A significant threshold of p<.05 was applied.
ADDICTION	*8. Piasecki et al. 2019*[45]	National Longitudinal Study of Adolescent to Adult Health, USA 5215 unrelated participants, age range 24–34 years. Sex	PRS calculation based on pT= 1	Gambling behavior and disordered gambling The two phenotypes were categorical: answering yes or no to "Have you ever bought lottery tickets, played video games or slot machines for money, bet on horses or sporting events, or taken part in any other kinds of gambling for	ADHD PRS was not associated with either gambling behavior or disordered gambling. Significance threshold of p<.05 was applied.

		ratio not provided. Population sample European, African, Hispanic and East Asian Ancestry. Genetic ancestry was strongly correlated (r = .89) with self-identified race/ethnicity. The self-identified race/ethnicity of the 9129 individuals was 5754 (63%) non-Hispanic White, 1940 (21%) non-Hispanic Black, 961 (11%) Hispanic, 449 (5%) Asian and 23 (<1%) Native American		money?"; and (if yes to the previous question), answer of yes or not to: "Has your gambling ever caused serious financial problems or problems in your relationships with any of your family members or friends?" Covariates: age, sex, PCs	

ASDt, NEUROPSYCH	*9. Torske et al. 2019*[64]	BUPGEN network, Norway 176 participants referred to a specialized hospital unit for evaluation of autism spectrum disorders (ASD), age range 5–22 years with full-scale intelligence quotient (IQ) above 70. Most (68%) had ASD. 24% female, 76% male Clinical sample European Ancestry	PRS calculation based on pT= 0.1	Diagnosis based on Autism Diagnostic Observation Schedule (ADOS), and/or the Autism Diagnostic Interview-Revised (ADI-R) Three executive function outcomes from the Behavior Rating Inventory of Executive Function (BRIEF)[80], a 86-item questionnaire. The Behavior Regulation Index (which incorporates 3 subscales: inhibit, shift, and emotional control) and the Metacognition Index (which incorporates 5 subscales: initiate, working memory, plan/organize, organization of materials, and monitor). The Global Executive Composite Index comprised all 8 above subscales. Social function was assessed using the Social Responsiveness Scale, a 65-item questionnaire[81]. Covariates: age, sex, PC's	ADHD PRS not associated with the any of the executive function outcomes or the autistic trait scale in a regression or when comparing high versus low ADHD PRS scoring groups (those in the top and bottom 15% of the PRS distribution, respectively). Significance threshold of p<.05 was applied.
ADHD, ADHDt, EXTERNALISING	*10. Nigg et al. 2020*[55]	Community recruited children, USA ADHD sample: 337 participants,	PRS calculation based on seven pT ($5x10^{-8}$ - 1)	A diagnostic evaluation using standardized, well-normed rating scales from parent and teacher, parent semistructured clinical interview, child intellectual testing, and clinical	Using a structural equation model, it was shown that the ADHD PRS was associated with ADHD severity (b = .171, 95% CI = 0.085–0.258; ΔR^2 = .029, p < .0001), irritability (b = .183, 95% CI = 0.087–0.280; ΔR^2 = .034, p < .0002) and also with surgency/sensation seeking (B = .146, 95%CI = 0.052–0.240, ΔR^2=.022, p = .002). These associations had adjusted for the major depression PRS[84] and for the sadness-

		28% female, 72% male Controls: 177 participants, 46% female, 54% male Age range 7-11 years Community sample enriched for children with ADHD Northern European Ancestry		observation. Best-estimate research diagnoses and final eligibility were established by two experienced clinicians (a child psychiatrist and a child psychologist), who independently assigned final diagnoses. Dimensional score on an ADHD latent variable captured from hyperactivity and inattention subscales of four published ADHD scales. Irritability captured with latent variable based on two subscale scores: anger and modified soothability from the Temperament in Middle Childhood Questionnaire (TMCQ)[82] and an oppositional defiant disorder irritable total score[83]. Latent variables were also created for surgency-approach and sadness-anxiety A person-centred approach compared different group definitions of ADHD with	anxiety scores and their association with ADHD. The ADHD PRS was not associated with the sadness/anxiety latent variable. In the person-centred analyses (i.e. looking at ADHD subgroups), the ADHD PRS was elevated in the ADHD versus not ADHD group (OR = 1.43, 95% CI = 1.17–1.75, ΔR^2 =.033 p = .0004). The emotion dysregulation ADHD group had elevated ADHD PRS versus other ADHD children (OR = 1.44, 95% CI = 1.03–2.20, Nagelkerke Δ R^2 = .013, p = .033) but the ADHD PRS did not differentiate irritable or other ADHD profiles. All effects were independent of variation in ADHD severity across traits or groups. Sensitivity analysis suggested changes in latent variable indicators or covariate handling did not influence results. Significance threshold of p<.01 was applied.

				and without irritability and emotion dysregulation Covariates: sex, age, lifetime mood disorder and PCs	
EA, MH	*11. Dickinson et al. 2019*[54]	National Institute of Mental Health Clinical Center, USA 540 participants with DSM-IV schizophrenia disorders, mean age 34.1 years (10.1 sd). 24.6% female, 75.4% male 247 siblings with no history of psychotic disorder (limited to one per family), 52.6% female, 47.4% male. 844 community control participants, 53.8% female, 46.2% male Clinical sample	PRS calculation based on 10 pT reduced to a single score through principal components . Analyses repeated with the 10 pT (0.0001-0.5)	Participants with schizophrenia and their siblings were assigned to one of 3 clusters based on trajectories of cognitive development: cognitively stable (CS), adolescent decline (AD), preadolescent impairment (PI). Wide-Range Achievement Test [WRAT] reading subtest[85] and Wechsler Adult Intelligence Scale [WAIS][86] used for cognitive assessments. Covariates: sex, age, PC's	The ADHD PRS did not differ significantly between schizophrenia patients, siblings and controls. Within the participants with schizophrenia, the ADHD PRS showed significant association with cognitive trajectory group ($F=5.1$ df = 2,525 $p = 0.007$, $R^2 = 0.019\%$). Pairwise comparisons showed PI>AD=CS (at $p<.05$). Within the siblings, the ADHD PRS did not show a significant association with cognitive trajectory group ($F=0.3$ df = 2,232) and no pairwise comparisons were significant at $p<.05$.

		European Ancestry			
ADDICTION	*12. Cabana-Domínguez et al. 2019*[40]	SAGE (USA) and three other dbGAP sample datasets 2083 cases, age range unknown, 41.6% male 4287 controls 44% female, 56.0% male Clinical sample European Ancestry	PRS calculation based on nine pT ($1x10^{-4}$ - 1) reduced to single score with PCA	Cocaine dependence, as measured by the DSM-IV[74].	ADHD-PRS was significantly associated with cocaine dependence (pseudo- R^2=1.39%, p =$4.5e^{-17}$). SNP threshold of p<5.7e-04 applied to account for multiple testing
MH	*13. Ohi et al. 2020*[59]	The Schizophrenia Non-Affected Relative Project, Japan 332 participants 130 patients with	PRS calculation based on six pT (0.01-1)	Schizophrenia (based on the criteria of the DSM5[72]) or being a first degree relative of someone with schizophrenia.	ADHD PRS were not significantly different between all the groups (patients with schizophrenia, their first-degree relatives and controls) or between any pairwise comparisons at p<.01. Significance threshold of p<.01 applied to correct for multiple testing

		schizophrenia, 38.2% female, 61.8% male, mean age: 42.9 SD: 13.1 years 56 unaffected first degree relatives (41 parents/12 siblings/4 offspring), 68.4% female, 31.6% male, mean age: 59.7 SD: 13.6 years, 146 controls, 33.3% female, 66.6% male, mean age: 37.2 SD: 14.1 years Clinical sample Japanese descent		Covariates: PC's	
BRAIN	*14. Mooney et al. 2020*[49]	312 Participants, age range: 7–15 years (mean age: 10.2 years), USA ADHD sample: n= 199 (30% female, 70%	PRS calculation based on pT = 0.5	Diagnosis by Conners' Rating Scales-3rd Edition short form, Strengths and Difficulties Questionnaire long form including the impairment module (SDQ), the ADHD Rating Scale ADHD-RS	ADHD PRS was negatively associated with TBV [β = −0.147 (−0.27 to −0.03)] and this remained significant after controlling for ADHD diagnosis. TBV accounted for 16% of the association between ADHD PRS and ADHD diagnosis after accounting for sex and age. ADHD PRS was not significantly associated with subcortical brain structures

		male); control sample: n = 113 (47% female, 53% male) Community sample enriched for ADHD Northern European Ancestry		MRI: Total brain volume (TBV) and subcortical structures Covariates: motion during MRI scan, PCs, age, sex, average FD (i.e., motion during the scan [average framewise displacement]), sex interaction effect, diagnosis. TBV also a covariate in analyses on subcortical structures	Among females only, the ADHD PRS was significantly associated with increased putamen volume [β = 0.224 (0.09–0.36)]. FDR correction (α = 0.05) for the 9 volumes tested
ADHD, ADHDt, ADDICTION, ASDt, EA, EXTERNALISING, NEUROPSYCH	*15. Vuijk et al. 2019*[33]	Longitudinal Study of Genetic Influences on Cognition (LOGIC) 433 participants, age range 7-18 years, mean age: 11.5, SD: 3.1 years. Clinical sample with wide range of diagnoses including ADHD. ADHD participants compared to individuals with other DSM-IV	PRS calculation based on 10 pT	DSM-IV[74] Axis 1 diagnoses; a range of parent-rated dimensional published scales of psychopathology Somatic complaints measured with the CBCL[75] Social cognition measured with the SRS[81] IQ and working memory from the Wechsler Intelligence Scale for Children–Fourth Edition for 7- 16-year-olds and the Wechsler Adult Intelligence Scale–4th Edition 17-18 year olds. [86] [87] Academic achievement with the Word Reading and Numerical Operations of the Wechsler Individual	In this clinical sample including a wide mix of psychiatric diagnoses, ADHD PRS was associated with broad ADHD diagnosis (OR 1.44, 95% CI 1.14-1.81; Pseudo R^2 2.01; permuted p .0011) as well as ADHD traits (b = 1.46; R^2 = 2.93%; F = 11.83, permuted p = .0007) and with Hyperactivity/Impulsivity subscale (b = .97; R^2 = 2.00%; F = 8.81, permuted p = .0063) but not with Inattention. For non-ADHD outcomes, the ADHD PRS predicted word reading (b = -2.11; R^2 = 2.05%; F = 8.68, permuted p = .0043) and numerical operations (b = -2.20; R^2 = 2.27%; F = 9.25, permuted p = .0030). ADHD PRS was also associated with aggressive behavior (b = 1.58; R^2 = 2.59; F = 10.52, permuted p = .0019) and working memory index (b = -2.17; R^2 = 2.47; F = 10.10, permuted p = .0016). Controlling for ADHD and stimulant use did not change the above non-ADHD outcome findings. ADHD PRS did not significantly predict somatic complaints measured with the CBCL [75]or social cognition measured with the SRS[81], considered to demonstrate discriminant validity of the ADHD PRS. Results are reported for the most significant pT. The adult psychiatric sample showed similar results, ADHD PRS was associated with ADHD diagnosis (OR 1.21, 95% CIs 1.07 – 1.37,

		Axis 1 diagnoses 37.2% female, 62.8% male Clinical sample Second sample for replication: n=5,140 19-60 year old adult patients from a local health system biobank European ancestry		Achievement Test–Third Edition[88] (WIAT-III). The adult replication cohort outcomes were ICD-10 ADHD, whether education was completed by age 23 years or not, and presence of substance use disorder history. Covariates: age, sex, genotyping wave (in biobank analyses), PCs	Pseudo R^2 0.42%, p = .0028) reduced likelihood of college completion (OR 1.23, 95% CIs 1.12 – 1.35, Pseudo R^2 0.72%, p <.0001) and substance use disorder (OR 1.18, 95% CIs 1.10 – 1.26, Pseudo R^2 0.40%, p <.0001). Division of youth sample into high (>30%), medium (middle 40%) and low (<30%) PRS scoring groups showed that the high group had a more severe multivariate pattern of psychopathology compared to the low group (b = .21, p =.01). No significant differences between the medium and low groups. Bonferroni correction for multiple outcomes
ADHDt, EXTERNALISING	*16. Li 2019*[56]	National Longitudinal Study of Adolescent to Adult Health (Add Health), USA 7,674 participants, age 7-12 (wave 1) age range 18-32 years (later waves). 54% female, 46% male	PRS calculation based on pT= 1	Latent classes were derived for externalizing behaviors (which included aggressive behaviors, non-aggressive rule breaking and substance use behaviors) assessed at Waves 3 and 4 by in-person interviews. 4 mediators selected from wave 1 assessment: Supportive parenting, school connectedness and sensation seeking assessed with questionnaires; Peer closeness assessed in relation to 10 named friends	ADHD PRS correlated .084 with ADHD symptoms (p<.01) ADHD PRS predicted 17.0% increased odds in the High Decreasing (OR = 1.17 95% CI = 1.002, 1.366, p=.05) and 8.0% increased odds in the Moderate (OR = 1.08, 95% CI = 1.004, 1.163, p=.03) externalizing trajectories, but was not associated with the Low Increasing (95% CI = 0.868, 1.265) trajectory, relative to the Normal trajectory group. There was no longer evidence of direct associations between ADHD PRS on externalising trajectory groups relative to the Normal trajectory group once mediators were added to the models. School connectedness either partially or fully mediated the effects. Significance threshold was p<.05.

		Population sample 63.2% Caucasian, 21.2% African-American, 5.1% Asian, and 10.6% Hispanic.		ADHD assessed retrospectively with DSM-IV items at Wave 3. Covariates: PCs, sex, age, highest level of education, income	
EXTERNALISING	*17. Riglin et al. 2019*[57]	Avon Longitudinal Study of Parents and Children (ALSPAC), UK 7924 participants, age range 7-15 years. Population sample European ancestry	PRS calculation based on pT=.05 in primary analyses; analyses repeated on multiple thresholds	Growth mixture modelling gave 5 distinct irritability trajectory classes: low, decreasing, increasing, late-childhood limited, and high-persistent Parent-reported data on irritability from the oppositional defiant disorder section of the Development and Well-Being Assessment (DAWBA)[1]—a structured research diagnostic interview—at ages 7, 10, 13 and 15 years. DAWBA also used to diagnose ADHD, oppositional defiant disorder, conduct disorder, generalized anxiety disorder and depression	ADHD PRS was associated with an increased likelihood of being in both the high-persistent (odds ratio=1.31, 95% CI=1.09–1.58, p=0.005) and the increasing (odds ratio=1.28, 95% CI=1.11–1.48, p=0.001) trajectory classes relative to the low irritability trajectory class. The odds were similar for being in either trajectory (high-persistent compared with increasing trajectory class: odds ratio=1.02, 95% CI=0.81–1.29, p=0.854). The ADHD PRS did not predict being in the decreasing or late childhood limited trajectory groups. Results were consistent when sex was controlled for and when individuals with diagnoses were excluded. PCs were not controlled for. Significance threshold was p<.05.

ADHD, MH, OTHER	*18. Grigoroiu-Serbanescu et al. 2019*[29]	Romania and UK case-control samples. Romanian sample: 470 bipolar disorder (BP) cases (all BP type 1) (60% female; 40% male 2%); 329 controls (57% female; 43% male). 43% of BP cases has childhood ADHD. UK sample: 472 BP cases with childhood ADHD data (67% BP type 1, 33% BP type-2) (65% female; 35% female) and 1287 controls (34% male; 66% female). 34% of the BP cases has childhood ADHD. Romanian and UK sample	PRS calculation based on 10 pT (0.01-0.5)	Bipolar disorder in the UK sample was assessed using the ICD-10, and in the Romanina sample with DSM-IV[74] criteria, based on Diagnostic Interview for Genetic Studies (DIGS) and medical records. Childhood ADHD within BP cases was assessed retrospectively using the Wender Utah Rating Scale (WURS)[89] and for some Romanian cases also using items from the Kiddie-SADS[90] clinical interview. Assessment of childhood ADHD was made by clinicians. Earl- and late-onset BP defined as age of onset under or over 22 years, respectively. No covariates	ADHD PRS differentiated BP cases with childhood ADHD from controls in the meta- analysis of both samples (OR = 0.2 (0.08–0.32) z =3.23, FDR-corrected p = 0.024). The ADHD PRS differentiated BP cases with childhood ADHD from BP cases without childhood ADHD in the meta-analysis but this did not survive FDR-correction (OR = 0.18 (0.04–0.31) z = 2.55 p = 0.011 FDR-p = 0.055). ADHD PRS associated with the continuous measure of ADHD symptoms (based on WURS and Kiddie-SADS) within the BP cases in the meta-analysis (b = 1.7 (0.7–2.69) z = 3.34 p = 0.0008 FDR-corrected p = 0.024). This result remained when sex or BP age of onset were included as covariates. This association was found to be driven by BP cases with early onset (<22 years). ADHD PRS did not differentiate all BP cases from controls at either nominal or FDR-corrected significance (OR=0.085, (0-0.17) z = 1.95, p = .051, FDR-corrected p = .105). However, it did differentiate early-onset BP cases from controls (OR = 2.51 (1.04–3.97), z =3.36, p =0.0008, FDR-corrected p = 0.024) but not late onset cases. ADHD PRS predicted earlier age of onset within BP group (b=-.92, (-1.61--0.23) z = -2.62, p = .009, FDR-corrected p = .049). Results given here for most significant PRS pT. FDR correction was used to adjust significance for multiple testing.

		results were meta-analysed. Clinical sample European ancestry			
ADDICTION, EXT, OTHER, SES	*19. Wimberley et al. 2019*[41]	IPSYCH Sample, Denmark, born 1981-2003. 13116 participants with ADHD, 26% female, 74% male Of these, 2368 (18.1%) developed SUD (27% female, 73% male). Median age at first SUD diagnosis was 19.4 years (IQR 17.2–22.3 years). Clinical sample from population cohort. Due to overlap with Demontis et al[17] discovery	PRS calculation based on pT 0.2	At least one substance use disorder (ICD-8 and ICD-10-Diagnostic Criteria for Research (DCR)[23]) in Danish registers after 13th birthday. Categorized by type into alcohol, cannabis, and other illicit drugs and second categorized into severity into use, abuse and addiction. Nicotine use not included. Other known SUD risk factors (presence of comorbid oppositional defiant disorder/conduct disorder (ODD/CD), parental SUD, parental mental disorder, paternal income, maternal education, obtained from IPSYCH and Danish registers. Covariates: observation time (to account time at risk for SUD given varying ages of participants), sex, age and calendar	ADHD PRS were associated with any SUD (OR = 1.30, 95% CI: 1.11–1.51; Nagelkerke R^2= .14). For types of SUD, associations were observed for alcohol (OR = 1.26, 95% CI: 1.04–1.53), cannabis (OR = 1.34, 95% CI: 1.10–1.64) but not illicit drugs (OR = 1.21, 95% CI: 0.99–1.50). For severity of SUD, associations were observed for use (OR = 1.36, 95% CI: 1.02–1.80), addiction (OR = 1.30, 95% CI: 1.07–1.57) but not abuse (OR = 1.21, 95% CI: 0.88–1.65). Stratified by sex, the point estimate for the ADHD PRS-SUD association was higher in females but CIs overlapped with CIs for males. The other known SUD risk factors were all themselves associated with ADHD PRS (at p<.001). Nevertheless, the above SUD associations still remained with the ADHD PRS when controlling for these known SUD risk factors. Sensitivity analyses repeated with different pT, different assumed prevalences of ADHD and SUD, and variation in population structure showed similar results. Significance threshold was Bonferroni corrected to p<.007

		sample, participants split into 5 groups, with each group consecutively used as target sample, and remaining 4 groups plus other Psychiatric Genomic consortium samples as the discovery sample. European Ancestry		year at first ADHD diagnosis and PCs	
MH	*20. Riglin et al. 2020*[60]	Avon Longitudinal Study of Parents and Children (ALSPAC), UK n = 5518 at age 7 years and n = 7017 at age 13 years Population sample European ancestry	PRS calculation based on pT <0.05 in primary analyses; repeated on multiple thresholds	A 'general psychopathology' ("p") factor for ages 7 and 13 years Emotional, behavioral and neurodevelopmental problems were determined with the DAWBA[70]. Additionally, the Social and Communication Disorders Checklist[91] (SCDC) was used for social-communication problems related to ASD. No covariates	ADHD PRS was associated with the general psychopathology "p" factor at age 7 (B 0.087, se 0.019, p <0.001), and age 13 (B 0.095, se 0.020, p <0.001) while including the above other 3 PRS in the models. Without other PRS in the model, the ADHD PRS predicted the p factor at age 7 (B 0.093, se 0.019, p <0.001, R^2 = .009%) and age 13 (B 0.095, se 0.019, p <0.001, R^2 = .009%) Results were consistent when the other PRS were excluded from the model and analyses repeated using inverse probability weighting to address potential bias due missing genetic data revealed similar results, as did analyses at other pT.

BRAIN, EXTERNALISING, PHYSICAL	*21. Barker et al. 2019*[50]	IMAGEN Study, France, UK, Ireland, Germany 604-874 participants Population sample European ancestry	PRS calculation based on pT 0.05	BMI derived from height and weight measurements at age 19 Voxel-based morphometry measures of whole-brain grey matter at age 19 Neural responses to reward anticipation and reward outcome from activation maps from a Monetary Incentive Delay fMRI task at age 19 A neural endophenotype created which was made up of grey matter regions and regions of activation derived from the fMRI task. Impulsivity symptoms at age 19 assessed using self-reported Barratt Impulsivity Scale (BIS)[92]. Covariates: sex, imaging site, age, PC's and total intracranial volume	ADHD PRS correlated with impulsivity symptoms (r = 0.10, p = 0.014 FWE corrected). ADHD PRS was correlated with the neural endophenotype (r = 0.087, p = 0.036 FWE corrected). In mediation analyses, the ADHD PRS associated via the neuroimaging substrate with impulsivity symptoms (b = 0.006, 90% CIs = 0.001, 0.019) and BMI (b = 0.009, 90% CIs = 0.001, 0.025). Significance levels ascertained from permutation testing, one-sided tests, and corrected for multiple testing.

ADHDt, EA	*22. De Zeeuw et al. 2019*[34]	The Netherlands Twin Register (NTR) Trios (i.e. one offspring and both parents). N = 1120–2518 Population sample European ancestry	PRS based on transmitted and nontransmitted alleles for eight pT (0.0001 - 0.5)	ADHD symptoms (CBCL and TRF Attention Problems scale[75]) were assessed at age 10 or 12 years. Academic achievement was assessed with the Cito score, a Dutch nationwide standardized educational achievement test[93] Educational attainment in adults assessed as self-reported highest degree. Covariates: sex, year of birth (only for EA), the interaction between sex and year of birth (only for EA), PCs, genotyping platform.	EA PRS and ADHD PRSs correlated for both the transmitted and non-transmitted PRS (r = − 0.27 and r = − 0.23, respectively). ADHD transmitted and nontransmitted PRS were not significantly associated with academic achievement (R^2 ~ 0.6%). ADHD transmitted PRS was associated with ADHD symptoms (R^2 = 1–2%). The transmitted ADHD PGS was associated with ADHD symptoms at home (β = 0.17 CIs .12-.21, R^2 = 2.7%, p = 2 x 10 -13) and at school (β = 0.13 CIs .08-.17, R^2 = 1.6%, p = 3 x 10 -7) but not with academic achievement (β = − 0.08 CIs -.14--.01, R^2 = .6%, p = 0.022). In a model that included both the EA PRS and ADHD PRS, the above effects remained between ADHD PRS and ADHD symptoms at home and school but the association between ADHD PRS and academic achievement was no longer significant. The non-transmitted ADHD PGS was not associated with any of above three the outcomes. Significance threshold of p<.01 employed.

MH	*23. Yao et al. 2019*[61]	Child and Adolescent Twin Study in Sweden (CATSS) N = 13,472 participants, assessed at age 15 years. Population sample European ancestry	PRS calculation based on pT <1 for primary analyses, and on seven pT (0.00001 - 1) for sensitivity analyses	Self- reported ED symptoms were measured by 3 subscales (Drive for Thinness, Bulimia, and Body Dissatisfaction) from the Eating Disorder Inventory-2 (EDI-2)[94], at 15 years Covariates: sex, birth year, and PCs	ADHD PRS was associated with the EDI-2 full scale (b = .027, 95% CI = .005, .049, R^2 = .0012%, p = .015) and subscales Drive for Thinness (b = .032, 95% CI = .005, .059, R^2 = .0010%, p = .022) and Body Dissatisfaction (b = .042, 95% CI = .011, .072, R^2 = .0013%, p = .007) but not the Bulimia subscale (b = .004, 95% CI = -.013, .021, R^2 = .0000% p = .654). Results were consistent at other pT; significant sex differences were not significant. Significance threshold was p<.05
ADDICTION, OTHER	*24. Rabinowitz et al. 2018*[42]	Sample from urban school district in the Mid-Atlantic region, USA N = 1,050 participants 56% female, 44% male Population sample African American	PRS calculation based on pT < 0.05	To assess past year marijuana abuse and dependence at age 20, Composite International Diagnostic Interview-University of Michigan Version (CIDI-UM)[95] was used in 2 cohorts. In the third cohort, National Survey on Drug Use and Health (NSDUH)[96] was used. The Structured Interview of Parent Management Skills and Practices Youth-Version (SIPMSP)[97] was used to assess parental	The ADHD PRS correlated negatively with parental monitoring (r = -.07, p<.05) but was not significantly correlated with community disadvantage (r = -.04, p>.05). ADHD PRS was not associated with marijuana use disorders and the ADHD PRS × community disadvantage and ADHD PRS × parental monitoring interactions were also not significant, nor were 3-way interactions involving sex, ADHD PRS, and either community disadvantage or parental monitoring. Significance threshold was p<.05

				monitoring (proximal contextual factor). The community disadvantage score was calculated using census-tract level items from the 1990 and 2000 Decennial census[98] (distal contextual factor). Covariates: PCs	
ADHDt	*25. Taylor et al. 2019*[39]	Child and Adolescent Twin Study in Sweden (CATSS) 13 391 participants 50% females, 50% male Population sample European ancestry	PRS calculation based on pT 0.5. Analyses repeated on 5 other pT	ADHD traits were measured with The Autism-Tics, AD/HD and Other Comorbidities Inventory (A-TAC)[99] assessed by parents at ages 9 and 12 years Covariates: sex, age, PCs	ADHD PRS was associated with ADHD traits at ages 9 and 12 years (β [SE] = 0.27 [0.03], R^2 = 8.4 x 10−3, p-value $5.9x10^{-19}$) and ADHD trait subscales hyperactivity/impulsivity (β [SE] = 0.14 [0.02], R^2 = 7.7 x 10−3, p-value $1.9x10^{-19}$) and inattention (β [SE] = 0.13 [0.02], R^2 = 6.0 x 10−3, p-value $2.9x10^{-15}$) After excluding children with ICD-10 diagnosed ADHD, ADHD PRS was still associated with ADHD traits (β [SE] = 0.21 [0.03], R^2 = 6.2 x 10−3, p-value 2.2 x 10^{-13}) and the ADHD subscales. FDR-corrections applied to adjust for multiple testing.
ADHDt, BRAIN	*26. Alemany et al. 2019*[47]	Generation R Study, The Netherlands 1053-1139 participants, the mean age: 10.16, SD: 0.60, age	PRS calculation based on six pT "priors" (0.01 - infinitesimal)	Structural MRIs; Image processing using FreeSurfer to extract cortical and subcortical brain volumes. Ten volumetric brain measures employed as outcomes: total brain volume (TBV), cortical gray matter (GM),	ADHD PRS was associated with attention problems subscale (b . 0.12, SE 0.00, p = 5.36 x 10-5). ADHD PRS was associated with smaller caudate volume (result for strongest prior: (b =-0.08, SE 0.03, $p_{uncorrected}$=7.49 10^4) across all priors except prior 1 at p<.05 and one prior was significant after FDR correction.

		range: 8.72–11.9 years. 49% female, 51% male Population sample European ancestry		total white matter, subcortical GM, ventricular volume, cerebellum, amygdalahippocampus complex, caudate, putamen and thalamus (final 3 are subcortical brain volumes) Assessed on CBCL[75] attention problems subscale at ages 8-11 years Covariates: sex, age, total intracranial volume (for all except TBV analysis), PCs	In subsequent mediation analyses, no evidence of caudate volume acting as a mediator between ADHD PRS and attention problems in full sample. Stratified by sex, mediation was significant for boys, indicating that 11% of the association between ADHD PRS (prior .0.01) and attention problems was mediated by differences in caudate volume. ADHD PRS was associated with smaller TBV (result for strongest prior: ß =-0.07, SE 0.03, $p_{uncorrected}$ = .006) across all priors except prior 0.01 at p<.05, but none significant after FDR correction. FDR correction at p<.05 used as significance threshold.
ADDICTION	*27. Gurriarán et al. 2018*[43]	Sample from the Addictive Disorders Assistance Units from Galicia health care areas, Spain N= 534 substance abuse/dependence patients (mean age 44.89, SD 9.73) 13% female, 87% male n = 587 Control subjects recruited from blood donors at	PRS calculation based on six pT (0.001 - 1)	DSM-IV[74] criteria for substance use disorder. Covariates: sex, age, PCs	ADHD PRS was not associated with substance use disorders after multiple testing correction (Pseudo R^2 ~0.4, .p<.05, p > 0.002) Results similar when MHC included. Permutation based p-value of P < 0.0022 employed.

		Santiago de Compostela, Galicia. Mean age 40.26 (SD: 10.70; range: 18-65). Not checked for substance use 50% female, 50% male Clinical sample European ancestry			
BRAIN	*28. Szekely et al. 2018*[51]	The LONG Cohort, USA 119 cases, 339 controls Mean age at first scan 11.47 years, SD 3.54; mean age at second scan 16.13 years, SD 4.72. 41% female, 59% male Population sample	PRS calculation based on seven pT (0.0005 – 0.5)	ADHD ascertained using clinician-administered Parent Diagnostic Interview for Children and Adolescents[100]. Longitudinal growth in volume across 2 time points modeled linearly for 4 brain divisions: cerebral cortex, basal ganglia, cerebellum, cerebral white matter, and one region of interest: the right lateral prefrontal cortex. Covariates: adjusted for age at baseline scan, interscan interval, sex and PCs	ADHD PRS was not associated with any brain growth phenotypes (all $P > 0.1$). Significance threshold not reported.

		enriched for ADHD cases 404 European Americans, 31 African Americans, 8 Asian Americans, and 15 participants of mixed race.			
ADHD, ADHDt, NEUROPSYCH	*29. Nigg et al. 2018*[65]	Community recruited sample, USA European-only sample n = 514 (337 ADHD, 71% male; 177 non-ADHD, 52% male) age range: 7-11 years Full sample n = 656 22% non-European, 78% European ancestry Community sample enriched for children with ADHD	PRS calculation based on pT 0.5 Results checked for another 6 pT	ADHD diagnoses made using DSM-IV criteria and a best estimate procedure. Separate parent and teacher-rated ADHD symptom latent variables derived from data on 3-4 published ADHD measures that capture inattention and hyperactivity. Cognitive latent variables were captured using PCA models from data on laboratory measures of working memory, response inhibition, executive functioning, arousal/attention, temporal information processing, and processing speed. Covariates: sex, age, PCs	ADHD PRS was associated with ADHD diagnosis (Nagelkerke R^2 =0.045%; b = 0.233, SE = 0.053, p = .000011) and both parent and teacher-rated ADHD symptom latent variables (R^2 =0.033%; b = 0.185, SE = 0.043 p = 1.69E-05 and R^2 =0.027%; b = 0.165, SE = 0.042, p = 8.55E-05 respectively). Of the five latent cognitive variables, ADHD PRS only predicted working memory (b = 0.227, SE = 0.040, p = 1.39E-08) and vigilance/arousal (b = 0.130, SE = 0.049, p = .0079). It did not predict slow output speed, mental clock or response inhibition. In mediation models, the ADHD PRS effect on ADHD diagnosis was statistically mediated by working memory (indirect effect, b = 0.101, SE = 0.029, p = .00049, 43% of genetic effect accounted for) and arousal/alertness (indirect effect b = 0.115, SE = 0.041, p = .005, 49% of genetic effect accounted for). The same was found for models with ADHD PRS predicting parent and teacher-rated ADHD symptom latent variables, with 43-51% of the genetic effect accounted for by the latent cognitive variables. Direct PRS tests had a Hochberg correction p<.05. Mediation models used p<.05. Analyses repeated including non-European LONG sample participants, and changing the discovery sample to be European-only, both led to similar conclusions.

ADHD	*30. Hawi et al. 2018*[30]	Participants recruited in Australia, UK and Ireland. N = 480 ADHD cases aged 5-18 years (mean age = 10.27 years, SD= 3.03). 13% female, 87% male N = 1208 controls, age 7-60 years (mean age = 20.61 years, SD= 6.76) 51% female, 49% male European ancestry	1000 pT from 0.0005 to 0.5	ADHD status using DSM-IV criteria determined with parental semi-structured interview and the Conners' Parent Rating Scale[107] Covariates: gender, age2 , age x gender, PCs	ADHD PRS explained 3.25% variance in ADHD case–control status (Nagelkerke' s R^2 = 0.03, p = 7.6E− 15) Significance threshold p=.001 applied.
OTHER	31. *Taylor et al. 2018*[68]	Avon Longitudinal Study of Parents and Children (ALSPAC), UK 7486 mothers, 7508 children Population sample	PRS calculation based on 5 pT (0.0005 – 0.5) as well as just genome-wide significant SNPs	9 participation phenotypes derived. Participation defined as responding to a questionnaire or attending a clinic for which the whole cohort was eligible to participate. Continuous phenotypes calculated by summing the number of questionnaires/ clinics completed and or clinics attended	ADHD PRS was negatively associated with all 9 mother and children participation phenotypes. For example, ADHD PRS predicted mother total participation score negatively (ES = -2.18, 95% CI -2.71-1.64) and it predicted the child total participation score negatively (ES = -2.14, 95% CI -2.63-1.64). Significance threshold not given: results reported as effect sizes.

		European ancestry		Covariates: child sex, PCs	
ADHDt, EA, PHYSICAL, MH, SES	*32. Selzam et al. 2019*[35]	Twins Early Development Study, UK 789-2962 dizygotic (DZ) twin pairs, assessed from 12-21 years. Population sample European ancestry	PRS calculation based on pT 1 (using a prior)	Parents reported on twins' ADHD traits via the Strength and Difficulties Questionnaire[71] hyperactivity subscale and the Conners' rating scales[107] at ages 12 and/or 16 years. Educational attainments based on standardized tests taken at the end of compulsory education in the United Kingdom (General Certificate of Secondary Education; GCSE) as obtained for twins at age 16 years. BMI and height were self-reported. IQ involved verbal and nonverbal ability using WISC-III assessments. Psychotic experiences assessed using the Specific Psychotic Experiences Questionnaire[108] at age 16.	The ADHD PRS effect was split into between family and within family effects using DZ twin data. The between family ADHD PRS effect, which is estimated independent of the within family effect, significantly predicted more ADHD traits (b = .11, CI .08-.14; p = 6.8 x 10-9), higher BMI (b = .07, CI .03-.11; p = .008), lower IQ (b = -.09, CI -.12--.05; p = 4.5 x 10-4) and lower GCSEs (b = -.18, CI -.21--.15; p = 7.3 x 10-17). The within family ADHD PRS effect showed that, within pairs, the twin with higher ADHD PRS had more ADHD traits than their co-twins (b = 0.12, CI .08-.17, p = $1.50e^{-7}$). Within pairs, the twin with higher ADHD PRS also lower GCSE grades than their co-twins (b = -0.06, CI -.10--.03 p = .001). The ADHD GPS within-family prediction was significantly lower than between-family prediction for GCSEs (b =-.12, CI -.16--.07, p = $4.95e^{-5}$, Diff = 65.4%). The between family ADHD PRS effect on GCSEs significantly reduced when socioeconomic status was controlled for (p = 7.69 x e-4) but was still significant. The ADHD PRS also significantly predicted lower SES (b =-.17, CI -.21--.13, p = $1.32e^{-13}$) The ADHD PRS did not significantly predict (either as within or between family effect): height, self-rated health, neuroticism, psychotic experiences. Results were stable when analyses were rerun on the sample split by same-sex/opposite-sex twins, based on differences in chip, using a

				Neuroticism assessed using a Big Five questionnaire [109]. Self rated health assessed using the RAND Short-Form Health Survey[110]. Socio Economic Status: based on maternal age at birth of the first child, maternal and paternal highest education level, and maternal and paternal occupation. Covariates: PCs, chip, plate, and phenotypes were corrected for age and sex	prior pT of 0.1, and using PRS's with British samples removed, and results Statistical significance was p<.01, based on an Benjamini Hochberg false discovery rate (FDR) adjustment
OTHER	*33. Schoeler et al. 2019*[69]	Avon Longitudinal Study of Parents and Children (ALSPAC), UK 5028 participants Assessed at age 8, 10 and 13 years. 51% female, 49% male	PRS calculation based on 99 pT (0.01 – 1)	Exposure to bullying was assessed based on child reports at 8, 10, and 13 years of age using a modified version of the Bullying and Friendship Interview Schedule (BFIS)[111]. Mean score of exposure to bullying across ages was used. Covariates: Sex, PCs	ADHD PRS was significantly associated with bullying (standardized *b*, 0.085; 95% CI, 0.056-0.113, P<.001). In a multi-PRS analysis with 10 other significant PRS predictors, ADHD PRS was still significantly associated with bullying (standardized *b*, 0.062; 95% CI, 0.032-0.092, p<.001). Repeated multi-PRS analysis which looked at chronicity of bullying showed similar results. There was no evidence of an interaction effect of sex. The multi-PRS association of ADHD PRS and bullying was no longer significant when bullying perpetration was included in as a covariate. Permutation and false discovery rate–corrected p values were applied to estimate significance thresholds.

		Population sample European ancestry			
OTHER	*34. Mooney et al. 2020*[112]	Community volunteers, USA 472 participants: 302 with ADHD (72.5% male), mean age 9.9 years (sd 1.4); 170 without ADHD (54.1% male), mean age 9.8 years (sd 1.4) Community sample enriched for ADHD European ancestry	PRS calculation based on pT 0.5	Diagnosis based on: diagnostic parent interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version [KSAD-S-E]), parent and teacher standardized rating forms that assessed symptoms and impairment, clinician observations A total of 568,281 probes assessed for DNA methylation on the MethylationEPIC BeadChip. Differential global methylation (average methylation across all probes), as well as differentially methylated positions (DMPs) derived from saliva. Cell-type adjusted beta values were the outcome variables Covariates: sex, age, PCs, medication usage, maternal smoking, number of missing	The ADHD PRS was associated with reduced DNA methylation at one probe, cg15472673 at genome-wide significance ($p = 6.71E–8$) and this association remained ($p = 9.76e–8$) when including ADHD status in the regression model, suggesting that the effect was not driven by elevated polygenic burden in ADHD cases. The probe is located between the GART and SON genes in a CpG island of a bivariate promoter. The SNPs in the ADHD PRS are not direct methylation quantitative trait loci for cg15472673, as such the association with the PRS is not thought to be a genetic effect on DNA methylation. The ADHD PRS was associated with DNA methylation levels at 12 other probes at $p < 1.0e–5$. No sex interactions were significant at the EWAS significance threshold. In terms of differentially methylated regions, one region on chromosome 6 within the major histocompatibility complex was identified, in which the ADHD PRS associated with 8 probes associated with the ADHD PRS. The association was sex-specific: in females a higher PRS was associated with higher methylation levels, and the opposite was found for males.

				SNPs in the PRS calculation for each patient and a sex interaction term	
ADHDt, BRAIN, EA, NEUROPSYCH	*35. Sudre et al. 2018*[36]	544 participants (mean 21 years, 212 (39%) with ADHD). Majority European ancestry. Subpopulations with white non-Hispanic ancestry and African American ancestry. Clinical sample	PRS calculation based on 7 pT (0.01 – 0.5)	Inattention and hyperactivity disorder symptoms measured using clinician administered Diagnostic Interview for Children and Adolescents for parents [2]. Adult symptoms of ADHD were measured by clinicians using the Conners' Adult ADHD Diagnostic Interview for DSM-IV [3]. Neuroanatomic imaging, and imaging of white matter tract microstructure Other disorders in adults were ascertained through the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [4]. Working memory spans assessed through number of correctly recalled digits/tapping patterns. Processing speed assessed using visual matching task (from the Woodcock	ADHD PRS predicted symptoms of hyperactivity–impulsivity (b =0.11 SE = 0.046, p=.02, at FDR q < 0.05), but not inattention (at FDR q < 0.05). Of the neuroanatomic mediators (White matter microstructure and cortical anatomy), the following emerged as partial or complete mediators: axial diffusivity within regions of the right anterior (29% of the genetic effect) and right superior corona radiate (21% of the genetic effect); For thickness, a region within the left dorsomedial prefrontal cortex (24% of the genetic effect); For surface area, a region within the right lateral temporal cortex (22% of the genetic effect). Of the 6 cognitive domains, 3 emerged as significant mediators of ADHD PRS → hyperactivity–impulsivity symptoms: working memory (28% of the genetic effect), IQ (20% of the genetic effect) and focused attention (17% of the genetic effect). These mediators fully explained the association between ADHD PRS and hyperactivity–impulsivity symptom. Sustained attention, processing speed and perseverative/impulsive responding were not significant mediators. In serial mediation analyses (polygenic risk → brain regions → cognition → symptoms); two potential pathways emerged. For mediation analyses of neuroimaging data, used permutation and voxel-wise p<.05 Results mostly held when analyses repeated combining the two largest subpopulations; with medication as a covariate, excluding those with comorbid disorders and confining analyses to one member of each family

				Johnson III Test of Cognitive Abilities[113]). IQ was assessed using an age appropriate version of the Wechsler scales[104] . Attentional processes measured using the Conners' Continuous Performance Test[114], from which focused attention, perseverative/impulsive responding and sustained attention were derived. Covariates: Age, sex. Also for imaging data: motion and quality control scores	Applied a false discovery rate and indicate the results that survived at $q < 0.05$.
ASDt, OTHER	*36. Serdarevic et al (2020)*[46]	Generation R study, the Netherlands 1174-1921 participants The children were assessed in infancy (9-20 weeks) and at age 6 years 49% female, 51% male	PRS calculation based on six pT (0.01 - 1)	Neuromotor functioning assessed during in person home visits using modified Touwen's Neurodevelopmental Examination[115]. Separate versions used for 9-15 week olds and 16-20 week olds. Overall scale and Senses, Responses, Hypertone, Hypotone, Tone subscales. Tone included both active and passive muscle strength. Parent-rated autistic traits at age 6 years using the Social Responsiveness Scale	The ADHD PRS did not predict neuromotor functioning total or subscales after Bonferroni correction; it predicted "Senses and other" subscale nominally (b=0.43, CIs .001-.06; p=.04, R^2 =0.01%). ADHD PRS did not predict autistic traits in whole sample. ADHD PRS predicted autistic traits in boys only (pT<.10; b=.176, CIs .09-.27, p=<.001) after correction for multiple testing but not girls. Models that were adjusted for the autism or schizophrenia PRS did not change results. Bonferroni corrected significance threshold of p<.005 applied.

		Population sample European ancestry		Covariates: age, sex, PCs	
ADHDt, BRAIN, NEUROPSYCH	*37. Shen et al (2020)*[52]	IMAGEN Study, France, UK, Ireland, Germany 1790 participants Assessed at baseline at age 14 years and at follow up at 16 years 49% female; 51% male Population sample Ancestry not described	pT <.50	Parent-rated Strengths and Difficulties Questionnaire hyperactivity-inattention subscale[71] ages 14 and 16 years. Neuropsychological variables: Working memory errors assessed using Cambridge Neuropsychological Testing Automated Battery[116] through a self-ordered searching task at age 14. Delay discounting assessed using the Monetary Choice Questionnaire[117] which includes items pitting a smaller intermediate reward against a larger delayed reward at age 14. Intrasubject variability was the standard deviation of reaction time in successful go tasks in the stop signal functional MRI task[118]. Covariates: age, sex, and site. Analyses on GMV also	ADHD PRS was associated with higher ADHD total trait score at age 14 (r=.14, df=1779, p<.001, 95% CI .097-.188), working memory errors (r=0.07, df=1779, p=0.002, 95% CI=0.026, 0.121) and delay discounting rate (r=0.06, df=1779, p=0.007, 95% CI=0.021, 0.109). For lower gray matter volume, the ADHD PRS associated only with the posterior occipital cluster (r=-0.06, df=1777, p=0.009, 95% CI=-0.106, -0.015). Nonsignificant associations are not described in publication. Significance threshold not given.

				controlled for handedness and total intracranial volume	
ADHD*, ADHDt, BRAIN, NEUROPSYCH	*38. Hermosillo et al (2019)*[37]	Community recruited children, USA n =196 ADHD participants, 28% female, 72% male n = 119 Non-ADHD control participants, 46% female, 54% male Age range 7-13 years, m=10.38 years (1.55 sd) Community sample enriched for ADHD European ancestry	PRS calculation based on pT 0.5 (4 other thresholds tested in replications)	ADHD diagnoses were best estimate research diagnoses from parent semi-structured clinical interviews, clinical observation and parent/teacher rating scales. Parent-reported ADHD traits using a latent variable derived from five commonly used scales. Teacher-reported ADHD traits using a latent variable derived from three commonly used scales. Working memory assessed using digit span backward, spatial span backward, and N-back task. MRI-based resting functional connectivity in a targeted set of subcortical structures. In total, 6 circuits involving	PRS statistically predicted ADHD diagnosis (b = .153 [.073 SE], p = .038) and parent-reported symptoms (b = .138 [.059], p = .020) but not teacher-rated symptoms. ADHD PRS did predict working memory (b = 2.194 [.060], p = .001) ADHD PRS associated significantly with connectivity between the left caudate nucleus and a cluster within the intraparietal sulcus (b = .467 [.152 SE], p = .002), also reported as a significant correlation (r = .026, .162 SD) and significantly associated with a cluster of regions in the right nucleus accumbens with connectivity to cortex (b = .270 [.117 SE], p = .021). No significant associations of the ADHD PRS with: connectivity of the right caudate nucleus; with connectivity between brain regions and either the left or the right amygdala; or with the connectivity of different clusters correlated to the left nucleus accumbens. A mediation model showed that the PRS-ADHD diagnosis association was suppressed by 60% when the connectivity of a circuit (the connectivity between the left caudate nucleus and the right parietal cortex) was included in the model. Effect sizes were similar for both sexes. No other mediation models showed a significant impact of any of the other connectivity circuits on the ADHD PRS-ADHD diagnosis, ADHD PRS-ADHD symptoms or ADHD PRS-working memory associations. Results reported as similar when current or previous medication use included in the models, when the sample was sex-matched and with other PRS pT. Permutation testing was applied.

				subcortical regions: left and right caudate, left and right nucleus accumbens, left and right amygdala. Covariates: age, sex, PCs	
ADHD, ASD	*39. LaBianca et al (2020)*[31]	Families with multiple individuals with ASD or ADHD recruited through adult psychiatric clinics, Denmark 39 multiplex families with 268 individuals, including 1st and 2nd degree relatives of all ages up to 4 generations. Age range 7-13 years, m=10.38 years (1.55 sd) Northern European ancestry Clinical sample and family relatives	No pT significance threshold	Diagnoses of ASD, ASD or combined ASD and ADHD, based on ICD-10 Affected status contingent on PRS score PRS score had Danish samples removed. Covariates: sex, age	The ADHD PRS significantly predicted ASD, ADHD and combined ASD and ADHD. No further information provided. A significant association was found between the ADHD PRS and being a patient, an affected relatives and unaffected relatives (p = .03) using the Kruskal-Wallis ranked sum test.

ADHD	*40. Demontis et al (2019)*[17]	iPSYCH, a population based case-cohort sample including all singletons born in Denmark between May 1981-December 2005. European ancestry Psychiatric Genomic Consortium (PGC) includes trio and case control samples. Only European ancestry individuals included in PRS analyses n = 18,298 biologically independent PGC individuals (n = 5599 cases; n = 12699 controls) n = 37,076 biologically independent	10 pT were employed (from 5 X 10-8-1). PRS in the iPSYCH sample were achieved with five leave-one-out analyses i.e. 4 of 5 groups used as training datasets for estimation of SNP weights while estimating PRS for the excluded target group.	PRS prediction considered a) within iPSYCh b) within PGC c) across all using leave-one-out analysis. iPSYCH cases diagnosed by psychiatrists at in- or out-patient clinics mostly with ICD-10 identified using a Danish Psychiatric Register. Controls randomly selected from iPSYCH without ADHD or moderate/severe mental retardation. Individuals with a diagnosis of moderate to severe mental retardation were excluded from both cases and controls. Diagnoses of ADHD derived from range of published instruments in PGC samples. Covariates: Batch effects, genotyping wave and PCs	ADHD PRS predicted ADHD across all target samples compared to controls or pseudocontrols. Within iPSYCH (using five-fold cross-validation), mean of maximum variance explained by ADHD PRS using estimated PRS Nagelkerke's R^2 was 5.5% (SE = 0.0012), range .047-.06. Within iPSYCH, OR = 1.56, 95% confidence interval (CI): 1.53–1.60. Within PGC (with iPSYCH as discovery sample), OR = 1.26 (1.22-1.31) variance explained on liability scale .0103, p = 2.4 E-35) Across PGC and iPSYCH waves, average variance explained on liability scale = .0371 (se = .0029) Increasing deciles of ADHD PRS associated with increasing OR for ADHD, both for iPSYCH and PGC.

		iPSYCH individuals (n = 14584 cases; n = 22492 controls)			
ADDICTION, EA, EXTERNALISING, MH, PHYSICAL	*41. Du Rietz et al 2018*[44]	UK Biobank, UK. n = 135,726, age 40-73 years (M = 56.79 years SD 7.96 years) 53% female, 47% male European ancestry Population sample In analyses, controls were individuals without ICD-10 or self-reported diagnosis of alcohol dependency, anxiety disorder, depressive disorder, BD, or schizophrenia	PRS calculation based on multiple pT between 0 and 0.5 at increments of .001	BMI using height and weight General cognitive ability obtained by 2-minute verbal-numerical reasoning test Neuroticism measured with Eysenck Personality Inventory Neuroticism Scale–Revised[119]. Anxiety and depressive disorders, bipolar disorder and schizophrenia identified either through self-report or ICD-10 codes. Alcohol intake frequency (via self report question); alcohol-related diagnosis through either self-report or ICD-10 codes. Smoking accessed through hospital records Risk taking coded dichotomously based on	ADHD PRS significantly positively predicted BMI (R^2 = .45%; p = 4.5 x 10-129), cognitive ability (R^2 = .38%; p = 4.5 x 10-36), alcohol intake frequency (R^2 = .09%; p = 8.1 x 10-29), alcohol dependency (R^2 = .21%; p = 4.5 x 10-6), tobacco use (R^2 = .33%; p = 4.2 x 10-21), risk taking (R^2 = .12%; p = 9.3 x 10-25), neuroticism (R^2 = .09%; p = 2.2 x 10-24), depressive disorder (R^2 = .11%; p = 2.2 x 10-13), height (R^2 = .03%; p = 8.7 x 10-20). ADHD PRS did not significantly predict anxiety disorder, bipolar disorder or schizophrenia. Within neuroticism, the items were also studied. ADHD PRS significantly predicted mood swings (R^2 = .002%), fed-up feelings (R^2 =.20%), feelings of loneliness and isolation (R^2 = .19%), miserableness (R^2 = .13%), irritability (R^2 = .09%), being tense/highly strung (R^2 = .07%), guilty feelings (R^2 = .05%), and having easily hurt feelings (R^2 = .05%). It did not predict being a nervous person or a worrier, suffering from nerves or often worrying after embarrassment. Secondary analyses showed there were not significant sex x PRS interaction effects. Of 8 control phenotypes, included to check for specificity, ADHD PRS significantly and negatively predicted height (R^2 = .03%) and age (R^2 = .03%), but not the other 6 control phenotypes. Significance threshold of p < 4.5 x 10-4 applied.

		and did not take lithium, antidepressants, or antipsychotics		yes/no answer to "Would you describe yourself as someone who takes risks?" Covariates: birthplace, age, sex, batch, PCs	
ADHD, MH	*42. Martin et al., 2018*[63]	The Child and Adolescent Twin Study in Sweden (CATSS), Sweden. CATSS Registry diagnoses n = 217-443; unaffected n = 13029- 13247 CATSS screening diagnoses n = 296- 1226; unaffected n = 2083- 12228 Avon Longitudinal Study of Parents and Children (ALSPAC), UK.	Primary analyses using pT p<0.1; analyses repeated on 4 other pT	ADHD, any anxiety disorder, any depression disorder or any anxiety or depressive disorder. CATSS had both registry-based ICD-10 clinical diagnoses (captured from ages 9-22yrs) and screening-based diagnoses based on parent-/self-rated items from the Autism-Tics, ADHD and Other Comorbidities inventory (ATAC) (assessed at ages 9 or 12 years)[99]. ALSPAC had algorithm-based diagnoses based on a semistructured interview, the Development and Well-Being Assessment (DAWBA[70] at ages 7,10,13 and 15 years from parents. Self ratings were also obtained for anxiety and depression at 15 and 18 years.	The ADHD PRS consistently predicted ADHD diagnoses using registry clinical diagnoses (OR = 1.39 (1.26–1.54) p =7.2E-11), screening research diagnoses (OR = 1.25 (1.17–1.34) p =2.8E-11) and algorithm-based research diagnoses (OR = 1.76 (1.51–2.05) p = 4.9E-13). The ADHD PRS predicted anxiety disorders using registry clinical diagnoses (OR = 1.16 (1.02–1.32) p = .020), and algorithm-based research diagnoses (OR = 1.20 (1.08–1.33) p =.00046) but not screening research diagnoses. The ADHD PRS predicted depressive disorders only using algorithm-based research diagnoses (OR = 1.19 (1.06–1.33) p =.0027) and not using registry clinical or screening research diagnoses. The ADHD PRS consistently predicted any anxiety or depressive disorder using registry clinical diagnoses (OR = 1.16 (1.04–1.29) p = .0062), screening research diagnoses (OR = 1.12 (1.01–1.25) p = .031) and algorithm-based research diagnoses (OR = 1.17 (1.07–1.27) p = .00063). Repeated analyses using other pT showed similar results. Significance threshold of p<.05 was applied

		ALSPAC algorithm diagnosed n = 199-724; unaffected n = 1728- 2732 Both population samples Both European ancestry		Covariates: age, PCs	
MH	*43. Rice et al. 2019*[62]	The Avon Longitudinal Study of Parents and Children (ALSPAC), UK n = 5416 adolescents with PRS scores and depression data on more than 1 assessment point between 10 and 18 years 47% male; 53% female Population sample	pT<.50	Self-report depressive symptoms using the short Mood and Feelings Questionnaire[120] 6 ages (10.5, 12.5, 13.5, 16.5, 17.5, 18.5 years). Categorized individuals scoring above/below clinical cut-off of scale. Family history measured as the number of family members with a history of depression or schizophrenia weighted by relatedness (first or second-degree relative) Three trajectory classes identified: persistently low (73.7%), later-adolescence onset (17.3%), and early-adolescence onset (9.0%).	The AHDH PRS did not correlate significantly with family history for major depression or schizophrenia (both p>.05). ADHD PRS predicted the early-adolescence–onset depression class (OR, 1.32; 95%CI, 1.13-1.54; P < .001) In multi-PRS analyses including also the schizophrenia and MDD PRS, the ADHD PRS still predicted the early (OR = 1.27 95% CI 1.08-1.50, p=.003) ADHD PRS did not predict the later-onset depression trajectory class in either the univariate analysis or the multi-PRS analysis. Analyses that were rerun including PCS, adjusting for missing phenotypic data, and adjusting for missing genetic data, showed similar findings. Significance threshold of p<.05 applied.

		European ancestry			
ADHDt, EA, EXTERNALISING, OTHER, SES	*44. Zwicker et al. 2020*[58]	Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) study, Canada n= 297 participants age 5-27 years (mean = 13.5, SD = 4.4) 53% female; 47% male Sample enriched for offspring of parents with depression, bipolar disorder and schizophrenia. 90% European ancestry; 10% non-European ancestry	pT<.50. Analyses repeated using other pT	Total adversity score calculated as mean of 10 binary indicators: (1) biological mother's education, (2) biological father's education, (3) homeownership status, (4) annual household income, (5) emotional abuse, (6) physical abuse, (7) sexual abuse, (8) neglect, (9) exposure to violence at home (10) bullying. Socio-economic and victimization adversity subscales also studied. ADHD symptoms: Under 18 years: Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS)–Present and Lifetime Version Over 18 years: Structured Clinical Interview for DSM-5 Externalizing symptoms score from KSADS interview	ADHD PRS was associated with ADHD symptoms (ß = 0.21, 95% CI 0.10 to 0.32, p < 0.001, R^2 = 3.0%) and externalising behaviors (ß = 0.23, 95% CI 0.12 to 0.34, p < 0.0001; R^2 = 4.0%; r= .22, p<.05). ADHD PRS was associated with adversity (b = 0.23, 95% CI 0.13 to 0.34, p < .0001. R^2= 4.0%) as well as the socio-economic adversity (b = 0.10, 95% CI 0.01 to 0.20, p = .028; R^2= 2.0%) and victimization adversity subscales (b = 0.24, 95% CI 0.12 to 0.35, p < .0001 R^2= 3.3%). ADHD PRS did not significantly associate with IQ or with family history for schizophrenia. Mediation models to test the ADHD PRS→adversity association showed that externalizing symptoms mediated 22% of the total effect of ADHD PGS on adversity. IQ did not mediate the ADHD PRS→adversity association. Associations held when run separately in individuals with and without ADHD; on the subset of participants under age 17; after excluding offspring of control parents; among the subset of participants who have a biological parent with mental illness and on the subset with self-reported European descent. Univariate PRS analyses employed p < 0.003 (Bonferroni significance threshold corrected for multiple tests)

				IQ assessed with Wechsler Abbreviated Scale of Intelligence – Second Edition[121] or Wechsler Preschool and Primary Scale of Intelligence. Covariates: age, sex, time in the study, PCs	

Note. Sample n are given for genotyped PRS sample used in analyses. PCs, principal components to control for population stratification. pT, single nucleotide polymorphism p-value threshold for PRS. If authors did not select a primary pT, results reported for most significant pT.

Outcome categories: ADHD*, attention deficit hyperactivity disorder diagnosis; ADHDt, ADHD traits; ADDICTION, substance and non-substance-based addiction phenotypes ASD, autism diagnosis; ASDt, autistic traits, BIOLOGICAL, genetic or methylation phenotypes including other PRS; BRAIN, imaging-based assessments of brain variables including structure, function and connectivity; EA, educational attainment phenotypes; EXTERNALISING, externalizing behaviors; MH, mental health phenotypes; NEUROPSYCH, neuropsychological phenotypes; PHYSICAL, physical health phenotypes; OTHER, uncategorized phenotypes.

AHPVT: Add Health Picture Vocabulary Test
BFIS: The Bullying and Friendship Interview Schedule
BRIEF: The Behavior Rating Inventory of Executive Function
CBCL: Child Behavior Check- list/6–18
CES-D: The Center for Epidemiologic Studies Depression Scale
DAWBA: The Development and Well-Being Assessment
EDI-2: The Eating Disorder Inventory-2
ICD: International Statistical Classification of Diseases and Related Health Problems
PCA: Principal Component Analysis
PT: p-value threshold of discovery GWAS as used for ADHD PRS
SCDC: The Social and Communication Disorders Checklist
SDQ: The Strengths and Difficulties Questionnaire
SWAN: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale
WURS: The Wender Utah Rating Scale

Table

Table 2:

Criteria list for the quality assessment of studies on the association between the ADHD PRS and outcomes measures

Criteria
1. Study participation; Study sample adequately represents the population of interest
(A) Description of the key characteristics of the study population (distribution by age, gender and ancestry/ethnicity)
(B) The sampling frame and recruitment are described, including characteristics of the place of recruitment or authors clearly reference where this information can be found
(C) Inclusion and exclusion criteria are described or authors clearly reference where this information can be found
(D) Information about participation at baseline and potential attrition (for genetic data) are described or authors clearly reference where this information can be found
2. Predictor measurement; *ADHD PRS is adequately measured*
(E) Description of genetic data collection (e.g., blood, saliva) and genotyping (array) is provided, and target sample was not part of GWAS
(F) Genetic data were subject to adequate quality control (minor allele frequency, missing rate, relatedness participants, sex mismatch, and genotype quality), an up to date imputation method and an established reference panel was used
(G) The ADHD PRS is adequately calculated (e.g., pruning/clumping of SNPs)
3. Outcome measurement; Outcome of interest is measured in a similar way for all participants
(H) A clear definition of the outcome measures is provided
(I) Several indications are provided for the validity and reliability of the outcome measure, or a reference is provided.
(J) The method and setting of outcome measurement is the same for all study participants
4. Confounding measurement; Important potential confounders are appropriately accounted for
(K) Age, gender and Socio Economic Status are accounted for in the analysis
(L) Population stratification and potential batch effects are accounted for in the analysis
(M) In case of clinical samples, treatment and comorbidity are accounted for in the analyses
5. Analysis and data presentation; Statistical analysis is appropriate
(N) Sufficient presentation of the data to assess the adequacy of the analytic strategy

(O) The number of participants in the target sample supports sufficient statistical power (N > 400)
(P) The selected statistical model is adequate for the design of the study
(Q) There is not evidence of selective reporting of results, and proper correction for multiple testing was applied.

Table 3:

Definitions of levels of evidence

Level of evidence	
Strong	Consistent findings (≥ 75%) in at least two high quality studies
Moderate	Consistent findings (≥ 75%) in one high quality study *and* at least one study of lower quality
Weak	Findings in one high quality study *or* consistent findings (≥ 75%) in at least 3 or more studies of lower quality
Inconclusive	Inconsistent findings irrespective of study quality, or less than 3 lower quality studies available

Note: (≥ 75%): within a category, at least 75% of the findings of studies had to agree on existence and direction of the relation between the ADHD PRS and the outcome measure.

Table

Table 4: Quality assessment results

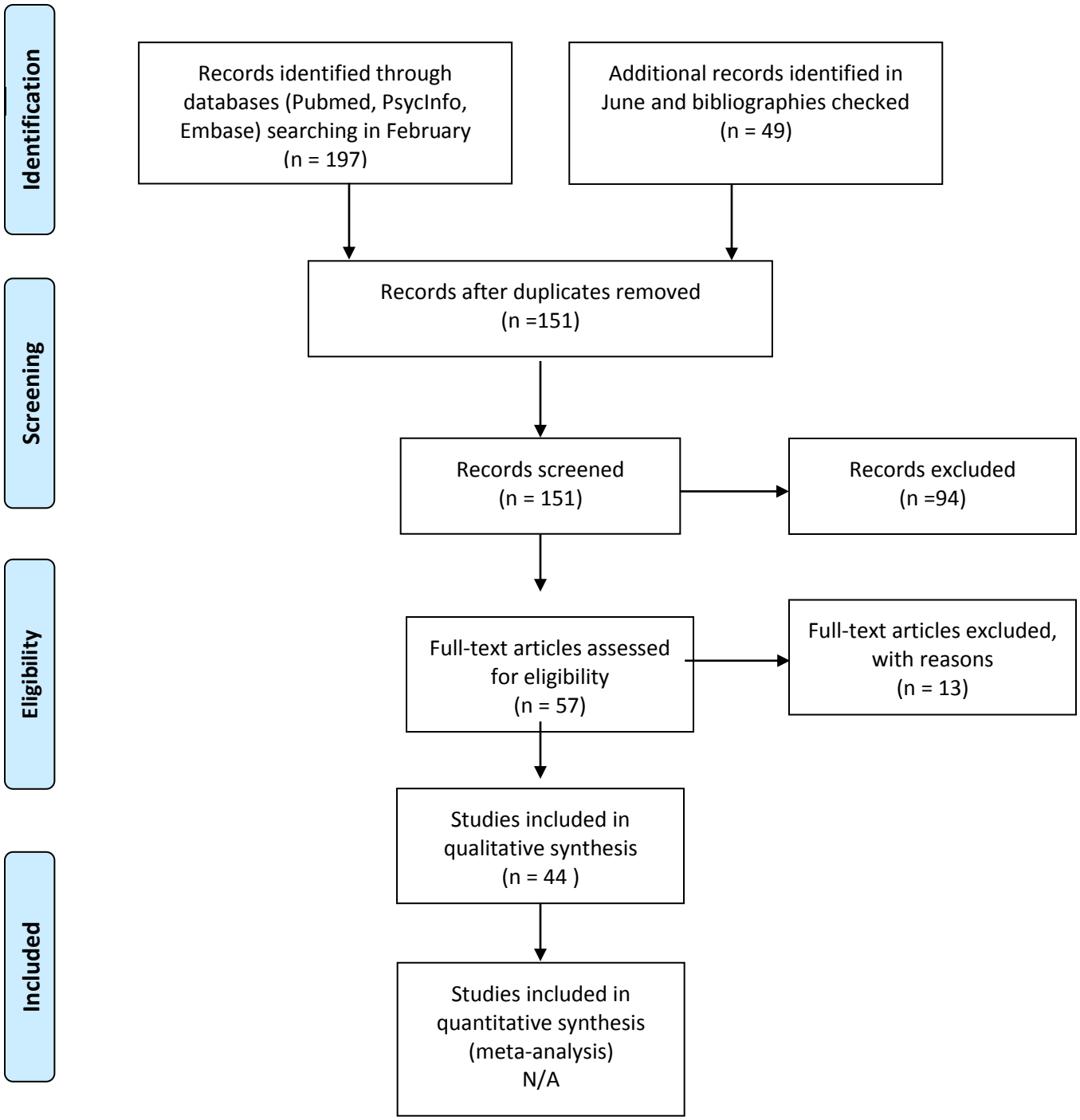
	1) Study sample				2) ADHD PRS			3) Outcomes			4) Confounders			5) Analysis, data presentation				N
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	bias
Stojanovski et al. 2019	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	0
Albaugh et al. 2019	+	+	+	+	-/+	+	+	+	-/+	+	+	+	NA	+	+	+	+	0
Burton et al. 2019	+	+	+	+	+	+	+	+	+	+	-/+	+	-	+	+	+	+	0
Jansen et al. 2019	+	+	-/+	+	+	+	+	+	+	+	-/+	+	-/+	+	+	+	+	0
Li 2019a	+	+	+	+	+	+	+	+	-	+	+	+	NA	+	+	+	+	0
Gialluisi et al. 2019	+	-	+	-	+	+	-/+	+	-	-	-	-+	-	+	+	+	+	2
Rietveld & Patel 2019	+	-	-/+	-	-	-	-	+	-/+	-/+	+	+	NA	+	+	+	+	2
Piasecki et al. 2019	+	+	+	+	+	+	+	+	-	+	-/+	+	NA	+	+	+	-/+	0
Torske et al. 2019	+	+	+	+	+	+	+	+	-/+	+	-/+	+	-	+	-	-/+	-	1
Nigg et al. 2019	+	+	+	+	+	+	+	+	-	+	-/+	+	+	+	-/+	+	-/+	0
Dickinson et al. 2019	+	+	+	-	+	+	+	+	+	+	-/+	+	-	+	-/+	+	-/+	0
Cabana-Domínguez et al. 2019	+	+	+	+	+	+	+	+	+	-/+	-	+	-	-/+	+	+	-/+	0
Ohi et al. 2020	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+	-/+	0
Mooney et al. 2020a	+	-/+	+	+	+	-/+	+	+	+	+	-/+	+	-/+	+	-	+	+	0
Vuijk et al. 2019	+	-+	+	+	+	+	+	+	+	+	-/+	+	+	+	-	+	+	0
Li 2019b	+	+	+	+	+	+	+	+	+	+	+	+	NA	+	+	+	-/+	0
Riglin et al. 2019	+	+	+	+	+	+	+	+	+	+	+	-	NA	+	+	+	-/+	0
Grigoroiu-Serbanescu et al. 2019	+	-/+	-/+	-	-/+	-/+	+	+	+	-/+	-	-	-	-/+	+	-/+	+	1
Wimberley et al. 2019	+	+	+	+	+	+	+	+	+	+	+	+	-/+	+	+	+	+	0

	1				2			3			4			5				
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	#
Riglin et al. 2020	+	+	-/+	+	+	+	+	+	+	+	-	-	NA	+	+	+	-/+	1
Barker et al. 2019	+	+	-/+	+	-/+	+	+	+	+	+	-/+	+	NA	+	+	+	+	0
De Zeeuw et al. 2019	-/+	+	+	+	+	+	+	+	+	+	-/+	+	NA	+	+	+	+	0
Yao et al. 2019	+	+	+	+	+	+	+	+	+	+	-/+	+	-	+	+	+	-/+	0
Rabinowitz et al. 2018	+	+	-/+	+	+	+	+	+	+	-/+	-/+	+	-	+	+	+	+	0
Taylor et al. 2019	+	+	+	+	+	+	+	+	+	+	-/+	+	NA	+	+	+	+	0
Alemany et al. 2019	+	+	+	+	+	+	+	+	+	+	-/+	+	NA	+	+	+	+	0
Gurriarán et al. 2018	+	+	+	+	+	+	+	+	+	-/+	-/+	+	-	+	+	+	+	0
Szekely et al. 2018	+	-/+	-/+	+	+	+	+	+	+	-	-/+	+	NA	-/+	+	+	+	0
Nigg et al. 2018	+	+	+	+	+	+	+	+	+	+	-/+	-/+	+	+	+	+	+	0
Hawi et al. 2018	+	-	+	+	+	+	+	+	+	+	-/+	+	-	+	-	+	+	0
Taylor et al. 2018	+	+	+	+	+	+	+	+	-	+	-/+	+	NA	+	+	+	-/+	0
Selzam et al. 2019	+	+	+	+	+	+	+	+	-/+	+	+	+	NA	+	+	+	+	0
Schoeler et al. 2019	+	+	+	+	+	+	+	+	-	+	-/+	+	NA	+	+	+	+	0
Mooney et al. 2020b	+	-/+	+	-/+	+	+	+	+	+	+	-/+	+	-/+	+	-/+	+	+	0
Sudre et al. 2018	-	-	+	-	+	-/+	+	+	+	+	-/+	-/+	+	+	-/+	+	+	1
Hermosillo et al. 2020	+	+	-/+	+	+	+	+	+	+	+	-/+	+	-/+	+	-/+	+	+	0
LaBianca et al. 2020	-	+	-	+	-	-	+	+	+	+	-/+	-	-	-/+	-/+	+	+	2

	1				2			3			4			5				
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**#**
Serdarevic et al. 2020	-/+	+	+	+	+	+	+	+	+	+	+	+	NA	+	+	+	+	0
Shen et al. 2020	+	+	+	+	-/+	+	+	+	-/+	-	-/+	-	-/+	+	+	+	-/+	1
Demontis et L. 2019	+	+	-/+	-/+	+	+	+	+	+	-	-	+	-	+	+	+	+	0
Du Rietz et al. 2018	+	+	+	+	+	+	+	+	-/+	+	-/+	+	NA	+	+	+	+	0
Martin et al. 2018	+	+	+	+	+	+	+	+	+	-	-/+	+	NA	+	+	+	-/+	0
Rice et al. 2019	+	+	+	+	+	+	+	+	+	+	-/+	+	NA	+	+	+	-/+	0
Zwicker et al. 2019	+	+	+	+	+	+	+	+	-/+	+	-/+	+	NA	+	-/+	+	+	0

Figure

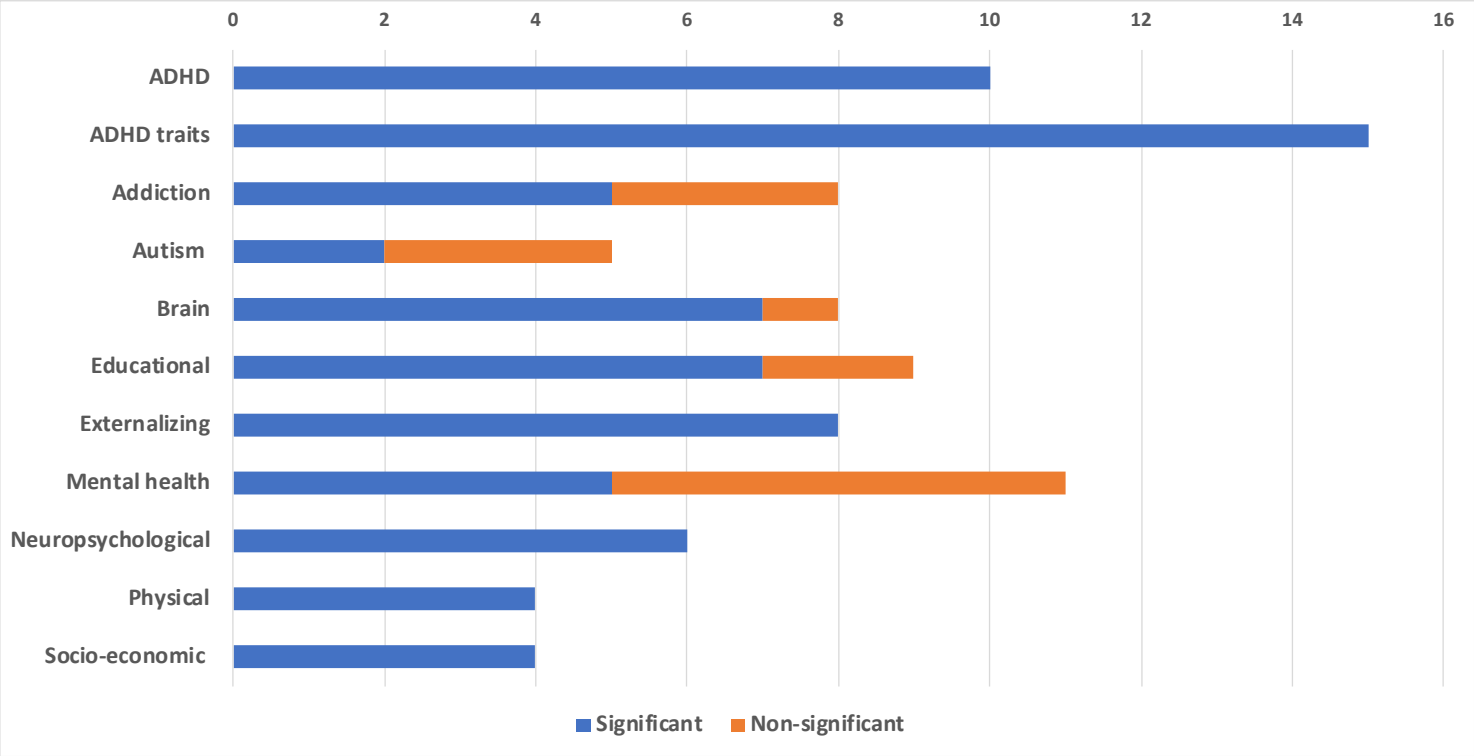
Figure 1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplementary Figure 1. Bar chart summarising number of studies per category, and strenght of association.



Supplementary Table 1: Measured traits for each category

Category (N studies)	**Measured traits (study number in Table 1)**
ADHD diagnosis (10)	• Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (3#, 18#, 29#, 30#) • Retrospectively self-reported ADHD symptoms keyed to the DSM-IV (4) • ICD-10 (15#, 39#, 40#, 42) • Retrospectively Wender Utah Rating Scale (WURS), Kiddie-SADS clinical interview. Assessment of childhood ADHD was made by clinicians (18#) • Conners' Parent Rating Scale (30#) • Best estimate research diagnoses from parent semi-structured clinical interviews, clinical observation and parent/teacher rating scales (38#) • Autism-Tics, ADHD and Other Comorbidities inventory (ATAC) (42) • Development and Well-Being Assessment (DAWBA) (42)
ADHD traits (16)	• Composite score of the Development and Well-Being Assessment (DAWBA) and the Strengths and Difficulties Questionnaire (SDQ) (1) • Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM5) (2) • Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) score: Total, inattentive and hyperactive/impulsive subscales (5) • Dimensional score on an ADHD latent variable captured from hyperactivity and inattention subscales of four published ADHD scales (10#) • DSM-IV Axis 1 diagnoses; a range of parent-rated dimensional published scales of psychopathology (15#) • DSM-IV items retrospectively (16) • Wender Utah Rating Scale (WURS) and items from the Kiddie-SADS clinical interview (18#) • Child Behavior Checklist (CBCL) Attention Problem scales (22, 26) • Teacher Report Form (TRF) Attention Problem scales (22) • The Autism-Tics, AD/HD and Other Comorbidities Inventory (A-TAC) (25) • Separate parent and teacher-rated ADHD symptom latent variables derived from data on 3-4 published ADHD measures that capture inattention and hyperactivity (29#) • SDQ (32)

	• Conners' Parent Rating Scale (32) • Inattention and hyperactivity disorder symptoms by clinician administered Diagnostic Interview for Children and Adolescents for parents (35[#]) • Strengths and Difficulties Questionnaire (SDQ) (37) • Parent-reported ADHD traits using a latent variable derived from five commonly used scales (38[#]) • Teacher-reported ADHD traits using a latent variable derived from three commonly used scales (38[#]) • ADHD symptoms: under 18 yrs: Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS)– Present and Lifetime Version; over 18 yrs: Structured Clinical Interview for DSM-5 (44)
Addiction (8)	• 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 12-month period (4) • Gambling: answering yes or no to "Have you ever bought lottery tickets, played video games or slot machines for money, bet on horses or sporting events, or taken part in any other kinds of gambling for money?"; and (if yes to the previous question), answer of yes or not to: "Has your gambling ever caused serious financial problems or problems in your relationships with any of your family members or friends?" (8) • Cocaine dependence DSM-IV (12[#]) • Presence of substance use disorder history (15[#]) • Addiction categorized first by alcohol, cannabis, and other illicit drugs and second categorized into severity into use, abuse and addiction (nicotine use not included) (19) • Composite International Diagnostic Interview-University of Michigan Version (CIDI-UM), National Survey on Drug Use and Health (NSDUH) (24) • Substance use disorder DSM-IV (27[#]) • Alcohol addiction ICD-10 (41) • Smoking through hospital records (41)
Autism/autistic traits (5)	• DSM-IV ASD diagnosis (3[#])

	• Social Responsiveness Scale (9[#], 15[#], 36) • ICD-19 (39[#])
Brain measures (8)	• Neuroanatomic imaging, and imaging of white matter tract microstructure (1) • Total brain volume (TBV) and subcortical structures (14[#]) • Voxel-based morphometry measures of whole-brain grey matter (21) • Neural responses to reward anticipation and reward outcome from activation maps from a Monetary Incentive Delay fMRI task (21) • Total brain volume (TBV), cortical gray matter (GM), total white matter, subcortical GM, ventricular volume, cerebellum, amygdalahippocampus complex, caudate, putamen and thalamus (26) • Longitudinal growth in volume across 2 time points modeled linearly for 4 brain divisions: cerebral cortex, basal ganglia, cerebellum, cerebral white matter, and one region of interest: the right lateral prefrontal cortex (28[#]) • Neuroanatomic imaging, and imaging of white matter tract microstructure (35) • Stop signal functional MRI task (37) • MRI-based resting functional connectivity in left and right caudate, left and right nucleus accumbens, left and right amygdala (38[#])
Educational attainment (9)	• Cognitive ability, measured by Add Health Picture Vocabulary Test (AHPVT) (4) • Educational attainment, measured by the question 'what is the highest level of education that you have achieved to date? (4, 22) • Eight outcomes relating to word reading, spelling, rapid naming, and phonology that are considered core deficits in dyslexia: Word reading (WRead), nonword reading (NWRead), and word spelling (WSpell), Phoneme awareness (PA), digit span (DigSpan, a measure of verbal short-term memory), and rapid automatized naming of letters (RANlet), digits (RANdig), and pictures (RANpic) (6) • Wide-Range Achievement Test [WRAT] reading subtest and Wechsler Adult Intelligence Scale [WAIS] used for cognitive assessments (11[#]) • Wechsler Intelligence Scale for Children–Fourth Edition and the Wechsler Adult Intelligence Scale–4th Edition (15[#], 35[#])

	• Word Reading and Numerical Operations of the Wechsler Individual Achievement Test–Third Edition (WIAT III) (15[#]) • Whether education was completed by age 23 years or not (15[#]) • Cito score, a Dutch nationwide standardized educational achievement test (22) • Wechsler Intelligence Scale III, verbal and nonverbal ability (32) • UK General Certificate of Secondary Education; GCSE (32) • General cognitive ability obtained by 2-minute verbal-numerical reasoning test (41) • IQ assessed with Wechsler Abbreviated Scale of Intelligence – Second Edition or Wechsler Preschool and Primary Scale of Intelligence (44)
Externalizing behaviors (8)	• Irritability captured with latent variable based on two subscale scores: anger and modified soothability from the Temperament in Middle Childhood Questionnaire (TMCQ, and an oppositional defiant disorder irritable total score. Latent variables were also created for surgency-approach and sadness-anxiety (10[#]) • DSM-IV Axis 1 diagnoses; a range of parent-rated dimensional published scales of psychopathology (15[#]) • Aggressive behaviors, non-aggressive rule breaking and substance use behaviors assessed by in-person interviews (16) • Parent-reported data on Development and Well-Being Assessment (DAWBA)[1]—a structured research diagnostic interview—at ages 7, 10, 13 and 15 years (17) • Comorbid oppositional defiant disorder/conduct disorder (ODD/CD) (19[#]) • Impulsivity symptoms at age 19 assessed using self-reported Barratt Impulsivity Scale (BIS) (21) • Risk taking coded dichotomously based on yes/no answer to “Would you describe yourself as someone who takes risks?” (41) • Externalizing symptoms score from KSADS interview (44)
Mental health (11)	• Diagnoses based on the DSM-IV, the Center for Epidemiologic Studies Depression (CES-D) Scale, and an abbreviated 4-item version of the Cohen’s Perceived Stress Scale (4) • Whether participant was ‘ever arrested’ (4) • Diagnoses based on the DSM-IV (11[#], 15[#], 18[#])

	• Diagnoses based on DSM5 (13[#]) • P-factor based on DAWBA, the Social and Communication Disorders Checklist (SCDC) (20) • 3 subscales (Drive for Thinness, Bulimia, and Body Dissatisfaction) from the Eating Disorder Inventory-2 (EDI-2) (23) • Specific Psychotic Experiences Questionnaire (32) • Neuroticism assessed by Big Five questionnaire (32) • Eysenck Personality Inventory Neuroticism Scale–Revised (41) • Diagnoses based on ICD-10 codes (41, 42) • Development and Well-Being Assessment (DAWBA) (42) • Mood and Feelings Questionnaire (43) • Family history measured as the number of family members with a history of depression or schizophrenia weighted by relatedness (first or second-degree relative) (43)
Neuropsychological constructs (6)	• Behavior Rating Inventory of Executive Function (BRIEF), a 86-item questionnaire. The Behavior Regulation Index (which incorporates 3 subscales: inhibit, shift, and emotional control) and the Metacognition Index (which incorporates 5 subscales: initiate, working memory, plan/organize, organization of materials, and monitor). The Global Executive Composite Index comprised all 8 above subscales (9[#]) • Working memory index from the Wechsler Intelligence Scale for Children–Fourth Edition (15[#]) • Laboratory measures of working memory, response inhibition, executive functioning, arousal/attention, temporal, information processing, and processing speed (29[#]) • Working memory spans assessed through number of correctly recalled digits/tapping patterns (35[#]) • Processing speed assessed using visual matching task (from the Woodcock Johnson III Test of Cognitive Abilities) (35[#]) • Conners' Continuous Performance Test (35[#]) • Cambridge Neuropsychological Testing Automated Battery (37) • Monetary Choice Questionnaire (37) • Working memory assessed using digit span backward, spatial span backward, and N-back task (38[#])

Physical health (4)	• Body mass index (BMI) (4, 21, 32, 41) • Patient-reported hypertension or high blood cholesterol as assessed by a doctor (4) • Height (32) • Self-rated health (RAND Short-Form Health Survey) (32)
Socio-economic variables (4)	• Six later-life US labor market outcomes: currently working for pay, individual earnings (gross individual income), total household wealth (net value of total wealth, excluding second home, if applicable), receiving governmental assistance in the form of social security disability insurance, receiving unemployment or workers' compensation, receiving other governmental transfers (7) • paternal income, maternal education (19[#]) • Socio Economic Status: based on maternal age at birth of the first child, maternal and paternal highest education level, and maternal and paternal occupation (32) • Socio-economic adversity scale (biological mother's education, biological father's education, homeownership status, annual household income) (44[#])
Other (9)	• Mild traumatic brain injury (2) • Age of onset BP (18[#]) • Parental Substance Use Disorder, parental mental disorder (19[#]) • The Structured Interview of Parent Management Skills and Practices Youth-Version (SIPMSP) (24) • The community disadvantage score was calculated using census-tract level items from the 1990 and 2000 Decennial census (24) • Study participation defined as responding to a questionnaire or attending a clinic for which the whole cohort was eligible to participate (31) • Bullying and Friendship Interview Schedule (BFIS) (33) • 568,281 probes assessed for DNA methylation on the MethylationEPIC BeadChip (34[#]) • Neuromotor functioning: Touwen's Neurodevelopmental Examination (36) • Victimization adversity scale (emotional abuse, physical abuse, sexual abuse, neglect, exposure to violence at home, bullying (44[#])

Note: [#]clinical sample, or enriched sample