



BIROn - Birkbeck Institutional Research Online

Polderman, T.J.C. and De Bode, N. and Ronald, Angelica (2020) Systematic review: How the ADHD polygenic risk score adds to our understanding of ADHD and associated traits. *Journal of the American Academy of Child & Adolescent Psychiatry* 59 (10 (S)), S158. ISSN 0890-8567.

Downloaded from: <https://eprints.bbk.ac.uk/id/eprint/42156/>

Usage Guidelines:

Please refer to usage guidelines at <https://eprints.bbk.ac.uk/policies.html> or alternatively contact lib-eprints@bbk.ac.uk.

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

Angelica Ronald¹ Ph.D., Nora de Bode^{2,3} BSc., & Tinca J.C. Polderman^{2, 3,*} Ph.D.

¹ Department of Psychological Sciences, Birkbeck University of London, London, United Kingdom

² Complex Trait Genetics, Center for Neuroscience and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

³ Amsterdam UMC, Vrije Universiteit Amsterdam, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Public Health

*Correspondence to: Tinca J.C. Polderman, Ph.D., Amsterdam UMC, Vrije Universiteit Amsterdam, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Public Health, De Boelelaan 117, Amsterdam, The Netherlands. Tel: +31 20 8901545, e-mail: tinca.polderman@amsterdamumc.nl

Acknowledgements: We are grateful to Professor Martijn van den Heuvel, Ph.D., for his assistance in evaluating the included MRI studies.

Disclosures: The authors report no financial interests or potential conflicts of interest

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

1 Objective: To investigate, by systematically reviewing the literature, if the ADHD polygenic
2 risk score (PRS) associates with ADHD and related traits in independent clinical and
3 population samples.
4
5
6

7 Method: Pubmed, Embase and PsychoInfo were systematically searched, alongside study
8 bibliographies. Quality assessments were conducted, and a best-evidence synthesis was
9 applied. Studies were excluded when 1) predictor was not based on the latest ADHD genome-
10 wide association study; 2) PRS was not based on genome-wide results; 3) study was a review.
11 Initially, 197 studies were retrieved [dd. Feb 22nd 2020]; a second search [dd June 3rd 2020]
12 retrieved a further 49 studies; from both searches, 57 studies were eligible and 44 studies met
13 inclusion criteria.
14
15
16
17
18
19
20
21

22 Results: Included studies were published in the last three years. Over 80% of the studies were
23 rated excellent based on a standardized quality assessment. Evidence of associations between
24 ADHD PRS and the following categories was strong: ADHD, ADHD traits brain structure,
25 education, externalizing behaviors, neuropsychological constructs, physical health and socio-
26 economic status. Evidence for associations with addiction, autism and mental health are
27 mixed and were, so far, inconclusive. Odds ratios for PRS associating with ADHD ranged
28 from 1.22-1.76; variance explained in dimensional assessments of ADHD traits was 0.7%-
29 3.3%.
30
31
32
33
34
35
36
37

38 Conclusion: A new wave of high quality research using the ADHD PRS has emerged.
39 Eventually, symptoms may be partly identified based on PRS, but the current ADHD PRS is
40 useful for research purposes only. This review shows the ADHD PRS is robust and reliable,
41 associating not just ADHD but many outcomes and challenges known to be linked to ADHD.
42
43
44
45
46
47
48

49 Keywords: Attention Deficit/Hyperactivity Disorder, genetics, neurodevelopment,
50 comorbidity, psychiatry
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

ADHD is a neurodevelopmental disorder that affects approximately 5% of children and 2.5% of adults¹. Decades of past research have established the significant twin heritability of ADHD and family studies demonstrate its high familiarity^{2,3}. More recently, significant SNP heritability estimates for ADHD have been reported⁴. Together this evidence supports the hypothesis that common genetic variants acting additively play a role in the causes of ADHD³. 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 traits¹⁶. 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 ADHD¹⁷. 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 al¹⁷ 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

1 ADHD. PRS's can be calculated in any genotyped sample and thus the degree to which the
2 ADHD PRS associates both with ADHD as well as other phenotypes can be explored. The
3 latter is interesting given the reported co-occurrence and genetic overlap of ADHD with many
4 other traits like autism and substance use, as described above.
5
6
7
8

9 A PRS is thus a major methodological development, not only for the genetic field, but
10 in terms of potential utility in a range of other research fields due to the fact that they can be
11 easily calculated in any genotyped sample. The potential of PRS for clinical utility, screening
12 and personalized health is currently a major topic of debate^{18,19}.
13
14
15
16
17
18

19 Here we present a systematic review of all studies using the ADHD PRS based on the
20 largest ADHD GWAS to date¹⁷ and provide a systematic quality assessment of all included
21 studies. In our review, we structured our results by the following outcome domains:
22 diagnosed ADHD and ADHD traits (dimensional assessments of ADHD symptoms or traits),
23 addiction, autism and autistic traits, brain-based (imaging) measures, educational attainment,
24 externalizing behaviors, , mental health, neuropsychological constructs, physical health,
25 socioeconomic variables and other (uncategorized) outcomes. Please see Table S1 for the
26 complete list of outcomes per category. We also note the ancestry of the samples used in the
27 literature to date.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

METHODS

1
2
3
4
5 Details of the outline of our review and methods applied were preregistered with PROSPERO
6
7 Framework (<https://www.crd.york.ac.uk/PROSPERO>) with registration number
8
9 CRD42020176391 on April 28 2020, and followed as registered except the following: 1) The
10
11 study by Hayden et al. (2013), on which we based our quality assessments, proposes six
12
13 quality domains. However, given some overlap in items of domains 1 and 2, we combined
14
15 these, and thus used five domains instead of six. 2) Given the sheer amount of studies
16
17 resulting from the latest GWAS (n= 44), and the importance of an adequately powered
18
19 GWAS to use the PRS reliably, we decided to exclude a systematic overview of studies based
20
21 on older GWAS's.
22
23
24
25
26
27
28

Study selection

29
30 PubMed, Embase, and PsychInfo were systematically searched for published, peer reviewed
31
32 studies written in English using the search terms: (“ADHD”[Title/Abstract] OR “Attention
33
34 Deficit”[Title/Abstract] OR “Attention-Deficit”[Title/Abstract] OR
35
36 “Hyperactivity”[Title/Abstract] OR “Hyperactive”[Title/Abstract] OR “attention deficit
37
38 hyperactivity disorder”[Title/Abstract] OR “Attention problems”[Title/Abstract]) AND
39
40 (“Polygenic risk score”[Title/Abstract] OR “Polygenic score”[Title/Abstract]). Bibliographies
41
42 of selected studies were also searched (by NB). A first search was conducted February 22nd
43
44 2020, and a second search on June 3rd 2020. All abstracts were inspected by two reviewers
45
46 (TJCP and NB). Studies were excluded when a) the predictor was not an ADHD PRS b) the
47
48 PRS was not based on genome-wide results (but e.g., on a certain selection of SNPs) c) the
49
50 ADHD PRS was not based on the latest GWAS results of ADHD¹⁷, or c) the study was a
51
52 review.
53
54
55
56
57
58
59
60
61
62
63
64
65

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

1 series of quality assessment criteria, clustered in five domains, to evaluate the quality of
2 studies that we included in the current review.
3
4
5
6

7 1. Study participation 8

9 A clear description of characteristics of the sample under study is key to evaluate how
10 adequately the sample represents the population of interest, and how potential attrition may
11 lead to selection bias affecting a proper representation.
12
13
14
15
16

17 2. The ADHD PRS 18

19 The validity and statistical power of a PRS depends on two crucial conditions. The first one is
20 a powerful GWAS discovery sample, and the second one is proper quality control (QC) of the
21 genetic data of the target sample under study. With the publication of the summary statistics
22 of the largest GWAS on ADHD three years ago¹⁷, for the first time, a reasonably powerful
23 ADHD PRS became possible. Standard QC protocols are available²⁶ to ensure that genetic
24 data are correctly processed, and that important data checks are applied. Furthermore, when
25 analysing PRS data, a proper correction for population stratification should be applied.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 3. Assessment of outcome measures 42

43 The current review includes multiple outcome measures that were tested for an association
44 with the ADHD PRS. In the quality assessment, the validity and reliability of these outcome
45 measures, either tested in the study, or as citation to earlier publication, were the focus of
46 evaluation.
47
48
49
50
51
52
53
54
55

56 4. Confounding factors 57 58 59 60 61 62 63 64 65

1 Several confounding factors can play a role in the relation between the genetic risk for ADHD
2 and the outcome measures. Given the variety of outcome measures the focus of evaluation
3 was on the following generic confounders: gender, age, socioeconomic status (SES), use of
4 medication and co-occurring disorders.
5
6
7
8
9

10 5. Analysis and data presentation 11

12 For a reader to judge the quality of a study, a proper presentation of the statistical analyses
13 and results is required. Of importance is also the target sample size, as sufficient statistical
14 power is required to provide accurate conclusions on the relation between the ADHD PRS
15 and outcome measures. Lastly, multiple testing correction should be applied when more than
16 one outcome measure is tested for an association with the predictor variable (i.e., ADHD
17 PRS).
18
19
20
21
22
23
24
25
26
27
28
29
30

31 A checklist consisting of criteria as described above was used to evaluate the quality of the 44
32 selected studies. Every item was rated positive (+), negative (-), or +/- (i.e., fulfilling part of
33 the criterium) by two independent reviewers (TJCP and NB). In case of any disagreement
34 between the reviewers, consensus was achieved by discussion. Studies were then ranked
35 based on the number of biases. A bias was present when more than 50% of the criteria of one
36 domain had a negative score. The highest quality was attained if at least 50% of the items of
37 each domain were rated as being positive^{24,25}. Of note, since item M (treatment and
38 comorbidity) could only be rated for the clinical samples, and not applicable (NA) for the
39 population samples, this item was excluded from the bias count.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57

58 *Best-evidence synthesis* 59 60 61 62 63 64 65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 studies²⁷.

Based on this evaluation, four increasing levels of evidence can be defined²⁸.

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-

1 substance-based addiction phenotypes (n=8), autism spectrum disorders or autistic traits
2 (n=5), brain-based (imaging) variables (n=8), educational attainment (n=9), externalizing
3 behaviors (n=8), mental health (n=11), neuropsychological constructs (n=6), physical health
4 (n=4), socio-economic variables (n=4) and “other” (uncategorized outcomes) (n=9).
5
6
7
8

9
10 Across the 44 studies, a total of 48 samples were used. Four studies included two
11 samples and note that these 48 samples are not all independent (see below). In terms of
12 sample characteristics, 25 of the 48 samples (52%) were population samples, 16 (33%) were
13 clinical samples and 7 (15%) were community samples enriched for individuals with ADHD
14 or mental illness. Children (under 18’s) made up just over half the samples (n=25; 52%), 13
15 (27%) were adult samples and the remaining (n = 10, 21%) included both children and adults.
16
17 It was most common for samples to come from Europe (n = 25, 52%) followed by North
18 America (n = 17, 35%), a mix of continents (n= 4, 9%), Asia (n = 1, 2%) and one had missing
19 country of origin (2%). The samples employed in more than one study were ALSPAC (6
20 studies), IMAGEN (3 studies), National Longitudinal Study of Adolescent to Adult Health (3
21 studies), Child and Adolescent Twin Study in Sweden (3 studies), Generation R (2 studies),
22 community based sample recruited close to Oregon Health & Science University USA (2
23 studies), and iPSYCH (2 studies).
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 *Diagnosed ADHD.* The ADHD PRS consistently associated with diagnosed ADHD in
42 all 10 studies. The odds ratios ranged from 1.22-1.76. This range omits one study which
43 associated with ADHD within a cohort with bipolar disorder²⁹ and two studies which did not
44 provide enough information to calculate odds ratios^{30,31}. Several studies^{17,32} showed, using
45 deciles or groups based on low/medium/high scorers, that the ADHD PRS operated in a dose
46 dependent manner in terms of its influence on ADHD status.
47
48
49
50
51
52
53
54
55

56 In terms of ADHD and co-occurring conditions, ADHD PRS was associated with
57 having combined ADHD and ASD in a multiplex family design including unaffected relatives
58
59
60
61
62
63
64
65

1 and relatives with either or both conditions³¹. The ADHD PRS did not differentiate bipolar
2 disorder cases with ADHD from bipolar disorder cases without ADHD²⁹. In the context of
3
4 other psychiatric disorders, ADHD PRS was associated with ADHD when controls were
5
6 individuals with other psychiatric disorders³³;
7
8

9
10 *ADHD Traits.* This was the most commonly studied outcome and all studies found
11 positive significant associations with the ADHD PRS (16 studies). Percent variance explained
12 in ADHD traits by the ADHD PRS ranged from 0.7-3.3%. These values were either directly
13 reported, or converted from correlations provided in the studies. Five studies that reported on
14 ADHD traits^{29,34,35,36,37} are omitted from this range because their study designs were different
15 (e.g. they only investigated subscales, they investigated familial effects, the sample was
16 bipolar disorder cases).
17
18

19
20 Four of these studies investigated the ADHD trait subscales separately, namely
21 hyperactivity/impulsivity and inattention. Two (50%) studies found that the ADHD PRS was
22 positively associated with higher scores on both subscales^{38,39} whereas two (50%) found that
23 the ADHD PRS was positively associated with the hyperactivity/impulsivity subscale but not
24 significantly associated with inattention^{33,36}.
25
26

27
28 *Addiction.* A range of addiction phenotypes were studied: seven studies on substance
29 related addiction^{32,40,33,41,42,43,44} and one study on a non-substance related addiction –
30 gambling⁴⁵. Three studies did not find the ADHD PRS associated with their addiction
31 phenotypes (which focused on gambling behaviors, substance abuse and marijuana use
32 disorders). The other five studies reported all or some significant positive associations,
33 including with cocaine dependence, substance use disorders, alcohol (intake frequency and
34 alcohol-related diagnoses), smoking, cannabis use disorder, use of illicit drugs, and severity of
35 addiction.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 provided³¹. 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 females⁴⁶.

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 alleles³⁴ 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 adults⁴⁴, and more perceived stress in another study³² but was not associated with neuroticism in a youth sample. The ADHD PRS positively associated with depression in a study of older adults⁴⁴. In a study of children, the ADHD PRS was positively associated with any anxiety or depressive disorder but there were some nonsignificant associations for specific disorders dependent on the type of diagnostic tool that was used⁶³. 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 depression⁶². The ADHD PRS also positively associated with a range of eating disorder traits in youth⁶¹.

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

1 methods, see Table 1). The other physical health phenotypes studied were height⁴⁴ (mixed
2 evidence), hypertension and blood cholesterol³² (no associations for either in PRS group
3 comparisons).
4
5

6
7 Socio-economic Status (SES). Four studies^{35,41,58,66} tested whether the PRS associated
8 with variables related to socioeconomic status. All studies showed a significant association
9 with the ADHD PRS being negatively associated with SES. The study by Selzam et al³⁵.
10 showed a significant negative association with SES in both their between and within family
11 design.
12
13
14
15
16
17

18
19 *Other (uncategorized) outcomes.* In terms of the nine uncategorized
20 outcomes^{29,35,41,42,49,58,67,68,69}, the ADHD PRS was positively associated with being bullied⁶⁹,
21 bullying chronicity⁶⁹ and a victimization adversity scale⁵⁸, a total adversity scale⁵⁸, earlier age
22 of onset of bipolar disorder²⁹, reduced participation in research studies⁶⁸, selected methylation
23 probes, reduced parental monitoring, and risk of parental mental disorder or substance use
24 disorder⁴¹. The ADHD PRS did not associate with infant neuromotor functioning⁴⁶,
25 community disadvantage and did not associate with ADHD traits in youth with mild traumatic
26 brain injury⁶⁷.
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 *Quality assessments*

42 Table 2 shows the items of the quality assessment (QA), and Table 3 the levels of
43 evidence. The results of the QA for each study are presented in Table 4. Three studies had
44 two biases, and five studies had one bias, leaving 36 studies without any notable bias. Studies
45 that did have one or two biases were randomly distributed across categories. Item K
46 (correction for age, gender, and socio-economic status) was rated most often as -/+ since the
47 majority of studies did not correct for socio-economic status and this criteria was not relevant
48 for the SES outcome category. Furthermore, sample sizes of target samples were in some
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 studies $n < 500$ which we considered small, although expected effect sizes may differ between
2 outcome measures.
3

4 The criteria from the best-evidence synthesis (Table 2) suggested that the evidence for
5 an association between the ADHD PRS and the following outcome categories was ‘strong’:
6 diagnosed ADHD, ADHD traits, brain-based imaging phenotypes, education, externalizing
7 behaviors, neuropsychological constructs, physical health and socioeconomic status. The
8 criteria from the best-evidence synthesis (Table 2) suggested that the evidence was
9 ‘inconclusive’ for the addiction, autism and autistic traits and mental health categories. The
10 ‘Other’ category was not included in the best-evidence synthesis.
11
12
13
14
15
16
17
18
19
20
21
22
23

24 INSERT TABLE 2

25
26 INSERT TABLE 3

27
28
29 INSERT TABLE 4
30
31
32
33

34 DISCUSSION

35
36 Overall, our literature review demonstrates that the ADHD PRS is reliable, robust, and
37 operates in a dose dependent manner. We found strong evidence from our best-evidence
38 synthesis that the common genetic variants underlying ADHD, as captured by the ADHD
39 polygenic risk score, associated with not only diagnosed ADHD but also with more
40 dimensional ADHD traits, more externalizing behaviors, impaired working memory and
41 education attainment, reduced brain volume, higher BMI and reduced SES. These findings
42 illustrate that the well-known phenotypic associations between ADHD and many of these
43 phenotypes, stemming from decades of research in epidemiology and developmental
44 psychology, may partly be explained by shared genetic effects. There is an emerging
45 literature, albeit not with conclusive evidence according to our best-evidence synthesis,
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 suggesting outcomes beyond childhood, such as addiction and adult mental health, may also
2 associate with the ADHD PRS. Some phenotypic outcomes are less researched than others;
3
4 this led to quite broad outcome categories in some instances (e.g., physical health) whereas
5
6 others were able to be more specific because of the larger literature (diagnosed ADHD;
7
8 ADHD traits, externalizing behaviors and addiction).
9
10

11
12
13
14
15
16
17 The ADHD PRS appears to carry a degree of specificity both in relation to other PRS's, in
18
19 terms of the wider context of neurodevelopment and mental health, and in its capacity to
20
21 significantly associate with only ADHD-relevant phenotypes. Illustrating this, some studies
22
23 used a multi-PRS model and found that the signal from the ADHD PRS remained significant
24
25 when controlling for other PRS's^{60,69,62}. In the wider context of neurodevelopment and mental
26
27 health, the ADHD PRS often did not associate with other conditions such as autism and
28
29 schizophrenia^{73,59,31,44} or family history for mental health conditions^{62,58}, and it only
30
31 associated with bipolar disorder when it co-occurred with ADHD²⁹. When studies included
32
33 negative control traits they invariably did not, as predicted, associate with the ADHD
34
35 PRS^{33,44}. Yet, there were also some surprising and novel cross-disorder findings: for example,
36
37 the ADHD PRS was associated with eating disorder traits in adolescents⁶¹. However, note that
38
39 the effect sizes of these eating disorder trait associations (.10-.13%) were at least five times
40
41 lower than the lowest estimated effect size for ADHD PRS associating with ADHD traits
42
43 (0.7%, the range being 0.7-3.3%). Thus, the literature supports the validity of the ADHD
44
45 PRS: the most consistent and strongest associations were with diagnosed ADHD and ADHD
46
47 traits.
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34 Within the studies on non-ADHD disorders, the ADHD PRS appears useful for predicting
35 trajectories. Specifically, the ADHD PRS appears to have transdiagnostic utility in
36 characterizing subgroups of individuals with early onset symptoms in non-ADHD conditions.
37 For example, while ADHD PRS did not associate with schizophrenia, within a schizophrenia
38 sample it associated with cognitive trajectory from adolescence into adulthood, being most
39 strongly associated with the subgroup with (earliest) preadolescent cognitive impairment⁵⁴.
40
41 The ADHD PRS did not associate with bipolar disorder, but it associated with an earlier age
42 of onset within bipolar disorder cases²⁹. Finally, the ADHD PRS associated with an early
43 onset depression trajectory class but not a later-onset depression trajectory class in youth
44 assessed longitudinally at ages 10 to 18 years⁶².

1 The ADHD PRS has been used in several studies to investigate gene-environment correlation,
2 namely, genetic influences on environmental exposure. Direct effects of the ADHD PRS are
3 reported on lower socioeconomic status³⁵, lower parental education and income⁴¹, worse labor
4 market outcomes⁶⁶, adversity⁵⁸ and bullying victimization^{69,58}. Two studies went beyond
5 direct genetic effects by applying within family analytic designs. De Zeeuw et al (2019) split
6 the ADHD PRS into transmitted and nontransmitted alleles to test for a process termed
7 “genetic nurture”^{34,122}. They did not find that the parents’ nontransmitted ADHD PRS (the
8 part of the ADHD PRS inherited by parents but not transmitted to their offspring), influenced
9 the offspring’s ADHD symptoms. Selzam et al’s more elaborate design involved splitting up
10 the covariance within their sample of twin siblings into between-family and within-family
11 effects³⁵. They conclude that some of the association between the ADHD PRS and
12 educational attainment might be due to passive gene-environment correlation effects. It is
13 important to note going forwards that part of the signal in a PRS may be correlated with
14 socioeconomic factors.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 The reviewed literature included multiple studies investigating PRS-brain-behavior pathways
40 relevant to ADHD. This new literature is worth highlighting in part because most attempts
41 pre-GWAS to link neuroimaging data simultaneously to both genetics and behavior was a
42 noble failure, beset with issues of multiple testing and low power^{123,124}. The studies in our
43 review demonstrate that reduced brain volume mediates the association between the ADHD
44 PRS and ADHD. For example, in one recent study, the ADHD PRS was negatively associated
45 with total brain volume and total brain volume accounted for 16% of the association between
46 ADHD PRS and ADHD diagnosis⁴⁹. Mediation was also employed successfully in other
47 categories. For example, in the neuropsychological category ⁶⁵, the association between the
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 adversity⁵⁸.

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 subgroups⁵⁵.

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 association¹²⁵. 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

1 diagnosed ADHD (e.g., ¹²⁶) and studies using older ADHD PRS (e.g. reviewed by ³³) and
2 studies using a cross-disorder PRS that includes the ADHD PRS. Not all of the 44 studies are
3 completely independent due to some partially or completely overlapping samples. For most
4 categories, every study was based on a different sample. However, it should be noted that
5 three of the 10 studies on mental health outcomes used the ALSPAC sample and two used the
6 CATSS sample. However, given that the evidence for the mental health category was mixed
7 and inconclusive, the repeated use of the ALSPAC and CATSS sample in this category does
8 not appear to have inflated the consistency of the evidence for these categories. In terms of
9 the other categories, two of the 16 ADHD trait studies and three of the eight studies on brain-
10 based outcomes employed the IMAGEN sample and two of the eight addiction studies
11 employed the Add Health sample. Lastly, we included studies based on clinical, enriched,
12 and population-based samples. We found no differences between the samples in their
13 associations with the outcome measures: In the outcome measures for which we observed
14 inconclusive results, (i.e., autism, addiction, and mental health) significant associations did
15 not cluster by sample type.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 While emphasizing the high quality of most of the reviewed literature and the strong evidence
40 that has emerged for associations of the ADHD PRS with outcomes, a number of limitations
41 and suggestions for improvements in this field of research are noted. Ideally, field standard
42 approaches in terms of the method of analyzing PRS's would be devised and pre-registration
43 is essential. At present, there are multiple approaches and methods which are only beginning
44 to be formally compared¹²⁷. The selected pT and the justifications for selection of pT varied
45 widely across studies: some selected $p < .05$ to avoid over-fitting, some selected the pT that
46 most accurately predicted ADHD in Demontis et al¹⁷, some use $pT=1$ to capture all variance,
47 and others applied ranges of multiple pT. When studies did not specify their selected p-value
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 threshold, we had to select one from which to report the results and this may exacerbate false
2 positives. A reference-standardized approach may be needed to compare PRS across different
3 target samples, to avoid factors often specific to the target sample influencing PRS, including
4 the variants considered, LD and allele frequency estimates¹²⁷. It will be exciting to see future
5 work that combines the ADHD PRS with rare variation and copy number variation or that
6 incorporates the sex chromosomes.
7
8
9
10
11
12

13
14
15
16
17 As shown in Table 1, the majority of this literature was conducted on European ancestry
18 samples: of the 44 studies, 77% (n =34 studies) had European ancestry, 91% (n = 41) had
19 most or all European ancestry, one study had missing ancestry and 5% (n=2) had non-
20 European ancestry participants (Japanese and African American, respectively). To maximize
21 the value of the data, some studies ran sensitivity analyses on their samples based on different
22 ancestral populations^{32,65}. Major initiatives in terms of both sample ascertainment and method
23 development are needed to ensure the genetic architecture of ADHD is understood regardless
24 of ancestry of the population under study¹²⁸. At present, the literature on the ADHD PRS only
25 offers partial insight globally because roughly only one in twenty studies on the current
26 ADHD PRS to date employs non-European ancestry participants.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 It is noted that some of the associations identified here are largely supported by studies
44 employing LD score regression as well as from past twin studies. LD score regression
45 provides an estimate of the degree of shared genetic effects in common genetic architecture.
46
47
48
49

50 PRS studies are distinguishable for several reasons, including that they allow tests for
51 association between ADHD and other phenotypes that currently lack a large GWAS.
52
53
54

55 Furthermore, as seen in this review, PRS can also easily be manipulated within more complex
56
57
58
59
60
61
62
63
64
65

1 analytic frameworks to test more complex hypotheses, such as analyses involving trajectory
2 modelling or mediation models.
3

4
5
6
7 In terms of individual prediction, the existing literature only goes so far as to compare groups
8 scoring high, medium and low on the ADHD PRS in a small number of our reviewed studies.
9

10 The ADHD PRS cannot yet accurately predict individual outcomes, and a PRS is only as
11 accurate as the discovery sample from which it is computed. Anyone who has used direct-to-
12 consumer testing can upload their genetic data on a new tool to calculate their own ADHD
13 PRS¹²⁹. Most individuals who score high on the current ADHD PRS will not develop ADHD
14 because the signal is too weak. There is a strong need for public engagement and public
15 debates on the clinical usability of PRS¹³⁰. It is possible that a more predictive ADHD PRS
16 will be used in the future, in combination with other known risk factors and clinical features,
17 to support health services with prediction, diagnosis and intervention¹³¹. As pointed out
18 elsewhere, there are some similarities between existing successful health screening practices -
19 - such as the newborn APGAR score and neonatal blood spot screening -- with how a PRS
20 would be obtained and could work in practice¹⁹.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 In sum, our review identified 44 relevant studies and demonstrates that strong evidence has
42 accumulated that the ADHD PRS associates with not only ADHD and ADHD traits, but also
43 reduced brain volume, lower education attainment, more externalizing behaviors, impaired
44 working memory, higher BMI and lower socioeconomic status. Alongside these direct effects,
45 the ADHD PRS is being used to reveal more complex processes such gene-environment
46 correlation and that the ADHD PRS influences ADHD symptoms via effects on brain
47 structure. Genetic associations that might have been expected based on past literature, such as
48 between the ADHD PRS and addiction, autism and mental health, are so far inconclusive
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 from the available evidence. In the context of other known risk factors for ADHD, the
2 ADHD PRS does not have the largest effect size. Nevertheless, the ADHD PRS brings
3 advantages in terms of being based on genetic variants, and thus being biologically-based,
4 possessing a degree of causality and being unchanging across the lifespan (unlike most other
5 risk factors). The estimated SNP heritability of ADHD is larger than the percent variance
6 explained by the current ADHD PRS. We can expect, therefore, that with a larger GWAS of
7 ADHD, a more accurate and predictive PRS will emerge going forward.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References:

1. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. *Lancet Lond Engl.* 2020;395(10222):450-462. doi:10.1016/S0140-6736(19)33004-1
2. Polderman TJC, Benyamin B, de Leeuw CA, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet.* 2015;47(7):702-709. doi:10.1038/ng.3285
3. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry.* 2019;24(4):562-575. doi:10.1038/s41380-018-0070-0
4. Pettersson E, Lichtenstein P, Larsson H, et al. Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls - CORRIGENDUM. *Psychol Med.* 2019;49(2):351. doi:10.1017/S0033291718002945
5. Ronald A, Larsson H, Anckarsäter H, Lichtenstein P. Symptoms of autism and ADHD: a Swedish twin study examining their overlap. *J Abnorm Psychol.* 2014;123(2):440-451. doi:10.1037/a0036088
6. Grove J, Ripke S, Als TD, et al. Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet.* 2019;51(3):431-444. doi:10.1038/s41588-019-0344-8
7. Stergiakouli E, Davey Smith G, Martin J, et al. Shared genetic influences between dimensional ASD and ADHD symptoms during child and adolescent development. *Mol Autism.* 2017;8:18. doi:10.1186/s13229-017-0131-2
8. Taylor MJ, Charman T, Ronald A. Where are the strongest associations between autistic traits and traits of ADHD? evidence from a community-based twin study. *Eur Child Adolesc Psychiatry.* 2015;24(9):1129-1138. doi:10.1007/s00787-014-0666-0
9. Ronald A, Edelson LR, Asherson P, Saudino KJ. Exploring the relationship between autistic-like traits and ADHD behaviors in early childhood: findings from a community twin study of 2-year-olds. *J Abnorm Child Psychol.* 2010;38(2):185-196. doi:10.1007/s10802-009-9366-5
10. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry.* 2008;49(5):535-542. doi:10.1111/j.1469-7610.2007.01857.x
11. Chang Z, Lichtenstein P, Larsson H. The effects of childhood ADHD symptoms on early-onset substance use: a Swedish twin study. *J Abnorm Child Psychol.* 2012;40(3):425-435. doi:10.1007/s10802-011-9575-6
12. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet.* 2019;51(2):237-244. doi:10.1038/s41588-018-0307-5
13. Eilertsen EM, Hannigan LJ, McAdams TA, et al. Parental Prenatal Symptoms of Depression and Offspring Symptoms of ADHD: A Genetically Informed Intergenerational Study. *J Atten Disord.* Published online April 26, 2020:1087054720914386. doi:10.1177/1087054720914386
14. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu, Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell.* 2019;179(7):1469-1482.e11. doi:10.1016/j.cell.2019.11.020
15. Hosang GM, Lichtenstein P, Ronald A, Lundström S, Taylor MJ. Association of Genetic and Environmental Risks for Attention-Deficit/Hyperactivity Disorder With Hypomanic Symptoms in Youths. *JAMA Psychiatry.* Published online August 14, 2019. doi:10.1001/jamapsychiatry.2019.1949
16. Visscher PM, Wray NR, Zhang Q, et al. 10 Years of GWAS Discovery: Biology,

Function, and Translation. *Am J Hum Genet.* 2017;101(1):5-22.

doi:10.1016/j.ajhg.2017.06.005

17. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* 2019;51(1):63-75. doi:10.1038/s41588-018-0269-7

18. Bogdan R, Baranger DAA, Agrawal A. Polygenic Risk Scores in Clinical Psychology: Bridging Genomic Risk to Individual Differences. *Annu Rev Clin Psychol.* 2018;14:119-157. doi:10.1146/annurev-clinpsy-050817-084847

19. Ronald A. Editorial: Polygenic scores in child and adolescent psychiatry - strengths, weaknesses, opportunities and threats. *J Child Psychol Psychiatry.* 2020;61(5):519-521. doi:10.1111/jcpp.13246

20. Wray NR, Lee SH, Mehta D, Vinkhuyzen AAE, Dudbridge F, Middeldorp CM. Research review: Polygenic methods and their application to psychiatric traits. *J Child Psychol Psychiatry.* 2014;55(10):1068-1087. doi:10.1111/jcpp.12295

21. Martin AR, Daly MJ, Robinson EB, Hyman SE, Neale BM. Predicting Polygenic Risk of Psychiatric Disorders. *Biol Psychiatry.* 2019;86(2):97-109. doi:10.1016/j.biopsych.2018.12.015

22. World Health Organizaton. ICF Browser. Published 2017. Accessed July 14, 2020. <https://apps.who.int/classifications/icfbrowser/>

23. World Health Organizaton. International Statistical Classification of Diseases and Related Health Problems 10th Revision. Published 2010. Accessed April 6, 2020. <https://icd.who.int/browse10/2010/en>

24. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med.* 2006;144(6):427-437. doi:10.7326/0003-4819-144-6-200603210-00010

25. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med.* 2013;158(4):280-286. doi:10.7326/0003-4819-158-4-201302190-00009

26. Anderson CA, Pettersson FH, Clarke GM, Cardon LR, Morris AP, Zondervan KT. Data quality control in genetic case-control association studies. *Nat Protoc.* 2010;5(9):1564-1573. doi:10.1038/nprot.2010.116

27. Kuijpers T, van der Windt DAWM, van der Heijden GJMG, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. *Pain.* 2004;109(3):420-431. doi:10.1016/j.pain.2004.02.017

28. Sackett DL, ed. *Evidence-Based Medicine: How to Practice and Teach EBM.* 2nd ed., reprinted. Churchill Livingstone; 2001.

29. Grigoriou-Serbanescu M, Giaroli G, Thygesen JH, et al. Predictive power of the ADHD GWAS 2019 polygenic risk scores in independent samples of bipolar patients with childhood ADHD. *J Affect Disord.* 2020;265:651-659. doi:10.1016/j.jad.2019.11.109

30. Hawi Z, Yates H, Pinar A, et al. A case-control genome-wide association study of ADHD discovers a novel association with the tenascin R (TNR) gene. *Transl Psychiatry.* 2018;8(1):284. doi:10.1038/s41398-018-0329-x

31. LaBianca S, LaBianca J, Pagsberg AK, et al. Copy Number Variants and Polygenic Risk Scores Predict Need of Care in Autism and/or ADHD Families. *J Autism Dev Disord.* Published online May 27, 2020. doi:10.1007/s10803-020-04552-x

32. Li JJ. The positive end of the polygenic score distribution for ADHD: a low risk or a protective factor? *Psychol Med.* Published online October 29, 2019:1-10. doi:10.1017/S0033291719003039

33. Vuijk PJ, Martin J, Braaten EB, et al. Translating Discoveries in Attention-Deficit/Hyperactivity Disorder Genomics to an Outpatient Child and Adolescent Psychiatric

Cohort. *J Am Acad Child Adolesc Psychiatry*. Published online August 14, 2019.

doi:10.1016/j.jaac.2019.08.004

34. de Zeeuw EL, Hottenga J-J, Ouwens KG, et al. Intergenerational Transmission of Education and ADHD: Effects of Parental Genotypes. *Behav Genet*. Published online February 6, 2020. doi:10.1007/s10519-020-09992-w

35. Selzam S, Ritchie SJ, Pingault J-B, Reynolds CA, O'Reilly PF, Plomin R. Comparing Within- and Between-Family Polygenic Score Prediction. *Am J Hum Genet*. 2019;105(2):351-363. doi:10.1016/j.ajhg.2019.06.006

36. Sudre G, Frederick J, Sharp W, et al. Mapping associations between polygenic risks for childhood neuropsychiatric disorders, symptoms of attention deficit hyperactivity disorder, cognition, and the brain. *Mol Psychiatry*. Published online January 30, 2019. doi:10.1038/s41380-019-0350-3

37. Hermosillo RJM, Mooney MA, Fezcko E, et al. Polygenic Risk Score–Derived Subcortical Connectivity Mediates Attention-Deficit/Hyperactivity Disorder Diagnosis. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2020;5(3):330-341. doi:10.1016/j.bpsc.2019.11.014

38. Burton CL, Wright L, Shan J, et al. SWAN scale for ADHD trait-based genetic research: a validity and polygenic risk study. *J Child Psychol Psychiatry*. Published online March 25, 2019;jcpp.13032. doi:10.1111/jcpp.13032

39. Taylor MJ, Martin J, Lu Y, et al. Association of Genetic Risk Factors for Psychiatric Disorders and Traits of These Disorders in a Swedish Population Twin Sample. *JAMA Psychiatry*. 2019;76(3):280. doi:10.1001/jamapsychiatry.2018.3652

40. Cabana-Domínguez J, Shivalikanjli A, Fernández-Castillo N, Cormand B. Genome-wide association meta-analysis of cocaine dependence: Shared genetics with comorbid conditions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;94:109667. doi:10.1016/j.pnpbp.2019.109667

41. Wimberley T, Agerbo E, Horsdal HT, et al. Genetic liability to ADHD and substance use disorders in individuals with ADHD. *Addiction*. 2020;115(7):1368-1377. doi:10.1111/add.14910

42. Rabinowitz JA, Musci RJ, Milam AJ, et al. The interplay between externalizing disorders polygenic risk scores and contextual factors on the development of marijuana use disorders. *Drug Alcohol Depend*. 2018;191:365-373. doi:10.1016/j.drugalcdep.2018.07.016

43. Gurriarán X, Rodríguez-López J, Flórez G, et al. Relationships between substance abuse/dependence and psychiatric disorders based on polygenic scores. *Genes Brain Behav*. 2019;18(3):e12504. doi:10.1111/gbb.12504

44. Du Rietz E, Coleman J, Glanville K, Choi SW, O'Reilly PF, Kuntsi J. Association of Polygenic Risk for Attention-Deficit/Hyperactivity Disorder With Co-occurring Traits and Disorders. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(7):635-643. doi:10.1016/j.bpsc.2017.11.013

45. Piasecki TM, Gizer IR, Slutske WS. Polygenic Risk Scores for Psychiatric Disorders Reveal Novel Clues About the Genetics of Disordered Gambling. *Twin Res Hum Genet*. 2019;22(5):283-289. doi:10.1017/thg.2019.90

46. Serdarevic F, Tiemeier H, Jansen PR, et al. Polygenic Risk Scores for Developmental Disorders, Neuromotor Functioning During Infancy, and Autistic Traits in Childhood. *Biol Psychiatry*. 2020;87(2):132-138. doi:10.1016/j.biopsych.2019.06.006

47. Alemany S, Jansen PR, Muetzel RL, et al. Common Polygenic Variations for Psychiatric Disorders and Cognition in Relation to Brain Morphology in the General Pediatric Population. *J Am Acad Child Adolesc Psychiatry*. 2019;58(6):600-607. doi:10.1016/j.jaac.2018.09.443

48. Albaugh MD, Hudziak JamesJ, Ing A, et al. White matter microstructure is associated

with hyperactive/inattentive symptomatology and polygenic risk for attention-deficit/hyperactivity disorder in a population-based sample of adolescents. *Neuropsychopharmacology*. 2019;44(9):1597-1603. doi:10.1038/s41386-019-0383-y

49. Mooney MA, Bhatt P, Hermosillo RJM, et al. Smaller total brain volume but not subcortical structure volume related to common genetic risk for ADHD. *Psychol Med*. Published online January 24, 2020:1-10. doi:10.1017/S0033291719004148

50. IMAGEN Consortium, Barker ED, Ing A, et al. Do ADHD-impulsivity and BMI have shared polygenic and neural correlates? *Mol Psychiatry*. Published online June 21, 2019. doi:10.1038/s41380-019-0444-y

51. Szekely E, Schwantes-An T-HL, Justice CM, et al. Genetic associations with childhood brain growth, defined in two longitudinal cohorts. *Genet Epidemiol*. 2018;42(4):405-414. doi:10.1002/gepi.22122

52. Shen C, Luo Q, Jia T, et al. Neural Correlates of the Dual-Pathway Model for ADHD in Adolescents. *Am J Psychiatry*. Published online May 7, 2020:appi.ajp.2020.1. doi:10.1176/appi.ajp.2020.19020183

53. Gialluisi A, Andlauer TFM, Mirza-Schreiber N, et al. Genome-wide association scan identifies new variants associated with a cognitive predictor of dyslexia. *Transl Psychiatry*. 2019;9(1):77. doi:10.1038/s41398-019-0402-0

54. Dickinson D, Zaidman SR, Giangrande EJ, Eisenberg DP, Gregory MD, Berman KF. Distinct Polygenic Score Profiles in Schizophrenia Subgroups With Different Trajectories of Cognitive Development. *Am J Psychiatry*. 2020;177(4):298-307. doi:10.1176/appi.ajp.2019.19050527

55. Nigg JT, Karalunas SL, Gustafsson HC, et al. Evaluating chronic emotional dysregulation and irritability in relation to ADHD and depression genetic risk in children with ADHD. *J Child Psychol Psychiatry*. 2020;61(2):205-214. doi:10.1111/jcpp.13132

56. Li JJ. Assessing phenotypic and polygenic models of ADHD to identify mechanisms of risk for longitudinal trajectories of externalizing behavior. *J Child Psychol Psychiatry*. 2019;60(11):1191-1199. doi:10.1111/jcpp.13071

57. Riglin L, Eyre O, Thapar AK, et al. Identifying Novel Types of Irritability Using a Developmental Genetic Approach. *Am J Psychiatry*. 2019;176(8):635-642. doi:10.1176/appi.ajp.2019.18101134

58. Zwicker A, MacKenzie LE, Drobinin V, et al. Neurodevelopmental and genetic determinants of exposure to adversity among youth at risk for mental illness. *J Child Psychol Psychiatry*. 2020;61(5):536-544. doi:10.1111/jcpp.13159

59. Ohi K, Nishizawa D, Shimada T, et al. Polygenic Risk Scores for Major Psychiatric Disorders Among Schizophrenia Patients, Their First-Degree Relatives, and Healthy Participants. *Int J Neuropsychopharmacol*. 2020;23(3):157-164. doi:10.1093/ijnp/pyz073

60. Riglin L, Thapar AK, Leppert B, et al. Using Genetics to Examine a General Liability to Childhood Psychopathology. *Behav Genet*. Published online December 11, 2019. doi:10.1007/s10519-019-09985-4

61. Yao S, Kuja-Halkola R, Martin J, et al. Associations Between Attention-Deficit/Hyperactivity Disorder and Various Eating Disorders: A Swedish Nationwide Population Study Using Multiple Genetically Informative Approaches. *Biol Psychiatry*. 2019;86(8):577-586. doi:10.1016/j.biopsych.2019.04.036

62. Rice F, Riglin L, Thapar AK, et al. Characterizing Developmental Trajectories and the Role of Neuropsychiatric Genetic Risk Variants in Early-Onset Depression. *JAMA Psychiatry*. 2019;76(3):306-313. doi:10.1001/jamapsychiatry.2018.3338

63. Martin J, Taylor MJ, Rydell M, et al. Sex-specific manifestation of genetic risk for attention deficit hyperactivity disorder in the general population. *J Child Psychol Psychiatry*. 2018;59(8):908-916. doi:10.1111/jcpp.12874

64. Torske T, Nærland T, Bettella F, et al. Autism spectrum disorder polygenic scores are associated with every day executive function in children admitted for clinical assessment. *Autism Res.* 2020;13(2):207-220. doi:10.1002/aur.2207
65. Nigg JT, Gustafsson HC, Karalunas SL, et al. Working Memory and Vigilance as Multivariate Endophenotypes Related to Common Genetic Risk for Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry.* 2018;57(3):175-182. doi:10.1016/j.jaac.2017.12.013
66. Rietveld CA, Patel PC. ADHD and later-life labor market outcomes in the United States. *Eur J Health Econ.* 2019;20(7):949-967. doi:10.1007/s10198-019-01055-0
67. Stojanovski S, Felsky D, Viviano JD, et al. Polygenic Risk and Neural Substrates of Attention-Deficit/Hyperactivity Disorder Symptoms in Youths With a History of Mild Traumatic Brain Injury. *Biol Psychiatry.* 2019;85(5):408-416. doi:10.1016/j.biopsych.2018.06.024
68. Taylor AE, Jones HJ, Sallis H, et al. Exploring the association of genetic factors with participation in the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol.* 2018;47(4):1207-1216. doi:10.1093/ije/dyy060
69. Schoeler T, Choi SW, Dudbridge F, et al. Multi-Polygenic Score Approach to Identifying Individual Vulnerabilities Associated With the Risk of Exposure to Bullying. *JAMA Psychiatry.* 2019;76(7):730. doi:10.1001/jamapsychiatry.2019.0310
70. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: Description and Initial Validation of an Integrated Assessment of Child and Adolescent Psychopathology. *J Child Psychol Psychiatry.* 2000;41(5):645-655. doi:10.1111/j.1469-7610.2000.tb02345.x
71. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry.* 1997;38(5):581-586. doi:10.1111/j.1469-7610.1997.tb01545.x
72. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* Fifth Edition. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596
73. Jansen AG, Dieleman GC, Jansen PR, Verhulst FC, Posthuma D, Polderman TJC. Psychiatric Polygenic Risk Scores as Predictor for Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in a Clinical Child and Adolescent Sample. *Behav Genet.* Published online July 25, 2019. doi:10.1007/s10519-019-09965-8
74. American Psychiatric Association, American Psychiatric Association, eds. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR.* 4th ed., text revision. American Psychiatric Association; 2000.
75. Achenbach TM, Rescorla L. *Manual for the ASEBA School-Age Forms & Profiles: An Integrated System of Multi-Informant Assessment.* ASEBA; 2001.
76. Harris KM. The Add Health Study: Design and Accomplishments. Published 2013. Accessed April 6, 2020. <https://www.cpc.unc.edu/projects/addhealth/documentation/guides/DesignPaperWIIV.pdf>
77. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas.* 1977;1(3):385-401. doi:10.1177/014662167700100306
78. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. *J Health Soc Behav.* 1983;24(4):385. doi:10.2307/2136404
79. Swanson J, Deutsch C, Cantwell D, et al. Genes and attention-deficit hyperactivity disorder. *Clin Neurosci Res.* Published online 2001:10.
80. Gioia GA, Isquith PK, Guy SC, Kenworthy L. TEST REVIEW Behavior Rating Inventory of Executive Function. *Child Neuropsychol.* 2000;6(3):235-238. doi:10.1076/chin.6.3.235.3152

81. Constantino JN. Social Responsiveness Scale. In: Volkmar FR, ed. *Encyclopedia of Autism Spectrum Disorders*. Springer New York; 2013:2919-2929. doi:10.1007/978-1-4419-1698-3_296
82. Simonds J, Rothbard MK. The Temperament in Middle Childhood Questionnaire (TMCQ): A Computerized Self-Report Instrument for Ages 7-10. Published online 2004.
83. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50(3):216-223. doi:10.1111/j.1469-7610.2008.01989.x
84. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet*. 2018;50(5):668-681. doi:10.1038/s41588-018-0090-3
85. Dumont R, Willis JO. Wide Range Achievement Test—Third Edition. In: Reynolds CR, Fletcher-Janzen E, eds. *Encyclopedia of Special Education*. John Wiley & Sons, Inc.; 2008:spced2214. doi:10.1002/9780470373699.spced2214
86. Wechsler D, ed. *Wechsler Adult Intelligence Scales-Fourth Edition*. 4th edition. Pearson; 2008.
87. Wechsler D. *The Wechsler Intelligence Scale for Children—Fourth Edition*. 4th Edition. PsychCorp; 2003.
88. Wechsler D. *Wechsler Individual Achievement Test—Third Edition*. 3rd Edition. Pearson; 2009.
89. The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder [published erratum appears in *Am J Psychiatry* 1993 Aug;150(8):1280]. *Am J Psychiatry*. 1993;150(6):885-890. doi:10.1176/ajp.150.6.885
90. Kiddie-Sads-Present and Lifetime Version (K-SADS-PL). Published online Version 1.0 of October1996. <http://www.wpic.pitt.edu/ksads>.
91. Skuse DH, Mandy WPL, Scourfield J. Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *Br J Psychiatry*. 2005;187(6):568-572. doi:10.1192/bjp.187.6.568
92. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology*. 1995;51(6):768-774.
93. Cito. Centrale Eindtoets. Published 2020. Accessed April 6, 2020. <https://www.cito.nl/onderwijs/primair-onderwijs/centrale-eindtoets>
94. Garner DM. *Eating Disorder Inventory-2: Professional Manual*. Psychological Assessment Resources; 1991.
95. Kessler RC. Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States: Results From the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8. doi:10.1001/archpsyc.1994.03950010008002
96. Substance Abuse and Mental Health Administration (SAMHSA). 2007 National Survey on Drug Use and Health Questionnaire. Published 2001. Accessed April 15, 2020. <http://datafiles.samhsa.gov/study/national-survey-drug-use-and-health-nsduh-2007-nid1353>
97. Capaldi DM, Patterson GR. *Psychometric Properties of Fourteen Latent Constructs from the Oregon Youth Study*. Springer New York; 1989. Accessed April 15, 2020. <http://dx.doi.org/10.1007/978-1-4612-3562-0>
98. American Community Survey 5-year estimates: 2005. United States Census Bureau. Published 2009. Accessed April 15, 2020. <http://www.census.gov/programssurveys/acs/data/summary-file.2009.html>.
99. Hansson SL, Svanströmrvall A, Rastam M, Gillberg C, Gillberg C, Anckarsäter H. Psychiatric telephone interview with parents for screening of childhood autism – tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): Preliminary reliability and validity. *Br J Psychiatry*. 2005;187(3):262-267. doi:10.1192/bjp.187.3.262
100. Reich W. Diagnostic Interview for Children and Adolescents (DICA). *J Am Acad*

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
- Child Adolesc Psychiatry*. 2000;39(1):59-66. doi:10.1097/00004583-200001000-00017
101. Nigg JT. The ADHD Response-Inhibition Deficit as Measured by the Stop Task: Replication With DSM-IV Combined Type, Extension, and Qualification. *J Abnorm Child Psychol*. 1999;27(5):393-402. doi:10.1023/A:1021980002473
102. Keilp JG, Herrera J, Stritzke P, Cornblatt BA. The continuous performance test, identical pairs version (CPT-IP) : III: Brain functioning during performance of numbers and shapes subtasks. *Psychiatry Res Neuroimaging*. 1997;74(1):35-45. doi:10.1016/S0925-4927(96)02881-8
103. De Luca CR, Wood SJ, Anderson V, et al. Normative Data From the Cantab. I: Development of Executive Function Over the Lifespan. *J Clin Exp Neuropsychol*. 2003;25(2):242-254. doi:10.1076/jcen.25.2.242.13639
104. Climie EA, Rostad K. Test Review: Wechsler Adult Intelligence Scale. *J Psychoeduc Assess*. 2011;29(6):581-586. doi:10.1177/0734282911408707
105. Fine EM, Delis DC. Delis–Kaplan Executive Functioning System. In: Kreutzer JS, DeLuca J, Caplan B, eds. *Encyclopedia of Clinical Neuropsychology*. Springer New York; 2011:796-801. doi:10.1007/978-0-387-79948-3_1539
106. Wing AM. Voluntary Timing and Brain Function: An Information Processing Approach. *Brain Cogn*. 2002;48(1):7-30. doi:10.1006/breg.2001.1301
107. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. 1998;26(4):257-268. doi:10.1023/a:1022602400621
108. Ronald A, Sieradzka D, Cardno AG, Haworth CMA, McGuire P, Freeman D. Characterization of psychotic experiences in adolescence using the specific psychotic experiences questionnaire: findings from a study of 5000 16-year-old twins. *Schizophr Bull*. 2014;40(4):868-877. doi:10.1093/schbul/sbt106
109. Mullins-Sweatt SN, Jamerson JE, Samuel DB, Olson DR, Widiger TA. Psychometric properties of an abbreviated instrument of the five-factor model. *Assessment*. 2006;13(2):119-137. doi:10.1177/1073191106286748
110. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
111. Wolke D, Woods S, Stanford K, Schulz H. Bullying and victimization of primary school children in England and Germany: Prevalence and school factors. *Br J Psychol*. 2001;92(4):673-696. doi:10.1348/000712601162419
112. Mooney MA, Ryabinin P, Wilmot B, Bhatt P, Mill J, Nigg JT. Large epigenome-wide association study of childhood ADHD identifies peripheral DNA methylation associated with disease and polygenic risk burden. *Transl Psychiatry*. 2020;10(1):8. doi:10.1038/s41398-020-0710-4
113. Blackwell TL. Test Review: Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). Woodcock-Johnson® III Test. Riverside Publishing Company. Itasca, IL. *Rehabil Couns Bull*. 2001;44(4):232-235. doi:10.1177/003435520104400407
114. Homack S, Riccio CA. Conners' Continuous Performance Test (2nd ed.; CCPT-II). *J Atten Disord*. 2006;9(3):556-558. doi:10.1177/1087054705283578
115. Touwen B. *Examination of the Child with Minor Neurological Dysfunction*. Heinemann; 1979.
116. Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *J R Soc Med*. 1992;85(7):399-402.
117. Kirby KN, Petry NM, Bickel WK. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol Gen*. 1999;128(1):78-87. doi:10.1037/0096-3445.128.1.78
118. D'Alberto N, Charani B, Orr CA, et al. Individual differences in stop-related activity

- are inflated by the adaptive algorithm in the stop signal task. *Hum Brain Mapp.* 2018;39(8):3263-3276. doi:10.1002/hbm.24075
119. Eysenck H, Eysenck S. *Manual for the Eysenck Personality Questionnaire (EPQ-R Adult)*. Hodder & Stoughton; 1994.
120. Thabrew H, Stasiak K, Bavin L-M, Frampton C, Merry S. Validation of the Mood and Feelings Questionnaire (MFQ) and Short Mood and Feelings Questionnaire (SMFQ) in New Zealand help-seeking adolescents. *Int J Methods Psychiatr Res.* 2018;27(3):e1610. doi:10.1002/mpr.1610
121. Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. PsychCorp; 1999.
122. Kong A, Thorleifsson G, Frigge ML, et al. The nature of nurture: Effects of parental genotypes. *Science.* 2018;359(6374):424-428. doi:10.1126/science.aan6877
123. Sullivan PF. Spurious genetic associations. *Biol Psychiatry.* 2007;61(10):1121-1126. doi:10.1016/j.biopsych.2006.11.010
124. Button KS, Ioannidis JPA, Mokrysz C, et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci.* 2013;14(5):365-376. doi:10.1038/nrn3475
125. Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet.* 2013;9(3):e1003348. doi:10.1371/journal.pgen.1003348
126. Brikell I, Larsson H, Lu Y, et al. The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. *Mol Psychiatry.* Published online June 22, 2018. doi:10.1038/s41380-018-0109-2
127. Pain O, Glanville KP, Hagenaars S, et al. *Evaluation of Polygenic Prediction Methodology within a Reference-Standardized Framework*. Genomics; 2020. doi:10.1101/2020.07.28.224782
128. Peterson RE, Kuchenbaecker K, Walters RK, et al. Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. *Cell.* 2019;179(3):589-603. doi:10.1016/j.cell.2019.08.051
129. Folkersen L, Pain O, Ingasson A, Werge T, Lewis CM, Austin J. *Impute.Me: An Open Source, Non-Profit Tool for Using Data from DTC Genetic Testing to Calculate and Interpret Polygenic Risk Scores*. Genetics; 2019. doi:10.1101/861831
130. Austin JC. Evidence-Based Genetic Counseling for Psychiatric Disorders: A Road Map. *Cold Spring Harb Perspect Med.* 2020;10(6):a036608. doi:10.1101/cshperspect.a036608
131. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* 2020;12(1):44. doi:10.1186/s13073-020-00742-5

Table 1: Description of included studies

Category	Study	Sample	ADHD PRS p-value threshold(s) (pT)	Outcome measures and covariates	Results
ADHDt, BRAIN	1. <i>Albaugh et al. 2019</i> ⁴⁸	<p>IMAGEN Study, France, UK, Ireland, Germany</p> <p>n=1471-1597 participants, age range: 12-16 years</p> <p>52% female, 48% male</p> <p>Population sample</p> <p>Western European ancestry</p>	PRS calculation based on pT= 0.05	<p>MRI: neuroanatomic imaging, and imaging of white matter tract microstructure correlates of ADHD symptomatology</p> <p>ADHD traits: composite score of the Development and Well-Being Assessment (DAWBA)⁷⁰ and the Strengths and Difficulties Questionnaire⁷¹ (SDQ)</p> <p>Covariates: Age, sex, site, socioeconomic status, pubertal stage, total brain volume, PCs</p>	<p>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 ($r = 0.137$, $p < 0.001$).</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>ADHD PRS not associated with cortical thickness in the cortical areas that were significantly associated with ADHD traits</p>

					Statistical thresholds were $p < .05$ family-wise error corrected and brain data was threshold-free cluster enhancement corrected.
ADHDt, OTHER	2. <i>Stojanovski et al. 2019</i> 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 ($t_{1224} = 3.5, \Delta R^2 = .009\%, p = .004$) and no association with ADHD symptom score in those with mild TBI ($t_{196} = 20.4, \Delta R^2 = 2.004\%, p = .70$). 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.

<p>ADHD, ASD</p>	<p>3. Jansen et al. 2019⁷³</p>	<p>Inside Out Sample, The Netherlands</p> <p>Clinical sample age range: 2–18 years (mean: 9.06, SD: 2.66)</p> <p>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.</p> <p>All European Ancestry</p> <p>Control sample from the Netherlands, n= 943, age range</p>	<p>PRS calculation based on eight pT (0.01 - 1)</p>	<p>DSM-IV⁷⁴ ADHD diagnosis, ASD diagnosis, and combined(either ASD, ADHD or both diagnoses)</p> <p>Parent-rated Child Behavior Check- list/6–18 (CBCL)⁷⁵.</p> <p>Covariates: Age, PCs</p>	<p>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.</p> <p>Planned sensitivity analyses between ADHD symptom severity scales and PRS were not run due to low correlations.</p> <p>Significance threshold was $p < .05$ Bonferroni corrected for 72 tests.</p>
-------------------------	---	---	---	--	--

		17-79 years, 37% male, 63% female.			
ADHD, ADDICTION, EA, MH, PHYSICAL	4. Li 2019 ³²	<p>National Longitudinal Study of Adolescent to Adult Health (Add Health), USA</p> <p>7088 participants, mean age: 29.00 years (SD: 1.74)</p> <p>54% female, 46% male</p> <p>Population sample</p> <p>63.6% Caucasian (including Hispanic), 20.7% African American, 0.2% Native American, 5.1% Asian, and 10.3% 'Other.'</p>	<p>PRS calculation based on $pT= 1$. PRS groups defined as low (<20th percentile), medium (21st–70th percentiles), and high (>80th percentile) compared on outcomes</p>	<p>ADHD diagnosis based on retrospectively self-reported ADHD symptoms keyed to the DSM-IV⁷⁴.</p> <p>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.</p> <p>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').</p> <p>Cognitive ability, measured by Add Health Picture Vocabulary Test (AHPVT)⁷⁶.</p>	<p>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 $p < .005$.</p> <p>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 $p < .005$).</p> <p>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.</p> <p>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.</p> <p>Bonferroni corrected significance threshold of $p < .005$ applied throughout.</p> <p>Secondary analyses demonstrated consistent results in European-ancestry subsample of total sample.</p>

				<p>Mental health, measured by diagnoses based on the DSM-IV⁷⁴, the Center for Epidemiologic Studies Depression (CES-D) Scale⁷⁷, and an abbreviated 4-item version of the Cohen's Perceived Stress Scale⁷⁸. Also, it was asked whether participant was 'ever arrested'.</p> <p>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.</p> <p>Covariates: age, sex PCs</p>	
ADHDt	5. <i>Burton et al. 2019</i> ³⁸	<p>Spit for Science sample, USA</p> <p>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</p>	<p>PRS calculation based on 10 pT (0.00001 - 0.5)</p> <p>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</p>	<p>Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) score⁷⁹: Total, inattentive and hyperactive/impulsive subscales.</p> <p>ADHD PRS was significantly associated with SWAN total score (b= .005, p = 1.7 x 10⁻¹¹, R² = .009), separately for parent-report (b= .0045, p = 9.0 x 10⁻⁹, R² = .009) and self-report (b= .042, p = 6 x 10⁻⁴, R² = .016) and separately for inattentive (b= .004, p = 1.6 x 10⁻¹⁰, R² = .008) and hyperactive/impulsive subscales (b= .004, p = 1.3 x 10⁻⁹, R² = .007). The association with the total score was still significant after excluding individuals with an ADHD community diagnosis.</p> <p>Comparisons of ADHD PRS in the categorized SWAN-scoring groups showed low<high, medium<high but low=medium.</p> <p>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.</p> <p>Significance threshold corrected for multiple testing throughout.</p>	

		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. <i>Gialluisi et al. 2019</i> 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%, $p \sim [10^{-5} - 10^{-7}]$). ADHD PRS was not significantly associated with the other 5 outcomes. A significance threshold of 6.94×10^{-5} was applied to correct for multiple testing due to multiple other PRS being tested in parallel.
SES	7. <i>Rietveld</i>	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

	<p><i>& Patel 2019</i>⁶⁶</p>	<p>Retirement Study (HRS), USA</p> <p>N=9033 including participants and spouses, age range: 50-65 years</p> <p>54% female, 46% male</p> <p>Population sample</p> <p>European Ancestry</p>		<p>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.</p> <p>Educational attainment included as mediator and measured by years of education.</p> <p>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</p>	<p>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).</p> <p>For all six outcomes, some of the association was reduced when educational attainment was added as a mediator.</p> <p>Most results were highly consistent when split by sex and when split by assessments conducted at ages 50-55 and 50-59 years.</p> <p>A significant threshold of $p < .05$ was applied.</p>
<p>ADDICTI ON</p>	<p>8. <i>Piasecki et al. 2019</i>⁴⁵</p>	<p>National Longitudinal Study of Adolescent to Adult Health, USA</p> <p>5215 unrelated participants, age range 24–34 years. Sex</p>	<p>PRS calculation based on $pT = 1$</p>	<p>Gambling behavior and disordered gambling</p> <p>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</p>	<p>ADHD PRS was not associated with either gambling behavior or disordered gambling.</p> <p>Significance threshold of $p < .05$ was applied.</p>

	<p>ratio not provided.</p> <p>Population sample</p> <p>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</p>		<p>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?"</p> <p>Covariates: age, sex, PCs</p>	
--	--	--	---	--

<p>ASDt, NEUROPSYCH</p>	<p>9. <i>Torske et al. 2019</i>⁶⁴</p>	<p>BUPGEN network, Norway</p> <p>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.</p> <p>24% female, 76% male</p> <p>Clinical sample</p> <p>European Ancestry</p>	<p>PRS calculation based on pT= 0.1</p>	<p>Diagnosis based on Autism Diagnostic Observation Schedule (ADOS), and/or the Autism Diagnostic Interview-Revised (ADI-R)</p> <p>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.</p> <p>Social function was assessed using the Social Responsiveness Scale, a 65-item questionnaire⁸¹.</p> <p>Covariates: age, sex, PC's</p>	<p>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).</p> <p>Significance threshold of p<.05 was applied.</p>
<p>ADHD, ADHDt, EXTERNALISING</p>	<p>10. <i>Nigg et al. 2020</i>⁵⁵</p>	<p>Community recruited children, USA</p> <p>ADHD sample: 337 participants,</p>	<p>PRS calculation based on seven pT (5x10⁻⁸ - 1)</p>	<p>A diagnostic evaluation using standardized, well-normed rating scales from parent and teacher, parent semistructured clinical interview, child intellectual testing, and clinical</p>	<p>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; $\Delta R^2 = .029$, p < .0001), irritability (b = .183, 95% CI = 0.087–0.280; $\Delta R^2 = .034$, p < .0002) and also with surgency/sensation seeking (B = .146, 95%CI = 0.052–0.240, $\Delta R^2 = .022$, p = .002). These associations had adjusted for the major depression PRS⁸⁴ and for the sadness-</p>

	<p>28% female, 72% male</p> <p>Controls: 177 participants, 46% female, 54% male</p> <p>Age range 7-11 years</p> <p>Community sample enriched for children with ADHD</p> <p>Northern European Ancestry</p>	<p>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.</p> <p>Dimensional score on an ADHD latent variable captured from hyperactivity and inattention subscales of four published ADHD scales.</p> <p>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 score⁸³.</p> <p>Latent variables were also created for surgency-approach and sadness-anxiety</p> <p>A person-centred approach compared different group definitions of ADHD with</p>	<p>anxiety scores and their association with ADHD. The ADHD PRS was not associated with the sadness/anxiety latent variable.</p> <p>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, $\Delta R^2 = .033$ $p = .0004$). The emotion dysregulation ADHD group had elevated ADHD PRS versus other ADHD children (OR = 1.44, 95% CI = 1.03–2.20, Nagelkerke $\Delta R^2 = .013$, $p = .033$) but the ADHD PRS did not differentiate irritable or other ADHD profiles.</p> <p>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.</p> <p>Significance threshold of $p < .01$ was applied.</p>
--	---	--	--

				and without irritability and emotion dysregulation	
				Covariates: sex, age, lifetime mood disorder and PCs	
EA, MH	11. <i>Dickinson et al. 2019</i> ⁵⁴	<p>National Institute of Mental Health Clinical Center, USA</p> <p>540 participants with DSM-IV schizophrenia disorders, mean age 34.1 years (10.1 sd). 24.6% female, 75.4% male</p> <p>247 siblings with no history of psychotic disorder (limited to one per family), 52.6% female, 47.4% male.</p> <p>844 community control participants, 53.8% female, 46.2% male</p> <p>Clinical sample</p>	<p>PRS calculation based on 10 pT reduced to a single score through principal components</p> <p>Analyses repeated with the 10 pT (0.0001-0.5)</p>	<p>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).</p> <p>Wide-Range Achievement Test [WRAT] reading subtest⁸⁵ and Wechsler Adult Intelligence Scale [WAIS]⁸⁶ used for cognitive assessments.</p> <p>Covariates: sex, age, PC's</p>	<p>The ADHD PRS did not differ significantly between schizophrenia patients, siblings and controls.</p> <p>Within the participants with schizophrenia, the ADHD PRS showed significant association with cognitive trajectory group (F=5.1 df = 2,525 p = 0.007, R² = 0.019%). Pairwise comparisons showed PI>AD=CS (at p<.05).</p> <p>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.</p>

		European Ancestry			
ADDICTI ON	12. Cabana-Dominguez 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 ($1 \times 10^{-4} - 1$) 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

		<p>schizophrenia, 38.2% female, 61.8% male, mean age: 42.9 SD: 13.1 years</p> <p>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,</p> <p>146 controls, 33.3% female, 66.6% male, mean age: 37.2 SD: 14.1 years</p> <p>Clinical sample</p> <p>Japanese descent</p>		Covariates: PC's	
BRAIN	14. Mooney et al. 2020 ⁴⁹	<p>312 Participants, age range: 7–15 years (mean age: 10.2 years), USA</p> <p>ADHD sample: n= 199 (30% female, 70%</p>	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	<p>ADHD PRS was negatively associated with TBV [$\beta = -0.147$ (-0.27 to -0.03)] and this remained significant after controlling for ADHD diagnosis.</p> <p>TBV accounted for 16% of the association between ADHD PRS and ADHD diagnosis after accounting for sex and age.</p> <p>ADHD PRS was not significantly associated with subcortical brain structures</p>

		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 [$\beta = 0.224$ (0.09–0.36)]. FDR correction ($\alpha = 0.05$) for the 9 volumes tested
ADHD, ADHDt, ADDICTI ON, ASDt, EA, EXTERN ALISING, NEUROPSYCH	15. Vуйjk 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,

		<p>Axis 1 diagnoses</p> <p>37.2% female, 62.8% male</p> <p>Clinical sample</p> <p>Second sample for replication: n=5,140 19-60 year old adult patients from a local health system biobank</p> <p>European ancestry</p>		<p>Achievement Test–Third Edition⁸⁸ (WIAT-III).</p> <p>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.</p> <p>Covariates: age, sex, genotyping wave (in biobank analyses), PCs</p>	<p>Pseudo R² 0.42%, p = .0028) reduced likelihood of college completion (OR 1.23, 95% CIs 1.12 – 1.35, Pseudo R² 0.72%, p <.0001) and substance use disorder (OR 1.18, 95% CIs 1.10 – 1.26, Pseudo R² 0.40%, p <.0001).</p> <p>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.</p> <p>Bonferroni correction for multiple outcomes</p>
ADHDt, EXTERN ALISING	16. Li 2019 ⁵⁶	<p>National Longitudinal Study of Adolescent to Adult Health (Add Health), USA</p> <p>7,674 participants, age 7-12 (wave 1) age range 18-32 years (later waves).</p> <p>54% female, 46% male</p>	<p>PRS calculation based on pT= 1</p>	<p>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.</p> <p>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</p>	<p>ADHD PRS correlated .084 with ADHD symptoms (p<.01)</p> <p>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.</p> <p>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.</p> <p>Significance threshold was p<.05.</p>

		<p>Population sample</p> <p>63.2% Caucasian, 21.2% African-American, 5.1% Asian, and 10.6% Hispanic.</p>		<p>ADHD assessed retrospectively with DSM-IV items at Wave 3.</p> <p>Covariates: PCs, sex, age, highest level of education, income</p>	
EXTERN ALISING	17. <i>Riglin et al. 2019</i> ⁵⁷	<p>Avon Longitudinal Study of Parents and Children (ALSPAC), UK</p> <p>7924 participants, age range 7-15 years.</p> <p>Population sample</p> <p>European ancestry</p>	<p>PRS calculation based on pT=.05 in primary analyses; analyses repeated on multiple thresholds</p>	<p>Growth mixture modelling gave 5 distinct irritability trajectory classes: low, decreasing, increasing, late-childhood limited, and high-persistent</p> <p>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.</p> <p>DAWBA also used to diagnose ADHD, oppositional defiant disorder, conduct disorder, generalized anxiety disorder and depression</p>	<p>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.</p> <p>Results were consistent when sex was controlled for and when individuals with diagnoses were excluded. PCs were not controlled for.</p> <p>Significance threshold was p<.05.</p>

<p>ADHD, MH, OTHER</p>	<p>18. <i>Grigori u- Serbane scu et al. 2019</i>²⁹</p>	<p>Romania and UK case-control samples.</p> <p>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.</p> <p>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.</p> <p>Romanian and UK sample</p>	<p>PRS calculation based on 10 pT (0.01-0.5)</p>	<p>Bipolar disorder in the UK sample was assessed using the ICD-10, and in the Romanina sample with DSM-IV⁷⁴ criteria, based on Diagnostic Interview for Genetic Studies (DIGS) and medical records.</p> <p>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-SADS⁹⁰ clinical interview. Assessment of childhood ADHD was made by clinicians.</p> <p>Earl- and late-onset BP defined as age of onset under or over 22 years, respectively.</p> <p>No covariates</p>	<p>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).</p> <p>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).</p> <p>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).</p> <p>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.</p> <p>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).</p> <p>Results given here for most significant PRS pT.</p> <p>FDR correction was used to adjust significance for multiple testing.</p>
---------------------------------------	---	---	--	---	---

		<p>results were meta-analysed.</p> <p>Clinical sample</p> <p>European ancestry</p>			
ADDICTION, EXT, OTHER, SES	19. <i>Wimberley et al. 2019</i> ⁴¹	<p>IPSYCH Sample, Denmark, born 1981-2003.</p> <p>13116 participants with ADHD, 26% female, 74% male</p> <p>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).</p> <p>Clinical sample from population cohort.</p> <p>Due to overlap with Demontis et al¹⁷ discovery</p>	<p>PRS calculation based on pT 0.2</p>	<p>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.</p> <p>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.</p> <p>Covariates: observation time (to account time at risk for SUD given varying ages of participants), sex, age and calendar</p>	<p>ADHD PRS were associated with any SUD (OR = 1.30, 95% CI: 1.11–1.51; Nagelkerke R²= .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).</p> <p>Stratified by sex, the point estimate for the ADHD PRS-SUD association was higher in females but CIs overlapped with CIs for males.</p> <p>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.</p> <p>Sensitivity analyses repeated with different pT, different assumed prevalences of ADHD and SUD, and variation in population structure showed similar results.</p> <p>Significance threshold was Bonferroni corrected to p<.007</p>

		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.		year at first ADHD diagnosis and PCs	
		European Ancestry			
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.

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

<p>ADHDt, EA</p>	<p>22. De Zeeuw et al. 2019³⁴</p>	<p>The Netherlands Twin Register (NTR)</p> <p>Trios (i.e. one offspring and both parents). N = 1120–2518</p> <p>Population sample</p> <p>European ancestry</p>	<p>PRS based on transmitted and nontransmitted alleles for eight pT (0.0001 - 0.5)</p>	<p>ADHD symptoms (CBCL and TRF Attention Problems scale⁷⁵) were assessed at age 10 or 12 years.</p> <p>Academic achievement was assessed with the Cito score, a Dutch nationwide standardized educational achievement test⁹³</p> <p>Educational attainment in adults assessed as self-reported highest degree.</p> <p>Covariates: sex, year of birth (only for EA), the interaction between sex and year of birth (only for EA), PCs, genotyping platform.</p>	<p>EA PRS and ADHD PRSs correlated for both the transmitted and non-transmitted PRS ($r = -0.27$ and $r = -0.23$, respectively).</p> <p>ADHD transmitted and nontransmitted PRS were not significantly associated with academic achievement ($R^2 \sim 0.6\%$). ADHD transmitted PRS was associated with ADHD symptoms ($R^2 = 1-2\%$).</p> <p>The transmitted ADHD PGS was associated with ADHD symptoms at home ($\beta = 0.17$ CIs .12-.21, $R^2 = 2.7\%$, $p = 2 \times 10^{-13}$) and at school ($\beta = 0.13$ CIs .08-.17, $R^2 = 1.6\%$, $p = 3 \times 10^{-7}$) but not with academic achievement ($\beta = -0.08$ CIs -.14--0.01, $R^2 = .6\%$, $p = 0.022$). 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.</p> <p>The non-transmitted ADHD PGS was not associated with any of above three the outcomes.</p> <p>Significance threshold of $p < .01$ employed.</p>
-----------------------------	--	--	--	--	---

MH	23. Yao <i>et al.</i> 2019 ⁶¹	<p>Child and Adolescent Twin Study in Sweden (CATSS)</p> <p>N = 13,472 participants, assessed at age 15 years.</p> <p>Population sample</p> <p>European ancestry</p>	<p>PRS calculation based on pT <1 for primary analyses, and on seven pT (0.00001 - 1) for sensitivity analyses</p>	<p>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</p> <p>Covariates: sex, birth year, and PCs</p>	<p>ADHD PRS was associated with the EDI-2 full scale (b = .027, 95% CI = .005, .049, R² = .0012%, p = .015) and subscales Drive for Thinness (b = .032, 95% CI = .005, .059, R² = .0010%, p = .022) and Body Dissatisfaction (b = .042, 95% CI = .011, .072, R² = .0013%, p = .007) but not the Bulimia subscale (b = .004, 95% CI = -.013, .021, R² = .0000% p = .654).</p> <p>Results were consistent at other pT; significant sex differences were not significant.</p> <p>Significance threshold was p<.05</p>
ADDICTION, OTHER	24. Rabino <i>witz et al.</i> 2018 ⁴²	<p>Sample from urban school district in the Mid-Atlantic region, USA</p> <p>N = 1,050 participants</p> <p>56% female, 44% male</p> <p>Population sample</p> <p>African American</p>	<p>PRS calculation based on pT < 0.05</p>	<p>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.</p> <p>The Structured Interview of Parent Management Skills and Practices Youth-Version (SIPMSP)⁹⁷ was used to assess parental</p>	<p>The ADHD PRS correlated negatively with parental monitoring (r = -.07, p<.05) but was not significantly correlated with community disadvantage (r = -.04, p>.05).</p> <p>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.</p> <p>Significance threshold was p<.05</p>

				<p>monitoring (proximal contextual factor).</p> <p>The community disadvantage score was calculated using census-tract level items from the 1990 and 2000 Decennial census⁹⁸ (distal contextual factor).</p> <p>Covariates: PCs</p>	
ADHDt	25. <i>Taylor et al. 2019</i> ⁹⁹	<p>Child and Adolescent Twin Study in Sweden (CATSS)</p> <p>13 391 participants</p> <p>50% females, 50% male</p> <p>Population sample</p> <p>European ancestry</p>	<p>PRS calculation based on pT 0.5. Analyses repeated on 5 other pT</p>	<p>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</p> <p>Covariates: sex, age, PCs</p>	<p>ADHD PRS was associated with ADHD traits at ages 9 and 12 years (β [SE] = 0.27 [0.03], $R^2 = 8.4 \times 10^{-3}$, p-value 5.9×10^{-19}) and ADHD trait subscales hyperactivity/impulsivity (β [SE] = 0.14 [0.02], $R^2 = 7.7 \times 10^{-3}$, p-value 1.9×10^{-19}) and inattention (β [SE] = 0.13 [0.02], $R^2 = 6.0 \times 10^{-3}$, p-value 2.9×10^{-15})</p> <p>After excluding children with ICD-10 diagnosed ADHD, ADHD PRS was still associated with ADHD traits (β [SE] = 0.21 [0.03], $R^2 = 6.2 \times 10^{-3}$, p-value 2.2×10^{-13}) and the ADHD subscales.</p> <p>FDR-corrections applied to adjust for multiple testing.</p>
ADHDt, BRAIN	26. <i>Aleman y et al. 2019</i> ⁴⁷	<p>Generation R Study, The Netherlands</p> <p>1053-1139 participants, the mean age: 10.16, SD: 0.60, age</p>	<p>PRS calculation based on six pT "priors" (0.01 - infinitesimal)</p>	<p>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),</p>	<p>ADHD PRS was associated with attention problems subscale ($b = 0.12$, SE 0.00, $p = 5.36 \times 10^{-5}$).</p> <p>ADHD PRS was associated with smaller caudate volume (result for strongest prior: ($b = -0.08$, SE 0.03, $p_{uncorrected} = 7.49 \times 10^{-4}$) across all priors except prior 1 at $p < .05$ and one prior was significant after FDR correction.</p>

		<p>range: 8.72–11.9 years.</p> <p>49% female, 51% male</p> <p>Population sample</p> <p>European ancestry</p>		<p>total white matter, subcortical GM, ventricular volume, cerebellum, amygdalahippocampus complex, caudate, putamen and thalamus (final 3 are subcortical brain volumes)</p> <p>Assessed on CBCL⁷⁵ attention problems subscale at ages 8-11 years</p> <p>Covariates: sex, age, total intracranial volume (for all except TBV analysis), PCs</p>	<p>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.</p> <p>ADHD PRS was associated with smaller TBV (result for strongest prior: $\beta = -0.07$, SE 0.03, $p_{uncorrected} = .006$) across all priors except prior 0.01 at $p < .05$, but none significant after FDR correction.</p> <p>FDR correction at $p < .05$ used as significance threshold.</p>
ADDICTI ON	27. Gurriarán et al. 2018 ⁴³	<p>Sample from the Addictive Disorders Assistance Units from Galicia health care areas, Spain</p> <p>N= 534 substance abuse/dependence patients (mean age 44.89, SD 9.73)</p> <p>13% female, 87% male</p> <p>n = 587 Control subjects recruited from blood donors at</p>	<p>PRS calculation based on six pT (0.001 - 1)</p>	<p>DSM-IV⁷⁴ criteria for substance use disorder.</p> <p>Covariates: sex, age, PCs</p>	<p>ADHD PRS was not associated with substance use disorders after multiple testing correction (Pseudo $R^2 \sim 0.4$, $p < .05$, $p > 0.002$) Results similar when MHC included.</p> <p>Permutation based p-value of $P < 0.0022$ employed.</p>

		<p>Santiago de Compostela, Galicia. Mean age 40.26 (SD: 10.70; range: 18-65). Not checked for substance use</p> <p>50% female, 50% male</p> <p>Clinical sample</p> <p>European ancestry</p>			
BRAIN	28. <i>Szekely et al. 2018</i> ⁵¹	<p>The LONG Cohort, USA</p> <p>119 cases, 339 controls</p> <p>Mean age at first scan 11.47 years, SD 3.54; mean age at second scan 16.13 years, SD 4.72.</p> <p>41% female, 59% male</p> <p>Population sample</p>	<p>PRS calculation based on seven pT (0.0005 – 0.5)</p>	<p>ADHD ascertained using clinician-administered Parent Diagnostic Interview for Children and Adolescents¹⁰⁰.</p> <p>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.</p> <p>Covariates: adjusted for age at baseline scan, interscan interval, sex and PCs</p>	<p>ADHD PRS was not associated with any brain growth phenotypes (all $P > 0.1$).</p> <p>Significance threshold not reported.</p>

		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	<p>Community recruited sample, USA</p> <p>European-only sample n = 514 (337 ADHD, 71% male; 177 non-ADHD, 52% male) age range: 7-11 years</p> <p>Full sample n = 656</p> <p>22% non-European, 78% European ancestry</p> <p>Community sample enriched for children with ADHD</p>	<p>PRS calculation based on pT 0.5</p> <p>Results checked for another 6 pT</p>	<p>ADHD diagnoses made using DSM-IV criteria and a best estimate procedure.</p> <p>Separate parent and teacher-rated ADHD symptom latent variables derived from data on 3-4 published ADHD measures that capture inattention and hyperactivity.</p> <p>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.</p> <p>Covariates: sex, age, PCs</p>	<p>ADHD PRS was associated with ADHD diagnosis (Nagelkerke R² =0.045%; b = 0.233, SE = 0.053, p = .000011) and both parent and teacher-rated ADHD symptom latent variables (R² =0.033%; b = 0.185, SE = 0.043 p = 1.69E-05 and R² =0.027%; b = 0.165, SE = 0.042, p = 8.55E-05 respectively).</p> <p>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.</p> <p>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.</p> <p>Direct PRS tests had a Hochberg correction p<.05. Mediation models used p<.05.</p> <p>Analyses repeated including non-European LONG sample participants, and changing the discovery sample to be European-only, both led to similar conclusions.</p>

ADHD	30. <i>Hawi et al. 2018</i> ⁸⁰	<p>Participants recruited in Australia, UK and Ireland.</p> <p>N = 480 ADHD cases aged 5-18 years (mean age = 10.27 years, SD= 3.03). 13% female, 87% male</p> <p>N = 1208 controls, age 7-60 years (mean age = 20.61 years, SD= 6.76) 51% female, 49% male</p> <p>European ancestry</p>	1000 pT from 0.0005 to 0.5	<p>ADHD status using DSM-IV criteria determined with parental semi-structured interview and the Conners' Parent Rating Scale¹⁰⁷</p> <p>Covariates: gender, age² , age x gender, PCs</p>	<p>ADHD PRS explained 3.25% variance in ADHD case-control status (Nagelkerke' s R² = 0.03, p = 7.6E- 15)</p> <p>Significance threshold p=.001 applied.</p>
OTHER	31. <i>Taylor et al. 2018</i> ⁶⁸	<p>Avon Longitudinal Study of Parents and Children (ALSPAC), UK</p> <p>7486 mothers, 7508 children</p> <p>Population sample</p>	PRS calculation based on 5 pT (0.0005 – 0.5) as well as just genome-wide significant SNPs	<p>9 participation phenotypes derived. Participation defined as responding to a questionnaire or attending a clinic for which the whole cohort was eligible to participate.</p> <p>Continuous phenotypes calculated by summing the number of questionnaires/clinics completed and or clinics attended</p>	<p>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).</p> <p>Significance threshold not given: results reported as effect sizes.</p>

		European ancestry		Covariates: child sex, PCs	
ADHDt, EA, PHYSICAL, MH, SES	32. Selzam <i>et al.</i> 2019 ³⁵	<p>Twins Early Development Study, UK</p> <p>789-2962 dizygotic (DZ) twin pairs, assessed from 12-21 years.</p> <p>Population sample</p> <p>European ancestry</p>	<p>PRS calculation based on pT 1 (using a prior)</p>	<p>Parents reported on twins' ADHD traits via the Strength and Difficulties Questionnaire⁷¹ hyperactivity subscale and the Conners' rating scales¹⁰⁷ at ages 12 and/or 16 years.</p> <p>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.</p> <p>BMI and height were self-reported.</p> <p>IQ involved verbal and nonverbal ability using WISC-III assessments.</p> <p>Psychotic experiences assessed using the Specific Psychotic Experiences Questionnaire¹⁰⁸ at age 16.</p>	<p>The ADHD PRS effect was split into between family and within family effects using DZ twin data.</p> <p>The between family ADHD PRS effect, which is estimated independent of the within family effect, significantly predicted more ADHD traits ($b = .11$, CI $.08-.14$; $p = 6.8 \times 10^{-9}$), higher BMI ($b = .07$, CI $.03-.11$; $p = .008$), lower IQ ($b = -.09$, CI $-.12--.05$; $p = 4.5 \times 10^{-4}$) and lower GCSEs ($b = -.18$, CI $-.21--.15$; $p = 7.3 \times 10^{-17}$).</p> <p>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 $-.10--.03$ $p = .001$).</p> <p>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 ($p = 7.69 \times e^{-4}$) but was still significant.</p> <p>The ADHD PRS also significantly predicted lower SES ($b = -.17$, CI $-.21--.13$, $p = 1.32e^{-13}$)</p> <p>The ADHD PRS did not significantly predict (either as within or between family effect): height, self-rated health, neuroticism, psychotic experiences.</p> <p>Results were stable when analyses were rerun on the sample split by same-sex/opposite-sex twins, based on differences in chip, using a</p>

				<p>Neuroticism assessed using a Big Five questionnaire ¹⁰⁹.</p> <p>Self rated health assessed using the RAND Short-Form Health Survey¹¹⁰.</p> <p>Socio Economic Status: based on maternal age at birth of the first child, maternal and paternal highest education level, and maternal and paternal occupation.</p> <p>Covariates: PCs, chip, plate, and phenotypes were corrected for age and sex</p>	<p>prior pT of 0.1, and using PRS's with British samples removed, and results</p> <p>Statistical significance was p<.01, based on an Benjamini Hochberg false discovery rate (FDR) adjustment</p>
OTHER	33. <i>Schoele r et al. 2019</i> ⁶⁹	<p>Avon Longitudinal Study of Parents and Children (ALSPAC), UK</p> <p>5028 participants</p> <p>Assessed at age 8, 10 and 13 years.</p> <p>51% female, 49% male</p>	<p>PRS calculation based on 99 pT (0.01 – 1)</p>	<p>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.</p> <p>Covariates: Sex, PCs</p>	<p>ADHD PRS was significantly associated with bullying (standardized <i>b</i>, 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 <i>b</i>, 0.062; 95% CI, 0.032-0.092, p<.001).</p> <p>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.</p> <p>Permutation and false discovery rate–corrected p values were applied to estimate significance thresholds.</p>

		Population sample			
		European ancestry			
OTHER	34. <i>Mooney et al. 2020</i> 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. <i>Sudre et al. 2018</i> 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)	<p>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.</p> <p>Neuroanatomic imaging, and imaging of white matter tract microstructure</p> <p>Other disorders in adults were ascertained through the Structured Clinical Interview for DSM-IV-TR Axis I Disorders ⁴.</p> <p>Working memory spans assessed through number of correctly recalled digits/tapping patterns.</p> <p>Processing speed assessed using visual matching task (from the Woodcock</p>	<p>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 $q < 0.05$).</p> <p>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).</p> <p>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.</p> <p>In serial mediation analyses (polygenic risk → brain regions → cognition → symptoms); two potential pathways emerged.</p> <p>For mediation analyses of neuroimaging data, used permutation and voxel-wise $p < .05$</p> <p>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</p>

				<p>Johnson III Test of Cognitive Abilities¹¹³).</p> <p>IQ was assessed using an age appropriate version of the Wechsler scales¹⁰⁴ .</p> <p>Attentional processes measured using the Conners' Continuous Performance Test¹¹⁴, from which focused attention, perseverative/impulsive responding and sustained attention were derived.</p> <p>Covariates: Age, sex. Also for imaging data: motion and quality control scores</p>	<p>Applied a false discovery rate and indicate the results that survived at $q < 0.05$.</p>
ASDt, OTHER	36. <i>Serdarevic et al (2020)</i> ⁴⁶	<p>Generation R study, the Netherlands</p> <p>1174-1921 participants</p> <p>The children were assessed in infancy (9-20 weeks) and at age 6 years</p> <p>49% female, 51% male</p>	<p>PRS calculation based on six pT (0.01 - 1)</p>	<p>Neuromotor functioning assessed during in person home visits using modified Touwen's Neurodevelopmental Examination¹¹⁵. 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.</p> <p>Parent-rated autistic traits at age 6 years using the Social Responsiveness Scale</p>	<p>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; $p=.04$, $R^2=0.01\%$).</p> <p>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.</p> <p>Models that were adjusted for the autism or schizophrenia PRS did not change results.</p> <p>Bonferroni corrected significance threshold of $p<.005$ applied.</p>

		Population sample		Covariates: age, sex, PCs	
ADHDt, BRAIN, NEUROPSYCH	37. Shen et al (2020) ⁵²	<p>IMAGEN Study, France, UK, Ireland, Germany</p> <p>1790 participants</p> <p>Assessed at baseline at age 14 years and at follow up at 16 years</p> <p>49% female; 51% male</p> <p>Population sample</p> <p>Ancestry not described</p>	pT <.50	<p>Parent-rated Strengths and Difficulties Questionnaire hyperactivity-inattention subscale⁷¹ ages 14 and 16 years.</p> <p>Neuropsychological variables: Working memory errors assessed using Cambridge Neuropsychological Testing Automated Battery¹¹⁶ through a self-ordered searching task at age 14.</p> <p>Delay discounting assessed using the Monetary Choice Questionnaire¹¹⁷ which includes items pitting a smaller intermediate reward against a larger delayed reward at age 14.</p> <p>Intrasubject variability was the standard deviation of reaction time in successful go tasks in the stop signal functional MRI task¹¹⁸.</p> <p>Covariates: age, sex, and site. Analyses on GMV also</p>	<p>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).</p> <p>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).</p> <p>Nonsignificant associations are not described in publication. Significance threshold not given.</p>

				controlled for handedness and total intracranial volume	
ADHD*, ADHDt, BRAIN, NEUROPSYCH	38. <i>Hermosillo et al (2019)</i> ³⁷	<p>Community recruited children, USA</p> <p>n =196 ADHD participants, 28% female, 72% male</p> <p>n = 119 Non-ADHD control participants, 46% female, 54% male</p> <p>Age range 7-13 years, m=10.38 years (1.55 sd)</p> <p>Community sample enriched for ADHD</p> <p>European ancestry</p>	<p>PRS calculation based on pT 0.5 (4 other thresholds tested in replications)</p>	<p>ADHD diagnoses were best estimate research diagnoses from parent semi-structured clinical interviews, clinical observation and parent/teacher rating scales.</p> <p>Parent-reported ADHD traits using a latent variable derived from five commonly used scales.</p> <p>Teacher-reported ADHD traits using a latent variable derived from three commonly used scales.</p> <p>Working memory assessed using digit span backward, spatial span backward, and N-back task.</p> <p>MRI-based resting functional connectivity in a targeted set of subcortical structures. In total, 6 circuits involving</p>	<p>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)</p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Permutation testing was applied.</p>

				<p>subcortical regions: left and right caudate, left and right nucleus accumbens, left and right amygdala.</p> <p>Covariates: age, sex, PCs</p>	
ADHD, ASD	39. <i>LaBianca et al (2020)</i> ³¹	<p>Families with multiple individuals with ASD or ADHD recruited through adult psychiatric clinics, Denmark</p> <p>39 multiplex families with 268 individuals, including 1st and 2nd degree relatives of all ages up to 4 generations.</p> <p>Age range 7-13 years, m=10.38 years (1.55 sd)</p> <p>Northern European ancestry</p> <p>Clinical sample and family relatives</p>	No pT significance threshold	<p>Diagnoses of ASD, ASD or combined ASD and ADHD, based on ICD-10</p> <p>Affected status contingent on PRS score</p> <p>PRS score had Danish samples removed.</p> <p>Covariates: sex, age</p>	<p>The ADHD PRS significantly predicted ASD, ADHD and combined ASD and ADHD. No further information provided.</p> <p>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.</p>

<p>ADHD</p>	<p>40. Demontis <i>et al</i> (2019)¹⁷</p>	<p>iPSYCH, a population based case-cohort sample including all singletons born in Denmark between May 1981-December 2005. European ancestry</p> <p>Psychiatric Genomic Consortium (PGC) includes trio and case control samples. Only European ancestry individuals included in PRS analyses</p> <p>n = 18,298 biologically independent PGC individuals (n = 5599 cases; n = 12699 controls)</p> <p>n = 37,076 biologically independent</p>	<p>10 pT were employed (from 5 X 10⁻⁸-1).</p> <p>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.</p>	<p>PRS prediction considered a) within iPSYCH b) within PGC c) across all using leave-one-out analysis.</p> <p>iPSYCH cases diagnosed by psychiatrists at in- or out-patient clinics mostly with ICD-10 identified using a Danish Psychiatric Register.</p> <p>Controls randomly selected from iPSYCH without ADHD or moderate/severe mental retardation.</p> <p>Individuals with a diagnosis of moderate to severe mental retardation were excluded from both cases and controls.</p> <p>Diagnoses of ADHD derived from range of published instruments in PGC samples.</p> <p>Covariates: Batch effects, genotyping wave and PCs</p>	<p>ADHD PRS predicted ADHD across all target samples compared to controls or pseudocontrols.</p> <p>Within iPSYCH (using five-fold cross-validation), mean of maximum variance explained by ADHD PRS using estimated PRS Nagelkerke's R² was 5.5% (SE = 0.0012), range .047-.06. Within iPSYCH, OR = 1.56, 95% confidence interval (CI): 1.53–1.60.</p> <p>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)</p> <p>Across PGC and iPSYCH waves, average variance explained on liability scale = .0371 (se = .0029)</p> <p>Increasing deciles of ADHD PRS associated with increasing OR for ADHD, both for iPSYCH and PGC.</p>
--------------------	--	--	--	---	--

		iPSYCH individuals (n = 14584 cases; n = 22492 controls)			
ADDICTI ON, EA, EXTERN ALISING, MH, PHYSICA L	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 ($R^2 = .45\%$; $p = 4.5 \times 10^{-129}$), cognitive ability ($R^2 = .38\%$; $p = 4.5 \times 10^{-36}$), alcohol intake frequency ($R^2 = .09\%$; $p = 8.1 \times 10^{-29}$), alcohol dependency ($R^2 = .21\%$; $p = 4.5 \times 10^{-6}$), tobacco use ($R^2 = .33\%$; $p = 4.2 \times 10^{-21}$), risk taking ($R^2 = .12\%$; $p = 9.3 \times 10^{-25}$), neuroticism ($R^2 = .09\%$; $p = 2.2 \times 10^{-24}$), depressive disorder ($R^2 = .11\%$; $p = 2.2 \times 10^{-13}$), height ($R^2 = .03\%$; $p = 8.7 \times 10^{-20}$). 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 $p < 4.5 \times 10^{-4}$ applied.

		and did not take lithium, antidepressants, or antipsychotics		yes/no answer to “Would you describe yourself as someone who takes risks?”	
ADHD, MH	42. <i>Martin et al., 2018</i> ⁶³	<p>The Child and Adolescent Twin Study in Sweden (CATSS), Sweden.</p> <p>CATSS Registry diagnoses n = 217-443; unaffected n = 13029- 13247</p> <p>CATSS screening diagnoses n = 296- 1226; unaffected n = 2083- 12228</p> <p>Avon Longitudinal Study of Parents and Children (ALSPAC), UK.</p>	Primary analyses using pT p<0.1; analyses repeated on 4 other pT	<p>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.</p> <p>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.</p>	<p>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).</p> <p>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.</p> <p>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.</p> <p>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).</p> <p>Repeated analyses using other pT showed similar results.</p> <p>Significance threshold of p<.05 was applied</p>

		<p>ALSPAC algorithm diagnosed n = 199-724; unaffected n = 1728- 2732</p> <p>Both population samples</p> <p>Both European ancestry</p>		Covariates: age, PCs	
MH	43. Rice et al. 2019 ⁶²	<p>The Avon Longitudinal Study of Parents and Children (ALSPAC), UK</p> <p>n = 5416 adolescents with PRS scores and depression data on more than 1 assessment point between 10 and 18 years</p> <p>47% male; 53% female</p> <p>Population sample</p>	pT<.50	<p>Self-report depressive symptoms using the short Mood and Feelings Questionnaire¹²⁰ 6 ages (10.5, 12.5, 13.5, 16.5, 17.5, 18.5 years).</p> <p>Categorized individuals scoring above/below clinical cut-off of scale.</p> <p>Family history measured as the number of family members with a history of depression or schizophrenia weighted by relatedness (first or second-degree relative)</p> <p>Three trajectory classes identified: persistently low (73.7%), later-adolescence onset (17.3%), and early-adolescence onset (9.0%).</p>	<p>The ADHD PRS did not correlate significantly with family history for major depression or schizophrenia (both p>.05).</p> <p>ADHD PRS predicted the early-adolescence–onset depression class (OR, 1.32; 95%CI, 1.13-1.54; P < .001)</p> <p>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)</p> <p>ADHD PRS did not predict the later-onset depression trajectory class in either the univariate analysis or the multi-PRS analysis.</p> <p>Analyses that were rerun including PCS, adjusting for missing phenotypic data, and adjusting for missing genetic data, showed similar findings.</p> <p>Significance threshold of p<.05 applied.</p>

		European ancestry			
ADHDt, EA, EXTERN ALISING, OTHER, SES	44. Zwickler et al. 2020 ⁵⁸	<p>Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) study, Canada</p> <p>n= 297 participants age 5-27 years (mean = 13.5, SD = 4.4)</p> <p>53% female; 47% male</p> <p>Sample enriched for offspring of parents with depression, bipolar disorder and schizophrenia.</p> <p>90% European ancestry; 10% non-European ancestry</p>	<p>pT<.50. Analyses repeated using other pT</p>	<p>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.</p> <p>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</p> <p>Externalizing symptoms score from KSADS interview</p>	<p>ADHD PRS was associated with ADHD symptoms ($\beta = 0.21$, 95% CI 0.10 to 0.32, $p < 0.001$, $R^2 = 3.0\%$) and externalising behaviors ($\beta = 0.23$, 95% CI 0.12 to 0.34, $p < 0.0001$; $R^2 = 4.0\%$; $r = .22$, $p < .05$).</p> <p>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, $p < .0001$ $R^2 = 3.3\%$).</p> <p>ADHD PRS did not significantly associate with IQ or with family history for schizophrenia.</p> <p>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.</p> <p>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.</p> <p>Univariate PRS analyses employed $p < 0.003$ (Bonferroni significance threshold corrected for multiple tests)</p>

				<p>IQ assessed with Wechsler Abbreviated Scale of Intelligence – Second Edition¹²¹ or Wechsler Preschool and Primary Scale of Intelligence.</p> <p>Covariates: age, sex, time in the study, PCs</p>	
--	--	--	--	--	--

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 2:

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

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

- (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 ($\geq 75\%$) in at least two high quality studies
Moderate	Consistent findings ($\geq 75\%$) in one high quality study <i>and</i> at least one study of lower quality
Weak	Findings in one high quality study <i>or</i> consistent findings ($\geq 75\%$) 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: ($\geq 75\%$): 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 4: Quality assessment results

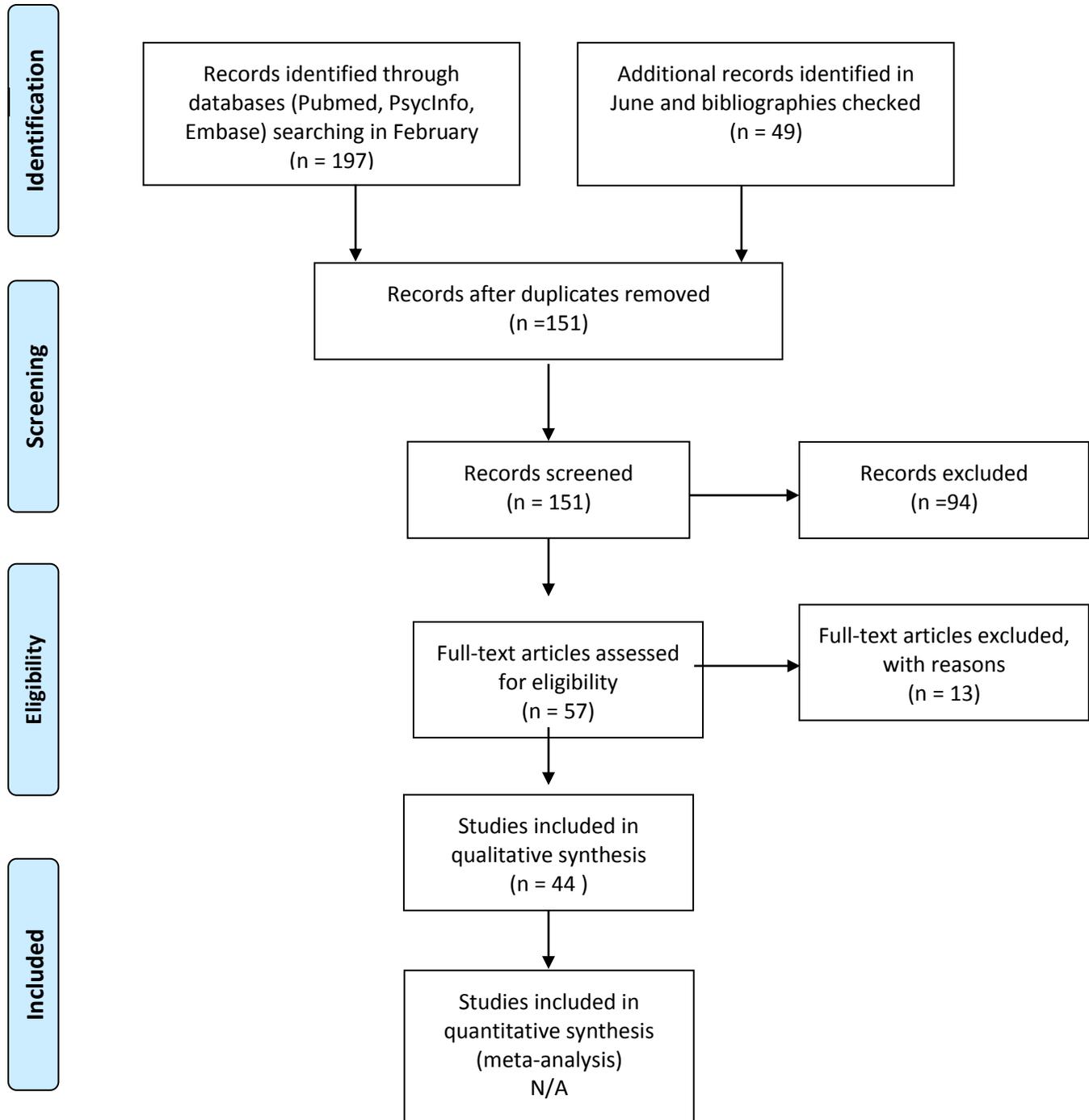
	1) Study sample				2) ADHD PRS			3) Outcomes			4) Confounders			5) Analysis, data presentation				N bias
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	
Stojanovski et al. 2019	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	0
Albaugh et al. 2019	+	+	+	+	-/+	+	+	+	-/+	+	+	+	NA	+	+	+	+	0
Burton et al. 2019	+	+	+	+	+	+	+	+	+	+	-/+	+	-	+	+	+	+	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
Grigoriou-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
Alemaný 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



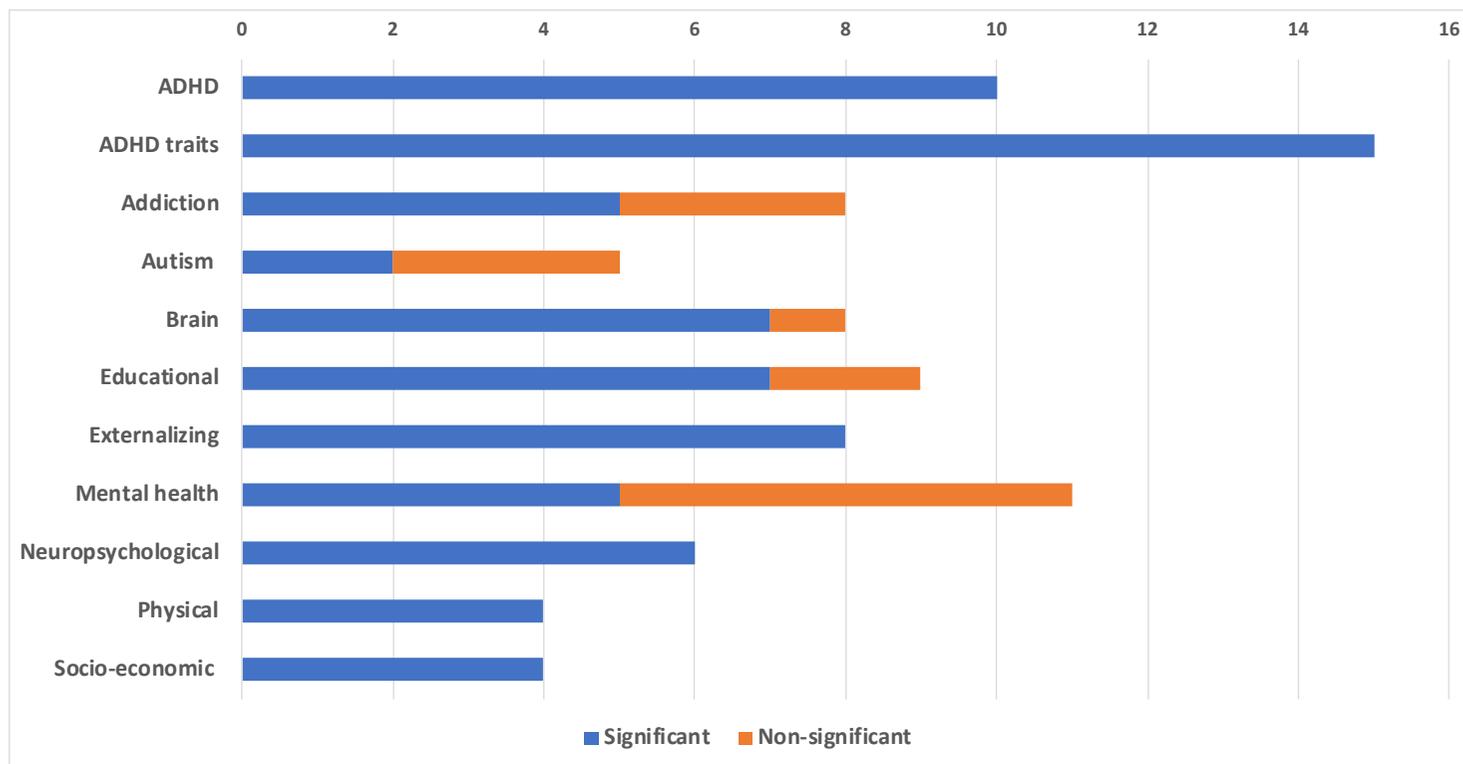
Figure 1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)

	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • DSM-IV ASD diagnosis (3#)

	<ul style="list-style-type: none"> • Social Responsiveness Scale (9[#], 15[#], 36) • ICD-19 (39[#])
Brain measures (8)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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[#])

	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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#)

	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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