Attention-Deficit/Hyperactivity Disorder Polygenic Risk Scores Predict Attention Problems in a Population-Based Sample of Children

Maria M. Groen-Blokhuis, MD, PhD, Christel M. Middeldorp, MD, PhD, Kees-Jan Kan, PhD, Abdel Abdellaoui, MSc, Catharina E.M. van Beijsterveldt, PhD, Erik A. Ehli, PhD, Gareth E. Davies, PhD, Paul A. Scheet, PhD, Xiangjun Xiao, MSc, James J. Hudziak, MD, Jouke-Jan Hottenga, PhD, Psychiatric Genomics Consortium ADHD Working Group, Ben M. Neale, PhD, Dorret I. Boomsma, PhD

Objective: Clinically, attention-deficit/hyperactivity disorder (ADHD) is characterized by hyperactivity, impulsivity, and inattention and is among the most common childhood disorders. These same traits that define ADHD are variable in the general population, and the clinical diagnosis may represent the extreme end of a continuous distribution of inattentive and hyperactive behaviors. This hypothesis can be tested by assessing the predictive value of polygenic risk scores derived from a discovery sample of ADHD patients in a target sample from the general population with continuous scores of inattention and hyperactivity. In addition, the genetic overlap between ADHD and continuous ADHD scores can be tested across rater and age.

Method: The Psychiatric Genomics Consortium has performed the largest genome-wide analysis (GWA) study of ADHD so far, including 5,621 clinical patients and 13,589 controls. The effects sizes of single nucleotide polymorphisms (SNPs) estimated in this meta-analysis were used to obtain individual polygenic risk scores in an independent population-based cohort of 2,437 children from the Netherlands Twin Register. The variance explained in Attention Problems (AP) scale scores by the polygenic risk scores was estimated by linear mixed modeling.

Results: The ADHD polygenic risk scores significantly predicted both parent and teacher ratings of AP in preschool- and school-aged children.

Conclusion: These results indicate genetic overlap between a diagnosis of ADHD and AP scale scores across raters and age groups and provides evidence for a dimensional model of ADHD. Future GWA studies on ADHD can likely benefit from the inclusion of population-based cohorts and the analysis of continuous scores. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(10):1123–1129. Key Words: ADHD, attention problems, polygenic scores, genetics, dimensional models

Attention-deficit/hyperactivity disorder (ADHD) is a condition characterized by age-inappropriate hyperactivity/impulsivity and inattention, resulting in significant impairment in about 5% of children. In the diagnostic manuals used in clinical practice, for example, the International Classification of Diseases, 10th Revision (ICD-10), DSM-IV, and the DSM-5, a clinical diagnosis of ADHD is a binary trait that can be useful for guiding treatment and care. At the population level, ADHD may represent the extreme end of a continuous distribution of inattentive and hyperactive behaviors. Classical twin studies support the validity of the dimensional model, but at this point in time, an additional approach to test for a dimensional model of ADHD is to assess whether genetic risk factors for an ADHD diagnosis influence behavior across the entire spectrum of inattentive and hyperactive behavior. Such an approach also may clarify apparent differences in the ADHD
assessment across raters and age groups. Correlations between parent and teacher ratings are generally only moderate, as are correlations within maternal ratings across preschool and school age.\textsuperscript{8,10} Previous studies indicate that the extent to which assessment from different raters and across different ages overlap is due to overlap of genetic effects across both raters and time,\textsuperscript{8,12} but these results are based on, for example, latent variable modeling approaches rather than on measured genetic variants. ADHD diagnoses and continuous measures of ADHD behaviors are highly heritable in childhood, with about 60% to 80% of the variance due to genetic factors.\textsuperscript{13-17} Despite this high heritability, current genome-wide association (GWA) studies have thus far been unsuccessful in detecting genetic risk variants for ADHD at genome-wide significant levels, suggesting a high degree of polygenic inheritance.\textsuperscript{18} A study by the Psychiatric Genomics Consortium (PGC) showed that 28% of the liability to ADHD is explained by single nucleotide polymorphisms (SNPs) present on platforms that are commonly used for genome-wide genotyping.\textsuperscript{19} These observations imply that many common variants of small effect stay undetected in current GWA studies due to limited sample size but very likely contribute to the genetic liability of ADHD. The effect sizes obtained in ADHD GWA studies can be used to estimate the genetic risk of the individual; so-called polygenic risk scores are obtained by multiplying the measured number of risk alleles at a particular locus by the effect size observed in a GWA study summing over all SNPs that surpass a certain threshold of significance.\textsuperscript{20,21} With regard to ADHD, polygenic risk scores based on the results of the PGC ADHD meta-analysis published in 2010 significantly predicted ADHD status in an independent sample of 452 clinical patients with ADHD and 5,081 controls, with higher polygenic risk scores in patients with ADHD and comorbid aggression.\textsuperscript{19,22} Polygenic risk scores can also be used to assess the genetic overlap across traits. For example, polygenic risk scores based on a GWA study on schizophrenia predict quantitative measures of psychosis.\textsuperscript{23} Similarly, polygenic risk scores based on a GWA study in patients with major depressive disorder (MDD) are predictive of continuous scores of anxiety and depression in a general population sample.\textsuperscript{24} In the current study, we obtained polygenic risk scores to assess the genetic overlap between clinically assessed ADHD and attention problems (AP) in a general population sample of children who were rated by their parent at preschool age and by their parents and teachers at school age.

**METHOD**

Genotype and phenotype data were available in a sample of 2,437 children of Dutch descent who are registered with the Netherlands Twin Register (NTR).\textsuperscript{25,26} In the Young NTR (YNTR), surveys assessing the health and behavior of newborn twins are sent out to their parents at registration and at age 2, 3, 5, 7, 10, and 12 years. At age 7, 10, and 12 years, parents are asked for their consent to invite the teachers of the twins to provide ratings of the children’s behavior.

**AP**

Age-appropriate versions of the Achenbach System of Empirically Based Assessment (ASEBA) have been included in the YNTR surveys.\textsuperscript{27,28} At ages 3, 7, 10, and 12 years the Child Behavior Checklist (CBCL) was collected from parents. At ages 7, 10, and 12 years, the Teacher Report Form (TRF) was included in teacher surveys. Respondents were asked to rate the child’s behavior on \~120 items on a 3-point scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true). The AP scale describes hyperactive and inattentive behavior. The AP scale contains 5 items at preschool age, and at school age, 10 items for parents, and 26 items for teachers. When multiple measures were available for the school-age (age 6–13 years) mother or teacher ratings, the measure closest to age 10 was chosen. There were 2,132 twins with maternal AP ratings at school age; for 1,888 twins (89%), AP was assessed between age 9 and 11, for 50 twins at age 12, and for 194 twins, at age 7 or 8 years. Teacher ratings were available at age 9 to 11 for 1,018 twins, at age 7 to 8 for 152 twins, and at age 12 for 442 twins. Maternal and paternal ratings were highly correlated ($r = 0.71$ and 0.73 for preschool and school age) and gave similar results; therefore, we report only on the larger set of maternal ratings.

**Genotype Data**

All participants were genotyped on the Affymetrix 6.0 platform, which contains more than 900,000 SNPs. Quality control and imputation were performed on a larger dataset ($N = 14,003$) that also included genotype data from the parents of the twins. SNP data were cleaned with the following criteria: Hardy–Weinberg equilibrium (HWE) $p$ value $>0.0001$, minor allele frequency (MAF) $>0.01$, call rate $>0.95$, concordance rate in duplicate samples $>0.98$, Mendelian error rate $<0.02$, and allele frequency difference with reference set $<0.20$. C/G and A/T SNPs

\footnotesize

\textsuperscript{1124} www.jaacap.org VOLUME 53 NUMBER 10 OCTOBER 2014
were only included if MAF was <0.35. Samples were cleaned on the following criteria: call rate >0.90, heterozygosity −0.10 < F < 0.10, consistency of X chromosome genotypes with known gender, consistency of expected and observed family relations, and Mendelian error rate <0.02. Ethnic outliers were excluded from the association analyses. Next, imputation was done by using known haplotypes from the 1000 Genomes Project (http://www.1000genomes.org/). The SNP data were phased in Mach 1.0 and imputed with Minimac using all ethnicity panels of the 1000 Genomes Phase I Integrated Release Version 3 build 37 (2010-11-23 sequence data freeze, 2012-03-14 haplotypes).

Within the Psychiatrics Genomics Consortium, a meta-analysis of 5,621 clinical patients with ADHD and 13,589 controls was conducted (F. Holmans for the PGC: presentation 21st World Congress of Psychiatric Genetics, October 2013, Boston, MA). These data were imputed using CEU+TSI Hapmap Phase 3 build 36 as the reference set (http://hapmap.ncbi.nlm.nih.gov/). Polygenic risk scores were calculated in Plink. SNPs were selected on the following criteria: info score >0.30 (a measure of imputation quality) in both the discovery and the target set, MAF >0.02 in both sets, consistency of reported alleles across sets, and a frequency difference across sets <.15. SNPs with C/G or A/T alleles were included only if MAF was <0.35. For each individual, the number of observed risk alleles at a particular locus (0,1,2) was multiplied with the ln(OR) observed in the PGC meta-analysis and summed over all SNPs. Several sets of polygenic risk scores were created based on different p value thresholds in the discovery set (thresholds .0001, .001, .01, .05, .1, .2, .3, .4, .5, and 1).

Data Analyses

AP scores were regressed on the polygenic risk scores in a linear mixed model, as implemented in SPSS (version 20). AP was predicted from the polygenic risk scores, plus sex and age at measurement and 4 principal components (PCs) that reflect Dutch population structure.29 These predictors were included as fixed effects in the model. The dependency between measures in related individuals were accounted for by including a random effect of family. Because families consist of monozygotic (MZ) and dizygotic (DZ) twin pairs who differ in their genetic relatedness (monozygotic twins share all additive [A] and dominance [D] genetic variation, whereas dizygotic twins do not), the effect of family was allowed to be different for MZ and DZ families. A script detailing the analyses is included in Supplement 1 (available online). Within each analysis, polygenic risk scores and AP scales were standardized, that is, the mean of the subsample was subtracted from each score and divided by the standard deviation. The variance explained by the polygenic risk scores was obtained by squaring the regression coefficient. All AP measures showed significant skewness and kurtosis (Figure S1, available online). To test whether the violation of distributional assumptions influenced the results, all analyses were repeated on quantile normalized scores (van der Waerden transformation,30 ranks averaged for tied data). This led to similar conclusions (Table S1, available online). To further corroborate these findings and to obtain corrected robust (“Huber–White”) standard errors of the regression coefficients, analyses were replicated in R (version 2.15). This was accomplished by respecification of the mixed model (in R package lavaan). This approach, which is detailed in Supplement 1 (available online), also led to similar conclusions. A detailed overview of the results can be found online in Supplement 1 (Figure S2 and Table S1).

Finally, the analyses were repeated to a subset of independent SNPs present in both the discovery and target set by using the clumping procedure in Plink (option −clump, with settings −clump-p1 1 −clump-p2 1 −clump-r2 0.25 −clump-kb 500). Results can be found in Figure S3, available online, where the explained variance was lower.

RESULTS

Table 1 shows the number of individuals and the means and standard deviations of age at measurement, and AP scores for the mother and teacher ratings at preschool and school age. Because of the longitudinal structure of the data, there is substantial overlap of individuals across these measures; 1,899 of 2,132 children with maternal ratings at school age also had ratings at preschool age (phenotypic correlation 0.44), and 1,516 of 1,612 children with teacher ratings also had school-age maternal ratings (phenotypic correlation 0.49). In Figure 1, the variance in AP explained by the polygenic risk

<table>
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<th>Measure</th>
<th>n</th>
<th>Age, Mean (SD)</th>
<th>AP Score, Mean (SD)</th>
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</thead>
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<td>3.32 (0.26)</td>
<td>2.29 (2.00)</td>
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<td>mother rating, CBCL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AP school; age 7–13 y;</td>
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<td>9.93 (0.88)</td>
<td>3.26 (3.38)</td>
</tr>
<tr>
<td>mother rating, CBCL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP school; age 7–13 y;</td>
<td>1,612</td>
<td>10.61 (1.40)</td>
<td>6.73 (7.92)</td>
</tr>
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<td>teacher rating, TRF</td>
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</table>

Note: CBCL = Child Behavior Checklist; SD = standard deviation; TRF = Teacher Report Form; y = years.
scores is shown for the mother and teacher ratings at preschool and school age, for different \( p \)-value bins. The polygenic risk scores based on the GWA meta-analysis results of clinical patients with ADHD versus controls significantly predicted maternal ratings of AP at preschool and school age, as well as teacher ratings at school age. All significant effects were in the expected direction, that is, higher polygenic risk scores were associated with higher AP scores. The maximum explained variance for each of the ratings varied between 0.5% and 0.6%, with no clear difference across preschool and school age or mother and teacher ratings.

**DISCUSSION**

Polygenic risk scores based on a GWA meta-analysis of clinical patients with ADHD significantly predicted AP in an independent population-based sample of children, indicating a genetic overlap between ADHD assessed as a categorical disorder and AP assessed as a continuous trait in a general population sample. Other studies that examined whether ADHD should be considered a category or a continuum have used latent class analysis (LCA), factor analysis (FA), factor mixture models (FMM), and taxometric procedures on item-level data to detect the underlying structure. Whereas some studies found evidence for distinct subtypes (e.g., predominantly inattentive, predominantly hyperactive/impulsive, or combined inattentive and hyperactive/impulsive symptoms), others found evidence for the existence of a continuum within or across subtypes. The current study provides evidence in support of a dimensional model of ADHD at the genetic level. Although categorical models of ADHD are necessary in clinical contexts where one needs to answer categorical questions with regard to treatment, for example, future research on the underlying continuous trait could provide the necessary information to decide on the appropriate cutoffs for these categories. The National Institute of Mental Health has therefore launched the Research Domain Criteria (RDoC) project that aims to develop a research classification system for mental disorders based on dimensions of neurobiology and observable behavior. Meanwhile, awareness of the dimensional nature of ADHD may already have an impact on clinical practice, as shown by clinics that have successfully incorporated dimensional models in their daily clinical practice.

Our findings of significant prediction of AP based on a clinical discovery set have important implications for gene-finding studies. Despite the lack of genome-wide significant findings in current GWA studies of ADHD, such studies apparently contain relevant signals. The small proportion of explained variance by the genetic risk scores does not preclude this conclusion. The estimated explained variance is similar to the estimates of
Hamshere et al.\textsuperscript{22} that predicted patient-with-
ADHD status by ADHD GWA meta-analysis
results, and to other studies using genetic risk
scores to investigate the genetic architecture of
other psychiatric phenotypes.\textsuperscript{38-40} The explained
variance is mostly dependent on the sample size
of the discovery set; when this sample size is
large, the effects detected in the GWA contain
less noise, leading to more accurate predictions
in the target sample. Genetic Complex Trait
Analyses (GCTA), such as those performed for
ADHD in PGC,\textsuperscript{19} generally provide higher es-
timates of the variance explained by all SNPs.
This is due to the difference in approaches, as
the GCTA method does not rely on imprecise
effect estimates but on a regression of phenotypic
similarities on genotypic similarities.\textsuperscript{41}
However, the different approaches all imply
that GWA studies on ADHD can be successful.
Moreover, our results for continuous ADHD-
related traits indicate that patient–control co-
horts may benefit from an increase in power by
including the available information on symp-
tom severity in their analyses,\textsuperscript{42} although this
gain in power could be limited by the nonuni-
formity of measurement error across the distri-
bution. In practice, the choice of study design
will likely depend on the costs of genotyping
and phenotyping and the availability of already
existent datasets. In this context, it is worth-
while to note that many population-
base cohort studies have both genome-wide
SNP data and continuous measures of ADHD
available, but are currently underused for gene-
finding studies on ADHD and other psychiatric
phenotypes. Although patient–control studies
benefit from the ascertainment of individuals
from the extreme end of the distribution, the
power to find genetic variants for ADHD is
roughly equal in an equal-sized population-
base cohort with a continuous measure of
ADHD, as in the latest PGC meta-analysis of
ADHD, because of the relatively high prevalence
of ADHD and the somewhat small proportion
of patients in the latest PGC meta-analysis.\textsuperscript{43}
Other advantages of population-based studies
include the richness of available phenotypic
information allowing for multivariate analyses
and the investigation of gene–environment
interactions.\textsuperscript{44}

Given the small predictive value of the
polygenic risk scores on AP, they cannot be
used to predict patient or control status at the
individual level or be used as biomarkers.
However, they are still informative on the
population level, as polygenic risk score ana-
lyses and GCTA do provide information on the
genetic architecture of traits and on the associ-
ation between traits.\textsuperscript{19} The current study not
only showed genetic overlap between clinical
diagnoses and continuously measured traits,
but also indicated that this overlap was present
at both preschool and school age and for
different raters. This similarity of genetic effects
across age is in line with twin studies that
demonstrate a high genetic stability of
maternal-rated AP in childhood,\textsuperscript{10,11} and the
finding that the behavior that parents and
teachers rate in common is highly heritable
de spite a moderate phenotypic correlation.\textsuperscript{8,45}
Moreover, an ADHD diagnosis requires the
behavior to be present in multiple settings, and
it is therefore expected that the genetic factors
that influence a clinical diagnosis of ADHD
 correlate with both parent and teacher ratings
of ADHD symptoms. The results from the
clumping analyses in which a smaller set of SNPs
limited to independent SNP sets (Figure S3,
available online) also speak to the highly poly-
genetic nature of ADHD and AP: by leaving out
SNPs (based on a statistical criterion), the var-
iance that is explained by polygenic scores de-
creases. When correlated SNPs are analyzed, it
is not the case that such correlation results in
inflation or bias in the amount of variance
explained. In the regression of the phenotype on
the polygenetic scores, the collinearity due to
correlations among predictors does not actually
affect the estimates; that is, in least-squares
regression, these remain best, linear, unbiased
estimates (BLUE). If regression estimates are un-
biased, then the estimate of the explained vari-
ance is also unbiased.\textsuperscript{46}

Thus, ADHD/AP can be predicted from
ADHD polygenic risk scores at the population
level, and it is clear that the PGC ADHD meta-
analysis picks up genetic variation relevant to
ADHD. Next, these GWA results can be used to
investigate the genetic overlap between ADHD
and other disorders and gene–environment
interplay. Our study supports the use of
dimensional models of ADHD and indicates
that future GWA studies can benefit from the
inclusion of both population-based and patient–
control studies, and by analyzing ADHD as a
quantitative rather than a categorical trait.\textsuperscript{c}


REFERENCES


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SUPPLEMENT 1

SPSS Syntax for Mixed Model

Glossary of Terms. 
- **Twin**: 1: first twin, 2: second twin
- **MZ**: 0: monozygotic twin, 1: dizygotic twin
- **A**: additive genetic effect
- **D**: dominant genetic effect
- **Fam nr**: family identifier
- **Zscore_AP10_m**: Z-score Attention Problems at age 10 as rated by mother
- **Zscore_sum_S1**: Z-score of the genetic risk profile for the first set of SNPs
- **PC1 to PC4**: principal components controlling for stratification

Syntax. **Dummy coding is used to decompose the variance into additive genetic and dominant genetic effects.**

```spss
compute Ac = 0.
compute Atw1 = 0.
compute Atw2 = 0.
compute Dc = 0.
compute Dtw1 = 0.
compute Dtw2 = 0.
execute.
if (twin = 1) Ac = sqrt(.5).
if (twin = 1) Atw1 = sqrt(.5).
if (twin = 1) Dc = sqrt(.25).
if (twin = 1) Dtw1 = sqrt(.75).
if (twin = 2) Ac = sqrt(.5).
if (twin = 2) Atw1 = sqrt(.5).
if (twin = 2 and MZ = 0) Atw2 = sqrt(.5).
if (twin = 2 and MZ = 1) Atw1 = sqrt(.5).
if (twin = 2) Dc = sqrt(.25).
if (twin = 2) Dtw2 = sqrt(.75).
execute.
MIXED Zscore_AP10_m with Zscore_sum_S1 PC1 PC2 PC3 PC4 sex age Ac Atw1 Atw2 Dc Dtw1 Dtw2 int /FIXED = Zscore_sum_S1 PC1 PC2 PC3 PC4 sex age int | SSTYPE(3) noint /METHOD = ML /PRINT = CORB SOLUTION TESTCOV /random Ac Atw1 Atw2 | SUBJECT(famnr) COVTYPE(id) /random Dc Dtw1 Dtw2 | SUBJECT(famnr) COVTYPE(id).
```
FIGURE S1 (A) Distribution of maternal Attention Problems z scores at age 3 years. (B) Distribution of maternal Attention Problems z scores at age 10 years. (C) Distribution of teacher-rated Attention Problems z scores at age 10 years.
FIGURE S2  Graphical representation of the statistical model as used in R. Attention problem (AP) scores of twins are regressed on the polygenic risk scores (regression coefficients $\beta$) as well as on latent additive genetic (A), nonadditive genetic (D), and unique environmental (E) factors with unit variance (and factor loadings $a$, $d$, and $e$). Note: the standardized $\beta$ is reported in Table S1. Covariates sex, age, and the principal components were also included as predictors (regression coefficients $s$, $b_{age}$, $pc_{1}$, $pc_{2}$, $pc_{3}$, and $pc_{4}$). To estimate the intercept ($i$) of AP and the means ($\mu$) of the risk scores and the covariates, these variables were regressed on a unit vector. Note that the means of the principal components are 0 (but were allowed to be estimated freely). The model was identified by fixing the correlation between the latent genetic factors to 1 in the group consisting of monozygotic twin pairs, and to 0.5 (A) and 0.25 (D) in the group consisting of dizygotic twin pairs. These constants reflect the (average) proportion of the twins’ shared segregating genes.
FIGURE S3  Proportion of variance explained in attention problems by polygenic risk scores based on different p value bins after selection of independent single nucleotide polymorphisms (SNPs) using the clumping procedure in Plink (option –clump, with settings –clump-p1 1 –clump-p2 1 –clump-r2 0.25 –clump-kb 500). Note: The number displayed below the bins is the upper threshold of p values for inclusion; the lower threshold is always 0.
TABLE S1  Standardized β and p Values of the Regression Linear Mixed Model of the Polygenic Risk Scores on the z Scores and the Normalized Attention Problem (AP) Scores and Robust Additive, Dominance, Nonshared Environmental Genetic Effects (ADE) Twin Model Analyses on the z Scores, for the Different Sets of Single Nucleotide Polymorphisms (SNPs)

<p>| AP-Preschool- | z Scores | Normalized Scores | z Scores (Twin Model, Robust) |</p>
<table>
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<th>Mother</th>
<th>p Value Bin</th>
<th>Standardized β</th>
<th>p Value</th>
<th>Standardized β</th>
<th>p Value</th>
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<th>p Value</th>
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<th>Normalized Scores</th>
<th>z Scores (Twin Model, Robust)</th>
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<td>p Value Bin</td>
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### TABLE S1  Continued

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Note: SE = standard error.