SWAN Scale for ADHD Trait-Based Genetic Research: A Validity and Polygenic Risk Study

Running Head: SWAN for ADHD population genetics

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Abstract

Background. Population-based samples with valid, quantitative and genetically-informative trait measures of psychopathology could be a powerful complement to case/control genetic designs. We report the convergent and predictive validity of the parent- and self-report versions of the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN). We tested if SWAN scores were associated with ADHD diagnosis, ADHD polygenic risk, as well as traits and polygenic risk for disorders that co-occur with ADHD: anxiety and obsessive-compulsive disorder (OCD). **Methods.** We collected parent- and self-report SWAN scores in a sample of 15,560 children and adolescents (6-17 years) recruited at a science museum (Spit for Science sample). We established age and sex norms for the SWAN. Sensitivity-specificity analyses determined SWAN cut-points that discriminated those with and without a reported ADHD diagnosis. These cut-points were validated in a clinic sample (266 ADHD cases; 36 controls). Convergent validity was established using the Conners' parent- and self-report scales. Using Spit for Science participants with genome-wide data (n=5,154), we tested if low, medium and high SWAN scores were associated with polygenic risk for ADHD, OCD and anxiety disorders. **Results.** Parent- and self-report SWAN scores showed high convergent validity with Conners' scales and distinguished ADHD participants with high sensitivity and specificity in the Spit for Science sample. In a clinic sample, the Spit for Science cut-points discriminated ADHD cases from controls with a sensitivity of 84% and specificity of 92%. High SWAN scores and scores above the Spit for Science cut-points were significantly associated with polygenic risk for ADHD. SWAN scores were not associated with polygenic risk for OCD or anxiety disorders. **Conclusion**. Our study supports the validity of the parent- and self-report SWAN scales and their potential in ADHD population-based genetic research.

Keywords: ADHD, SWAN, psychometric validity, polygenic risk score, standardized norms

Abbreviations: Obsessive-compulsive (OC), Obsessive-compulsive Disorder (OCD), Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN), SWAN parent-report scale (SWAN-Parent), SWAN self-report scale (SWAN-Self), inattentive subscale (IA), hyperactive/impulsive subscale (HI), SWAN total z-score (z-SWAN-Total), SWAN inattentive subscale z-score, (z-SWAN-IA), SWAN hyperactive/impulsive z-scores (z-SWAN-HI), Conners' ADHD Rating Scale-Revised (CPRS-R), Conners-Wells Adolescent Self Report Scale (CASS-L), Child Behavior Checklist (CBCL), Toronto Obsessive-Compulsive Scale (TOCS).

Attention-deficit/hyperactivity disorder (ADHD) is an impairing and common disorder (5% prevalence; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Despite high heritability (70-80%; Faraone et al., 2015), we are just beginning to identify genetic variants for ADHD (Demontis et al., 2018). Several obstacles impede more rapid progress. First, genome-wide association studies (GWAS) typically compare controls to ADHD cases, identified by clinical interviews using diagnostic criteria. This is a slow and costly process. Second, the severity of ADHD traits can overlap considerably in cases and controls (Fair, Bathula, Nikolas, & Nigg, 2012). ADHD is now widely considered to be the extreme end of widely distributed, quantitative traits (Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997). Although diagnostic categories are useful in clinical practice, dichotomizing continuously distributed traits into case/control reduces statistical power in research (Fair et al., 2012; Pain, Dudbridge, & Ronald, 2018; van der Sluis, Posthuma, Nivard, Verhage, & Dolan, 2013). Thus, quantitative trait population-based approaches should be considered in ADHD genetic research.

Quantitative traits can be derived from summing the number of symptoms on symptom scales. However, these scales often generate skewed distributions, especially in the general population where the base-rate of most disorders are low, which results in a cluster of scores at zero. To accelerate genetic discovery in ADHD, we need genetically-informative measures that efficiently generate reliable, heritable, widely and preferably normally distributed scores in the general population. Measures of this type would facilitate rapid accrual of samples and would complement case/control methods.

The Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN; Swanson et al., 2012) is a unique trait measure. The SWAN is based on the ADHD

criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition (American Psychiatric Association, 1994). What makes the SWAN different is that it rates ADHD symptoms on a seven-point Likert scale with -3 indicating low traits (e.g., highly attentive) and +3 indicating high traits (highly inattentive). The SWAN meets many criteria of a genetically-informative trait measure. It is reliable, generates normally distributed scores in the general population, has high internal consistency, high test-retest reliability, converges reasonably with ADHD symptom measures and diverges from measures of emotionality (Arnett et al., 2013; Crosbie et al., 2013; Lai et al., 2013; Lakes, Swanson, & Riggs, 2012; Stroud et al., 2009; Swanson et al., 2012). The parent- and self-report SWAN are heritable (h^2=0.24-0.94; Couvy-Duchesne et al., 2016; Crosbie et al., 2013; Greven et al., 2016; Hay, Bennett, Levy, Sergeant, & Swanson, 2007; Peng et al., 2016; Polderman et al., 2007; Smit & Anokhin, 2017). An underpowered GWAS (n=1851) using the SWAN identified suggestive genome-wide significant hits (Ebejer et al., 2013).

Some questions remain about the SWAN's suitability for genetic research. First, can the SWAN discriminate ADHD cases from controls with high sensitivity and specificity in the general population? The question is not if SWAN can substitute for a diagnosis of ADHD, which would not be possible because it does not capture traits across settings or functional impairment. The question is whether the high extreme of distributed ADHD traits converges and shares genetic risk with ADHD diagnosis (Crosbie et al., 2013; Plomin, Haworth, & Davis, 2009). People with extremely high traits should have ADHD, while people with low trait scores should not have ADHD. Second, do low ADHD traits, such as hyper-attentiveness and lack of fidgeting, represent another type of psychopathology? Low SWAN scores might be associated with increased risk for obsessive-compulsive disorder (OCD) and/or anxiety because these disorders

are partially characterized by over-attention to threatening stimuli or underactivity due to shyness or fear (Muller & Roberts, 2005; Roy et al., 2008). Third, is the SWAN self-report version valid? Previous studies have used a self-report version in youth (Couvy-Duchesne et al., 2016; Ebejer et al., 2015; Greven et al., 2016), but did not validate or generate norms for the measure. A validated self-report SWAN for adolescents is critical for population genetics research because parents are not always available. Fourth, are parent- and self-report SWAN scores associated with genetic risks that predispose to diagnosed ADHD (polygenic risk)? Finally, are SWAN scores associated with polygenic risk for disorders that co-occur with ADHD including OCD and anxiety (Abramovitch, Dar, Mittelman, & Wilhelm, 2015; Jensen et al., 2001)?

To address the gaps in the existing literature, we examined the convergent and predictive validity in parent- and self-report SWAN scales, as well as established norms. We established cut-points in a population-based sample and validated them in a clinic sample. We tested if ADHD traits share genetic risk with diagnosed ADHD as previously demonstrated (Brikell et al., 2018; Groen-Blokhuis et al., 2014; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Middeldorp et al., 2016; Riglin et al., 2016; Stergiakouli et al., 2015); as polygenic risk for diagnosed ADHD should increase with an increase in ADHD traits. Finally, we examined if ADHD traits were associated with traits and genetic risk for disorders that commonly co-occur with ADHD. We hypothesized that high ADHD traits would be associated with traits for disorders that co-occur with ADHD: anxiety and OCD (Abramovitch et al., 2015; Jensen et al., 2001). Low ADHD trait scores would not be associated with anxiety and obsessive-compulsive (OC) traits - indicating that the “strength” end of the ADHD distribution does not represent another psychopathology. ADHD traits may be associated with polygenic risk for co-occurring disorders, although less than polygenic risk for diagnosed ADHD or not at all.

Methods

Samples

Figure 1 outlines all samples used in the study.

Insert Figure 1

Spit for Science sample. Spit for Science recruited 17,263 participants (ages 6-17 years) at the Ontario Science Centre in Toronto, Canada (see Crosbie et al., 2013 for details). Complete information was available for 15,560 participants (parent-report: ages 6-15 years n=12,797, self-report: ages 13-17 years n=2,763) that included 3,714 families with at least one sibling. Consistent with the reported prevalence of childhood ADHD (CDC, 2015), 972 (6.2%) reported a diagnosis of ADHD (referred to as community diagnosis). The mean age was 11.0 ± 2.8 years and 50.8% were male (n=7901).

The parent- (SWAN-Parent) and self-report (SWAN-Self) versions of the SWAN included the same 18 items but with different referents ("your child" instead of "me") with a possible total score from -54 to 54. There are two 9-item subscales (range of -27 to 27): an inattentive subscale (IA) and a hyperactive/impulsive subscale (HI).

To assess convergent validity, a random subset of parents and youth completed a widely-used ADHD measure: Conners' ADHD Rating Scale-Revised (CPRS-R – parent-rated; n=841) or Conners-Wells Adolescent Self Report Scale (CASS-L; n=172). Each measure generates four scales in T-score format: Inattentive (L-scale), Hyperactive-Impulsive (M-scale), Total (N-scale) and ADHD Index (H-scale) (Conners, Sitarenios, Parker, & Epstein, 1998).

Parents and youth completed anxiety (Child Behavior Checklist [CBCL] anxiety problems sub-scale; Achenbach & Rescorla, 2001) and OC trait measures (Toronto Obsessive-Compulsive Scale – TOCS; Park et al., 2016). The anxiety scale has 11 items scored from 0 ("not true") to 2 ("very true or often true"). The TOCS has 21 items scored on a seven-point Likert scale ranging from -3 ("far less often than others of the same age") to +3 ("far more often than others of the same age").

Validation ADHD Clinic Sample. This sample consisted of 266 children (6-17 years old) diagnosed with ADHD and 36 control children assessed in a tertiary care mental health clinic (mean age = 9.1 ± 2.2 years, 84.5% male [n=225]). ADHD diagnoses were based on consensus between a psychiatrist and clinical psychologist following a rigorous assessment described elsewhere (McAuley, Chen, Goos, Schachar, & Crosbie, 2010). We excluded individuals with an IQ <80 on both verbal and non-verbal domains. SWAN-Parent scores were not considered when formulating the diagnosis and SWAN-Self scales were not used because most of the sample was pre-adolescent.

Ethical Considerations

Informed consent, and verbal assent when applicable, approved by The Hospital for Sick Children Research Ethics Board were obtained from all participants.

Statistical analyses

We reversed the SWAN items such that high scores reflected high ADHD traits and low scores reflected low ADHD traits. We standardized SWAN scores for age, gender and respondent because of their association with SWAN scores (p's < 0.0001). Participants were divided into 30 groups according to age, gender, and respondent. Parent-report groups included integer ages

from 6-15 and self-report groups included integer ages from ages 13-17. Standardized scores corresponding to the empirical percentile of each individual were assigned within each of the 30 groups separately. Standardization of scores allows for combination of parent- and self-report ratings in analyses where appropriate. Analyses non-standardized SWAN scores are described in the supplemental methods. We created standardized z-scores for the total score (z-SWAN-Total), each subscale (z-SWAN-IA and z-SWAN-HI), TOCS total score and CBCL anxiety problem total scores. Bootstrap analysis using SAS 9.3 established confidence intervals. We accounted for sibling relatedness in the models using random effects.

Phenotypic Analyses in Spit for Science and Clinic Samples

We used t-tests to compare SWAN scores in those with and without a community diagnosis of ADHD (Spit for Science) or those with and without a clinical diagnosis of ADHD and controls (clinic sample). Parent- and self-report participants were analyzed separately in Spit for Science, while only parent-report was available in the clinic.

We used receiver operating characteristic (ROC) analyses to identify the optimal cut-point for discriminating those with and without a community ADHD diagnosis in the Spit for Science sample. Area under the curve (AUC) of ≥0.80 indicates good discrimination of cases from controls. The Youden Index indicates the optimal cut-points in an ROC curve. We validated the ability of these Spit for Science cut-points for standardized SWAN scores to correctly classify ADHD cases in the clinic sample. We compared the predictive validity of Spit for Science cut-points with cut-points recommended by Swanson et al. (1.65 SD; 2012). ROC analyses were conducted using MedCalc. All other statistical tests were performed using SPSS 21 or SAS v9.4.

Internal consistency was assessed in the Spit for Science sample using Cronbach's α for the SWAN-Parent and SWAN-Self ($\alpha \geq 0.80$ are considered good). To assess convergent validity, z-SWAN subscales were correlated with their corresponding CPRS-R and CASS-L subscales in the subset that completed both SWAN and appropriate Conners' measures for the informant. Spearman's rho was used to assess correlations because CPRS-R and CASS-L scores were not normally distributed.

To examine the relationship of OC and anxiety traits across the spectrum of ADHD traits, we divided the z-SWAN-Total distribution into thirds to create three groups: low (z-score <-1.11; n=2076), medium (z-score=-1.11 to 1.11; n=11403) and high (z-score >1.11; n=2081). We used three groups to ensure large enough sample sizes in each group in the phenotype and subsequent genetic analyses that used a smaller subset of participants. Analyses of Variance (ANOVAs) tested mean differences in TOCS total score and CBCL anxiety total score across SWAN groups.

Genetic Analyses in Spit for Science Sample

Genetic analyses focused on 5,154 Caucasians from the Spit for Science sample that passed standard quality control analyses (see supplemental methods). Polygenic risk scores were calculated in three European discovery samples: ADHD (European-only, cases=19,099, controls=34,194; Demontis et al., 2018), OCD (cases=2,688 and controls=7,037; International Obsessive Compulsive Disorder Foundation Genetics Collaborative & Studies, 2017) and anxiety disorders (ANGST; 17,310 cases and controls; Otowa et al., 2016). From each discovery set, we selected a subset of pruned SNPs across various p-value thresholds ($p<1x10^{-5}$, $1x10^{-4}$, $1x10^{-3}$, 0.05, 0.01, 0.10, 0.20, 0.30, 0.40 and 0.50). Pruning was conducted in plink 1.9 (Purcell et al., 2007; http://pngu.mgh.harvard.edu/purcell/plink/ref) on unambiguous variants from the discovery sets. Standardized polygenic risk scores (mean=0, SD=1) were sums of the allele

counts from the Spit for Science sample weighted by the effect size from each discovery set. The number of SNPs for each analysis is reported in Table S1.

We developed a script based on PRSice (Euesden, Lewis, & O'Reilly, 2015) to test the association between z-SWAN-Total scores with polygenic risk scores at each p-value threshold. In all polygenic risk score analyses we included array and principal components to account for population stratification (see supplemental methods). We selected the p-value threshold that accounted for the most variance in z-SWAN-Total using r^2 for each discovery set for subsequent analyses. To test if polygenic risk for ADHD, OCD and anxiety disorders were associated with high and low SWAN scores, we divided genotyped participants into three groups as described above (low: z-score <-1.11, n=670; medium: z-score -1.11 to 1.11, n= 3745, and high: z-score <1.11, n=739). We used ANOVAs to test if SWAN groups differed in their mean standardized polygenic risk scores based on ADHD, OCD and anxiety disorder discovery sets. We then used Tukey's post-hoc test to identify specific group differences. We also used regression to compare polygenic risk scores derived from the ADHD discovery set in participants above and below the Spit for Science cut-points identified in the ROC analyses for z-SWAN-Total for parent-report (n=4,426) and self-report data (n=728) separately. We conducted similar analyses using the Swanson recommended cut-point (1.65 SD; Swanson et al., 2012) in all genotyped participants (n=5,154). The significance alpha threshold was adjusted to account for multiple testing (0.05/30=0.001). We also conducted polygenic risk score analyses for SWAN scores to examine differences among respondent, SWAN sub-scales and effect of removing participants with an ADHD community diagnosis (see supplemental methods).

Results

Phenotypic Analyses in Spit for Science and Validation Clinic Sample

SWAN-Parent and SWAN-Self scores were significantly higher in participants with compared to without an ADHD community diagnosis in the Spit for Science sample (Table 1). SWAN-Parent scores were also significantly higher in ADHD patients compared to healthy controls in the clinic sample (Table 1). SWAN scores showed high sensitivity and specificity for community-reported ADHD diagnosis in the Spit for Science sample (Table 2). Sensitivity and specificity was greater for SWAN-Parent (AUC=0.85-0.88) than for SWAN-Self (AUC=0.71-0.75). In the Spit for Science sample, differences between z-SWAN-Total and non-standardized SWAN scores in predicting ADHD community diagnoses were small (see Table S2 and S3). Results from analyses with non-standardized SWAN scores are described in supplemental results (Table S2-S3).

Insert Table 1-2

Next, we validated the Spit for Science cut-point based on parent-report data in a clinic sample. In the clinic, the Spit for Science cut-point (z-SWAN-Total cut-point>0.74) correctly identified 222 of 266 ADHD cases (sensitivity: 84%) and misclassified three controls into the ADHD group (specificity = 92%). In the same clinic sample, when we applied the Swanson cut-point (2012) to the z-SWAN-Total, 95 of 266 ADHD clinic cases were correctly identified (sensitivity: 36%) and no controls were misclassified (specificity: 100%).

SWAN-Parent and SWAN-Self scores from the Spit for Science sample showed high internal consistency (SWAN-Parent-Total α=0.95, SWAN-Parent-IA α=0.92 and SWAN-Parent-HI α=0.93; SWAN-Self-Total α=0.88, SWAN-Self-IA α=0.82 and SWAN-Self-HI α=0.84). For SWAN-Parent, convergence was high between corresponding parent-reported z-SWAN-Total and CPRS-R scale scores: CPRS-R Inattentive and z-SWAN-IA (rho=0.70, p<0.01), CPRS-R

Total and z-SWAN-Total (rho=0.72, $p<0.01$), CPRS-R ADHD Index and z-SWAN-Total (rho=0.71, $p<0.01$). CPRS-R Hyperactive/Impulsive scale had a slightly lower convergence with the z-SWAN-HI (rho=0.67, $p<0.01$). For SWAN-Self, convergence was moderate for the z-SWAN-IA and the CASS-L Inattention subscale (rho=0.52, $p<0.01$) and the z-SWAN-HI and the self-reported CASS-L Hyperactivity/Impulsivity subscale (rho=0.58, $p<0.01$).

z-SWAN-Total scores were significantly associated with TOCS z-scores ($F_{(2,15557)}=8.11$, $p=0.0003$; Figure S1a), although the effect size was small (Cohen's d=0.10). Higher z-SWAN-Total scores were associated with higher CBCL anxiety total scores ($F_{(2,15557)}=18.33$, $p<.0001$). Anxiety traits were significantly higher in the group with the highest compared to the lowest z-SWAN-Total scores (low vs. high group: $p<0.0001$; Cohen's d=0.47) and intermediate scores (medium vs. high group: $p<0.0001$; Cohen's d=0.37; Figure S1b).

Insert Figure 2

Genetic Analyses in Spit for Science Sample

The estimated parameters for all polygenic risk score analyses are reported in Table S4. Figure 2 shows that ADHD polygenic risk was significantly associated with z-SWAN-Total scores. Neither polygenic risk scores based on OCD nor anxiety disorders were associated with z-SWAN-Total (Figure 2). Next, we examined if polygenic risk scores differed across low, medium and high z-SWAN-Total groups. For these analyses, we used the p-value threshold that explained the most variance for each discovery set (ADHD: $p=0.30$ [$r^2=8.74\text{x}10^{-3}$]; OCD: p=0.01 [$r^2=2.27\text{x}10^{-4}$]; Anxiety: $p<10^{-5}$ [$r^2=1.98\text{x}10^{-4}$]). Groups based on the z-SWAN-Total scores were associated with ADHD polygenic risk ($F_{(5145, 5143)}=12.97$, $p=2.4 \text{ x } 10^{-6}$). ADHD polygenic risk was significantly higher in groups with the highest SWAN scores than in groups with low and

mid-range scores (low vs. high, $p=1.21x10^{-5}$; medium vs. high, $p=2.8x10^{-4}$; medium vs. low, $p=0.09$; Figure 3). Neither OCD nor anxiety disorder polygenic risk scores were associated with z-SWAN-Total group ($F_{(5145, 5143)}=2.38$, $p=0.09$ and $F_{(5145, 5143)}=2.7$, $p=0.07$ respectively, data not shown). ADHD polygenic risk was significantly higher in participants above, compared to below, the optimal cut-points identified in the ROC analyses for parent-report z-SWAN (z-SWAN-Total score >0.74 [n=1,105] vs. score <0.74 n=3,321: $t(4409)=5.67$; $p=1.5x10^{-8}$) and the Swanson cut-point (z-SWAN-Total score >1.65 [n=270], score <1.65 [n=4,884]: $t(5144)=3.77$; $p<0.0001$; data not shown). The same trend was observed for the cut-point for self-report z-SWAN (score >0.81 n=154, score <0.81 n=574, $t(721)=1.75$; $p=0.07$; data not shown). Results from polygenic risk scores based on respondent, ADHD sub-scales and without an ADHD community diagnosis are reported in supplemental results (Table S4, Figure S2-4).

Insert Figure 2 & 3

Discussion

Ascertaining sufficiently large samples for well-powered GWAS analyses is expensive and time-consuming. Alternative and complementary strategies that use valid and genetically-informative quantitative trait measures to collect population-based samples could accelerate genetic discovery and manage costs. The current study adds to the previous literature to support the SWAN as a valid tool for use in quantitative genetic research. The SWAN generates heritable trait scores that are widely and virtually normally distributed in the general population (Couvy-Duchesne et al., 2016; Crosbie et al., 2013; Greven et al., 2016; Hay et al., 2007; Peng et al., 2016; Polderman et al., 2007; Smit & Anokhin, 2017). In this study, we showed that high SWAN scores converged with a diagnosis of ADHD in both Spit for Science and clinical samples

consistent with the notion that ADHD is the extreme of a quantitative trait. SWAN (both parent- and self-report) scores show convergence with an established measures of ADHD. We demonstrated that high ADHD trait scores were associated with anxiety traits while low ADHD trait scores were not associated with either OCD or anxiety traits. Finally, we found that both parent- and self-report SWAN scores were associated with polygenic risk for ADHD, but not OCD or anxiety disorder consistent with the notion that ADHD is the extreme of a quantitative trait.

The current study used the largest sample to date to confirm the high internal consistency of the SWAN as previously reported (Lai et al., 2013; Lakes et al., 2012; Stroud et al., 2009). We found high convergent validity of the SWAN with a gold-standard measure of ADHD. High ADHD traits were associated with anxiety traits, which often co-occur with ADHD (Jensen et al., 2001). SWAN scores, whether parent- or self-report, discriminated those with and without a community diagnosis of ADHD with high sensitivity and specificity supporting the validity of the SWAN as a measure of ADHD traits. The optimal cut-point derived in the Spit for Science sample was validated in a clinic sample as they discriminated ADHD cases from controls with good sensitivity and specificity. However, prediction of an ADHD diagnosis from SWAN scores was imperfect, which is not surprising given the range of information and informants required for a diagnosis. The Spit for Science cut-points for the SWAN-Parent (score >0.74) predicted diagnosis better than a widely used cut-point recommended by Swanson et al. (1.65 SD; 2012). The Swanson cut-point is higher than our identified cut-point resulting in higher specificity, but markedly lower sensitivity.

The SWAN-Self in adolescents also had good sensitivity and specificity for diagnosis, high internal consistency and good convergence with an accepted self-report ADHD scale – CASS-L.

Finally, parent-report SWAN scores were associated with ADHD polygenic risk. The non-significant association of ADHD polygenic risk with self-report of ADHD was likely related to power (n=728 total, n=154 above cut-point). Future studies with larger samples should investigate if parent- and self-report ADHD traits in youth have the same or different genetic architectures. Together our results suggest that although correlations between parent- and self-report ADHD symptoms are often low to moderate (Parker, Bond, Reker, & Wood, 2005), the SWAN self-report is a valid measure of ADHD traits and is associated with ADHD genetic risk.

SWAN scores were associated with polygenic risk for ADHD indicating that ADHD traits measured by the SWAN share genetic risks with diagnosed ADHD. This association was significant for both inattentive and hyperactive/impulsive subscales and remained significant after excluding individuals with a community diagnosis of ADHD, suggesting that these individuals were not driving the association. Together our results add to mounting evidence that ADHD traits and diagnosis share genetic risk (Brikell et al., 2018; Groen-Blokhuis et al., 2014; Martin et al., 2014; Middeldorp et al., 2016; Riglin et al., 2016; Stergiakouli et al., 2015).

High ADHD traits alone do not constitute or replace a diagnosis of ADHD. Under some circumstances, high ADHD traits could be a strength in the right context and would not warrant a diagnosis. A diagnosis of ADHD requires a comprehensive clinical assessment and should not be based solely on questionnaire information, especially from a single informant. However, our results indicate that high ADHD traits converge with ADHD diagnosis in a clinical sample and share genetic risk with diagnosed ADHD, which suggest an overlap between high ADHD traits and diagnosis. Therefore, SWAN could be useful for genetic studies of ADHD traits especially in large samples where rapid collection of samples at low cost is desirable. These studies could help identify genetic variants for ADHD in complement with existing case/control studies. The

SWAN could also play an important role in clinical practice and research. With the available age and gender norms, the SWAN could be used for screening of ADHD symptoms as part of a comprehensive assessment, for establishing a treatment baseline and for monitoring progress.

One critique of the use of trait measures such as the SWAN in research or clinical practice is the presumption that the low extreme of a trait represents a strength (Plomin et al., 2009). Low ADHD traits could reflect above average impulse, motor and attention control (Fair et al., 2012) or hypo-activity, inertia, over-focusing, or perseveration of the type seen in OCD or anxiety disorders. In our study, participants with low trait ADHD scores did not have elevated scores for anxiety or for OC traits, supporting the hypothesis that low ADHD trait scores are most likely strengths rather than evidence of a different disorder. The finding that SWAN scores were not associated with polygenic risk for anxiety or OCD further supports this hypothesis. Similarly, in recent larger, better-powered studies ADHD polygenic risk scores were only weakly or not associated with anxiety (Brikell et al., 2018; Du Rietz et al., 2018).

Our study has various strengths. It is the largest population-based study of the SWAN and the first study to calculate general population-based cut-points and validate them in a clinic sample. Age and gender standardized SWAN scores were used to create scoring software, the ADHD Calculator of Traits (ACT©; https://synapse.research.sickkids.ca/act/welcome). Limitations of our study include that our sample was slightly biased towards higher socio-economic status (SES); however, SES was not associated with traits in our sample (Crosbie et al., 2013). We were also unable to assess the association of ADHD traits with conduct and oppositional-defiant disorder traits, as they were not measured in our Spit for Science sample because of time constraints. For the polygenic risk score analyses, the discovery set for OCD and anxiety were smaller than for ADHD, which implies that a lack of power may have affected our results.

However, these discovery samples were sufficient to show significant associations with other traits previously (International Obsessive Compulsive Disorder Foundation Genetics Collaborative & Studies, 2017; Meier et al., 2018; Taylor et al., 2017) suggesting that lack of power may not be driving the results. As in all other polygenic risk studies, the variance explained in the trait were small, which is likely the result of several factors including the size of discovery and target sample sets and the role of rare variants, epistasis and gene by environment interactions (Mistry, Harrison, Smith, Escott-Price, & Zammit, 2018; van der Sluis et al., 2013).

Conclusion

This study indicates that the SWAN is a valid quantitative trait measure that is sensitive to genetic variation in ADHD, but not genetic variation in other disorders. Our results suggest the utility of the SWAN for the study of ADHD traits in population-based designs where increased speed and reduced costs could make genetic studies more feasible.

Key Points

- Valid and genetically-informative quantitative trait measures in population-based samples are a viable complement for gene discovery in ADHD.
- Both the parent- and self-report SWAN scales had sound psychometric properties.
- High ADHD traits were associated with diagnosed ADHD and anxiety traits while low ADHD traits were not associated with anxiety or OCD traits.
- ADHD traits shared polygenic risk with diagnosed ADHD but not OCD or anxiety disorders.

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Table 1. Mean parent- and self-report SWAN by reported ADHD diagnosis in the Spit for Science and clinic ADHD samples.

Spit for Science Sample*					
	Without ADHD diagnosis	**With ADHD diagnosis**	**t-value**	**p-value**	**Cohen's d**
N	14,588	972			
SWAN-Parent (mean, SD)					
N	11,987	810			
Age	10.06 (2.08)	10.77 (2.08)			
Male (N, %)	6203 (51.75)	613 (75.68)			
z-SWAN					
z-SWAN-Total	-0.09 (0.94)	1.37 (0.79)	-50.30	<0.0001	1.57
z-SWAN-IA	-0.09 (0.95)	1.27 (0.84)	-43.75	<0.0001	1.44
z-SWAN-HI	-0.08 (0.95)	1.25 (0.85)	-42.85	<0.0001	1.36
SWAN-Self (mean, SD)					
N	2,601	162			
Age	15.34 (1.29)	15.41(1.22)			
Male (N, %)	983 (37.79)	104 (64.20)			
z-SWAN					
z-SWAN-Total	-0.05 (0.97)	0.88 (0.98)	-11.84	<0.0001	0.96
z-SWAN-IA	-0.05 (0.98)	0.80 (0.97)	-10.71	<0.0001	0.87
z-SWAN-HI	-0.05 (0.98)	0.75 (1.04)	-9.97	<0.0001	0.81
Validation Clinic Sample					
	Controls	**ADHD cases**	**t-value**	**p-value**	**Cohen's d**
N	36	266			
Age	8.92 (1.87)	9.15 (2.26)			
Male (N, %)	16 (44.44)	209 (78.57)			
SWAN-Parent (mean, SD)					
z-SWAN					
z-SWAN-Total	-0.51 (1.05)	1.36 (0.68)	-10.38	<0.0001	2.55
z-SWAN-IA	-0.55 (1.08)	1.38 (0.83)	-10.35	<0.0001	2.24
z-SWAN-HI	-0.41 (1.00)	1.12 (0.78)	-8.80	<0.0001	1.89

No self-report scales were collected in the validation ADHD clinic sample. SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale, SD = standard deviation; z-SWAN-Total = Standardized SWAN total score; z-SWAN- IA = Standardized SWAN, inattentive subscale; z-SWAN-HI = Standardized SWAN, hyperactive/impulsive subscale. *Community diagnosis was parent or self-reported.

Table 2. Area under the curve (AUC), optimal cut-points, sensitivity and specificity for classifying ADHD (Spit for Science sample)

	AUC	Optimal cut-point	Sensitivity	Specificity
Parent-report				
z-SWAN-Total	0.88	>0.74	82.3	81.1
z-SWAN- IA	0.86	>0.60	81.2	76.2
z-SWAN- HI	0.85	>0.72	77.0	80.0
Self-report				
z-SWAN-Total	0.75	>0.81	57.4	81.4
z-SWAN-IA	0.73	>0.51	63.0	71.6
z-SWAN-HI	0.71	>0.56	60.5	73.2

z-SWAN-Total = Standardized SWAN score combined; z-SWAN- IA = Standardized SWAN inattentive subscale; z-SWAN-HI = Standardized SWAN hyperactive/impulsive subscale

Figure Captions

Figure 1: Overview of samples and SWAN variables.

The Spit for Science population-based sample contained 15,560 participants with complete data (12,797 with parent-reported data, 2,673 with self-reported data). The SWAN-Parent and SWAN-Self each have inattentive (SWAN-Parent-IA, SWAN-Self-IA) and hyperactive/impulsive subscales (SWAN-Parent-HI; SWAN-Self-HI) that can be summed to generate a total score (SWAN-Parent-Total and SWAN-Self-Total). We also created standardized scores that accounted for age, gender and respondent for the total score and both subscales (z-SWAN-Total, z-SWAN-IA, z-SWAN-HI). We also genotyped the Caucasian sub-sample of the Spit for Science sample (n=5,366), of which 5,154 passed standard quality control analyses (parent-report n=4,426, self-report n=728). Our clinic validation sample had 266 pediatric ADHD patients and 36 health controls. For the polygenic risk score (PGRS) analyses, we used three Caucasian European discovery samples: ADHD from the Psychiatric Genomics Consortium and iPSYCH meta-analysis (European-only), OCD from the International OCD Foundation Genetics Collaborative (IOCDF) and OCD Collaborative Genetics Association Studies meta-analysis (OCGAS) and anxiety disorders from the Anxiety Neuro Genetics Study (ANGST).

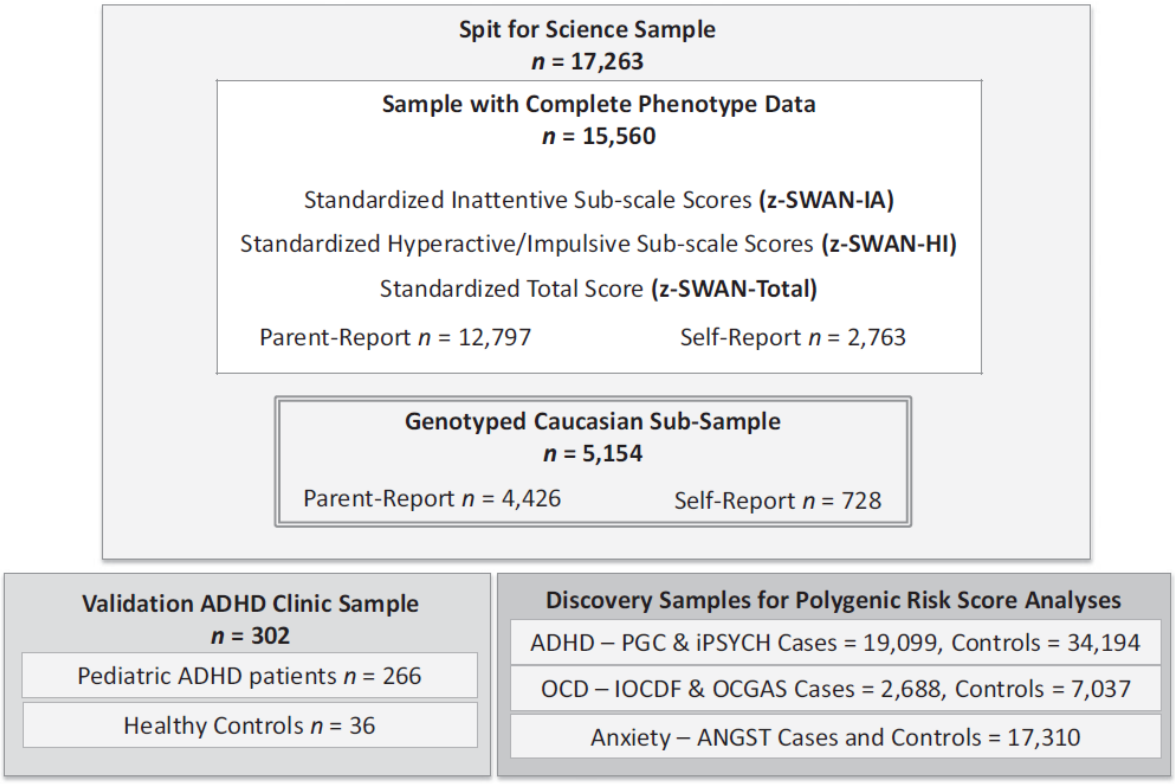

Spit for Science Sample
n = 17,263
Sample with Complete Phenotype Data
n = 15,560
Standardized Inattentive Sub-scale Scores (z-SWAN-IA)
Standardized Hyperactive/Impulsive Sub-scale Scores (z-SWAN-HI)
Standardized Total Score (z-SWAN-Total)
Parent-Report n = 12,797
Self-Report n = 2,763
Genotyped Caucasian Sub-Sample
n = 5,154
Parent-Report n = 4,426
Self-Report n = 728
Validation ADHD Clinic Sample
n = 302
Pediatric ADHD patients n = 266
Healthy Controls n = 36
Discovery Samples for Polygenic Risk Score Analyses
ADHD – PGC & iPSYCH Cases = 19,099, Controls = 34,194
OCD – IOCDF & OCGAS Cases = 2,688, Controls = 7,037
Anxiety – ANGST Cases and Controls = 17,310

Figure 2: Association of SWAN Scores and Polygenic Risk for ADHD, OCD and Anxiety

Polygenic risk scores (PGRS) derived from clinical attention-deficit/hyperactivity disorder (ADHD, * $p < 0.001$), but not obsessive-compulsive disorder (OCD) or anxiety disorder, discovery samples were significantly associated with ADHD traits (standardized total Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale [z-SWAN-Total] score). P-value thresholds refer to parameters from discovery sample statistics (ADHD, OCD, Anxiety disorders). r^2 = variance explained in z-SWAN-Total by polygenic risk from the respective discovery sample. P-value in legend reflects the association of PGRS and z-SWAN-Total.

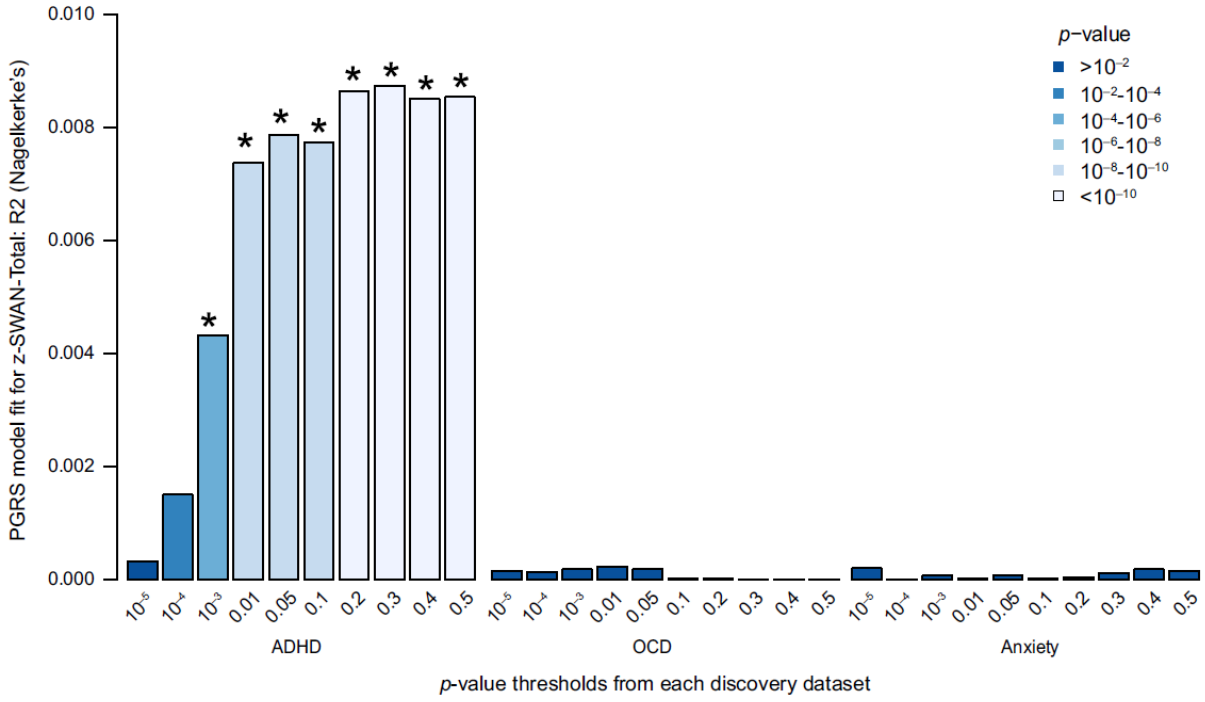
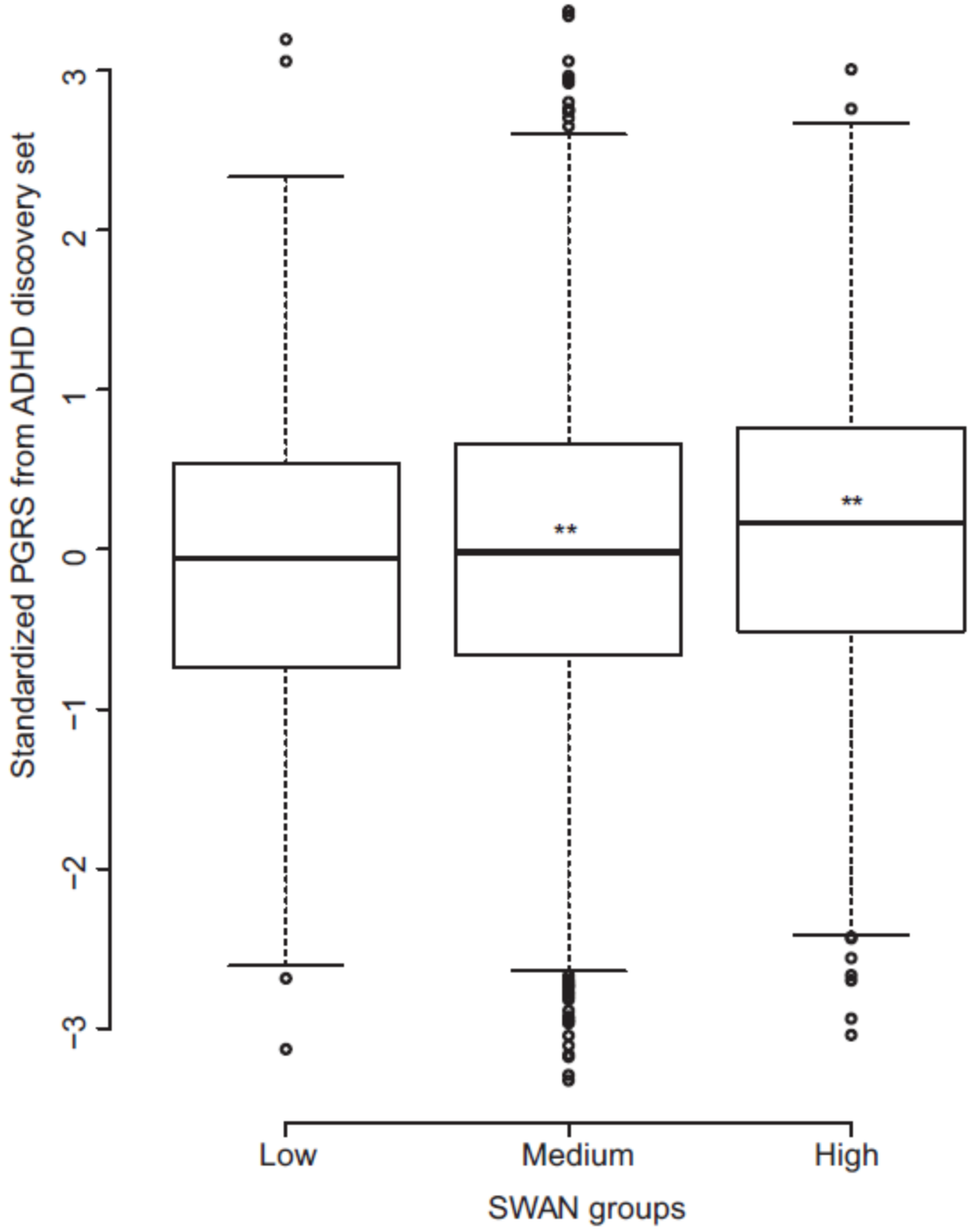


Figure 3. ADHD Polygenic Risk Scores across Low to High ADHD traits.

Attention-deficit/hyperactivity disorder (ADHD) polygenic risk was highest in the group with the highest Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale standardized total score (z-SWAN-Total) scores (** low vs. high, $p=1.21 \times 10^{-5}$; medium vs. high, $p=2.8 \times 10^{-4}$; medium vs. low, *ns*). Low group: z-score <-1.11, n=670; medium group: z-score -1.11 to 1.11, n=3745, and high group: z-score <1.11, n=739). PGRS = polygenic risk score.


Standardized PGRS from ADHD discovery set
3
2
1
0
−1
−2
−3
**
**
Low
Medium
High
SWAN groups