Utility of Attention-Deficit/Hyperactivity Disorder Trait Measure in Population Genetics: A Polygenic Risk Study

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Abstract

Background: We tested the utility of the SWAN (Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale) for measuring attention-deficit/hyperactivity disorder (ADHD) traits in population-based genetics. We examined the convergent, predictive, and discriminant validity of the SWAN parent- and new youth-report scale while creating norms and clinical cut-offs. We tested if high ADHD traits were associated with ADHD diagnosis and polygenic risk and if low ADHD traits pointed to another psychopathological phenotype or genetic risk.

Methods: We collected parent- and youth-reported SWAN scores in a community sample (n=15,560; 6-18 years of age). Sensitivity-specificity analyses determined SWAN scores that discriminated a community ADHD diagnosis (n=972). Cut-offs were validated in a clinic sample (266 ADHD patients; 36 controls). We examined the relationship of SWAN scores with anxiety, obsessive-compulsive (OC) traits as well as ADHD, obsessive-compulsive disorder (OCD), and anxiety disorder using polygenic risk scores.

Results: SWAN scores showed high convergent validity and distinguished ADHD participants with high sensitivity and specificity in the community sample. The community-based threshold discriminated ADHD clinic cases from controls with a sensitivity of 86% and specificity of 94%. High ADHD traits were associated with high anxiety, but not OC, traits. High SWAN scores and those above the community-based cut-off were only associated with ADHD polygenic risk.

Conclusions: The SWAN is useful for genetic research because it predicts ADHD diagnoses with high sensitivity and specificity and is associated with ADHD polygenic risk. Cut-off

values and norms are presented. Low ADHD traits were not associated with other psychopathology.

Introduction

Characterized by marked restlessness, inattentiveness, and impulsiveness, attention-deficit/hyperactivity disorder (ADHD) is an impairing disorder affecting 5% of children (1). Genetics strongly influence ADHD (2) and polygenic analyses show that many common variants acting together contribute significantly to the genetic risk (3). Progress in identifying genome-wide significant associations has been slow in part because ADHD is both genetically and phenotypically complex. The Psychiatric Genetics Consortium (PGC) recently identified the first genome-wide significant associations for ADHD by amalgamating clinical samples (>20,000 cases; 4). Over 100,000 participants will likely be needed to identify the majority of genetic risk variants for complex disorders like ADHD (5).

One strategy for efficiently increasing sample size and statistical power for genetic discovery is studying ADHD traits in non-clinical samples. The rationale for this strategy is that clinical ADHD can be considered the extreme of continuously distributed traits of activity, attention, and impulsiveness (6, 7). This hypothesis is supported by substantial overlap in genetic risk between diagnosed ADHD and ADHD trait scores (6, 7) and a dose-dependent relationship between ADHD symptom severity in the general population and polygenic risk scores based on ADHD case-control studies (8).

Trait measures must be carefully designed because genetic analyses are sensitive to the measurement of ADHD traits (3). A genetically-informative trait measure should be reliable, heritable, and generate widely and normally distributed trait scores. Symptom rating scales are the most widely used to measure ADHD traits. These scales ask informants

to rate the severity of individual symptoms from no symptoms (e.g., "0") to marked, severe and persistent symptoms ("3"). A score of 2 or greater on these scales is considered a symptom. Summing across all 18 symptoms based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; 9) ADHD criteria provides a score from 0-18 symptoms. Examples of symptom-based scales are the Conner's Parent Rating Scale and the Swanson, Nolan, and Pelham (SNAP-IV; 10, 11). However, these scales do not provide information about the full distribution of ADHD traits that are believed to vary widely in the general population. Using these measures, people with no ADHD symptoms get a score of "0" whether they are highly attentive and reflective or have no symptoms (12). In the general population sample, the distribution of scores aggregates at zero creating a "J-shaped" distribution which cannot be normalized and ignores potentially meaningful variation in the lower ranges of scores. Combining normally attentive and highly attentive individuals overlooks the opportunity to identify risk and protective factors and to distinguish individuals with few risk factors from those who have many (12, 13).

If ADHD represents the extreme of a trait, then a genetically-informed trait measures should show high, but not complete, convergence between trait extremes and ADHD diagnosis (12, 14). Trait-based measures are also assumed to tap into a single construct. People with extreme high traits have the disorder of interest while people with low trait scores may have strengths in those areas. Alternatively, low trait scores could indicate a weakness in another area. For example, being able to sit still, be reflective, and highly attentive under all circumstances could connote a strength or reflect different disorders such as anxiety or obsessive compulsive disorder (OCD) that are partially characterized by

over-attention to threatening stimuli (15, 16), or underactivity due to shyness or fear, respectively.

The Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN; 17) is unique among ADHD trait measures. The SWAN is based on the 18 ADHD items from the DSM-IV (17, 18) and generates a total score and two subscales for inattentive and hyperactive/impulsive traits. Items are worded to permit informants to report both "strengths" and "weaknesses" on a seven-point scale. For example, -3 = far above average indicates low ADHD trait scores to +3 = far below average indicates the presence of an ADHD trait. Values of 0 indicate average levels of each item (17). The SWAN is typically completed by parents although a teacher-report version has been used (19). To date, no youth self-report version of the SWAN exists but is needed since youth and their parents often disagree about symptoms (20, 21) and youth can be the only available informant in population research.

The SWAN meets many criteria of a potential genetically-informative trait measure. It is reliable and generates normally distributed scores for ADHD traits in the general population (17, 19, 22-27). The SWAN has strong psychometric properties (28) with high internal consistency (α = .88-.98 for the SWAN total and subscales (19, 25, 26, 29, 30)), high test-retest reliability (intraclass correlations [ICCs] ranging from .84-.90; Pearson's r ranging from .72-.90; (19, 22, 25)), and reasonable convergent validity with ADHD measures (22, 23, 25-27, 29). Low correlation with measures of emotions suggests discriminant validity (25) although correlations with the SWAN total score does not explicitly address the presence of other traits at the extremes. The heritability of the

parent-report SWAN total scores [h^2=0.38], hyperactivity-impulsivity [h^2=0.40] and inattention [h^2=0.24] subscales has also been established (14).

Nevertheless, questions remain about the SWAN's ability to discriminate ADHD cases from controls with adequate sensitivity and specificity. This is a critical point given that ADHD is assumed to represent the extreme of ADHD traits. Although high ADHD trait scores may also correlate to some degree with other disorders that are comorbid with ADHD (e.g., anxiety; 31), we do not know if people with low trait scores for activity, attention, and impulse control have internalizing symptoms such as obsessiveness, compulsiveness, or anxiety. SWAN scores should scale with polygenic risk for ADHD (i.e., higher SWAN scores with higher polygenic risk for ADHD) and not with polygenic risk for OCD or anxiety. Finally, the availability of a youth self-report SWAN would be useful for population-based genetic research.

In a large community sample (15,560 individuals ages 6-18 years), we assessed the psychometric properties of a new youth self-report version of the SWAN and validated norms for parent and youth versions. We tested the hypothesis that the SWAN discriminates individuals with a self-reported community diagnosis of ADHD and that the same threshold can discriminate clinic cases (n=266) from age-matched controls (n=36). We expected participants above compared to below this community-based cut-off would have higher ADHD polygenic risk scores. We hypothesized that ADHD traits would be associated with average to low levels of anxiety and obsessive-compulsive traits (OC) and high ADHD traits would be associated with elevated anxiety and OC traits based on the high rate of comorbidity in ADHD (31). We predicted that SWAN scores would be associated

with ADHD, but not OCD or anxiety, polygenic risk scores and that ADHD polygenic risk would be highest with high SWAN scores.

Methods and Materials

Community sample

We studied 17,263 youth (ages 6-18 years) at the Ontario Science Centre in Toronto, Canada (see (14) for description of sampling method). Participants were de-identified at the time of data collection. We collected information about demographics, history of ADHD or treatment with stimulants and ADHD traits from parents of 12,797 children (6-14 years) and 2,763 youth (ages 14-18 years). 15,560 had complete information. 972 (6.2%) had received a diagnosis of ADHD (community diagnosis); a rate consistent with the generally-accepted childhood prevalence of ADHD (32, 33). Both the parent- (SWAN-Par) and self-reported SWAN (SWAN-Self) consist of two subscales that measure hyperactive/impulsive (SWAN-Par-HI or SWAN-Self-HI) and inattentive (SWAN-Par-IA or SWAN-Self-IA) traits and a total or combined score (SWAN-Par-Com or SWAN-Self-Com). To assess convergent validity, we had a random subset of participants complete a second widely-used ADHD rating scale Conners' ADHD Rating Scale-Revised (CPRS-R; n=841) or Conners-Wells Adolescent Self Report Scale (CASS-L; n=172). The CPRS-R and the Conners-Wells' Adolescent Self Report Scale generate four ADHD related scales in T-score format: The Inattentive scale (L-scale), Hyperactive-Impulsive scale (M-scale), Total scale (N-scale), and an ADHD Index scale (H-scale) which is comprised of items that have a demonstrated relationship with ADHD symptoms and identifies children 'at risk' for ADHD (11).

Parents and youth also completed questionnaires that measure anxiety (Child Behavior Checklist – CBCL; 34) and obsessive-compulsive (OC) traits (Toronto Obsessive Compulsive Scale – TOCS; 35). The CBCL anxiety problems sub-scale (34) has 11 items that each range from 0 ('not true') to 2 ('very true or often true'). Similar to the SWAN, the TOCS has 21-items scored on a 7-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').

ADHD Clinic Sample

The clinic sample consisted of 266 children (6-18 years old) with a clinician-confirmed diagnosis of ADHD and 36 controls children assessed in a tertiary care mental health clinic. Diagnoses were based on consensus between a psychiatrist and clinical psychologist following a rigorous assessment described in detail elsewhere (36, 37). Individuals with an IQ <80 in both verbal and non-verbal domains were excluded. Parent-reported SWAN scores were not taken into consideration during the diagnostic process. Self-report SWANs were not collected on the clinic sample because most participants were pre-adolescent.

Ethics

Informed consent and verbal assent when applicable approved by the Hospital for Sick Children Research Ethics Board were obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. No compensation was given to participants.

Statistical analyses

We refer to scores as high or low ADHD traits. We reversed the scoring of the SWAN items. As such, for SWAN-Par-Com and SWAN-Self-Com; the maximum score of +54 indicated the *highest* ADHD trait score while the minimum of -54 represented the *lowest* ADHD trait score. For SWAN-Par-HI, SWAN-Self-HI, SWAN-Par-IA and SWAN-Self-IA, the minimum was -27 and the maximum was +27.

We standardized SWAN scores for age and gender. Participants were divided into 30 groups according to respondent (parent- or self-report), gender, and age. 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. Standardized scores were created for the overall total (zSWAN-Com) and each subscale (zSWAN-IA and zSWAN-HI). Bootstrap analysis using SAS 9.3 established confidence intervals. The same methods created standardized TOCS total score (zTOCS) and CBCL anxiety problem sub-scale total scores.

We compared participants with and without a community-reported diagnosis of ADHD on SWAN scores in parent- and self-respondents separately using t-tests. In analyses without standardized zSWAN scores, we included age and gender as covariates. The sample was highly enriched for siblings so relatedness was accounted for in the model using random effects.

Receiver operating characteristic curves (ROC) were used to select optimal models for predicting an ADHD diagnosis. We calculated optimal cut-points for SWAN-Par-Com,

SWAN-Self-Com, and zSWAN-Com by comparing scores of participants with and without a community diagnosis of ADHD. Area under the curve (AUC) of 0.8 indicates good discrimination of cases from non-cases. The Youden Index indicates the optimal cut-off point in an ROC curve. Cut-offs derived from the community sample were tested in the clinic sample to validate their ability to correctly classify those diagnosed with ADHD. We compared the optimal threshold derived from the above analyses with the threshold recommended by Swanson (1.65 SD; 17). ROC analyses were conducted using MedCalc Application. All other statistical tests were performed using SPSS 21 and SAS v9.4.

Internal consistency was assessed using Cronbach's α for both the parent- and self-report versions of the SWAN. Internal consistency values where $\alpha \geq 0.80$ are considered good. Because the CPRS-R and CASS-L create standardized scores, the correlation between the z-SWAN subscales and their corresponding CPRS-R subscales (Total, Inattentive, Hyperactive/Impulsive, and ADHD Index) and CASS-L subscales were calculated in the 841 participants who completed two measures to assess convergent validity. Spearman's rho was used to assess correlations because CPRS and CASS-L scores were not normally distributed.

To examine the phenotypic relationship of parent- and self-report zSWAN-Com scores across their continuum with OC and anxiety traits, we divided participants into 5 groups based on their SWAN scores (group 1 [low ADHD traits] n=357, group 2 n=3,607, group 3 n=7,739, group 4 n=3,515, group 5 [high ADHD traits] n=342). We used ANOVAs to assess mean differences in standardized OC (TOCS total score) and anxiety (CBCL anxiety problem

scale total score) trait scores across SWAN groups. Relatedness was accounted for in the model using random effects.

A subset of the sample (n=5,366) was genotyped on the Illumina HumanCoreExome and OMNI1M arrays. Details about extraction, genotyping and quality control can be found online in supplemental information. A total of 5,154 participants that passed standard QC were used in the analyses. Polygenic risk scores were calculated based on three discovery samples: 1) ADHD from the PGC ADHD sample (4; cases = 20,183, controls = 35,191), 2) OCD from the recent GWAS meta-analysis (38; cases = 2688 and controls = 7037) and anxiety disorders from Anxiety Neuro Genetics Study (ANGST (39); 17,310 cases and controls). From each discovery set, we selected a subset of pruned SNPs based on a range of p-value thresholds ($p < 1*10^{-5}$, $1*10^{-4}$, $1*10^{-3}$, 0.05, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5). Pruning was conducted in plink 1.9 (40; http://pngu.mgh.harvard.edu/purcell/plink/ref) on all unambiguous variants from the discovery sets. The polygenic risk score was constructed as a weighted sum of the expected allele counts from our community-based sample weighted by the effect size from the discovery set. For each discovery set, standardized polygenic risk scores were created (mean=0, SD=1).

Based on PRSice (41) we developed a script to identify the p-value cut-off for each discovery set that explained the most variation of the zSWAN-Com scores. We tested the association between zSWAN-Com scores with polygenic risk scores at each p-value cut-off while correcting for potential genotyping batch effect as well as population stratification using the principal components as described in the supplemental methods. We then selected the p-value threshold that accounted for the most variance in zSWAN using r^2 for each respective discovery set for subsequent analyses. To understand if polygenic risk for

psychiatric disorders were associated with SWAN scores across the continuum from low to high ADHD traits, we divided genotyped participants equally into 3 groups based on their zSWAN-Com scores (low, medium, high) and compared the pair-wise mean polygenic risk score differences across the 3 groups using Tukey's test within each discovery set (ADHD, OCD and anxiety). We also compared polygenic risk scores derived from the ADHD discovery set in participants above and below the optimal threshold identified in the ROC analyses for zSWAN-Com with parent-reported data (n=4,426) using a two-sided t-test. We only examined parent-report because the number of genotyped participants with self-reported SWAN data was small (n=728). We conducted similar analyses using the threshold of 1.65 SD recommended by Swanson (17) in all genotyped participants (n=5,154).

Results

As shown in Table 1, participants with ADHD community diagnoses had significantly higher SWAN scores than those without ADHD community diagnoses, whether parent- or self-reported. The ADHD clinic sample had comparable SWAN scores to that of the community-ADHD cases and clinic controls had lower SWAN scores than community controls (i.e. those without self-reported ADHD diagnoses, Table 2). SWAN scores showed high sensitivity and specificity to discriminate between community-reported ADHD and control participants (Table 3). Sensitivity and specificity were greater for parent-report (AUC=0.85-0.90) than self-report (AUC=0.71-0.76). Differences between zSWAN-Com and non-standardized SWAN scores in predicting ADHD community diagnoses were small. When the Swanson cut-point (1.65 SD; 17) for both zSWAN –Com was applied in the community sample,

sensitivity and specificity decreased (sensitivity 57 and 70 respectively; specificity 92 and 90 respectively).

In the clinic sample, a SWAN-Par-Com threshold of >6 resulted in sensitivity of 86 and specificity of 94, correctly identifying 228 of 266 ADHD cases (86%) while misclassifying one control case into ADHD group (3%).

SWAN-Par and SWAN-Self scores showed high internal consistency (SWAN-Par-Com α = .95, SWAN-Par-IA α = .92, and SWAN-Par-HI α = .93; SWAN-Self-C α = 0.88, SWAN-Self-IA α = 0.82, and SWAN-Self-HI α = 0.84). In participants with parent-reported ratings, convergence was high between corresponding zSWAN-Com and CPRS scale scores: CPRS-R Inattentive and zSWAN-IA (rho =.70, $p < 0.01$), CPRS-R Total and zSWAN-Com (rho =.72, p < 0.01); CPRS-R ADHD Index and zSWAN-Com (rho =.71, $p < 0.01$). CPRS-R Hyperactive/Impulsive scale had a slightly lower convergence with the zSWAN-HI (rho = .67, $p < 0.01$). In participants with self-reported ratings, convergence between zSWAN-IA and the CASS-L Inattention subscale was moderate (rho = 0.52, $p <0.01$), as was the convergence between the zSWAN-HI and the CASS-L Hyperactivity/Impulsivity subscale (rho = 0.58, $p <0.01$).

SWAN groups were significantly associated with standardized TOCS total scores reflecting OC traits ($df = 6$, $F = 8.45$, $p < .0001$; Figure 1a). Groups with the lowest (groups 1 and 2) and highest zSWAN-Com scores (group 5) tended to have the lowest zTOCS scores and those with mid-range zSWAN-Com scores had somewhat higher TOCS scores (groups 3-4) although the effect size was small (cohen's d = 0.33). As shown in Figure 1b, higher zSWAN-Com scores were associated with higher CBCL anxiety problem scale total scores ($df = 6$, $F =$

18.33, $p < .0001$). The group with the highest zSWAN-Com scores had higher anxiety traits than the group with the lowest ($p < 0.01$; cohen's d = 0.85) and intermediate z-SWAN-Com scores ($p < 0.01$; cohen's d = 0.67).

Figure 2 shows that polygenic risk from ADHD was significantly associated with zSWAN-Com scores and the most variance explained was using the p-value = 0.3 threshold from the discovery set (r2 =$8.74*10^{-3}$ $p = 1.73x10^{-11}$). Neither polygenic risk scores based on OCD nor anxiety disorders predicted zSWAN-Com (*ns*). The p-value thresholds that explained the most variance in each trait were 0.01 for OCD (r2 = $2.27*10^{-4}$) and 10^{-5} for anxiety (r2 =$1.98*10^{-4}$). As shown in Figure 3a, when comparing polygenic risk scores across 3 groups from low to high zSWAN-Com scores, ADHD polygenic risk was significantly higher in the participants with the highest SWAN scores than those with low and mid-range scores (low vs. high, $p = 1.48*10\text{-}^{10}$; medium vs. high, $p = 4.27*10^{-5}$; medium vs. low, $p = 0.07$). There were no significant differences in polygenic risk scores derived from OCD or anxiety across the SWAN categories respectively (Supplementary Figures 1a and 1b, $p > 0.4$). Polygenic risk scores based on ADHD were significantly higher in participants above, compared to below, the optimal thresholds identified in the ROC analysis (zSWAN-Com score>=0.54: t=5.5; $p = 3.015e*10^{-8}$) and the threshold set by Swanson (17; using zSWAN-Com score>=1.65: t=3.5; $p = 0.0006$; data not shown).

Discussion

Our results show that SWAN scores, whether raw or standardized, parent- or self-report, discriminate cases from controls with high sensitivity and specificity and show convergent validity with a gold-standard measure of ADHD. Validating cut-offs derived from the

community in an ADHD clinic sample strengthens evidence for sensitivity and specificity of the SWAN and supports the use of the SWAN as a measure of traits underlying an ADHD diagnosis. Prediction of an ADHD diagnosis from SWAN scores was not perfect which is not surprising given the range of factors and informants that must be taken into account in a diagnosis. The current cut-points for the SWAN (score of 7) yielded better AUC thresholds than the 1.65 SD cut-off recommended by Swanson (17). The 1.65 SD threshold is higher than what the current research identified, resulting in higher specificity but markedly lower sensitivity. Both cut-points were associated with genetic risk for ADHD, which supports that ADHD traits measured by the SWAN share some underlying biology with ADHD. We also confirmed in the largest sample to date the high internal consistency and convergent validity of the SWAN with other measures of ADHD and generated standardized norms for parent- and youth self-reported SWAN measure. SWAN scores were also associated with genetic risk for ADHD, but not other common childhood psychiatric disorders demonstrating the utility of the SWAN for ADHD genetic research.

One critique of the use of strength to weakness trait measures such as the SWAN in research or clinical practice is the presumption that the low extreme of a trait represents a strength (12). Extreme low ADHD traits could reflect above average impulse, motor, and attention control. However, extremely low traits could reflect hypo-activity, inertia, over-focusing, or perseveration seen in OCD or anxiety disorders. In our study, participants with low trait ADHD scores did not have elevated scores for anxiety or for obsessive-compulsive traits, supporting the hypothesis that low ADHD trait scores are indeed strengths. Similarly, Greven (42) et al. found that low SWAN scores were associated with better cognitive performance, fewer behavior problems, more positive traits. Further, extremely low traits

on the SWAN were largely influenced by shared environmental factors (e.g., less parental negativity, less chaotic homes) and less so by genetic influences. In our study, high SWAN scores not only reflected high ADHD traits but also elevated anxiety in keeping with the well-known comorbidity of these traits (31). OC traits tended to be lowest with high and low SWAN scores but the effect size was small. Polygenic risk scores for OCD and anxiety disorder were similar across the range of SWAN scores which suggests that neither low or high ADHD traits are associated with elevated genetic risk for these two disorders. Together our findings indicate that the SWAN is sensitive and specific to ADHD traits both phenotypically and genetically.

Trait-based questionnaires can play an important role in clinical practice and research. Questionnaires with appropriate age and gender norms could be useful for screening of ADHD symptoms as part of a comprehensive assessment, for establishing a treatment baseline, and for monitoring progress. Diagnosing ADHD requires a comprehensive clinical assessment that carefully weighs the presence of inclusion and exclusion criteria as delineated in diagnostic manuals. Diagnosis should never be based solely on questionnaire information, especially from a single informant.

The current study has various strengths: it is the largest population-based study of the SWAN; it is the first study to calculate general population-based thresholds and validate them in a clinic sample; and it generated age and gender standardized scores of the SWAN, which have been used to create scoring software, the ADHD Calculator of Traits (ACT)© that can be accessed by clinicians, researchers, and parents at http://www.sickkids.ca/Research/schachar-lab/index.html. Future research should

explore differences between the self-report and parent-report SWAN on comorbid traits and polygenic risk when larger samples are available.

Although clinical diagnosis is the gold standard for clinical practice, it could lack the level of precision required for research into the mechanism of disease. Quantitative traits that measure ADHD strengths and weaknesses open the possibility of finding not only genetic risks for ADHD but also protective factors (12). In addition, the collection of clinically diagnosed participants on the necessarily large scales for genetic research is expensive, time consuming, and likely to result in low inter-rater reliability and decreased statistical power. Collection of a large, rigorously-diagnosed sample of affected individuals with the adequate power to detect genetic effects is the rate-limiting step in psychiatric genetics both in terms of time and cost (43). Growing evidence demonstrates that ADHD diagnosis is consistent with extreme scores of continuously distributed inattention, hyperactivity and impulsivity traits. This assumption is supported by the results of the current study showing that individuals in the general community reporting a diagnosis of ADHD scored significantly higher on the SWAN ADHD trait measure and high SWAN scores were associated with ADHD polygenic risk. This trait measure is also associated with cognitive deficits in ADHD believed to share genetic risk with the disorder (14). The SWAN affords an alternative phenotyping strategy for gene discovery in ADHD.

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Table/Figure Legends

Table 1: Mean Parent- and Self-report SWAN scores (total and subscales) for community sample with and without self-reported community ADHD diagnosis.

* indicates that $p < 0.0001$. SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale, ADHD = attention-deficit/hyperactivity disorder; SD = standard deviation; SWAN-Par-Com = Parent-report SWAN, combined; SWAN-Par-IA = Parent-report SWAN, inattentive subscale; SWAN-Par-HI = Parent-report SWAN, hyperactive/impulsive subscale; SWAN-Self-Com = Self-report SWAN, combined; SWAN-Self-IA = Self-report SWAN, inattentive subscale; SWAN-Self-HI = Self-report SWAN, hyperactive subscale; zSWAN-Com = Standardized SWAN score, combined; zSWAN- IA = Standardized SWAN for both informants, inattentive subscale; zSWAN-HI = Standardized SWAN, hyperactive/impulsive subscale.

Table 2. Mean parent-report SWAN scores (total and subscales) for clinic sample with clinician-confirmed ADHD diagnoses and controls.

* indicate that $p < 0.0001$; no self-report scales were collected in clinic sample or clinic controls; SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale, ADHD = attention-deficit/hyperactivity disorder; SD = standard deviation; SWAN-Par-Com = Parent-report SWAN, combined; SWAN-Par-IA = Parent-report SWAN, inattentive subscale; SWAN-Par-HI = Parent-report SWAN, hyperactive/impulsive subscale; zSWAN-Com = Standardized SWAN score, combined; zSWAN- IA = Standardized SWAN for both informants, inattentive subscale; zSWAN-HI = Standardized SWAN, hyperactive/impulsive subscale.

Table 3. Area under the curve (AUC), optimal cut-off scores, sensitivity and specificity for classifying ADHD (community diagnosis) in general population sample

ADHD = attention-deficit/hyperactivity disorder; SWAN-Par-Com = Parent report SWAN, combined; SWAN-Par-IA = Parent report SWAN, inattentive subscale; SWAN-Par-HI = Parent report SWAN, hyperactive/impulsive subscale; SWAN-Self-Com = Self report SWAN, combined; SWAN-Self-IA = Self report SWAN, inattentive subscale; SWAN-SELF-HI = Self report SWAN, hyperactive subscale; zSWAN-Com = Standardized SWAN score for both informants, combined; zSWAN- IA = Standardized SWAN for both informants, inattentive subscale; zSWAN-HI = Standardized SWAN for both informants, hyperactive/impulsive subscale.

Figure 1. Relationship of ADHD traits with OCD and anxiety traits

Figure 1a) Obsessive-compulsive traits (Toronto Obsessive-Compulsive standardized total score – z-score) were not meaningfully different as a function of Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) scores (group 1 = low SWAN scores, 5 = high SWAN scores). Figure 1b) Higher attention-deficit/hyperactivity disorder (ADHD) traits were associated with higher anxiety traits (Standardized total score on CBCL-Anxiety problems scale $p < .001$). The group with the highest z-SWAN scores had significantly higher anxiety traits than all other SWAN groups (group 5 vs. group 1, 2, 3 or 4, p's < 0.01). OCD = obsessive compulsive disorder.

Figure 2: Predicting SWAN Scores from Polygenic Risk for ADHD, OCD, and Anxiety

Polygenic risk scores derived from clinical attention-deficit/hyperactivity disorder (ADHD), but not obsessive-compulsive disorder (OCD) or anxiety, discovery samples significantly predicted ADHD traits (standardized total Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale combined [SWAN-Com] score). P-value thresholds refer to parameters from clinical discovery sample statistics (ADHD, OCD, Anxiety = anxiety disorders). r2 = variance explained by polygenic risk in predicting zSWAN-COM.

Figure 3. ADHD, OCD and Anxiety polygenic risk scores across low to high ADHD traits.

Attention-deficit/hyperactivity disorder (ADHD) polygenic risk was highest in the group with the highest standardized Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale combined (SWAN-com) scores (** low vs. high group $p = 1.48\text{x}10\text{-}^{10}$; * medium vs. high, $p = 4.27\text{x}10^{-5}$; medium vs. low, *ns*). n = 1805 in each SWAN group. PGRS = polygenic risk score.

Table 1.

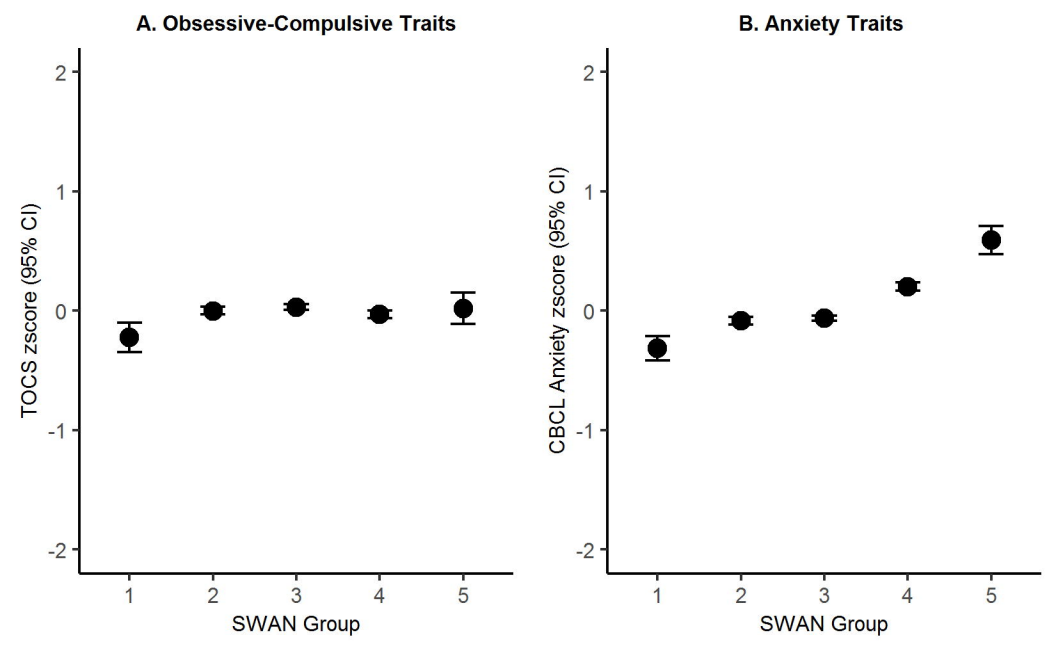
	Without community ADHD diagnosis	With community ADHD diagnosis	*t*-value	Effect Size (cohen's d)
Total N	14588	972		
Parent SWAN				
N	11987	810		
Age (SD)	10.06 (2.08)	10.77 (2.08)		
Male (N, %)	6203 (51.75)	613 (75.68)		
SWAN-Par				
SWAN-Par-Com (SD)	-6.55 (16.06)	20.29 (14.52)	-45.21*	1.68
SWAN-Par-IA (SD)	-2.64 (8.66)	10.99 (8.20)	-41.87*	1.58
SWAN-Par-HI (SD)	-3.91(8.89)	9.30 (8.59)	-40.40*	1.49
zSWAN				
zSWAN-Com (SD)	-0.09 (0.94)	1.37 (0.79)	-43.41*	1.57
zSWAN-IA (SD)	-0.09 (0.95)	1.27 (0.84)	-39.74*	1.44
zSWAN-HI (SD)	-0.08 (0.95)	1.25 (0.85)	-39.37*	1.36
Self-report SWAN				
N	2601	162		
Age (SD)	15.34 (1.29)	15.41(1.22)		
Male (N, %)	983 (37.79)	104 (64.20)		
SWAN-Self				
SWAN-Self-Com (SD)	-5.58 (13.96)	8.06 (14.27)	-12.26*	.98
SWAN-Self-IA (SD)	-3.00 (7.55)	3.85 (7.69)	-11.37*	.91
SWAN-Self-HI (SD)	-2.58 (8.47)	4.21 (8.86)	-10.00*	.80
zSWAN				
zSWAN-Com (SD)	-0.05 (0.97)	0.88 (0.98)	-11.87*	.96
zSWAN-IA (SD)	-0.05 (0.98)	0.80 (0.97)	-10.70*	.87
zSWAN-HI (SD)	-0.05 (0.98)	0.75 (1.04)	-9.99*	.81

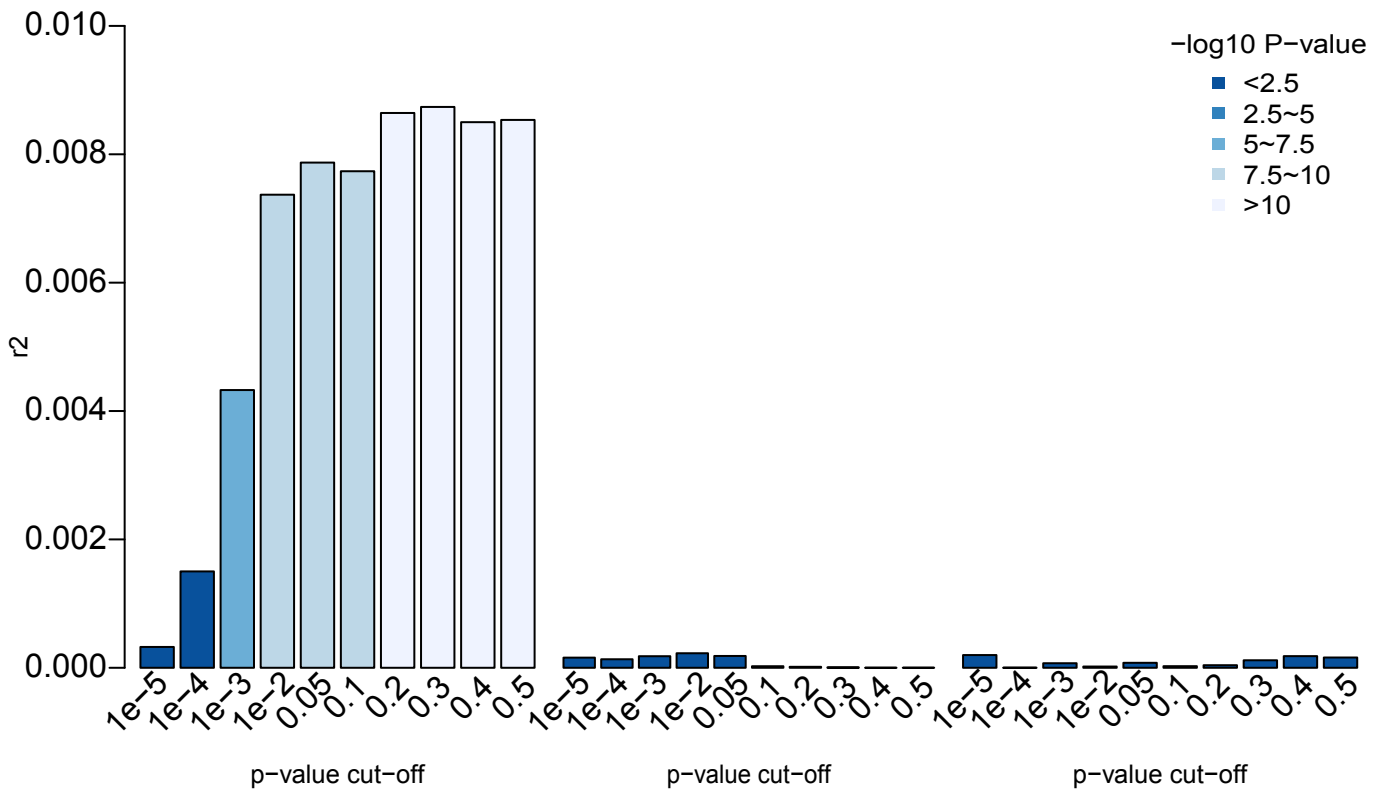
Table 2.

	Controls	ADHD cases	*t*-value	Effect Size (cohen's d)
N	36	266		
Age (SD)	8.92 (1.87)	9.15 (2.26)		
Male (N, %)	16 (44.44)	209 (78.57)		
SWAN-Par				
SWAN-Par-Com (SD)	-14.47 (17.98)	20.35 (13.27)	-11.21*	2.50
SWAN-Par-IA (SD)	-7.44 (9.85)	12.19 (8.26)	-13.07*	2.32
SWAN-Par-HI (SD)	-7.03 (9.13)	8.16 (8.16)	-10.33*	1.83
zSWAN				
zSWAN-Com (SD)	-0.51 (1.05)	1.36 (0.68)	-10.38*	2.55
zSWAN-IA (SD)	-0.55 (1.08)	1.38 (0.83)	-10.35*	2.24
zSWAN-HI (SD)	-0.41 (1.00)	1.12 (0.78)	-8.80*	1.89

Table 3.

	AUC	Optimal cut-off	Sensitivity	Specificity
Parent-report				
SWAN-Par-Com	0.90	>6	83.7	83.3
SWAN-Par-IA	0.88	>4	78.6	82.9
SWAN-Par-HI	0.86	>2	77.2	81.0
zSWAN- Com	0.88	>0.74	82.5	81.0
zSWAN- IA	0.86	>0.60	81.2	76.3
zSWAN- HI	0.85	>0.72	77.0	81.0
Self-report				
SWAN-Self-Com	0.76	>4	59.9	78.9
SWAN-Self-IA	0.74	>0	66.7	69.0
SWAN-Self-HI	0.71	>2	58.6	75.2
zSWAN-Com	0.75	>0.81	57.4	81.4
zSWAN-IA	0.73	>0.51	64.2	71.4
zSWAN-HI	0.71	>0.56	61.7	73.1


A. Obsessive-Compulsive Traits
TOCS zscore (95% CI)
2
1
0
-1
-2
1
2
3
4
5
SWAN Group
B. Anxiety Traits
CBCL Anxiety zscore (95% CI)
2
1
0
-1
-2
1
2
3
4
5
SWAN Group


0.010
0.008
0.006
0.004
0.002
0.000
r2
−log10 P−value
<2.5
2.5~5
5~7.5
7.5~10
>10
1e−5
1e−4
1e−3
1e−2
0.05
0.1
0.2
0.3
0.4
0.5
p−value cut−off
p−value cut−off
p−value cut−off

Standardized PGRS from ADHD meta−analysis
3
2
1
0
−1
−2
−3
*
**
Low
Medium
High
SWAN Group