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Youth Team Sports Participation Associates With Reduced Dimensional Psychopathology Through Interaction With Biological Risk Factors

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ABSTRACT

BACKGROUND: Physical activity is associated with mental health benefits in youth. Here, we used causal inference and triangulation with 2 levels of biology to substantiate relationships between sports participation and dimensional psychopathology in youths.

METHODS: Baseline data from the Adolescent Brain Cognitive Development (ABCD) Study, which recruited children from 9 to 10 years of age across the United States, were included in multilevel regression models to assess relationships between lifetime participation in team sports (TS), individual sports, and nonsports activities and Child Behavior Checklist (CBCL) scores. We calculated polygenic risk scores for 8 psychiatric disorders to assess interactions with sports exposure on CBCL scores among European descendants. Following rigorous quality control, FreeSurfer-extracted brain magnetic resonance imaging structural data were examined for mediation of CBCL–activities relationships.

RESULTS: Among those with complete data (N = 10,411), causal estimates using inverse probability weighting associated lifetime TS exposure with a 1.05-point reduction in CBCL total (95% CI, −1.54 to −0.56, $p < .0001$) a relationship that was specific to TS and strengthened with more years of exposure. Associations of attention-deficit/hyperactivity disorder polygenic loading with CBCL total weakened in European children with TS exposure (n = 4041; beta = −0.93, SE = 0.38, p = .013). Furthermore, TS participation and lower CBCL each associated with increased subcortical volumes (n = 8197). Subcortical volume mediated 5.5% of TS effects on CBCL total.

CONCLUSIONS: Our findings support prior associations of TS participation with lower psychopathology in youths through additional studies that demonstrate specificity, dose response, and coherence across 2 levels of biology. Longitudinal studies that further clarify causal relationships may justify interventional studies of TS for high-risk youth.

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Among the ∼50% of Americans with a lifetime history of mental illness, the median age of onset is 14 years (1). Childhood psychiatric symptoms are known to adversely affect adult functioning, even if they do not develop into full-fledged diagnoses or persist into adulthood (2). Strategies to prevent the onset of mental illness, particularly in at-risk children, are urgently needed (3).

Physical activity is a potentially modifiable factor that can influence mental health outcomes in children. A recent meta-analysis of pediatric and adolescent cohorts reported small but significant associations between sedentary behavior and poor mental health (4). Conversely, the positive impact of physical activity on mental health, especially on depressive symptoms and anxiety, has been suggested in cross-sectional and longitudinal studies of children and adolescents (5). Higher frequency, greater intensity, longer duration, and earlier initiation of sports involvement have also been associated with positive mental health outcomes. Echoing results from large adult cohorts (6), school-based studies have shown that team sports (TS) associate more positively with mental health than do individual sports (IS), especially among girls (7). A small number of randomized controlled trials evaluating physical activity interventions for children with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have also demonstrated benefits for executive function, motor skills, and inattention (8,9).

However, the strength of available evidence linking physical activity to mental health benefits in youth is limited by the small number of randomized controlled trials and the likelihood of residual confounding with measured or unmeasured variables (e.g., socioeconomic variables). Large data sets from diverse and well-characterized populations, such as the ongoing Adolescent Brain Cognitive Development (ABCD) Study, enable isolation of specific sports exposures versus other activities and control of potential confounders. Hoffmann *et al.* (10) associated TS exposure in the ABCD Study with significant reduction in a range of psychopathology, after controlling for numerous potential demographic confounders. However, a

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firmer case for causality can be made through triangulation with underlying biological mechanisms. For example, in an analysis limited to hippocampal volumes, Gorham *et al.* (11) found that variance volume mediated the relationship between TS and depression symptoms in the ABCD cohort. Broader exploration of mechanisms that could transmit potential neuroprotective effects of sports exposure against psychopathology, coupled with additional analyses that probe causality, could further justify interventional studies.

Here, we leveraged baseline (age 9–10 years) data from the ABCD Study to further validate the relationship between sports exposure and mental health, including both statistical methods to assess causal inference (dose effects and inverse probability weighting) and triangulation with 2 levels of biology (whole-brain magnetic resonance imaging [MRI] analysis and polygenic risk scores [PRSs]). Furthermore, because there are known sex differences in the expression of dimensional psychopathology in youth (12), timing of pubertal development, and activity participation rates, additional analyses considered whether associations between activities, Child Behavior Checklist (CBCL) scores, and underlying biological mediators differed by sex.

METHODS AND MATERIALS

Study Design and Population

The ABCD Study enrolled 11,875 children of ages 9 to 10 across 22 U.S. sites. Institutional review board approval for the study is described in Auchter *et al.* (13). All parents provided written informed consent and all youths provided assent. Enrolled participants match the racial and ethnic composition of the United States and were enriched for siblings (including twins and other multiples). A full description of study procedures can be found elsewhere (13,14). Here, we used cross-sectional baseline data obtained directly from youth participants (brain MRI and genomics) and primary caregivers (demographics, developmental history, symptom inventories, sports, and activities) (Table S1).

Dimensional Psychopathology

The CBCL measures youth dimensional psychopathology during the preceding 6 months (15). The CBCL is a widely used survey that measures 113 items across 8 domains (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, somatic complaints, social problems, thought problems, and withdrawn/depressed) as well as broad-band indices of internalizing, externalizing, and total psychopathology. We used CBCL total as the primary outcome because it captures diffuse psychopathology.

Sports and Other Activities

Youth participants' physical activity was assessed with the Sports and Activities Involvement Questionnaire. We categorized these activities into 3 types: TS, IS, and nonsports activities (NSA) (see Supplemental Methods). While IS could entail team membership, they were categorized as individual due to their stronger reliance on individual-level results. These 3 sets of measurements were dichotomized to create a lifetime participation variable (yes/no). TS participation was also calculated as a continuous variable for number of activities × years participated (e.g., 2 years of baseball and 1 year of soccer totals 3 activity years).

Polygenic Risk Score

Genome-wide genotype data from individuals of European ancestry were used for PRS analyses. For every sibling pair, one was randomly selected for inclusion; see Supplemental Methods for additional quality control (QC)–based exclusions. With PLINK version 1.9 (16), single nucleotide polymorphisms were filtered according to minor allele frequency, data missingness, deviation from Hardy–Weinberg equilibrium, and linkage disequilibrium. Shapeit version 2 (17) was used for prephasing, with genotyping data from the 1000 Genomes Project used as a reference panel. IMPUTE version 2 (18) was used for imputation.

We generated PRSs using a Bayesian approach (19). In PLINK, the resultant posterior effect sizes were applied to individual-level genotype data to generate PRSs for each subject. PRSs were calculated for 8 specific psychiatric disorders—ADHD, ASD, anorexia nervosa, bipolar disorder, major depressive disorder (MDD), obsessive-compulsive disorder, schizophrenia, and Tourette syndrome—using summary statistics from the Psychiatric Genomics Consortium (20–28) (see Supplemental Methods).

Brain MRI

Brain T1-weighted images were obtained at 3T on Siemens MAGNETOM Prisma, GE Healthcare Discovery MR750, and Philips Achieva scanners. Detailed scanning methods are described elsewhere (29). For this analysis, we downloaded minimally processed volumes from the National Institute of Mental Health Data Archive, which we subjected to strict QC through inspection of each scan, as described in Supplemental Methods. To correct low frequency intensity nonuniformity, we used the N4 bias field correction algorithm (30). Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite, version 7 (http://surfer.nmr.mgh.harvard.edu/). We extracted cortical region of interest (ROI) values (surface area, thickness, and volume), subcortical volumes, and related global values (mean surface area, mean cortical thickness; and total cortical, subcortical, and gray matter volumes) with the Desikan-Killiany cortical atlas (31,32).

Socioeconomic Status

As an indicator of socioeconomic status, income-to-needs ratio (INR) was included as a covariate (33). We took a midpoint of total combined family income categories (see Supplemental Methods) and divided by its corresponding federal poverty level, according to household sizes.

Puberty Scale

We used the body hair scale from the Pubertal Development Scale and Menstrual Cycle Survey History from both parents and youths as indicators of puberty stage. Their responses were recorded in 4 categories (see Supplemental Methods for additional details).

Statistical Analysis

TS and Psychopathology. First, we assessed associations between lifetime activity participation and dimensional psychopathology. Then, we tested a TS-focused model with CBCL total score as the primary outcome (model 1). Exploratory analyses separately tested associations between TS and individual and broad-band CBCL scores, using the false discovery rate (FDR) to correct for 10 comparisons. Multilevel regression models were adjusted for age, sex, race, ethnicity, INR, and puberty scale as fixed effects and family identifier (ID) and site ID as random effects. Sensitivity analyses assessed specificity of TS association among 8 activity participation patterns using 3-way interaction among 3 types of activities (TS × IS × NSA) with CBCL total, as well as dose dependency of TS participation, based on activity years. Additionally, we used inverse probability weighting (IPW) methods to estimate causal effects of TS participation on psychiatric symptoms. With IPW, we made a pseudopopulation by weighting individual data, using the probability of TS exposure. The same set of variables was used to calculate stabilized inverse probability weights of TS participation. IPW enabled us to minimize confounding by measured covariates, so we could compare the weighted averages of CBCL scores between TS+ and TS− groups.

Genetics. Next, we assessed whether lifetime TS participation could offset genetic risk for psychopathology among participants of European ancestry. We first compared the mean PRS of each of the 8 psychiatric disorders (see above) by activity participation. In exploratory analyses, we regressed these 8 PRSs on CBCL total, using FDR to correct for 8 comparisons, adjusting for age, sex, INR, and puberty scales; their interactions with PRS and TS; and 5 principal components as fixed effects and site ID as a random effect (model 2). For those PRSs which were significantly associated with CBCL total, we then included TS and its interaction with PRS into the regression models (model 3). Sensitivity analyses added IS and NSA as well as their respective cross-product interactions with PRS. In instances when we identified a significant interaction term (i.e., statistical interaction between the PRS and TS on CBCL total), we also ran separate regression models to examine possible interactions on each of the CBCL syndrome-specific and broad-band scales.

Imaging. We tested whether brain volume features mediated the effects of TS participation on dimensional psychopathology, using an iterative set of analyses that focused first on global and then regional MRI data. First, we examined associations between 6 global MRI measurements (mean cortical thickness, total surface area, cortical volume, subcortical gray matter volume, cerebellum gray matter volume, and total gray matter volume) and CBCL total (model 4) and associations between TS participation and the same 6 global MRI measurements (model 5), using multilevel linear regression models with FDR correction for 6 comparisons. For global MRI measures that associated with both CBCL total and TS exposure, we conducted mediation analyses (34) to determine whether brain volumes mediated effects of TS exposure on CBCL total score (model 6). Mediation analysis decomposed the total effect into 2 components, the causal mediation effects and the direct effects. Furthermore, to achieve greater regional specificity, global MRI measurements that associated with both CBCL total and TS exposure were subject to ROI-based analyses, using the same approach as models 4 and 5. ROIs showing nominally significant relationships in both models were then subject to mediation analyses, as in model 6. For all analyses, we included age, sex, race, ethnicity, INR, number of surface holes, puberty scale, and estimated total intracranial volume (only for ROI values) as fixed effects and family ID, site ID, and MRI scanner type as random effects.

Sex Differences. Finally, to explore potential sex differences, we included an additional interaction term (sex × independent variable of interest) in models 1, 3, 4, and 5 (i.e., model 1s, 3s, 4s, and 5s).

Statistical analyses were conducted with R version 4.1.2 (https://www.R-project.org/). We used the lme4 package (35) for multilevel regression model, geepack package (https://cran.r-project.org/package=geepack) for IPW analysis, and mediation package (https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf) for mediation analysis. All continuous covariates except CBCL scores were z-standardized prior to analysis. We used two-sided $p < .05$ as the significance threshold for all analyses. The same threshold was used for the between model FDR correction in exploratory analyses.

RESULTS

Demographics

Among 11,875 ABCD Study participants, 9638 participants had complete data for all covariates, 4014 met the criteria for PRS calculation, and 8197 cleared MRI QC rating criteria, without missing data (Figure S1). Among 9638 youths, 6201 (64.3%) had lifetime TS participation, 6668 (69.2%) had IS exposure, and 5577 (57.9%) had NSA exposure. Demographics of the study population are shown in Table 1 and Table S2.

TS and CBCL

Among the 3 types of activities, only TS was significantly and negatively associated with CBCL total T score (Table S3a), echoing results of Hoffmann *et al.* (10), but now using linear rather than negative binomial regression. In model 1, we observed a significant negative association between lifetime TS and CBCL total T score (beta = −0.93 [Cohen's d = 0.083], 95% CI, −1.41 to −0.44, p = .00016) (Table S3b). Among the CBCL subscales in exploratory analyses, anxious/depressed, withdrawn/depressed, social problems, thought problems, attention problems, and internalizing scores were negatively associated with TS status (Table S4).

A series of novel sensitivity analyses consistently supported the findings in model 1. The negative association between lifetime TS and CBCL total persisted when the 8 activity participation patterns (TS × IS × NSA) were added into the model (Figure S2; Table S3c). To assess dose response, we calculated the history of TS participation (number of sports type × years of participation). A gradual decrease in CBCL

Table 1. Demographics by Lifetime Team Sports Participation (n = 9638)

Participant Characterstics	Team Sports−, n = 3437	Team Sports+, n = 6201
Age, Months, Mean (SD)	118.53 (7.52)	119.39 (7.40)
Female, n (%)	2220 (64.6%)	2271 (38.2%)
Race, White, n (%)	2469 (71.8%)	5119 (82.6%)
Ethnicity, Hispanic, n (%)	764 (22.2%)	1004 (16.2%)
Income-to-Needs Ratio, Mean (SD)	3.11 (2.39)	4.19 (2.39)
Individual Sports, n (%)	2119 (61.7%)	4549 (73.4%)
Cultural Activities, n (%)	1753 (51.0%)	3824 (61.7%)
Body Hair Scale, Parent-Report, n (%)		
1	2025 (58.9%)	4200 (67.7%)
2	637 (18.5%)	1124 (18.1%)
3	670 (19.5%)	780 (12.6%)
4	105 (3.1%)	97 (1.6%)
Body Hair Scale, Youth-Report, n (%)		
1	1654 (48.1%)	3025 (51.7%)
2	1088 (31.7%)	2015 (32.5%)
3	469 (13.6%)	696 (11.2%)
4	226 (6.6%)	285 (4.6%)

total score was observed as TS exposure activity year increased (beta = −0.271, 95% CI, −0.335 to −0.208, $p <$ .0001) (Figure 1). With IPW, we estimated causal effects of TS on CBCL total score. Lifetime TS exposure was estimated to reduce CBCL total T score by 1.05 points (95% CI, −1.54 to −0.56, $p <$ .0001).

TS and Polygenic Risk for Psychiatric Disorders

The 8 psychiatric disorder PRS values were unassociated with activity participation, except lower mean ASD PRS in TS participants and lower ADHD PRS in IS participants (Table S5). Consistent with a recent report, which controlled for other

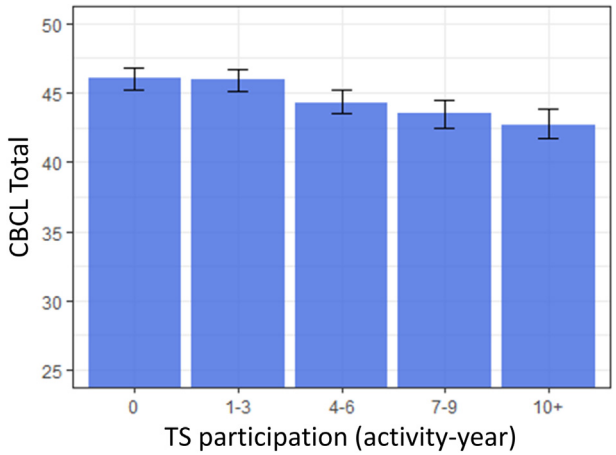

Figure 1. Team sports (TS) participation history and Child Behavior Checklist (CBCL) total. Estimated marginal means of CBCL total score by activity years category (0, 1–3, 4–6, 7–9, 10+ activity years) (n = 9638) ($p <$ .0001). Error bars indicate 95% CIs. Covariates included age, sex, race, ethnicity, income-to-needs ratio, puberty scales (fixed effects), family identifier, site identifier (random effects).

Table 2. Team Sports by PRSs Interaction on CBCL (Model 3) (n = 4014)

Factor	Beta	SE	p Values
Interactions of TS With Disorder-Specific PRSs on CBCL Total			
ADHD	−0.932	0.375	.013[a]
ASD	−0.121	0.378	.75[a]
BIP	−0.496	0.381	.19[a]
MDD	−0.190	0.381	.62[a]
SCZ	0.030	0.374	.94[a]
AN	0.191	0.385	.62[a]
TrS	−0.383	0.376	.31[a]
OCD	−0.024	0.373	.95[a]
Main Effects of ADHD PRS and TS in the ADHD × TS Interaction Model			
ADHD PRS	2.63	0.545	<.0001
TS	−0.790	1.038	.00062
ADHD PRS × TS	−0.932	0.375	.013

Covariates: age, sex, income-to-needs ratio, puberty scales, 5 principal components (fixed effects), site identifier (random effect).

ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; CBCL, Child Behavior Checklist; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PRS, polygenic risk score; SCZ, schizophrenia; TrS, Tourette syndrome; TS, team sports.

[a]Unadjusted p values.

indices of socioeconomic status but not for INR (33), PRSs for ADHD, MDD, and ASD positively associated with CBCL total score in the exploratory analyses, while no such association was reported for other PRSs after FDR correction for multiple comparisons (model 2) (Table S6a).

Including a cross-product interaction term (TS × PRS) in model 3 for ADHD, MDD, and ASD PRSs indicated that only ADHD PRS had a nominally significant interaction with TS in association with CBCL total score. While ADHD PRS positively associated with CBCL total across TS participation status, the slope for TS+ youths was smaller than that of TS− youths (beta = −0.93, SE = 0.38, p = .013) (Figure 2; Table 2). Notably, this interaction survives correction for 3 PRSs that showed a main effect on CBCL total, but not for all 8. Another sensitivity analysis that also included IS and NSA and their interactions with PRS retained interaction of TS and PRS on CBCL total and showed an oppositely signed interaction of NSA and PRS on CBCL total (Table S7).

Among CBCL subscales, ADHD PRS associated positively with all the CBCL subscales, except for anxious/depressed and withdrawn/depressed, after FDR correction (Table S6b); however, ADHD PRS did not significantly interact with TS on any of the CBCL subscales (Table S8).

Magnetic Resonance Imaging

CBCL total score associated significantly and inversely with all 6 global volume measurements except cortical thickness (model 4) (Table S9a). Among global MRI indices, only subcortical gray matter volume was significantly associated with TS after FDR correction (beta = 0.061, SE = 0.209, p = .0035) (model 5) (Table S10a). These associations were robust to sensitivity analysis with IS and NSA included in the model

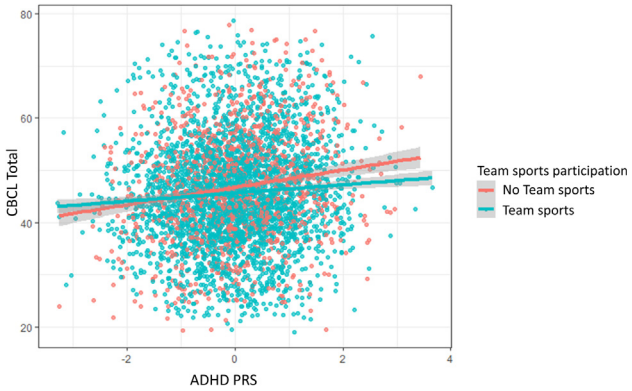

Figure 2. Interactive effect of team sports exposure and attention-deficit/hyperactivity disorder (ADHD) polygenic risk scores (PRSs) on Child Behavior Checklist (CBCL) total. Red line: association between ADHD PRS (*z*-standardized) and CBCL among children with no lifetime team sports participation. Green line: association between ADHD PRS and CBCL among children with team sports participation. Covariates included age, sex, income-to-needs ratio, puberty scales, and 5 principal components as fixed effects and site identifier as a random effect (n = 4014).

(Tables S11a and S12a). Subsequent mediation analyses indicated a significant mediating effect of total subcortical volume on the relationship between TS exposure and CBCL total score, with total subcortical volume accounting for 5.5% of the variance in this relationship (model 6) (Figure 3).

In post hoc analyses of subcortical ROI, nominally significant associations emerged between CBCL total and 9 ROIs, although none reached FDR significance (model 5) (Table S9b). For TS, among subcortical ROIs, volume in 8 total regions associated with TS exposure, reaching FDR significance in 2 of them (left thalamus and left pallidum) (model 4) (Table S10b). We also tested mediation effects of subcortical ROIs that met inclusion criteria (nominally significant association both with TS and with CBCL). The left cerebellum cortex, left hippocampus [consistent with Gorham *et al.* (11)], and right accumbens area demonstrated significant mediation effects on CBCL total by TS (Table 3).

Sex Differences

There was a significant sex-dependent difference in TS and CBCL association represented with interaction term (model 1s) (beta = 1.10, 95% CI, 0.178 to 2.02, p = .019). TS participation associated with lower CBCL total among boys (beta = −1.57, SE = 0.38, $p < .0001$) but not among girls (beta = −0.46, SE = 0.327, p = .16) (Figure 4).

Sex did not interact with ADHD PRS to influence CBCL total (model 3s) (beta = 1.27, SE = 0.22, p = .16), and there was no significant sex × TS × PRS interaction with CBCL total (beta = −0.85, SE = 0.74, p = .26).

None of the associations between global MRI indices and CBCL total were significantly different by sex (model 4s) (Table S13). There was no sex-dependent association between TS and global MRI indices (model 5s) (Table S14) or interaction between TS and MRI indices on CBCL (Table S15).

Table 3. Mediation Effects by ROI on Estimated Causal Effects of Team Sports on CBCL Total Score (Model 6) (n = 8197)

Region	Estimate	Lower 95% CI	Upper 95% CI	p Value
Subcortical Volume	Proportion mediated: 0.0545 (95% CI, 0.016–0.19)			
ACME	−0.044	−0.08	−0.01	.010
ADE	−0.748	−1.28	−0.27	.004
Total effect	−0.792	−1.32	−0.31	.002
Left Cerebellum Cortex	Proportion mediated: 0.0378 (95% CI, 0.004–0.14)			
ACME	−0.031	−0.06	−0.00	.034
ADE	−0.753	−1.30	−0.23	.004
Total effect	−0.783	−1.33	−0.27	<.001
Left Hippocampus	Proportion mediated: 0.0379 (95% CI, 0.006–0.14)			
ACME	−0.031	−0.06	−0.00	.024
ADE	−0.756	−1.28	−0.23	.002
Total effect	−0.787	−1.31	−0.26	<.001
Right Accumbens Area	Proportion mediated: 0.0381 (95% CI, 0.006–0.14)			
ACME	−0.030	−0.06	−0.00	.016
ADE	−0.751	−1.30	−0.20	.010
Total effect	−0.781	−1.32	−0.23	.006

ROI values are *z*-standardized. ROIs that are nominally significant in both Tables S6 and S7 are listed. Left GC-ML-DG was the only left hippocampal subregion that showed nominally significant association between both TS—ROI and ROI—Child Behavior Checklist. Covariates: age, sex, race, ethnicity, income-to-needs ratio, puberty scales, estimated intracranial volume, surface holes (fixed effects), family identifier, site identifier, scanner type (random effects). Total effect is the sum of a mediation (indirect) effect and a direct effect.

ACME, average causal mediation effect; ADE, average direct effect; ROI, region of interest; TS, team sports.

DISCUSSION

Using cross-sectional data from 9- to 10-year-old participants in the ABCD Study, we examined the association between sports participation and dimensional psychopathology through novel validation analyses. First, using IPW, we demonstrated that the association of TS with lower CBCL scores is robust to potential confounders, such as socioeconomic status, study site, and puberty. Furthermore, associations of TS with psychopathology were strongest among individuals with more lifetime TS exposures, consistent with a dose effect. We then turned to analyses that examined TS-CBCL effects on 2 levels of brain biology. TS participation was associated with reduced effects of polygenic risk on psychopathology; and this relationship was mediated by volume differences in subcortical regions that themselves were associated with increased risk. These analyses of specificity, dose response, and coherence across 2 levels of biology provide convergent validation for the relationship between TS exposure and reduced psychopathology in youths.

These results provide biological context for beneficial effects of TS participation on children's overall mental health. Meta-analyses of prospective studies indicated that physical activity has mental health benefits, regarding the prevention of adult

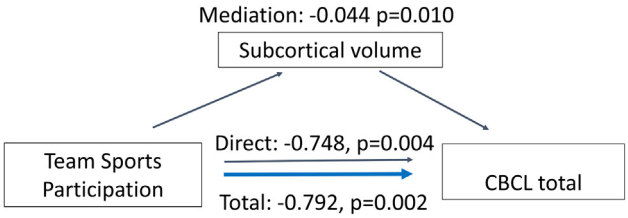

Figure 3. Mediation of team sports exposure effects on Child Behavior Checklist (CBCL) total via subcortical volume. Estimated total effect of team sports on CBCL total was −0.792 points. Five and a half percent of the total effect (beta = −0.002) was mediated by subcortical volume and direct effect of team sports was −0.748 points (n = 8197). Covariates included age, sex, race, ethnicity, income-to-needs ratio, number of surface holes, puberty scale, and estimated total intracranial volume as fixed effects and family identifier, site identifier, and magnetic resonance imaging scanner type as random effects.

depression and schizophrenia (36,37). The ABCD Study enables analysis of these patterns at a younger age, when psychiatric symptoms begin to emerge. Hoffman *et al.* (10) reported the incident rate ratio of TS by CBCL psychopathology from year 1 cross-sectional data. Our results also specifically link TS (compared with IS or NSA) more strongly to mental health, using mixed-effect linear models to estimate effect size. This specific result could reflect synergistic social, psychological, and physical benefits of TS. Previous studies indicated that TS may provide benefits beyond individualized sports through positive social interactions with peers that provide social support and acceptance, more self-esteem, and less body dissatisfaction (38–40). A systematic review has found limited evidence of benefits in mental health for organized NSAs (e.g., arts or music) among children and adolescents (5), which is consistent with our findings. These results may explain the heterogeneity of previous reports on effects of physical activity and warrant further examination of the mechanism behind the benefits of TS, including its physical and social components. Even though the effect size for the association between TS and CBCL is small

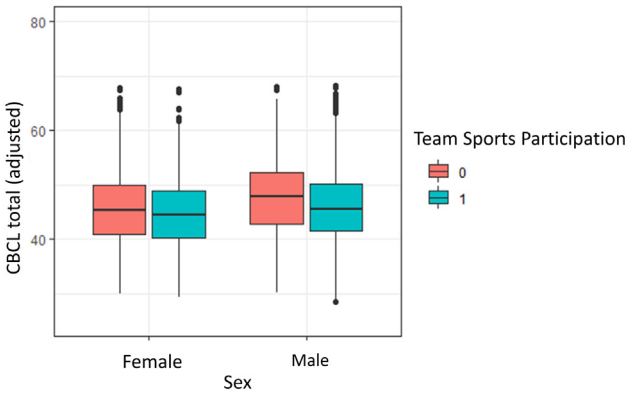

Figure 4. Effects of team sports participation and Child Behavior Checklist (CBCL) total by sex. Box plots for estimated mean CBCL total scores are displayed (n = 9638). Covariates included age, race, ethnicity, and income-to-needs ratio as fixed effects and family identifier and site identifier as random effects.

(Cohen's d = 0.083), the population-level impact of TS-based intervention could be substantial, with fairly low equipment and other costs (41).

To our knowledge, this study is the first to implicate polygenic loading in the relationship between TS and psychopathology. Though interactions with specific polymorphisms such as within *BDNF* have been reported (42); more robust, genome-wide approaches have not yet been deployed to study whether TS participation reduces psychopathology symptoms among children with high polygenic risk. Consistent with prior work that did not include socioeconomic status as a covariate (43,44), we observed the association between PRS and CBCL scores for ADHD, ASD, and MDD PRSs; however, TS only mitigated the relationship between ADHD PRS and psychopathology. Among CBCL subscales, this interaction was most pronounced for thought problems, although interaction of TS and ADHD PRS only reached nominal significance. Notably, the effect size of this interaction was small, and while its statistical significance survives correction for 3 comparisons (i.e., ADHD, ASD, and MDD × TS), it would not have survived had we not constrained the interaction analysis based on PRSs showing a main association with CBCL total. The fact that the summary statistics from Psychiatric Genomics Consortium used in this analysis (20–28) were derived predominantly from adult participants may influence their impact on psychopathology and their relevance to gene-environment interactions in childhood. However, given the likelihood that polygenic risk will continue to influence emergent psychiatric symptoms later in adolescence, longitudinal studies of youth TS participation on mental health outcomes against the background of polygenic risk are warranted.

Several previous MRI studies have associated physical activity in youths with increases in global brain volumes—whole brain (45), whole gray matter (46,47), and whole white matter (48). Previous reports also showed associations between subcortical volumes and physical activity, specifically with larger hippocampus (11,46,49,50) and nucleus accumbens (49–51). While the cellular biology underlying these associations remains unknown, increased cytogenesis and neuroplasticity have been associated with exercise, through a variety of specific mechanisms, in animal models (41). Two such possibilities include known effects of both physical activity and enriched environment on hippocampal neurogenesis, with potential downstream effects in other subcortical and cortical regions (52), and nucleus accumbens-mediated integration of rewarding stimuli and social interaction (53). Future translational studies may clarify region- and development-specific effects on sports participation on brain biology. Moreover, we found that these subcortical volumes mediate the relationship between TS and CBCL, extending the previously reported analysis that focused on hippocampal volumes (11). These results are consistent with the idea that TS participation alters brain development in regions that are relevant to psychopathology risk, although fully prospective studies would better enable causal inference.

The finding that both TS and ADHD PRSs associated more strongly with dimensional psychopathology in boys than in girls extends previous literature on sex differences in how youth sports participation influences psychopathology. A prior study indicated a similar association among boys, with TS

exposure predicting fewer internalizing problems and less depressed mood (54). Conversely, sports exposure has also been associated with prosocial behavior among girls (55), and another study suggests that physical education classes emphasizing self-efficacy and mastery are more beneficial for girls (56). Thus, considering our results and data from these previous studies, more work is needed to connect exercise, the mechanism underlying resilience, psychopathology, and sex-dependent outcomes.

Studies of psychopathology and MRI phenotypes in children can be confounded by a number of factors, including socioeconomic differences, puberty stage, and motion-related and other MRI artifacts. As an index of socioeconomic status, we adjusted for INR, a measure that incorporates U.S. poverty statistics and household size. In the ABCD cohort, INR captures effects of numerous individual economic and psychosocial factors that have been associated with neurodevelopmental differences (33,57). We additionally adjusted for puberty, given previously reported effects of pubertal status on psychopathology and brain morphology, especially subcortical volumes (58–60). For analyses with MRI outcomes, we filtered out low quality images by manual QC of all 11,263 T1 scans available after excluding scans needing clinical consultation or failing the FreeSurfer processing pipeline. Furthermore, we adjusted for the number of surface holes to eliminate bias due to image and segmentation quality (61,62).

There are several limitations to this study. First, sports experience was measured using data reported retrospectively by parents, making it subject to recall bias. Second, because of the cross-sectional nature of the data, the possibility of reverse causality (e.g., children with more psychopathology may be less interested in sports) cannot be ruled out, especially regarding psychopathology and MRI outcomes. While prospective data on TS participation and psychopathology are currently available (through year 2) in the ABCD cohort, year 2 MRI scans have not yet undergone the rigorous QC that was applied to baseline scans; furthermore, TS were substantially disrupted by the COVID-19 pandemic during this window, complicating longitudinal analyses. However, the fact that baseline findings persisted through IPW and other sensitivity analyses may somewhat alleviate this concern. Third, despite controlling for INR and puberty stage, unmeasured confounders likely influence the relationship between TS and psychopathology. Additionally, while the ABCD Study population mirrors the racial and ethnic composition of the U.S. population, there are selection biases with regard to socioeconomic status and geographical distribution, which could affect the access to TS activities (63). Finally, as with numerous population genetics studies, results from participants of European ancestry may not generalize to other populations, and more inclusive genome-wide association studies involving non-European individuals are needed.

Despite these limitations, the results of this study indicate the promise of TS participation as a modifiable, protective factor for psychopathology risk and point to potential intermediate biological mechanisms. It will be of interest to revisit effects of TS exposure longitudinally in ABCD Study participants as they approach late adolescence, a time of heightened risk for emergence of mental illness, in concert with other neurodevelopmental changes. This additional work may provide additional support for TS-based interventions for youth who are at increased biological risk for psychopathology.

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REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.
2. Copeland WE, Wolke D, Shanahan L, Costello EJ (2015): Adult functional outcomes of common childhood psychiatric problems: A prospective, longitudinal study. JAMA Psychiatry 72:892–899.
3. Choi KW, Smoller JW (2020): Making the right moves to prevent depression in young people. Lancet Psychiatry 7:221–222.
4. Rodriguez-Ayllon M, Cadenas-Sánchez C, Estévez-López F, Muñoz NE, Mora-Gonzalez J, Migueles JH, *et al.* (2019): Role of physical activity and sedentary behavior in the mental health of preschoolers, children and adolescents: A systematic review and meta-analysis. Sports Med 49:1383–1410.
5. Boelens M, Smit MS, Raat H, Bramer WM, Jansen W (2022): Impact of organized activities on mental health in children and adolescents: An umbrella review. Prev Med Rep 25:101687.
6. Chekroud SR, Gueorguieva R, Zheutlin AB, Paulus M, Krumholz HM, Krystal JH, Chekroud AM (2018): Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: A cross-sectional study. Lancet Psychiatry 5:739–746.
7. McMahon EM, Corcoran P, O'Regan G, Keeley H, Cannon M, Carli V, *et al.* (2017): Physical activity in European adolescents and associations with anxiety, depression and well-being. Eur Child Adolesc Psychiatry 26:111–122.
8. Xie Y, Gao X, Song Y, Zhu X, Chen M, Yang L, Ren Y (2021): Effectiveness of physical activity intervention on ADHD symptoms: A systematic review and meta-analysis. Front Psychiatry 12:706625.
9. Zhang M, Liu Z, Ma H, Smith DM (2020): Chronic physical activity for attention deficit hyperactivity disorder and/or autism spectrum disorder in children: A meta-analysis of randomized controlled trials. Front Behav Neurosci 14:564886.
10. Hoffmann MD, Barnes JD, Tremblay MS, Guerrero MD (2022): Associations between organized sport participation and mental health

difficulties: Data from over 11,000 US children and adolescents. PLoS One 17:e0268583.
11. Gorham LS, Jernigan T, Hudziak J, Barch DM (2019): Involvement in sports, hippocampal volume, and depressive symptoms in children. Biol Psychiatry Cogn Neurosci Neuroimaging 4:484–492.
12. Loso HM, Dube SL, Chaarani B, Garavan H, Albaugh M, Ivanova M, Potter A (2021): Sex differences in psychopathology in a large cohort of nine and ten-year-olds. Psychiatry Res 302:114026.
13. Auchter AM, Hernandez Mejia M, Heyser CJ, Shilling PD, Jernigan TL, Brown SA, *et al.* (2018): A description of the ABCD organizational structure and communication framework. Dev Cogn Neurosci 32:8–15.
14. Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, *et al.* (2018): The conception of the ABCD study: From substance use to a broad NIH collaboration. Dev Cogn Neurosci 32:4–7.
15. Achenbach TM (2009): The Achenbach System of Empirically Based Assessment (ASEBA): Development, Findings, Theory, and Applications. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.
16. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015): Second-generation PLINK: Rising to the challenge of larger and richer datasets. GigaScience 4:7.
17. Delaneau O, Marchini J, 1000 Genomes Project Consortium, 1000 Genomes Project Consortium (2014): Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. Nat Commun 5:3934.
18. Howie BN, Donnelly P, Marchini J (2009): A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet 5:e1000529.
19. Ge T, Chen CY, Ni Y, Feng Y-CA, Smoller JW (2019): Polygenic prediction via Bayesian regression and continuous shrinkage priors [no. 1]. Nat Commun 10:1776.
20. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, *et al.* (2022): Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604:502–508.
21. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) (2018): Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. Mol Psychiatry 23:1181–1188.
22. Yu D, Sul JH, Tsetsos F, Nawaz MS, Huang AY, Zelaya I, *et al.* (2019): Interrogating the genetic determinants of Tourette's syndrome and other tic disorders through genome-wide association studies. Am J Psychiatry 176:217–227.
23. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 50:668–681.
24. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, *et al.* (2019): Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 51:1207–1214.
25. Cross-Disorder Group of the Psychiatric Genomics Consortium (2019): Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 179:1469–1482.e11.
26. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, *et al.* (2019): Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 51:793–803.
27. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51:63–75.
28. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51:431–444.
29. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, *et al.* (2018): The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. Dev Cogn Neurosci 32:43–54.
30. Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, Gee JC (2010): N4ITK: Improved N3 bias correction. IEEE Trans Med Imaging 29:1310–1320.
31. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.
32. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, *et al.* (2002): Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355.
33. Gonzalez MR, Palmer CE, Uban KA, Jernigan TL, Thompson WK, Sowell ER (2020): Positive economic, psychosocial, and physiological ecologies predict brain structure and cognitive performance in 9–10-year-old children. Front Hum Neurosci 14:578822.
34. Imai K, Keele L, Tingley D (2010): A general approach to causal mediation analysis. Psychol Methods 15:309–334.
35. Bates D, Mächler M, Bolker B, Walker S (2015): Fitting linear mixed-effects models using lme4 [no. 1]. J Stat Softw 67:1–48.
36. Brokmeier LL, Firth J, Vancampfort D, Smith L, Deenik J, Rosenbaum S, *et al.* (2020): Does physical activity reduce the risk of psychosis? A systematic review and meta-analysis of prospective studies. Psychiatry Res 284:112675.
37. Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, *et al.* (2018): Physical activity and incident depression: A meta-analysis of prospective cohort studies. Am J Psychiatry 175:631–648.
38. Jewett R, Sabiston CM, Brunet J, O'Loughlin EK, Scarapicchia T, O'Loughlin J (2014): School sport participation during adolescence and mental health in early adulthood. J Adolesc Health 55:640–644.
39. Doré I, O'Loughlin JL, Beauchamp G, Martineau M, Fournier L (2016): Volume and social context of physical activity in association with mental health, anxiety and depression among youth. Prev Med 91:344–350.
40. Boone EM, Leadbeater BJ (2006): Game on: Diminishing risks for depressive symptoms in early adolescence through positive involvement in team sports. J Res Adolesc 16:79–90.
41. Halperin JM, Bédard AC, Curchack-Lichtin JT (2012): Preventive interventions for ADHD: A neurodevelopmental perspective. Neurotherapeutics 9:531–541.
42. Uher R (2014): Gene–environment interactions in severe mental illness. Front Psychiatry 5:48.
43. Vainieri I, Martin J, Rommel A, Asherson P, Banaschewski T, Buitelaar J, *et al.* (2022): Polygenic association between attention-deficit/hyperactivity disorder liability and cognitive impairments. Psychol Med 52:3150–3158.
44. Wainberg M, Jacobs GR, Voineskos AN, Tripathy SJ (2022): Neurobiological, familial and genetic risk factors for dimensional psychopathology in the Adolescent Brain Cognitive Development study. Mol Psychiatry 27:2731–2741.
45. Herting MM, Keenan MF, Nagel BJ (2016): Aerobic fitness linked to cortical brain development in adolescent males: Preliminary findings suggest a possible role of BDNF genotype. Front Hum Neurosci 10:327.
46. Herting MM, Nagel BJ (2012): Aerobic fitness relates to learning on a virtual Morris water task and hippocampal volume in adolescents. Behav Brain Res 233:517–525.
47. Esteban-Cornejo I, Cadenas-Sanchez C, Contreras-Rodriguez O, Verdejo-Roman J, Mora-Gonzalez J, Migueles JH, *et al.* (2017): A whole brain volumetric approach in overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project. Neuroimage 159:346–354.
48. Esteban-Cornejo I, Mora-Gonzalez J, Cadenas-Sanchez C, Contreras-Rodriguez O, Verdejo-Román J, Henriksson P, *et al.* (2019): Fitness, cortical thickness and surface area in overweight/obese children: The mediating role of body composition and relationship with intelligence. Neuroimage 186:771–781.
49. Chaddock L, Erickson KI, Prakash RS, Kim JS, Voss MW, VanPatter M, *et al.* (2010): A neuroimaging investigation of the association between

aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res 1358:172–183.
50. Ruotsalainen I, Renvall V, Gorbach T, Syväoja HJ, Tammelin TH, Karvanen J, Parviainen T (2019): Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents. Behav Brain Res 362:122–130.
51. Chaddock L, Erickson KI, Prakash RS, VanPatter M, Voss MW, Pontifex MB, *et al.* (2010): Basal ganglia volume is associated with aerobic fitness in preadolescent children. Dev Neurosci 32:249–256.
52. Ho NF, Hooker JM, Sahay A, Holt DJ, Roffman JL (2013): In vivo imaging of adult human hippocampal neurogenesis: Progress, pitfalls and promise. Mol Psychiatry 18:404–416.
53. Bendersky CJ, Milian AA, Andrus MD, De La Torre U, Walker DM (2021): Long-term impacts of post-weaning social isolation on nucleus accumbens function. Front Psychiatry 12:745406.
54. Isaksson J, Selinus EN, Åslund C, Nilsson KW (2020): Physical activity in early adolescence predicts depressive symptoms 3 years later: A community-based study. J Affect Disord 277:825–830.
55. Moeijes J, van Busschbach JT, Bosscher RJ, Twisk JWR (2018): Sports participation and psychosocial health: A longitudinal observational study in children. BMC Public Health 18:702.
56. McKercher C, Schmidt MD, Sanderson K, Dwyer T, Venn AJ (2012): Physical activity and depressed mood in primary and secondary school-children. Ment Health Phys Act 5:50–56.
57. Rakesh D, Zalesky A, Whittle S (2021): Similar but distinct – Effects of different socioeconomic indicators on resting state functional connectivity: Findings from the Adolescent Brain Cognitive Development (ABCD) Study®. Dev Cogn Neurosci 51:101005.
58. van Soelen ILC, Brouwer RM, van Baal GCM, Schnack HG, Peper JS, Chen L, *et al.* (2013): Heritability of volumetric brain changes and height in children entering puberty. Hum Brain Mapp 34:713–725.
59. Goddings AL, Mills KL, Clasen LS, Giedd JN, Viner RM, Blakemore SJ (2014): The influence of puberty on subcortical brain development. Neuroimage 88:242–251.
60. Graber JA (2013): Pubertal timing and the development of psychopathology in adolescence and beyond. Horm Behav 64:262–269.
61. Rosen AFG, Roalf DR, Ruparel K, Blake J, Seelaus K, Villa LP, *et al.* (2018): Quantitative assessment of structural image quality. Neuroimage 169:407–418.
62. Monereo-Sánchez J, de Jong JJA, Drenthen GS, Beran M, Backes WH, Stehouwer CDA, *et al.* (2021): Quality control strategies for brain MRI segmentation and parcellation: Practical approaches and recommendations – Insights from the Maastricht study. Neuroimage 237:118174.
63. Kamphuis C, Lenthe F, Giskes K, Huisman M, Brug J, Mackenbach J (2010): Socio-economic status, social capital and sports participation. Eur J Public Health 20:41–41.

Supplemental Methods

Sports and other activities

Youth participants' physical activity was assessed with the Sports and Activities Involvement Questionnaire (SAIQ). We categorized these activities into three types: *team sports* (TS; baseball, softball, basketball, field hockey, football, ice hockey, lacrosse, rugby, soccer, and volleyball), *individual sports,* (IS; dance, climbing, gymnastics, horseback riding, ice skating, martial arts, skateboarding, skiing, surfing, swimming, tennis, track, martial arts, wrestling, and yoga), and *non-sports activities* (NSA; music, painting, theater, crafts, competitive game like chess, and collecting stamps or coins).

Polygenic risk score

Genome-wide genotype data from a subset of youth participants (individuals of European ancestry) were used for polygenic risk score (PRS) analyses. For every sibling pair according to Family ID, one was randomly selected for the following analysis, which was conducted using PLINK v1.9(1). Single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) of less than 1%, with missingness greater than 5%, and with Hardy Weinberg equilibrium (HWE) $p< 1x10^{-5}$ were excluded. Variants in linkage disequilibrium were pruned using a window size of 50 kb, a step size of 5 kb, and an R^2 threshold of 0.5. To better control for population stratification artifacts, we calculated the first 4 principal components (PCs) and filtered individuals who fell outside 4 standard deviations from the mean of any of the 4 PCs calculated in a European reference population via the 1000 Genomes project.(2) We also removed participants who had an identity-by-descent (pi hat) value greater than 0.125 (i.e., third-

degree relatives), a sex mismatch, or who were missing more than 5% of their data. Shapeit v2 (3) was used for prephasing with genotyping data from the 1000 Genomes project used as a reference panel. IMPUTE v2 (4) was used for imputation.

We generated polygenic risk scores using a Bayesian approach (PRS-CS(5)). Due to the relatively small sample sizes (< 200,000) and high polygenicity of the tested psychiatric traits, ϕ, the global shrinkage parameter, was set at 0.02 for all traits except CROSS, for which ϕ was learned from the data. The remainder of the parameters were kept at the default setting. In PLINK, the resultant posterior effect sizes were applied to individual-level genotype data to generate PGS for each subject.– ADHD, ASD, anorexia nervosa (AN), bipolar disorder (BIP), major depressive disorder (MDD), obsessive compulsive disorder (OCD), schizophrenia (SCZ), and Tourette's syndrome (TRS), using summary statistics from the Psychiatric Genetics Consortium (PGC)(6–14).

Brain MRI quality control

A trained research coordinator individually assessed all 11,263 available T1 images and gave quality control (QC) ratings of "1" (best) to "4" (worst) for images that successfully went through the FreeSurfer recon-all process (Elyounssi et al., manuscript in preparation). The rating criteria was created to triage scans for manual edits, which are ongoing by our group. A rating of "1" was given to scans that require fewer and/or minor manual edits. A rating of "2" was given to scans that require several manual edits but can still be completed in several hours. A rating of "3" was given to scans with a larger number of manual edits needed that would take at least one day. A rating of "4" was given to unusable scans with severe motion or other artifacts. Scans with anatomical abnormalities such as cysts larger than 1 cm^3, or those with considerable

signal dropout (including after re-processing) were also excluded from the analysis. We also used total number of surface holes across the reconstructed cortical surface for each scan as an additional indicator of image quality.(15)

Covariates

INR calculation: We took a mid-point of total combined family income categories (~$5,000; $5,000 ~ $11,999; $12,000 ~ $15,999; $16,000 ~ $24,999; $25,000 ~ $34,999; $35,000 ~ $49,999; $50,000 ~ $74,999; $75,000 ~ $99,999; $100,000 ~ $199,999; $200,000~) and divided by 2017 federal poverty guideline according to household sizes (https://aspe.hhs.gov/topics/poverty-economic-mobility/poverty-guidelines/prior-hhs-poverty-guidelines-federal-register-references/2017-poverty-guidelines).

Puberty scale: Responses from Pubertal Development Scale and Menstrual Cycle Survey History (PDMS) were recorded in four categories (1 = has not yet begun to grow; 2 = has barely started to grow; 3 = is definitely underway; 4 = seems complete). Both values from youth and parents were included as covariates.

References

1. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015): Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* 4: s13742-015.
2. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, *et al.* (2015): A global reference for human genetic variation. *Nature* 526: 68–74.
3. Delaneau O, Marchini J (2014): Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel [no. 1]. *Nat Commun* 5: 3934.

4. Howie BN, Donnelly P, Marchini J (2009): A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS genetics* 5: e1000529.

5. Ge T, Chen C-Y, Ni Y, Feng Y-CA, Smoller JW (2019): Polygenic prediction via Bayesian regression and continuous shrinkage priors [no. 1]. *Nat Commun* 10: 1776.

6. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, *et al.* (2022): Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 1–13.

7. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) (2018): Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Mol Psychiatry* 23: 1181–1188.

8. Yu D, Sul JH, Tsetsos F, Nawaz MS, Huang AY, Zelaya I, *et al.* (2019): Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. *Am J Psychiatry* 176: 217–227.

9. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50: 668–681.

10. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, *et al.* (2019): Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* 51: 1207–1214.

11. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu, Cross-Disorder Group of the Psychiatric Genomics Consortium

(2019): Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* 179: 1469-1482.e11.

12. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, *et al.* (2019): Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet* 51: 793–803.
13. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 51: 63–75.
14. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet* 51: 431–444.
15. Rosen AFG, Roalf DR, Ruparel K, Blake J, Seelaus K, Villa LP, *et al.* (2018): Quantitative assessment of structural image quality. *Neuroimage* 169: 407–418.

Table S1. ABCD variables used in the analysis

Category	Variable	ABCD field	ABCD Survey	File Name
Demographics	Age	interview_age	Parent Demographics Survey	pdem02
	Sex	sex		
	Race	demo_prnt_race_a_v2___10		
	Ethnicity	demo_prnt_ethn_v2_l		
Socioeconomic Status	Household Income Level	demo_comb_income_v2_l		
	number of people in the household	demo_roster_v2_l	Longitudinal Parent Demographics Survey	abcd_lpds01
Child Psychopathology	Anxious/Depressed	cbcl_scr_syn_anxdep_t	Parent Child Behavior Checklist Scores Aseba (CBCL)	abcd_cbcls01
	Withdrawn/Depressed	cbcl_scr_syn_withdep_t		
	Somatic Complaints	cbcl_scr_syn_somatic_t		
	Social Problems	cbcl_scr_syn_social_t		
	Thought Problems	cbcl_scr_syn_thought_t		
	Attention Problems	cbcl_scr_syn_attention_t		
	Rule-Breaking Behavior	cbcl_scr_syn_rulebreak_t		
	Aggressive Behavior	cbcl_scr_syn_aggressive_t		
	Internalizing Problems	cbcl_scr_syn_internal_t		
	Externalizing Problems	cbcl_scr_syn_external_t		
	Total Problems	cbcl_scr_syn_totprob_t		
Activity	Team Sports	sai_p_activities___1, 2, 4, 5, 7, 11, 12, 15, 21	Parent Sports and Activities Involvement Questionnaire (SAIQ)	abcd_saiq02
	Individual Sports	sai_p_activities___0, 3, 6, 8, 9, 10, 13, 14, 16, 17, 18, 19, 20, 22		
	Non-sports Activity	sai_p_activities___23, 24, 25, 26, 27, 28		
	Activity History (year)	saip2_{activity name}_nyr		
Test Condition	Family ID	rel_family_id	ACS Post Stratification Weights	acspsw03
	Site ID	site_id_l	Longitudinal Tracking	abcd_lt01
	MRI scanner	mri_info_manufacturer	MRI Info	abcd_mri01

Puberty	Parent Body Hair Scale	pds_2_p	Parent Pubertal Development Scale and Menstrual Cycle Survey History (PDMS)	abcd_ppdms01
	Youth Body Hair Scale	pds_bdyhair	Youth Pubertal Development Scale and Menstrual Cycle Survey History (PDMS)	abcd_ypdms01

INR: income-to-needs ratio

Table S2. Demographics stratified by lifetime activities participation

Table S2a. Demographics stratified by lifetime individual sports participation

	Individual sports - (n=2,970)	Individual sports + (n=6,668)
Age	118.85 (7.36)	119.19 (7.49)
Sex (female: %)	1002 (33.7)	3589 (53.8)
Race (Caucasian: %)	2060 (69.4)	5529 (82.9)
Ethnicity (Hispanic: %)	691 (23.3)	1077 (16.2)
Income-to-needs ratio	2.65 (2.16)	4.32 (2.39)
Cultural activities (%)	1095 (36.9)	4482 (67.2)
Body hair scale (parents) (%)		
1	1873 (63.1)	4352 (65.3)
2	544 (18.3)	1217 (18.3)
3	475 (16.0)	975 (14.6)
4	78 (2.6)	124 (1.9)
Body hair scale (youth) (%)		
1	1428 (48.1)	3432 (51.5)
2	975 (32.8)	2127 (31.9)
3	344 (11.6)	821 (12.3)
4	223 (7.5)	288 (4.3)

N=9,638. Data are presented as mean (SD) or number (percentage).

Table S2b. Demographics stratified by lifetime cultural activities participation

	Cultural activities - (n=4,061)	Cultural activities + (n=5,577)
Age	118.43 (7.37)	119.56 (7.48)
Sex (female: %)	1688 (41.6)	2903 (52.1)
Race (Caucasian: %)	2993 (73.7)	4595 (82.4)
Ethnicity (Hispanic: %)	920 (22.7)	848 (15.2)
Income-to-needs ratio	3.08 (2.34)	4.33 (2.39)
Body hair scale (parents) (%)		
1	2558 (63.0)	3667 (65.8)
2	758 (18.7)	1003 (18.0)
3	650 (16.0)	800 (14.3)
4	95 (2.3)	107 (1.9)
Body hair scale (youth) (%)		
1	1974 (48.6)	2885 (51.7)
2	1296 (31.9)	1807 (32.4)
3	500 (12.3)	665 (11.9)
4	291 (7.2)	220 (3.9)

N=9,638. Data are presented as mean (SD) or number (percentage).

Table S3. Association between TS and CBCL

Table S3a. TS and CBCL association after adding IS and NSA

	beta	SE	p
TS	-1.04	0.580	<0.0001
IS	0.823	0.250	0.0022
NSA	-0.352	0.268	0.14
Age	-0.145	0.108	0.18
Sex	-2.62	0.240	<0.0001
Caucasian	1.59	0.314	<0.0001
Hispanic	-0.437	0.344	0.20
INR	-1.51	0.138	<0.0001
Puberty (parents)	0.470	0.150	0.0017
Puberty (youth)	0.279	0.125	0.026

N=9,638. Covariates: family ID, site ID (random effects). Continuous covariates were z-standardized.

Table S3b. Covariates for Association of TS status on CBCL Total score (*Model 1*)

	beta	SE	p
TS	-0.934	0.248	0.00016
Age	-0.126	0.107	0.24
Sex	-2.41	0.234	<0.0001
Caucasian	1.65	0.314	<0.0001
Hispanic	-0.487	0.343	0.16
INR	-1.38	0.134	<0.0001
Puberty (parents)	0.466	0.150	0.0020
Puberty (youth)	0.276	0.125	0.028

N=9,638. Covariates: family ID, site ID (random effects). Continuous covariates were z-standardized.

Table S3c. Sensitivity analysis of TS and CBCL association after adding IS and NSA and their interaction

	beta	SE	p
TS	-2.95	0.510	<0.0001
IS	-0.796	0.539	0.0020
NSA	-0.936	0.632	0.15
TS*IS	2.54	0.686	0.0013
TS*NSA	1.90	0.819	0.21
IS*NSA	1.41	0.790	0.67
TS*IS*NSA	-1.97	1.00	0.051
Age	-0.135	0.108	0.21

Sex	-2.63	0.240	<0.0001
Caucasian	1.64	0.314	<0.0001
Hispanic	-0.415	0.344	0.23
INR	-1.49	0.138	<0.0001
Puberty (parents)	0.378	0.126	0.0022
Puberty (youth)	0.230	0.110	0.023

N=9,638. Covariates: family ID, site ID (random effects). Continuous covariates were z-standardized.

Table S4. Association of TS status on CBCL subscales (*Model 1*)

	beta	SE	Unadjusted p	FDR
Anxious/Depressed	-0.603	0.137	<0.0001	<0.0001
Withdrawn/Depressed	-0.765	0.128	<0.0001	<0.0001
Somatic Complaints	-0.198	0.138	0.15	0.21
Social Problems	-0.535	0.105	<0.0001	<0.0001
Thought Problems	-0.471	0.134	0.00044	0.00073
Attention Problems	-0.536	0.139	0.000011	0.00022
Rule Breaking Behavior	-0.074	0.108	0.19	0.49
Aggressive Behavior	-0.162	0.124	0.20	0.24
Internalizing	-1.253	0.238	<0.0001	<0.0001
Externalizing	-0.168	0.230	0.47	0.49

N=9,638. Covariates: age, sex, race, ethnicity, INR, puberty scales (fixed effects), family ID, site ID (random effects).

Table S5. Association between Polygenic Risk Scores (PRS) and activity participation

	Team sports			**Individual sports**			**Non-sports activities**		
	No	**Yes**	**p**	**No**	**Yes**	**p**	**No**	**Yes**	**p**
n	1180	2834		945	3069		1406	2608	
ADHD	0.04 (1.00)	-0.03 (0.99)	0.033	0.06 (1.00)	-0.03 (1.00)	0.017	0.03 (1.01)	-0.03 (0.99)	0.051
ASD	0.06 (0.99)	-0.04 (1.00)	0.003	0.00 (0.99)	-0.01 (1.00)	0.76	-0.07 (1.00)	0.02 (1.00)	0.004
BIP	0.03 (0.98)	-0.02 (1.01)	0.16	-0.07 (1.00)	0.01 (1.00)	0.042	-0.04 (1.00)	0.01 (1.00)	0.093
MDD	0.05 (0.98)	-0.02 (1.00)	0.041	0.00 (0.98)	0.00 (1.00)	0.81	0.01 (1.00)	-0.01 (1.00)	0.719
SCZ	0.00 (1.02)	0.00 (1.00)	0.86	-0.04 (1.01)	0.01 (1.00)	0.16	-0.01 (1.03)	0.01 (0.99)	0.518
AN	-0.05 (0.97)	0.02 (1.00)	0.036	0.04 (0.96)	-0.01 (1.00)	0.12	0.04 (0.98)	-0.02 (1.00)	0.05
TrS	0.03 (1.01)	-0.03 (1.00)	0.11	0.02 (0.97)	-0.02 (1.01)	0.31	0.01 (1.01)	-0.02 (0.99)	0.47
OCD	0.01 (1.02)	-0.01 (0.98)	0.70	-0.02 (1.02)	0.00 (0.99)	0.50	-0.01 (0.99)	0.01 (1.00)	0.583

N=4,014.

ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, BP: bipolar disorder, MDD: major depressive disorder, SCZ: schizophrenia, AN anorexia nervosa, TrS: Tourette Syndrome, OCD: obsessive-compulsive disorder. Asterisks (*) indicate comparisons that were significant after FDR correction.

Table S6. Association between PRS and CBCL (*Model 2*)

Table S6a. Association of PRS with CBCL Total

	beta	SE	Unadjusted p	FDR
ADHD	1.021	0.167	<0.0001	<0.0001
ASD	0.527	0.169	0.0018	0.0048
BIP	0.199	0.173	0.25	0.29
MDD	0.721	0.174	<0.0001	0.0001
SCZ	0.341	0.193	0.077	0.13
AN	-0.089	0.179	0.62	0.62
TrS	0.194	0.170	0.25	0.29
OCD	0.291	0.165	0.078	0.13

N=4,014. Covariates: age, sex, INR, puberty scales, 5 principal components (fixed effects), site ID (random effects)

ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, BP: bipolar disorder, MDD: major depressive disorder, SCZ: schizophrenia, AN anorexia nervosa, TrS: Tourette Syndrome, OCD: obsessive-compulsive disorder

Table S6b. Association of ADHD PRS with CBCL subscales

	beta	SE	Unadjusted p	FDR
Anxious/Depressed	0.198	0.097	0.042	0.047
Withdrawn/Depressed	0.047	0.087	0.59	0.59
Somatic Complaints	0.262	0.094	0.0052	0.0074
Social Problems	0.235	0.069	0.00064	0.0011
Thought Problems	0.431	0.093	<0.0001	<0.0001
Attention Problems	0.610	0.093	<0.0001	<0.0001
Rule Breaking Behavior	0.323	0.068	<0.0001	<0.0001
Aggressive Behavior	0.382	0.081	<0.0001	<0.0001
Internalizing	0.449	0.164	0.0063	0.0079
Externalizing	0.948	0.156	<0.0001	<0.0001

N=4,014. Covariates: age, sex, INR, 5 principal components (fixed effects), site ID (random effects)

Table S6c. Association of ASD PRS with CBCL subscales

	beta	SE	Unadjusted p	FDR
Anxious/Depressed	0.169	0.098	0.0859	0.1228
Withdrawn/Depressed	0.144	0.088	0.1011	0.1264
Somatic Complaints	0.131	0.095	0.1664	0.1849
Social Problems	0.058	0.069	0.4017	0.4017
Thought Problems	0.236	0.094	0.0115	0.0488
Attention Problems	0.227	0.094	0.0162	0.0488
Rule Breaking Behavior	0.135	0.068	0.0487	0.0811
Aggressive Behavior	0.192	0.082	0.0195	0.0488
Internalizing	0.331	0.166	0.0453	0.0811
Externalizing	0.434	0.157	0.0058	0.0488

N=4,014. Covariates: age, sex, INR, 5 principal components (fixed effects), site ID (random effects)

Table S6d. Associaton of MDD PRS with CBCL subscales

	beta	SE	Unadjusted p	FDR
Anxious/Depressed	0.239	0.102	0.019	0.027
Withdrawn/Depressed	0.280	0.091	0.0021	0.0042
Somatic Complaints	0.367	0.098	0.0002	0.0009
Social Problems	0.268	0.072	0.0002	0.0009
Thought Problems	0.154	0.097	0.11	0.11
Attention Problems	0.202	0.098	0.039	0.046
Rule Breaking Behavior	0.214	0.071	0.0025	0.0042
Aggressive Behavior	0.174	0.085	0.041	0.046
Internalizing	0.625	0.171	0.0003	0.0009
Externalizing	0.576	0.163	0.0004	0.0010

N=4,014. Covariates: age, sex, INR, 5 principal components (fixed effects), site ID (random effects)

Table S7. Interaction between TS and ADHD PRS on CBCL, adjusted with other activities

	beta	SE	p
ADHD PRS	2.451	0.633	<0.0001
TS	-0.9384	1.041	0.00021
IS	1.784	1.109	0.00056
NSA	1.601	0.997	0.61
Team sports x ADHD PRS	-0.951	0.376	0.011
Individual sports x ADHD PRS	0.261	0.413	0.53
Cultural activities x ADHD PRS	0.558	0.358	0.12

N=4,014. Covariates: age, sex, INR, puberty scales, 5 principal components (fixed effects), site ID (random effects)

Table S8. TS PRS interaction on CBCL subscales with ADHD PRSs

	Interaction			
	beta	SE	Unadjusted p	FDR
Anxious/Depressed	-0.309	0.219	0.16	0.23
Withdrawn/Depressed	-0.387	0.196	0.048	0.16
Somatic Complaints	-0.178	0.211	0.40	0.50
Social Problems	-0.090	0.155	0.56	0.57
Thought Problems	-0.420	0.208	0.044	0.16
Attention Problems	-0.336	0.210	0.11	0.22
Rule Breaking Behavior	-0.281	0.153	0.066	0.17
Aggressive Behavior	-0.104	0.183	0.57	0.57
Internalizing	-0.769	0.369	0.037	0.16
Externalizing	-0.493	0.350	0.16	0.23

N=4,014. Covariates: age, sex, INR, puberty scales, 5 principal components (fixed effects), site ID (random effects)

Table S9. Association between CBCL Total and structural MRI (*Model 4*)

Table S9a. Association between CBCL Total and structural MRI summary values

	beta	SE	Unadjusted p	FDR
Mean cortical thickness	-0.098	0.127	0.44	0.44
Total surface area	-1.061	0.146	<0.0001	<0.0001*
Cortex volume	-1.046	0.144	<0.0001	<0.0001*
Subcortical gray matter volume	-0.755	0.136	<0.0001	<0.0001*
Cerebellum gray matter volume	-0.636	0.143	<0.0001	<0.0001*
Total gray matter volume	-1.094	0.147	<0.0001	<0.0001*

N=8,197. Global values are z-standardized. Covariates: age, sex, race, ethnicity, INR, puberty scales77, surface holes (fixed effects), family ID, site ID, scanner type (random effects). Asterisks (*) indicate comparisons that were significant after FDR correction.

Table S9b. Association between CBCL Total and subcortical ROI volumes

	beta	SE	Unadjusted p	FDR
R Accumbens area	-0.42	0.142	0.003	0.060
Brain Stem	-0.418	0.166	0.012	0.095
R Hippocampus	-0.357	0.154	0.02	0.095
L Caudate	-0.322	0.147	0.028	0.095
R Cerebellum Cortex	-0.343	0.165	0.038	0.095
L Cerebellum Cortex	-0.34	0.165	0.04	0.095
R Thalamus	-0.337	0.164	0.04	0.095
L Accumbens area	-0.312	0.153	0.041	0.095
L Hippocampus	-0.318	0.158	0.045	0.095
L Thalamus	-0.328	0.17	0.054	0.10
R Caudate	-0.276	0.147	0.06	0.10
L Pallidum	-0.239	0.154	0.121	0.19
R Amygdala	-0.219	0.15	0.144	0.21
R Pallidum	-0.195	0.144	0.175	0.24
L Amygdala	-0.185	0.145	0.203	0.26
L Putamen	-0.17	0.142	0.231	0.27
R Putamen	-0.116	0.141	0.412	0.46
R Ventral DC	-0.09	0.161	0.575	0.61
L Ventral DC	-0.074	0.162	0.646	0.65

N=8,197. ROI values are z-standardized. Covariates: age, sex, race, ethnicity, INR, puberty scale, estimated intracranial volume, surface holes (fixed effects), family ID, site ID, scanner type (random effects).

DC: ventral diencephalon, CC: Corpus Callosum.

Table S10. TS association with structural MRI (*Model 5*)

Table S10a. TS association with structural MRI summary values

	beta	SE	Unadjusted p	FDR
Mean cortical thickness	0.0120	0.0231	0.6034	0.60
Total surface area	0.0272	0.0201	0.1757	0.21
Cortex volume	0.0277	0.0205	0.1780	0.21
Subcortical gray matter volume	0.0626	0.0218	0.0040	0.024*
Cerebellum gray matter volume	0.0471	0.0206	0.0224	0.067
Total gray matter volume	0.0355	0.0200	0.076	0.15

N=8,197. QC rating 1,2,3 only. Global values are z-standardized. Covariates: age, sex, race, ethnicity, INR, puberty scale, surface holes (fixed effects), family ID, site ID, scanner type (random effects). Asterisks (*) indicate comparisons that were significant after FDR correction.

Table S10b. TS association with subcortical ROI volumes

	beta	SE	Unadjusted p	FDR
L Thalamus	0.0571	0.017	0.0008	0.015*
L Pallidum	0.0547	0.0189	0.0037	0.036*
R Thalamus	0.0409	0.0175	0.02	0.12
R Pallidum	0.043	0.0202	0.033	0.12
L Hippocampus	0.0385	0.0184	0.036	0.12
R Accumbens area	0.0392	0.0196	0.045	0.12
L Ventral DC	0.0354	0.0178	0.047	0.12
L Cerebellum Cortex	0.0352	0.0179	0.049	0.12
Brain Stem	0.0322	0.0177	0.069	0.15
R Cerebellum Cortex	0.0294	0.0179	0.1	0.17
L Putamen	0.0332	0.0206	0.11	0.17
R Amygdala	0.0305	0.019	0.11	0.17
L Amygdala	0.0244	0.0195	0.21	0.31
R Putamen	0.0247	0.0208	0.24	0.31
R Hippocampus	0.0219	0.0189	0.25	0.31
R Caudate	0.0209	0.0201	0.3	0.36
R Ventral DC	0.0154	0.0179	0.39	0.44
L Accumbens area	0.0142	0.0175	0.42	0.44
L Caudate	0.0055	0.0201	0.78	0.78

N=8,197. ROI values are z-standardized. Covariates: age, sex, race, ethnicity, INR, puberty scale, estimated intracranial volume, surface holes (fixed effects), family ID, site ID, scanner type (random effects). Asterisks (*) indicate comparisons that were significant after FDR correction.

Table S11. Association between CBCL total and structural MRI adjusted for other activities (IS and NSA)

Table S11a. Global value adjusted for other activities

	beta	SE	Unadjusted p
Total surface area	-1.082	0.146	<0.0001
Cortex volume	-1.064	0.144	<0.0001
Subcortical gray matter volume	-0.774	0.136	<0.0001
Cerebellum gray matter volume	-0.650	0.143	<0.0001
Total gray matter volume	-1.115	0.147	<0.0001

N=8,197. Global values are z-standardized. Covariates: IS, NSA, age, sex, race, ethnicity, INR, puberty scale, surface holes (fixed effects), family ID, site ID, scanner type (random effects). Asterisks (*) indicate comparisons that were significant after FDR correction.

Table S11b. Subcortical ROIs for other activities

	beta	SE	Unadjusted p
R Accumbens area	-0.4204	0.142229	0.003119
L Cerebellum Cortex	-0.34495	0.165174	0.036764
L Thalamus	-0.339	0.16995	0.046077
L Caudate	-0.32966	0.146978	0.024903
Brain Stem	-0.41246	0.165797	0.012855
L Hippocampus	-0.32203	0.158359	0.041995
L Accumbens area	-0.30453	0.152529	0.045873
R Cerebellum Cortex	-0.35016	0.165017	0.03384
R Thalamus	-0.34005	0.164255	0.03843
R Hippocampus	-0.35906	0.153811	0.019574
R Caudate	-0.28433	0.146576	0.052405
L Pallidum	-0.2485	0.153868	0.106301
R Amygdala	-0.22384	0.149501	0.13433
R Pallidum	-0.19957	0.143791	0.165172
L Amygdala	-0.18652	0.145009	0.19834
L Putamen	-0.17487	0.142125	0.218555
R Putamen	-0.12272	0.141021	0.384178
R VentralDC	-0.095	0.161359	0.556013
L VentralDC	-0.07483	0.161767	0.643673

N=8,197. ROI values are z-standardized. ROIs that were nominally significant in Table S6 were listed. Covariates: IS, NSA, age, sex, race, ethnicity, INR, puberty scale, estimated intracranial volume, surface holes (fixed effects), family ID, site ID, scanner type (random effects). Asterisks (*) indicate comparisons that were significant after FDR correction.

Table S12. TS association with structural MRI adjusted for other activities (IS and NSA)

Table S12a. Global value adjusted for other activities

	beta	SE	p
Subcortical gray matter volume	0.0539	0.0219	0.014

N=8,197. Global values are z-standardized. Covariates: IS, NSA, age, sex, race, ethnicity, INR, puberty scale, surface holes (fixed effects), family ID, site ID, scanner type (random effects)

Table S12b. Subcortical ROIs for other activities

	beta	SE	Unadjusted p
L Thalamus	0.0543	0.0172	0.0016
L Pallidum	0.0516	0.0190	0.0066
Brain Stem	0.0346	0.0178	0.053
L Hippocampus	0.0369	0.0185	0.046
L VentralDC	0.0350	0.0179	0.051
R Thalamus	0.0401	0.0177	0.023
R Pallidum	0.0415	0.0203	0.041
R Accumbens area	0.0402	0.0197	0.042
L Cerebellum Cortex	0.0337	0.0180	0.061
L Putamen	0.0314	0.0208	0.131
R Cerebellum Cortex	0.0272	0.0180	0.131
R Amygdala	0.0284	0.0192	0.138
L Amygdala	0.0237	0.0197	0.229
R Hippocampus	0.0210	0.0191	0.271
R Putamen	0.0217	0.0209	0.301
L Accumbens area	0.0175	0.0176	0.322
R Caudate	0.0173	0.0203	0.394
R VentralDC	0.0135	0.0181	0.454
L Caudate	0.0022	0.0202	0.913

N=8,197. ROI values are z-standardized. Covariates: IS, NSA, age, sex, race, ethnicity, INR, puberty scale, estimated intracranial volume, surface holes (fixed effects), family ID, site ID, scanner type (random effects). Asterisks (*) indicate comparisons that were significant after FDR correction.

DC: ventral diencephalon.

Table S13. Interaction between global MRI measurements and sex on CBCL total (*Model 4s*)

	beta	SE	Unadjusted p	FDR
Mean cortical thickness	0.0610	0.2337	0.79	0.79
Total surface area	0.3243	0.2650	0.22	0.27
Cortex volume	0.3635	0.2596	0.16	0.26
Subcortical gray matter volume	0.3499	0.2565	0.17	0.26
Cerebellum gray matter volume	0.567	0.259	0.029	0.17
Total gray matter volume	0.439	0.264	0.097	0.26

N=8,197. Global values are z-standardized. Covariates: global MRI measurements, age, sex, race, ethnicity, INR, puberty scales, surface holes (fixed effects), family ID, site ID, scanner type (random effects).

Table S14. Interaction between TS and sex on global MRI measurements (*Model 5s*)

	beta	SE	Unadjusted p
Mean cortical thickness	-0.0202	0.0446	0.65
Total surface area	-0.0115	0.0386	0.77
Cortex volume	-0.0225	0.0393	0.57
Subcortical gray matter volume	-0.0068	0.0417	0.87
Cerebellum gray matter volume	-0.0211	0.0394	0.59
Total gray matter volume	-0.0230	0.0387	0.55

N=8,197. Global values are z-standardized. Covariates: TS, age, sex, race, ethnicity, INR, puberty scales, surface holes (fixed effects), family ID, site ID, scanner type (random effects).

Table S15. 3-Way Interaction between TS, global MRI measurements, and sex on CBCL total

	beta	SE	Unadjusted p
Mean cortical thickness	0.0012	0.4925	0.99
Total surface area	-0.9362	0.5668	0.099
Cortex volume	-0.7018	0.5531	0.20
Subcortical gray matter volume	0.1956	0.5476	0.72
Cerebellum gray matter volume	-0.306	0.556	0.58
Total gray matter volume	-0.645	0.563	0.25

N=8,197. Global values are z-standardized. Covariates: TS, global MRI measurements, sex, and these interactions, age, race, ethnicity, INR, puberty scales, surface holes (fixed effects), family ID, site ID, scanner type (random effects).

Figure S1. Flow diagram for the population used for the analysis

Among total 11,875 data available, we used data from 9,638 participants for the analysis testing TS effects, 4,014 for genetic analysis, and 8,197 for MRI analysis.

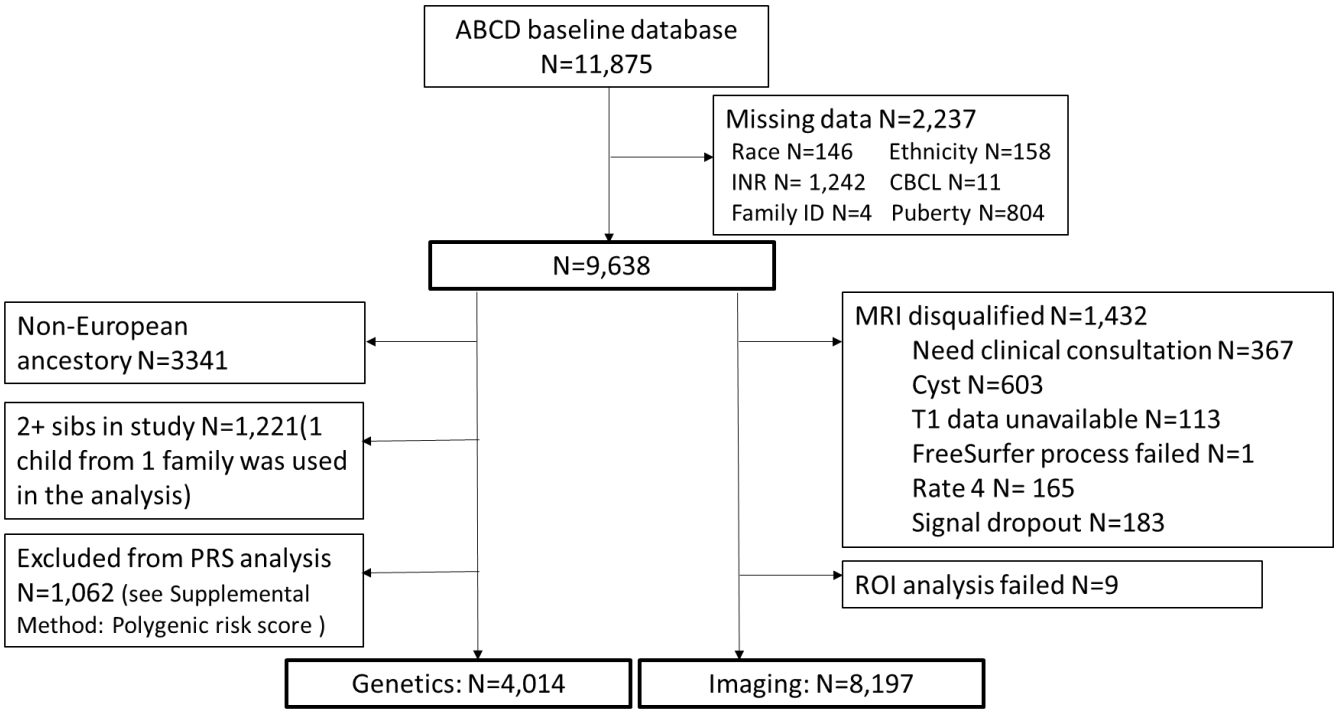

Figure S2. Estimated differences in CBCL total score by activity participation

N=9,637. T=team sports; I=individual sports; N=non-sports activity. The no activity participation group was used as a reference. Covariates: age, sex, race, ethnicity, INR, puberty scales, (fixed effects), family ID, site ID (random effects)