Supplementary Information for

Early-Initiated Childhood Reading for Pleasure: Associations with Better Cognitive Performance, Mental Well-being and Brain Structure in Young Adolescence

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This supplementary file includes:

1. Supplementary methods S1 - S5 Pages 3 – 9
2. Supplementary diagram 1 Page 10
3. Figures S1 – S10 Pages 11 - 20
4. Tables S1 - S16 Pages 21 - 38
5. Other supplementary materials 1 - 2 Pages 39 - 42
6. References Pages 43 - 44

1. Supplementary Methods

Method.S1. Participants

In this study, data from the latest 3rd and 4th updates of the ABCD research project (https://abcdstudy.org/) were used, which is an ongoing longitudinal project launched in 21 research sites across the US (a list of all sites was in supplementary material.2). The ABCD cohort recruited 11,878 participants aged 9(107 months) to 11(133 months) for baseline recording and 10,414 participants aged 11(127 months) to 13(168 months) for 2 years follow-up recordings. Participants were recruited from local schools in this study. It was defined by the World Health Organization (WHO) that the adolescence began at the 10th birthday, and since the majority of ABCD participants were close to or exceeded this age, we refer to them as young adolescents. The ABCD project tracks participants through young adolescence to adulthood across multiple domains related to health and development, in order to investigate how individual, family, environmental and cultural factors influence brain development and health outcomes. All of the participants had signed written consent forms (for parents or caregivers) or informed consent forms (for young adolescents) before participation in the study. The institutional review committee of the University of California, San Diego (UCSD), is responsible for the ethical oversight of the ABCD research.

Samples failing these criteria were excluded from this study: 1). common MRI contraindications; 2). inability to communicate fluently in English; 3). hearing/sensorimotor impairments; 4). a history of major neurological disorders. 5). a history of traumatic brain injury; 6). refusal to complete assessments. Additional information about the study design and research participants is available on the (https://abcdstudy.org/scientists/protocols/) ABCD project's website, and the data collection processes have been detailed in previous publications(Casey et al., 2018; Karcher & Barch, 2021). 1635 participants who had no records of RfP measurements and incomplete demographic data were excluded from this study, as well as according to the above criteria. Finally, 10,243 participants were included in the study and their demographic characteristics were summarized in **Table 1.**

Method.S2. Structural neuroimaging of ABCD

High resolution sMRI data of all participants were obtained through the following 3T scanners with a 32-channel head coil: 1) Discovery MR750 (GE Healthcare, Wisconsin), 2) Achieva dStream and Ingenia CX (Philips, Massachusetts) or 3) Prisma (Siemens Medical, Germany). The sequence and imaging parameters included: 1) Prisma VE11B-C: Matrix 256×256, Slices 176, FOV 256×256, Resolution (mm) 1.0×1.0×1.0, TR (ms) 2500, TE (ms) 2.88, TI (ms) 1060, Flip Angle (deg) 8, Acquisition Time 07:12; 2) Achieva dStream, Ingenia:

Matrix 256×256, Slices 225, FOV 256×240, Resolution (mm) 1.0×1.0×1.0, TR (ms) 6.31, TE (ms) 2.9, TI (ms) 1060, Flip Angle (deg) 8, Acquisition Time 05:38; (3) MR750, DV25-26: Matrix 256×256, Slices 208, FOV 256×256, Resolution (mm) 1.0×1.0×1.0, TR (ms) 2500, TE(ms) 2, TI(ms) 1060, Flip Angle (deg) 8, Acquisition Time 06:09.

The ABCD research team performed the data preprocessing procedures, which mainly included the following steps: (1)Image processing: 1. Gradient nonlinearity distortions in T1w and T2w structural images were corrected; 2. T2w images were registered to T1w images using mutual information; 3. Intensity normalization was performed using tissue segmentation and sparse spatial smoothing; 4. Resampled with 1 mm isotropic voxels into rigid alignment using a custom, in-house atlas created specifically for participants of this age by the ABCD data preprocessing team; (2)Cortical surface reconstruction was performed using FreeSurfer (https://surfer.nmr.mgh.harvard.edu), with the following major steps: 1.Skull-stripping; 2.Segmentation of white matter and initial mesh creation. 3.Correction of topological defects; 4. Optimization of the surface; 5. Nonlinear registration to a spherical surface-based atlas via the sulcal/gyral pattern alignment.

For quality control (QC) of FreeSurfer cortical surface reconstruction processes, QC score in the freesqc01 file indicates whether inclusion or exclusion is recommended: 0 score indicates failing quality control and rejection. Five types of artifacts were evaluated for their severity: motion, intensity inhomogeneity, white matter underestimation, pial overestimation, and magnetic susceptibility artifact. Additional parameters for data collection and preprocessing can be found on the ABCD website (https://abcdstudy.org/scientists/protocols/) and in previous publications(Casey et al., 2018; Hagler et al., 2019).

Method.S3. The GWAS-derived exposure and outcome data for Mendelian randomization (MR) and MR sensitivity analyses

(1) The exposure and outcome data

In the process of obtaining genetic instrument data for MR analysis, the SNP-exposure and SNP-outcome were from independent GWAS results that were derived from separate studies. We have made sure that there's no participant overlapping between the samples utilized to calculate genetic associations between SNP-exposure and SNP-outcome in the two- sample MR analysis, in order to avoid this source of bias(Burgess, Davies, & Thompson, 2016; Choi et al., 2019; Rosoff et al., 2021). In this study, SNP-exposure were obtained from GWAS analysis from the ABCD cohort. The SNP-outcome data were obtained from **a)** ID:ebi-a-GCST006572, UK-Biobank and Cognitive Genomics Consortium (COGENT) participants (for cognitive performances)(Lee et al., 2018); **b)** ID: ubm-a-2819, UK-Biobank participants (for

adult left superior temporal cortical area)(Elliott et al., 2018); **c)** ID: ieu-a-1183, the GWAS meta-analysis from 12 cohorts including the Denmark Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) and Psychiatric Genomics Consortium (PGC) participants (for ADHD case-control)(Demontis et al., 2019). All GWAS data were available for ancestry-matched 4445 young adolescents (early RfP), 257841 adults (cognitive performances), and 55374 children & adults (ADHD case-control) participants.

Detailed information:

(a) The exposure data for the MR analysis were SNPs associated with early RfP identified in the ABCD study. The imputed ABCD genotype data had been quality controlled and processed with linkage disequilibrium (LD) based SNP pruning (zzz.bwh.harvard.edu/plink/summary.shtml). The covariates of GWAS analysis included sex, age, and 10 PCs generated from principle component analysis (PCA). The top associated SNPs identified through GWAS for further MR analysis conformed to a relatively more relaxed threshold ($P < 5\times10^{-6}$) than the genome-wide significant threshold ($P < 5\times10^{-8}$). Consistently, previous psychiatric MR studies had applied the method of relaxing the threshold for genetic instruments when there were too few significant SNPs available(Choi et al., 2019; Gage et al., 2017). Our significance level for the SNPs associated with early RfP exceeded the suggestive significant level of $P < 1\times10^{-5}$, but did not exceed genome-wide significant level of $P < 5\times10^{-8}$, which was consistent with previously published GWAS studies on reading related measurements(Davis et al., 2014; Luciano et al., 2013). Similar to early RfP, previous study indicated that SNPs showed strongest signals of association with reading (as well as and mathematics) were at the significant level of $P < 5\times10^{-5}$ (reading, N=2,243; mathematics, N=2,772) in participants at age 12(Davis et al., 2014). Also, for reading and spelling, gene-based analyses showed significant association ($P < 2.8 \times 10^{-6}$)(Luciano et al., 2013). Association for reading measures and non-word repetition was indicated with the greatest associated SNPs in the pseudogene ABCC13 ($P = 7.34\times10^{-8}$), and the gene DAZAP1 ($P = 1.32\times10^{-6}$)(Luciano et al., 2013). The top SNPs associated with early RfP were further clumped for independence and used as exposure genetic instruments for subsequent MR analysis;

(b) The outcome data for MR analysis were obtained from GWAS summaries associated with **1)** adult cognitive performance (ID: ebi-a-GCST006572), which was based on UK-Biobank and Cognitive Genomics Consortium (COGENT) cohorts(Lee et al., 2018), **2)** adult left superior temporal cortical area (ID: ubm-a-2819), which was based on UK-Biobank cohort(Elliott et al., 2018), as well as **3)** ADHD disorder in children and adults (ID: ieu-a-1183), which was based on iPSYCH & PGC cohorts(Demontis et al., 2019), and details of the children and adults participants included in the GWAS meta-analyses of diagnosed ADHD were listed in supplementary table 1 of the previous study(Demontis et al., 2019). These published

summary-level data for MR outcome data preparation were publicly available on GWAS databases websites: (https://www.ebi.ac.uk/gwas/, or http://gwas-api.mrcieu.ac.uk/).

(2) MR sensitivity analyses

We used the standard inverse variance weighted (IVW) method of MR analysis to determine potential causal relationships. We then compared IVW results with two other established MR methods, including **1)** a weighted median analysis that allows for half of the instrument variables to be invalid in the causal estimation(Bowden, Smith, Haycock, & Burgess, 2016) and **2)** the MR–Egger regression with its intercept representing average pleiotropic bias and slope representing the causal estimate(Bowden, Smith, & Burgess, 2015), which are recognized as being more robust to horizontal pleiotropy but at the expense of decreased statistical power(Hemani, Bowden, & Davey Smith, 2018). The Steiger-directionality test was further applied to test the causal direction between the hypothetical SNP exposures and SNP outcomes(Hemani, Tilling, & Smith, 2017)

For sensitivity analyses, the MR-PRESSO (MR_Pleiotropy_Residual_Sum_and Outlier) test was applied to detect pleiotropic outliers(Verbanck, Chen, Neale, & Do, 2018). Horizontal pleiotropy and heterogeneity were also tested using the MR–Egger intercept test and modified Q-statistics(Hemani, Zheng, et al., 2018).

During sensitivity analysis of those MR evaluations, across all genetic instruments, no horizontal pleiotropy or heterogeneity was observed using the MR–Egger intercept test or modified Q statistics, and no SNP outliers were detected by the MR-PRESSO test.

Method.S4. The *LMM* model

The *LMM* model listed below was applied to investigate associations between RfP measurements (early RfP or RfP durations) and dependent variables of interest (*Y*), including cognition scores and mental problem scores (**formula I**), as well as brain structure (**formula II**, the different types of MRI scanners were also added as covariates in sMRI-related analysis). In these formulas, let *j*, *k* and *i* denote the random effects of 1) ABCD site (*j*); 2) family structures (family ID) (*k*) nested within ABCD sites (*j*); and 3) a young adolescent participant (*i*):

Formula I:

$$\begin{aligned} Y_{jki} = {} & \beta_0 + \beta_1 RfP\ measurements_{jki} + \beta_2 Age_{jki} + \beta_3 Sex_{jki} + \beta_4 BMI_{jki} \\ & + \beta_5 Puberty_{jki} + \beta_6 Race/Ethnicity_{jki}(dummy\ variables) \\ & + \beta_7 Parental\ education_{jki} + \beta_8 Family\ income_{jki} + U_{j[k]} + U_j + \varepsilon_{jki} \end{aligned}$$

Formula II (for structural neuroimaging analysis)**:**

$$Y_{jki} = \beta_0 + \beta_1 RfP\ measurements_{jki} + \beta_2 Age_{jki} + \beta_3 Sex_{jki} + \beta_4 BMI_{jki} + \beta_5 Puberty_{jki} + \beta_6 Race/Ethnicity_{jki}(dummy\ variables) + \beta_7 Parental\ education_{jki} + \beta_8 Family\ income_{jki} + \beta_9 MRI\ scanners(dummy\ variables)_{jki} + U_{j[k]} + U_j + \varepsilon_{jki}$$

The t value, *df* (DFE value in *LMM* results), β value and *P* value were obtained from the LMM model for each association analysis, and the *r* value was calculated using *t* and *df* values:

$$r_{LMM} = \frac{t_{LMM}}{\sqrt{t_{LMM}^2 + df_{LMM}}}$$

The calculated *r* values from the *LMM* models represent the effect sizes of associations between early RfP and cognition or mental health scales and brain morphological measures. *P* values of associations were Bonferroni-corrected ($P < 0.05$) for multiple comparisons to test significance.

Details of demographic covariates included: Parental education was defined by the highest education level achieved by both parents, corresponding to 3 categories of 7 scores: **1.** ≤HS Diploma/GED: 1) 6th grade or less; 2) 7th-9th grade; 3) 10th-12th grade; 4) high-school, general educational development exam (GED) or equivalent; **2.** College and Bachelor: 5) some college; 6) bachelor's degree; and **3.** Post Graduate Degree: 7) master's degree, professional degree or PhD. Family income levels per year included: **1.** Low: < $50,000; **2.** Middle: >= $50,000 & <100,000; **3.** High >= $100,000. Race/ethnicity comprised four main groups (in alphabetical order): 1: 'Asia', 2: 'Black', 3: 'Hispanic', 4: 'Other' and 5: 'White'. Sex (female/male, in alphabetical order). Categorical factors were race/ethnicity, sex, and MRI scanner types. Early RfP, age (in months), BMI and family SES were continuous factors

Method.S5. Longitudinal and mediation analyses, and twin study

(A) Longitudinal analysis

A longitudinal analysis was conducted on more than half of the participants (6738) who had complete recordings on the variables of interest, using RfP measurements and cognitive/psychiatric assessments obtained in the 2-year follow up after the baseline recordings. A cross-lagged panel structural model (CLPM) implemented in Mplus 7.4(Quach, Nguyen, Williams, & Sciberras, 2018) was used to examine the relative strength of cross-lagged correlations between early RfP and cognitive/psychiatric scores. Maximum likelihood estimation was used to determine the model parameters. We reported the standardized regression coefficients and their standard errors throughout. As in the *LMM* association analysis, covariates were all controlled in these CLPM models.

The CLPM model:

$$\boldsymbol{X_{t+2} = \alpha_t X_t + \beta_t Y_t + \eta_1 z_t + \varepsilon_1}$$
$$\boldsymbol{Y_{t+2} = \delta_t Y_t + \gamma_t X_t + \eta_2 z_t + \varepsilon_2}$$

In this model, X_t and Y_t denote the baseline RfP measurements and a cognitive/psychiatric assessment score of a participant, and X_{t+2} and Y_{t+2} represent their 2-years follow-up recordings. The coefficients of the model are $\boldsymbol{\alpha_t}$, $\boldsymbol{\beta_t}$, $\boldsymbol{\delta_t}$, $\boldsymbol{\gamma_t}$, $\boldsymbol{\eta_1}$ and $\boldsymbol{\eta_2}$. The covariate variable is $\boldsymbol{z_t}$, and $\boldsymbol{\varepsilon 1}$ and $\boldsymbol{\varepsilon 2}$ represent the error term.

(B) Mediation analysis

The Mediation toolbox (https://github.com/canlab/MediationToolbox) developed by Tor Wager's team was used for mediation analysis, which has been validated and applied in previous neuroimaging research(Lim, Padmala, & Pessoa, 2009; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). In the 3-factor pathway mediation model, we investigated whether the associations between early RfP (independent predictor) and cognitive or psychiatric scores (predicted dependent variable) were mediated by brain structure (proposed mediator of the indirect path AB), adjusting for all covariates. Methodological details of this standard mediation analysis are presented in the supplementary information of a previous paper(Wager et al., 2008). Mean values derived from brain structure measures (Bonferroni-corrected $P < 0.05$) that were both significantly associated with early RfP and cognitive/psychiatric scores were included in the mediation model. The P values of indirect, direct and total effects calculated from mediation analysis were bias-corrected and also further estimated by bootstrapping with a 10000-random samplings approach.

(C) Twin study analysis

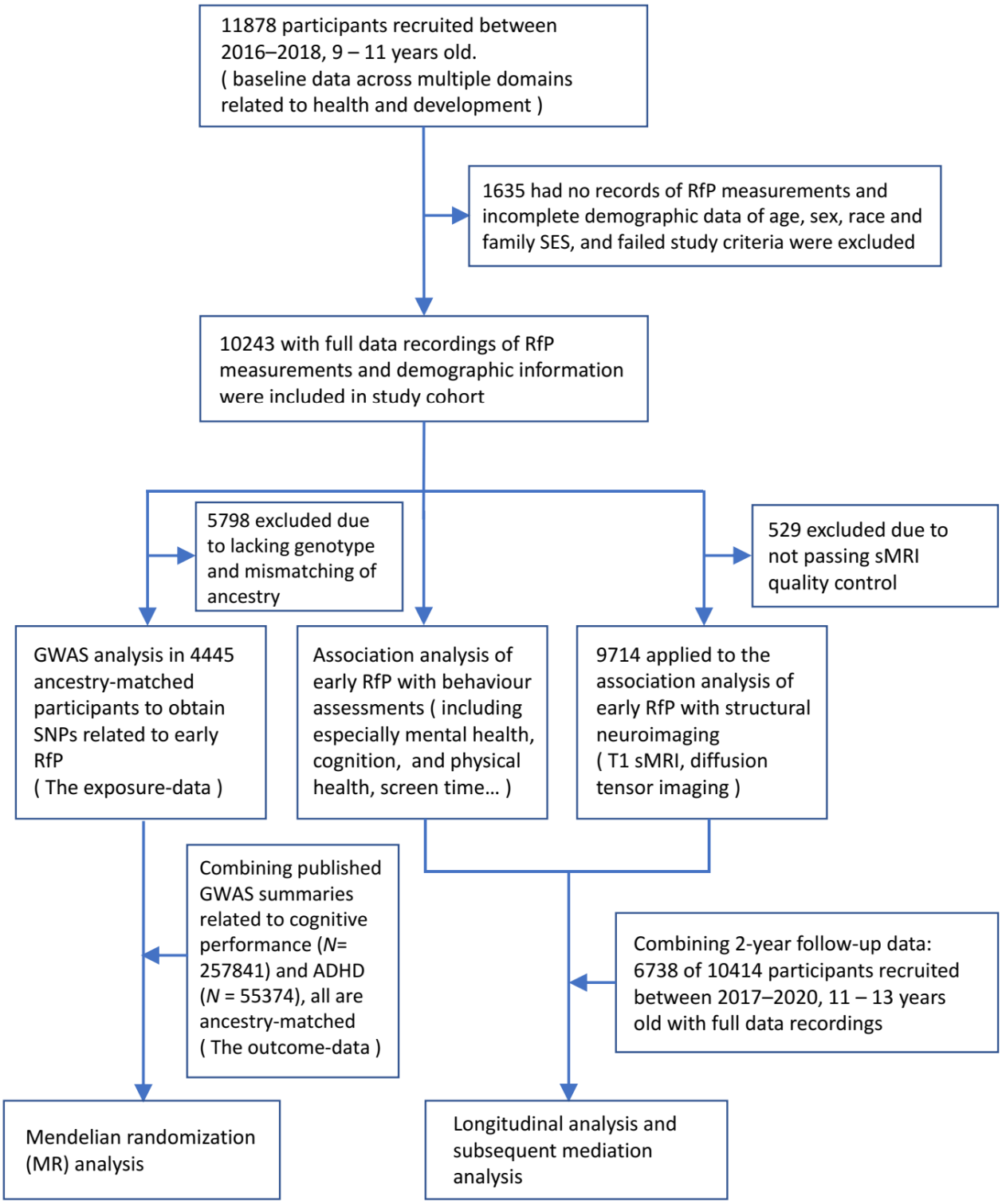
Basically, the variability in an observed variable or phenotype can be explained by differences in genetic and environmental factors, which includes: 1) The A represents additive genetic factors, 2) the C represents shared or common environmental factors, and 3) the E represents unique or specific environmental factors. Therefore, in order to calculate the 3 sources of variance, we must collect data from relatives with different levels of genetic and environmental similarity to identify the parameters. One such important design is the standard twin study to assess the relative significance of genetic and environmental factors. Generally, it compares the similarity of identical (monozygotic, MZ, sharing essentially 100% of their genes) and fraternal (dizygotic, DZ, sharing only about 50% of their genes) twins to infer the role of A, C and E.

The twin study analysis on heritability was performed using the OpenMx V 2.20.6. R statistical package with structural equation modelling of the standard twin ACE statistical model controlled for cofounders, which has been validated and applied in previous twin

study(Koncz et al., 2022).

2. Supplementary.diagram.1

Flow diagram of cohort selection and study design



3. Supplementary Figures

Figure S1

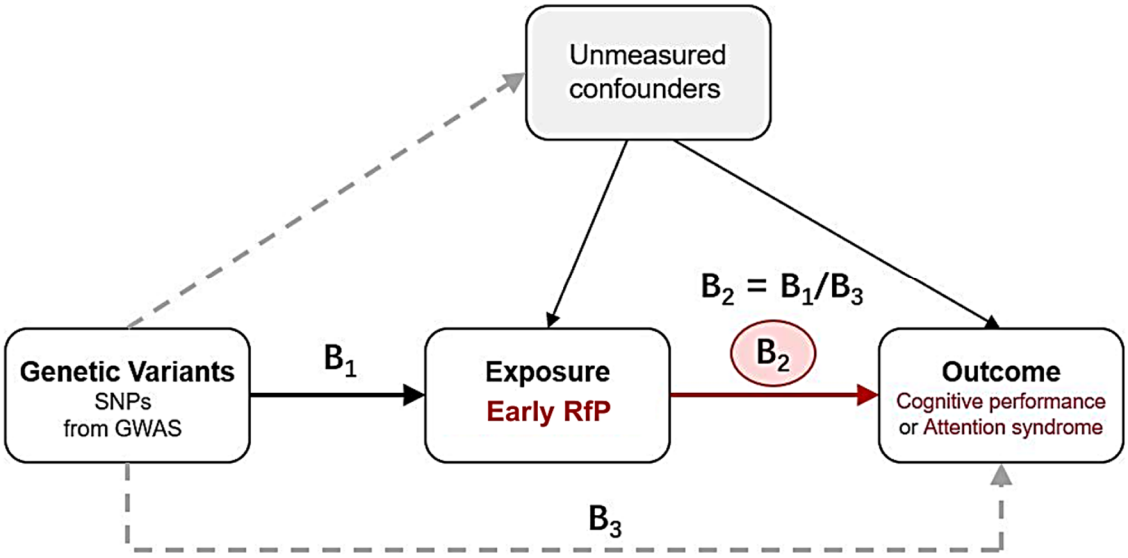


Figure S1. Model of the MR study

Genetic variants (SNPs) significantly associated with the exposure were used as instruments to determine whether the exposure had a significant causal relationship ($\mathbf{B_2}$) with the outcome. $\mathbf{B_1}$ and $\mathbf{B_3}$ demonstrate the estimated direct effects of a SNP on the exposure (early RfP) and outcome (adult cognitive performance or attention syndrome later in life), respectively. According to MR assumptions, dashed-line pathways indicate that the genetic instrument should not be associated with confounders (independence assumption) or the outcome (exclusion restriction assumption).

Figure modified from the previous study(Choi et al., 2019).

Figure S2

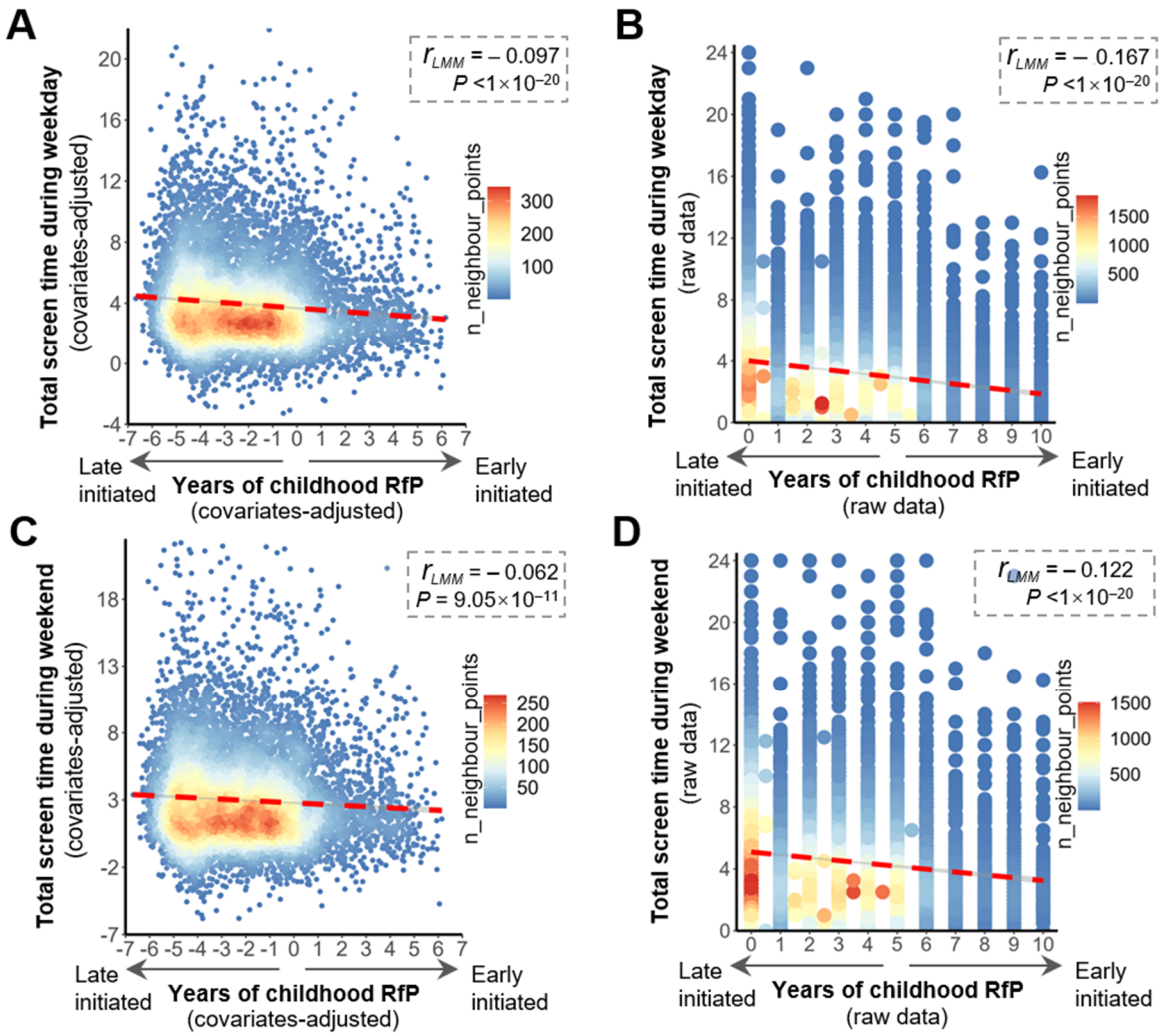


Figure S2. Correlations between early RfP and youth total screen time

(A, B) Density-scatter plots demonstrated the significant negative correlations between early RfP and youth total screen time (per day) during their weekdays. **(C, D)** The significant negative correlations between early RfP and youth total screen time during the weekends. Each individual datapoint is coloured by the number of neighbouring datapoints (n_neighbour_points) to represent the density of the overall data distribution.

(for **A** and **C,** datapoints with all covariates adjusted; for **B** and **D,** raw data distribution). $P_{\text{Bonferroni}}$<0.05.

Figure S3

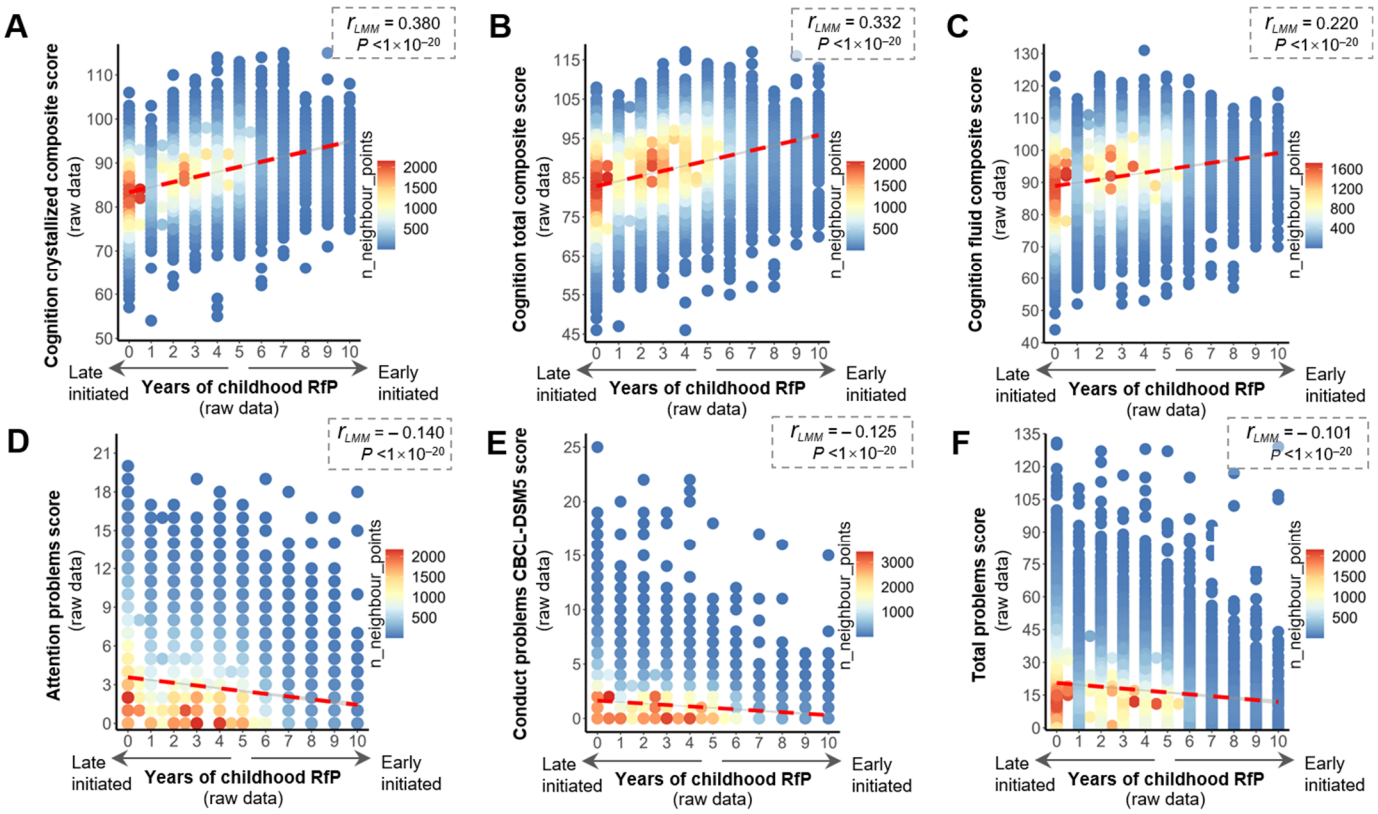


Figure S3. Scatter plots of raw data consistently demonstrated the representative most significantly correlated subscales of cognitive and psychopathology scores with early RfP

(A-C) Density-scatter plots and analysis of raw data showing that the crystallized composite, total composite and fluid composite were the top 3 positively correlated cognitive subscales. **(D-F)** The attention problem, conduct problem and total problems were the top-ranked negatively correlated psychopathological subscales. n_neighbour_points shows the number of neighbouring datapoints around each datapoint to represent the density of the overall data distribution. Bonferroni-corrected P ($P_{\text{Bonferroni}}$)<0.05.

Figure S4

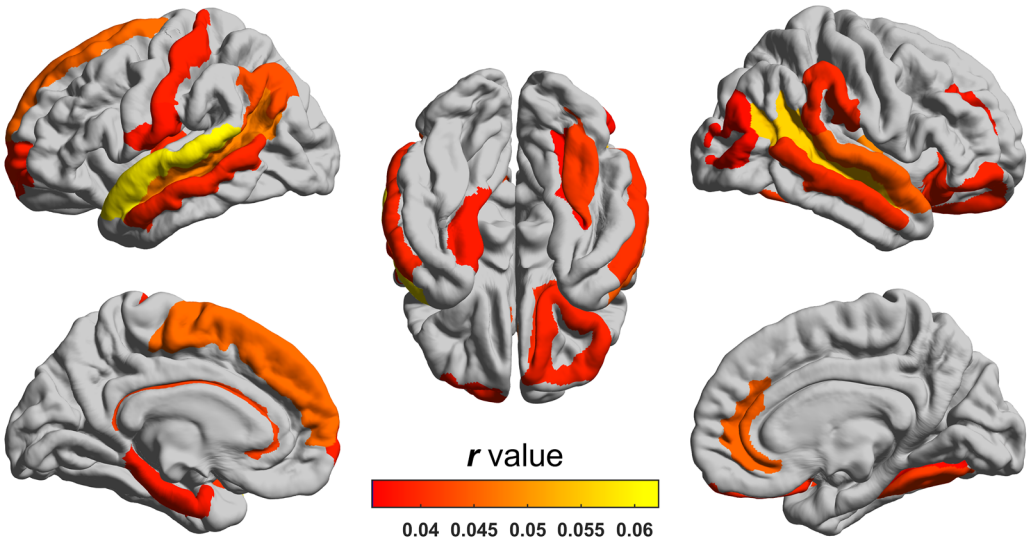


Figure S4. Youth brain cortical areas were significantly correlated with early RfP in the typically developing (TD) participants

Brain map showing the specific cortical areas that were modestly significantly increased in participants of TD group with higher levels of early RfP. Brain regions with larger areas positively associated with early RfP are represented by the red colour. $P_{Bonferroni}<0.05$.

Figure S5

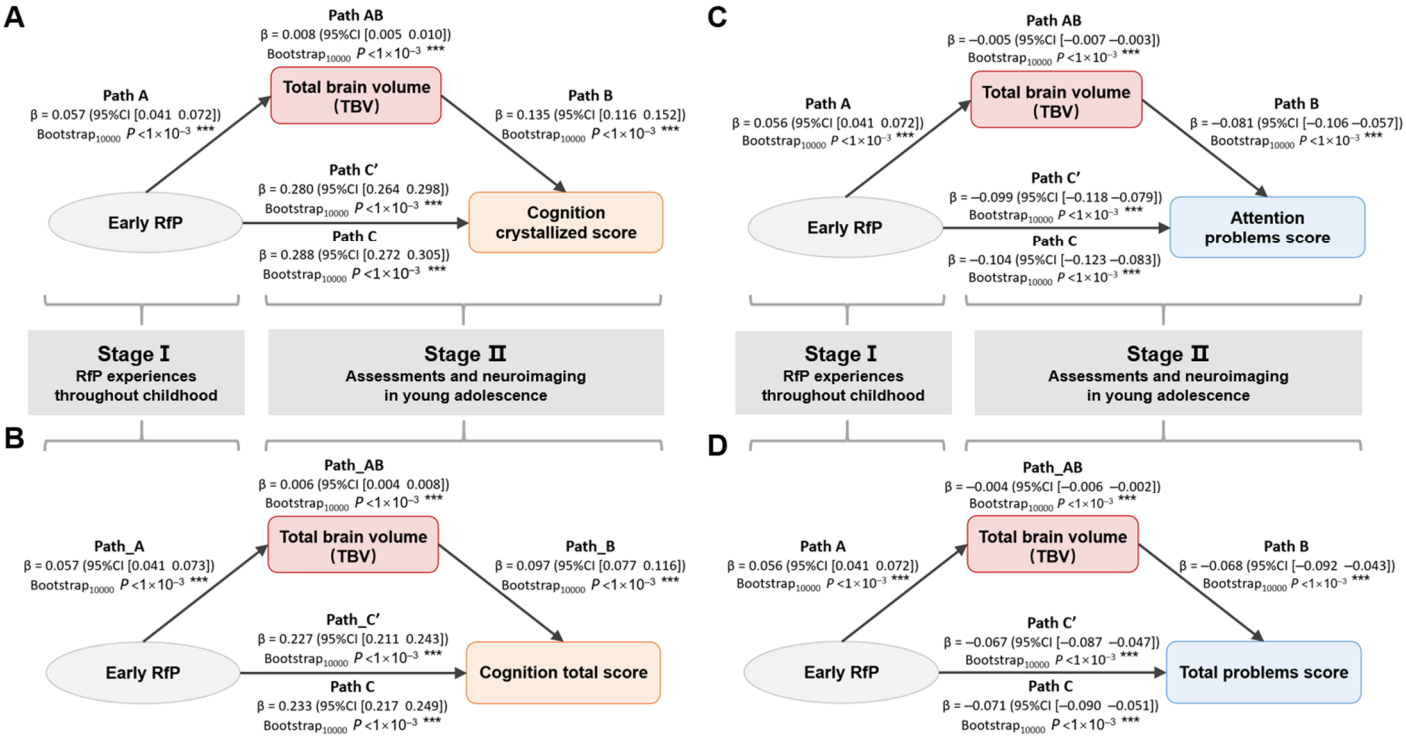


Figure S5. Mediation analysis between early RfP and cognitive and psychopathological symptoms scores through TBV.

The mediation effects (path_AB) implemented by TBV between the early RfP and youth cognitive or psychopathological scores were all significant (bias-corrected *P* and bootstrap *P* <0.001). Path AB is the product of path A and path B ($\beta_{path\_AB} = \beta_{path\_A} * \beta_{path\_B}$), indicating the mediation effect between the predictor factor (early RfP) and the young adolescent clinical assessments through the subcortical structures. The β values represent regression coefficients of the effect of the independent variables on the dependent variables.

TBV, total brain volume.

Figure S6

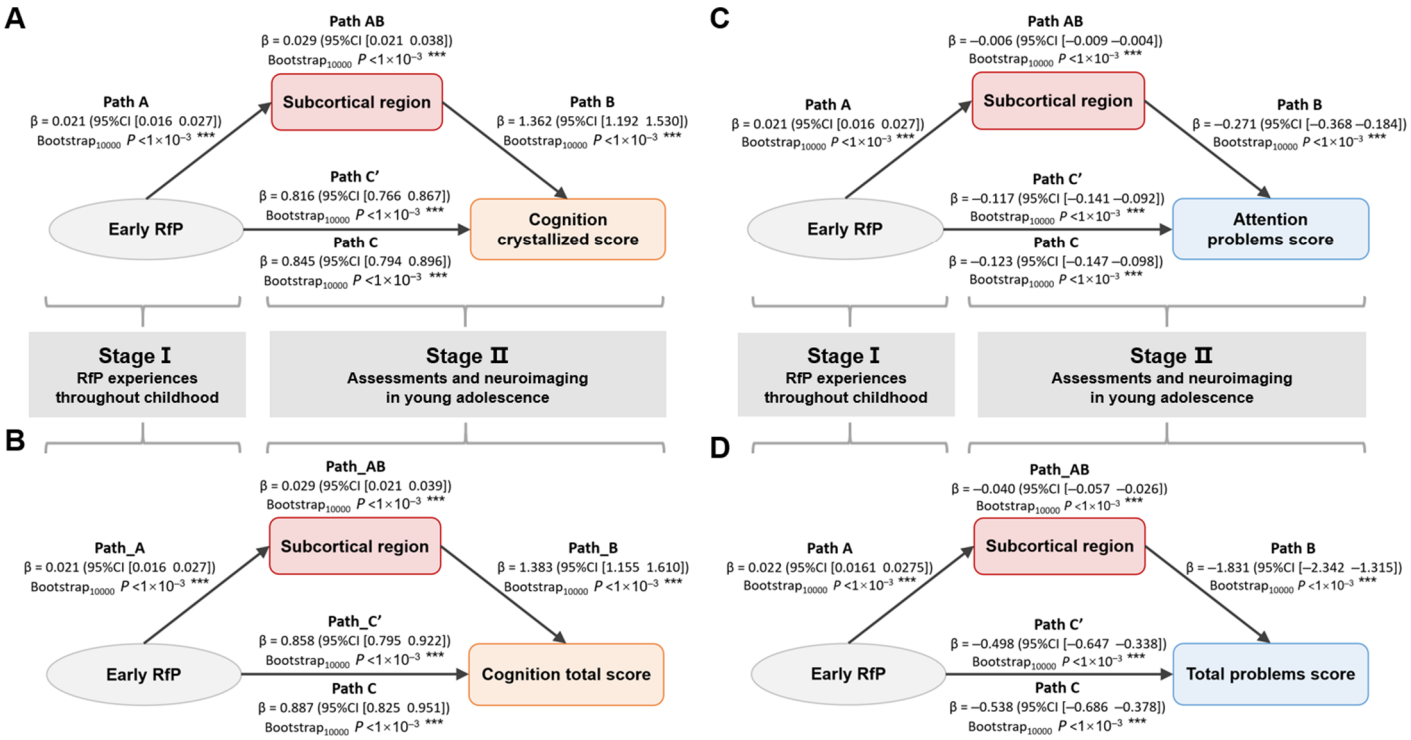


Figure S6. Mediation analysis between early RfP and cognitive and psychopathological symptoms scores through mean significant subcortical structure

(A-D) It was consistent with the results of brain cortical mediation analysis in **Figure 3** that the mediation effects (path_AB) implemented by brain subcortical regions between the early RfP and youth cognitive or psychopathological scores were all significant (bias-corrected *P* and bootstrap *P* <0.001). Analysis method was identical to these described above.

Figure S7

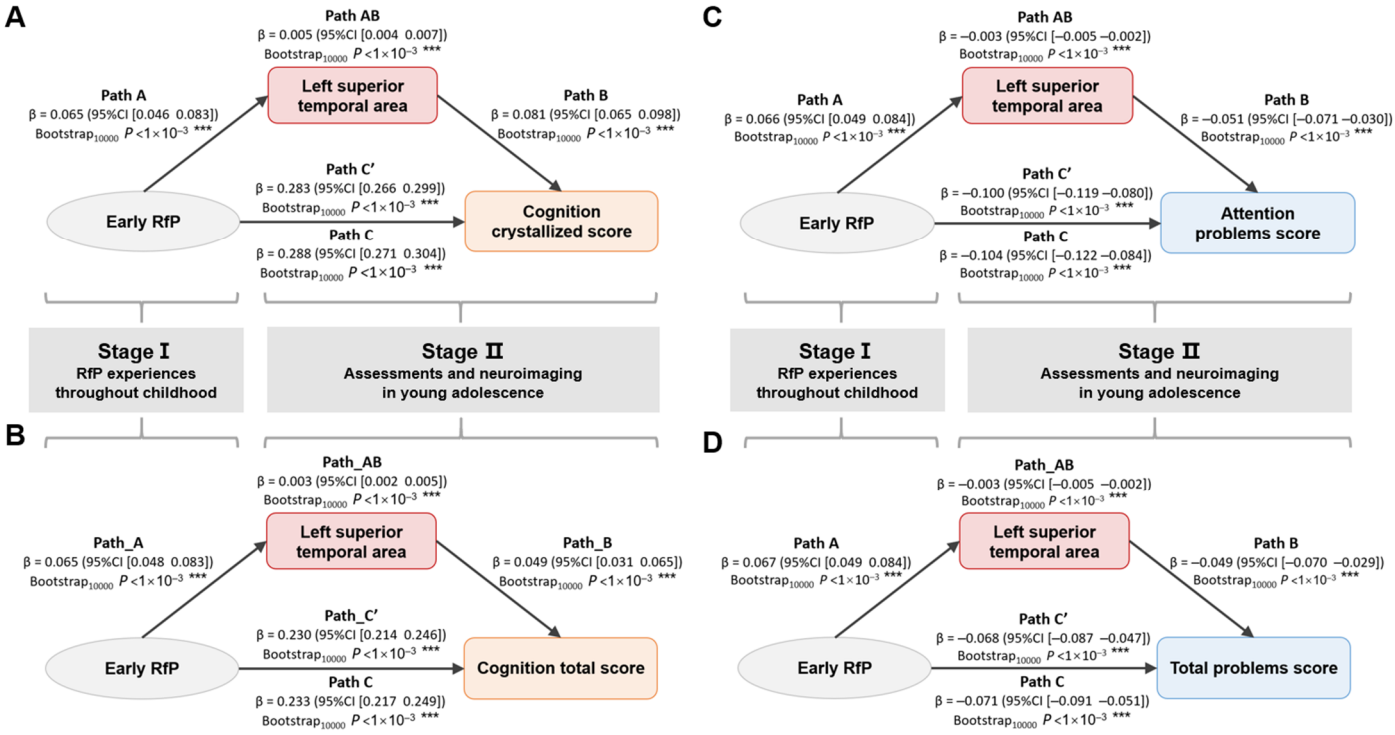


Figure S7. Mediation analysis between early RfP and cognitive and psychopathological symptoms scores through the left superior temporal cortical area region.

The mediation effects (path_AB) implemented by the left superior temporal cortical area between the early RfP and youth cognitive or psychopathological scores were all significant (bias-corrected *P* and bootstrap *P* <0.001). Analysis method was identical to these described above.

Figure S8

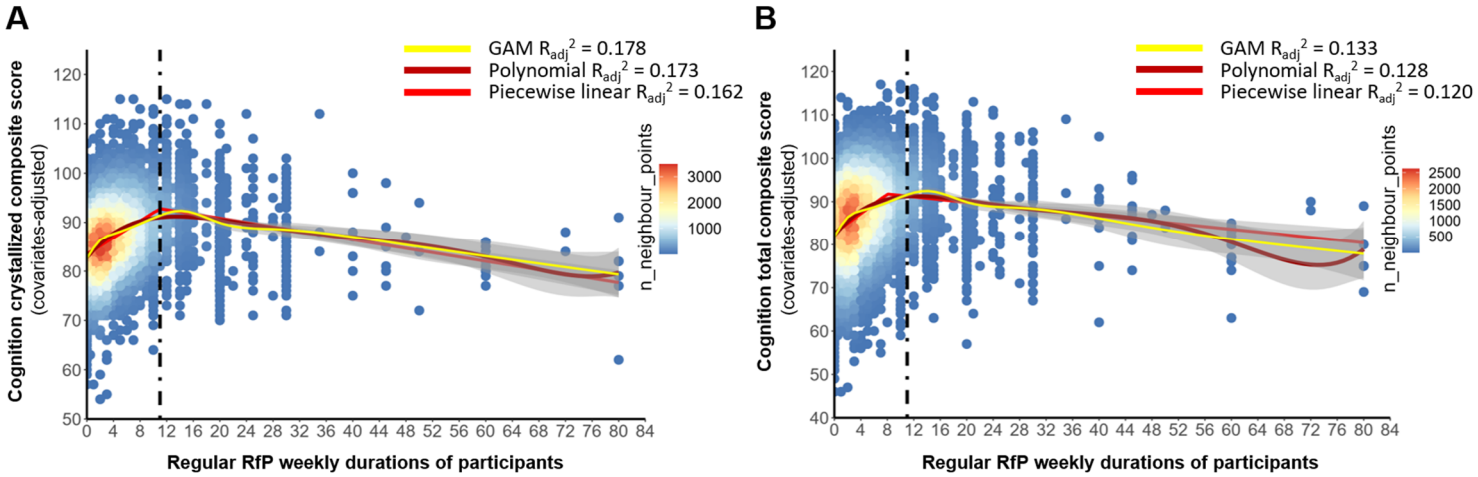


Figure S8. Nonlinear associations between weekly RfP durations and cognition in young adolescents.

(A, B) Density-scatter plots showing the nonlinear associations between participants' regular RfP durations (indicated by RfP h/week) and their cognitive assessment scores in young adolescence. Nonlinear-fitting results indicated that the optimal RfP duration for cognitive scores, including the cognition crystallized composite and total cognition score, was approximately 12 h/week, as represented by the black dotted line. For the condition of less than or equivalent to 12 hours of RfP per week, the cognition assessment scores improved with increasing RfP time (**A,** cognition crystallized composite: r_{LMM} =0.323, P<1×10^{-20}; **B,** total cognition score: r_{LMM} =0.253, P<1×10^{-20}). For the condition of more than 12 hours of RfP per week, cognition scores decreased slowly with increasing RfP time. n_neighbour_points shows the number of neighbouring datapoints around each datapoint to represent the density of the overall data distribution. $P_{\text{Bonferroni}}$<0.05.

GAM: Generalized additive models with integrated smoothness estimation.

R_{adj}^2: adjusted R-square

Figure S9

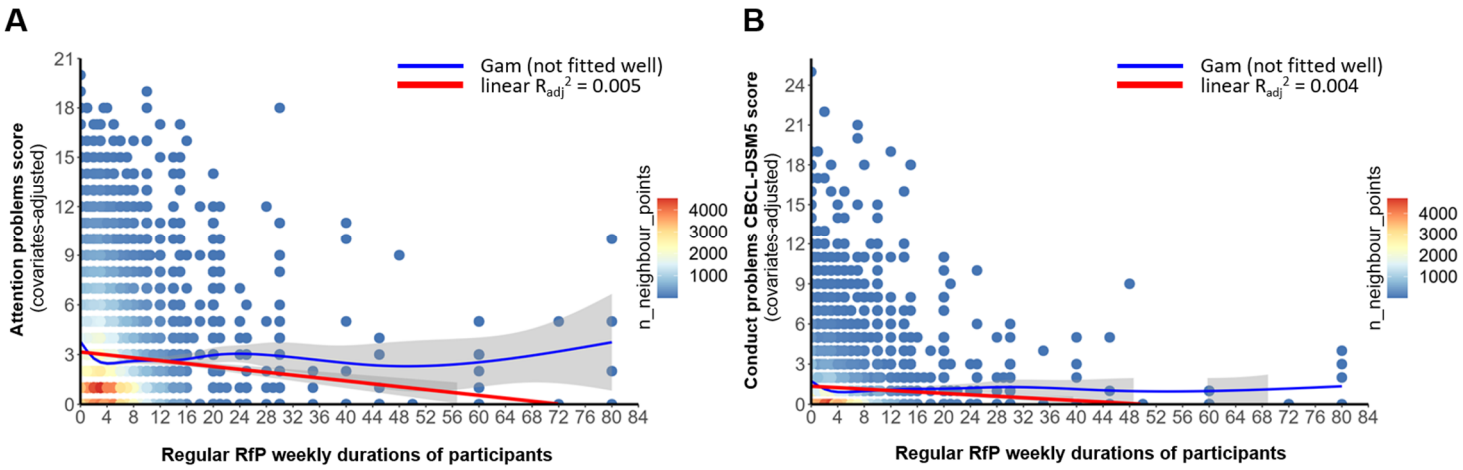


Figure S9. Mild negative linear associations between weekly RfP durations and youth psychopathological problems

(A, B) Density-scatter plots showing the mild significantly negatively correlated subscales between participants' regular weekly RfP durations and their psychopathological scores in young adolescence, which were attention problems score (**A,** $r_{LMM} = -0.045$, $P = 3.53\times10^{-4}$) and conduct problems score (**B,** $r_{LMM} = -0.038$, $P = 0.007$). n_neighbour_points shows the number of neighbouring datapoints around each datapoint to represent the density of the overall data distribution. $P_{Bonferroni}<0.05$.

Figure S10

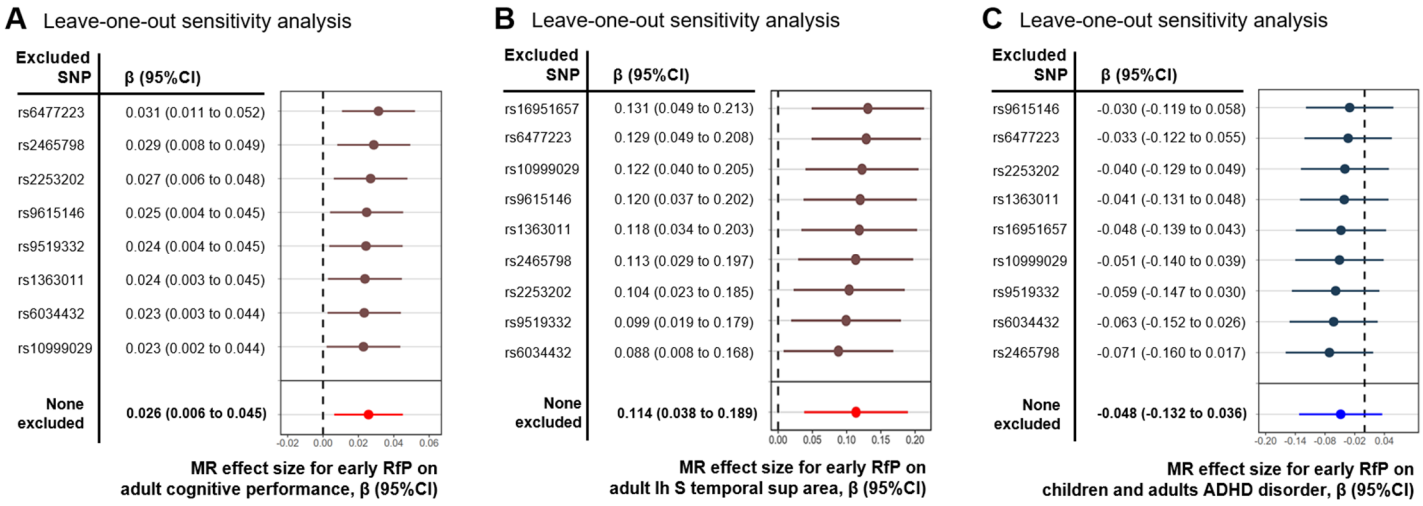


Figure S10. The leave-one-out sensitivity test confirmed no influence of individual SNP on the Mendelian randomization effect.

(A) Validation analysis that sequentially excluded each SNP from the estimation of the MR causal effect between RfP and cognitive performance using the IVW method. **(B)** Validation analysis between early RfP and adult left superior temporal cortical area. **(C)** Validation analysis between early RfP and ADHD disorder in children and adults.

4. Supplementary Tables

Table S1. Basic information on cognitive and psychopathological summary scales

10 core subscales of the cognitive summary scale, abcd_tbss01 (mean score ±SD)						
nihtbx_cardsort _age corrected	nihtbx_cryst _age corrected	nihtbx_flanker _age corrected	nihtbx_fluidcomp _age corrected	nihtbx_list _age corrected	nihtbx_pattern _age corrected	nihtbx_picture _age corrected
(96.712±15.162)	(105.506±18.303)	(95.425±13.674)	(95.552±17.352)	(100.547±14.786)	(93.783±22.092)	(100.961±16.103)
nihtbx_picvocab _age corrected	nihtbx_reading _age corrected	nihtbx_totalcomp _age corrected				
(106.798±16.998)	(102.518±19.128)	(100.374±17.957)				

20 core subscales of the psychopathology symptoms summary scale, abcd_cbcls01 (mean score ±SD)						
cbcl_scr_dsm5 _adhd	cbcl_scr_dsm5 _anxdisord	cbcl_scr_dsm5 _conduct	cbcl_scr_dsm5 _depress	cbcl_scr_dsm5 _opposit	cbcl_scr_dsm5 _somaticpr	cbcl_scr_syn _aggressive
(2.625±2.974)	(2.060±2.433)	(1.283±2.355)	(1.268±2.010)	(1.766±2.038)	(1.082±1.508)	(3.263±4.353)
cbcl_scr_syn _anxdep	cbcl_scr_syn _attention	cbcl_scr_syn _external	cbcl_scr_syn _internal	cbcl_scr_syn _rulebreak	cbcl_scr_syn _social	cbcl_scr_syn _somatic
(2.517±3.064)	(2.977±3.493)	(4.454±5.864)	(5.046±5.528)	(1.191±1.860)	(1.624±2.279)	(1.494±1.954)
cbcl_scr_syn _totprob	cbcl_scr_syn _thought	cbcl_scr_syn _withdep	cbcl_scr_07_ocd	cbcl_scr_07_sct	cbcl_scr_07 _stress	
(18.181±17.966)	(1.620±2.195)	(1.034±1.708)	(1.344±1.815)	(0.524±1.001)	(2.903±3.347)	

Full names: nihtbx_cardsort NIH Toolbox Dimensional Change Card Sort Test Ages 8–11 v2.0 Age-Corrected Standard Score; **nihtbx_cryst** Crystallized Composite Age-Corrected Standard Score; **nihtbx_flanker** NIH Toolbox Flanker Inhibitory Control and Attention Test Ages 8–11 v2.0 Age-Corrected Standard Score; **nihtbx_fluidcomp** Cognition Fluid Composite Age-Corrected Standard Score; **nihtbx_list** NIH Toolbox List Sorting Working Memory Test Age 7+ v2.0 Age-Corrected Standard Score; **nihtbx_pattern** NIH Toolbox Pattern Comparison Processing Speed Test Age 7+ v2.0 Age-Corrected Standard Score; **nihtbx_picture** NIH Toolbox Picture Sequence Memory Test Age 8+ Form A v2.0 Age-Corrected Standard Score, **nihtbx_picvocab** NIH Toolbox Picture Vocabulary Test Age 3+ v2.0 Age-Corrected Standard Score, **nihtbx_reading** NIH Toolbox Oral Reading Recognition Test Age 3+ v2.0 Age-Corrected Standard Score; **nihtbx_totalcomp** Cognition Total Composite Score Age-Corrected Standard Score; **cbcl_scr_dsm5_adhd_r** ADHD CBCL-DSM-5 Scale; **cbcl_scr_dsm5_anxdisord_r** Anxiety Problems CBCL-DSM-5 Scale; **cbcl_scr_dsm5_conduct_r** Conduct Problems CBCL-DSM-5 Scale; **cbcl_scr_dsm5_depress_r** Depressive Problems CBCL-DSM-5 Scale; **cbcl_scr_dsm5_opposit_r** Oppositional Defiant Problems CBCL-DSM-5 Scale; **cbcl_scr_dsm5_somaticpr_r** Somatic Problems CBCL-DSM-5 Scale; **cbcl_scr_syn_aggressive_r** Aggressive Behavior CBCL Syndrome Scale; **cbcl_scr_syn_anxdep_r** Anxious/Depressed CBCL Syndrome Scale; **cbcl_scr_syn_attention_r** Attention Problems CBCL Syndrome Scale; **cbcl_scr_syn_external_r** Externalizing Problems CBCL Syndrome Scale; **cbcl_scr_syn_internal_r** Internalizing Problems CBCL Syndrome Scale; **cbcl_scr_syn_rulebreak_r** Rule-Breaking Behavior CBCL Syndrome Scale; **cbcl_scr_syn_social_r** Social Problems CBCL Syndrome Scale; **cbcl_scr_syn_somatic_r** Somatic Complaints CBCL Syndrome Scale; **cbcl_scr_syn_totprob_r** Total Problems CBCL Syndrome Scale; **cbcl_scr_syn_thought_r** Thought CBCL Syndrome Scale; **cbcl_scr_syn_withdep_r** Withdrawn/Depressed CBCL Syndrome Scale; **cbcl_scr_07_ocd_r** Obsessive-Compulsive Problems (OCD) CBCL Scale2007 Scale; **cbcl_scr_07_sct_r** Sluggish Cognitive Tempo (SCT) CBCL Scale2007 Scale; **cbcl_scr_07_stress_r** Stress Problems CBCL Scale2007 Scale.

Table S2. Young adolescent assessment scales that were most significantly associated with early RfP

Category	Short name	Full scale name	Range of *LMM* t values	Range of *LMM P* values	Range of calculated *LMM r* values
Cognition (Positive correlated)	abcd_tbss01	NIH TB cognition summary scale	4.289 to 36.955	$P = 9.225\times10^{-4}$ to $P < 1\times10^{-20}$	**0.041 - 0.331**
	absd_ps01 [a]	Pearson scores of the verbal learning and immediate memory scale	–3.564 to –5.929 [a] ∪3.695 to 16.355	$P = 0.021$ to $P < 1\times10^{-20}$	–0.034 to –0.056[a] ∪ **0.035 to 0.154**
Mental problems (Negative correlated)	abcd_cbcl01 [b]	Dimensional psychopathology and adaptive functioning assessed by the parent-reported child behaviour checklist (CBCL)	–3.594 to –14.943 ∪6.799	$P = 0.039$ to $P < 1\times10^{-20}$	**–0.034 to –0.139** ∪ 0.064[b]
	abcd_cbcls01	Summary scores of psychopathology symptoms reported in abcd_cbcl01	–4.285 to –11.198	$P = 7.380\times10^{-4}$ to $P < 1\times10^{-20}$	**–0.040 to –0.105**
	abcd_bpmt01	Brief problem monitor (BPM) scores reported by the teacher	–3.256 to –8.182	$P = 0.022$ to $P < 1\times10^{-20}$	**–0.047 to –0.118**
	abcd_ksad01	Parent interview for the diagnostic and statistical manual of mental disorders 5th edition (DSM-5) full mental health diagnosis. (for parents)	–4.111 to –11.181	$P = 0.036$ to $P < 1\times10^{-20}$	**–0.034 to –0.130**
	abcd_ssbpmtf 01	Summary scale of normed children's functioning reported by the teacher	–3.501 to –7.483	$P = 0.013$ to 2.406×10^{-12}	**–0.057 to –0.110**
	abcd_upps01	UPPS-P for children short form (impulsivity)	–3.24 to –7.68	$P = 0.0243$ to 3.60×10^{-13}	**–0.032 to –0.072**
Screen time (Negative correlated)	abcd_stq01	ABCD youth screen time survey	–3.383 to –9.767	$P = 0.010$ to $P < 1\times10^{-20}$	**–0.033 to –0.098**
Physical health (Positive correlated)	abcd_saiq02 [c]	Scores of the parent-reported young adolescents' daily sports and activities [c]	3.56 to 33.80	$P = 0.046$ to $P < 1\times10^{-20}$	0.034 to 0.304

[a] Several subscales (6 of 30) of absd_ps01 showing negative r_{LMM} values were the recorded total intrusion and repetition times in cognitive evaluation trials, included: RAVLT Short/Long Delay Trials Total Intrusions (pea_ravlt_sd_trial_ ii_ti ~ pea_ravlt_sd_trial_ vi_ti, and a pea_ravlt_ld_trial_ vii_ti).

[b] The only one positive associated subscale of abcd_cbcl01 was that "Feels he/she has to be perfect" (cbcl_q32_p).

[c] The scale (abcd_saiq02) belonging to the physical health category was also positively associated with early RfP, which were the scale of the parent-reported young adolescents' daily sports and activities that contained RfP-related scores themselves.

Bonferroni corrected, $P<0.05$.

Table S3. Early RfP was significantly correlated with youth school academic performance

School Grades	**β**	**95% CI**	**SE**	***t* Stat**	**r_{LMM} value (calculated)**	***P* value**
Intercept	4.005	[3.631, 4.380]	0.191	20.982	0.195	$< 1\times10^{-20}$
Early RfP	**0.104**	[0.094, 0.113]	4.85×10^{-3}	**21.365**	**0.199**	$\mathbf{< 1\times10^{-20}}$
Age	0.002	$[-1.274\times10^{-3}, 4.30\times10^{-3}]$	1.42×10^{-3}	1.065	0.010	0.287
Sex	–0.148	[–0.194, –0.102]	0.023	–6.330	–0.060	2.55×10^{-10}
Parents Education	0.031	[0.0130, 0.042]	5.86×10^{-3}	5.246	0.050	1.58×10^{-7}
Family Income	0.019	$[5.10\times10^{-3}, 0.032]$	6.88×10^{-3}	2.702	0.026	6.91×10^{-3}
BMI	3.72×10^{-5}	$[-5.342\times10^{-4}, 6.087\times10^{-4}]$	2.92×10^{-4}	0.128	0.001	0.898
Race_2	–0.288	[–0.462, –0.114]	0.088	–3.243	–0.031	0.001
Race_3	–0.094	[–0.261, 0.074]	0.086	–1.094	–0.010	0.274
Race_4	–0.087	[–0.258, 0.085]	0.087	–0.992	–0.009	0.321
Race_5	–0.015	[–0.175, 0.145]	0.082	–0.182	–0.002	0.855
Puberty	0.010	[–0.040, 0.060]	0.026	0.388	0.004	0.698
School Performance	**β**	**95% CI**	**SE**	***t* Stat**	**r_{LMM} value (calculated)**	***P* value**
Intercept	3.38	[3.194, 3.578]	0.097	34.457	0.313	$< 1\times10^{-20}$
Early RfP	**0.071**	[0.067, 0.076]	2.41×10^{-3}	**29.219**	**0.269**	$\mathbf{< 1\times10^{-20}}$
Age	-4.04×10^{-3}	$[5.51\times10^{-3}, -2.57\times10^{-3}]$	7.44×10^{-4}	-5.392	-0.052	7.11×10^{-8}
Sex	–0.081	[–0.104, –0.058]	0.012	-6.828	-0.065	9.04×10^{-12}
Parents Education	0.021	[0.016, 0.027]	2.85×10^{-3}	7.573	0.072	3.94×10^{-14}
Family Income	0.022	[0.015, 0.028]	3.29×10^{-3}	6.603	0.063	4.22×10^{-11}
BMI	-6.13×10^{-5}	$[-3.50\times10^{-4}, 2.17\times10^{-4}]$	1.45×10^{-4}	–0.461	–0.004	0.645
Race_2	–0.099	[–0.183, -0.016]	0.043	–2.329	–0.022	0.020
Race_3	–0.045	[–0.125, 0.036]	0.041	–1.090	–0.010	0.276
Race_4	–0.071	[–0.153, 0.012]	0.042	–1.675	–0.016	0.094
Race_5	0.007	[–0.070, 0.084]	0.039	0.171	0.002	0.864
Puberty	0.018	$[-7.56\times10^{-3}, 0.043]$	0.013	1.378	0.013	0.168

A linear-mixed effects (*LMM*) model was conducted.

Sex and race/ethnicity were categorical factors (dummy variables).

Table S4. The correlations between early RfP and all the core subscales of youth cognitive (abcd_tbss01) and psychopathology symptoms (abcd_cbcls01) assessment summaries

Cognition subdomain scores	β_{LMM}	r_{LMM}	***P* value**	**Cognition subdomain scores**	β_{LMM}	r_{LMM}	***P* value**
nihtbx_**cryst**	0.848	0.329	$< 1\times10^{-20}$	nihtbx_**list**	0.679	0.138	$< 1\times10^{-20}$
nihtbx_**reading**	0.855	0.312	$< 1\times10^{-20}$	nihtbx_**picture**	0.519	0.101	$< 1\times10^{-20}$
nihtbx_**totalcomp**	0.887	0.267	$< 1\times10^{-20}$	nihtbx_**cardsort**	0.367	0.093	$< 1\times10^{-20}$
nihtbx_**picvocab**	0.724	0.242	$< 1\times10^{-20}$	nihtbx_**flanker**	0.317	0.083	1.24×10^{-16}
nihtbx_**fluidcomp**	0.631	0.150	$< 1\times10^{-20}$	nihtbx_**pattern**	0.383	0.062	3.50×10^{-9}
Psychopathology subdomain scores	β_{LMM}	r_{LMM}	***P* value**	**Psychopathology subdomain scores**	β_{LMM}	r_{LMM}	***P* value**
cbcl_scr_syn_**attention**	–0.160	–0.106	$< 1\times10^{-20}$	cbcl_scr_dsm5_**depress**	–0.036	-0.041	6.61×10^{-4}
cbcl_scr_dsm5_**adhd**	–0.126	–0.098	$< 1\times10^{-20}$	cbcl_scr_syn_withdep	–0.022	-0.029	ns
cbcl_scr_dsm5_**conduct**	–0.086	–0.085	5.10×10^{-18}	cbcl_scr_dsm5_somaticpr	–0.019	-0.029	ns
cbcl_scr_syn_**external**	–0.206	–0.082	1.52×10^{-16}	cbcl_scr_dsm5_anxdisord	–0.030	-0.028	ns
cbcl_scr_syn_**rulebreak**	–0.063	–0.080	1.13×10^{15}	cbcl_scr_syn_internal	–0.053	-0.022	ns
cbcl_scr_dsm5_**opposit**	–0.070	–0.078	3.53×10^{-15}	cbcl_scr_syn_somatic	–0.018	-0.021	ns
cbcl_scr_syn_**aggressive**	–0.143	–0.076	2.67×10^{-14}	cbcl_scr_syn_thought	–0.019	-0.020	ns
cbcl_scr_syn_**totprob**	–0.538	–0.070	4.59×10^{-12}	cbcl_scr_syn_anxdep	–0.017	-0.012	ns
cbcl_scr_07_**stress**	–0.093	–0.064	5.84×10^{-10}	cbcl_scr_07_sct	–0.005	-0.011	ns
cbcl_scr_syn_**social**	–0.054	-0.055	2.34×10^{-7}	cbcl_scr_07_ocd	0.008	0.010	ns

Early RfP was significantly positively associated with all of the neurocognition subscales, and was positively associated with 11 behavioural psychopathological symptom subscales.

P values were Bonferroni-corrected. The ns represents non-significant result after Bonferroni correction.

Table S5. Subgroup analysis of correlations in young adolescent females and males

Cognition subdomain scores in **females**	β_{LMM}	r_{LMM}	***P* value**	Cognition subdomain scores in **females**	β_{LMM}	r_{LMM}	***P* value**
nihtbx_cryst	0.790	0.308	$< 1\times10^{-20}$	nihtbx_list	0.585	0.122	4.284×10^{-17}
nihtbx_reading	0.783	0.293	$< 1\times10^{-20}$	nihtbx_picture	0.458	0.089	4.291×10^{-9}
nihtbx_totalcomp	0.799	0.247	$< 1\times10^{-20}$	nihtbx_flanker	0.284	0.076	1.629×10^{-6}
nihtbx_picvocab	0.687	0.225	$< 1\times10^{-20}$	nihtbx_cardsort	0.275	0.073	4.545×10^{-6}
nihtbx_fluidcomp	0.540	0.132	3.03×10^{-20}	nihtbx_pattern	0.344	0.057	1.67×10^{-3}
Cognition subdomain scores in **males**	β_{LMM}	r_{LMM}	***P* value**	Cognition subdomain scores in **males**	β_{LMM}	r_{LMM}	***P* value**
nihtbx_cryst	0.904	0.348	$< 1\times10^{-20}$	nihtbx_list	0.757	0.151	$< 1\times10^{-20}$
nihtbx_reading	0.915	0.326	$< 1\times10^{-20}$	nihtbx_picture	0.572	0.111	6.65×10^{-16}
nihtbx_totalcomp	0.957	0.282	$< 1\times10^{-20}$	nihtbx_cardsort	0.437	0.106	1.90×10^{-14}
nihtbx_picvocab	0.767	0.260	$< 1\times10^{-20}$	nihtbx_flanker	0.343	0.087	1.07×10^{-9}
nihtbx_fluidcomp	0.700	0.163	$< 1\times10^{-20}$	nihtbx_pattern	0.423	0.067	1.74×10^{-5}
Psychopathology subdomain scores in **females**	β_{LMM}	r_{LMM}	***P* value**	Psychopathology subdomain scores in **females**	β_{LMM}	r_{LMM}	***P* value**
cbcl_scr_syn_attention	–0.141	–0.104	1.20×10^{-12}	cbcl_scr_dsm5_depress	–0.032	–0.039	ns
cbcl_scr_dsm5_adhd	–0.117	–0.100	9.33×10^{-12}	cbcl_scr_dsm5_anxdisord	–0.030	–0.028	ns
cbcl_scr_dsm5_conduct	–0.081	–0.095	1.62×10^{-10}	cbcl_scr_dsm5_somaticpr	–0.019	–0.028	ns
cbcl_scr_dsm5_opposit	–0.075	–0.091	1.22×10^{-9}	cbcl_scr_syn_thought	–0.023	–0.026	ns
cbcl_scr_syn_external	–0.197	–0.088	5.51×10^{-9}	cbcl_scr_syn_withdep	–0.016	–0.022	ns
cbcl_scr_syn_rulebreak	–0.058	–0.084	3.48×10^{-8}	cbcl_scr_syn_internal	–0.045	–0.019	ns
cbcl_scr_syn_aggressive	–0.139	–0.082	7.45×10^{-8}	cbcl_scr_syn_somatic	–0.016	–0.018	ns
cbcl_scr_syn_totprob	–0.467	–0.065	6.69×10^{-5}	cbcl_scr_07_ocd_r	0.010	0.013	ns
cbcl_scr_07_stress	–0.084	–0.061	3.50×10^{-4}	cbcl_scr_syn_anxdep	–0.016	–0.012	ns
cbcl_scr_syn_social	–0.050	–0.053	3.78×10^{-3}	cbcl_scr_07_sct	–0.004	–0.009	ns
Psychopathology subdomain scores in **males**	β_{LMM}	r_{LMM}	***P* value**	Psychopathology subdomain scores in **males**	β_{LMM}	r_{LMM}	***P* value**
cbcl_scr_syn_attention	–0.172	-0.105	2.01×10^{-14}	cbcl_scr_dsm5_depress	–0.038	–0.041	0.056
cbcl_scr_dsm5_adhd	–0.132	-0.096	6.96×10^{-12}	cbcl_scr_syn_withdep	–0.026	–0.034	ns
cbcl_scr_dsm5_conduct	–0.087	-0.078	9.44×10^{-8}	cbcl_scr_dsm5_anxdisord	–0.029	–0.027	ns
cbcl_scr_syn_external	–0.209	-0.076	1.81×10^{-7}	cbcl_scr_dsm5_somaticpr	–0.017	–0.026	ns
cbcl_scr_syn_rulebreak	–0.064	-0.074	4.84×10^{-7}	cbcl_scr_syn_internal	–0.059	–0.024	ns
cbcl_scr_syn_aggressive	–0.145	-0.071	1.65×10^{-6}	cbcl_scr_syn_somatic	–0.018	–0.021	ns
cbcl_scr_syn_totprob	–0.568	-0.069	3.79×10^{-6}	cbcl_scr_syn_thought	–0.015	–0.014	ns
cbcl_scr_dsm5_opposit	–0.064	-0.068	6.58×10^{-6}	cbcl_scr_syn_anxdep	–0.018	–0.013	ns
cbcl_scr_07_stress	–0.098	-0.064	2.90×10^{-5}	cbcl_scr_07_sct	–0.005	–0.010	ns
cbcl_scr_syn_social	–0.054	-0.052	2.61×10^{-3}	cbcl_scr_07_ocd	0.007	0.008	ns

P values were Bonferroni-corrected.

Table S6. Comparison of the correlations between early RfP and cognitive (upper-panel) and psychopathology symptoms (lower-panel) assessments while more covariates were included

Excluding all covariates	r_{LMM}	*P* value	Including family SES	r_{LMM}	*P* value	Including all covariates (raw)	r_{LMM}	*P* value
nihtbx_cryst	0.329	$< 1\times10^{-20}$	nihtbx_cryst	0.363	0	nihtbx_reading	0.366	0
nihtbx_reading	0.312	$< 1\times10^{-20}$	nihtbx_reading	0.344	$< 1\times10^{-20}$	nihtbx_cryst	0.380	0
nihtbx_totalcomp	0.267	$< 1\times10^{-20}$	nihtbx_totalcomp	0.303	$< 1\times10^{-20}$	nihtbx_totalcomp	0.332	$< 1\times10^{-20}$
nihtbx_picvocab	0.242	$< 1\times10^{-20}$	nihtbx_picvocab	0.278	$< 1\times10^{-20}$	nihtbx_picvocab	0.301	$< 1\times10^{-20}$
nihtbx_fluidcomp	0.150	$< 1\times10^{-20}$	nihtbx_fluidcomp	0.180	$< 1\times10^{-20}$	nihtbx_fluidcomp	0.220	$< 1\times10^{-20}$
nihtbx_list	0.138	$< 1\times10^{-20}$	nihtbx_list	0.172	$< 1\times10^{-20}$	nihtbx_list	0.195	$< 1\times10^{-20}$
nihtbx_picture	0.101	$< 1\times10^{-20}$	nihtbx_picture	0.120	$< 1\times10^{-20}$	nihtbx_picture	0.152	$< 1\times10^{-20}$
nihtbx_cardsort	0.093	$< 1\times10^{-20}$	nihtbx_cardsort	0.115	$< 1\times10^{-20}$	nihtbx_cardsort	0.152	$< 1\times10^{-20}$
nihtbx_flanker	0.083	1.24×10^{-16}	nihtbx_flanker	0.104	$< 1\times10^{-20}$	nihtbx_flanker	0.126	$< 1\times10^{-20}$
nihtbx_pattern	0.062	3.50×10^{-09}	nihtbx_pattern	0.072	1.94×10^{-12}	nihtbx_pattern	0.107	$< 1\times10^{-20}$
Excluding all covariates	r_{LMM}	*P* value	**Including SES**	r_{LMM}	*P* value	**Including all covariates (raw)**	r_{LMM}	*P* value
cbcl_scr_syn_attention	–0.106	$< 1\times10^{-20}$	cbcl_scr_syn_attention	–0.116	$< 1\times10^{-20}$	cbcl_scr_syn_attention	–0.140	$< 1\times10^{-20}$
cbcl_scr_dsm5_adhd	–0.098	$< 1\times10^{-20}$	cbcl_scr_dsm5_adhd	–0.108	$< 1\times10^{-20}$	cbcl_scr_dsm5_adhd	–0.134	$< 1\times10^{-20}$
cbcl_scr_dsm5_conduct	–0.085	5.10×10^{-18}	cbcl_scr_dsm5_conduct	–0.104	$< 1\times10^{-20}$	cbcl_scr_dsm5_conduct	–0.125	$< 1\times10^{-20}$
cbcl_scr_syn_external	–0.082	1.52×10^{-16}	cbcl_scr_syn_rulebreak	–0.098	$< 1\times10^{-20}$	cbcl_scr_syn_rulebreak	–0.121	$< 1\times10^{-20}$
cbcl_scr_syn_rulebreak	–0.080	1.13×10^{-15}	cbcl_scr_syn_external	–0.098	$< 1\times10^{-20}$	cbcl_scr_syn_external	–0.118	$< 1\times10^{-20}$
cbcl_scr_dsm5_opposit	–0.078	3.53×10^{-15}	cbcl_scr_syn_aggressive	–0.090	2.62×10^{-20}	cbcl_scr_syn_aggressive	–0.107	$< 1\times10^{-20}$
cbcl_scr_syn_aggressive	–0.076	2.67×10^{-14}	cbcl_scr_dsm5_opposit	–0.088	3.59×10^{-19}	cbcl_scr_dsm5_opposit	–0.103	$< 1\times10^{-20}$
cbcl_scr_syn_totprob	–0.070	4.59×10^{-12}	cbcl_scr_syn_totprob	–0.085	6.03×10^{-18}	cbcl_scr_syn_totprob	–0.101	$< 1\times10^{-20}$
cbcl_scr_07_stress	–0.064	5.84×10^{-10}	cbcl_scr_07_stress	–0.077	8.74×10^{-15}	cbcl_scr_07_stress	–0.089	1.01×10^{-19}
cbcl_scr_syn_social	–0.055	2.34×10^{-07}	cbcl_scr_syn_social	–0.074	1.71×10^{-13}	cbcl_scr_syn_social	–0.088	4.59×10^{-19}
cbcl_scr_dsm5_depress	–0.041	6.61×10^{-4}	cbcl_scr_dsm5_depress	–0.053	8.62×10^{-07}	cbcl_scr_dsm5_depress	–0.058	2.08×10^{-08}
cbcl_scr_syn_withdep	–0.029	ns	cbcl_scr_syn_withdep	–0.046	3.57×10^{-05}	cbcl_scr_syn_withdep	–0.056	8.90×10^{-08}
cbcl_scr_dsm5_somaticpr	–0.029	ns	cbcl_scr_dsm5_somaticpr	–0.038	2.74×10^{-03}	cbcl_scr_syn_thoughtr	–0.039	1.20×10^{-03}
cbcl_scr_dsm5_anxdisord	–0.028	ns	cbcl_scr_dsm5_anxdisord	–0.035	9.25×10^{-03}	cbcl_scr_dsm5_anxdisord	–0.034	0.010
cbcl_scr_syn_internal	–0.022	ns	cbcl_scr_syn_internal	–0.032	0.028	cbcl_scr_syn_internal	–0.030	ns
cbcl_scr_syn_somatic	–0.021	ns	cbcl_scr_syn_somatic	–0.030	ns	cbcl_scr_dsm5_somaticpr	–0.029	ns
cbcl_scr_syn_thought	–0.020	ns	cbcl_scr_syn_thought	–0.030	ns	cbcl_scr_07_sct	–0.028	ns
cbcl_scr_syn_anxdep	–0.012	ns	cbcl_scr_07_sct	–0.021	ns	cbcl_scr_syn_somatic	–0.024	ns
cbcl_scr_07_sct	–0.011	ns	cbcl_scr_syn_anxdep	–0.015	ns	cbcl_scr_syn_anxdep	–0.012	ns
cbcl_scr_07_ocd	0.010	ns	cbcl_scr_07_ocd	0.007	ns	cbcl_scr_07_ocd	0.005	ns

P values were Bonferroni-corrected

Table S7. Sensitivity analysis of the correlations between early RfP and youth cognitive and psychopathology scores in typically developing (TD) and ADHD groups

Analysis results in typically developing participants without comorbidities (TD group, *N*=9313)

Cognition subdomain scores	**β_{LMM}**	**r_{LMM}**	***P* value**	**Cognition subdomain scores**	**β_{LMM}**	**r_{LMM}**	***P* value**
nihtbx_cryst	0.799	0.314	$<1\times10^{-20}$	nihtbx_list	0.611	0.126	$<1\times10^{-20}$
nihtbx_reading	0.797	0.297	$<1\times10^{-20}$	nihtbx_picture	0.475	0.093	5.77×10^{-18}
nihtbx_totalcomp	0.823	0.255	$<1\times10^{-20}$	nihtbx_cardsort	0.327	0.085	3.58×10^{-15}
nihtbx_picvocab	0.687	0.231	$<1\times10^{-20}$	nihtbx_flanker	0.273	0.073	3.24×10^{-11}
nihtbx_fluidcomp	0.574	0.140	$<1\times10^{-20}$	nihtbx_pattern	0.366	0.060	2.78×10^{-7}
Psychopathology subdomain scores	**β_{LMM}**	**r_{LMM}**	***P* value**	**Psychopathology subdomain scores**	**β_{LMM}**	**r_{LMM}**	***P* value**
cbcl_scr_syn_attention	–0.075	–0.085	2.42×10^{-15}	cbcl_scr_syn_rulebreak	–0.031	–0.054	3.39×10^{-6}
cbcl_scr_dsm5_adhd	–0.064	–0.078	4.68×10^{-13}	cbcl_scr_07_stress	–0.048	–0.046	2.91×10^{-4}
cbcl_scr_dsm5_opposit	–0.048	–0.065	4.90×10^{-9}	cbcl_scr_syn_totprob	–0.199	–0.039	0.004
cbcl_scr_dsm5_conduct	–0.044	–0.065	6.26×10^{-9}	cbcl_scr_07_ocd	0.019	0.031	ns
cbcl_scr_syn_external	–0.111	–0.064	1.49×10^{-8}	cbcl_scr_07_sct	0.008	0.030	ns

Analysis results in participants met the diagnostic criteria for ADHD (ADHD group, *N*=930)

Cognition subdomain scores	**β_{LMM}**	**r_{LMM}**	***P* value**	**Cognition subdomain scores**	**β_{LMM}**	**r_{LMM}**	***P* value**
nihtbx_cryst	1.008	0.380	$<1\times10^{-20}$	nihtbx_fluidcomp	0.718	0.160	6.83×10^{-5}
nihtbx_reading	1.027	0.353	$<1\times10^{-20}$	nihtbx_cardsort	0.532	0.121	0.012
nihtbx_picvocab	0.866	0.291	1.53×10^{-17}	nihtbx_flanker	0.477	0.110	0.045
nihtbx_totalcomp	1.030	0.288	4.59×10^{-17}	nihtbx_picture	0.472	0.097	ns
nihtbx_list	0.979	0.191	3.59×10^{-7}	nihtbx_pattern	0.128	0.020	ns
Psychopathology subdomain scores	**β_{LMM}**	**r_{LMM}**	***P* value**	**Psychopathology subdomain scores**	**β_{LMM}**	**r_{LMM}**	***P* value**
cbcl_scr_07_ocd	0.155	0.112	0.029	cbcl_scr_syn_thought	0.123	0.071	ns
cbcl_scr_07_sct	0.089	0.106	0.050	cbcl_scr_syn_anxdep	0.159	0.070	ns
cbcl_scr_syn_rulebreak	–0.119	-0.080	ns	cbcl_scr_dsm5_anxdisord	0.112	0.055	ns
cbcl_scr_dsm5_conduct	–0.156	-0.076	ns	cbcl_scr_syn_external	–0.198	-0.054	ns

P values were Bonferroni-corrected.

Table S8. The correlations of early RfP with psychopathology scores in TD and ADHD groups using different reading media or devices

Psychopathology subdomain scores	β_{LMM}	r_{LMM}	*P* value	Psychopathology subdomain scores	β_{LMM}	r_{LMM}	*P* value
TD group who usually read on electronic screen devices (*N*=2350)							
cbcl_scr_syn_attention	–0.059	–0.073	0.017	cbcl_scr_dsm5_opposit	–0.039	–0.059	ns
cbcl_scr_syn_rulebreak	–0.033	–0.067	ns	cbcl_scr_syn_external	–0.086	–0.057	ns
cbcl_scr_dsm5_conduct	–0.035	–0.060	ns	cbcl_scr_07_ocd	0.032	0.055	ns
cbcl_scr_dsm5_adhd	–0.042	–0.060	ns	cbcl_scr_syn_withdep	0.031	0.046	ns
TD group who usually read printed materials (*N*=4161)							
cbcl_scr_syn_attention	–0.086	–0.119	7.12×10^{-13}	cbcl_scr_syn_rulebreak	–0.040	–0.081	6.76×10^{-6}
cbcl_scr_dsm5_adhd	–0.067	–0.108	9.91×10^{-11}	cbcl_scr_syn_aggressive	–0.080	–0.078	2.27×10^{-5}
cbcl_scr_dsm5_opposit	–0.050	–0.086	1.26×10^{-6}	cbcl_scr_syn_totprob	–0.231	–0.057	0.010
cbcl_scr_syn_external	–0.119	–0.085	1.57×10^{-6}	cbcl_scr_07_ocd	0.027	0.047	ns
cbcl_scr_dsm5_conduct	–0.046	–0.084	2.55×10^{-6}	cbcl_scr_07_stress	–0.038	–0.045	ns
ADHD group who usually read on electronic screen devices (*N*=248)							
cbcl_scr_dsm5_somaticpr	–0.143	–0.183	ns	cbcl_scr_syn_withdep	–0.057	–0.060	ns
cbcl_scr_syn_somatic	–0.139	–0.138	ns	cbcl_scr_syn_attention	–0.053	–0.057	ns
cbcl_scr_syn_rulebreak	–0.101	–0.093	ns	cbcl_scr_syn_internal	–0.165	–0.057	ns
cbcl_scr_dsm5_conduct	–0.086	–0.062	ns	cbcl_scr_syn_external	–0.152	–0.050	ns
ADHD group who usually read printed materials (*N*=440)							
cbcl_scr_07_ocd	0.130	0.129	ns	cbcl_scr_syn_attention	–0.074	–0.074	ns
cbcl_scr_syn_anxdep	0.157	0.099	ns	cbcl_scr_dsm5_anxdisord	0.082	0.068	ns
cbcl_scr_syn_thought	0.106	0.086	ns	cbcl_scr_dsm5_depress	0.072	0.060	ns
cbcl_scr_07_sct	0.046	0.074	ns	cbcl_scr_07_stress	0.087	0.057	ns

P values were Bonferroni-corrected.

Table S9. Cortical and subcortical brain structures of young adolescents that were moderately significantly correlated with early RfP

Total brain	β_{LMM}	r_{LMM}	***P* value**	**Total brain**	β_{LMM}	r_{LMM}	***P* value**
Intracranial volume	3030.831	0.061	1.66×10^{-7}	Total brain cortical area	371.313	0.059	8.11×10^{-7}
Total brain volume	2355.864	0.060	7.74×10^{-7}	Total brain cortical volume	1056.506	0.055	1.95×10^{-5}
Cortical brain area	β_{LMM}	r_{LMM}	***P* value**	**Cortical brain area**	β_{LMM}	r_{LMM}	***P* value**
Left lateral aspect of the **superior temporal** gyrus	5.198	0.064	2.37×10^{-8}	Left **subcentral** gyrus and sulci	3.170	0.042	0.007
Right **superior temporal** sulcus	14.039	0.057	2.21×10^{-6}	Right anterior segment of the circular sulcus of the **insula**	1.408	0.041	0.010
Left **angular** gyrus	6.526	0.051	9.47×10^{-5}	Left **middle frontal** sulcus	4.426	0.041	0.011
Left **superior temporal** sulcus	11.534	0.050	1.05×10^{-4}	Left **middle temporal** gyrus	5.322	0.041	0.013
Left inferior segment of the circular sulcus of the **insula**	2.331	0.049	2.07×10^{-4}	Left **middle frontal** gyrus	9.106	0.041	0.014
Right long insular gyrus and central sulcus of the **insula**	1.177	0.049	2.62×10^{-4}	Left **postcentral** sulcus	6.122	0.041	0.014
Right **middle occipital** gyrus	5.871	0.048	3.13×10^{-4}	Left lateral **occipito-temporal** gyrus	4.186	0.040	0.021
Right **middle temporal** gyrus	6.033	0.048	4.24×10^{-4}	Right **middle frontal** gyrus	8.361	0.039	0.024
Right lateral aspect of the **superior temporal** gyrus	3.572	0.047	5.47×10^{-4}	Left **supramarginal** gyrus	6.185	0.039	0.026
Right **anterior part of the cingulate** gyrus and sulcus **(ACC)**	5.050	0.047	5.96×10^{-4}	Left **precentral** gyrus	4.352	0.039	0.028
Left **superior frontal** gyrus	12.113	0.047	6.87×10^{-4}	Left long insular gyrus and central sulcus of the **insula**	0.908	0.039	0.029
Right **supramarginal** gyrus	6.974	0.046	1.05×10^{-3}	Left **inferior temporal** gyrus	5.344	0.039	0.032
Left **parahippocampal** gyrus	3.284	0.046	1.27×10^{-3}	Right **medial occipito-temporal** sulcus and **lingual** sulcus	3.682	0.039	0.034
Left **postcentral** gyrus	4.864	0.045	2.09×10^{-3}	Right **temporal pole**	2.358	0.038	0.040
Left **temporal pole**	2.849	0.044	2.70×10^{-3}	Right medial **orbital** sulcus	1.729	0.038	0.042
Right **orbital** gyri	3.860	0.044	2.71×10^{-3}	Left **posterior-dorsal part of the cingulate** gyrus	1.612	0.038	0.044
Right inferior segment of the circular sulcus of the **insula**	1.899	0.043	3.79×10^{-3}	Left **central** sulcus	4.108	0.038	0.048
Subcortical brain volume	β_{LMM}	r_{LMM}	***P* value**	**Subcortical brain volume**	β_{LMM}	r_{LMM}	***P* value**
Left **ventral diencephalon (DC)**	9.077	0.058	2.25×10^{-6}	Right **putamen**	13.243	0.051	1.60×10^{-4}

Right **thalamus** proper	15.218	0.056	8.50×10^{-6}	Right **pallidum**	3.991	0.050	2.14×10^{-4}
Right cerebral white matter	477.642	0.052	5.90×10^{-5}	Right **accumbens** area	1.876	0.047	1.22×10^{-3}
Right **ventral DC**	8.759	0.051	7.70×10^{-5}	Left **putamen**	12.825	0.045	2.32×10^{-3}
Left cerebral white matter	492.309	0.051	8.99×10^{-5}	Right **caudate**	9.982	0.045	3.44×10^{-3}
Brain stem	41.722	0.050	1.11×10^{-4}	Left **pallidum**	4.726	0.044	5.06×10^{-3}
Left **thalamus** proper	15.020	0.049	1.54×10^{-4}	Left **hippocampus**	6.892	0.039	0.022
Left **caudate**	9.855	0.047	1.20×10^{-3}				

Results using the cortical FreeSurfer Destrieux atlas and subcortical ASEG atlas were shown after analysing the participants' brain segmentation data.
Bonferroni corrected, $P<0.05$. Brain cortical area in mm^2. Brain volume in mm^3.

Table S10. The total brain and subcortical regions modestly related to early RfP in table S9 were overlapping regions that were significantly correlated with young adolescent cognitive scores and negatively correlated with their psychopathology scores

Subcortical regions correlated with **cognition total score**	β_{LMM}	r_{LMM}	***P* value**	Subcortical regions correlated with **cognition total score**	β_{LMM}	r_{LMM}	***P* value**
Total brain volume	1451.552	0.1203	$< 1\times10^{-20}$	Right putamen	7.302	0.096	3.73×10^{-20}
Left thalamus proper	9.785	0.114	$< 1\times10^{-20}$	Right pallidum	2.227	0.092	1.98×10^{-18}
Intracranial volume	1686.283	0.113	$< 1\times10^{-20}$	Left putamen	7.927	0.092	2.80×10^{-18}
Left cerebral white matter	304.536	0.112	$< 1\times10^{-20}$	Left hippocampus	4.693	0.0903	1.40×10^{-17}
Right cerebral white matter	302.452	0.111	$< 1\times10^{-20}$	Left caudate	5.742	0.086	4.97×10^{-16}
Right thalamus proper	8.718	0.106	$< 1\times10^{-20}$	Right caudate	5.794	0.085	1.68×10^{-15}
Left ventral DC	4.955	0.105	$< 1\times10^{-20}$	Left pallidum	2.367	0.074	2.73×10^{-11}
Right ventral DC	4.937	0.103	$< 1\times10^{-20}$	Right accumbens area	0.856	0.070	4.05×10^{-10}
Brain-stem	23.666	0.103	$< 1\times10^{-20}$				
Subcortical regions correlated with **cognition crystallized score**	β_{LMM}	r_{LMM}	***P* value**	Subcortical regions correlated with **cognition crystallized score**	β_{LMM}	r_{LMM}	***P* value**
Total brain volume	2446.298	0.157	$< 1\times10^{-20}$	Right pallidum	3.621	0.117	$< 1\times10^{-20}$
Intracranial volume	2922.059	0.152	$< 1\times10^{-20}$	Right putamen	11.110	0.114	$< 1\times10^{-20}$
Left thalamus proper	15.327	0.139	$< 1\times10^{-20}$	Left hippocampus	7.550	0.113	$< 1\times10^{-20}$
Left cerebral white matter	470.985	0.135	$< 1\times10^{-20}$	Right caudate	9.757	0.111	$< 1\times10^{-20}$
Right ventral DC	8.327	0.135	$< 1\times10^{-20}$	Left caudate	9.220	0.108	$< 1\times10^{-20}$
Right cerebral white matter	473.494	0.134	$< 1\times10^{-20}$	Left putamen	11.228	0.101	1.39×10^{-22}
Left ventral DC	8.174	0.134	$< 1\times10^{-20}$	Left pallidum	3.660	0.089	4.73×10^{-17}
Brain stem	39.135	0.132	$< 1\times10^{-20}$	Right accumbens area	1.241	0.079	2.57×10^{-13}
Right thalamus proper	13.900	0.131	$< 1\times10^{-20}$				
Subcortical regions correlated with **total problems**	β_{LMM}	r_{LMM}	***P* value**	Subcortical regions correlated with **total problems**	β_{LMM}	r_{LMM}	***P* value**
Total brain volume	–369.874	–0.071	1.83×10^{-10}	Left cerebellum cortex	–12.799	–0.049	3.51×10^{-4}
Right cerebral white matter	–72.077	–0.061	2.43×10^{-7}	Right cerebellum cortex	–12.892	–0.048	6.10×10^{-4}

Left cerebral white matter	–67.890	–0.058	1.72×10^{-6}	Left hippocampus	–1.045	–0.047	0.001
Brain stem	–5.651	–0.056	3.77×10^{-6}	Left ventral DC	–0.950	–0.046	0.001
Left thalamus proper	–2.073	–0.056	5.62×10^{-6}	Left caudate	–1.230	–0.043	0.007
Intracranial volume	–356.564	–0.055	8.65×10^{-6}	Right caudate	–1.188	–0.040	0.021
Right accumbens area	–0.281	–0.053	2.32×10^{-5}	Right putamen	–1.318	–0.040	0.023
Right thalamus proper	–1.823	–0.051	7.94×10^{-5}				

Subcortical regions correlated with **attention problems scores**	β_{LMM}	r_{LMM}	***P* value**	Subcortical regions correlated with **attention problems scores**	β_{LMM}	r_{LMM}	***P* value**
Total brain volume	–2132.44	–0.069	7.02×10^{-10}	Left hippocampus	–6.099	–0.046	0.002
Intracranial volume	–2264.61	–0.059	6.83×10^{-7}	Left caudate	–7.382	–0.043	0.006
Right cerebral white matter	–397.630	–0.057	3.40×10^{-6}	Left ventral DC	–5.092	–0.042	0.011
Left cerebral white matter	–385.223	–0.055	7.44×10^{-6}	Right thalamus proper	–8.658	–0.041	0.016
Brain stem	–32.072	–0.054	1.49×10^{-5}	Right caudate	–7.157	–0.041	0.016
Left thalamus proper	–11.668	–0.053	3.28×10^{-5}	Left cerebellum white matter	–27.559	–0.041	0.016
Right accumbens area	–1.507	–0.048	4.88×10^{-4}	Right putamen	–7.823	–0.040	0.024

Bonferroni corrected, $P<0.05$. Subcortical volume in mm^3.

Table S11. Young adolescents from both low- and high-income families showed positive correlations between early RfP and brain structures

High income families (n=4174)				Low income families (n=2873)			
Cortical and subcortical brain structure	**β_{LMM}**	**r_{LMM}**	***P* value**	**Cortical and subcortical brain structure**	**β_{LMM}**	**r_{LMM}**	***P* value**
Intracranial volume	4.147×10^{3}	0.082	3.88×10^{-5}	Left lateral aspect of the superior temporal gyrus	6.799	0.079	0.012
Left ventral DC volume	12.607	0.080	7.14×10^{-5}	Right parahippocampal gyrus	4.556	0.078	0.016
Right ventral DC volume	12.038	0.077	2.08×10^{-4}	Left posterior-dorsal part of the cingulate gyrus	2.952	0.077	0.021
Right thalamus proper volume	20.896	0.073	7.95×10^{-4}	Left transverse frontopolar gyri and sulci	3.051	0.075	0.030
Left lateral aspect of the superior temporal gyrus	6.145	0.069	0.0027	Right pericallosal sulcus	5.983	0.075	0.031
Whole brain	4.797×10^{3}	0.069	0.0032	Right superior segment of the circular sulcus of the insula	3.729	0.074	0.040
Right middle temporal gyrus	8.848	0.068	0.0035	Right orbital gyri	7.153	0.073	0.051
Right superior temporal sulcus	17.360	0.063	0.015	Left superior segment of the circular sulcus of the insula	3.997	0.073	0.054

Sub-group analysis based on their family incomes per year (low income <$50,000, high income ⩾$100,000, the middle income group was not compared here). Each group showed significant associations between early RfP and brain structure. Bonferroni corrected, $P<0.05$. Cortical area in mm^2. Subcortical volume in mm^3.

Table S12. Neural fiber tract volumes measured by DTI were significantly associated with their early RfP

DTI fiber tract volume	β_{LMM}	r_{LMM}	*P* value	DTI fiber tract volume	β_{LMM}	r_{LMM}	*P* value
Left corticospinal /pyramidal	24.379	0.060	4.95×10^{-5}	All fiber tracts	658.006	0.053	9.66×10^{-4}
Right temporal superior longitudinal fasiculus	29.808	0.059	5.67×10^{-5}	Left inferior-fronto-occipital fasiculus	35.971	0.053	1.24×10^{-3}
Right fornix	15.458	0.059	6.36×10^{-5}	Left anterior thalamic radiations	33.784	0.052	1.57×10^{-3}
Right hemisphere fiber tracts without corpus callosum	246.848	0.057	1.72×10^{-4}	Right hemisphere fiber tracts	323.771	0.052	1.90×10^{-3}
Right inferior-fronto-occipital fasiculus	41.545	0.056	2.51×10^{-4}	Right anterior thalamic radiations	31.797	0.052	2.11×10^{-3}
Left hemisphere fiber tracts without corpus	242.487	0.056	2.90×10^{-4}	Left superior longitudinal fasiculus	31.377	0.049	5.33×10^{-3}
Left fornix	15.024	0.056	3.39×10^{-4}	Left temporal superior longitudinal fasiculus	26.644	0.049	5.35×10^{-3}
Right superior longitudinal fasiculus	37.354	0.056	3.53×10^{-4}	Right parietal superior longitudinal fasiculus	30.579	0.047	0.013
Left hemisphere fiber tracts	337.406	0.054	7.30×10^{-4}	Left inferior longitudinal fasiculus	34.693	0.046	0.022
Right corticospinal/ pyramidal	21.551	0.053	9.36×10^{-4}	Left superior corticostriate-parietal cortex only	27.797	0.046	0.022

Results from the DTI analysis were shown after analysing the participants' brain segmentation data. Bonferroni corrected, $P<0.05$. Fiber tract volume in mm^3.

Table S13. Regular RfP weekly durations (within 12h/week) were significantly associated with their increased brain cortical and subcortical volumes

Cortical brain volume	β_{LMM}	r_{LMM}	***P* value**	**Cortical brain volume**	β_{LMM}	r_{LMM}	***P* value**
Left superior temporal sulcus	24.892	0.052	2.35×10^{-4}	Right long insular gyrus and central sulcus of the insula	3.070	0.042	0.023
Right superior temporal sulcus	26.913	0.051	3.93×10^{-4}	Right superior frontal gyrus	30.737	0.042	0.023
Right precentral gyrus	15.350	0.049	1.10×10^{-3}	Left middle-posterior part of the cingulate gyrus and sulcus	6.243	0.042	0.025
Left postcentral gyrus	13.804	0.047	3.27×10^{-3}	Left lateral aspect of the superior temporal gyrus	12.913	0.041	0.031
Left precentral gyrus	13.560	0.044	0.011	Right inferior temporal sulcus	7.164	0.041	0.034
Subcortical brain volume	**β**	r_{LMM}	***P* value**	**Subcortical brain volume**	β_{LMM}	r_{LMM}	***P* value**
Right putamen	9.79	0.052	2.44×10^{-4}	Right pallidum	2.61	0.044	0.012
Right ventral DC	6.00	0.050	5.23×10^{-4}	Brain stem	25.11	0.044	0.012
Right amygdala	3.25	0.050	5.93×10^{-4}	Left amygdala	2.73	0.043	0.014
Left ventral DC	5.49	0.047	2.79×10^{-3}	Right cerebral white matter	287.30	0.042	0.021
Left putamen	9.85	0.046	4.25×10^{-3}	Left caudate	6.97	0.042	0.022
Left thalamus proper	9.56	0.045	6.79×10^{-3}	Left cerebral white matter	280.22	0.042	0.029
Intracranial volume	1659.15	0.045	7.55×10^{-3}				

Results from associations between RfP durations (within 12 h/week) and brain structure.

Table S14. Result of twin analysis on the heritability (h^2) of early RfP, cognition, attention problems and representative brain cortical structure

Variables of interest	h^2 (95% CI)	h^2 P value	C	E	MZ ICC	DZ ICC
Early RfP	0.315(0.272 – 0.358)	<0.001	0.505	0.180	0.821	0.660
Crystallized composite of cognition	0.461(0.456 – 0.467)	0.001	0.245	0.294	0.651	0.352
Fluid composite of cognition	0.608(0.602 – 0.614)	<0.001	0	0.392	0.692	0.367
Attention problems score	0.671(0.652 – 0.691)	<0.001	0	0.329	0.652	0.177
Left superior temporal sulcus area	0.261(0.220 – 0.301)	<0.001	0.599	0.140	0.552	0.431

Heritability were estimated under the ACE model. *P* values for heritability estimates were obtained by comparing the ACE model with the E model. C, common environmental component; E, unique environmental component; MZ, monozygotic; DZ, dizygotic. ICC, intraclass correlation coefficient;

Table S15. Results of Mendelian randomization (MR) analyses

MR analysis: the relationship between early RfP and adult cognitive performances						
id.exposure	**id.outcome**	**Method**	**No. of SNPs**	**β**	**se**	***P* Value**
Early RfP	ebi-a-GCST006572 [a]	IVW	8	0.026	0.010	**0.009**
Early RfP	ebi-a-GCST006572	Weighted median	8	0.035	0.013	**0.006**
Early RfP	ebi-a-GCST006572	MR Egger	8	0.054	0.044	0.266
MR analysis: the relationship between early RfP and adult left superior temporal cortical area						
id.exposure	**id.outcome**	**Method**	**No. of SNPs**	**β**	**se**	***P* Value**
Early RfP	ubm-a-2819 [b]	IVW	9	0.114	0.039	**0.003**
Early RfP	ubm-a-2819	Weighted median	9	0.070	0.054	0.198
Early RfP	ubm-a-2819	MR Egger	9	0.119	0.161	0.487
MR analysis: the relationship between early RfP and ADHD disorder in children and adults						
id.exposure	**id.outcome**	**Method**	**No. of SNPs**	**β**	**se**	***P* Value**
Early RfP	ieu-a-1183 [c]	IVW	9	–0.048	0.043	0.259
Early RfP	ieu-a-1183	Weighted median	9	–0.050	0.058	0.394
Early RfP	ieu-a-1183	MR Egger	9	–0.167	0.169	0.355
Steiger MR directionality test						
Early RfP → Adult cognitive performance	**id.exposure**	**id.outcome**	**snp_r2. exposure**	**snp_r2. outcome**	**correct_causal_ direction**	**steiger_*P*val**
	Early RfP	ebi-a-GCST006572	0.041	4.23×10^{-5}	TRUE	1.88×10^{-40}
Early RfP → Adult left superior temporal cortical area	**id.exposure**	**id.outcome**	**snp_r2. exposure**	**snp_r2. outcome**	**correct_causal_ direction**	**steiger_*P*val**
	Early RfP	ubm-a-2819	0.046	2.1×10^{-3}	TRUE	1.16×10^{-20}
Early RfP → ADHD in children and adults	**id.exposure**	**id.outcome**	**snp_r2. exposure**	**snp_r2. outcome**	**correct_causal_ direction**	**steiger_*P*val**
	Early RfP	ieu-a-1183	0.047	1.42×10^{-4}	TRUE	9.74×10^{-37}

[a] ebi-a-GCST006572: Adult cognitive performances, [b] ubm-a-2819: adult a2009s lh superior temporal area, [c] ieu-a-1183: Children & adults ADHD disorder. β statistics were converted from OR by log-transformation in the ADHD case-control MR analysis. Effect size indicates β for cognitive performance, brain structure, or ADHD disorder per 1-SD increase in early RfP score.

IVW, inverse variance–weighted MR analysis.

Table S16. MR sensitivity tests to detect horizontal pleiotropy and heterogeneity

1) MR-Egger intercept pleiotropy test

id.exposure	id.outcome	Egger_intercept	se	*P* Value
Early RfP	ebi-a-GCST006572 [a]	–0.004	0.005	0.533
Early RfP	ubm-a-2819 [b]	–0.001	0.020	0.928
Early RfP	ieu-a-1183 [c]	0.016	0.021	0.491

2) MR heterogeneity test

	id.exposure	id.outcome	Method	Q	Q_df	Q_*P*Value
Early RfP & Adult cognition	Early RfP	ebi-a-GCST006572	IVW	4.151	7	0.762
	Early RfP	ebi-a-GCST006572	MR Egger	3.713	6	0.715
Early RfP & Adult lh superior temporal	Early RfP	ubm-a-2819	IVW	7.753	8	0.458
	Early RfP	ubm-a-2819	MR Egger	7.752	7	0.355
Early RfP & ADHD in children and adults	Early RfP	ieu-a-1183	IVW	6.636	8	0.576
	Early RfP	ieu-a-1183	MR Egger	6.106	7	0.527

3) MR-PRESSO test

id.exposure	id.outcome	MR-PRESSO Global test RSSobs	MR-PRESSO Global test *P* Value
Early RfP	ebi-a-GCST006572	5.366	0.779
Early RfP	ubm-a-2819	9.806	0.493
Early RfP	ieu-a-1183	8.201	0.587

No horizontal pleiotropy, heterogeneity, or outlier was detected in the MR sensitivity tests. (All statistical results of the sensitivity tests were non-significant)

[a] ebi-a-GCST006572: Adult cognitive performances, [b] ubm-a-2819: adult a2009s lh superior temporal area. [c] ieu-a-1183: Children & adults ADHD disorder,

5. Other Supplementary Materials

Supplementary material 1. All the assessment scales of young adolescents in the ABCD database that were analysed in the study

NDA Short Name	Full name of assessment scale	Description
Physical Health		
abcd_devhxss01	ABCD Sum Scores Developmental History	ABCD Developmental History Questionnaire
abcd_ehis01	ABCD Youth Edinburgh Handedness Inventory Short Form	Handedness, laterality quotient
abcd_hsss01	ABCD Hormone Saliva Salimetric Scores	Pubertal hormone levels (estradiol, testosterone, and DHEA)
abcd_medhxss01	ABCD Sum Scores Parent Medical History	ABCD Parent Medical History Questionnaire
abcd_mx01	ABCD Parent Medical History Questionnaire	Medical history and health services utilization
abcd_otbi01	ABCD Parent Ohio State Traumatic Brain Injury Screen-Short Modified	Traumatic brain injury of youth
abcd_ppdms01	ABCD Parent Pubertal Development Scale and Menstrual Cycle Survey History	Pubertal stage and menstrual phase (for postmenarcheal girls) - parent survey
abcd_saiq02	ABCD Parent Sports and Activities Involvement Questionnaire	Involvement in sports, music and hobbies, TBI risk
abcd_sds01	ABCD Parent Sleep Disturbance Scale for Children	Sleep and sleep disorders
abcd_spacss01	ABCD Sum Scores Parent Sports and Activities Involvement	ABCD Parent Sports and Activities Involvement Questionnaire .
abcd_ssphp01	ABCD Sum Scores Physical Health Parent	Physical Health summary scores - parent surveys
abcd_ssphy01	ABCD Sum Scores Physical Health Youth	Physical Health summary scores - youth surveys
abcd_stq01	ABCD Youth Screen Time Survey	Screen time utilization - youth
abcd_svs01	ABCD Youth Snellen Vision Screener	Vision screening
abcd_tbi01	ABCD Sum Scores Traumatic Brain Injury	Traumatic brain injury of youth summary scores
abcd_ypdms01	ABCD Youth Pubertal Development Scale and Menstrual Cycle Survey History	Pubertal stage and menstrual phase (for postmenarcheal girls) - youth survey
abcd_yrb01	ABCD Youth Risk Behavior Survey Exercise Physical Activity	Physical exercise
dhx01	ABCD Developmental History Questionnaire	Prenatal exposure before and during pregnancy - medications, drugs alcohol, tobacco
medsy01	ABCD Parent Medications Survey Inventory Modified from PhenX	Medications taken in the last two weeks
pdem02	ABCD Parent Demographics Survey	Demographics, race, gender, family structure, SES, education, occupation (includes Native American Acculturation Scale)
sph01	ABCD Pubertal Hormone Saliva	Information collected by RAs at the time of collecting oral fluid to indicate current estradiol, testosterone, and DHEA levels (e.g., time of day of collection)
Neurocognition		
absd_ps01	ABCD Pearson Scores	Measures included in Pearson Scores: Rey Auditory Verbal Learning Test, Matrix Reasoning Test, and Rey Delayed Recall Test
abcd_tbss01	ABCD Youth NIH TB Summary Scores	Measures included in NIH TB Summary Scores: NIH TBX

		Picture Vocabulary; NIH Tbx Flanker Inhibitory Control and Attention; NIH Tbx List Sorting Working Memory; NIH Tbx Dimensional Change Card Sort; NIH Tbx Pattern Comparison Processing Speed;NIH Tbx Picture Sequence Memory; NIH Tbx Oral Reading Recognition
cct01	ABCD Cash Choice Task	Impulsivity, delayed gratification
lmtp201	ABCD Little Man Task	Visuospatial processing flexibility, attention
Mental Health		
abcd_asrs01	Adult Self Report Scores	Adult Self Report summary scores
abcd_bisbas01	ABCD Youth Behavioral Inhibition/Behavioral Approach System Scales Modified from PHENX	Inhibition and reward seeking
abcd_bpmt01	ABCD Brief Problem Monitor Teacher Form	Normed multi-informant monitoring of children's functioning/teacher report
abcd_cbcl01	ABCD Parent Child Behavior Checklist Raw Scores Aseba	Dimensional psychopathology, adaptive functioning
abcd_cbcls01	Child Behavior Check List Scores	Child Behavior Check List summary scores, summary of cbcl01
abcd_ksad01	ABCD Parent Diagnostic Interview for DSM-5 Full	Mental health diagnosis - parent questions
abcd_ksad501	ABCD Youth Diagnostic Interview for DSM-5	Mental health diagnosis - youth questions
abcd_mhp02	ABCD Sum Scores Mental Health Parent	Mental Health summary scores - parent surveys
abcd_mhy02	ABCD Sum Scores Mental Health Youth	Mental Health summary scores - youth surveys
abcd_pgbi01	ABCD Parent General Behavior Inventory-Mania	Subsyndromal mania
abcd_pksadscd01	ABCD Parent KSADS Conduct Disorder	KSADS - conduct disorder raw values
abcd_ptsd01	Parent Diagnostic Interview for DSM-5 (KSADS) Traumatic Events	KSADS - PTSD raw values
abcd_ssbpmtf01	ABCD Summary Scores Brief Problem Monitor Teacher Form	Normed multi-informant monitoring of children's functioning/teacher report summary scores
abcd_upps01	UPPS-P for Children Short Form (ABCD-version)	Impulsivity
abcd_yksad01	ABCD Youth Diagnostic Interview for DSM-5 Background Items	School, sexual orientation
abcd_ysr01	ABCD Other Resilience	Resilience (friends)
dibf01	ABCD Parent Diagnostic Interview for DSM-5 Background Items Full	School, family, social relations
fhxp102	ABCD Family History Assessment Part 1	Family history of psychopathology and substance use
pasr01	ABCD Parent Adult Self Report Raw Scores Aseba	Parent dimensional psychopathology
pps01	ABCD Prodromal Psychosis Scale	Prodromal psychosis levels
Substance Use		
abcd_crpf01	ABCD Parent Community Risk and Protective Factors (CRPF)	Beliefs about drug availability (alcohol, nicotine, marijuana, "other" drugs) along with questions about access and exposure to medical marijuana
abcd_hers01	ABCD Youth Hair Sample	Information collected by RAs at the time of collecting
abcd_plus01	ABCD Youth Participant Last Use Survey Day 1 2 3 4	Tobacco/caffeine/medication usage in the last 24 hours - youth answers
abcd_suss01	Summary Scores Substance Use	Caffeine summary scores

abcd_yhr01	ABCD Youth Hair Results	Metabolites of past 3 month substance use
abcd_ysu02	ABCD Youth Substance Use Interview	Measures included in Substance Use Interview are described below
abcd_ytt01	ABCD Youth Toxicology Test	Past day drug use - Oral Fluid Draeger
plus01	ABCD Parent Participant Last Use Survabcd_ysuip01ey Day 2 3 4	Tobacco/caffeine/medication usage in the last 24 hours - parent answers
prq01	ABCD Parental Rules on Substance Use	Parental substance use approval and rules
yalcs01	ABCD Youth Alcohol Screen	Past day alcohol use - Breathalyzer
Culture and Environment		
abcd_fes01	ABCD Youth Family Environment Scale-Family Conflict Subscale Modified from PhenX	Family dynamics, cohesion, expressiveness, conflict
abcd_meim01	ABCD Parent Multi-Group Ethnic Identity-Revised Survey	Cultural affiliation
abcd_nsc01	ABCD Youth Neighborhood Safety/Crime Survey Modified from PhenX	Neighborhood risk and protective factors, crime
abcd_pnsc01	ABCD Parent Neighborhood Safety/Crime Survey Modified from PhenX	Neighborhood risk and protective factors, crime
abcd_psb01	Youth Prosocial Behavior Survey	Resilience
abcd_sscep01	ABCD Sum Scores Culture & Environment Parent	Culture and environment summary scores - parent surveys
abcd_sscey01	ABCD Sum Scores Culture & Environment Youth	Culture and environment summary scores - youth surveys
abcd_via01	ABCD Parent Vancouver Index of Acculturation-Short Survey	Acculturation
crpbi01	ABCD Children's Report of Parental Behavioral Inventory	Environment - family and religion
fes02	ABCD Parent Family Environment Scale-Family Conflict Subscale Modified from PhenX	Family dynamics, cohesion, expressiveness, conflict
macv01	ABCD Parent Mexican American Cultural Values Scale Modified	Familism, religion, independence, self-reliance
pacc01	ABCD Parent Acculturation Survey Modified from PhenX*	Cultural factors
pmq01	ABCD Parental Monitoring Survey	Parental monitoring and supervision
psb01	Parent Prosocial Behavior Survey	Resilience
srpf01	ABCD School Risk and Protective Factors Survey	School risk and protective factors
yacc01	ABCD Youth Acculturation Survey Modified from PhenX	Cultural factors
Mobile Using (Screen time)		
abcd_ssmty01	ABCD Sum Scores Mobile Tech Youth	Mobile Tech Youth summary scores
abcd_stq01	ABCD Youth Screen Time Survey	Screen time utilization - youth
stq01	ABCD Parent Screen Time Survey	Screen time utilization - parent

All detailed information was obtained from the ABCD project and can be found at its website (https://abcdstudy.org/scientists-protocol.html) and (https://nda.nih.gov/abcd/abcd-annual-releases.html).

Supplementary material 2. Subjects were recruited across 21 ABCD research sites in the USA

(1) Children's Hospital Los Angeles, Los Angeles, California; (2) Florida International University, Miami, Florida; (3) Laureate Institute for Brain Research, Tulsa, Oklahoma; (4) Medical University of South Carolina, Charleston, South Carolina; (5) Oregon Health and Science University, Portland, Oregon; (6) SRI International, Menlo Park, California; (7) University of California San Diego, San Diego, California; (8) University of California, Los Angeles (UCLA). California; (9) University of Colorado Boulder, Boulder, Colorado; (10) University of Florida, Gainesville, Florida; (11) University of Maryland at Baltimore, Baltimore, Maryland; (12) University of Michigan, Ann Arbor, Michigan; (13) University of Minnesota, Minneapolis, Minnesota; (14) University of Pittsburgh, Pittsburgh, Pennsylvania; (15) University of Rochester, Rochester, New York; (16) University of Utah, Salt Lake City, Utah; (17) University of Vermont, Burlington, Vermont; (18) University of Wisconsin-Milwaukee, Milwaukee, Wisconsin; (19)Virginia Commonwealth University, Richmond, Virginia; (20)Washington University in St. Louis, St. Louis, Missouri; and (21) Yale University, New Haven, Connecticut

More information at: https://abcdstudy.org/study-sites/
Subjects were recruited at the school level through a probability sampling, within the defined catchment areas of the nationally distributed set of 21 recruitment sites

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