Supplementary Online Content

French L, Gray C, Leonard G, et al. Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. *JAMA Psychiatry*. Published online August 26, 2015. doi:10.1001/jamapsychiatry.2015.1131.

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Characteristics of the Study Participants

A. All Study Participants					
	SYS		ALSPAC	IMAGEN	
	Males	Females	Males	Males	Females
Participants (n)	459	490	295	145	188
Age in months at scan (SD)	180 (21)	181 (23)	235 (10)	174 (5)	174 (5)
Age at Time point 2	NA	NA	NA	228 (7)	228 (6)
Risk Score (SD)	-0.063 (0.55)	-0.061 (0.54)	0.26 (0.54)	-0.32 (0.55)	-0.47 (0.55)
Used cannabis by age 16	142 (31%)	171 (35%)	91 (31%)	37 (26%)	45 (24%)

B. Characteristics of the Male Adolescents (SYS) by Cannabis Use (Never/Ever) and Polygenic Risk Score (below median [Low] and above median [High])				
	Low Risk		High Risk	
	Never	Ever	Never	Ever
Participants (n)	153	73	164	69
Age in months at scan (SD)	174 (21)	194 (17)	173 (20)	192 (18)
Youngest age in months at first use	N/A	132	N/A	108
Mean age in months at first use (SD)	N/A	171 (17)	N/A	165 (25)

eTable 2. Top-5 Clusters for the Interaction Between Schizophrenia Risk Score and Cannabis Groups Vis-à-Vis Cortical Thickness in SYS Male Adolescents

Hemisphere	Cluster Number	Difference	Vertex Max	Cluster Size (mm^2)	TalX	TalY	TalZ	Annotation
Left	1	-3.5962	56377	133.85	-54.4	-9.3	12.0	postcentral
Left	2	-3.4979	46461	473.41	-22.2	-69.9	-6.8	lingual[a]
Left	3	-3.4615	49164	112.07	-40.3	-66.5	34.8	inferior parietal
Left	4	-3.2799	48897	159.87	-37.3	52.0	1.5	rostral middle frontal
Left	5	-3.2355	4376	259.15	-26.4	-93.9	-15.9	lateral occipital
Right	1	-3.8352	33819	1002.91	39.7	-81.1	18.5	inferior parietal[a]
Right	2	-3.2439	55497	334.08	5.5	-76.6	19.4	cuneus
Right	3	-3.0101	66935	68.10	34.3	-44.6	56.8	superior parietal
Right	4	-2.9960	131281	109.77	29.0	3.3	51.8	caudal middle frontal
Right	5	-2.9569	112310	102.01	52.4	-51.9	8.5	inferior parietal

Each person's FreeSurfer data were sampled into a common space (fsaverage) and spatially smoothed using a 10mm FWHM. A different-offset, different-slope (DODS) design matrix was used to compare the cannabis groups (Ever vs. Never) x Schizophrenia Risk Score. Two types of corrections for multiple comparisons were applied: cluster-wise correction using Monte Carlo simulation and voxel-wise correction using False Discovery Rate ([1]Hagler DL, Saygin AP, & Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *NeuroImage.* 2006; 33(4): 1093:1103).

[a] Cluster meets cluster-wide significance using a Monte Carlo simulation (threshold = 2.0, $p<0.01$).

No vertices remained significant after correction for multiple comparisons using a False Discovery Rate of 0.05 (difference left hemisphere > 3.64 and difference right hemisphere > 3.88).

eTable 3. Regional Variations in Group Differences in Cortical Thickness and *CNR1* Expression

			Group Difference (Ever – Never)	
Region	Lobe	*CNR1* Expression	Low Risk Males	High Risk Males
bankssts	temporal	5.87	0.0010	-0.0120
caudalanteriorcingulate	frontal	6.83	-0.0052	-0.1070
caudalmiddlefrontal	frontal	6.06	0.0252	-0.0496
cuneus	occipital	5.48	0.0202	-0.0243
entorhinal	temporal	6.52	-0.0613	-0.1530
frontalpole	frontal	6.24	-0.0381	-0.0687
fusiform	temporal	6.38	0.0178	-0.0496
inferiorparietal	parietal	5.80	0.0263	-0.0517
inferiortemporal	temporal	6.17	-0.0036	-0.0698
insula	frontal	6.32	-0.0237	-0.0712
isthmuscingulate	frontal	6.30	0.0276	-0.0713
lateraloccipital	occipital	5.65	0.0241	-0.0602
lateralorbitofrontal	frontal	6.27	-0.0285	-0.0473
lingual	occipital	5.50	0.0177	-0.0284
medialorbitofrontal	frontal	6.50	-0.0283	-0.0361
middletemporal	temporal	6.16	-0.0148	-0.0970
paracentral	parietal	6.17	0.0283	-0.0598
parahippocampal	temporal	6.33	-0.0810	-0.0281
parsopercularis	frontal	6.02	0.0267	-0.0486
parsorbitalis	frontal	6.33	-0.0288	-0.0690
parstriangularis	frontal	5.91	-0.0013	-0.0452
pericalcarine	occipital	5.00	0.0191	-0.0096

postcentral	parietal	5.48	0.0268	-0.0092
posteriorcingulate	parietal	6.39	0.0089	-0.0733
precentral	frontal	6.03	0.0081	-0.0489
precuneus	parietal	5.85	0.0203	-0.0791
rostralanteriorcingulate	frontal	6.68	-0.0242	-0.0062
rostralmiddlefrontal	frontal	6.07	0.0004	-0.0597
superiorfrontal	frontal	6.17	0.0238	-0.0613
superiorparietal	parietal	5.78	0.0454	-0.0477
superiortemporal	temporal	6.11	0.0133	-0.0523
supramarginal	parietal	6.06	0.0175	-0.0705
temporalpole	temporal	6.51	-0.0265	-0.1852
transversetemporal	temporal	5.67	0.0400	-0.0232

Group differences in age-adjusted cortical thickness between “Ever” and “Never” users in the Low Risk and High Risk groups of male adolescents from the Saguenay Youth Study.

eTable 4. Correlations in SYS Male Cannabis Users (n=142) Between Age-Adjusted Cortical Thickness and Risk Scores Calculated From Different *P* Value Thresholds

P-value Threshold	SNPs	Correlation	R^2	P-value
0.00000005	111	-0.25307	0.06404	0.002376
0.000001	246	-0.16296	0.02656	0.052660
0.00001	1278	-0.09501	0.00903	0.260694
0.001	3419	-0.10683	0.01141	0.205737
0.01	10648	-0.03230	0.00104	0.702788
0.05	24727	-0.00106	0.00000	0.989983

Odds ratios from the discovery and replication cohorts combined were used for calculating risk scores with the set of 111 SNPs. Odds ratios from the discovery cohort were used for the remaining risk score calculations due to data availability (see eMethods, Polygenic Risk Score section).

eMethods. Additional Details of the Study Methods

Saguenay Youth Study (SYS): Recruitment, Cannabis Assessment, MRI and Genotyping

Between 2003 and 2012, we assessed adolescents and their parents recruited from a population with a known founder effect, namely Saguenay-Lac-Saint-Jean region of Quebec, Canada[1]. Both maternal and paternal grandparents of the adolescents were of French-Canadian ancestry born in the region; as such, all adolescents are of a single ethnicity, namely white Caucasians of French Canadian ancestry. This is a community-based sample recruited in local high schools. The main *exclusion criteria* were: (1) positive medical history for meningitis, malignancy, and heart disease requiring heart surgery; (2) treatment for schizophrenia or bipolar disorder; (3) severe mental illness (e.g. autism) or mental retardation (IQ<70); (4) premature birth (< 35 weeks) and (5) MRI contraindications. Given the availability of cannabis self-reports and following quality control of MR and genetic data, a total of 949 adolescents were included in the analysis of the relationship between cannabis use, cortical thickness and genetic risk of schizophrenia (459 males, 180±21 months of age (Mean±SD]; 490 females, 181±23 months of age). Age ($p = 0.31$) and variance in age ($p=0.45$, Kolmogorov-Smirnov test) were not different between the male and female adolescents. The Research Ethics Committee of the Chicoutimi Hospital approved the study protocol; the parents and adolescents provided written informed consent and assent, respectively.

Lifetime exposures to cannabis and other illicit substances were obtained through self-reports using a questionnaire adapted from the National Longitudinal Survey of Children and Youth (NLSCY) and Quebec Longitudinal Study of Child Development (QLSCD) protocols[1]. In this questionnaire, we asked “As-tu déjà essayé les drogues suivantes?” (Have you tried the following drugs?), followed by a list of illicit substances including “Marijuana, haschich, pot, grass”. Participants were provided the following options for their answers: “Non” (Never) or “Oui, au cours…” (Yes, in…). If they answered Yes, we asked the participant to specify the time period as follows: “des derniers 30 jours” (the last 30 days), “des derniers 12 mois” (the last 12 months) or “de ma vie” (in my life). Cannabis use rates were not different between the sexes ($p=0.21$).

T1-weighted images were acquired on a Phillips 1.0-T superconducting magnet (Gyroscan NT; Philips Medical Systems, Best, the Netherlands) using the following parameters: 3D RF-spoiled gradient echo scan with 140–160 sagittal slices, 1-mm isotropic resolution, TR=25 ms, TE=5 ms, and flip angle=30°.

All adolescents were genotyped with the Illumina Human610-Quad BeadChip (610K SNPs) or Illumina HumanOmniExpress BeadChip (700k SNPs). Imputations were used to combine the two platforms. We employed an imputation protocol developed by the ENIGMA Working Group, and imputed genotypes using a reference file created by the ENIGMA2 Genetics Support Team. This reference file is based on the 1kG Project (phase 1, release v3; ~41M SNPs)[2] and includes only ~13M SNPs that are polymorphic in Caucasians and have been observed more than once in European samples. Haplotype phasing was performed with SHAPEIT[3] using an overlapping subset of 313,653 post-quality-control SNPs that were present on both genotyping platforms and the above reference panel. Imputation was conducted on the phased data with IMPUTE2[4]. Markers with low imputation quality (information score <0.5) or low minor allele frequency (<0.01) were removed.

ALSPAC: Recruitment, Cannabis Assessment, MRI and Genotyping

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based longitudinal birth cohort ascertained in the former Avon Health Authority in southwest England based on expected dates of delivery 1st April 1991 to 31st December 1992[5]. Out of 14,062 live births, 13,988 were alive at 1 year. Between November 2011 and October 2012, a subset of 510 male participants was recruited for an MRI study. These individuals were selected based on the availability of multiple (> 3) blood samples obtained during their early and mid puberty (9, 11, 13 and 15 yr), and their current residence being in the Southwestern England. When compared with all males included in the cohort, the subsample studied here differs on a number of variables in a manner consistent with being from families with a higher parental education[6]. Similar patterns of attrition have been observed in other studies[7]. Given the availability of cannabis self-reports (at both 16.5 and 18-21 years of age) and following quality control of MR and genetic data, a total of 295 male youth were included in the analysis of the relationship between cannabis use, cortical thickness and genetic risk of schizophrenia (235±10 months of age (Mean±SD] at the time of MR imaging). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees; participants provided written informed consent for their participation in this substudy. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Participants' use of cannabis was assessed via self-reports at seven time points, from 10 to 16.5 years of age. Using either an interview (age 10, 12.5 and 13.5 years) or a questionnaire (age 14, 15.5, 16.5 and at scan [18-21.5] years), participants were asked "Have you ever tried cannabis (also called marijuana, hash, dope, pot, skunk, puff, grass, draw, ganja, spliff, joints, smoke, weed)?". Those who had answered "Yes" were then asked additional questions, including one about the number of times they have used or taken cannabis in total (lifetime). The latter question was asked at age 16.5; to answer it, participants were offered the following options: <5, 5-20, 21-60, 61-100, >100 occasions of cannabis use in lifetime. Given the low frequency of the last two options (i.e., 61-100 and >100), for the purpose of our analyses we grouped these two categories together under ≥61 occasions.

T1-weighted images were acquired on a General Electric 3.0-T magnet (General Electric Medical Systems, Milwaukee, WI) using the following parameters: 3D fast spoiled gradient echo scan with 180 oblique-axial slices, 1-mm isotropic resolution, TR-7.9 ms, TE=3.0 ms, TI=450ms and flip angle=20°.

All participants were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, USA. Quality control steps consisted in removing samples with incorrect sex assignment, minimal or excessive heterozygosity, high levels of individual missingness, cryptic relatedness and non-European ancestry (evidenced from principal component analysis). SNPs with minor allele frequencies less than 1% and call rate >95% were removed and SNPs that did not pass an exact test of Hardy-Weinberg equilibrium at P <

$5x10^{-7}$ were ignored. Imputation was carried with SHAPEIT[3] and IMPUTE2[4] using the 1KG Project[2] as reference set.

IMAGEN: Recruitment, Cannabis Assessment, MRI and Genotyping

Between 2007 and 2011, the IMAGEN consortium has recruited and assessed over 2,000 adolescents through local high schools in eight European cities across four countries: France (Paris), Germany (Mannheim, Hamburg, Dresden and Berlin), Ireland (Dublin) and United Kingdom (London and Nottingham). Exclusion criteria included events likely to affect normal brain development, such as premature birth, personal history of serious medical, neurological and/or psychiatric conditions, and low general intelligence (IQ <70)[8]. This sample was assessed at Time 1 (~ 14 years of age) with the full protocol, as described elsewhere[9]. A follow-up of the sample with an identical protocol is under way (Time 2; ~ 19 years of age). In between the two time-points (~ 16 years of age), all participants have been contacted and asked to answer a series of questions about substance use using a web-based questionnaire (see below). As of December 2014, we have acquired full dataset from the two on-site visits (Time 1 and Time 2) for 426 participants. Given the availability of cannabis self-reports (at 16 years of age), and following quality control of MR and genetic data, a total of 333 participants were included in the analysis of the relationship between cannabis use, cortical thickness and genetic risk of schizophrenia (145 males: 174±5 (Time 1), 198±5 (Cannabis follow-up) and 228±7 (Time 2) months of age; 188 females, 174±5 (Time 1), 198±7 (Cannabis follow-up) and 228±6 (Time 2) months of age). There were no differences in age ($p = 0.31$) or variance of age between the sexes ($p=0.45$, Kolmogorov-Smirnov test). Local ethics boards approved the study protocol; the parents and adolescents provided written informed consent and assent, respectively.

Lifetime exposures to cannabis and other illicit substances were obtained through self-reports using a questionnaire adapted from the European School Survey Project on Alcohol and Other Drugs (ESPAD). Cannabis use and its frequency have been captured using the following two questions. First, participants were asked “Have you ever used marijuana (grass, pot) or hashish (hash, hash oil)?” If they answered “Yes”, they were also asked a number of other questions including “On how many occasions IN YOUR WHOLE LIFETIME have you used marijuana (grass, pot) or hashish (hash, hash oil)?”; to answer it, the following options were provided: 0, 1-2, 3-5, 6-9, 10-19, 20-39 and 40 or more occasions. To make the lower ranges comparable to those used in ALSPAC (see above), we grouped together 3-5, 6-9 and 10-19 occasions into a “3-19 occasions” cell (ALSPAC: 5-19). Furthermore, given the low number of adolescents reporting the use of cannabis at 20-39 and 40 or more occasions, we grouped these two cells into a single one, namely “20 or more occasions”. Thus, participants we classified into the following four groups, based on their lifetime use of cannabis by age 16: “never users” and “users”, the latter having had used cannabis on “1-2”, “3-19” or “20 or more” occasions. Cannabis use rates were not different between the sexes ($p=0.47$).

T1-weighted images were acquired on 3 Tesla scanners from four different manufacturers (Siemens: 4 sites, Philips: 2 sites, General Electric: 1 site, and Bruker: 1 site) using 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence based on the ADNI-1 protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/), with voxel size set to 1.1x1.1x1.1 mm.

All adolescents were genotyped with the Illumina Human610-Quad Beadchip or Illumina Human660-Quad Beadchip in three batches. For all three batches, a PCA approach was used to identify (and exclude) individuals with non-European ancestry[10]. SNPs with call rates >95%, minor allele frequencies less than 5% and SNPs that did not pass an exact test of Hardy-Weinberg equilibrium at $P < 5x10^{-4}$ were excluded. Following these quality-control procedures, 477,218 SNPs were used, in turn, for imputations using a reference file created by the ENIGMA2 Genetics Support Team (same as for the SYS imputations described above). Haplotype phasing and imputation was performed using, respectively, Mach1 and Minimac codes from the MaCH software suit[11], as specified in the ENIGMA2 protocol (http://enigma.ini.usc.edu/wp-content/uploads/2012/07/ENIGMA2_1KGP_cookbook_v3.pdf).

Allen Brain Atlas

Gene-expression data were obtained postmortem in human brains and made available through the Allen Human Brain Atlas (Allen Institute for Brain Science; http://www.brain-map.org/)[12]. This atlas provides anatomically comprehensive coverage of the normal adult brain (3,702 samples). Expression data from left hemispheres of six donors were extracted for all cortical regions (age: 24-57 years, 1 female); data from the right hemisphere were available only in 2/6 donors. Based on blood samples acquired after death, all donors were free of drugs prescribed for psychiatric disorders.

Expression of *CNR1* gene was obtained by averaging the 89 relevant probes on the expression arrays. Spatially, we mapped 1,697 of the 1,950 cortical expression profiles to the cortical parcellations defined by the Desikan-Killiany atlas of the human cerebral cortex[13]; the unmapped samples are primarily in the hippocampus, which is not included in the Desikan-Killiany atlas. In the left hemisphere, 1,269 mapped samples remained after the mapping. First, we performed an automatic mapping through which expression samples were assigned to Desikan-Killiany cortical regions based on the sample's MNI coordinates (within one voxel). These assignments were reviewed manually for their accuracy. For samples that were not assigned a Desikan-Killiany region through the automatic procedure, we completed assignments following anatomic annotations provided by the Allen Institute.

We averaged expression values from the mapped samples to provide a single *CNR1* expression value for each of the 34 Desikan-Killiany regions in the left hemisphere. Within an individual brain and Desikan-Killiany region, we calculated the median values. Across individual brains, we used the median expression value to provide the final expression value for that region. The number of donors assayed per Desikan-Killiany region varied slightly; data from all six donors were used for 28 of the 34 regions.

We note that CNR1 expression in the human cerebral cortex does not differ between adults of similar age of the Allen Brain Atlas donors (age 23 to 40 years) and adolescents (12-21 years old). We examined CNR1 expression levels in three postmortem datasets and observed no differences in CNR1 expression between these two age ranges (BrainSpan: 12 cortical regions [brainspan.org], 12 brains; BrainCloud: 152 prefrontal cortex samples[14]; and Braineac: 3 cerebral lobes, 57 brains[15]).

Analysis of magnetic resonance images

For all participants in all three samples, we extracted cortical thickness using FreeSurfer, a set of automated tools for the reconstruction of the cortical surface[16]. Version 5.0.0

was used for the SYS and IMAGEN cohorts and 5.3.0 was used for the ALSPAC cohort. For every MR image, FreeSurfer segments the cerebral cortex, the white matter, and other subcortical structures, and then computes meshes with ≈160,000 triangles that recover the geometry and the topology of the pial surface and the gray/white interface of the left and right hemispheres. The local cortical thickness is measured as a distance between the position of homologous vertices in the pial and gray/white surfaces. A correspondence between the cortical surfaces across participants is established using a nonlinear alignment of the principal sulci in each participant's brain with an average brain[13].

For each participant and time point, we calculated the average cortical thickness as the mean of the average cortical thickness of the left and right hemispheres, as provided by FreeSurfer. In addition, we used regional values of cortical thickness computed by FreeSurfer for the 34 Desikan-Killiany regions in each hemisphere. In SYS and ALSPAC, the average and regional values of cortical thickness served as outcomes. In IMAGEN, we calculated a difference in these values between Time 2 and Time 1 and used this difference as the outcome measure. We adjusted these thickness differences by scanner manufacturer (Siemens, Philips and General Electric), separately for males and females.

Polygenic Risk Score

Risk scores for the 108 schizophrenia-associated loci were obtained from a large genome-wide association study (GWAS) by the Schizophrenia Working Group of the Psychiatric Genomics Consortium; 36,989 patients with schizophrenia and 113,075 controls were compared in this GWAS[17]. We used the 114 single nucleotide polymorphisms (SNPs) and corresponding odds ratios (ratios from discovery and replication cohorts combined) as reported in Table S2 of this report[17]. Odds ratios for the 24,834 SNPs with $p<0.05$ in the GWAS were obtained from the scz2.prs.txt.gz file provided by the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/downloads). In all three samples (SYS, ALSPAC. IMAGEN), for each SNP and individual we calculated the risk score by multiplying the natural log of the odds ratio by the frequency of the reference or maker allele. These values were then summed across SNP's to provide an individual score. Missing genotype values were ignored at an individual level (due to uncertain imputation probability or non imputed SNPs); most genotype values were available. In SYS, for example, 111 SNPs were in the imputed dataset with 98% of the individuals having non-missing genotypes for at least 100 SNPs.

Statistical Analysis

All statistical analysis was performed with JMP (version 10.0; SAS Institute Inc). Effect sizes were calculated using R software, version 3.1.2.[18]

eResults. Results of Additional Analyses Performed in the SYS and IMAGEN Samples

In SYS there was no difference in risk scores between males and females (p=0.95). In IMAGEN there was a sex difference in the risk score (p = 0.016), with males having slightly higher risk scores than females (p = 0.016, males: -0.32±0.55, females: -0.47±0.55). We did not observe relationships between risk score and cannabis use in any of the three samples (SYS: p > 0.7, t-test, males or females; ALSPAC: Spearman correlation = 0.1, p=0.099; IMAGEN: Spearman correlation < 0.052, p > 0.3, males or females).

Saguenay Youth Study:

We have re-analyzed the SYS data using the median-based groups (Figure 2A). As expected, in males, we observed an interaction between Cannabis use (Never/Ever) and the Risk Score (High/Low) on age-adjusted cortical thickness (t(455)=-2.97, p=0.003). In female adolescents (n=490), neither the interaction (t(486)=-0.34, p=0.7) nor the main effects of Cannabis use (t(486)= 0.17, p=0.9) or the Risk score (t(486)=-0.92, p=0.4) were significant (full model R^2=0.004, p=0.56). Following up the significant Cannabis-Risk Score interaction in male adolescents, we have tested for differences between "ever users" and "never users" in age-adjusted cortical thickness separately in the Low Risk (t(224)=-0.47, p=0.7) and High Risk (t(231)=3.77, p=0.0002) groups; these results are depicted in Figure 2A. Effect size (Cohen's *d*) of the difference between "ever users" and "never users" are: High Risk group: *d*=0.53; Low Risk group: *d*=0.067.

Cannabis use, risk score and their interaction do not predict differences in cortical thickness in the subset of 139 males older than 16 years old. In this subset, we found no difference in age-adjusted cortical thickness between "ever users" and "never users" in either Low Risk (t(68)=1.1, p=0.26, *d*=0.27) or High Risk (t(64)=0.90, p=0.36, *d*=0.22) groups. In female adolescents (n=490), neither the interaction (t(486)=-1.1, p=0.28) nor the main effects of Cannabis use (t(486)=-0.25, p=0.8) or the Risk score (t(486)=-0.93, p=0.4) were significant. Similar results are observed in median-based group analyses (eFigure 1). Nonetheless, as shown in Figure 1C, age-adjusted cortical thickness decreases as a function of risk score slightly in (female) cannabis users (R^2=0.02, p=0.045) but not in non-users (R^2=0.00, p=0.4). We also tested risk scores based on 24,384 SNPs that reached nominal significance in a meta-analysis reported by the Psychiatric Genomics Consortium (p < 0.05, uncorrected). This score correlates weakly with the score based on the 108 top loci (females: r = 0.23; males: r=0.16). We observed no interactions between this score and Cannabis use on age-adjusted cortical thickness in males or females (R^2 < 0.02, p > 0.15).

Finally, we performed a post-hoc vertex-wise analysis in SYS males to determine whether the observed interaction between Cannabis use and Risk Score in global cortical thickness has any local maxima; this is not the case when using corrections based on False Discovery Rate (eTable 3).

IMAGEN

As shown in Figure 2C, in the High Risk group (males) we observed differences in the adjusted change of cortical thickness between "never users" and "most-frequent users" (i.e., ≥20 occasions), with a difference of 0.078 (Lower Confidence Limit=0.005, Upper Confidence Limit=0.15, p=0.037, *d*=0.85). We also observed a similar difference between "never users" and "medium users" (3-19 occasions), with a difference of 0.073

(Lower Confidence Limit=0.004, Upper Confidence Limit=0.14, p=0.036, *d*=0.76). If we collapse the three levels of cannabis users into a grouping of “ever users”, we also observe a difference in comparison to “never users” (Lower Confidence Limit=0.010, Upper Confidence Limit=0.10, p=0.016, *d*=0.60). Such cannabis-related differences in the adjusted change of cortical thickness over time were observed neither in the Low Risk male adolescents (p=0.26, *d*=0.36) nor in female adolescents (Low Risk group: p=0.38, *d*=0.21; High Risk group: p=0.41, *d*=0.21, Figure S1).

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eFigure. Dot Plots Showing the Mean Cortical Thickness for Different Groups of Cannabis Users in High- and Low-Risk females in SYS and IMAGEN Samples

Thickness values are binned and stacked horizontally within each grouping. Age-adjusted cortical thickness is presented for SYS (A). For IMAGEN (B), change in cortical thickness (Time 2 minus Time 1) is displayed. Mean thickness values are marked with solid bars.