Supplementary Text

Cohort description

ABCD

Data for this study comes from the ABCD-Genetic Enrichment (ABCD-GE) study, a sub-study of 1 192 ethnic Dutch children. Approval of the study was obtained from the Central Committee on Research Involving Human Subjects in the Netherlands, the medical ethics review committees of the participating hospitals, and the Registration Committee of the Municipality of Amsterdam and written consent was obtained from participating parents and children of the phenotypes. Regarding the DNA collection and analysis, an opt-out procedure was used (METC approval 2002_039#B2013531).

ALSPAC

Data for this study were obtained for children of the ALSPAC study, a UK population-based longitudinal pregnancy-ascertained birth cohort (estimated birth date: 1991-1992)[1, 2]. Ethical approval was obtained from the ALSPAC Law-and-Ethics Committee (IRB00003312) and the Local Research-Ethics Committees. Written informed consent was obtained from a parent or individual with parental responsibility and assent (and for older children consent) was obtained from the child participants. The study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

BREATHE

Participants were drawn from the BREATHE project (European Commission: FP7-ERC-2010-AdG, ID 268479), a population-based cohort of primary schoolchildren designed to analyze the association between air pollution and behavior, cognitive function and brain morphology [3]. A total of 2 897

children aged 7 to 11 years accepted the invitation and participated in the project. Genotype data were available for 1 667 children of European ethnic origin.

All parents or legal guardians gave written informed consent, and the study was approved by the IMIM-Parc de Salut Mar Research Ethics Committee (No. 2010/41221/I), Barcelona, Spain; and the FP7-ERC-2010-AdG Ethics Review Committee (268479-22022011).

CATSS

The Child and Adolescent Twin Study in Sweden (CATSS) is an ongoing longitudinal twin study targeting all twins born in Sweden since July 1, 1992 [4, 5]. Parents of twins are interviewed regarding the children's somatic and mental health and social environment in connection with their 9th or 12th birthdays and followed up over time. The response rate was 75%. Follow-ups were conducted when the twins were 15 years of age (response rate, 61%) and 18 years of age (response rate, 59%). All responding parents, legal guardians or twins provided informed consent; digitally, written or by participation, to the study, and all data were deidentified. This study received ethical approval from the Karolinska Institutet Ethical Review Board. DNA samples (from saliva) were obtained from the participants at study enrollment, see Brikell *et al* [6]. A total of 11 081 samples passed quality control assessment; MZ twins were then imputed, resulting in 13 576 samples and 6 981 993 imputed SNPs that passed all quality control assessments.

CHDS

The New Zealand arm of the Gene-Environment-Development Initiative (GEDI) utilized data from the Christchurch Health and Development Study, a longitudinal study of the life course development of a birth cohort of 1 265 children born in the Christchurch (New Zealand) urban region in mid-1977 [7–10].

For this analysis phenotypic data on childhood aggression/ODD gathered via parental and self-report were combined with gene chip data for a sample of 626 participants of European ancestry.

COGA

The Collaborative Studies on the Genetics of Alcoholism (COGA) is an eleven-center research project in the United States designed to identify and understand the genetic basis of alcoholism. Research is conducted at University of Connecticut, Indiana University, University of Iowa, SUNY Downstate Medical Center at Brooklyn, Washington University in St. Louis, University of California at San Diego, Rutgers University, University of Texas Health Science Center at San Antonio, Virginia Commonwealth University, Icahn School of Medicine at Mount Sinai, and Howard University.

COGA investigators have collected data on more than 2 255 extended families in which many members are affected by alcoholism. The researchers collected extensive clinical, neuropsychological, electrophysiological, biochemical, and genetic data on the more than 17 702 individuals who are represented in the database. The researchers also have established a repository of cell lines from these individuals to serve as a permanent source of DNA for genetic studies.

COPSAC

The Copenhagen Prospective Studies on Asthma in Childhood is a clinical study with multiple cohorts (COPSAC2000 and COPAC2010). The COPSAC2010 cohort is a population based prospective mother-child cohort comprising 700 children born to unselected mothers (during 2009-10) from Zealland, Denmark. The cohort was enrolled at age 1 week and attended the research clinic for clinical examinations at ages 1, 3, 6, 9, 12, 18, 24, 30 and 36 month and yearly hereafter till age 8 years. The Ethics Committee for Copenhagen and the Danish Data Protection Agency approved this study. This has been described

elsewhere [11]. The GWAS was run in the COPSAC 2010 birth cohort (n=459) where the phenotypes were extracted from the Strengths and Difficulty Questionnaire (SDQ) at the 8 years visit.

Dunedin Study

Participants were members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a representative birth cohort [12]. Study members (n = 1 037; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible for the longitudinal study based on residence in the province at 3 years of age and who participated in the first follow-up assessment at 3 years of age. The cohort represented the full range of socioeconomic status on NZ's South Island. On adult health, the cohort matches the NZ National Health and Nutrition Survey (e.g., BMI, smoking, GP visits)[12]. Cohort members are primarily white; approximately 7% self-identify as having partial non-Caucasian ancestry, matching the South Island. Assessments were carried out at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years, when 95% of the 1 007 study members still alive took part. The Dunedin Study was approved by the NZ-HDEC (Health and Disability Ethics Committee) and informed consent was obtained from all study members.

E-Risk

Participants were members of E-Risk, which tracks the development of a 1994-95 birth cohort of 2,232 British children [13]. Briefly, the E-Risk sample was constructed in 1999-2000, when 1,116 families (93% of those eligible) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprised 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs; sex was evenly distributed within zygosity (49% male). The study sample represents the full range of socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighborhood-level socioeconomic index (ACORN [A

Classification of Residential Neighborhoods], developed by CACI Inc. for commercial use): 25.6% of E-Risk families live in “wealthy achiever” neighborhoods compared to 25.3% nationwide; 5.3% vs. 11.6% live in “urban prosperity” neighborhoods; 29.6% vs. 26.9% in “comfortably off” neighborhoods; 13.4% vs. 13.9% in “moderate means” neighborhoods; and 26.1% vs. 20.7% in “hard-pressed” neighborhoods. E-Risk underrepresents “urban prosperity” neighborhoods because such households are often childless. Home visits were conducted when participants were aged 5, 7, 10, 12 and most recently, 18 years (93% participation). The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed written consent and twins gave written assent between 5-12 years and then informed written consent at age 18.

At age 18, 2 066 participants were assessed, each twin by a different interviewer. The average age at the time of assessment was 18.4 years (SD = 0.36); all interviews were conducted after the 18th birthday.

FinnTwin12

FinnTwin12 is a population-based cohort of Finnish twins born 1983–1987 that was established to track health and behavioral habits [14–16]. Identified through the Finnish Central Population Registry, families with twins were contacted and initially enrolled when the twins were 11–12 years old (N=5600 twins; 87% response rate). Questionnaires were collected from multiple informants over time: from the twins themselves at ages 12, 14, and 17; from parents at age 12; and from teachers at ages 12 and 14. DNA samples (from blood or saliva) for genotyping were taken in young adulthood (mean age 22 yrs), for which written informed consent was obtained. Study protocols were approved by the local ethics committee in Helsinki, and the IRB of Indiana University (Bloomington).

Generation R Study

The Generation R Study is a prospective cohort study from fetal life onwards that included pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 (n = 9,778). The main aim of this study is to identify early environmental and genetic factors that affect growth, health and development [17]. The Generation R Study is multidisciplinary and both prenatal and postnatal measures have included multiple domains of growth, health and development. Rotterdam is an ethnically diverse city and this is reflected in the Generation R participants. Of the enrolled mothers, 42% was of non-Dutch ethnic background, largely made by mothers from Surinamese (9%), Turkish (7%) and Moroccan (3%) background [17, 18]. Data has been collected in children up until the mean age of 10 years, with current on-going data collection at mean age 13 years. Study protocols were approved by the local ethics committee, and written informed consent and assent was obtained from all parents and children.

GINIplus/LISA

The influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany (LISA) Study is a population-based birth cohort study. A total of 3 094 healthy, full-term neonates were recruited between 1997 and 1999 in Munich, Leipzig, Wesel and Bad Honnef. The participants were not pre-selected based on family history of allergic diseases.

A total of 5 991 mothers and their newborns were recruited into the German Infant study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) between September 1995 and June 1998 in Munich and Wesel. Infants with at least one allergic parent and/or sibling were allocated to the interventional study arm investigating the effect of different hydrolysed formulas for allergy prevention in the first year of life. All children without a family history of allergic diseases and children whose parents did not give consent for the intervention were allocated to the non-interventional arm. Detailed descriptions of the LISA and GINIplus studies have been

published elsewhere [19, 20]. DNA was collected at the age 6 and 10 years. During the 10- and 15-year follow-ups, information on aggressive behavior was collected based on the conduct problems subscale from the strength and difficulties (SDQ) questionnaire. At 10 years, the questionnaire was administered to the parents and at 15 years, to the participants themselves. For both studies, approval by the local Ethics Committees and written consent from participants and their families were obtained.

GSMS

The Great Smoky Mountains Study is a longitudinal, representative study of 1 420 children in 11 predominantly rural counties in Southeastern United States [21, 22]. Annual assessments on psychopathology and associated factors were completed on the 1 420 children until age 16 (6 674 observations of 1 420 individuals; 1993 to 2000) and then again at ages 19, 21, 25, and 30 (4 556 observations of 1 336 participants; 1999 to 2015) for a total of 11,230 total assessments.

IBG

Two cohort studies supplied information for this project: The Colorado Adoption Project (http://ibgwww.colorado.edu/cap/) and the Colorado Twin Registry (https://www.colorado.edu/ibg/research/human-research-studies/colorado-twin-registry). [23–25]

INMA

The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project is a network of birth cohorts in Spain that aim to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development (http://www.proyectoinma.org/) [26]. The study has been approved by Ethical Committee of each

participating centre and written consent was obtained from participating parents. Data for this study comes from INMA Sabadell subcohort.

The study was approved by the Ethical Committee of the Municipal Institute of Medical Investigation and by the Ethical Committee of the hospitals involved in the study. The pregnant women received information of the study both written and orally. Their informed consent of the participants was asked in each of the visits.

INSchool

The INSchool cohort consist of 3, 557 children from 23 schools in Catalonia (age range: 5-17 years; mean age: 9.8 years, s.d.=2.9). 57.5% of the participants (n=2 046) were males. Screening included the Achenbach System of Empirically Based Assessment (ASEBA) with the Child Behavior Checklist CBCL/4-18 (completed by parents or surrogates), the Teacher Report Form TRF/5-18 (completed by teachers and other school staff) and the Youth Self-Report YSR/11-18 (completed by youths); the Strengths and Difficulties Questionnaire (SDQ) and the Conner's ADHD Rating Scales (Parents and Teachers). The study was approved by the Clinical Research Ethics Committee (CREC) of Hospital Universitari Vall d'Hebron, all methods were performed in accordance to the relevant guidelines and regulations and written informed consent was obtained from participant parents before inclusion into the study.

MCTFR

Data for this study come from the Minnesota Center for Twin and Family Research (MCTFR), and consists of three cohorts of same-sex twins from the birth years 1971-91, 1977-85 [27], and 1988-94 [28]. Approval for all studies was obtained through the University of Minnesota Institutional Review Board.

MOBA

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [29]. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114.500 children, 95.200 mothers and 75.200 fathers. The current study is based on version 11 of the quality-assured data files released for research on ADHD. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is based on regulations based on the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (number 2016/1702).

MSUTR

Data for this study comes from the Michigan State University Twin Registry (MSUTR), a large, population-based twin registry comprised of thousands of twins throughout Michigan, aged 3-55 (current N~31 300) [30]. The overall focus of the MSUTR is on understanding developmental changes in genetic, environmental, and neurobiological influences on internalizing and externalizing disorders. Recruitment for the MSUTR is ongoing via the identification of birth records through the Michigan Department of Health and Human Services (MDHHS). Because birth records are confidential in Michigan, recruitment packets are mailed directly from MDHHS to eligible twin pairs. Twins indicating interest in participation via pre-stamped postcards or e-mails/calls to the MSUTR project office are then contacted by study staff to determine study eligibility and to schedule their assessments. Participants in the registry complete a family health and demographic questionnaire via mail. Families are then recruited for one or more of the intensive, in-person studies based on their answers to relevant items in the registry questionnaire. In-person assessments target a variety of biological, genetic, and environmental phenotypes, including

multi-informant measures of psychiatric and behavioral phenotypes, census and neighborhood informant reports of twin neighborhood characteristics, buccal swab and salivary DNA samples, assays of adolescent and adult steroid hormone levels, and/or videotaped interactions of child twin families. Approval for all studies was obtained through the Michigan State University Institutional Review Board and the Michigan Department of Health and Human Services Institutional Review Board. All methods were performed in accordance to relevant guidelines and regulations.

MUSP

This study is of 7 223 women recruited early in pregnancy over the period 1981-1983 and the live singleton children to whom they subsequently gave birth. There were follow-up of the mothers at 5, 14, 21 and 27 years after recruitment. Children were also followed-up in the mothers' questionnaire and independently at 21 and 30 years of age. The CBCL and YSR were administered to children at 5, 14 and 21 years of age. The CIDI was administered to mothers at 27 years after recruitment and the children at 21 and 30 years after recruitment. The cohort comprises both mothers (to 27 years after the birth) and children (to 30 years of age). Three papers describing the recruitment methodology and sample details have been published [31–33].

NFBC1986

Northern Finland Birth Cohort 1986 (NFBC1986) is a prospective longitudinal birth cohort which included pregnant women with expected date of delivery between July 1985 and June 1986 in the two Northern most provinces of Finland. In total, 9 432 children were live-born in the cohort [34]. At approximately age 16 years, the cohort members were asked to complete a postal questionnaire, including the Youth Self-Report (YSR). Items on aggression are used here. At age 16 years blood samples taken for DNA extraction for 6 266 adolescents attending the clinical examination. All participants and their parents provided

consent to use their data and received Institutional Review Board approval by University of Oulu, and the Ethics committee of the Ostrobotnia Hospital district.

More information may be found at: http://www.oulu.fi/nfbc.

NTR

The Netherlands Twin Register (NTR) is a population-based prospective cohort study which includes newborn twins and multiples from the Netherlands. Recruitment started with birth year 1986 [35]. NTR data collection has a focus on growth, development, emotional and behavioral problems and health. Phenotype data on aggression were collected by surveys, in which parents and teachers were asked to rate their offspring / pupils' behavior using standardized instruments [36, 37]. At age 14 years and after, twins and their siblings were asked for self-assessments [38]. Buccal cells and blood for DNA isolation were collected in multiple sub-projects [39]. See: http://www.tweelingenregister.org/ for more information. The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Centre, Amsterdam, an Institutional Review Board certified by the U.S. Office of Human Research Protections (IRB number IRB00002991 under Federal-wide Assurance-FWA00017598; IRB/institute codes, NTR 03-180).

QIMR

The QIMR *Retrospective DSM III Conduct Disorder* contribution draws on data from a number of studies (phenotypic and genotypic) undertaken from the 1980s onward by the Genetic Epidemiology group at QIMR (QIMR Berghofer Medical Research Institute or QIMRB), with recruitment predominantly from families with adult twins who registered for research purposes with the Australian Twin Registry (https://www.twins.org.au) [40–42]. Phenotype data were self-report, with study overlap resolved by using the questionnaire completed at the youngest age. The largest contributions were from (1) SS1, an

interview study of adult twins born before 1964 using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) instrument (N=4 046 twins used, conducted 1993-1995) and SP, a follow-up of their spouses (N=584, conducted 1998-1999); (2) Twin-89, an interview study on personality and drinking habits of the twins born 1964-1972 (N=2 040, conducted 1996-2000); (3) the NIH-funded Nicotine Addiction Genetics (NAG) and three Interactive *Research* Project Grant (IRPG) interview studies (N=4 017, from both cohorts, conducted 2003-2005). Closely similar or identical questions approximating the items in the DSM-III CD diagnosis (testing aggressive and highly anti-social behavior), were scored for all studies and combined into a 14 or 15-item symptom score, rescaled by 15/14 if there were 14 items.

TCHAD

The twin study of Child and Adolescent Development (TCHAD) followed 1 500 twin pairs from age 8 to age 26 [5]. The genotyping followed the same procedure as for CATSS; see Brikell *et al* [6].

The Raine Study

The Raine Study is a prospective pregnancy cohort where 2 900 mothers (Gen1) where recruited between 1989 and 1991 [43, 44]. Recruitment took place at Western Australia's major perinatal centre, King Edward Memorial Hospital, and nearby private practices. Women who had sufficient English language skills, an expectation to deliver at King Edward Memorial Hospital, and an intention to reside in Western Australia to allow for future follow-up of their child (Gen2) were eligible for the study.
The Raine Study is known to be one of the largest successfully prospective cohorts richly phenotyped at multiple time points over pregnancy, infancy, childhood adolescence, and young adult. The mothers (Gen1) completed questionnaires regarding their children (Gen2) and the children (Gen2) had physical examinations at ages 1, 2, 3, 6, 8, 10, 14, 17, 20 and 22 years.

TEDS

The Twins Early Development Study (TEDS) is a longitudinal twin study that recruited over 16 000 twin pairs born between 1994 and 1996 in England and Wales through national birth records [45]. More than 10 000 of these families are still involved in study. TEDS was and still is a representative sample of the population in England and Wales. Rich cognitive and behavioural data have been collected from the twins from infancy to emerging adulthood with data collection at ages 2, 3, 4, 7, 8, 9, 10, 12, 14, 16, 18, 19 and 21, enabling longitudinal genetically sensitive study designs. Data have been collected from twins themselves (including extensive web-based cognitive testing), from their parents and teachers, and from the UK National Pupil Database. Genotyped DNA data are available for 10 346 individuals (who are unrelated except for 3 320 dizygotic co-twins). TEDS data have contributed to over 400 scientific papers involving more than 140 researchers in 50 research institutions.

TRAILS

Tracking Adolescents' Individual Lives Survey (TRAILS) is a large prospective population study of Dutch adolescents with bi- or triennial measurements from age 11 years onwards. TRAILS participants were selected from five municipalities in the Northern part of the Netherlands [46]. The cohort's characteristics and database are described in detail elsewhere [47] and at http://www/trails.nl/. DNA was extracted from blood samples or (in a few cases) buccal swaps, collected at about age 16. In total, 1 491 children of white European descent were genotyped. The study was approved by the Dutch Central Committee on Research Involving Human subjects (CCMO), and all measurements were carried out with participants' adequate understanding and written consent.

VTSABD

The VCU arm of the NIDA-funded Gene-Environment-Development Initiative (GEDI) combined existing phenotypic and environmental data from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) study, a population-based multi-wave, cohort-sequential twin study of adolescent psychopathology and its risk factors, with genome-wide genotyping, generating a genotyped sample of ~900 subjects [10, 48–51].

YFS

The Young Finns study (YFS) is an on-going longitudinal population-based cohort study that includes 3 596 healthy Finnish children and adolescents from six birth cohorts (aged 3, 6, 9, 12, 15, and 18 years at the study baseline in 1980)[52, 53]. The study was approved by the ethical committee of the Varsinais-Suomi's hospital district's federation of municipalities. For the current study, we selected a subsample of 1 784 participants from the five oldest age groups (aged 6, 9, 12, 15, and 18 at baseline) who had parent-reported aggressive behavior data and genetic data available.

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ABCD

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CATSS

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CHDS (GEDI)

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COGA

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COPSAC

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Dunedin

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FinnTwin12

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Generation R Study

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GINIplus/LISA

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GSMS (GEDI)

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IBG

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INMA

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Supplementary Methods

Sample description

Cohorts with assessment of AGG in children and adolescents aged 1.5 - 18 years – and adult retrospective assessment of adolescent CD – with genotyping, that collaborate within the ACTION (Aggression in Children: unraveling gene-environment interplay to inform Treatment and InterventiON strategies) (54, 55) and the EAGLE (EArly Genetics and Lifecourse Epidemiology; Middeldorp et al. 2019) consortia and additional childhood cohorts took part in the meta-analysis. Each cohort received a standard operation protocol (https://www.action-euproject.eu/content/data-protocols). Cohorts could contribute one or multiple GWASs for AGG, for every combination of rater, instrument, and age. For more information on the cohorts see Supplementary Table 1 and Supplementary Text. As limited data was available on individuals of non-European ancestry and to avoid inducing population stratification, we restricted the analysis to individuals of European ancestry. In total, 29 cohorts contributed 164 GWASs, resulting in a total of 328 935 observations on 87 485 unique individuals (Supplementary Table 2).

Measurement of Aggressive Behavior

AGG was rated by mothers, fathers, teachers, and by self-report. GWASs where no distinction was made between mother or father report were included with mother-reported data. In total, the meta-analysis included AGG assessed with 26 instruments (see Supplementary Table 3). The instruments covered various childhood behaviors and disorders with an aggressive component (e.g. conduct disorder and oppositional defiant disorder). Items included content such as “hot tempers” and “gets in many fights”. For all instruments and raters, AGG was assessed on a continuous scale, with higher scores indicating higher levels of AGG. The most commonly employed instruments came from the Achenbach System of Empirically Based Assessment (ASEBA; 41%; Achenbach et al. 2017) and the Strengths and Difficulties Questionnaire (SDQ; 34%; Goodman 2001).

Genotyping and quality control

Genotyping was performed within each cohort on common genotyping arrays (see Supplementary Table 4), followed by cohort-specific quality control based on variant- and individual-based call rate, minor allele frequency, Hardy-Weinberg equilibrium, and excessive heterozygosity (see Supplementary Table 5). Cohorts removed samples with non-European ancestry or mismatched sex. The most commonly used genotyping array across cohorts were the Illumina 660K, Illumina 670K, and Affymetrix 6.0 arrays. Cohorts were asked to use genotypes imputed to the 1000 Genomes (1000G) reference set, mapped to build 37 of the human Genome Reference Consortium assembly (GRCh37). 75.9% of the cohorts used 1000G phase 3 version 5 as reference set for the imputation, while the remaining ones imputed to 1000G phase 1 version 3 (see Supplementary Table 6).

GWAS model

For all cohorts, local analysts performed univariate GWASs where AGG was regressed on the SNP with sex, age, and first five ancestry-based principal components as covariates, and, if necessary, cohort-specific covariates (see Supplementary Table 7). GWASs included autosomal SNPs. Cohorts with a sample that included only unrelated subjects applied a linear regression model. To correct for non-independence of observations, cohorts with a sample containing related individuals applied a mixed linear model. Alternatively, cohorts with a sample containing related individuals could apply a sandwich correction of the standard errors [59].

Genome-wide association analyses were stratified by (1) rater, (2) instrument, and (3) age, selecting strata such that every stratum contained at least 450 observations. In total, summary statistics for 164 GWASs analyses were uploaded. Descriptive statistics for each uploaded GWAS are shown in Supplementary Table 8. Each cohort supplied the phenotypic correlations (Supplementary Table 10) between the AGG measures within the different strata and the degree of sample overlap between strata

(Supplementary Table 11). These statistics allowed us to account for dependence within cohort (see "Meta-analysis method").

Pre-GWAMA QC

Each uploaded file underwent QC using the EasyQC software package [60]. SNPs with a genotyping rate below 95% were removed. Additionally, based on the sample size of the GWAS, we applied variable QC filter on MAF and HWE *p*-value (see Supplementary Figure 1). A high-pass cutoff of 0.6 and 0.7 was applied to SNPs that were imputed using MACH and IMPUTE, respectively [61]. Reported allele frequencies were compared with an imputation-matched reference file (see URLs) and variants with an absolute difference larger than 0.2 were removed. Supplementary Table 9 reports the number of remaining SNPs before and after QC.

Meta-analysis method

Within cohort, the measures of AGG may be dependent as a result of including repeated measures and/or AGG as assessed by multiple raters. Any covariance between test statistics within cohort and across GWASs is therefore a sum of (1) a truly shared genetic signal and (2) sample overlap [62]:

$$E\left[Z_{ji}Z_{jk}|\ell_j\right] = \frac{\sqrt{N_{ji}N_{jk}}\varrho_g}{M}\ell_j + \frac{N_s r_p}{\sqrt{N_{ji}N_{jk}}}$$

Note, this function is a sum of two elements: the truly shared genetic effect on the left side of the plus sign and the cross-trait-intercept (CTI) on the right side. The CTI reflects the expected dependence between two GWASs that arises from sample overlap and phenotypic correlation. Here Z_{ji} and Z_{jk} are the Z-scores for SNP j in GWASs i and k, respectively; $\ell_j = \sum_l r_{jl}^2$ is the so-called "LD Score" of SNP j, which measures the amount of genetic variation tagged by j; N_{ji} and N_{jk} represent the sample sizes; ϱ_g is the genetic covariance between the traits analyzed in i and k; M stands for the number of overlapping

SNPs; N_s indicates the number of individuals that participated in both i and k; and r_p is the phenotypic correlation between i and k. The CTI between i and k is then:

$$CTI_{ik} = \frac{N_s r_p}{\sqrt{N_{ji} N_{jk}}}$$

To account for the effect of sample overlap, we applied a modified version of the multivariate meta-analysis approach developed by Baselmans *et al* (2019): instead of estimating the CTI using Linkage Disequilibrium SCore regression (LDSC; Bulik-Sullivan et al. 2015b, a), we calculated the expected CTI using the observed sample overlap and phenotypic covariance as reported by the cohorts. The multivariate test statistics are obtained from:

$$Z_{multi,j} = \frac{\sum_{i=1}^{P} w_{ji} Z_{ji}}{\sqrt{\sum_{i=1}^{P} w_{ji} V_{ji} + \sum_{i=1}^{P} \sum_{k=1}^{P} \sqrt{w_{ji} w_{jk}} CTI_{ik} \; for \; i \neq k}}$$

where P is the number of GWASs across which we run the meta-analysis; $w_{ji} = \sqrt{N_{ji} h^2_{SNP,i}}$ is the weight given to the jth SNP in GWAS i, with $h^2_{SNP,i}$ being the SNP-heritability of the trait analyzed in GWAS i; and $V_{ji} = 1$ represents the variance of the distribution of Z_{ji} under the null hypothesis of no effect. Finally, we approximate the effective sample size (N_{eff}) via:

$$N_{eff} = \sqrt{N}^{T} CTI^{-1} \sqrt{N}$$

where N is an P-sized vector of sample sizes, and CTI is the P x P matrix of cross-trait-intercepts. When there is no sample overlap (or a phenotypic correlation equal to zero) between the GWASs (i.e. CTI is an identity matrix), N_{eff} is equal to the sum of sample sizes.

Creating age-bins for the age-specific GWAMAs

Age-bins for the age-by-rater GWAMAs were created such that the total *univariate* number of observations exceeded 15 000. To do so, the GWAs were sorted on their mean age, from lowest to highest. For the first age-bin, the first GWA was used as starting point. Then, if the next GWA belonged

to another cohort, this was included in the age-bin. If the next GWA belonged to the same cohort, the GWA with the largest sample size was retained in the age-bin. This was repeated until the total univariate N_{obs} exceeded 15 000. Then, the lower bound of the age-bin was set to the mean age of the first GWA, rounded down to the nearest integer and the upper bound of the age-bin was set to the mean age of the last GWA, rounded up to the nearest integer. Finally, all GWAs with a mean age within the boundaries (up to and including the upper bound) were included in the age-by-rater GWAMA. For the next age-bin, the first available GWA was used as the starting point and the process was repeated until all GWAs were divided into age-bins. If the last age-bin contained N_{obs} < 15 000, the last two age-bins were combined.

Calculating polygenic scores

All data were meta-analyzed twice more, once omitting all data from the Netherlands Twin Register (NTR) and once omitting all Australian data (Queensland Institute for Medical Research [QIMR] and Mater-University of Queensland Study of Pregnancy [MUSP]). For the target sample in the NTR we considered mother-reported AGG at age 7 (*N*=4,491), which represents the largest NTR univariate stratum. In the QIMR participants (*N*=10,706), we tested whether our childhood AGG polygenic scores (PGS) predicted adult retrospective assessment of their own CD behavior during adolescence. We allowed for cohort-specific best practice in the polygenic score analysis.

In the NTR, we created 16 sets of PGSs in PLINK1.9 [65], with *P*-value thresholds between 1 and 1.0E-05 (Supplementary Table 13). The remaining SNPs were clumped in PLINK. We applied an r^2-threshold (high-pass) of 0.5 and minimum clumping distance of 250,000 base pair positions [65]. Age; age^2; sex; first five ancestry-based principal components (PCs); a SNP-array variable; and interaction terms between sex and age, and sex and age^2 were defined as fixed effects. To account for relatedness, prediction was performed using generalized equation estimation as implemented in the “gee” package

(version 4.13-19) in R (version 3.5.3)[66]. GEE applies a sandwich correction over the standard errors to account for clustering in the data [67]. To correct for multiple testing, we applied an FDR correction at α=0.05 for 16 tests.

QIMR excluded SNPs with low imputation quality (r^2=0.6) and MAF below 1%, and selected the most significant independent SNPs using PLINK1.9 (criteria linkage disequilibrium r^2=0.1 within windows of 10 Mbp). We calculated PGS for seven *P*-value thresholds (*P*<1.0E-05, *P*<0.001, *P*<0.01, *P*<0.05, *P*<0.1, *P*<0.5, and *P*<1.0) of the GWAS summary statistics. PGS were calculated from the imputed genotype dosages to the 1000 Genomes (Phase 3 Release 5) reference panel. We fitted linear mixed models, which controlled for relatedness using a genetic relatedness matrix (GRM) and covariates sex, age, two dummy variables for the GWAS array used, and the first five genetic PCs. The parameters of the model were estimated using GCTA 1.9 [68]. The linear model was as follows:

$$CD\ symptom\ score = intercept + Covariates * b + c * PGC + G$$

where b and c represent the vectors of fixed effects; and $G \sim N(0, GRM * \sigma 2G)$ represents the random effect that models the sample relatedness, with GRM being the N by N matrix of relatedness estimated from SNPs, and N=10,706 is the number of individuals.

Differential genetic correlation across rater-specific assessment of AGG and external outcomes

We separately computed genetic correlations between rater-specific assessment of AGG and a list of external phenotypes (*N*=46). Note, since the GWAMA on paternal assessment of AGG returned a non-significant SNP-heritability (h^2_{SNP}=0.0412; SE=0.0261), rater-specific genetic correlations with external outcomes were only computed for maternal-, self-, and teacher-reported AGG. We applied Genomic Structural Equation Modelling (Genomic SEM; Grotzinger et al. 2019) to test whether genetic correlations between AGG and external phenotypes are significantly different across rater. Specifically, we considered the genetic correlations between the outcome and tree rater-specific assessments of AGG

and fitted three models. In the first model, the genetic correlations between the outcome and all three rater-specific assessments of AGG were constrained at zero (null model). In the second model, the genetic correlations were allowed to differ from zero but constrained to be equal across raters (equal model). In the third model, the genetic correlations between rater-specific assessment of AGG and the outcome were freely estimated (free model). To facilitate model convergence, path loadings from the latent AGG variables on their respective observed variables, and genetic correlations between rater-specific assessment of AGG were constrained to be positive in all three models. Since the null model and equal model were nested inside the free model, model selection was performed based on a log-likelihood ratio test. To correct for multiple testing, we applied an FDR correction for 2 x 46 tests.

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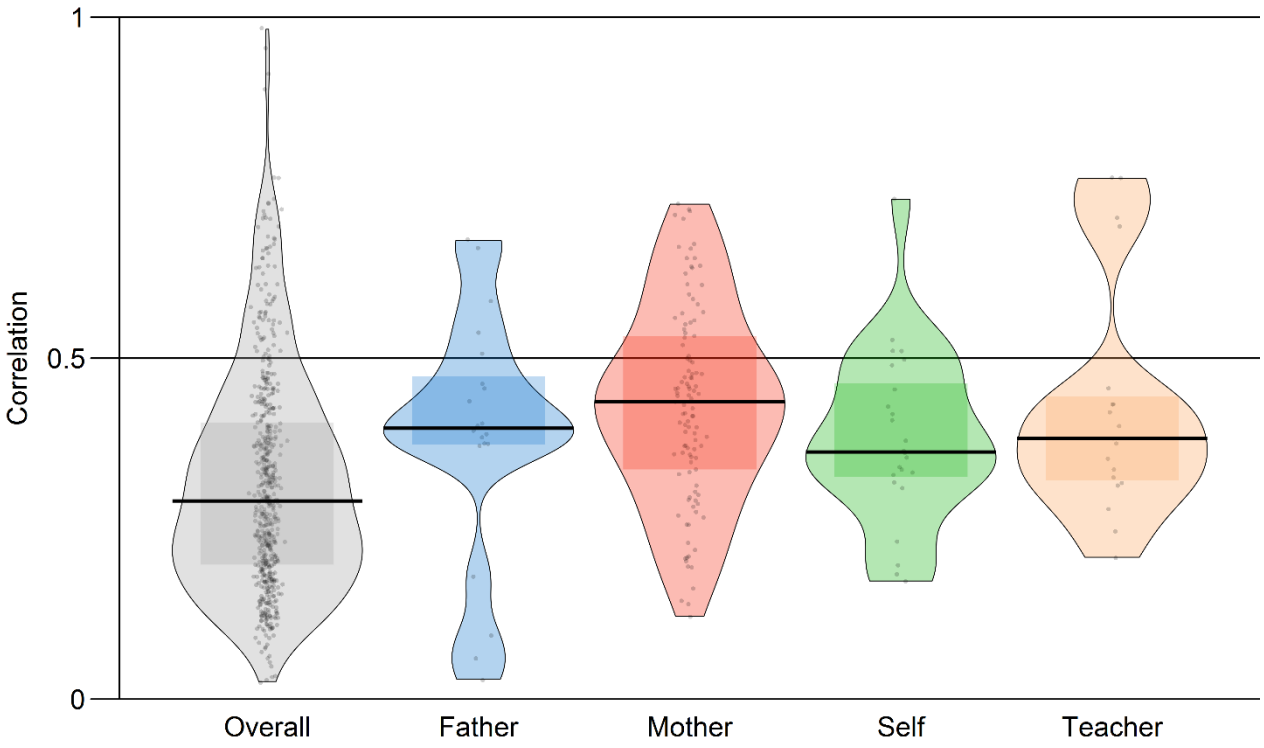
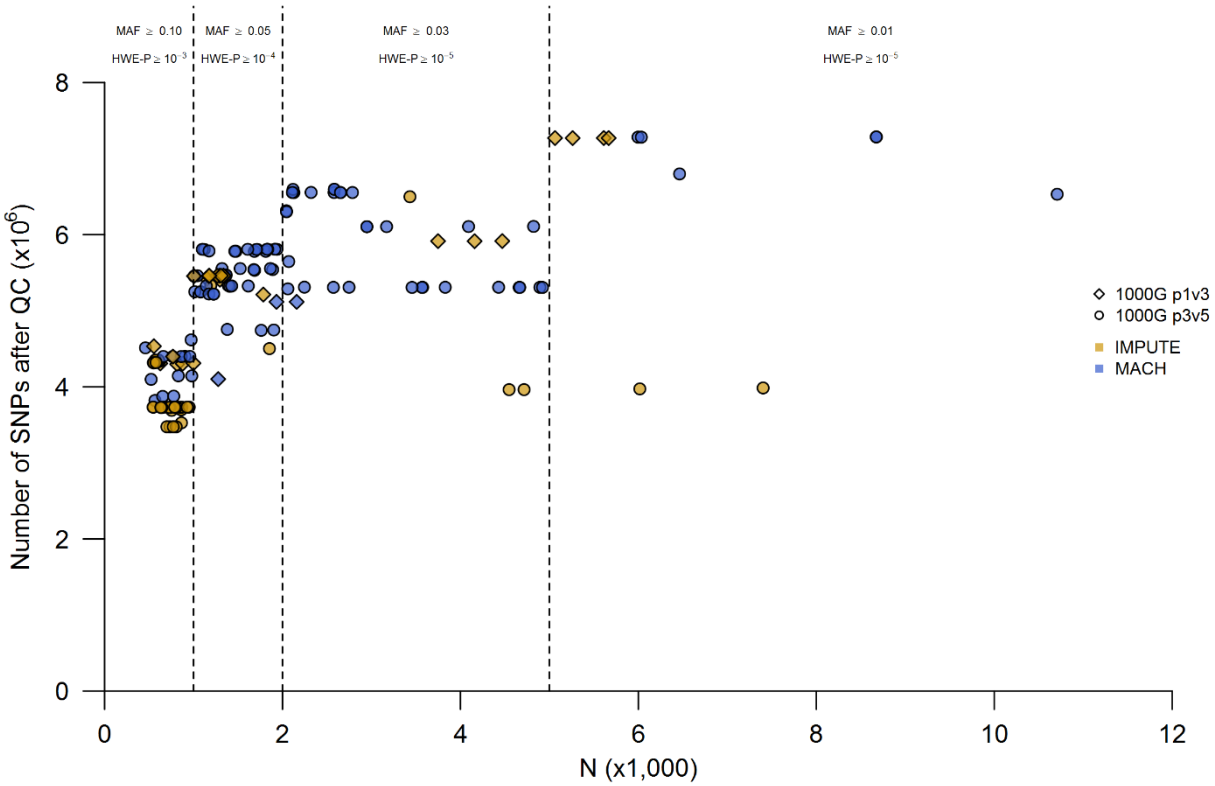
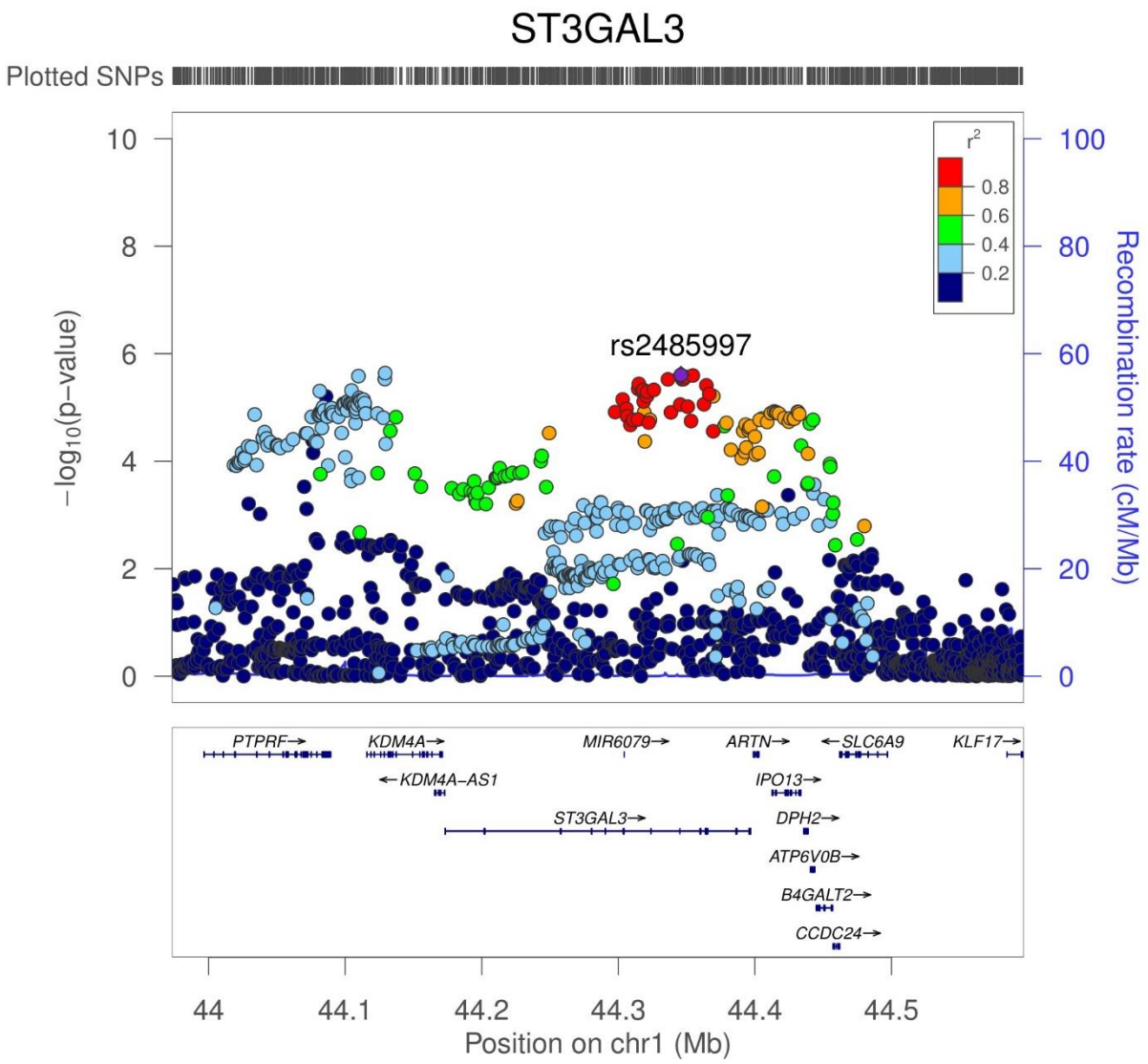
Supplementary Figures



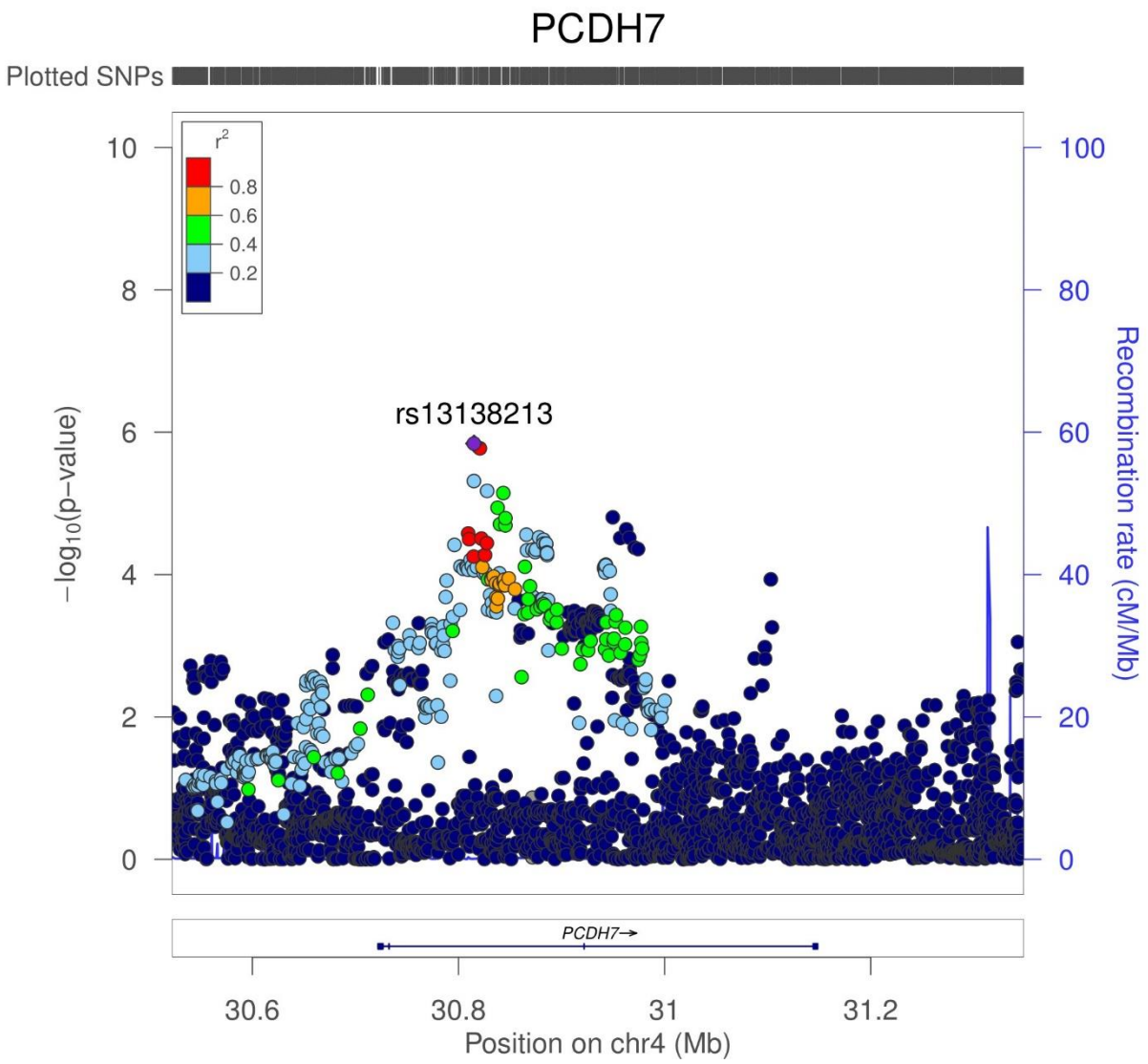
Supplementary Figure 1. Distribution of phenotypic correlations. From left to right, colors represent (1) correlations across all samples, (2) correlations within father-reported data, (3) mother-reported data, (4) self-reported data, and (5) teacher-reported data. Boxes represent the interquartile range.



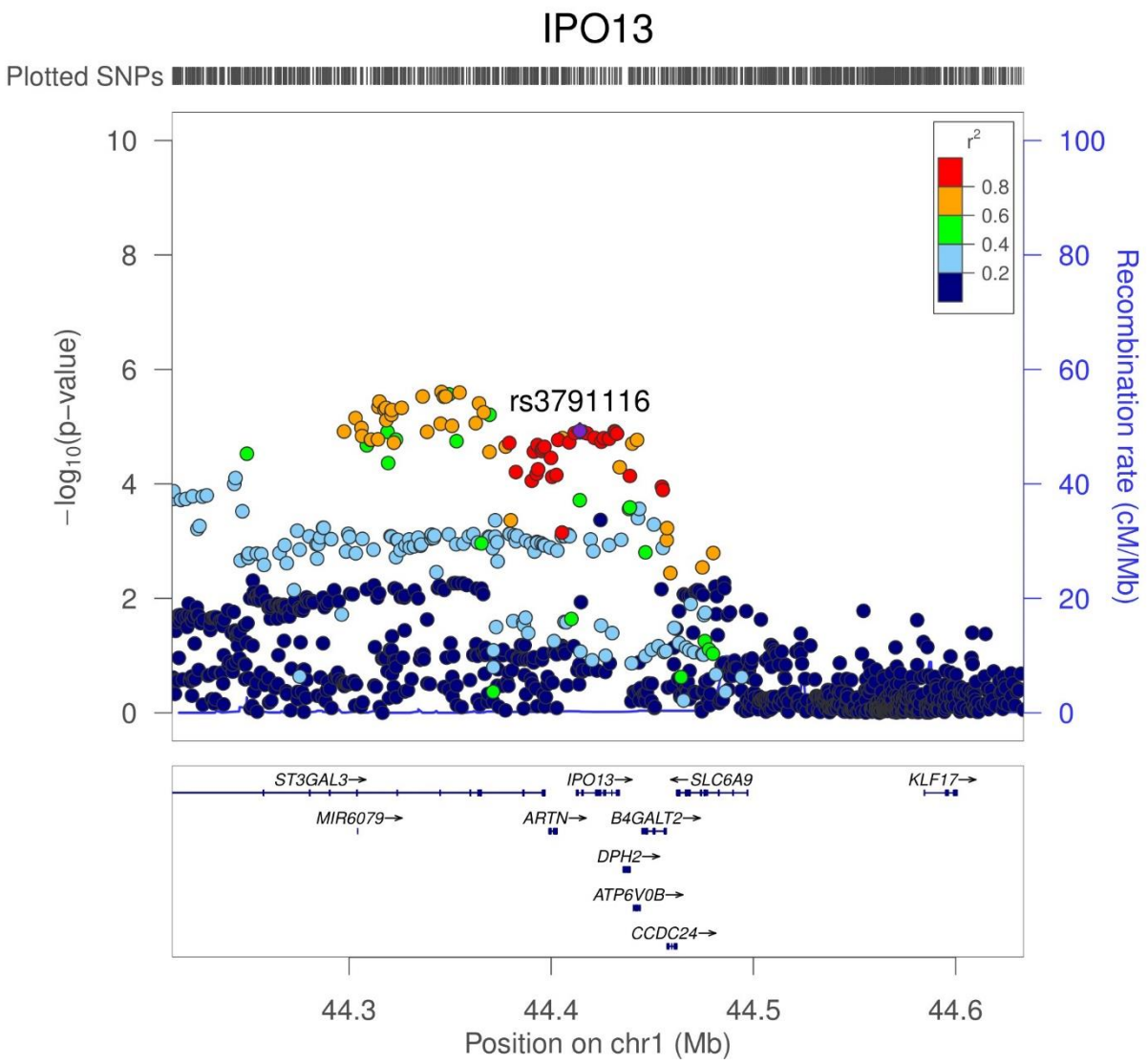
Supplementary Figure 2. Number of SNPs after QC per GWAS. Horizontal axis shows the (maximum) sample size. Vertical axis shows the number of SNPs after QC. Shape of the points correspond to imputation reference panel. Color of the points correspond to software used for imputation. Dotted vertical lines represent the upper limit of the sample-size-dependent QC filters. MAF=minor allele frequency; HWE-P=Hardy-Weinberg equilibrium test *P*-value.



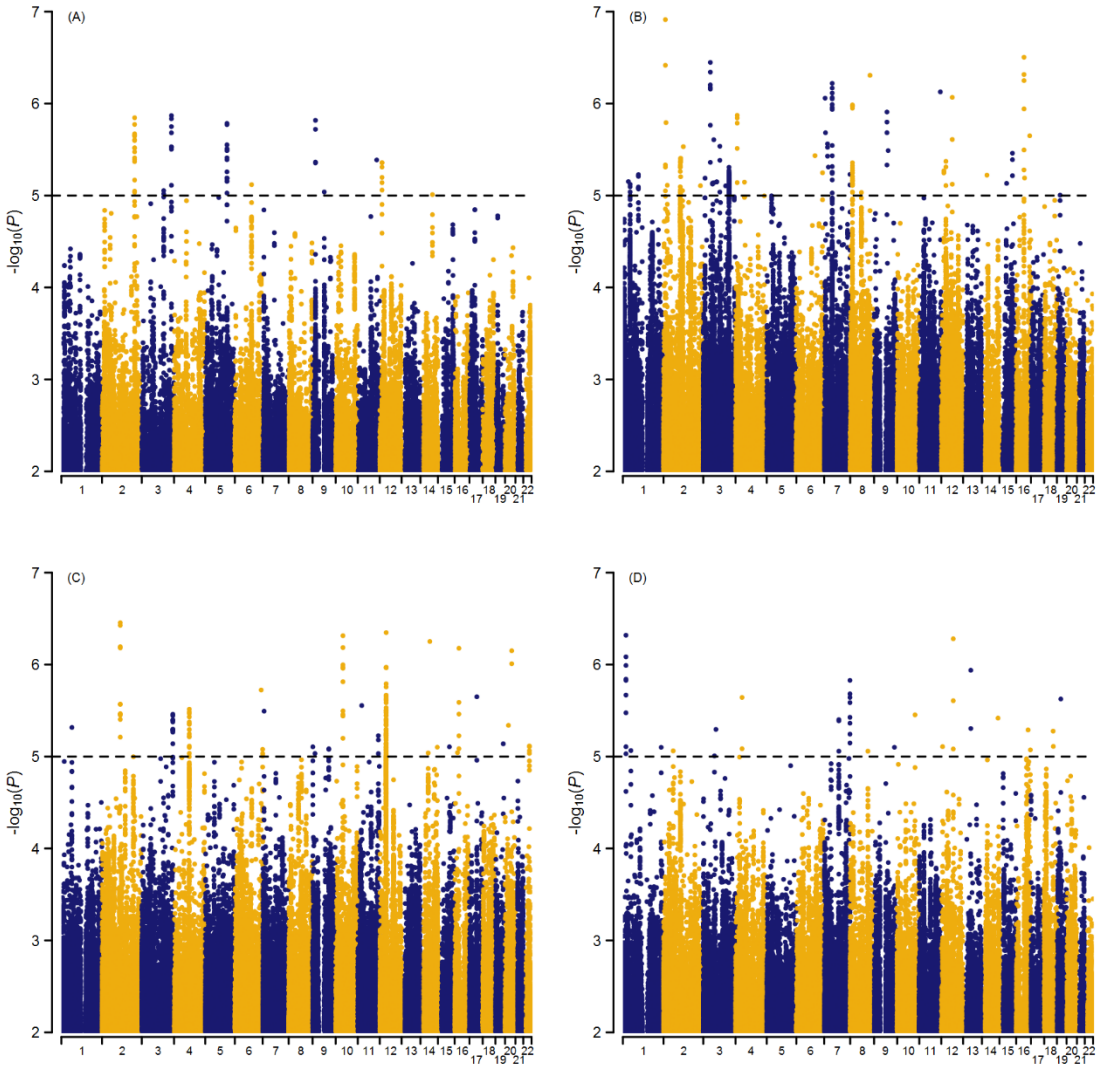
Supplementary Figure 3. Zoom plot of *ST3GAL3*. Plotting window was extended with 200Kbp on both sides of the gene. Purple diamond indicates the index variant inside the gene.



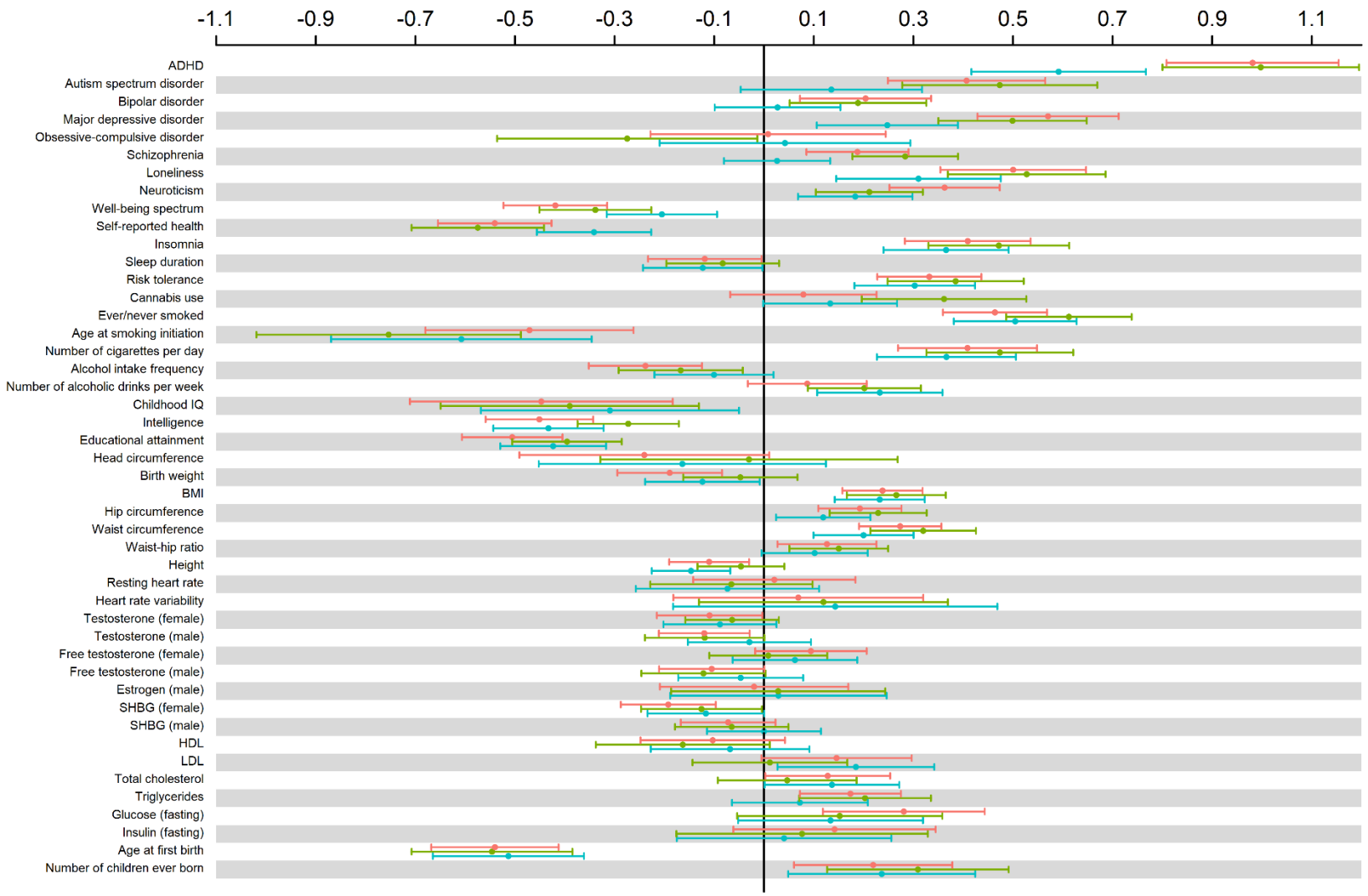
Supplementary Figure 4. Zoom plot of *PCDH7*. Plotting window was extended with 200Kbp on both sides of the gene. Purple diamond indicates the index variant inside the gene.



Supplementary Figure 5. Zoom plot of *IPO13*. Plotting window was extended with 200Kbp on both sides of the gene. Purple diamond indicates the index variant inside the gene.



Supplementary Figure 6. Manhattan plot per rater-specific GWAMA. (A) father. (B) mother. (C) self. (D) teacher. Dotted horizontal line represents threshold for suggestive association (P=10^{-5}).



Supplementary Figure 7. Genetic correlations between rater-specific assessment of AGG and external phenotypes. Phenotypes are sorted on domain. Colors represent raters: red=mother, green=self, blue=teacher. Bars indicate 95% confidence intervals.