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Genetic Associations Between Childhood Psychopathology and Adult Depression and Associated Traits in 42 998 Individuals
A Meta-Analysis

Wonuola A. Akingbuwa, MSc; Anke R. Hammerschlag, PhD; Eshim S. Jami, MSc; Andrea G. Allegrini, MSc; Ville Karhunen, MSc; Hannah Sallis, PhD; Helga Ask, PhD; Ragna B. Askeland, MSc; Bart Baselmans, PhD; Elizabeth Diemer, ScM; Fiona A. Hagenbeek, MSc; Alexandra Havdahl, PhD; Jouke-Jan Hottenga, PhD; Hamdi Mbarek, PhD; Fernando Rivadeneira, PhD; Martin Tesli, PhD; Catharina van Beijsterveldt, PhD; Gerome Breen, PhD; Cathryn M. Lewis, PhD; Anita Thapar, PhD; Dorret I. Boomsma, PhD; Ralf Kuja-Halkola, PhD; Ted Reichborn-Kjennerud, PhD, MD; Per Magnus, PhD, MD; Kaili Rimfeld, PhD; Eivind Ystrom, PhD; Marjo-Riitta Jarvelin, PhD, MD; Paul Lichtenstein, PhD; Sebastian Lundstrom, PhD; Marcus R. Munafò, PhD; Robert Plomin, PhD; Henning Tiemeier, PhD, MD; Michel G. Nivard, PhD; Meike Bartels, PhD; Christel M. Middeldorp, PhD, MD; and the Bipolar Disorder and Major Depressive Disorder Working Groups of the Psychiatric Genomics Consortium

IMPORTANCE Adult mood disorders are often preceded by behavioral and emotional problems in childhood. It is yet unclear what explains the associations between childhood psychopathology and adult traits.

OBJECTIVE To investigate whether genetic risk for adult mood disorders and associated traits is associated with childhood disorders.

DESIGN, SETTING, AND PARTICIPANTS This meta-analysis examined data from 7 ongoing longitudinal birth and childhood cohorts from the UK, the Netherlands, Sweden, Norway, and Finland. Starting points of data collection ranged from July 1985 to April 2002. Participants were repeatedly assessed for childhood psychopathology from ages 6 to 17 years. Data analysis occurred from September 2017 to May 2019.

EXPOSURES Individual polygenic scores (PGS) were constructed in children based on genome-wide association studies of adult major depression, bipolar disorder, subjective well-being, neuroticism, insomnia, educational attainment, and body mass index (BMI).

MAIN OUTCOMES AND MEASURES Regression meta-analyses were used to test associations between PGS and attention-deficit/hyperactivity disorder (ADHD) symptoms and internalizing and social problems measured repeatedly across childhood and adolescence and whether these associations depended on childhood phenotype, age, and rater.

RESULTS The sample included 42 998 participants aged 6 to 17 years. Male participants varied from 43.0% (1040 of 2417 participants) to 53.1% (2434 of 4583 participants) by age and across all cohorts. The PGS of adult major depression, neuroticism, BMI, and insomnia were positively associated with childhood psychopathology (β estimate range, 0.023-0.042 [95% CI, 0.017-0.049]), while associations with PGS of subjective well-being and educational attainment were negative (β, −0.026 to −0.046 [95% CI, −0.020 to −0.057]). There was no moderation of age, type of childhood phenotype, or rater with the associations. The exceptions were stronger associations between educational attainment PGS and ADHD compared with internalizing problems (Δβ, 0.0561 [Δ95% CI, 0.0318-0.0804]; ΔSE, 0.0124) and social problems (Δβ, 0.0528 [Δ95% CI, 0.0282-0.0775]; ΔSE, 0.0126), and between BMI PGS and ADHD and social problems (Δβ, −0.0001 [Δ95% CI, −0.0102 to 0.0100]; ΔSE, 0.0052), compared with internalizing problems (Δβ, −0.0310 [Δ95% CI, −0.0456 to −0.0164]; ΔSE, 0.0074). Furthermore, the association between educational attainment PGS and ADHD increased with age (Δβ, −0.0032 [Δ 95% CI, −0.0048 to −0.0017]; ΔSE, 0.0008).

CONCLUSIONS AND RELEVANCE Results from this study suggest the existence of a set of genetic factors influencing a range of traits across the life span with stable associations present throughout childhood. Knowledge of underlying mechanisms may affect treatment and long-term outcomes of individuals with psychopathology.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Bipolar Disorder and Major Depressive Disorder Working Groups of the Psychiatric Genomics Consortium members appear at the end of the article.

Corresponding Author: Wonuola A. Akingbuwa, MSc, Department of Biological Psychology, Vrije Universiteit Amsterdam, Van der Boechorststraat 7, 1081 BT Amsterdam, the Netherlands (o.a.akingbuwa@vu.nl).

Longitudinal studies indicate that the onset of mood disorders in adulthood, including depression and bipolar disorder (BD), is often preceded by childhood problems. These include not only internalizing problems, such as depression and anxiety,[1,2] but also externalizing traits, such as attention-deficit/hyperactivity disorder (ADHD) and aggression.[3-5] Moreover, both in prospective and retrospective studies, behavioral and emotional problems during childhood and adolescence have been associated with other adult outcomes that are associated with adult mood disorders, including educational attainment (EA),[6-9] insomnia,[10,11] subjective well-being (SWB),[12] personality,[13-16] and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared).[17-19]

Both twin/family and molecular genetic studies have reported heritability[20-22] and stability[23-25] of psychopathology over time. Studies of BD in high-risk families also show that children of parents with BD are susceptible to psychiatric disorders and symptoms in childhood,[26] adolescence, and early adulthood.[27,28] These results suggest that genetic factors may underlie the persistence of symptoms or the transition from one disorder to another between childhood and adulthood. Polygenic score (PGS) analyses enable the examination of the genetic association between adult traits and childhood symptoms of psychopathology.

Polygenic scores are aggregate scores of an individual's genetic risk for a trait, calculated by summing risk alleles from a discovery genome-wide association study (GWAS), weighted by their effect sizes.[29] For complex (ie, polygenic) traits influenced by many genetic variants, PGS summarize genetic risk across loci that are not individually significant in a GWAS. A statistically significant association between measured traits and PGS based on another trait suggests a shared genetic etiology. Results of studies using PGS to investigate the association of childhood psychopathology with mood disorders and associated traits vary. Analyses investigating depression and BD PGS have found no evidence of associations with emotional and behavior problems during childhood and adolescence, although there is evidence of association between depression PGS and emotional problems in adulthood.[30-32] Associations between PGS of EA and ADHD or attention problems have been more consistent, with multiple studies[30,32-34] showing strong genetic associations between EA and ADHD or attention problems in childhood and adolescence.

The last 2 years have seen ever-larger GWAS for traits, including major depression (MD),[35,36] BD,[37] EA,[38] and BMI,[39] consequently increasing accuracy of PGS.[40] Combined with the substantial increase in individuals genotyped in large longitudinal childhood cohorts that assess psychopathology, this provides an opportunity to rigorously investigate whether genetic factors underlie the associations between childhood psychopathology and adult mood disorders and associated nonpsychiatric traits (EA, insomnia, SWB, neuroticism, and BMI) and determine whether this association depends on age. Using 7 childhood population-based cohorts, we studied 42 998 individuals with repeated measures of ADHD symptoms, internalizing, and social problems. We performed meta-analyses to test whether PGS of adult traits are associated with childhood and adolescent psychopathology and whether this association depends on various factors, including age, type of psychopathology, type of scale used to measure psychopathology, and the informant.

Key Points

Question Do genetic factors underlie the association between childhood psychopathology and adult mood disorders and associated traits?

Findings This meta-analysis of longitudinal cohorts, which includes data on 42 998 participants, revealed significant associations between childhood psychopathology and adult polygenic scores of major depression, subjective well-being, neuroticism, insomnia, educational attainment, and body mass index but not bipolar disorder.

Meaning Per this analysis, shared genetic factors exist between childhood psychopathology traits from age 6 years onwards and adult depression and associated traits.

Methods

Participants and Measures

We obtained self-rated or maternal-rated measures of ADHD symptoms, internalizing, and social problems from 7 population-based cohorts (**Table 1**). Data collection was approved by each cohort's local institutional review or ethics board, waiving the need for informed consent for this study. The starting points of data collection varied, ranging from July 1985 to April 2002. Data analysis was performed from September 2017 to May 2019. Cohort descriptions can be found in the eAppendix 2 in the Supplement.

Genotyping and Polygenic Scores

Genotyping and quality control were performed by each cohort, following common standards (eAppendix 2 in the Supplement). In each cohort, PGS were constructed for the following adult traits: MD,[35] BD,[37] SWB,[41] neuroticism,[41] insomnia,[42] EA,[38] and BMI.[39] Height[39] was included as a control phenotype (eTable 1 in the Supplement contains the GWAS discovery sample size for each trait). To avoid overlap between discovery and target samples, summary statistics omitting the target cohort or cohorts were used. Analyses were limited to individuals of European ancestry.

Polygenic scores were estimated using LDpred, a method that takes into account the level of linkage disequilibrium between measured single-nucleotide variants (SNVs; often called single-nucleotide polymorphisms) to avoid inflation of effect sizes.[43] The method LDpred requires the inclusion of prior probabilities corresponding to the fraction of SNVs thought to be causal, which allows for testing varying proportions of SNVs associated with the outcome of interest. We thus tested a range of priors (0.75, 0.50, 0.30, 0.10, and 0.03) to assess the prior at which assessment was optimal. We restricted analyses to common variants, using SNV inclusion criteria of minor allele frequency greater than 5% and imputation quality of R^2 greater than 0.90.

Table 1. Sample Characteristics

Cohort	Approximate Age Groups, y	Scale(s)	Phenotype(s) Measured	Rater	Sample Size
Avon Longitudinal Study of Parents and Children	7, 10, 12, 14, 16	Strength and Difficulties Questionnaire	ADHD symptoms, internalizing problems, social problems	Maternal	6502
Child and Adolescent Twin Study in Sweden	9, 12, 15	Autism-Tics, ADHD and Other Comorbidities Inventory, Screen for Child Anxiety Repated Emotional Disorders, Short Mood and Feelings Questionnaire, Strength and Difficulties Questionnaire	ADHD symptoms, internalizing problems, social problems	Maternal, self	11 039
Generation R	6, 10	Achenbach System of Empirically Based Assessment (Child Behavior Checklist)	ADHD symptoms, internalizing problems, social problems	Maternal	2438
Norwegian Mother and Child Cohort Study	8	Screen for Child Anxiety Related Emotional Disorders, Short Mood and Feelings Questionnaire, Rating Scale for Disruptive Behavior Disorders	ADHD symptoms, internalizing problems	Maternal	4583
Northern Finland Birth Cohort of 1986	16	Achenbach System of Empirically Based Assessment (Youth Self Report)	ADHD symptoms, internalizing problems, social problems	Self	3409
Netherlands Twin Register	7, 10, 12, 14, 17	Achenbach System of Empirically Based Assessment (Child Behavior Checklist and Youth Self Report)	ADHD symptoms, internalizing problems, social problems	Maternal, self	5501
Twins Early Development Study	7, 8, 9, 12, 14, 16	Strength and Difficulties Questionnaire, Conners' Parent Rating Scale	ADHD symptoms, internalizing problems, social problems	Maternal, self	9526

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

Cohort-Specific Association Analyses

In each cohort, associations between childhood psychopathology and adult traits were estimated by regressing each outcome measure (ie, ADHD symptoms, internalizing, and social problems) stratified by age and rater, on the calculated PGS of the 8 adult traits at the 5 priors. A wide variety of surveys were used to further characterize the cohort.[44-50]

Where cohorts included related individuals, regressions were performed using the exchangeable model in generalized estimating equations to correct for relatedness in samples.[51] Scales were coded such that higher scores reflected more childhood problems. Both childhood psychopathology scores and PGS were standardized to a mean of 0 and an SD of 1, allowing for comparable βs across cohorts. Sex, age, batch effects, and genetic principal components (which correct for population stratification) were included as covariates in the regression (eAppendix 2 in the Supplement).

Multivariate Meta-analyses

Meta-analyses were performed using the metafor package in R version 3.6.0 (R Foundation for Statistical Computing).[52] To obtain the prior that provided the strongest estimate of the association with overall childhood psychopathology, we performed a random-effects meta-analysis for each of the 5 priors for each adult-trait PGS. Specifying random effects accounts for heterogeneity in the true associations attributable to factors that contribute to sample variation across cohorts, such as differences in measurements and sample characteristics. Subsequent analyses for each adult trait were conducted based on the selected prior from the previous analysis (ie, the one that provided the highest estimate of the association). As a sensitivity check, we repeated all analyses using a prior of 0.50 and compared these results to those using the prior with the highest estimate. We selected the prior of 0.50, because it represents a reasonable estimation of the proportion of associated SNVs across the different types of complex traits we tested.

To correct for dependency in the outcome variables attributable to repeated measures of the same individuals over time, we specified the variance-covariance matrix between their sampling errors. Because errors were assumed to be independent between cohorts, we combined variance-covariance matrices across cohorts by setting correlations between cohorts to 0 in the matrix, further accounting for differences between cohorts.[53] To test whether the error covariance matrix alone suitably accounted for differences between cohorts, we applied for each adult trait an analysis of variance (ANOVA) test to compare models with the random effects dropped with those where they were specified along with the error covariance matrix.

Subsequent meta-analyses to test the association between each adult-trait PGS and overall childhood psychopathology (ie, all 3 childhood measures analyzed jointly) were performed on the reduced model (no random effects), if dropping them did not result in a significant loss of fit compared with the full model (random effects plus error covariance matrix).

We also tested the association between the PGS and each individual childhood psychopathology measure.

Because both the childhood outcomes, and PGS measures are correlated, we estimated the effective number of tests between both sets of variables under the assumption that they are nonindependent.[54,55] We corrected the meta-analysis results for multiple testing by applying Bonferroni correction (P = .05/number of tests) to the effective number of tests (2015.04 effective tests; $\alpha = 2.48 \times 10^{-5}$) (eTable 2 in the Supplement).

Multimodel Inference Analyses to Identify Moderators

To ascertain whether the variables age, type of childhood psychopathology (ie, ADHD symptoms, internalizing problems, or social problems), measurement instrument (eg, Strength and Difficulties Questionnaire,[44] Achenbach System of Empirically Based Assessment[48]), and rater (ie, maternal or self) moderated association between childhood psychopathology and adult-trait PGS, we performed multimodel inference analyses using the glmulti package in R version 3.6.0.[56] The glmulti package allows the definition of a function that takes into account all potential moderators and generates all possible models for the association of interest, returning the best models based on a specified information criterion; in our study, this was Akaike information criterion.[57] Furthermore, it provides parameter estimates based on all possible models, rather than a single-top model, while considering the relative importance of each potential moderator by weighting them. The averaged model avoids relying too strongly on a single best model.

In summary, for each adult-trait PGS, we selected the prior that provide the strongest estimate of its association with childhood psychopathology by performing random-effects meta-analyses at each prior. This was followed by ANOVA tests to determine whether our error covariance matrix suitably accounted for differences between cohorts. We then performed multivariate meta-analyses testing the associations of PGS of adult traits with childhood psychopathology at all ages. Finally, we performed multimodel inference analyses to ascertain whether moderators affected the association between each adult-trait PGS and childhood psychopathology.

Results

The 7 included cohorts combined participants from the Netherlands, UK, Sweden, Norway, and Finland in a combined sample of 42 998 unique participants aged 6 to 17 years old. The percentage of male participants ranged from 43.0% (1040 of 2417 participants) to 53.1% (2434 of 4583 participants) by age and across all cohorts.

Cohort-Specific Association Analyses

Cohort-specific descriptive statistics and correlation matrices of the 3 psychopathology measures, ADHD symptoms, internalizing problems, and social problems are described in eTables 3, 4, 5, 6, 7, 8, and 9 in the Supplement. Correlation matrices show the observed variability or stability of childhood psychopathology over time. Based on cohorts with multiple or consistent measures of psychopathology across development, we observed moderate correlations across different ages. Estimates were highest for measurements of the same trait at adjacent ages, around 0.50, and lowest between self-rated and maternally rated measures, around 0.20. The results of the univariate analyses in each cohort are displayed in eTables 10, 11, 12, 13, 14, 15, and 16 in the Supplement.

Meta-analyses

Random-effects meta-analyses corresponding to the 5 priors showed that the prior that provided the strongest association estimates were 0.75 for EA and BMI; 0.50 for MD, insomnia, and height; 0.30 for neuroticism; 0.10 for BD; and 0.03 for SWB (eTable 17 in the Supplement). A reduced model (error matrix alone) was used in the multivariate and subsequent analyses for all traits except for the EA and BMI PGS, for which we used the full model (random effect plus the error covariance matrix). This was because ANOVA tests comparing the full model with the reduced model suggested that the error covariance matrix alone insufficiently accounted for differences between cohorts (ANOVA results, eTable 18 in the Supplement).

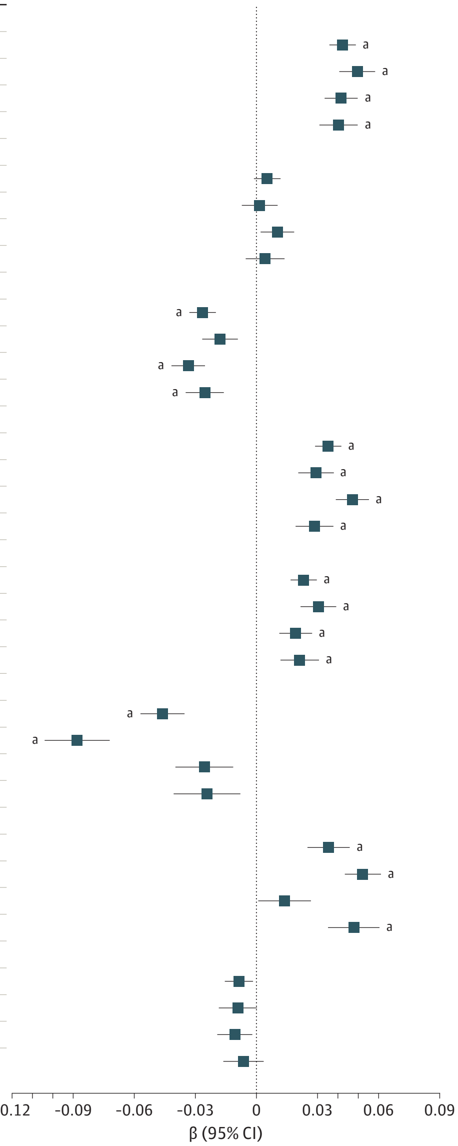
Subsequent meta-analyses of the association between PGS of each adult trait and overall childhood psychopathology (all 3 childhood measures in the same model) showed that the directions of associations were as expected (**Figure 1**). Significant positive associations were observed for PGS of MD (β, 0.042 [95% CI, 0.036-0.049]; SE, 0.003; $P = 2.48 \times 10^{-37}$; R^2, 0.002), neuroticism (β, 0.035 [95% CI, 0.029-0.042]; SE, 0.003; $P = 1.22 \times 10^{-26}$; R^2, 0.001), insomnia (β, 0.023 [95% CI, 0.017-0.030]; SE, 0.003; $P = 2.36 \times 10^{-12}$; R^2, 0.0005), and BMI (β, 0.035 [95% CI, 0.025-0.046]; SE, 0.005; $P = 2.23 \times 10^{-11}$; R^2, 0.001), while associations for SWB (β, −0.026 [95% CI, −0.020 to −0.033]; SE, 0.003; $P = 1.92 \times 10^{-15}$; R^2, 0.0006) and EA (β, −0.046 [95% CI, −0.035 to −0.057]; SE, 0.006; $P = 6.74 \times 10^{-17}$; R^2, 0.002) were negative. There was no evidence for association with BD PGS (β, 0.005 [95% CI, −0.001 to 0.012]; SE, 0.003; P = .11; R^2, 2.50×10^{-5}). No associations were found with the PGS of height.

Moderators

Using model averaging, we considered the effect of 4 moderators (ie, outcome, age, measurement instrument, and rater) across all possible models. Using a P value threshold of .0125 (α = .05/number of moderators), we found evidence of moderation for EA and BMI PGS (**Table 2**). The association between EA PGS and childhood psychopathology varied as a function of outcome, rater, and age. The EA PGS were associated with ADHD symptoms but not internalizing problems (Δβ, 0.0561 [Δ95% CI, 0.0318-0.0804]; ΔSE, 0.0124) or social problems (Δβ, 0.0528 [Δ95% CI, 0.0282-0.0775]; ΔSE, 0.0126); Figure 1). Additionally, the association between ADHD symptoms and EA PGS increased with age (Δβ, −0.0032 [Δ 95% CI, −0.0048 to −0.0017]; ΔSE, 0.0008) in maternal ratings, while self-ratings showed the opposite (Δβ, 0.0463 [Δ95% CI, 0.0315-0.0611]; ΔSE, 0.0075). However, the influence of rater on the associations appears to be driven by a single outlier aged around 17 years in the self-reported data (**Figure 2**). The association between BMI PGS and childhood psychopathology also varied across outcomes.

Figure 1. Multivariate Meta-analysis Estimates of the Associations Between Adult Traits and Overall Childhood Psychopathology

Source	β (95% CI)
Major depression	
Combined	0.0423 (0.0358 to 0.0488)
ADHD symptoms	0.0495 (0.0407 to 0.0583)
Internalizing problems	0.0416 (0.0334 to 0.0497)
Social problems	0.0403 (0.0309 to 0.0497)
Bipolar disorder	
Combined	0.0053 (-0.0012 to 0.0119)
ADHD symptoms	0.0016 (-0.0072 to 0.0104)
Internalizing problems	0.0103 (0.0021 to 0.0185)
Social problems	0.0043 (-0.0053 to 0.0138)
Subjective well-being	
Combined	-0.0264 (-0.0329 to -0.0199)
ADHD symptoms	-0.0179 (-0.0266 to -0.0091)
Internalizing problems	-0.0335 (-0.0417 to -0.0253)
Social problems	-0.0254 (-0.0348 to -0.0160)
Neuroticism	
Combined	0.0352 (0.0288 to 0.0417)
ADHD symptoms	0.0292 (0.0205 to 0.0379)
Internalizing problems	0.0471 (0.0390 to 0.0553)
Social problems	0.0285 (0.0192 to 0.0378)
Insomnia	
Combined	0.0232 (0.0167 to 0.0297)
ADHD symptoms	0.0304 (0.0216 to 0.0392)
Internalizing problems	0.0193 (0.0112 to 0.0273)
Social problems	0.0213 (0.0118 to 0.0307)
Educational attainment	
Combined	-0.0461 (-0.0569 to -0.0353)
ADHD symptoms	-0.0880 (-0.1040 to -0.0720)
Internalizing problems	-0.0256 (-0.0398 to -0.0114)
Social problems	-0.0243 (-0.0407 to -0.0079)
Body mass index	
Combined	0.0354 (0.0251 to 0.0458)
ADHD symptoms	0.0523 (0.0434 to 0.0612)
Internalizing problems	0.0138 (0.0009 to 0.0268)
Social problems	0.0478 (0.0352 to 0.0604)
Height	
Combined	-0.0086 (-0.0155 to -0.0017)
ADHD symptoms	-0.0091 (-0.0185 to -0.0002)
Internalizing problems	-0.0106 (-0.0192 to -0.0020)
Social problems	-0.0063 (-0.0163 to -0.0036)



Bars represent confidence intervals corresponding to α = .05. ADHD indicates attention-deficit/hyperactivity disorder. [a]Indicates significance after correction for multiple testing ($\alpha = 2.48 \times 10^{-5}$).

Associations were strongest with ADHD and social problems (Δβ, −0.0001 [Δ95%CI, −0.0102 to 0.0100]; ΔSE, 0.0052), compared with internalizing problems (Δβ, −0.0310 [Δ95% CI, −0.0456 to −0.0164]; ΔSE, 0.0074). Moderators did not influence associations between the other adult-trait PGS and childhood psychopathology (eTable 19 in the Supplement).

Sensitivity Analyses

Using a prior of 0.50 sensitivity analyses showed similar results to the main analyses, except for the moderation of outcome on the association with BMI PGS (intercept: β, 0.0439; SE, 0.0087 [95% CI, 0.0269-0.0609]; internalizing problems: Δβ, −0.0257; ΔSE, 0.0130 [Δ 95% CI, −0.0512 to −0.0003]; social problems: Δβ, −0.0018; ΔSE, 0.0055 [Δ 95% CI, −0.0126 to 0.0089]; eFigure in the Supplement). While this was nominally significant (*P* = .047), it did not remain after adjusting for the 4 moderators tested (α = .0125; eTable 20 in the Supplement). Results from the main analyses also remained the same when all meta-analyses included random effects.

Discussion

We investigated genetic associations between childhood psychopathology and adult mood disorders and associated traits over time. Using results of well-powered GWAS meta-analyses of adult traits, we calculated PGS in what is, to our knowledge, the largest childhood target sample to date for this type of study (N = 42 998). We revealed strong evidence of associations of PGS for adult MD, SWB, neuroticism, insomnia,

Table 2. Model-Averaged Moderator Effects for Educational Attainment and Body Mass Index[a]

Variable	Estimate (SE)	95% CI	z value	P value	Importance
Educational attainment					
Intercept	−0.0770 (0.0092)	−0.0950 to −0.0591	−8.4072	4.20×10^{-17}[b]	1.0000
Self-rating	0.0463 (0.0075)	0.0315 to 0.0611	6.1370	8.41×10^{-10}[b]	1.0000
Age	−0.0032 (0.0008)	−0.0048 to −0.0017	−4.0563	4.99×10^{-5}[b]	0.9896
Outcome measures					
Internalizing problems	0.0561 (0.0124)	0.0318 to 0.0804	4.5239	6.07×10^{-6}[b]	0.9606
Social problems	0.0528 (0.0126)	0.0282 to 0.0775	4.2076	2.58×10^{-5}[b]	0.9606
Scale					
A-TAC	0.0008 (0.0016)	−0.0023 to 0.0039	0.4956	0.6202	0.0194
Conners' Parent Rating Scale	0.0008 (0.0016)	−0.0023 to 0.0039	0.4898	0.6243	0.0194
RS-DBD	0.0007 (0.0015)	−0.0022 to 0.0037	0.4737	0.6357	0.0194
SCARED	0.0001 (0.0004)	−0.0007 to 0.0008	0.1861	0.8524	0.0194
SDQ	−0.0002 (0.0004)	−0.0010 to 0.0007	−0.4316	0.6660	0.0194
SMFQ	−0.0008 (0.0016)	−0.0038 to 0.0023	−0.4923	0.6225	0.0194
BMI					
Intercept	0.0468 (0.0064)	0.0343 to 0.0593	7.3531	1.94×10^{-13}[b]	1.0000
Outcome measure					
Internalizing problems	−0.0310 (0.0074)	−0.0456 to −0.0164	−4.1744	2.99×10^{-5}[b]	0.9374
Social problems	−0.0001 (0.0052)	−0.0102 to 0.0100	−0.0192	0.9847	0.9374
Self-rated	−0.0011 (0.0022)	−0.0055 to 0.0033	−0.5068	0.6123	0.0923
Age	7.48×10^{-6} (2.32×10^{-5})	-3.80×10^{-5} to 0.0001	0.3223	0.7473	0.0195
Scale					
A-TAC	-1.42×10^{-9} (3.35×10^{-9})	-7.99×10^{-9} to 5.14×10^{-9}	−0.4241	0.6715	8.21×10^{-8}
Conners' Parent Rating Scale	2.77×10^{-12} (1.62×10^{-9})	-3.18×10^{-9} to 3.19×10^{-9}	0.0017	0.9986	8.21×10^{-8}
RS-DBD	-1.03×10^{-9} (3.12×10^{-9})	-7.15×10^{-9} to 5.09×10^{-9}	−0.3290	0.7422	8.21×10^{-8}
SCARED	-3.32×10^{-9} (6.90×10^{-9})	-1.68×10^{-8} to 1.02×10^{-8}	−0.4809	0.6306	8.21×10^{-8}
SDQ	-1.05×10^{-9} (2.47×10^{-9})	-5.90×10^{-9} to 3.80×10^{-9}	−0.4260	0.6701	8.21×10^{-8}
SMFQ	2.69×10^{-10} (1.67×10^{-9})	-3.00×10^{-9} to 3.54×10^{-9}	0.1612	0.8720	8.21×10^{-8}

Abbreviations: A-TAC, Autism-Tics, ADHD, and Other Comorbidities Inventory; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); RS-DBD, Rating Scale for Disruptive Behavior Disorders; SCARED, Screen for Child Anxiety Related Emotional Disorders; SDQ, Strength and Difficulties Questionnaire; SMFQ, Short Mood and Feelings Questionnaire.

[a] The intercept estimate contains information from the reference variable of each moderator, selected in alphabetical order or with the lowest value, in the case of numerical moderators. Hence the intercept reflects the association estimate between educational attainment or BMI and Achenbach System of Empirically Based Assessment measured, maternally rated attention problems at approximately age 6 years. The other estimates show the change in association estimates depending on the moderator variable. The importance value for each moderator represents their overall support across all models. Moderators present in multiple models with large weights will have higher importance, and the closer this value is to 1, the more important the moderator is for the association being considered.

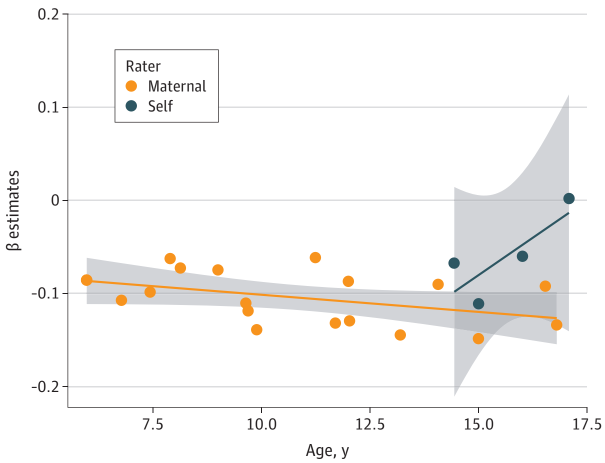
[b] Values were significant when adjusted for 4 moderators ($\alpha = .05/4 = .0125$).

EA, and BMI with childhood ADHD symptoms, internalizing problems, and social problems. We found no evidence of associations between BD PGS and childhood psychopathology. In addition, we found no evidence of the moderators age, outcome, measurement instrument, and rater on these associations, except for EA PGS and BMI PGS. While EA PGS was more strongly associated with ADHD symptoms compared with the 2 other outcomes, BMI PGS was more strongly associated with ADHD symptoms and social problems than with internalizing problems. The association between EA PGS and ADHD symptoms increased with age and was stronger for maternal-rated ADHD symptoms compared with self-rated ADHD symptoms.

Our results indicate a consistent pattern of genetic associations between PGS of adult depression and associated traits and childhood psychopathology across age. This has not been observed previously, which is likely partly attributable to the increased power of our larger discovery and target samples compared with previous studies.[31,32] Moreover, previous studies focused on separate childhood phenotypes[58,59] as opposed to our approach of simultaneously analyzing multiple childhood problems at different ages. Consistent genetic associations across age suggest a set of genetic variants that influence a range of traits across the life span.

The exceptions to these consistent associations were EA and BMI PGS, which showed moderation on the associations

Figure 2. Moderator Effects of Age and Rater on the Association Between Educational Attainment Polygenic Scores and Attention-Deficit/Hyperactivity Disorder



Each point represents β estimates from univariate analyses of the association between educational attainment polygenic scores and attention-deficit/hyperactivity disorder symptoms at different ages. Overall, the negative association becomes stronger with increasing age (Table 2). The gray shadow around the trend line represents the 95% CI of the age effect size.

by the different types of childhood outcome. While both were genetically associated with ADHD in accordance with previous research,[30,33,34,58] they were not associated with internalizing problems, or social problems, in the case of EA. The lack of association with internalizing problems was somewhat unexpected, given genetic correlations previously found for BMI and EA with adult MD.[35,36] These results suggest that genetic associations between EA and BMI and MD may become more apparent after adolescence, while they are already present for childhood ADHD and social problems (for BMI).

We did not identify associations between BD PGS and childhood psychopathology. This is intriguing because moderate genetic correlations with BD have been observed for MD and ADHD, as well as other behavioral-cognitive phenotypes, such as SWB and EA.[21] However, previous analyses of BD PGS also found no associations with continuous measures of psychopathology in childhood[32,60] or adolescence.[61] These results may be explained by less powerful BD GWAS compared with MD and other traits, which might result in underpowered PGS. Nevertheless, the lack of association with BD PGS may also suggest that genetic risk for BD does not manifest until later in development, but given the higher prevalence rates of childhood psychopathology in offspring of parents with BD, this seems less likely.[28,62,63] It will be interesting to see if the observation holds as more powerful GWAS become available for BD.

Limitations

A limitation of our study is that analyses are limited to European ancestry, and therefore results are not generalizable to populations of differing ancestry. Second, associations between PGS and childhood psychopathology measures may be confounded by unaccounted passive gene-environment correlations, an association between a child's genotype and familial environment resulting from parents providing environments that are influenced by their own (parental) genotypes.[64,65] Consequently, associations observed with adult PGS may be the result of both direct and indirect (environmentally-mediated) genetic effects. Third, dropout may have influenced our results. Previous analyses in longitudinal cohorts have reported negative associations between PGS for schizophrenia, ADHD, and depression and participation in childhood and adolescence.[66,67] Nonparticipation in adolescence is also associated with higher psychopathology scores at earlier ages.[53] These results suggest that individuals with higher genetic risk for psychiatric disorders and higher childhood psychopathology are more likely to drop out of longitudinal studies. Genetic associations and the magnitude of associations reported may therefore be underestimated. Finally, because we combined data from different cohorts, we introduced heterogeneity in the assessment of childhood psychopathology. However, the meta-regression showed in general, consistent effect sizes across scales and raters. Moreover, combining multiple cohorts resulted in a large sample size, increasing statistical power compared with previous studies, which is a strength of this study.

Conclusions

The general lack of an influence of age and type of childhood psychopathology on our identified associations supports evidence of a common genetic psychopathology factor that remains stable across development.[68] Polygenic scores by themselves are not sufficient to identify individual children at high risk for persistence (they explain <1% of the variance in childhood psychopathology in this study). Nevertheless, these findings are of major importance because the individuals who are affected across the life span with consequences on other outcomes, such as EA and BMI, should be the focus of attention for targeted treatment. Furthermore, PGS could be combined with other risk factors for risk assessment in clinical samples, as was recently done for psychosis risk using schizophrenia PGS.[69] Future studies focusing on samples from high-risk populations are warranted to investigate whether PGS for adult traits, together with other variables, can be used to build risk profiles with reasonable accuracy. These may allow for the stratification of children into high-risk and low-risk groups for persistence, as well as test whether early intervention or more intense treatments for the former group can prevent poor outcomes.[70]

In conclusion, we demonstrate the power of combining genetic longitudinal population data to elucidate developmental patterns in psychopathology. Our study provides novel evidence for the presence of shared genetic factors between childhood psychopathology and depression and associated adult traits, as well as their stability across development. Insight into these associations may aid identification of children at risk for a relatively chronic course of illness, ultimately facilitating targeted treatment to this vulnerable group.

ARTICLE INFORMATION

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Author Affiliations: Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (Akingbuwa, Hammerschlag, Jami, Baselmans, Hagenbeek, Hottenga, Mbarek, van Beijsterveldt, Boomsma, Nivard, Bartels, Middeldorp); Amsterdam Public Health Research Institute, Amsterdam, the Netherlands (Akingbuwa, Hammerschlag, Jami, Hagenbeek, Boomsma, Bartels); Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia (Hammerschlag, Middeldorp); Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (Allegrini, Breen, Lewis, Rimfeld, Plomin); Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom (Karhunen, Jarvelin); University of Bristol School of Psychological Science, Bristol, United Kingdom (Sallis, Munafò); MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom (Sallis, Havdahl, Munafò); Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom (Sallis); Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway (Ask, Askeland, Tesli, Ystrom); Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands (Diemer, Tiemeier); Nic Waals Institute, Lovisenberg Diaconal Hospital, Oslo, Norway (Havdahl); Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway (Havdahl); Qatar Genome Programme, Qatar Foundation, Doha, Qatar (Mbarek); The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands (Rivadeneira); Erasmus MC, Department of Epidemiology, University Medical Center Rotterdam, Rotterdam, the Netherlands (Rivadeneira); Erasmus MC, Department of Internal Medicine, University Medical Center Rotterdam, Rotterdam, the Netherlands (Rivadeneira); National Institute of Health Research Biomedical Research Centre, South London and Maudsley National Health Services Foundation Trust, London, London, United Kingdom (Breen); Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom (Thapar); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Kuja-Halkola, Lichtenstein); Norwegian Institute of Public Health, Oslo, Norway (Reichborn-Kjennerud); University of Oslo, Oslo, Norway (Reichborn-Kjennerud); Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway (Magnus); PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway (Ystrom); Medical Research Council–Public Health England Centre for Environment and Health, Imperial College London, London, United Kingdom (Jarvelin); Center for Life Course Health Research, University of Oulu, Oulu, Finland (Jarvelin); Medical Research Center Oulu, Oulu, Finland (Jarvelin); Institute of Biomedicine and Biocenter of Oulu, Oulu, Finland (Jarvelin); Department of Life Sciences, Brunel University London College of Health and Life Sciences, London, United Kingdom (Jarvelin); Centre for Ethics Law and Mental Health, Gillberg Neuropsychiatry Centre, University of Gothenburg, Gothenburg, Sweden (Lundstrom); National Institute of Health Research Biomedical Research Centre, University Hospitals Bristol National Health Services Foundation Trust, University of Bristol, Bristol, United Kingdom (Munafò); Department of Social and Behavioral Science, Harvard T. H. Chan School of Medicine, Boston, Massachusetts (Tiemeier); Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Services, Brisbane, Queensland, Australia (Middeldorp).

Author Contributions: Ms Akingbuwa and Dr Middeldorp had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Akingbuwa, Baselmans, Lewis, Reichborn-Kjennerud, Munafo, Plomin, Tiemeier, Nivard, Bartels, Middeldorp.
Acquisition, analysis, or interpretation of data: Akingbuwa, Hammerschlag, Jami, Allegrini, Karhunen, Sallis, Ask, Askeland, Diemer, Hagenbeek, Havdahl, Hottenga, Mbarek, Rivadeneira, Tesli, Van Beijsterveldt, Breen, Thapar, Boomsma, Kuja-Halkola, Reichborn-Kjennerud, Magnus, Rimfeld, Ystrom, Jarvelin, Lichtenstein, Lundstrom, Plomin, Nivard, Bartels, Middeldorp.
Drafting of the manuscript: Akingbuwa, Hammerschlag, Baselmans, Hottenga, Mbarek, Lewis, Munafo, Bartels, Middeldorp.
Critical revision of the manuscript for important intellectual content: Akingbuwa, Hammerschlag, Jami, Allegrini, Karhunen, Sallis, Ask, Askeland, Diemer, Hagenbeek, Havdahl, Hottenga, Rivadeneira, Tesli, Van Beijsterveldt, Breen, Lewis, Thapar, Boomsma, Kuja-Halkola, Reichborn-Kjennerud, Magnus, Rimfeld, Ystrom, Jarvelin, Lichtenstein, Lundstrom, Plomin, Tiemeier, Nivard, Bartels.
Statistical analysis: Akingbuwa, Jami, Allegrini, Karhunen, Sallis, Baselmans, Diemer, Mbarek, Breen, Rimfeld, Nivard, Bartels, Middeldorp.
Obtained funding: Breen, Boomsma, Magnus, Ystrom, Jarvelin, Lichtenstein, Lundstrom, Plomin, Tiemeier, Bartels, Middeldorp.
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Supervision: Hammerschlag, Lewis, Munafo, Plomin, Bartels, Middeldorp.
Other—data curation Van Beijsterveldt.

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The Bipolar Disorder Working Group of the Psychiatric Genomics Consortium: Eli A. Stahl,

Icahn School of Medicine at Mount Sinai, New York, New York, and Broad Institute, Cambridge, Massachusetts; Gerome Breen, King's College London, London, UK; Andreas J. Forstner, University of Basel and University Hospital Basel, Basel, Switzerland, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany, and University of Marburg, Marburg, Germany; Andrew McQuillin, University College London, London, UK; Stephan Ripke, Broad Institute, Cambridge, Massachusetts, Charité-Universitätsmedizin, Berlin, Germany, and Massachusetts General Hospital, Boston, Massachusetts; Vassily Trubetskoy, Charité-Universitätsmedizin, Berlin, Germany; Manuel Mattheisen, iSEQ, Aarhus University, Aarhus, Denmark, Karolinska Institutet, Stockholm, Sweden, University Hospital Würzburg, Würzburg, Germany, and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Yunpeng Wang, Mental Health Centre Sct. Hans, Copenhagen, Denmark, and University of Oslo, Oslo, Norway; Jonathan R. I. Coleman, King's College London, London, UK; Héléna A. Gaspar, King's College London, London, UK; Christiaan A. de Leeuw, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Stacy Steinberg, deCODE Genetics/Amgen, Reykjavik, Iceland; Jennifer M. Whitehead Pavlides, The University of Queensland, Brisbane, Queensland, Australia; Maciej Trzaskowski, The University of Queensland, Brisbane, Queensland, Australia; Enda M. Byrne, The University of Queensland, Brisbane, Queensland, Australia; Tune H. Pers, Broad Institute, Cambridge, Massachusetts, and Boston Children's Hospital, Boston, Massachusetts; Peter A. Holmans, Cardiff University, Cardiff, UK; Alexander L. Richards, Cardiff University, Cardiff, UK; Liam Abbott, Broad Institute, Cambridge, Massachusetts; Esben Agerbo, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Aarhus University, Aarhus, Denmark; Huda Akil, University of Michigan, Ann Arbor; Diego Albani, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy; Ney Alliey-Rodriguez, University of Chicago, Chicago, Illinois; Thomas D. Als, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Adebayo Anjorin, Berkshire Healthcare National Health Services Foundation Trust, Bracknell, UK; Verneri Antilla, Massachusetts General Hospital, Boston, Massachusetts; Swapnil Awasthi, Charité-Universitätsmedizin, Berlin, Germany; Judith A. Badner, Rush University Medical Center, Chicago, Illinois; Marie Bækvad-Hansen, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Statens Serum Institut, Copenhagen, Denmark; Jack D. Barchas, Weill Cornell Medical College, New York, New York; Nicholas Bass, University College London, London, UK; Michael Bauer, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Richard Belliveau, Broad Institute, Cambridge, Massachusetts; Sarah E. Bergen, Karolinska Institutet, Stockholm, Sweden; Carsten Bøcker Pedersen, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Aarhus University, Aarhus, Denmark; Erlend Bøen, Diakonhjemmet Hospital, Oslo, Norway; Marco P. Boks, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, the Netherlands; James Boocock, University of California Los Angeles, Los Angeles; Monika Budde, University Hospital, Ludwig Maximilian University of Munich, Munich, Denmark; William Bunney, University of California, Irvine, Irvine; Margit Burmeister, University of Michigan, Ann Arbor; Jonas Bybjerg-Grauholm, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Statens Serum Institut, Copenhagen, Denmark; William Byerley, University of California San Francisco, San Francisco; Miquel Casas, Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health, Madrid, Spain, Hospital Universitari Vall d'Hebron, Barcelona, Spain, Universitat Autònoma de Barcelona, Barcelona, Spain, Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d'Hebron Research Institut, Universitat Autònoma de Barcelona, Barcelona, Spain; Felecia Cerrato, Broad Institute, Cambridge, Massachusetts; Pablo Cervantes, McGill University Health Center, Montreal, QC, Canada; Kimberly Chambert, Broad Institute, Cambridge, Massachusetts; Alexander W. Charney, Icahn School of Medicine at Mount Sinai, New York, New York; Danfeng Chen, Broad Institute, Cambridge, Massachusetts; Claire Churchhouse, Broad Institute, Cambridge, Massachusetts and Massachusetts General Hospital, Boston, Massachusetts; Toni-Kim Clarke, University of Edinburgh, Edinburgh, UK; William Coryell, University of Iowa Hospitals and Clinics, Iowa City; David W. Craig, Translational Genomics Research Institute, USC, Phoenix, Arizona; Cristiana Cruceanu, McGill University Health Center, Montreal, QC, Canada, and Max Planck Institute of Psychiatry, Munich, Denmark; David Curtis, Centre for Psychiatry, Queen Mary University of London, London, UK, and UCL Genetics Institute, University College London, London, UK; Piotr M. Czerski, Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland; Anders M. Dale, University of California San Diego, La Jolla; Simone de Jong, King's College London, London, UK; Franziska Degenhardt, Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany; Jurgen Del-Favero, University of Antwerp, Antwerp, Belgium; J. Raymond DePaulo, Johns Hopkins University School of Medicine, Baltimore, Maryland; Srdjan Djurovic, Oslo University Hospital Ullevål, Oslo, Norway, and University of Bergen, Bergen, Norway; Amanda L. Dobbyn, Icahn School of Medicine at Mount Sinai, New York, New York; Ashley Dumont, Broad Institute, Cambridge, Massachusetts; Torbjørn Elvsåshagen, Oslo University Hospital, Oslo, Norway; Valentina Escott-Price, Cardiff University, Cardiff, UK; Chun Chieh Fan, University of California San Diego, La Jolla, California; Sascha B. Fischer, University of Basel, Basel, Switzerland, and University Hospital Basel, Basel, Switzerland; Matthew Flickinger, University of Michigan, Ann Arbor; Tatiana M. Foroud, Indiana University, Indianapolis; Liz Forty, Cardiff University, Cardiff, UK; Josef Frank, Heidelberg University, Mannheim, Germany; Christine Fraser, Cardiff University, Cardiff, UK; Nelson B. Freimer, University of California Los Angeles, Los Angeles; Louise Frisén, Karolinska University Hospital, Stockholm, Sweden and Child and Adolescent Psychiatry Research Center, Stockholm, Sweden; Katrin Gade, University Hospital, Ludwig Maximilian University of Munich, Munich, Germany, and University Medical Center Göttingen, Göttingen, Germany; Diane Gage, Broad Institute, Cambridge, Massachusetts; Julie Garnham, Dalhousie University, Halifax, Nova Scotia, Canada; Claudia Giambartolomei, University of California Los Angeles, Los Angeles; Marianne Giørtz Pedersen, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Aarhus University, Aarhus, Denmark; Jaqueline Goldstein, Broad Institute, Cambridge, Massachusetts; Scott D. Gordon, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; Katherine Gordon-Smith, University of Worcester, Worcester, UK; Elaine K. Green, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK; Melissa J. Green, University of New South Wales, Sydney, New South Wales, Australia, Neuroscience Research Australia, Sydney, New South Wales, Australia; Tiffany A. Greenwood, Department of Psychiatry, University of California San Diego, La Jolla; Jakob Grove, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Weihua Guan, University of Minnesota System, Minneapolis; José Guzman-Parra, University Regional Hospital, Biomedicine Institute, Málaga, Spain; Marian L. Hamshere, Cardiff University, Cardiff, UK; Martin Hautzinger, Eberhard Karls Universität Tübingen, Tubingen, Germany; Urs Heilbronner, University Hospital, Ludwig Maximilian University of Munich, Munich, Germany; Stefan Herms, University of Basel, Basel, Switzerland, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany, and University Hospital Basel, Basel, Switzerland; Maria Hipolito, Howard University Hospital, Washington, DC; Per Hoffmann, University of Basel, Basel, Switzerland, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany, University Hospital Basel, Basel, Switzerland; Dominic Holland, University of California San Diego, La Jolla; Laura Huckins, Icahn School of Medicine at Mount Sinai, New York, New York; Stéphane Jamain, INSERM U955, Créteil, France, and Université Paris Est, Créteil, France; Jessica S. Johnson, Icahn School of Medicine at Mount Sinai, New York, New York; Anders Juréus, Karolinska Institutet, Stockholm, Sweden; Radhika Kandaswamy, King's College London, London, UK; Robert Karlsson, Karolinska Institutet, Stockholm, Sweden; James L. Kennedy, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, University of Toronto, Toronto, Ontario, Canada, and University of Toronto, Toronto, Ontario, Canada; Sarah Kittel-Schneider, University Hospital Frankfurt, Frankfurt am Main, Germany; James A. Knowles, SUNY Downstate Medical Center College of Medicine, Brooklyn, New York; Manolis Kogevinas, ISGlobal, Barcelona, Spain; Anna C. Koller, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany; Ralph Kupka, Altrecht, Utrecht, the Netherlands, GGZ inGeest, Amsterdam, the Netherlands, Psychiatry, VU Medisch Centrum, Amsterdam, the Netherlands; Catharina Lavebratt, Karolinska University Hospital, Stockholm, Sweden; Jacob Lawrence, North East London National Health Services Foundation Trust, Ilford, UK; William B. Lawson, Howard University Hospital, Washington, DC; Markus Leber, University Hospital Cologne, Cologne, Germany; Phil H. Lee, Broad Institute, Cambridge, Massachusetts, Massachusetts General Hospital, Boston, Massachusetts; Shawn E. Levy, HudsonAlpha Institute for Biotechnology, Huntsville, Alabama; Jun Z. Li, University of Michigan, Ann Arbor; Chunyu Liu, University of Illinois at Chicago College of Medicine, Chicago; Susanne Lucae, Max Planck Institute of Psychiatry, Munich, Germany; Anna Maaser, Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital

Bonn, Bonn, Germany; Donald J. MacIntyre, National Health Services 24, Glasgow, UK, and Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK; Pamela B. Mahon, Johns Hopkins University School of Medicine, Baltimore, Maryland, Brigham and Women's Hospital, Boston, Massachusetts; Wolfgang Maier, University of Bonn, Bonn, Germany; Lina Martinsson, Karolinska University Hospital, Stockholm, Sweden; Steve McCarroll, Broad Institute, Cambridge, Massachusetts, and Harvard Medical School, Boston, Massachusetts; Peter McGuffin, King's College London, London, UK; Melvin G. McInnis, University of Michigan, Ann Arbor; James D. McKay, International Agency for Research on Cancer, Lyon, France; Helena Medeiros, SUNY Downstate Medical Center College of Medicine, Brooklyn, New York; Sarah E. Medland, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; Fan Meng, University of Michigan, Ann Arbor; Lili Milani, University of Tartu, Tartu, Estonia; Grant W. Montgomery, The University of Queensland, Brisbane, Queensland, Australia; Derek W. Morris, National University of Ireland, Galway, Galway, Ireland, and Trinity College Dublin, Dublin, Ireland; Thomas W. Mühleisen, Department of Biomedicine, University of Basel, Basel, Switzerland, Institute of Neuroscience and Medicine, Research Centre Jülich, Jülich, Germany; Niamh Mullins, Icahn School of Medicine at Mount Sinai, New York; Hoang Nguyen, Icahn School of Medicine at Mount Sinai, New York, New York; Caroline M. Nievergelt, University of California San Diego, La Jolla, Veterans Affairs San Diego Healthcare System, San Diego, California; Annelie Nordin Adolfsson, Umeå University Medical Faculty, Umeå, Sweden; Evaristus A. Nwulia, Howard University Hospital, Washington, DC; Claire O'Donovan, Dalhousie University, Halifax, Nova Scotia, Canada; Loes M. Olde Loohuis, University of California Los Angeles, Los Angeles; Anil P. S. Ori, University of California Los Angeles, Los Angeles; Lilijana Oruc, Clinical Center University of Sarajevo, Sarajevo, Bosnia-Herzegovina; Urban Ösby, Karolinska University Hospital, Stockholm, Sweden; Roy H. Perlis, Harvard Medical School, Boston, Massachusetts, and Massachusetts General Hospital, Boston, Massachusetts; Amy Perry, University of Worcester, Worcester, UK; Andrea Pfennig, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; James B. Potash, Johns Hopkins University School of Medicine, Baltimore, Maryland; Shaun M. Purcell, Icahn School of Medicine at Mount Sinai, New York, New York, and Brigham and Women's Hospital, Boston, Massachusetts; Eline J. Regeer, Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, the Netherlands; Andreas Reif, University Hospital Frankfurt, Frankfurt am Main, Germany; Céline S. Reinbold, University of Basel, Basel, Switzerland, and University Hospital Basel, Basel, Switzerland; John P. Rice, Washington University in St Louis, St Louis, Missouri; Fabio Rivas, University Regional Hospital, Biomedicine Institute, Málaga, Spain; Margarita Rivera, King's College London, London, UK, University of Granada, Granada, Spain; Panos Roussos, Icahn School of Medicine at Mount Sinai, New York, New York, Icahn School of Medicine at Mount Sinai, New York, New York; Douglas M. Ruderfer, Vanderbilt University Medical Center, Nashville, Tennessee; Euijung Ryu, Mayo Clinic, Rochester, Minnesota; Cristina Sánchez-Mora, Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health, Madrid, Spain, Hospital Universitari Vall d'Hebron, Barcelona, Spain, Vall d'Hebron Research Institut, Universitat Autònoma de Barcelona, Barcelona, Spain; Alan F. Schatzberg, Stanford University School of Medicine, Stanford, California; William A. Scheftner, Rush University Medical Center, Chicago, Illinois; Nicholas J. Schork, Scripps Translational Science Institute, La Jolla, California; Cynthia Shannon Weickert, University of New South Wales, Sydney, New South Wales, Australia, Neuroscience Research Australia, Sydney, New South Wales, Australia, SUNY Upstate Medical University, Syracuse, New York; Tatyana Shehktman, University of California San Diego, La Jolla; Paul D. Shilling, University of California San Diego, La Jolla; Engilbert Sigurdsson, University of Iceland, Reykjavik, Iceland; Claire Slaney, Dalhousie University, Halifax, Nova Scotia, Canada; Olav B. Smeland, University of California San Diego, La Jolla, Oslo University Hospital, Oslo, Norway; Janet L. Sobell, University of Southern California, Los Angeles; Christine Søholm Hansen, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Statens Serum Institut, Copenhagen, Denmark; Anne T. Spijker, PsyQ, Rotterdam, the Netherlands; David St Clair, Institute for Medical Sciences, University of Aberdeen, Aberdeen, UK; Michael Steffens, Federal Institute for Drugs and Medical Devices, Bonn, Germany; John S. Strauss, University of Toronto, Toronto, Ontario, Canada, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; Fabian Streit, Heidelberg University, Mannheim, Germany; Jana Strohmaier, Heidelberg University, Mannheim, Germany; Szabolcs Szelinger, TGen, Phoenix, Arizona; Robert C. Thompson, Department of Psychiatry, University of Michigan, Ann Arbor; Thorgeir E. Thorgeirsson, deCODE Genetics/Amgen, Reykjavik, Iceland; Jens Treutlein, Heidelberg University, Mannheim, Germany; Helmut Vedder, Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany; Weiqing Wang, Icahn School of Medicine at Mount Sinai, New York, New York; Stanley J. Watson, University of Michigan, Ann Arbor; Thomas W. Weickert, University of New South Wales, Sydney, New South Wales, Australia, Neuroscience Research Australia, Sydney, New South Wales, Australia, SUNY Upstate Medical University, Syracuse, New York; Stephanie H. Witt, Heidelberg University, Mannheim, Germany; Simon Xi, Pfizer Global Research and Development, Cambridge, Massachusetts; Wei Xu, Princess Margaret Cancer Centre, Toronto, Ontario, Canada, University of Toronto, Toronto, Ontario, Canada; Allan H. Young, King's College London, London, UK; Peter Zandi, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; Peng Zhang, Johns Hopkins University School of Medicine, Baltimore, Maryland; Sebastian Zöllner, University of Michigan, Ann Arbor; Rolf Adolfsson, Umeå University Medical Faculty, Umeå, Sweden; Ingrid Agartz, Karolinska Institutet, Stockholm, Sweden, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, Norway; Martin Alda, Dalhousie University, Halifax, Nova Scotia, Canada, National Institute of Mental Health, Klecany, Czech Republic; Lena Backlund, Karolinska University Hospital, Stockholm, Sweden; Bernhard T. Baune, Department of Psychiatry, University of Münster, Münster, Germany; Frank Bellivier, Department of Psychiatry and Addiction Medicine, Assistance Publique–Hôpitaux de Paris, Paris, France, Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, France, UMR-S1144 Team 1, INSERM, Paris, France, Université Paris Diderot, Paris, France; Wade H. Berrettini, University of Pennsylvania, Philadelphia; Joanna M. Biernacka, Mayo Clinic, Rochester, Minnesota; Douglas H. R. Blackwood, University of Edinburgh, Edinburgh, UK; Michael Boehnke, University of Michigan, Ann Arbor; Anders D. Børglum, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Aiden Corvin, Trinity College Dublin, Dublin, Ireland; Nicholas Craddock, Cardiff University, Cardiff, UK; Mark J. Daly, Broad Institute, Cambridge, Massachusetts, and Massachusetts General Hospital, Boston, Massachusetts; Udo Dannlowski, University of Münster, Münster, Germany; Tõnu Esko, Broad Institute, Cambridge, Massachusetts, Harvard Medical School, Boston, Massachusetts, University of Tartu, Tartu, Estonia, and Children's Hospital Boston, Boston, Massachusetts; Bruno Etain, Assistance Publique–Hôpitaux de Paris, Paris, France, UMR-S1144 Team 1, INSERM, Paris, France, Université Paris Diderot, Paris, France, and Institute of Psychiatry, Psychology and Neuroscience, London, UK; Mark Frye, Mayo Clinic, Rochester, Minnesota; Janice M. Fullerton, Neuroscience Research Australia, Sydney, New South Wales, Australia, and University of New South Wales, Sydney, New South Wales, Australia; Elliot S. Gershon, University of Chicago, Chicago, Illinois; Michael Gill, Trinity College Dublin, Dublin, Ireland; Fernando Goes, Johns Hopkins University School of Medicine, Baltimore, Maryland; Maria Grigoroiu-Serbanescu, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania; Joanna Hauser, Poznan University of Medical Sciences, Poznan, Poland; David M. Hougaard, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, and Statens Serum Institut, Copenhagen, Denmark; Christina M. Hultman, Karolinska Institutet, Stockholm, Sweden; Ian Jones, Cardiff University, Cardiff, UK; Lisa A. Jones, University of Worcester, Worcester, UK; René S. Kahn, Icahn School of Medicine at Mount Sinai, New York, New York, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, the Netherlands; George Kirov, Cardiff University, Cardiff, UK; Mikael Landén, Karolinska Institutet, Stockholm, Sweden, University of Gothenburg, Gothenburg, Sweden; Marion Leboyer, Faculté de Médecine, Université Paris Est, Créteil, France, Assistance Publique–Hôpitaux de Paris, Paris, France, and INSERM, Paris, France; Cathryn M. Lewis, King's College London, London, UK; Qingqin S. Li, Janssen Research and Development LLC, Titusville, New Jersey; Jolanta Lissowska, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland; Nicholas G. Martin, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia, The University of Queensland, Brisbane, Queensland, Australia; Fermin Mayoral, University Regional Hospital, Biomedicine Institute, Málaga, Spain; Susan L. McElroy, Lindner Center of HOPE, Mason, Ohio; Andrew M. McIntosh, University of Edinburgh, Edinburgh, UK; Francis J. McMahon, National Institute of Mental Health, Bethesda, Maryland; Ingrid Melle, Oslo University Hospital, Oslo, Norway, University of Oslo, Institute of Clinical Medicine, Oslo, Norway; Andres Metspalu, University of Tartu, Tartu, Estonia; Philip B. Mitchell, University of New South Wales, Sydney, New South Wales, Australia; Gunnar Morken, Norwegian University of Science and Technology, Trondheim, Norway, Psychiatry, St Olavs University Hospital, Trondheim, Norway; Ole Mors, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Aarhus University Hospital, Risskov, Denmark; Preben Bo

Mortensen, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Bertram Müller-Myhsok, Max Planck Institute of Psychiatry, Munich, Germany, Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, University of Liverpool, Liverpool, UK; Richard M. Myers, HudsonAlpha Institute for Biotechnology, Huntsville, Alabama; Benjamin M. Neale, Broad Institute, Cambridge, Massachusetts and Massachusetts General Hospital, Boston, Massachusetts; Vishwajit Nimgaonkar, University of Pittsburgh, Pittsburgh, Pennsylvania; Merete Nordentoft, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, University of Copenhagen, Copenhagen, Denmark; Markus M. Nöthen, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany; Michael C. O'Donovan, Cardiff University, Cardiff, UK; Ketil J. Oedegaard, Haukeland Universitetssjukehus, Bergen, Norway, University of Bergen, Bergen, Norway; Michael J. Owen, Cardiff University, Cardiff, UK; Sara A. Paciga, Pfizer Global Research and Development, Groton, Connectictu; Carlos Pato, SUNY Downstate Medical Center College of Medicine, Brooklyn, New York; Michele T. Pato, SUNY Downstate Medical Center College of Medicine, Brooklyn, New York; Danielle Posthuma, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; Josep Antoni Ramos-Quiroga, Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health, Madrid, Spain, Hospital Universitari Vall d'Hebron, Barcelona, Spain, Universitat Autònoma de Barcelona, Barcelona, Spain, Vall d'Hebron Research Institut, Universitat Autònoma de Barcelona, Barcelona, Spain; Marta Ribasés, Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health, Madrid, Spain, Hospital Universitari Vall d'Hebron, Barcelona, Spain, Vall d'Hebron Research Institut, Universitat Autònoma de Barcelona, Barcelona, Spain; Marcella Rietschel, Heidelberg University, Mannheim, Germany; Guy A. Rouleau, McGill University, Faculty of Medicine, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Martin Schalling, Karolinska University Hospital, Stockholm, Sweden; Peter R. Schofield, Neuroscience Research Australia, Sydney, New South Wales, Australia, School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Thomas G. Schulze, Ludwig Maximilian University of Munich, Munich, Germany, Johns Hopkins University School of Medicine, Baltimore, Maryland, Heidelberg University, Mannheim, Germany, University Medical Center Göttingen, Göttingen, Germany, and National Institute of Mental Health, Bethesda, Maryland; Alessandro Serretti, University of Bologna, Bologna, Italy; Jordan W. Smoller, Broad Institute, Cambridge, Massachusetts, and Massachusetts General Hospital, Boston, Massachusetts; Hreinn Stefansson, deCODE Genetics/Amgen, Reykjavik, Iceland; Kari Stefansson, deCODE Genetics/Amgen, Reykjavik, Iceland, and University of Iceland, Reykjavik, Iceland; Eystein Stordal, Hospital Namsos, Namsos, Norway, Norges Teknisk Naturvitenskapelige Universitet, Trondheim, Norway; Patrick F. Sullivan, Karolinska Institutet, Stockholm, Sweden, University of North Carolina at Chapel Hill, Chapel Hill; Gustavo Turecki, McGill University, Montreal, Quebec, Canada; Arne E. Vaaler, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway; Eduard Vieta, University of Barcelona, August Pi i Sunyer Biomedical Research Institute, Biomedical Research Networking Center for Mental Health Network, Barcelona, Spain; John B. Vincent, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; Thomas Werge, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Institute of Biological Psychiatry, Mental Health Services Copenhagen, Roskilde, Denmark, University of Copenhagen, Copenhagen, Denmak; John I. Nurnberger, Indiana University School of Medicine, Indianapolis; Naomi R. Wray, The University of Queensland, Brisbane, Queensland, Australia; Arianna Di Florio, Cardiff University, Cardiff, UK, University of North Carolina at Chapel Hill, Chapel Hill; Howard J. Edenberg, Indiana University School of Medicine, Indianapolis; Sven Cichon, University of Basel, Basel, Switzerland, Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany, Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland, Institute of Neuroscience and Medicine, Research Centre Jülich, Jülich, Germany; Roel A. Ophoff, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, the Netherlands, University of California Los Angeles, Los Angeles; Laura J. Scott, University of Michigan, Ann Arbor; Ole A. Andreassen, Oslo University Hospital, Oslo, Norway, and University of Oslo, Oslo, Norway; John Kelsoe, University of California San Diego, La Jolla; Pamela Sklar, Icahn School of Medicine at Mount Sinai, New York, New York.

The Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium: Naomi R. Wray, The University of Queensland, Brisbane, Queensland, Australia; Stephan Ripke, Broad Institute, Cambridge, Massachusetts, Massachusetts General Hospital, Boston, Massachusetts, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Germany; Manuel Mattheisen, Aarhus University, Aarhus, Denmark, Karolinska Institutet, Stockholm, Sweden, University of Würzburg, Würzburg, Germany; Maciej Trzaskowski, The University of Queensland, Brisbane, Queensland, Australia; Enda M. Byrne, The University of Queensland, Brisbane, Queensland, Australia; Abdel Abdellaoui, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Mark J. Adams, University of Edinburgh, Edinburgh, UK; Esben Agerbo, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Tracy M. Air, University of Adelaide, Adelaide, South Australia, Australia; Till F. M. Andlauer, Max Planck Institute of Psychiatry, Munich, Germany, Technical University of Munich, Munich, Germany; Silviu-Alin Bacanu, Virginia Commonwealth University, Richmond; Marie Bækvad-Hansen, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Statens Serum Institut, Copenhagen, Denmark; Aartjan T. F. Beekman, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; Tim B. Bigdeli, Virginia Commonwealth University, Richmond, Virginia Institute for Psychiatric and Behavior Genetics, Richmond; Elisabeth B. Binder, Emory University School of Medicine, Atlanta, Georgia, Max Planck Institute of Psychiatry, Munich, Germany; Julien Bryois, Karolinska Institutet, Stockholm, Sweden; Henriette N. Buttenschøn, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Jonas Bybjerg-Grauholm, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Statens Serum Institut, Copenhagen, Denmark; Na Cai, Helmholtz Zentrum München, Munich, Germany; Enrique Castelao, Lausanne University Hospital and University of Lausanne, Prilly, Vaud, Switzerland; Jane Hvarregaard Christensen, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Toni-Kim Clarke, University of Edinburgh, Edinburgh, UK; Jonathan R. I. Coleman, King's College London, London, UK; Lucía Colodro-Conde, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia; Hilary Coon, University of Utah, Salt Lake City; Baptiste Couvy-Duchesne, The University of Queensland, St Lucia, Queensland, Australia; Nick Craddock, Cardiff University, Cardiff, UK; Gregory E. Crawford, Duke University, Durham, North Carolina; Gail Davies, University of Edinburgh, Edinburgh, UK; Ian J. Deary, University of Edinburgh, Edinburgh, UK; Franziska Degenhardt, University of Bonn, Bonn, Nordrhein-Westfalen, Germany, University of Duisburg-Essen, University Hospital Essen, Essen, Nordrhein-Westfalen, Germany; Eske M. Derks, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia; Nese Direk, Dokuz Eylul University School Of Medicine, Izmir, Turkey, Erasmus MC, Rotterdam, the Netherlands; Conor V. Dolan, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Thalia C. Eley, King's College London, London, UK; Valentina Escott-Price, Cardiff University, Cardiff, UK; Farnush Farhadi Hassan Kiadeh, University of British Columbia, Vancouver, British Columbia, Canada; Hilary K. Finucane, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, Massachusetts Institute of Technology, Cambridge, Massachusetts; Jerome C. Foo, Heidelberg University, Mannheim, Germany; Andreas J. Forstner, University of Basel, Basel, Switzerland, University of Bonn, Bonn, Germany, University of Marburg, Marburg, Germany; Josef Frank, Heidelberg University, Mannheim, Germany; Héléna A. Gaspar, King's College London, London, UK; Michael Gill, Trinity College Dublin, Dublin, Ireland; Fernando S. Goes, Johns Hopkins University, Baltimore, Maryland; Scott D. Gordon, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; Jakob Grove, Aarhus University, Aarhus, Denmark,iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Lynsey S. Hall, Newcastle University, Newcastle upon Tyne, UK, University of Edinburgh, Edinburgh, UK; Christine Søholm Hansen, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Statens Serum Institut, Copenhagen, Denmark; Thomas F. Hansen, Rigshospitalet, Glostrup, Denmark, Mental Health Center Sct. Hans, Copenhagen, Denmark, The Lundbeck Foundation Initiative for Psychiatric Research, iPSYCH, Copenhagen, Denmark; Stefan Herms, University of Basel, Basel, Switzerland, University of Bonn, Bonn, Germany; Ian B. Hickie, University of Sydney, Sydney, New South Wales, Australia; Per Hoffmann, University of Basel, Basel, Switzerland, University of Bonn, Bonn, Germany; Georg Homuth, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Germany; Carsten Horn, F. Hoffmann-La Roche Ltd, Basel, Switzerland; Jouke-Jan Hottenga, Vrije Universiteit

Amsterdam, Amsterdam, the Netherlands; David M. Howard, University of Edinburgh, Edinburgh, UK, King's College London, UK; David M. Hougaard, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Statens Serum Institut, Copenhagen, Denmark; Marcus Ising, Max Planck Institute of Psychiatry, Munich, Germany; Rick Jansen, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; Ian Jones, Cardiff University, Cardiff, UK; Lisa A. Jones, University of Worcester, Worcester, UK; Eric Jorgenson, Kaiser Permanente Northern California, Oakland, California; James A. Knowles, University of Southern California, Los Angeles, California; Isaac S. Kohane, Boston Children's Hospital, Boston, Massachusetts, Brigham and Women's Hospital, Boston, Massachusetts, Harvard Medical School, Boston, Massachusetts; Julia Kraft, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Germany; Warren W. Kretzschmar, University of Oxford, Oxford, UK; Zoltán Kutalik, Swiss Institute of Bioinformatics, Lausanne, Switzerland, University Hospital of Lausanne, Lausanne, VD, Switzerland; Yihan Li, University of Oxford, Oxford, UK; Penelope A. Lind, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia; Jurjen J. Luykx, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, GGNet Mental Health, Apeldoorn, the Netherlands; Donald J. MacIntyre, National Health Services 24, Glasgow, UK, University of Edinburgh, Edinburgh, UK; Dean F. MacKinnon, Johns Hopkins University, Baltimore, Maryland; Robert M. Maier, The University of Queensland, Brisbane, Queensland, Australia; Wolfgang Maier, University of Bonn, Bonn, Germany; Jonathan Marchini, University of Oxford, Oxford, UK; Hamdi Mbarek, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Patrick McGrath, Columbia University College of Physicians and Surgeons, New York, New York; Peter McGuffin, King's College London, London, UK; Sarah E. Medland, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia; Divya Mehta, Queensland University of Technology, Brisbane, Queensland, Australia, The University of Queensland, Brisbane, Queensland, Australia; Christel M. Middeldorp, Children's Health Queensland Hospital and Health Service, South Brisbane, Queensland, Australia, University of Queensland, Brisbane, Queensland, Australia, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Evelin Mihailov, University of Tartu, Tartu, Estonia; Yuri Milaneschi, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; Lili Milani, University of Tartu, Tartu, Estonia; Francis M. Mondimore, Johns Hopkins University, Baltimore, Maryland; Grant W. Montgomery, The University of Queensland, Brisbane, Queensland, Australia; Sara Mostafavi, University of British Columbia, Vancouver, British Columbia, Canada, University of British Columbia, Vancouver, British Columbia, Canada; Niamh Mullins, King's College London, London, UK; Matthias Nauck, University Medicine Greifswald, Greifswald, Germany; Bernard Ng, University of British Columbia, Vancouver, British Columbia, Canada; Michel G. Nivard, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Dale R. Nyholt, Queensland University of Technology, Brisbane, Queensland, Australia; Paul F. O'Reilly, King's College London, London, UK; Hogni Oskarsson, Humus, Reykjavik, Iceland; Michael J. Owen, Cardiff University, Cardiff, UK; Jodie N. Painter, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia; Carsten Bøcker Pedersen, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Marianne Giørtz Pedersen, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Roseann E. Peterson, Virginia Commonwealth University, Richmond; Erik Pettersson, Karolinska Institutet, Stockholm, Sweden; Wouter J. Peyrot, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; Giorgio Pistis, Lausanne University Hospital and University of Lausanne, Prilly, Switzerland; Danielle Posthuma, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; Jorge A. Quiroz, Solid Biosciences, Boston, Massachusetts; Per Qvist, Aarhus University, Aarhus, Denmark, Aarhus University, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; John P. Rice, Washington University in St. Louis School of Medicine, St Louis, Missouri; Brien P. Riley, Virginia Commonwealth University, Richmond; Margarita Rivera, King's College London, London, UK, University of Granada, Granada, Spain; Saira Saeed Mirza, Erasmus MC, Rotterdam, the Netherlands; Robert Schoevers, University of Groningen, Groningen, the Netherlands; Eva C. Schulte, Medical Center of the University of Munich, Munich, Germany; Ling Shen, Kaiser Permanente Northern California, Oakland; Jianxin Shi, National Cancer Institute, Bethesda, Maryland; Stanley I. Shyn, Kaiser Permanente Washington, Seattle, Washington; Engilbert Sigurdsson, University of Iceland, Reykjavik, Iceland; Grant C. B. Sinnamon, James Cook University, Townsville, Queensland, Australia; Johannes H. Smit, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; Daniel J. Smith, University of Glasgow, Glasgow, UK; Hreinn Stefansson, deCODE Genetics/Amgen, Reykjavik, Iceland; Stacy Steinberg, deCODE Genetics/Amgen, Reykjavik, Iceland; Fabian Streit, Heidelberg University, Mannheim, Germany; Jana Strohmaier, Heidelberg University, Mannheim, Germany; Katherine E. Tansey, Cardiff University, Cardiff, UK; Henning Teismann, University of Münster, Münster, Germany; Alexander Teumer, University Medicine Greifswald, Institute Greifswald, Germany; Wesley Thompson, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Mental Health Center Sct. Hans, Copenhagen, Denmark, Oslo University Hospital, Oslo, Norway, University of California, San Diego, San Diego; Pippa A. Thomson, University of Edinburgh, Edinburgh, UK; Thorgeir E. Thorgeirsson, deCODE Genetics/Amgen, Reykjavik, Iceland; Matthew Traylor, University of Cambridge, Cambridge, UK; Jens Treutlein, Heidelberg University, Mannheim, Germany; Vassily Trubetskoy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Germany; André G. Uitterlinden, Erasmus MC, Rotterdam, the Netherlands; Daniel Umbricht, F. Hoffmann-La Roche Ltd, Basel, Switzerland; Sandra Van der Auwera, University Medicine Greifswald, Greifswald, Germany; Albert M. van Hemert, Leiden University Medical Center, Leiden, the Netherlands; Alexander Viktorin, Karolinska Institutet, Stockholm, Sweden; Peter M. Visscher, The University of Queensland, Brisbane, Queensland, Australia; Yunpeng Wang, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Mental Health Center Sct. Hans, Copenhagen, Denmark, Oslo University Hospital, Oslo, Norway; Bradley T. Webb, Virginia Commonwealth University, Richmond; Shantel Marie Weinsheimer, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Mental Health Center Sct. Hans, Copenhagen, Denmark; Jürgen Wellmann, University of Münster, Münster, Germany; Gonneke Willemsen, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Stephanie H. Witt, Heidelberg University, Mannheim, Germany; Yang Wu, The University of Queensland, Brisbane, Queensland, Australia; Hualin S. Xi, Pfizer Global Research and Development, Cambridge, Massachusetts; Jian Yang, The University of Queensland, Brisbane, Queensland, Australia; Futao Zhang, The University of Queensland, Brisbane, Queensland, Australia; Volker Arolt, University of Münster, Münster, Germany; Bernhard T. Baune, University of Münster, Münster, Germany, University of Melbourne, Melbourne, Victoria, Australia; Klaus Berger, University of Münster, Münster, Germany; Dorret I. Boomsma, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Sven Cichon, Research Center Juelich, Juelich, Germany, University of Basel, Basel, Switzerland, University of Basel, University Hospital Basel, Basel, Switzerland, University of Bonn, Bonn, Germany; Udo Dannlowski, University of Münster, Münster, Germany; EJC de Geus, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; J. Raymond DePaulo, Johns Hopkins University, Baltimore, Maryland; Enrico Domenici, Università degli Studi di Trento, Trento, Italy; Katharina Domschke, Faculty of Medicine, University of Freiburg, Freiburg, Germany; Tõnu Esko, Broad Institute, Cambridge, Massachusetts, University of Tartu, Tartu, Estonia; Hans J. Grabe, University Medicine Greifswald, Greifswald, Germany; Steven P. Hamilton, Kaiser Permanente Northern California, San Francisco; Caroline Hayward, University of Edinburgh, Edinburgh, UK; Andrew C. Heath, Washington University in St. Louis School of Medicine, St. Louis, Missouri; Kenneth S. Kendler, Virginia Commonwealth University, Richmond; Stefan Kloiber, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, Max Planck Institute of Psychiatry, Munich, Germany, University of Toronto, Toronto, Ontario, Canada; Glyn Lewis, University College London, London, UK; Qingqin S. Li, Janssen Research and Development LLC, Titusville, New Jersey; Susanne Lucae, Max Planck Institute of Psychiatry, Munich, Germany; Pamela A.F. Madden, Washington University in St. Louis School of Medicine, St. Louis, Missouri; Patrik K.E. Magnusson, Karolinska Institutet, Stockholm, Sweden; Nicholas G. Martin, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; Andrew M. McIntosh, University of Edinburgh, Edinburgh, UK; Andres Metspalu, University of Tartu, Tartu, Estonia; Ole Mors, Aarhus University Hospital, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric

Research, Denmark; Preben Bo Mortensen, Aarhus University, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Bertram Müller-Myhsok, Max Planck Institute of Psychiatry, Munich, Germany, Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, University of Liverpool, Liverpool, UK; Merete Nordentoft, Copenhagen University Hospital, Copenhagen, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Markus M. Nöthen, University of Bonn, Bonn, Germany; Michael C. O'Donovan, Cardiff, UK; Sara A. Paciga, Pfizer Global Research and Development, Groton, Connecticut; Nancy L. Pedersen, Karolinska Institutet, Stockholm, Sweden; Brenda WJH Penninx, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; Roy H. Perlis, Harvard Medical School, Boston, Massachusetts, Massachusetts General Hospital, Boston, Massachusetts; David J. Porteous, University of Edinburgh, Edinburgh, UK; James B. Potash, University of Iowa, Iowa City; Martin Preisig, Lausanne University Hospital and University of Lausanne, Prilly, Switzerland; Marcella Rietschel, Heidelberg University, Mannheim, Germany; Catherine Schaefer, Kaiser Permanente Northern California, Oakland; Thomas G. Schulze, Heidelberg University, Mannheim, Germany, Johns Hopkins University, Baltimore, Maryland, Medical Center of the University of Munich, Munich, Germany, NIMH Division of Intramural Research Programs, Human Genetics Branch, Bethesda, Maryland, University Medical Center Göttingen, Goettingen, Germany; Jordan W. Smoller, Broad Institute, Cambridge, Massachusetts, Massachusetts General Hospital, Boston, Massachusetts, Massachusetts General Hospital, Boston, Massachusetts; Kari Stefansson, deCODE Genetics/Amgen, Reykjavik, Iceland, University of Iceland, Reykjavik, Iceland; Henning Tiemeier, Erasmus MC, Rotterdam, Zuid-Holland, the Netherlands, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; Rudolf Uher, Dalhousie University, Halifax, Nova Scotia, Canada; Henry Völzke, University Medicine Greifswald, Greifswald, Germany; Myrna M. Weissman, Columbia University College of Physicians and Surgeons, New York, New York, New York State Psychiatric Institute, New York; Thomas Werge, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, Mental Health Center Sct. Hans, Copenhagen, Denmark, University of Copenhagen, Copenhagen, Denmark; Cathryn M. Lewis, King's College London, London, UK; Douglas F. Levinson, Stanford University, Stanford, California; Gerome Breen, King's College London, London, UK; Anders D. Børglum, Aarhus University, Aarhus, Denmark, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark; Patrick F. Sullivan, Karolinska Institutet, Stockholm, Sweden, University of North Carolina at Chapel Hill, Department of Genetics, Chapel Hill, North Carolina, University of North Carolina at Chapel Hill, Department of Psychiatry, Chapel Hill.

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