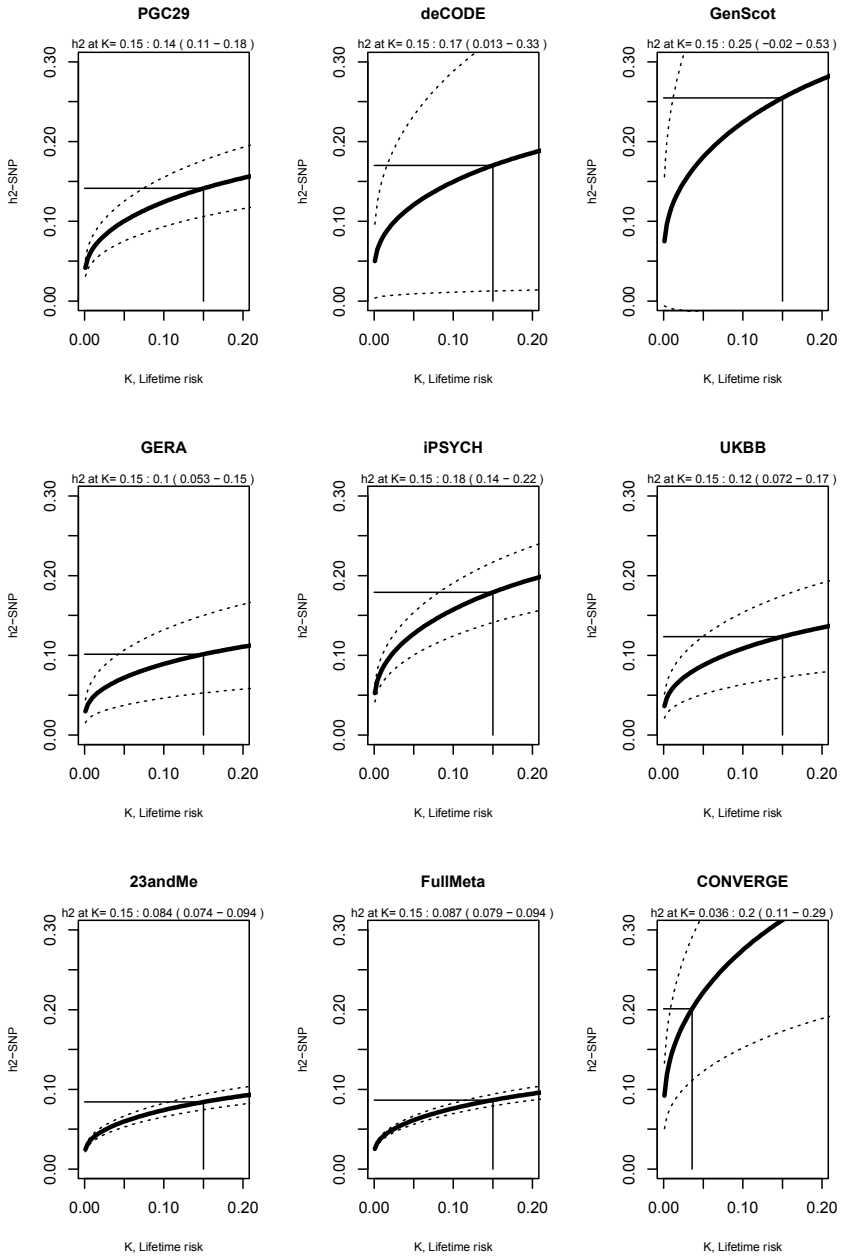
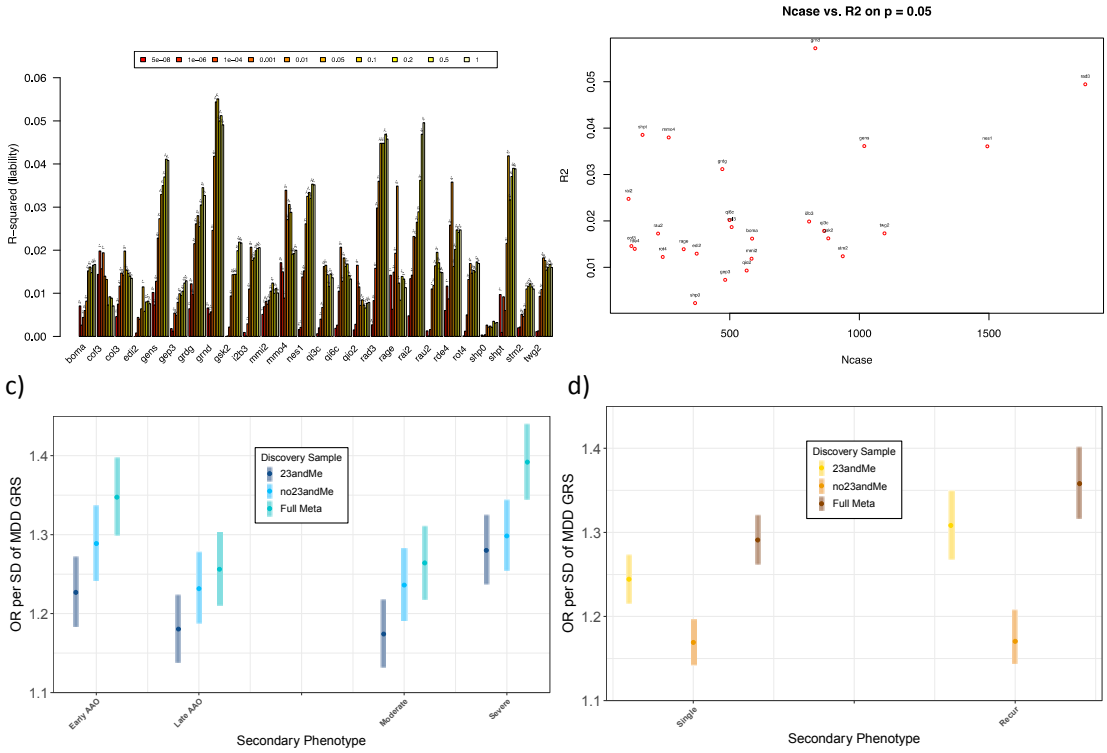
SUPPLEMENTARY FIGURES & SUPPLEMENTARY NOTE

Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression



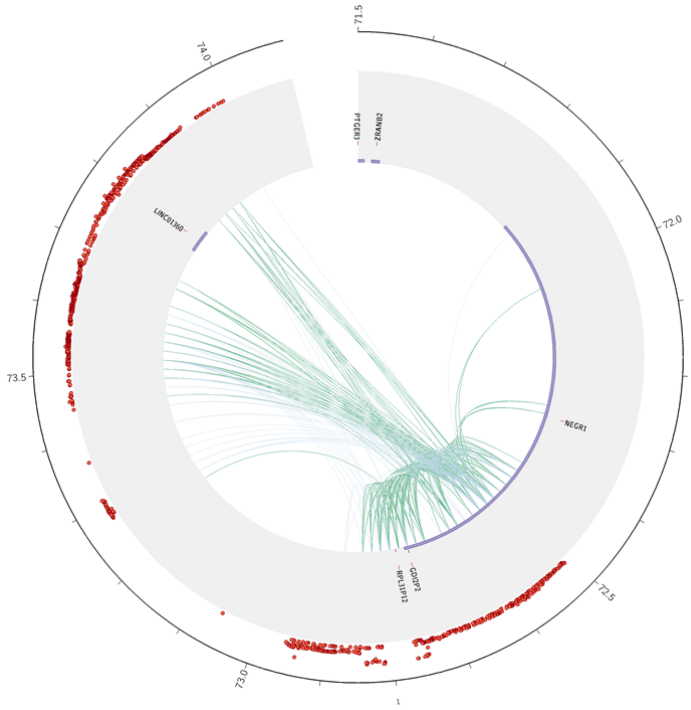
Supplementary Figure 1. SNP heritability estimates per cohort

SNP-heritability per cohort showing impact of lifetime risk assumptions (with 95% confidence intervals). Sample size: PGC29 (Ncas=16,823; Ncon=25,632); deCODE (Ncas=1,980; Ncon=9,536); GenScot (Ncas=997; Ncon=6,358); GERA (Ncas=7,162; Ncon=38,307); iPSYCH (Ncas=18,629; Ncon=17,841); UKBB (Ncas=14,260; Ncon=15,480); 23andMe (Ncas=70,813; Ncon=217,316); FullMeta (Ncas=130,664; Ncon=330,470); CONVERGE (Ncas=5,303; Ncon=5,337)

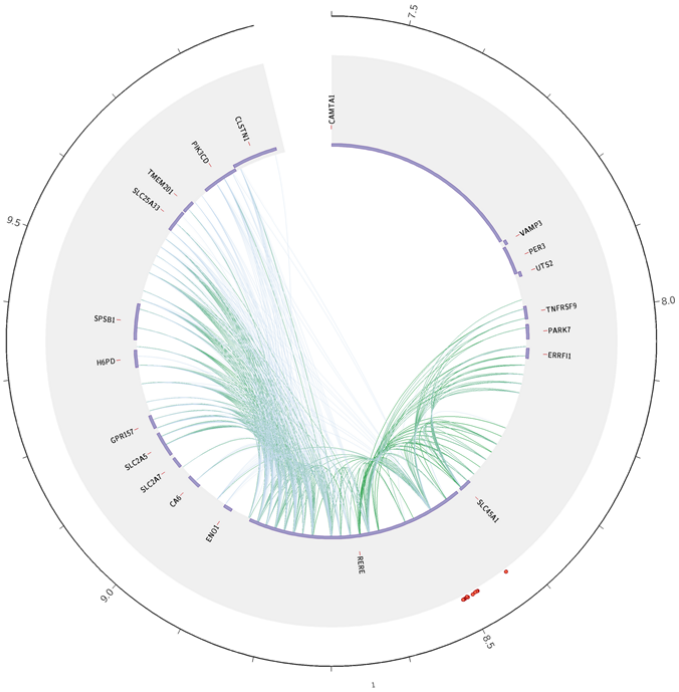


Supplementary Figure 2: Leave-one-out genetic risk score analyses of PGC29.

(a) Per sample R^2 at varying significance thresholds from logistic regression (1<0.05; 2*<0.01; 3*<0.005; 4*<0.001; 5*<1.0e-4; 6*<1.0e-8; 7*<1.0e-12). All but one of the samples in PGC29 yielded significant differences in case-control distributions of GRS. Across all PGC29 samples, GRS explained 1.9% of variance in liability. Sample size of all PGC29 cohorts: boma (Ncas=586; Ncon=1,062); cof3 (Ncas=120; Ncon=126); col3 (Ncas=507; Ncon=1,445); edi2 (Ncas=372; Ncon=285); gens (Ncas=1,019; Ncon=1,344); gep3 (Ncas=482; Ncon=2,836); grdg (Ncas=471; Ncon=470); grnd (Ncas=830; Ncon=474); gsk2 (Ncas=880; Ncon=861); i2b3 (Ncas=806; Ncon=1,067); jjp2 (Ncas=466; Ncon=1,380); mmi2 (Ncas=584; Ncon=517); mmo4 (Ncas=264; Ncon=371); nes1 (Ncas=1,494; Ncon=1,602); pfm2 (Ncas=281; Ncon=820); qi3c (Ncas=864; Ncon=579); qi6c (Ncas=499; Ncon=590); qio2 (Ncas=565; Ncon=526); rad3 (Ncas=1,872; Ncon=1,528); rage (Ncas=322; Ncon=227); rai2 (Ncas=109; Ncon=340); rau2 (Ncas=223; Ncon=378); rde4 (Ncas=133; Ncon=516); roc3 (Ncas=271; Ncon=92); rot4 (Ncas=241; Ncon=1,028); shp0 (Ncas=366; Ncon=1,087); shpt (Ncas=163; Ncon=484); stm2 (Ncas=936; Ncon=934); twg2 (Ncas=1,097; Ncon=2,663); (b) Relation between the number of cases and R^2, showing the expected positive correlation. (c) Major depression GRS (from out-of-sample discovery sets) were significantly higher in cases with: earlier age at onset; more severe symptoms (based on number of criteria endorsed); Target sample PGC29; Target sample size: cases with early Age At Onset (AAO)=3,950; cases with late AAO=3,950; cases with moderate MDD=4,958; cases with severe MDD=3,976; Discovery Sample size: 23andMeD (Ncas=70,813; Ncon=217,316); FMex23 (full meta-analysis excluding 23andMe and PGC29) (Ncas=43,028; Ncon=87,522); FullMeta (full meta-analysis excluding PGC29) (Ncas=113,841; Ncon=304,838); (d) Major depression GRS (from out-of-sample discovery sets) were significantly higher in cases with: recurrent compared to single episode. Error bars represent 95% confidence intervals. Target sample iPsych; Target sample size: 5,574 cases of recurrent and 12,968 single episode MDD Discovery Sample size: 23andMe (Ncas=70,813; Ncon=217,316); FMex23 (full meta-analysis excluding 23andMe and iPsych) (Ncas=41,222; Ncon=95,313); FullMeta (full meta-analysis excluding iPsych) (Ncas=112,035; Ncon=312,629).*



a)

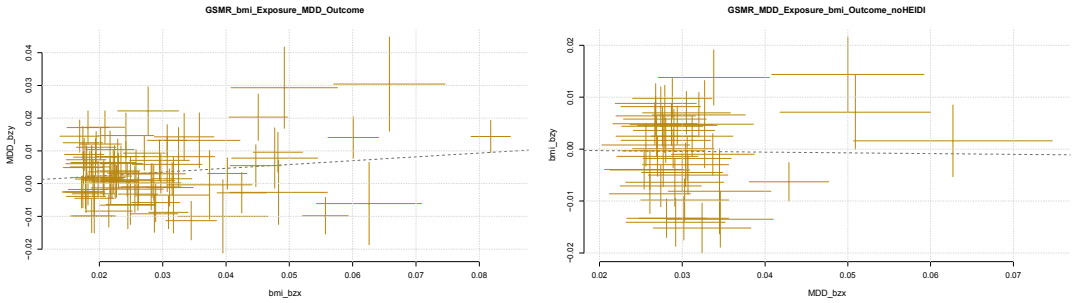


b)

<u>Supplementary Figure 3: Circular plots to illustrate DNA-DNA loops.</u>

From the outside, the tracks show hg19 coordinates in Mb, the positions of significant major depression associations (as -log$_{10}$(P), outward is more significant), the names and positons of GENCODE genes, and the arcs show significant DNA-DNA loops (q < 1e-4) from Hi-C on adult cortex (green) and fetal frontal cortex (blue). (a) chr1:71.5-74.1 Mb suggesting that the two statistically independent associations in the region both implicate NEGR1. (b) The association in RERE, in contrast, coincides with many DNA-DNA loops and may suggest that this region contains super-enhancer elements.

a)



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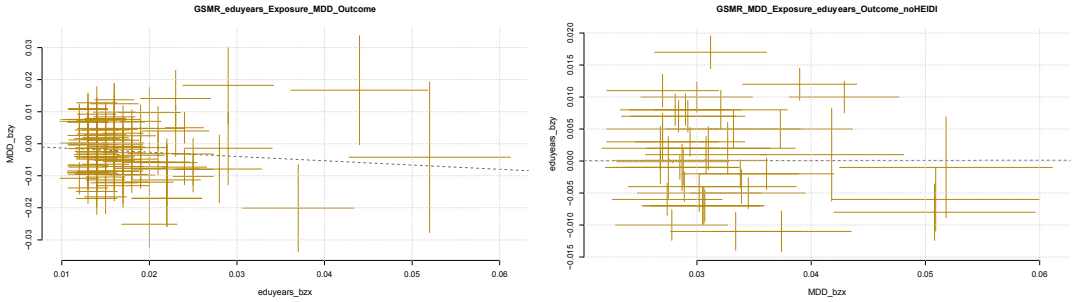

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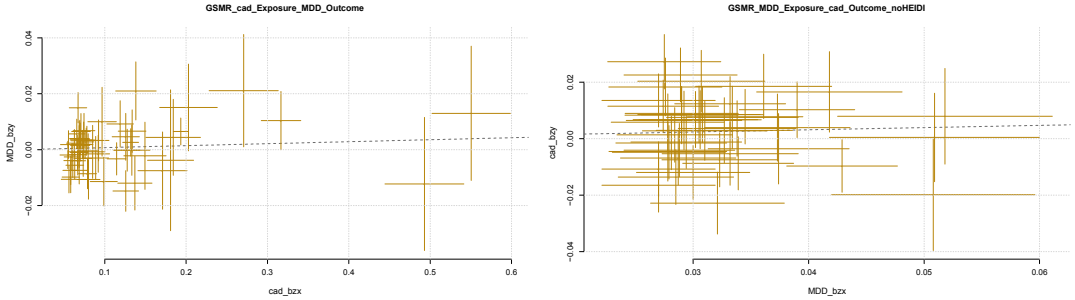

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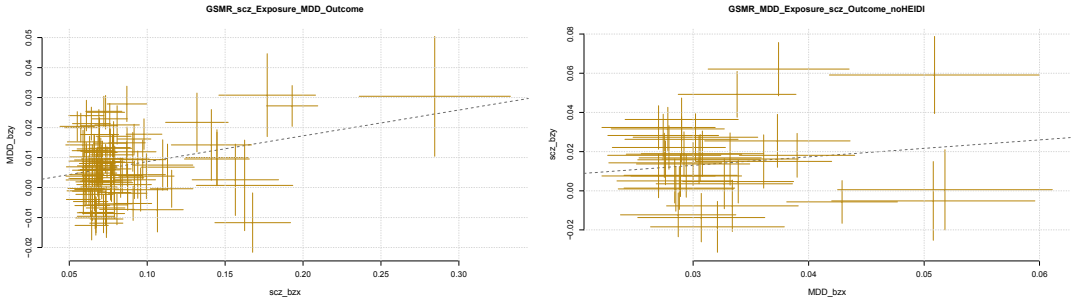

Supplementary Figure 4: Mendelian randomization analyses.

Supplementary Table 13 *shows the GSMR parameter estimates and significance, and these graphs show scatterplots of the instruments for major depression and (a) BMI, (b) years of education, (c) coronary artery disease, and (d) schizophrenia. Note the regression line is included for reference,* $\hat{b}_{xy}$ *are estimated as a generalized least squares estimates of* $\hat{b}_{zy}/\hat{b}_{zx}$ *. Sample size: BMI=322,135; EduY=405,072; CAD=184,305; SCZ=(Ncas=36,989; Ncon=113,075); MDD=(Ncas=130,664; Ncon=330,470).*

Genotyping and quality control.

Genotyping procedures can be found in the primary reports for each cohort (summarized in ***Supplementary Table 3***). Individual genotype data for all PGC29 samples, GERA, and iPSYCH were processed using the PGC "ricopili" pipeline (URLs) for standardized quality control, imputation, and analysis. [1] The cohorts from deCODE, Generation Scotland, UK Biobank, and 23andMe were processed by the collaborating research teams using comparable procedures. SNPs and insertion-deletion polymorphisms were imputed using the 1000 Genomes Project multi-ancestry reference panel (URLs).[2]

Quality control and imputation on the PGC29 samples were performed according to standards from the PGC. The default parameters for retaining SNPs and subjects were: SNP missingness < 0.05 (before sample removal); subject missingness < 0.02; autosomal heterozygosity deviation ($|F_{het}|<0.2$); SNP missingness < 0.02 (after sample removal); difference in SNP missingness between cases and controls < 0.02; and SNP Hardy-Weinberg equilibrium ($P>10^{-6}$ in controls or $P>10^{-10}$ in cases). These default parameters sufficiently controlled λ and false positive findings for 16 cohorts (boma, rage, shp0, shpt, edi2, gens, col3, mmi2, qi3c, qi6c, qio2, rai2, rau2, twg2, grdg, grnd). Two cohorts (gep3 and nes2) needed stricter SNP filtering and 11 cohorts needed additional ancestral matching (rot4, stm2, rde4) or ancestral outlier exclusion (rad2, i2b3, gsk1, pfm2, jjp2, cof3, roc3, mmo4). An additional cohort of inpatient MDD cases from Münster, Germany was processed through the same pipeline.

Genotype imputation was performed using the pre-phasing/imputation stepwise approach implemented in IMPUTE2 / SHAPEIT (chunk size of 3 Mb and default parameters). The imputation reference set consisted of 2,186 phased haplotypes from the 1000 Genomes Project dataset (August 2012, 30,069,288 variants, release "v3.macGT1"). After imputation, we identified SNPs with very high imputation quality (INFO >0.8) and low missingness (<1%) for building the principal components to be used as covariates in final association analysis. After linkage disequilibrium pruning ($r^2 > 0.02$) and frequency filtering (MAF > 0.05), there were 23,807 overlapping autosomal SNPs in the data set. This SNP set was used for robust relatedness testing and population structure analysis. Relatedness testing identified pairs of subjects with $\hat{\pi} > 0.2$, and one member of each pair was removed at random after preferentially retaining cases over controls. Principal component estimation used the same collection of autosomal SNPs.

Identification of identical samples is easily accomplished given direct access to individual genotypes. [3] Two concerns are the use of the same control samples in multiple studies (e.g., GAIN or WTCCC controls) [4,5] and inclusion of closely related individuals. For cohorts where the PGC central analysis team had access to individual genotypes (PGC29 and GERA), we used SNPs directly genotyped on all platforms to compute empirical relatedness, and excluded one of each duplicated or relative pair (defined as $\hat{\pi} > 0.2$). Within all other cohorts (deCODE, Generation Scotland, iPSYCH, UK Biobank, 23andMe, and CONVERGE), identical and relative pairs were identified and resolved using similar procedures. Identical individuals between PGC29, iPSYCH, UK Biobank, and Generation Scotland were identified using genotype-based checksums (URLs), [6] and an individual on the collaborator's side was excluded. Checksums were not available for the deCODE and 23andMe cohorts. Related pairs are not detectable by the checksum method but we did not find evidence of important overlap using LD score regression (the intercept between pairs of cohorts ranged from -0.01 to +0.01 with no evidence of important sample overlap).

Cohort comparability.

Supplementary Table 3 summarizes the numbers of cases and controls in PGC29 and the six expanded cohorts. The most direct and important way to evaluate the comparability of these cohorts for a GWA meta-analysis is using SNP genotype data. [7,8]

First, there was no indication of important sample overlap. This was directly evaluated as part of genotype quality control (see below), and confirmed as the LDSC regression intercepts between pairs of cohorts were always near zero.

Second, ***Supplementary Table 3*** and ***Supplementary Fig. 1*** show h^2_{SNP} on the liability scale for each cohort. In h^2_{SNP} methodology, the direct estimate is of variation explained in case-control status in the cohort, which are then transformed to the liability scale using an estimate of lifetime risk. Therefore, these estimates should be viewed as benchmarking rather than precise as lifetime risk estimate depends on the cohort and the transformation depends on the level of screening of controls. [9] These estimates demonstrate that common SNPs genome-wide contribute to variation but are not a suitable statistic for drawing strong conclusions about impact of phenotyping strategies. The h^2_{SNP} estimates range from 0.08 (SE 0.01) to 0.26 (SE 0.14) (for lifetime risk K=0.15) but the confidence intervals largely overlap (***Supplementary Fig. 1***).

Third, ***Supplementary Table 3b*** shows the r_g values for all pairs of cohorts. In contrast to h^2_{SNP}, r_g estimates are not dependent on estimates of lifetime risk. The median r_g was 0.80 (interquartile range 0.67-0.96), and the upper 95% confidence interval on r_g included 0.75 for all pairwise comparisons. These results indicate that the common variant genetic architecture of the cohorts overlap strongly, and provide critical support for the full meta-analysis of all cohorts.

For the PGC29 samples we could evaluate the comparability of the samples using individual level SNP genotype data. [7,8] The sample sizes were too small to evaluate the common variant genetic correlations (r_g) between all pairs of PGC29 samples (>3,000 subjects per sample are recommended). As an alternative, we used "leave one out" genetic risk scores (GRS, described below). We repeated this procedure by leaving out each PGC29 sample in turn so that we could evaluate the similarity of the common-variant genetic architectures of each sample to the rest of the cohort. ***Supplementary Fig. 2A*** and ***Supplementary Table 4*** shows that all but one of the samples in the PGC29 cohort yielded significant differences in case-control GRS distributions.

Because around half of the major depression cases were identified by self-report (i.e., diagnosis or treatment for clinical depression by a medical professional), we further evaluated the comparability of the 23andMe cohort with the other cohorts (full meta-analysis excluding 23andMe, "FMex23") as detailed in ***Supplementary Table 5***. At the most stringent level, of 11 SNPs reaching genome-wide significance in the 23andMe cohort, three replicate in FMex23 (at $P < 0.05/11$ comparisons). In the FMex23 cohorts, all five genome-wide significant loci replicate in 23andMe (at $P < 0.05/5$ comparisons). Next, of the independent loci associated at $P<10^{-6}$ in 23andMe, 19/44 (43%) had $P<0.05$ in FMex23 (P=8.0 x10^{-14}). Of the independent loci associated at $P<10^{-6}$ in FMex23, 13/24 (54%) had $P<0.05$ in 23andMe (P=1.8 x10^{-11}). Expanding these analyses further, we observed highly significant sign-test concordances at all tested P-value thresholds with 23andMe as the discovery sample and FMex23 as the target sample and vice versa. We repeated GRS analyses with 23andMe or FMex23 as discovery samples and the results showed significance (but explained less variance in out-of-sample prediction than when combined (***Fig. 2***). Moreover, GRS in 23andMe and FMex23 were higher in those with more severe MDD (***Supplementary Fig. 2***). We interpret these results as supporting this meta-analysis of GWA results for these seven cohorts. Sample size appeared to be a more potent determinant of the significance than how these phenotypes were assessed.

Trans-ancestry comparison with the Chinese CONVERGE cohort.

The Han Chinese CONVERGE study [10] included clinically ascertained females with severe, recurrent MDD, and is the largest non-European MDD GWA to date. Neither of the two genome-wide significant loci in CONVERGE had SNP findings ±250 kb with $P < 1x10^{-6}$ in the full European major depression results. We used LDSC with an ancestry-specific LD reference for within ancestry estimation, and POPCORN [11] for trans-ancestry estimation. In the CONVERGE sample, h^2_{SNP} was reported as 20-29%. [12] Its r_g with the seven European major depression cohorts was 0.33 (SE 0.03). [13] For comparison, r_g for CONVERGE with European results for schizophrenia was 0.34 (SE 0.05) and 0.45 (SE 0.07) for bipolar disorder. The weighted mean r_g between the CONVERGE cohort with the seven cohorts using was 0.31 (SE 0.03). These r_g estimates should be interpreted in light of the estimates of r_g within European MDD cohorts which are variable (***Table S3***).

Common genetic risk variants for complex biomedical conditions are likely to be shared across ancestries. [14,15] However, lower r_g have been reported likely reflecting different LD patterns by ancestry. For example,

European-Chinese r_g estimates were below one for ADHD (0.39, SE 0.15), [16] rheumatoid arthritis (0.46, SE 0.06), [11] and type 2 diabetes (0.62, SE 0.09), [11] and reflect population differences in LD and population-specific causal variants.

The discovery rate for major depression (44 associations per 135,458 cases or 1:3,078 cases) is similar to that for severe, recurrent MDD in the CONVERGE study (2 per 5,303 cases or 1:2,650 cases).

Definition of independent loci

The full criteria used for identifying independent loci are:

- All SNPs were high-quality (imputation INFO score ≥ 0.6 and allele frequencies ≥0.01 and ≤0.99).
- We used "clumping" to convert MDD-associated SNPs to associated regions. We identified an index SNP with the smallest *P*-value in a genomic window and other SNPs in high LD with the index SNP using PLINK (--clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.1 --clump-kb 3000). This retained SNPs with association $P < 0.0001$ and $r^2 < 0.1$ within 3 Mb windows. Only one SNP was retained from the extended MHC region due to its exceptional LD.
- We used bedtools (URLs) to combine partially or wholly overlapping clumps within 50 kb.
- We reviewed all regional plots, and removed two singleton associations (i.e., only one SNP exceeding genome-wide significance).
- We conducted conditional analyses. To identify independent associations within a 10 Mb region, we re-evaluated all SNPs in a region conditioning on the most significantly associated SNP using summary statistics [17] (superimposing the LD structure from the Atherosclerosis Risk in Communities Study sample).

Brief review of four key loci, *OLFM4, NEGR1, RBFOX1* and *LRFN5*

The two most significant SNPs are located in or near *OLFM4* and *NEGR1*, which were previously associated with obesity and body mass index. [18-23] *OLFM4* (olfactomedin 4) has diverse functions outside the CNS including myeloid precursor cell differentiation, innate immunity, anti-apoptotic effects, gut inflammation, and is over-expressed in diverse common cancers. [24] Many olfactomedins also have roles in neurodevelopment and synaptic function; [25] e.g., latrophilins form trans-cellular complexes with neurexins [26] and with *FLRT3* to regulate glutamatergic synapse number. [27] *Olfm4* was highly upregulated after spinal transection, possibly related to inhibition of subsequent neurite outgrowth. [28] *NEGR1* (neuronal growth regulator 1) influences axon extension and synaptic plasticity in cortex, hypothalamus, and hippocampus, [29-31] and modulates synapse formation in hippocampus [32,33] via regulation of neurite outgrowth. [34,35] High expression, modulated by nutritional state, is seen in brain areas relevant to feeding, suggesting a role in control of energy intake. [36] The same SNP alleles are associated with increased risk of obesity and MDD (see also Mendelian randomization analyses below) and are associated with *NEGR1* gene expression in brain (***Supplementary Table 6***). The associated SNPs may tag two upstream common deletions (8 and 43 kb) that delete transcription factor binding sites, [37] although reports differ on whether the signal is driven by the shorter [18] or the longer deletion. [22] Thus, the top two associations are in or near genes that influence BMI and may be involved in neurite outgrowth and synaptic plasticity.

Notable associations reported here include *RBFOX1* and *LRFN5*. There are independent associations with major depression at both the 5' and the 3' ends of *RBFOX1* (1.7 Mb, RNA binding protein fox-1 homolog 1). This convergence makes it a strong candidate gene. Fox-1 regulates the expression of thousands of genes, many of which are expressed at synapses and enriched for autism-related genes. [38] The Fox-1 network regulates neuronal excitability and prevents seizures. [39] It directs splicing in the nucleus and binds to 3' UTRs of target mRNAs in the cytoplasm. [39,40] Of particular relevance, Fox-1 participates in the termination of the corticotropin releasing hormone response to stress by promoting alternative splicing of the PACAP receptor to its repressive form. [41] Thus, *RBFOX1* as a risk gene for major depression may be consistent with chronic hypothalamic-pituitary-adrenal axis hyperactivation reported in MDD. [42] *LRFN5* (leucine rich repeat and fibronectin type III domain containing 5) encodes adhesion-like molecules involved in synapse formation.

Common SNPs in *LRFN5* were associated with depressive symptoms in older adults in a gene-based GWA analysis. [43] LRFN5 induces excitatory and inhibitory presynaptic differentiation in contacting axons and regulates synaptic strength. [44,45] LRFN5 also limits T-cell response and neuroinflammation (CNS "immune privilege") by binding to herpes virus entry mediator; a LRFN5-specific monoclonal antibody increases activation of microglia and macrophages by lipopolysaccharide and exacerbates mouse experimental acquired encephalitis; [46] thus, reduced expression (the predicted effect of eQTLs in LD with the associated SNPs) could increase neuroinflammatory responses.

Genetic risk score (GRS) analysis

To demonstrate the validity of our GWAS results, we conducted a series of GRS prediction analyses. The GWA summary statistics identified associated SNP alleles and effect sizes which were used to calculate GRS for each individual in a target sample (i.e., the sum of the count of risk alleles weighted by the natural log of the odds ratio of the risk allele). In some analyses the target sample had been included as part of PGC29; here, the discovery samples were meta-analyzed excluding this cohort. As in the PGC schizophrenia report, [1] we excluded uncommon SNPs (MAF < 0.1), low-quality variants (imputation INFO < 0.9), indels, and SNPs in the extended MHC region (chr6:25-34 Mb). We then LD pruned and "clumped" the data, discarding variants within 500 kb of, and in LD $r^2 > 0.1$ with the most associated SNP in the region. We generated GRS for individuals in target subgroups for a range of P-value thresholds (P_T: $5x10^{-8}$, $1x10^{-6}$, $1x10^{-4}$, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0).

For each GRS analysis, five ways of evaluating the regression of phenotype on GRS are reported (***Supplementary Table 4***). 1) The significance of the case-control score difference from logistic regression including ancestry PCs and a study indicator (if more than one target dataset was analyzed) as covariates. 2) The proportion of variance explained (Nagelkerke's R^2) computed by comparison of a full model (covariates + GRS) to a reduced model (covariates only). It should be noted that these estimates of R^2 reflect the proportion of cases in the case-control studies where this proportion may not reflect the underlying risk of in the population. 3) The proportion of variance on the liability scale explained by the GRS R^2 was calculated from the difference between full and reduced linear models and was then converted to the liability scale of the population assuming lifetime risk of 15%. These estimates should be approximately comparable across target sample cohorts, whatever the proportion of cases in the sample. 4) Area under the receiver operator characteristic curve (AUC; R library pROC) was estimated in a model with no covariates [1] where AUC can be interpreted as the probability of a case being ranked higher than a control. 5) Odds ratio for 10 GRS decile groups (these estimates also depend on both risk of MDD in the population and proportion of cases in the sample). We evaluated the impact of increasing sample size of the discovery sample GWA (***Fig. 2***) and also using the schizophrenia GWA study [1] as the discovery sample. We also undertook GRS analysis for a target sample of MDD cases and controls not included in the meta-analysis (a clinical inpatient cohort of MDD cases and screened controls collected in Münster, Germany).

We conducted GRS analyses based on prior hypotheses from epidemiology of MDD using clinical measures available in some cohorts (if needed, the target sample was removed from the discovery GWA). We used GRS constructed from P_T=0.05, selected as a threshold that gave high variance explained across cohorts. First, we used GRS analyses to test for higher mean GRS in cases with younger age at onset (AAO) of MDD compared to those with older AAO in PGC29. To combine analyses across samples, we used within-sample standardized GRS residuals after correcting for ancestry principal components. Heterogeneity in AAO in PGC29 has been noted, [47] which may reflect study specific definitions of AAO (e.g., age at first symptoms, first visit to general practitioner, or first diagnosis). Following Power et al., [47] we divided AAO into octiles within each cohort and combined the first three octiles into the early AAO group and the last three octiles into the late AAO group.

Second, we tested for higher mean GRS for cases in the PGC29 samples with clinically severe MDD (endorsing ≥8 of 9 DSM MDD criteria) compared to those with "moderate" MDD (endorsing 5-7 of 9 MDD criteria) following Verduijn et al. [48] Sample sizes are given in ***Supplementary Table 3***. Third, using iPSYCH as the target sample, we tested for higher mean GRS in recurrent MDD cases (ICD-10 F33, N=5,574) compared

to those with single episode MDD cases (ICD-10 F32, N=12,968) in analyses that included ancestry principal components and genotyping batch as covariates. Finally, following Verduijn et al. [48] using the NESDA sample (PGC label "nes1", an ongoing longitudinal study of depressive and anxiety disorders) as the target sample , we constructed clinical staging phenotypes in which cases were allocated to one of three stages: Stage 2 (n = 388) first episode MDD; stage 3 (n = 562) recurrent/relapse episode MDD; stage 4 (n = 705) persistent/unremitting chronic MDD, with an episode lasting longer than 2 years before baseline interview and/or ≥ 80% of the follow-up time with depressive symptoms. We tested for higher mean GRS in stage IV cases compared to stage II MDD cases.

Mendelian randomization (MR) analyses.

We used MR[49] to investigate the relationships between major depression and correlated traits. Epidemiological studies show that MDD is associated with environmental and life event risk factors as well as multiple diseases, yet it remains unclear whether such trait outcomes are causes or consequences of MDD (or prodromal MDD). Genetic variants are present from birth, and hence are far less likely to be confounded with environmental factors than in epidemiological studies.

Briefly in MR analyses, we take genome-wide significant SNPs for the exposure trait and test for a directional relationship with effect sizes of these SNPs estimated in the outcome trait Under pleiotropy, SNPs may be associated in the same direction in the two traits (consistent with the genetic correlation estimated from genome-wide SNPs), but causality would generate a directional relationship in the size of effect sizes (which is plausibly less likely under pleiotropy alone). A check for reverse causality takes genome-wide significant SNPs from major depression and tests for a directional relationship of effect sizes estimated in the exposure trait.

We conducted bi-directional MR analysis for four traits: years of education (EDY)[50], body mass index (BMI) [51], coronary artery disease (CAD)[52], and schizophrenia (SCZ)[53]. We denote z as a genetic variant (i.e., a SNP) that is significantly associated with x, an exposure or putative causal trait for y (the disease/trait outcome). The effect size of x on y can be estimated using a two-step least squares (2SLS) [54] approach: $\hat{b}_{xy} = \hat{b}_{zy}/\hat{b}_{zx}$, where $\hat{b}_{zx}$ is the estimated effect size for the SNP-trait association the exposure trait, and $\hat{b}_{zy}$ is the effect size estimated for the same SNP in the GWAS of the outcome trait.

Since SNP-trait effect sizes are typically small, power is increased by using multiple associated SNPs which allows simultaneous investigation of pleiotropy driving the epidemiologically observed trait associations. Causality of the exposure trait for the outcome trait implies a consistent relationship between the SNP association effect sizes of the exposure associated SNPs in the outcome trait.

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We used generalized summary statistics-based MR (GSMR) to estimate $\hat{b}_{xy}$ and its standard error from multiple SNPs associated with the exposure trait at a genome-wide significance level. We conducted bi-directional GSMR analyses for each pair of traits, and report results after excluding SNPs that fail the HEIDI-outlier heterogeneity test (which is more conservative than excluding SNPs that have an outlying association likely driven by locus-specific pleiotropy). GSMR is more powerful than inverse-weighted MR (IVW-MR) and MR-Egger because it takes account of the sampling variation of both $\hat{b}_{zx}$ and $\hat{b}_{zy}$. GSMR also accounts for

residual LD between the clumped SNPs. For comparison, we also conducted IVW-MR and MR-Egger analyses. [58]

Acknowledgements

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PGC	D Posthuma	480-05-003	Netherlands Scientific Organization	Netherlands
PGC	D Posthuma	–	Dutch Brain Foundation and the VU University Amsterdam	Netherlands
BiDirect	K Berger	01ER0816, 01ER1506	BMBF	Germany
BoMa	M Rietschel	RI 908/11-1	Deutsche Forschungsgemeinschaft	Germany
BoMa	MM Nöthen	NO246/10-1	Deutsche Forschungsgemeinschaft	Germany
BoMa	MM Nöthen	Excellence Cluster ImmunoSensation	Deutsche Forschungsgemeinschaft	Germany
BoMa	MM Nöthen, M Rietschel, S Cichon	01ZX1314A/01ZX1614A, 01ZX1314G/01ZX1614G,	BMBF Integrament	Germany
BoMa	MM Nöthen, M Rietschel, S Cichon	01GS08144, 01GS08147	BMBF NGFNplus MooDS	Germany
CoFaMS - Adelaide	BT Baune	APP1060524	NHMRC	Australia
Danish Radiant	T Werge	0001-2009-2	Højteknologifonden	Denmark
Danish Radiant	T Werge	R24-A3242	Lundbeck Foundation	Denmark
EDINBURGH	AM McIntosh	104036/Z/14/Z	Wellcome Trust	UK
EGCUT	A Metspalu	EstRC-IUT20-60, EU Project	European Union	Estonia

		No. 2014-2020.4.01.15-0012 and 692145		
GenPod/Newmeds	G Lewis, M O'Donovan	G0200243	MRC	UK
GenPod/Newmeds	R Uher	LSHB-CT-2003-503428	EU 6th framework	UK
GenPod/Newmeds	G Lewis	15008	EU IMI-JU	UK
GenScot	AM McIntosh, T-K Clarke, D Porteous	104036/Z/14/Z	Wellcome Trust	UK
GenScot	D Porteous	CZD/16/6	Chief Scientist Office	UK
GenScot	D Porteous	HR03006	Scottish Funding Council	UK
Harvard i2b2	JW Smoller	R01 MH085542	NIMH	USA
Harvard i2b2	RH Perlis	R01 MH086026	NIMH	USA
Münster MDD Cohort	BT Baune	N Health-F2-2008-222963	European Union	Germany
Münster MDD Cohort	TG Schulze	01ZX1314K	BMBF Integrament	Germany
Münster MDD Cohort	TG Schulze		Dr. Lisa Oehler Foundation	Germany
Münster MDD Cohort	TG Schulze	SCHU 1603/5-1	German Research Foundation (DFG)	Germany
Münster MDD Cohort	U Dannlowski	FOR2107 DA1151/5-1; SFB-TRR58, Project C09	German Research Foundation (DFG)	Germany
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NTR	DI Boomsma	480-15-001/674	N.W.O.	Netherlands
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PsyColaus	M Preisig	3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401	Swiss National Science Foundation	Switzerland
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RADIANT	G Breen	G0901245	MRC	UK
RADIANT	G Breen	U01 MH109528	NIMH	UK
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deCODE	K Stefansson	R01 DA017932	NIDA	USA
deCODE	TE Thorgeirsson	R01 DA034076	NIDA	USA
GERA	C Schaefer; N Risch	RC2 AG036607	NIA, NIMH, OD	USA
iPSYCH	T Werge, A Børglum, O Mors, M Nordentoft, D Hougaard, PB	R102-A9118, R155-2014-1724, R129-A3973, R24-A3243	Lundbeck Foundation	Denmark

	Mortesen			
iPSYCH	T Werge, A Børglum, O Mors, M Nordentoft, D Hougaard, PB Mortesen		Novo Nordisk Foundation	Denmark
iPSYCH	T Werge, A Børglum, O Mors, M Nordentoft, D Hougaard, PB Mortesen	R144-A5327	The Capital Region of Denmark	Denmark
iPSYCH	T Werge, A Børglum, O Mors, M Nordentoft, D Hougaard, PB Mortesen	iSEQ, GenomeDK HPC facility, CIRRAU	Aarhus University	Denmark
iPSYCH	T Werge, A Børglum, O Mors, M Nordentoft, D Hougaard, PB Mortesen	294838	EU	EU
iPSYCH	T Werge, A Børglum, O Mors, M Nordentoft, D Hougaard, PB Mortesen		Stanley Medical Research Institute	USA
UK Biobank	AM McIntosh	104036/Z/14/Z	Wellcome Trust	UK
CONVERGE	J Flint	WT090532/Z/09/Z, WT083573/Z/07/Z, WT089269/Z/09/Z	Wellcome Trust	UK
CONVERGE	K Kendler	MH100549	NIMH	USA

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