Supplementary text: Genetic structure of major depression symptoms in clinical and population cohorts

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Cohort information

Psychiatric Genomics Consortium (PGC): Data from the PGC drawn from 23 cohorts in the Wave 1 and Wave 2 datasets of the Major Depressive Disorder Working Group (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013; Wray et al., 2018). Symptoms were assessed by trained interviewers using structured diagnostic instruments and DSM checklists. Because information on symptom presence was not available for control participants in most cohorts, participants with a diagnosis of depression were selected for analysis (N = 12,821).

Australian Genetics of Depression Study (AGDS) (Byrne et al., 2020; Mitchell et al., 2022) is a study of depression and therapeutic response recruited using nationwide prescribing history and through publicity targeting adults who are or had ever been treated for clinical depression (N = 20,689). Symptoms experienced during the participant's worst period of depression were assessed using the Composite International Diagnostic Interview (CIDI) Short Form (Hickie et al., 2001) and administered through an online questionnaire. Because the study was enriched for participants with a history of being diagnosed with or treated for depression, AGDS was grouped as a Clinical cohort.

Avon Longitudinal Study of Parents and Children (ALSPAC): Pregnant women resident in Avon, UK with expected dates of delivery between 1st April 1991 and 31st December 1992 were invited to take part in the study (Boyd et al., 2013; Fraser et al., 2013). 20,248 pregnancies have been identified as being eligible and the initial number of pregnancies enrolled was 14,541. Of the initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the

oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above: The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented in the released data and reflecting enrolment status at the age of 24 is 906, resulting in an additional 913 children being enrolled (456, 262 and 195 recruited during Phases II, III and IV respectively). The phases of enrolment are described in more detail in the cohort profile paper and its update. The total sample size for analyses using any data collected after the age of seven is therefore 15,447 pregnancies, resulting in 15,658 foetuses. Of these 14,901 children were alive at 1 year of age.

Of the original 14,541 initial pregnancies, 338 were from a woman who had already enrolled with a previous pregnancy, meaning 14,203 unique mothers were initially enrolled in the study. As a result of the additional phases of recruitment, a further 630 women who did not enrol originally have provided data since their child was 7 years of age. This provides a total of 14,833 unique women (G0 mothers) enrolled in ALSPAC as of September 2021.

Participants were from the original children sample (N = 13,988) with symptoms present during the last two weeks assessed using the Clinical Interview Schedule Revised (CIS-R) (Lewis et al., 1992) collected during a clinical visit at age 18. Participants were considered to have had a symptom if they reported it at the occasion.

Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool" and reference the following webpage: http://www.bristol.ac.uk/alspac/researchers/our-data/.

Generation Scotland: Scottish Family Health Study (**GS:SFHS**) is a study of 7,000 families recruited from the general population of Scotland (Smith et al., 2012). Participants who screened reported seeking help for emotional or psychiatric problems were administered an in-person structured interview (Fernandez-Pujals et al., 2015; Smith et al., 2012); and a subset participated in an online follow-up that included a CIDI (Composite International Diagnostic Interview) questionnaire. Symptom data was analysed on participants who met DSM criteria for depression at either time point (N = 3,493).

Estonian Biobank (**EstBB**) is a population health cohort recruited from medical practitioners in Estonia (Leitsalu et al., 2015). Participants responded to a CIDI questionnaire of depression symptoms during the Mental Health online Survey (MHoS) recontact. Participants were first screened of the presence of low mood or anhedonia and then asked about symptoms during the worst period of depression (N = 84,079).

UK Biobank (**UKB**) is a population health cohort recruited from general practitioners in the United Kingdom (Sudlow et al., 2015). Lifetime depression symptoms were assessed during online recontact and taken from the CIDI portion of the Mental Health Questionnaire (Davis et al., 2020) (UKB-MHQ, N=157,366) and from assessments of low mood and anhedonia ("ever had [symptom] for a full week") from the touchscreen questionnaire (data fields 4598 and 4631) collected at baseline and during repeat and imaging assessments (UKB Touchscreen, N=222,061). For the CIDI, low mood and anhedonia were used as gating symptoms, where participants had to endorse at least one to be asked about the other symptoms. The symptom was present if the question was endorsed as "Yes", absent if answered as "No", and missing otherwise. For the touchscreen items, the symptom was considered present if it was endorsed ("Yes") at any assessment and absent if it was responded to with "No" at all available time points.

Genotyping, QC, and GWAS

Psychiatric Genomics Consortium (PGC). The analysis used data from 24 cohorts from the PGC MDD datasets that had symptom data on cases. Data was drawn from the following cohorts:

- BiDirect (bidi1)
- BOMA (boma)
- CoFams (cof3)
- PsyCoLaus (col3)
- GenRED (gens, grnd)
- GenPod/Newmeds (gep3)
- GSK (gsk2)
- Jannsen (janpy)
- MPIP/MARS (mmi2, mmo4)
- NESDA/NTR (nes1)
- QIMR (qi3c, qi6c, qio2)
- RADIANT (rad3, rage, rai2, rau2, rde4)
- Rotterdam (rot4)
- SHIP (shp0)
- STAR*D (stm2)
- TwinGene (twg2)

The genotypes were processed through Ricopili (Lam et al., 2020) with the following QC: SNP missingness < 0.05; sample missingness < 0.02; autosomal heterozygosity deviation (|Fhet|<0.2); and SNP Hardy-Weinberg equilibrium ($P>10^{-6}$ in controls, $P>10^{-10}$ in cases). QC'd genotypes were then imputed to the 1000 Genomes Reference Panel (The 1000 Genomes Project Consortium, 2015). Information on cohort genotyping and additional processing steps is available in (Wray et al., 2018).

Australian Genetics of Depression Study (AGDS). Genotyping was conducted using the Illumina Infinium Global Screening Array platform and QC'd for unknown or ambiguous map position and strand alignment, missingness >5%, HWE < 1×10^{-6}, MAF<1%. Genotypes were imputed to HRCr1.1. Individuals were excluded with missing rate > 3%, inconsistent sex, or if deemed ancestry outliers from the European population (6 standard deviations from the first two genetic principal components from 1000 Genomes). Imputed genotype dosages were used for the analyses. GWAS was carried out in SAIGE (Zhou et al., 2018) using a generalized linear mixed model with genotyping batch and 10 PCs as covariates. Variants with MAF<1% and imputation accuracy score <0.7 were excluded.

Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC children were genotyped using the Illumina HumanHap550 quad chip genotyping platforms. Individuals were excluded on the basis of gender mismatches; minimal or excessive heterozygosity; disproportionate levels of individual missingness (>3%) and insufficient sample replication (IBD < 0.8). Population stratification was assessed by multidimensional scaling analysis, removing samples that clustered outside the CEU HapMap2 population. SNPs with a minor allele frequency of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (P < 5E-7) were removed. Cryptic relatedness was measured as proportion of identity by descent (IBD > 0.1). Related subjects that passed all other quality control thresholds were retained during

subsequent phasing and imputation. 9,115 subjects and 500,527 SNPs passed these quality control filters. Imputation of the target data was performed using Impute V2.2.2 against 1000 genomes reference panel (Phase 1, Version 3) (all polymorphic SNPs excluding singletons), using all 2186 reference haplotypes (including non-Europeans). This resulted in 28,699,419 SNPs, with 8,282,911 SNPs with a MAF >0.01 and info score of >0.8. Analysis were conducted using SNPTEST v2.5.2, adjusting for sex and the first 10 principal components of ancestry.

Generation Scotland (GS:SFHS). GWAS data was obtained using the Illumina OmniExpress array, and imputed using the Haplotype Research Consortium (HRC) dataset. Further details of methods here https://pubmed.ncbi.nlm.nih.gov/28270201/. GWAS was conducted in regenie with 4 PCs removing SNPs with MAC < 100, genotype missingness > 10%, INFO < 0.1, and HWE p > 1e-15.

Estonian Biobank (EstBB). The samples from the Estonian Biobank have been genotyped at the Genotyping Core Facility of the Institute of Genomics, University of Tartu using the Global Screening Array (GSAv1.0, GSAv2.0, and GSAv2.0_EST) from Illumina. Altogether 155,772 samples have been genotyped and PLINK format files exported using GenomeStudio v2.0.4. Individuals were excluded from the analysis if their call-rate was <95% or if the sex defined based on heterozygosity of the X chromosome did not match the sex in the phenotype data. Variants were excluded if the call-rate was < 95% and HWE p-value <1e-4 (autosomal variants only). Variant positions were updated to genome build 37 and all alleles were switched to the TOP strand using tools and reference files provided at https://www.well.ox.ac.uk/~wrayner/strand/. After QC the dataset contained 154,201 samples for imputation. Before imputation variants with MAF<1% and indels were removed. Prephasing was done using the Eagle v2.3 software. The number of conditioning haplotypes Eagle2 uses when phasing each sample was set to: --Kpbwt=20000. Imputation was done using Beagle v.28Sep18.793 with effective population size ne=20,000. An Estonian population specific imputation reference of 2,297 WGS samples was used. The analysis was performed using the SAIGE software, including related individuals and adjusting for the first 10 principal components (PCs) of the genotype matrix, as well as for birth year, birth year squared and sex.

UK Biobank (UKB). Imputed genotypes were analysed from the version 3 release (Bycroft et al., 2018). Imputed genotypes were QC'd to INFO >= 0.1, MAC >= 100, HWE P > 1e-10, max alleles = 2, and duplicate markers removed. Association analysis was performed as a logistic regression in Plink2 (Chang et al., 2015) with genotyping array and 20 PCs as covariates.

GWAS Meta-analysis and LD Score. For input into LDSC we set the sample size equal to the sum of effective sample sizes of each cohort in the meta-analysis and then specified sample prevalences of 50% (Grotzinger, Fuente, et al., 2022). Symptoms' population prevalences were estimated for the Clinical cohorts by multiplying the observed sample prevalence by the prevalence of MDD (15%) and for the Community cohorts by multiplying by the proportion of participants in the UKB MHQ sample who were positive on either one the gating symptoms.

Ethics statements

Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the local research ethics committees (project number B3118). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

All participants in AGDS provided informed consent that they had read and understood the study information sheets and to confirm that they would be willing to provide a saliva sample for genotyping and

downstream generic analyses. All study protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee - approval numbers P2118, P1309 and P2304.

The activities of the EstBB are regulated by the Human Genes Research Act, which was adopted in 2000 specifically for the operations of the EstBB. Individual-level data analysis in the EstBB was carried out under ethical approvals [1.1-12/2860 & 1.1-12/624] from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs), using data according to the release application [3-10/GI-28207] from the Estonian Biobank.

Ethical approval for the GS:SFHS data collection was obtained from the Tayside Committee on Medical Research Ethics A (ref 05/S1401/89). Generation Scotland is currently approved as a Research Tissue Bank by the East of Scotland Research Ethics Service (ref 20/ES/0021).

UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382).

Confirmatory factor analysis model schematics

Figure S1. Schematic drawings of the CFA models

Schematics to illustrate factor structures of the models that were tested. Symptoms are grouped by those from Case-enriched/Clinical cohorts, those from Community cohorts, and those from the UKB Touchscreen. Residual variances omitted for clarity. See also Supplementary Tables S4 for factor structures.

Symptom abbreviations:

- Dep: Depressed mood
- Anh: Anhedonia
- AppDec: Weight loss / decrease in appetite
- AppInc: Weight gain / increase in appetite
- SleDec: Insomnia
- SleInc: Hypersomnia
- MotoInc: Psychomotor agitation
- MotoDec: Psychomotor slowing
- Fatig: Fatigue
- Guilt: Feelings of worthlessness / guilt
- Conc: Diminished concentration
- Sui: Recurrent thoughts of death or suicide

Figure S1. Diagrams of CFA models with parameter estimates.

See also Supplementary Tables S6 for parameter estimates.

Figure S1a: Model "Depr": Common factor

Figure S1b: Model "Case-Comm": Case-enriched (Clinical) and community factors

Figure S1c: Model "Depr-Gate": Gating measurement factor

Figure S1d: Model "Case-Comm-Gate": Clinical-Community-Gating factors

Figure S1e: Model "Psyc-Soma": Psychological-Somatic

Figure S1f: Model "Psyc-Neuv": Psychological- Neurovegetative

Figure S1g: Model "Affc-Neuv": Affective-Neurovegetative

Figure S1h: Model "Cog-Mood-Neuv": Cognitive-Mood-Neurovegetative

Figure S1i: Model "CogMood-App-Leth": Cognitive/Mood-Appetite-Lethargy

Figure S1j: Model "AffCog-Melc-Atyp": Affective/Cognitive-Melancholic-Atypical

Figure S1m: Model "CogMoodLeth-App Cog/Mood/Lethargy-Appetite-

Figure S1n: Model "CogMoodLeth-App [Res]": Cog/Mood/Lethargy-Appetite-Lethargy with residual correlations

Symptom genetic correlations

Figure S2. Genetic correlations between symptoms

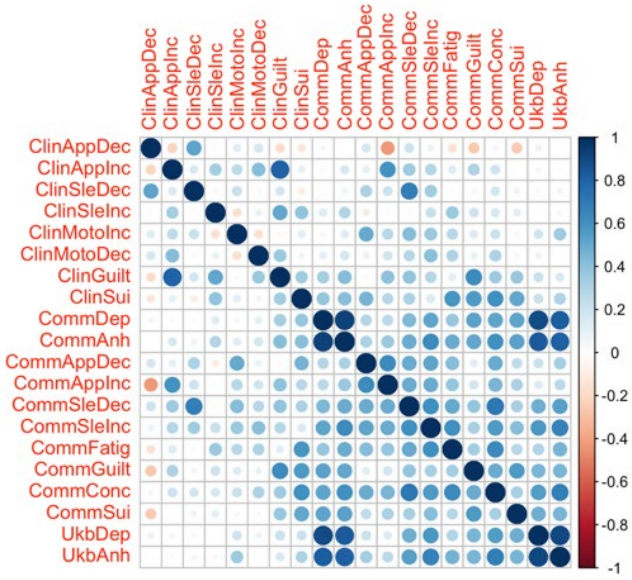


Figure S3. Model implied and residual proportions of genetic correlations
Variance and covariances scaled by total genetic variance of each symptom.

Figure S3a. Model implied proportions of genetic correlations for Case-Community-Gating factors (Model "Case-Comm-Gate")

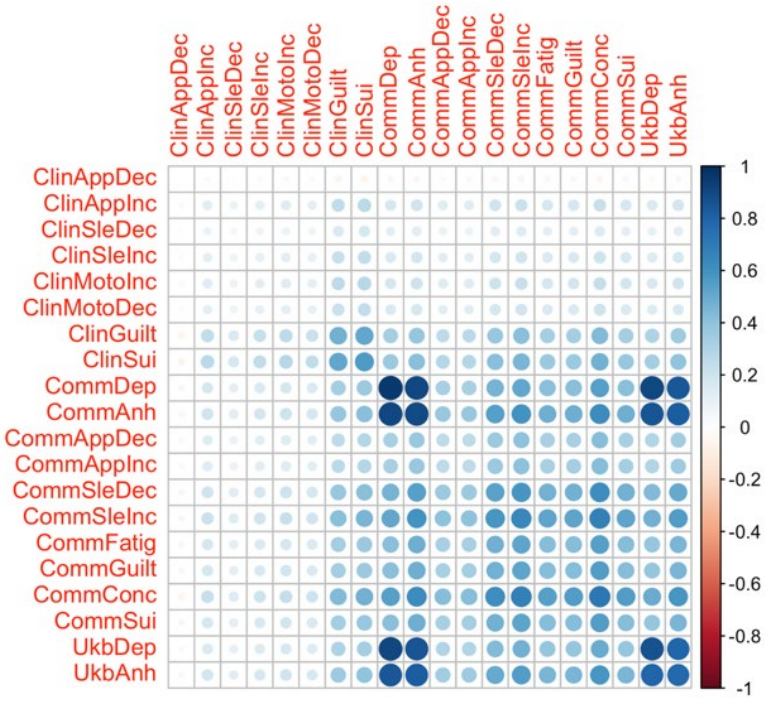


Figure S3b. Model residual proportions of genetic correlations for Case-Community-Gating factors (Model Case-Comm-Gate)

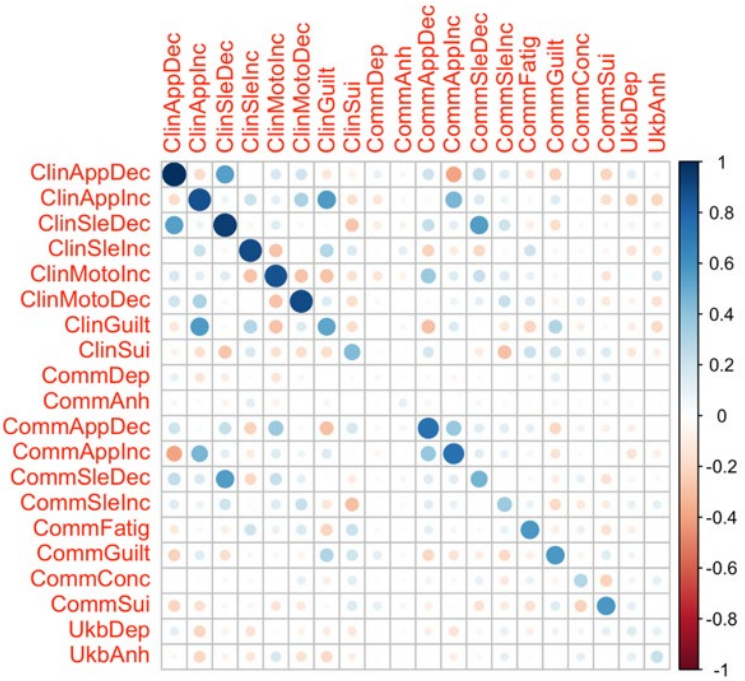


Figure S3c. Model implied proportions of genetic correlations for Cognitive/Mood-Appetite-Lethargy factors (Model "CogMood-App-Leth")

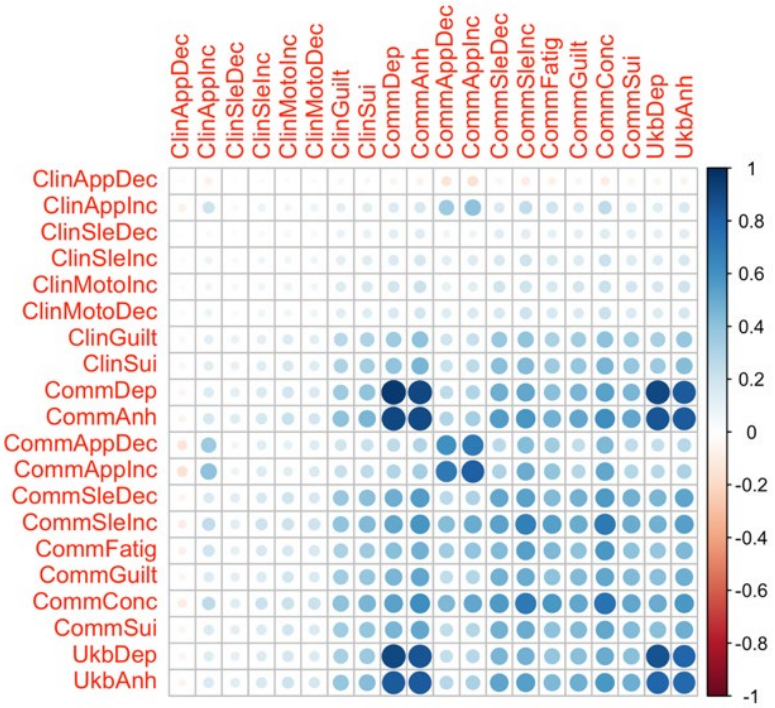
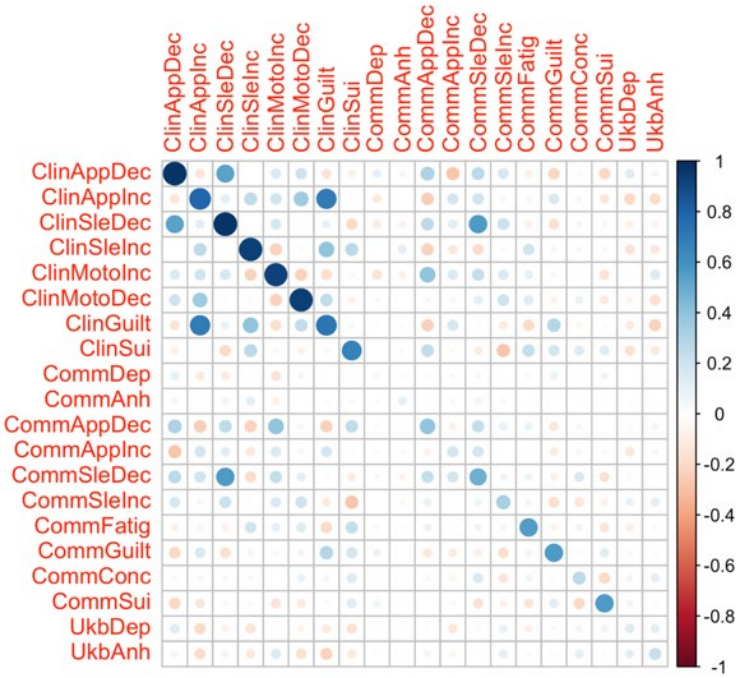


Figure S3d. Model residual proportions of genetic correlations for Cognitive/Mood-Appetite-Lethargy factors (Model "CogMood-App-Leth")



External phenotype summary statistics

For the genetic multiple regression analysis, we used the following summary statistics:

- Alcohol dependence (Walters et al., 2018)
- Anxiety (Grotzinger, Mallard, et al., 2022)
- Bipolar disorder (Mullins et al., 2021)
- Body mass index (Pulit et al., 2019)

- Educational attainment (Okbay et al., 2022)
- Major depression (Als et al., 2023)
- Major depressive disorder (Wray et al., 2018)
- Neuroticism (Nagel et al., 2018)
- Pain (multisite chronic pain) (Johnston et al., 2019)
- Post-traumatic stress disorder (Nievergelt et al., 2019)
- Sleep (long sleep duration) (Dashti et al., 2018)
- Smoking (cigarettes per day) (Liu et al., 2019)

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