ARTICLE

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Genetics of major depressive disorder in a homogeneous population with uniform phenotyping

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Harmonized phenotyping and diverse population-specific studies are crucial for advancing gene discovery in psychiatric genetics. We conducted a genome-wide association (GWAS) mega-analysis of DSM-defined lifetime major depressive disorder (MDD) in 64 941 participants (25.7% cases) from the Dutch BIObanks Netherlands Internet Collaboration (BIONIC) consortium. Liability-scale SNP-based heritability was 12.0% (SE = 1.4%) as estimated by LDSC (assuming a lifetime prevalence of 15%) and 26.6% (SE = 1.1%) when estimated by LDAK-REML on individual-level genotype data, indicating substantial common-variant signal in this clinically harmonized sample. The genetic correlation with the latest major depression GWAS from the Psychiatric Genomics Consortium (PGC-MD) was high ($r_G = 0.89$, SE = 0.048). Polygenic scores (PGSs) based on BIONIC predicted depression in UK Biobank, and PGSs derived from PGC-MD predicted MDD in BIONIC, supporting transferability of depression polygenic signal across cohorts and phenotype definitions. Within-family PGS analyses in twins suggested that the observed prediction was not primarily driven by detectable family-level confounding, and twin concordance for MDD increased with polygenic burden. We identified one genome-wide significant locus, indexed by rs3818852 in *PALMD*, but this finding currently lacks independent replication and should be interpreted cautiously. Finally, genetic correlation and latent causal variable analyses identified multiple traits showing shared or directionally consistent genetic associations with MDD. Together, these findings underscore the value of clinically harmonized phenotyping in regional biobank collaborations for studying the genetic architecture of MDD.

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Major depressive disorder (MDD) is among the most common psychiatric disorders with a lifetime prevalence that can reach up to 19%, and is a leading cause of disability worldwide [1, 2]. Episodes are frequently characterized by severe dysfunction and pervasiveness [3, 4]. MDD is a genetically complex trait with a twin-based heritability of 37% [5] and a polygenic architecture, characterized by the additive effect of many variants with small effects. In addition, MDD's intrinsic heterogeneity, heterogeneity in depression diagnoses and assessment, and the relatively modest heritability compared to other psychiatric conditions have all been suggested as contributing to low statistical power for genome-wide association studies [6, 7]. One successful approach to combating several of these problems is through large international collaborative efforts that bring together dozens of cohorts and millions of individuals [8–11].

Concurrently, a discussion has emerged regarding the trade-off in sample size and phenotypic definition in genetic studies. Larger

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sample sizes have led to finding large numbers of genetic variants associated with broad concepts of depression. Growing sample sizes often come at the expense of uniform phenotyping; combining samples across multiple studies tends to yield a lower adherence to clinical diagnostic criteria and phenotypic uniformity. The use of self-reported diagnosis or treatment for depression, or depressed mood derived from a cut-off applied to a self-report symptom questionnaire in research, coined 'minimal phenotyping', may not align with MDD according to diagnostic criteria or represent associated but different genetic vulnerabilities [12–15]. In a comparison of depression phenotypes derived from the UK Biobank, Cai et al. [15] found that minimal phenotyping definitions are epidemiologically distinct from strictly defined MDD, have lower SNP-based heritability (SNP-h^2) estimates (11% for self-reported depression vs. 26% for MDD following diagnostic criteria), and that GWAS hits from minimal phenotyping may not be specific to MDD, and instead apply to a broader range of psychopathology and personality measures [15]. Consequently, follow-up characterization of GWAS loci from minimal phenotyping studies may not inform on biology specific to MDD.

The inclusion of data based on heterogeneous phenotypic assessment is associated with a decay of SNP-h^2 estimates [16, 17]. This has led to a call for uniform phenotyping, for example by adherence to clinical diagnostic criteria. In addition to phenotypic heterogeneity, the genetic differences between cohorts, as combined in meta-analyses, are a source of heterogeneity. Most studies limit participation to participants of European ancestry. However, there can be considerable population stratification and admixture affecting heterogeneity and GWAS results [18], even after adjustments through ancestry-informative principal components. Tropf et al. [19] found that heterogeneity across populations is one of the contributing factors to missing heritability, the common difference between GWAS-derived SNP-h^2 estimates and heritability based on twin-based approaches.

To address these challenges, we initiated the BIObanks Netherlands Internet Collaboration (BIONIC) [20]. This nation-wide collaborative project combines genotype data from sixteen Dutch cohorts, and focuses on uniform phenotyping of MDD according to clinical criteria. The Netherlands has a population of 18 million people, with ~15.5 million of Dutch ancestry, and a population density of ~535 people per square kilometer. In such single populations, population stratification is smaller, although not entirely absent [21, 22]. We enriched the existing population and clinical cohorts in the Netherlands with an infrastructure for nation-wide depression phenotyping so that all MDD cases were defined based on DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) criteria [3, 23]. All cohorts agreed to share genotype and phenotype data in a central location for mega-analysis, where QC and genotype imputation were conducted simultaneously and harmonized across all arrays and participants.

Here, we investigated the genetic architecture of lifetime MDD in a clinically harmonized Dutch dataset with DSM-based phenotyping. We performed a genome-wide association mega-analysis of lifetime MDD case-control status in 64 941 individuals (16 655 cases and 48 286 controls) and evaluated the extent to which this design captured common-variant signal by estimating SNP-based heritability and genetic overlap with the latest Psychiatric Genomics Consortium major depression GWAS [10]. We extended the primary GWAS with complementary analyses, including follow-up of genome-wide association signals, polygenic score (PGS) prediction within BIONIC and out-of-sample in UK Biobank, within-family analyses to assess the robustness of polygenic prediction, PGS analyses within twin pairs, and analyses of genetic correlations and directionally informative genetic associations with other traits. Together, these analyses were intended to inform on the value of clinically harmonized phenotyping in a relatively homogeneous population for MDD.

METHODS

Sample and phenotype descriptions

This genome-wide association (GWAS) mega-analysis combines lifetime major depressive disorder (MDD) and genotype data from sixteen Dutch cohorts in the BIONIC (BIObanks Netherlands Internet Collaboration) project. Descriptions of the sixteen cohorts can be found in the Supplementary Information. All relevant ethical regulations for working with human participants were followed in the conduct of the study. Ethics approval was provided by the human research ethics boards of the 16 contributing studies and data were governed under UMCG DTA counter number 2019N1629. Written informed consent was obtained from all participants by the contributing cohorts.

The majority of phenotype data were collected through the Lifetime Depression Assessment Survey (LIDAS) [23], developed to assess DSM-5 MDD and validated against the Composite International Diagnostic Interview [24]. Additional data were derived from clinical interviews and questionnaires (see eMethods for a detailed description). Importantly, across all cohorts, MDD cases were defined according to the same DSM-5 criteria: a period of at least two weeks with five or more depression symptoms (including at least one cardinal symptom) causing dysfunction in life [25]. MDD controls were defined as having no such period. MDD controls that met diagnostic criteria or reported diagnosis and/or treatment for a range of psychopathologies were excluded from analyses (eMethods). The final analysis set included 64 941 European-ancestry individuals with non-missing MDD, covariate (sex, age) and genotype data, with 16 655 lifetime MDD cases and 48 286 screened controls.

Genotyping, quality control, and imputation

Details on the quality control (QC) procedure have been described previously [20]. In brief, the sixteen studies had collected genotype data on seven different arrays across multiple batches, resulting in nineteen datasets. This included some smaller datasets that could not be analyzed independently because they were too small or had an overrepresentation of cases. To include the largest number of individuals, SNP data genotyped on the same arrays were combined after basic sample and SNP quality control (details in eMethods). The resulting array groups were the units for further QC and imputation. Genotype data were imputed against the Human Reference Consortium (HRC) panel (v1.1) [26]. After imputation, the array groups had identical genome coverage, and were merged into a single set for mega-analysis. All arrays included genotype data on the 22 autosomes. The availability of X-chromosome data varied (Supplementary Fig. 1), with the first pseudo-autosomal region (PAR), non-PAR, and second PAR available in 55 141, 55 863, and 41 441 individuals, respectively.

Genome-wide association mega-analysis

We conducted a GWAS mega-analysis of lifetime MDD for SNPs in the merged BIONIC dataset. Analyses were conducted in fastGWA [27] from the Genome-wide Complex Trait Analysis (GCTA) software [28], with a generalized linear mixed model. SNPs with minor allele frequency <0.01 and imputation quality <0.40 were excluded from analysis. Analyses were adjusted for sex, age, 10 ancestry-informative principal components (PCs), and genotype array. We accommodated relatedness among the participants by means of the genetic relationship matrix. Independent GWAS signals were identified by conditional and joint analysis in GCTA [29], where the BIONIC GWAS MDD sample served as the LD reference sample, restricted to one individual per related pair (relatedness ≥0.125), as calculated in the KING software (V2.2.6) [30].

SNP-based heritability and genetic correlation

SNP-based heritability (SNP-h^2) was estimated by Linkage Disequilibrium score regression (v1.0.1; LDSC) [31] applied to GWAS summary statistics, and LDAK-REML (LDAK v6) applied to individual-level genotype data. Effective N was calculated following previous literature [32]. SNP-h^2 was estimated on the liability scale, specifying 15% as population prevalence [3] and sample prevalence as observed in the data (26% for the main GWAS model). LDAK SNP weightings were calculated via the LDAK-Thin model (--cut-weights), which accounts for linkage disequilibrium by down-weighting SNPs in high-LD regions. A genetic relatedness matrix (GRM) was constructed from HapMap3 SNPs using these weightings (--calc-kins-direct, --power −0.25). Heritability was then estimated by restricted maximum likelihood (REML), with sex, age at measurement, 10 principal components, and six genotyping array dummy-coded variables as fixed effects. Genetic correlations were estimated by LDSC (v1.0.1).

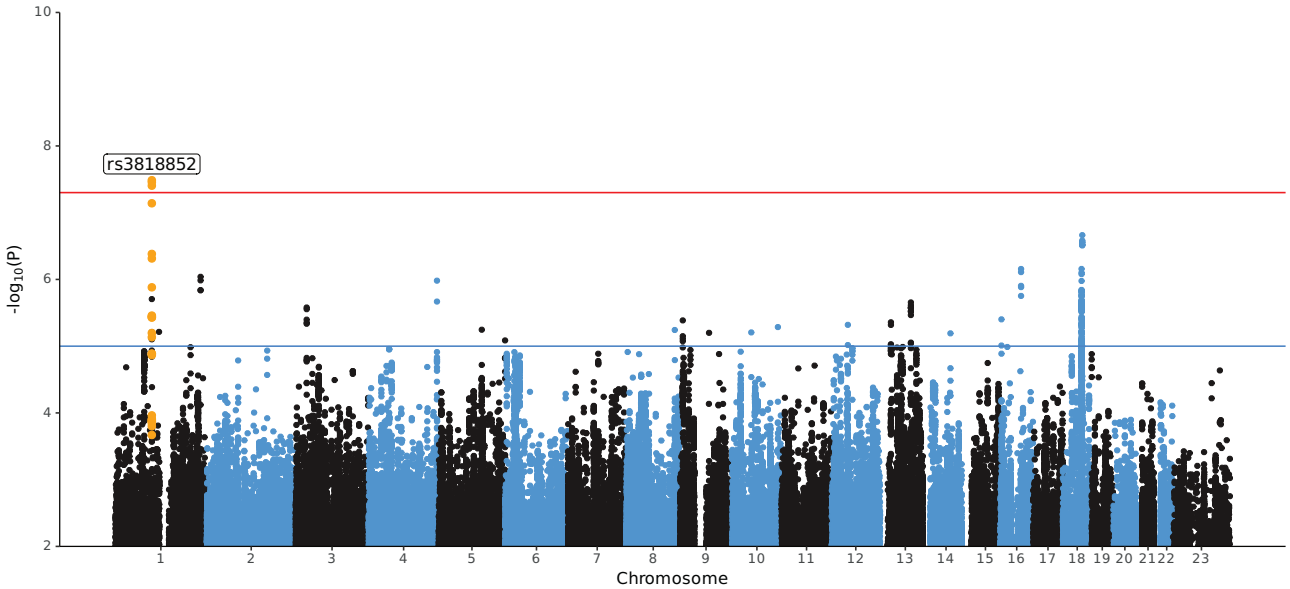

Fig. 1 Manhattan plots of the GWAS mega-analysis of major depressive disorder. Manhattan Plot of the genome-wide association mega-analysis of lifetime MDD in BIONIC. The x-axis indicates chromosomal position. Y-axis denotes -log10 p and indicates the strength of association between the SNP and outcome phenotype. The red line indicates Bonferroni-corrected genome-wide significance; $p < 5 \times 10^{-8}$. The blue line indicates suggestive singificance; $p < 1 \times 10^{-5}$.

GWAS-by-subtraction

As an exploratory secondary analysis to investigate overlap with broader depression liability, we carried out GWAS-by-subtraction as implemented in the genomic structural equation modeling (Genomic SEM) [33] software with the European GWAS summary statistics from the largest major depression (MD) GWAS to date [10] (PGC-MD, excluding Dutch samples) and the BIONIC MDD GWAS as input. GWAS-by-subtraction performs a GWAS of the unique genetic variance in the BIONIC MDD GWAS after regressing out the variance shared with the PGC-MD GWAS, i.e., the variance not shared between the two traits [34].

Polygenic score prediction

We explored genetic risk prediction of lifetime MDD through in-sample and out-of-sample polygenic score (PGS) prediction with PGSs generated in the PRScs software [35] and PLINK (v1.9) [36]. For in-sample prediction we generated MD PGSs in BIONIC based on the PGC-MD GWAS summary statistics (European samples and including 23andMe), excluding all datasets from the Netherlands [10]. The association between the MD PGS and lifetime MDD case-control status in BIONIC was estimated by logistic regression in unrelated individuals with age at assessment, sex, and 10 ancestry-informative PCs as covariates. The proportion of variance explained by the PGS on the liability scale for MDD case-control status was estimated according to Lee et al. [37].

We explored out-of-sample MD PGS prediction based on the BIONIC MDD GWAS summary statistics in the UK Biobank, for a strict definition of MDD (clinical criteria) and broad depression (clinical criteria, sum score cut-offs or self-report single item measures). Details on data field codes and genotype QC are in eMethods. A total of 23 755 and 132 122 individuals met the criteria for strict and broad phenotype definitions, respectively. PGSs were generated in similar fashion to the in-sample prediction in PRScs and PLINK (v1.9) [36] assuming an infinitesimal model. PGS prediction was estimated by logistic regression in unrelated individuals with age at measurement, sex, genotype array and 10 PCs as covariates. We repeated this approach for the PGC MDD summary statistics from [38] as a benchmark mega-analysis of similar size and phenotype definition to BIONIC.

Within-family designs are able to account for many sources of passive genotype-environment correlation, with dizygotic (DZ) twins having the additional benefit that all shared environmental factors are time-invariant among twins [39]. We sought to evaluate MD PGS prediction in a within-family design, following the approach of Selzam et al. [39] in 1141 dizygotic twin pairs with non-missing data (lifetime MDD and PGS) from the Netherlands Twin Register (NTR; a collaborating cohort in BIONIC). First, PGS prediction of MDD was assessed in DZ twin pairs through a logistic generalized linear mixed-effects model, correcting for sex and genotype array. Next, we defined between- and within-family PGS effects. Between-family PGS effects were estimated as the change in lifetime MDD risk associated with differences in the average PGS across families. Within-family PGS effects were estimated as the change in lifetime MDD risk associated with differences between an individual's PGS and their family's mean PGS. The two were fit as predictors of MDD in the same model, together with a random effect to accommodate the clustering of twins in twin pairs. The difference between the between- and within-family PGS effects was statistically tested through a chi-squared test of the difference between their coefficients divided by the standard deviations of the sampling distribution of the estimate differences [40, 41].

We computed MD PGS deciles in N = 2963 complete monozygotic and dizygotic twin pairs from the NTR cohort who took part in BIONIC [42], and distinguished three groups: concordantly affected (133) pairs, concordantly unaffected (2257) pairs and discordant (573) pairs. We hypothesized that concordantly affected twin pairs would be overrepresented in high MD PGS deciles. We repeated this approach in an independent sample for replication, the Australian Genetics of Depression Study [43] (Supplementary Information). We tested the association between the mean MD PGS in twin pairs and MDD concordance in an ordinal logistic regression model, correcting for two ancestry-informative PCs [42].

Genetic causal associations

We computed genetic correlations between the BIONIC MDD GWAS and 1461 disease, personality and lifestyle traits using bivariate LDSC in the Complex-Traits Genetics Virtual Lab (CTG-VL) analysis pipeline (https://vl.genoma.io/). Details on their derivation and acquisition are given in the eMethods. We then applied the bivariate latent causal variable (LCV) model to traits with a significant genetic correlation with MDD. The LCV method identifies potentially causal relationships among heritable traits [44], quantifying the degree to which a genetic correlation between two traits may be explained by (partial) genetic causality as opposed to full horizontal pleiotropy through the genetic causal proportion (GCP) metric. The Benjamini-Hochberg False Discovery Rate threshold of 5% was applied to correct for multiple testing at both the genetic correlation and LCV steps.

Gene-level analyses & tissue enrichment

We performed a gene-based test and gene-set analysis of MDD in the MAGMA (Multi-marker Analysis of GenoMic Annotation; v1.08) [45] tool, mapping SNPs from the BIONIC MDD GWAS to 19 210 protein-coding genes (eMethods). Gene sets were derived from categories C2 and C5 from

the publicly accessible MsigDB v7.0. Significance was set at the Bonferroni-corrected threshold of $p = 0.05/15\ 488 = 3.23 \times 10^{-6}$. We further performed tissue expression analysis for 53 tissue categories in MAGMA with the gene-based test results as input. Gene expression datasets were obtained from GTEx v8 RNAseq. Significance was defined as $p = 0.05/18\ 062 = 2.77 \times 10^{-6}$.

Gene prioritization

We fine-mapped significant loci in the BIONIC MDD GWAS in the Fine-mapped Locus Assessment Model of Effector geneS (FLAMES) [46] software, to predict the most likely effector gene in a locus (eMethods).

Sensitivity analyses

We ran a number of sensitivity analyses to assess the robustness of outcomes and the validity of the approach (eMethods). First, we ran a GWAS mega-analysis of height in the BIONIC data to benchmark our approach. Second, we compared a GWAS meta-analysis of lifetime MDD to the mega-analysis approach. Third, we repeated the GWAS mega-analysis for an alternative lifetime MDD phenotype definition in which control status was defined less strictly.

RESULTS

Genome-wide association mega-analysis of lifetime MDD

We ran a genome-wide association (GWAS) mega-analysis of lifetime major depressive disorder (MDD) in 64 941 Dutch individuals (16 655 lifetime MDD cases and 48 286 screened controls) (Fig. 1, Supplementary Figs. 2, 3). The majority of the sample was female (60.8% in the full sample) and average age was 50.7 (SD 16.0) (Supplementary Table 1). We detected a single significant SNP on chromosome 1. Specifically, rs3818852, an intronic variant of the *PALMD* gene, reached significance at the genome-wide-adjusted alpha level (OR = 0.93, $p = 3.26 \times 10^{-8}$). *PALMD* encodes the palmdelphin protein, which is involved in cellular processes including cytoskeletal organization and cell shape modulation. There have been no previous GWAS hits for rs3818852 registered in the GWAS catalogue, indicating a potentially novel association. Supplementary Table 2 lists the 10 most significant independent SNPs, with the summary statistics for the top 1000 loci available in the Supplementary Material.

SNP-based heritability and genetic correlation with PGC-MD

We estimated SNP-based heritability (SNP-h^2) of BIONIC lifetime MDD using two complementary approaches. Using LDSC [31] on the BIONIC lifetime MDD GWAS summary statistics, liability-scale SNP-h^2 was 0.120 (SE = 0.014; Neff = 63 743; Ncases = 16 655). Using LDAK-REML on individual-level genotype data, liability-scale SNP-h^2 was 0.266 (95% CI: 0.245–0.287). Both estimates were numerically higher than the estimate reported in the latest PGC-MD analysis (0.084) [10], although such comparisons should be interpreted cautiously given differences in estimation methods. The genetic correlation between the BIONIC MDD GWAS and the PGC-MD European GWAS (including 23andMe; Neff = 1 523 738) was high ($r_G = 0.869$; SE = 0.048), indicating substantial shared genetic liability between the two studies, while also being statistically distinguishable from 1.

GWAS-by-subtraction

We applied GWAS-by-subtraction as an exploratory secondary analysis to examine overlap between the BIONIC DSM-5-based MDD signal and broader depression liability captured in international summary statistics (Supplementary Fig. 4). No variants reached genome-wide significance in this analysis. The *PALMD*-region lead SNP from the primary BIONIC GWAS (rs3818852) remained among the more strongly associated signals (OR = 0.83, $p = 1.38 \times 10^{-6}$), but this analysis was not intended as replication and is interpreted descriptively.

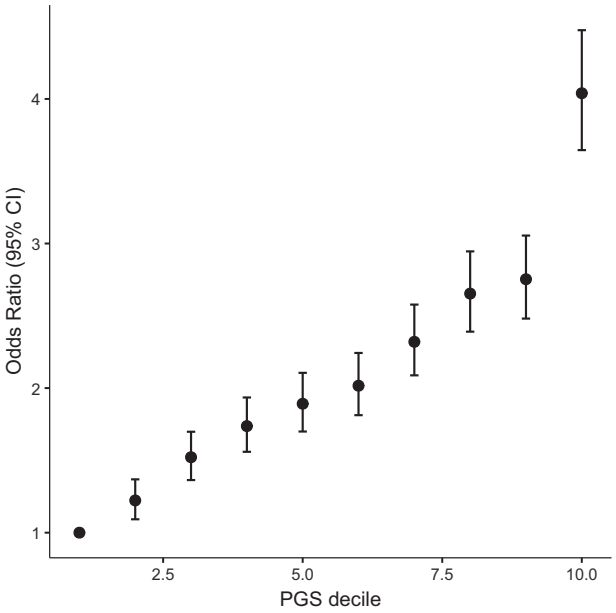

Fig. 2 MD PGS prediction of lifetime MDD. Predictive performance of the PGC major depression polygenic score of lifetime MDD in BIONIC ($N_{unrelated}$ = 44 144). The x-axis denotes the MD PGS decile. The y-axis denotes the odds ratio of each decile from the generalized estimating equations model where lifetime MDD status in the BIONIC sample was predicted by PGS decile. Odds ratios were estimated relative to decile 1. 95% confidence intervals are given.

Polygenic score prediction

We tested the predictive utility of the major depression polygenic score (MD PGS) based on PGC-MD in the BIONIC MDD GWAS sample (unrelated N = 44 144; 27% cases). The MD PGS was significantly associated with lifetime MDD status in BIONIC (OR = 1.490, 95% CI: 1.457–1.524, $p < 0.001$) and explained 4.59% (95% CI: 4.09–5.09%) of variance on the liability scale. Figure 2 displays the increasing risk for MDD at higher MD PGS deciles.

We then tested the predictive utility of a PGS based on the BIONIC MDD GWAS for two phenotypic definitions of depression in the UK Biobank: strict (ICD code for depression) and broad ('minimal phenotypic'). The BIONIC MDD PGS was significantly associated with both strict (N = 23 755, OR = 1.111, 95% CI: 1.095–1.126, Z = 15.1) and broad definitions of depression (N = 132 122, OR = 1.103, 95% CI: 1.095–1.111, Z = 27.5), explaining 0.30 and 0.26% of phenotypic variance on the liability scale, respectively. The BIONIC MDD PGS results marginally outperformed those of the similarly sized broad depression PGC PGS (eResults). These results highlight the transferability of the BIONIC MDD PGS, showing robust out-of-sample prediction for different phenotypic definitions.

Within- and between-family PGS prediction. Genotype-phenotype associations and the PGSs derived from them may arise through confounding effects, including population stratification, assortative mating and gene-environment correlation [39]. To assess whether PGS prediction of lifetime MDD may be subject to confounding, we evaluated MD PGS performance based on PGC-MD in a subset of dizygotic twins from the BIONIC MDD GWAS sample. In an unmatched binary logistic regression model of 2282 dizygotic twins (1141 complete pairs), the major depression PGS significantly predicted lifetime MDD (OR = 1.420, 95% CI: 1.257–1.606, $p = 2.08 \times 10^{-8}$). We then applied a random-effects logistic model to predict lifetime MDD with between- and within-family MD PGS effects, and family as a random variable. Both the between- and within-family MD PGSs were significantly associated with MDD (OR = 1.466, 95% CI: 1.238–1.736, $p = 9.149 \times 10^{-6}$;

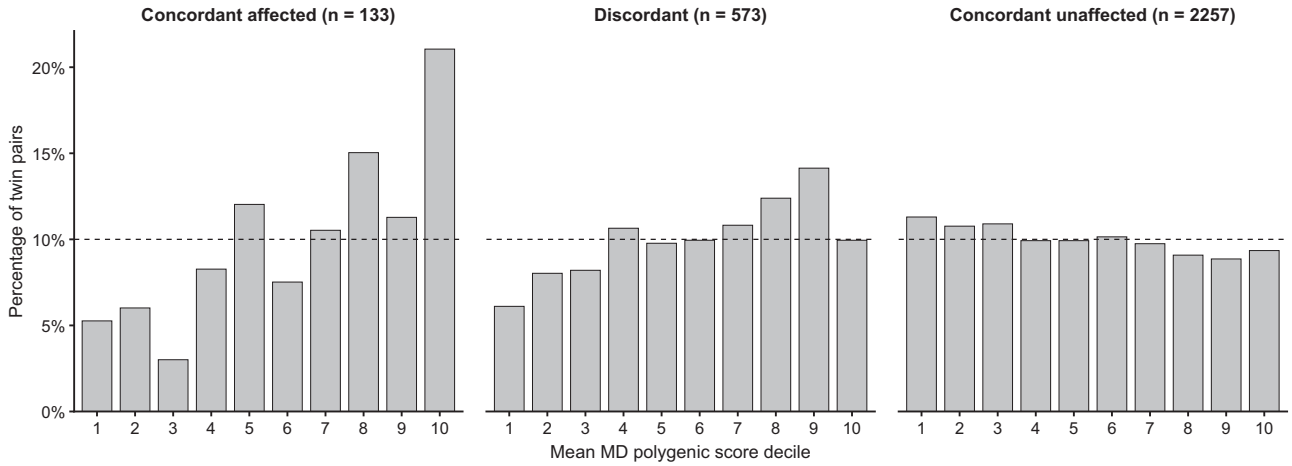

Fig. 3 MDD PGS distribution by twin concordance. Distribution of twin pairs across mean major depression polygenic score deciles, standardized within concordance group. Bars show the percentage of twin pairs within each concordance category falling into each mean MD PGS decile. Concordantly affected pairs were relatively overrepresented in higher deciles, concordantly unaffected pairs in lower deciles, and discordant pairs showed an intermediate pattern.

OR = 1.571, 95% CI: 1.214–2.032, $p = 0.001$, respectively). The between- and within-family PGS effects were not significantly different (χ^2 [1, N = 2282] = 0.193, $p = 0.661$), indicating that polygenic prediction of lifetime MDD was not primarily driven by family-level confounding. Sensitivity analyses confining analysis data to same-sex twins, same-microarray and opposite-sex twins corroborated these findings (Supplementary Information).

Twin concordance and PGS deciles. We computed MD PGS deciles in N = 2963 twin pairs in BIONIC. We distinguished three subsamples based on lifetime MDD concordance in the twin pairs: both twins affected (N = 133 pairs), both twins unaffected (N = 2257), and one twin affected with the co-twin unaffected (N = 573). We expected concordantly affected twin pairs to be overrepresented in the high PGS deciles, and concordantly unaffected twin pairs to be overrepresented in the low PGS deciles. Figure 3 presents the distribution of twin pairs across MD PGS deciles by MDD concordance status, showing that the number of concordantly affected twin pairs increases in the higher MD PGS deciles, and the number of concordantly unaffected twin pairs decreases in the higher MD PGS deciles. A similar pattern was observed in an independent replication sample from the Australian Genetics of Depression Study (Supplementary Information, Supplementary Figs. 6, 7).

We ran an ordinal logistic regression model with twin MDD concordance as outcome to test whether the mean MD PGS predicted twin MDD concordance status in the N = 2963 twin pairs in BIONIC. We found each increase of one standard deviation in mean MD PGS to be significantly associated with a 1.4-fold greater risk for concordant MDD status within twin pairs (OR = 1.381; 95% CI: 1.264–1.497).

Genetic causal associations

We computed genetic correlations between BIONIC lifetime MDD and 1461 complex traits and diseases, finding 388 significant genetic correlations (False Discovery Rate (FDR) < 5%) with well-established correlates including self-harm, substance use, anxiety, loneliness, neuroticism, irritable bowel syndrome, and chronic pain (Supplementary Material). With the latent causal variable (LCV) method [44, 47], we identified 33 traits with a putative causal genetic association with MDD at FDR < 5% (|genetic causal proportion (GCP)| >0.60), and 4 traits with limited partial genetic causality (|GCP| ≤0.60) (Table 1; Fig. 4). We identified 34 traits as putative risk factors for MDD, and 3 traits as putative outcomes of MDD. The putative causal genetic associations with MDD spanned a diverse range of traits, including well-known risk factors such as hypersomnia, stroke, and trauma. Several significant putative causal traits were related to one's work environment, including working with paints and chemicals and a workplace with very cold temperatures, which might also reflect differences in socio-economic status. Others included lifestyle traits such as vitamin D levels and vegetable consumption. Finally, associations with cardiometabolic traits were found, including stroke, ECG load, and HDL cholesterol.

Gene-level analyses & tissue enrichment

We ran a MAGMA [45] gene-based analysis on the BIONIC MDD GWAS results, mapping input SNPs to 19 210 protein-coding genes. Two genes were significantly associated with MDD at the genome-wide significance level: the *PALMD* gene on chromosome 1 (Z-score = 4.725, $p = 1.15 \times 10^{-6}$) and the *CIAPIN1* gene on chromosome 16 (Z-score = 4.627, $p = 1.85 \times 10^{-6}$) (Fig. 5). We ran a MAGMA gene-set analysis for pathway-specific enrichment for gene sets C2 and C5 from MsigDB v7.0. We found no significant gene-sets at the Bonferroni-corrected significance threshold (3.23×10^{-6}). The most significant gene sets were involved in regulation of T-cell migration (Beta = 1.61, $p = 6.75 \times 10^{-6}$) and vitamin binding (Beta = 0.31, $p = 7.75 \times 10^{-6}$). The full summary statistics of the gene-based test and gene-set test are available in the Supplementary Material. In the MAGMA tissue expression analysis, in which we compared SNP associations from the BIONIC MDD GWAS with gene expression levels from the GTEx v8 database for 53 tissue types, none of the investigated tissues showed significant enrichment after multiple testing correction (Supplementary Fig. 7).

Gene prioritization

We applied FLAMES [46] to identify the most likely effector gene for the genome-wide significant locus in the BIONIC MDD GWAS (lead variant: rs3818852 on chromosome 1). There were 23 SNPs with an LD > 0.60 implicated as potential alternative causal SNPs, which were used for credible set generation in FINEMAP. The *PALMD* gene was assigned the highest FLAMES score (0.436), suggesting it is the most likely effector gene for the genetic association between rs3818852 and MDD.

Sensitivity analyses

To study the feasibility of a GWAS of MDD in a relatively small sample, we conducted a GWAS mega-analysis of height in 52 893 individuals from the BIONIC dataset. Despite the modest sample

Table 1. Traits with an inferred putative causal relationship with MDD.

Phenotypes that cause MDD	GCP	GCP se	GCP *P*	r_G	r_G se	r_G *P*
Sleeping too much	−0.88	0.11	8.64e-16	0.65	0.16	4.01e-05
Workplace often full of chemical or other fumes	−0.86	0.13	2.32e-11	0.73	0.19	7.56e-05
Mouth ulcers	−0.83	0.13	5.31e-11	0.28	0.07	4.74e-05
ECG load	−0.85	0.13	2.03e-10	-0.68	0.18	1.68e-04
Had other major operations	−0.94	0.15	6.11e-10	0.41	0.10	7.53e-05
Triglycerides	−0.77	0.14	6.77e-08	0.20	0.07	6.87e-03
Self-reported cervical spondylosis	−0.80	0.15	1.86e-07	0.44	0.15	2.38e-03
Sometimes worked with paints, thinners or glues	−0.80	0.16	3.31e-07	0.54	0.12	1.18e-05
Mouth-teeth dental problems: Mouth ulcers	−0.49	0.10	1.10e-06	0.28	0.08	2.49e-04
Treatment/medication code: cod liver oil capsule	−0.79	0.17	4.97e-06	−0.66	0.22	3.08e-03
Ever had period of mania / excitability	−0.79	0.18	6.68e-06	0.60	0.12	5.69e-07
Vitamin and mineral supplements: Vitamin B	−0.76	0.18	1.56e-05	0.36	0.13	6.57e-03
Treatment/medication code: rosiglitazone	−0.90	0.21	1.89e-05	0.35	0.14	1.20e-02
Vegetable consumption	−0.60	0.14	2.21e-05	−0.43	0.17	1.30e-02
Vitamin D	−0.75	0.18	4.35e-05	−0.18	0.06	1.97e-03
Workplace often very cold	−0.75	0.18	4.45e-05	0.51	0.15	4.61e-04
HDL cholesterol	−0.67	0.18	1.73e-04	−0.12	0.04	3.22e-03
Workplace often very hot	−0.55	0.15	2.43e-04	0.50	0.15	5.84e-04
Did your sleep change?	−0.75	0.21	3.44e-04	0.69	0.27	1.13e-02
Difficulty concentrating during worst depression	−0.75	0.21	3.47e-04	0.75	0.14	1.60e-07
Illnesses of mother: None of the above (group 2)	−0.72	0.20	3.75e-04	−0.41	0.12	1.12e-03
Workplace had a lot of cigarette smoke from other people smoking: Often	−0.74	0.21	4.57e-04	0.65	0.16	6.64e-05
More creative or having more ideas than usual	−0.59	0.17	5.10e-04	0.51	0.17	2.24e-03
Probable Recurrent major depression (moderate)	−0.75	0.22	6.30e-04	0.76	0.14	2.40e-08
Diabetes diagnosed by doctor	−0.69	0.20	7.56e-04	0.24	0.07	3.16e-04
Self-reported stroke	−0.72	0.22	8.71e-04	0.64	0.20	1.35e-03
Treatment/medication code: ranitidine	−0.70	0.21	9.20e-04	0.46	0.14	8.28e-04
Treatment/medication code: diazepam	−0.72	0.22	1.03e-03	0.63	0.24	1.00e-02
Self-reported diabetes	−0.68	0.21	1.23e-03	0.23	0.07	1.38e-03
Stroke (European biobanks)	−0.84	0.26	1.47e-03	0.30	0.11	8.61e-03
Diaphragmatic hernia	−0.68	0.22	2.30e-03	0.49	0.14	3.52e-04
Age at menopause (last menstrual period)	−0.65	0.22	2.99e-03	−0.22	0.06	7.67e-04
Illnesses of mother: Chronic bronchitis/emphysema	−0.67	0.23	3.42e-03	0.41	0.11	2.23e-04
Stroke (global biobanks)	−0.64	0.23	4.74e-03	0.27	0.09	2.94e-03
Phenotypes caused by MDD						
Breathing problems improved/stopped away from workplace or on holiday	0.85	0.12	3.55e-13	0.69	0.17	4.71e-05
Been in a serious accident believed to be life-threatening	0.78	0.16	1.08e-06	0.68	0.17	4.94e-05
Back pain for 3+ months	0.53	0.12	5.32e-06	0.31	0.11	6.39e-03

This table displays 37 traits with a significant (FDR < 5%) genetic causal proportion with lifetime major depressive disorder (MDD). *P*s are before FDR correction, *P*s after FDR correction are listed in Supplementary Material. *GCP* genetic causal proportion, *se* standard error, r_G genetic correlation.

size, we identified 94 independent significant SNPs associated with height at the genome-wide significance level (Supplementary Figs. 8, 9). Height LDSC SNP-h^2 was estimated to be 0.379 (SE = 0.026; N_{eff} = 49 036), or 37.9% of phenotypic variance. The genetic correlation with the largest GWAS of height to date, Yengo et al. [48], was $r_G = 0.980$ (SE = 0.016).

As an alternative to the GWAS mega-analysis approach, we conducted a genome-wide association fixed-effect meta-analysis combining the seven array group GWAS results of lifetime MDD case-control status. Results were similar to those of the main model ($r_G = 1$, Supplementary Information, Supplementary Fig. 10).

We ran a GWAS mega-analysis of lifetime MDD with a less stringent screening process for psychopathology in control participants. This approach aimed to assess whether the screening criteria for controls may introduce bias into SNP-h^2 and r_G estimates. Expanding the total sample size to N = 67 440 (16 655 cases), we found that the relaxed control screening had minimal impact on the results ($r_G = 0.99$) compared to the main model; see Supplementary Information. The SNP-h^2 estimate in this model was 0.112 (SE = 0.014), closely aligning with the estimate from the main model (SNP-h^2 = 0.120). These findings suggest that the SNP-h^2 estimate in the main model was not artificially inflated by the stringent control screening criteria.

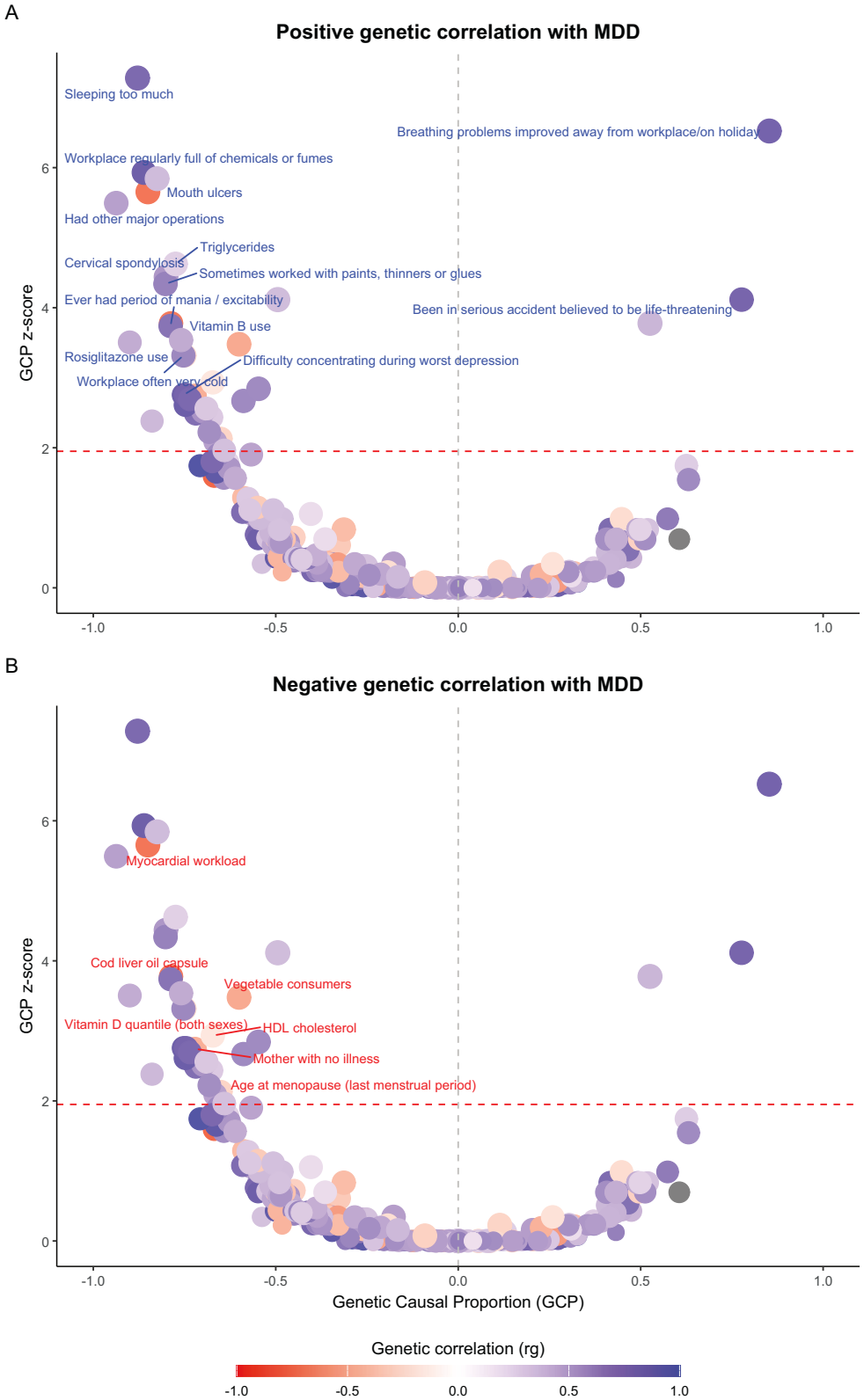

Fig. 4 Causal architecture plots for MDD. Causal architecture plots depicting the LCV phenome-wide analysis results for BIONIC MDD. Dots represent traits with a significant genetic correlation with MDD. The x-axis reflects the proportion of genetic causality (GCP). The y-axis shows the GCP absolute Z-score (statistical significance). The red-dashed line represents the statistical significance threshold (FDR <5%), while the gray-dashed line represents the division between traits causally influencing MDD (left) and traits causally being influenced by MDD (right). Dot size reflects estimate accuracy (se). Annotation is provided for traits with a |GCP| >0.60 that are significant at False Discovery Rate (FDR) <5%, and that have a positive (plot **A**) or negative (plot **B**) genetic correlation with MDD.

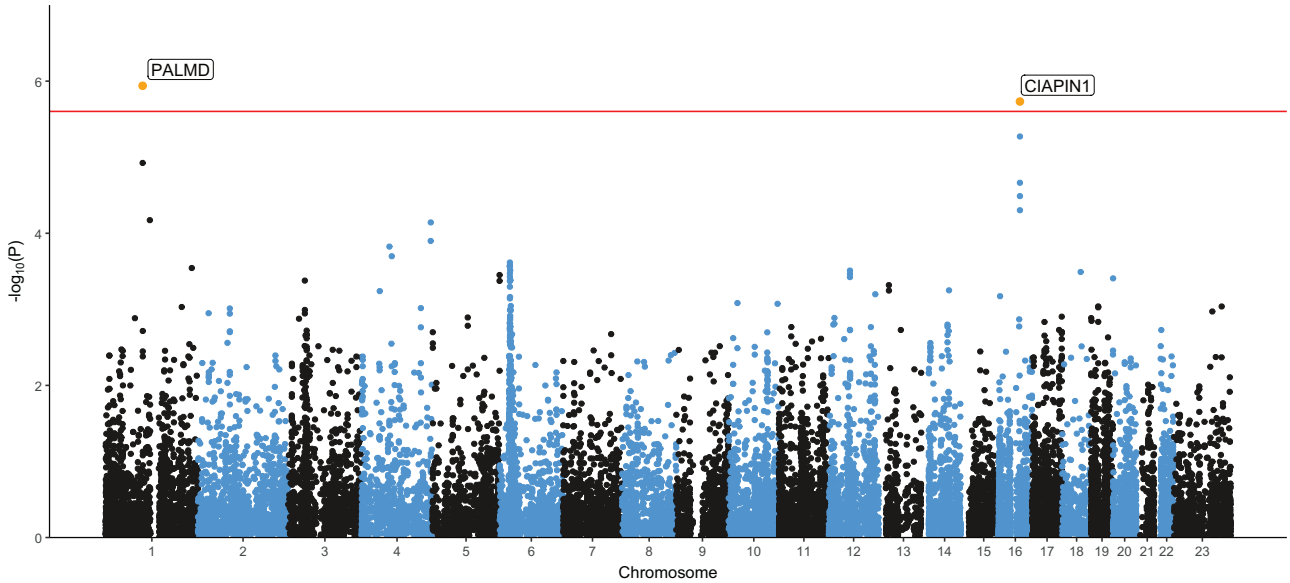

Fig. 5 Gene-based analysis of MDD. Manhattan Plot of the gene-based analysis of lifetime MDD in BIONIC. The x-axis indicates chromosomal position. The y-axis denotes -log10 *P* and indicates the strength of association between the gene and the outcome phenotype. The red line indicates Bonferroni-corrected genome-wide significance; $P < 2.50 \times 10^{-6}$ (based on 19 994 tested protein-coding genes).

DISCUSSION

This study represents, to our knowledge, the largest harmonized genetic analysis of clinically defined lifetime MDD to date. By combining genotype data with DSM-5-based phenotyping across multiple studies in the Netherlands, this approach provides a complementary design to the very large international depression GWAS efforts, which often need to rely on broader and more heterogeneous definitions. Our findings suggest that this harmonized approach captures meaningful common-variant signal for MDD, as reflected in SNP-based heritability, the high genetic correlation with international MDD GWAS, and robust polygenic prediction both within BIONIC and in external data.

Liability-scale SNP-h^2 for lifetime MDD in BIONIC was estimated at 12.0% by LDSC and 26.6% by LDAK-REML on individual-level genotype data. The higher estimate obtained with LDAK-REML relative to LDSC is not unexpected, as these methods make different assumptions about how heritability is distributed across the genome. The LDAK-REML estimate is also broadly in line with previous SNP-based heritability estimates reported for more clinically defined depression phenotypes [15, 49]. Both estimates were higher than those reported in recent large depression GWAS meta-analyses [9–11], although direct comparisons are hindered by differences in analytical approaches. One possible explanation is that harmonized DSM-5-based phenotyping in a relatively homogeneous setting improves the capture of genetic signal, in line with recent theoretical and empirical work emphasizing the importance of phenotypic and population heterogeneity in depression genetics [50, 51]. Our results do not directly establish this mechanism, but they are consistent with the view that clinically informed and relatively homogeneous designs remain valuable alongside very large-scale meta-analytic efforts [15, 17, 19]. The high genetic correlation with PGC-MD, while significantly lower than 1, further supports the view that BIONIC captures largely shared but not identical depression liability. As an additional benchmark of our design, a GWAS of height in the same sample recovered 94 genome-wide significant loci and showed near-perfect genetic correlation with the largest published height GWAS, demonstrating that BIONIC can robustly capture established polygenic signals.

The polygenic score analyses further support the validity and transferability of the BIONIC MDD phenotype. A major depression polygenic score derived from external GWAS robustly predicted lifetime MDD in BIONIC, while a BIONIC-based polygenic score significantly predicted both strict and broad depression definitions in UK Biobank. This suggests that the genetic signal captured in BIONIC generalizes beyond the discovery setting and is not specific to a single phenotype operationalization.

The inclusion of twin pairs allowed an examination of polygenic prediction in a within-family framework. Within-family polygenic score effects remained associated with lifetime MDD, and their magnitude did not significantly differ from between-family effects, providing evidence that the observed prediction was not driven by detectable family-level confounding in this sample, consistent with earlier work indicating limited assortative mating effects for MDD [30, 52, 53]. Twin concordance for MDD tracked polygenic burden, with concordantly affected pairs having higher mean polygenic scores than discordant pairs, and discordant pairs having higher scores than concordantly unaffected pairs, echoing results for schizophrenia and bipolar disorder [42]. Together, these analyses suggest that the BIONIC phenotype captures clinically relevant and transferable polygenic liability to MDD.

Against this broader polygenic background, we identified one genome-wide significant locus for MDD, indexed by rs3818852 in *PALMD* on chromosome 1. This locus has not previously been implicated in MDD. Independent replication in a comparable clinically ascertained cohort was not possible, because all eligible Dutch cohorts were already included in BIONIC. The finding should therefore be interpreted cautiously pending external replication. *PALMD* remains biologically interesting given prior work implicating it in cellular and neuronal processes [54–56], including hippocampal dendritic branching, and gene-based follow-up analyses also highlighted *PALMD* and *CIAPIN1* as candidate genes. While these findings await replication and should be interpreted with caution, they may help generate hypotheses for future replication and functional work.

We also examined the broader correlational and potentially directional genetic architecture of MDD. Genetic correlation and latent causal variable analyses identified a range of traits with signals consistent with partial genetic overlap or directional association with MDD, including sleep-related traits, cardiovascular indicators, lifestyle variables, and work-related exposures. Several of these align with previous work on broad depression,

while others may reflect aspects that become more visible when considering clinically defined lifetime MDD [47]. At the same time, these analyses should be interpreted cautiously: latent causal variable models are informative for prioritizing hypotheses, but they do not establish causal effects in the same sense as experimental or quasi-experimental designs. We therefore view these findings primarily as a guide for future etiological work.

Several limitations should be considered. First, harmonization reduced phenotypic heterogeneity relative to many large-scale depression GWAS, but residual heterogeneity across cohorts and assessment contexts may remain. Second, because all currently eligible Dutch cohorts with genotype data and clinical MDD assessment were included in this study, we were unable to perform an independent replication analysis of the *PALMD* locus. Third, our design does not allow us to disentangle the relative contributions of phenotypic harmonization and population homogeneity to the observed increase in genetic signal. Fourth, the ancestry composition of the sample limits generalizability to more diverse populations and potentially to culturally varying manifestations of depression. These limitations should be weighed against a major strength of the study: the integration of multiple Dutch cohorts into a clinically harmonized resource for studying the genetics of MDD. We are not the first to show that a strict phenotyping definition in a relatively homogeneous population benefits MDD genetic variant identification [57]. It is clear that such a strategy still holds promise for finding genome-wide significant associations with MDD.

Overall, our findings add to the growing evidence base on the genetic architecture of MDD and suggest that clinically informed, harmonized phenotyping remains valuable in psychiatric genetics. As genetic discovery from increasingly broad phenotyping strategies begins to plateau, complementary designs such as BIONIC may help improve signal capture, strengthen polygenic prediction, and refine the study of genetic overlap and etiological pathways in MDD.

DATA AVAILABILITY

Data are available upon reasonable request from the contributing cohorts. Code is available upon request from the corresponding author. Full summary statistics from the BIONIC GWAS mega-analysis of MDD can be found here on the GWAS catalog under GCP ID: GCP001649.

CODE AVAILABILITY

Analyses were performed using publicly available software, including GCTA/fastGWA (https://yanglab.westlake.edu.cn/software/gcta/), KING (https://www.kingrelatedness.com/), LDSC (https://github.com/bulik/ldsc), LDAK (https://dougspeed.com/ldak/), Genomic SEM (https://github.com/GenomicSEM/GenomicSEM), PRScs (https://github.com/getian107/PRScs), PLINK (https://www.cog-genomics.org/plink/), CTG-VL (https://vl.genoma.io/), MAGMA (https://cncr.nl/researchs/magma), and FLAMES (https://github.com/Marijn-Schipper/FLAMES. Custom analysis scripts are available upon request from the corresponding author.

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AUTHOR CONTRIBUTIONS

FH, DIB, YM, JJH, BWJHP, MB, BAPCdM and HvL: conceived and designed the study. JJH, RP and FH: developed the analysis pipeline and software. FH, BAPCdM and JH: performed the statistical analyses. TEG, MB, MLR, AALK, JJH, BAPCdM, SDG and BLM: prepared and curated the data. LM'tH, FR, MTB, DR, MV, IB, EF, CH, AO, EJCdG, LK, MH, HSJP, WMV, HMvL, BP and DIB: contributed cohort data. FH: created the visualizations. FH, DIB, YM, JJH and BWJHP: wrote the original draft. DIB and BWJHP: acquired funding. All authors reviewed and edited the manuscript.

COMPETING INTERESTS

The authors declare no competing interest.

ADDITIONAL INFORMATION

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