**Word Count:** 10,377 (including abstract, text, and references)

**Number of Figures:** 3

**Number of Tables:** 1

**Meta-Analyses of Genome-Wide Association Studies for Postpartum Depression**

**Corresponding Author:** Jerry Guintivano (guinti@email.unc.edu)

Jerry Guintivano, PhD [1]; Enda M Byrne, PhD [2,3]; Jacqueline Kiewa [2]; Shuyang Yao, PhD [4]; Anna E Bauer, PhD [1]; Karolina A Aberg, PhD [5]; Mark J Adams, PhD [6]; Archie Campbell [7,8]; Megan L Campbell [9,10]; Karmel W Choi, PhD [11,12,13]; Elizabeth C Corfield, PhD [14,15]; Alexandra Havdahl, PhD [15,16,17]; Donald Hucks [18]; Nastassja Koen, PhD [19]; Yi Lu, PhD [4]; Merete L Mægbæk, MSc [20]; Jimmy Mullaert, MD PhD [21,22]; Roseann E Peterson, PhD [23,24]; Laura M Raffield, PhD [25]; Hannah M Sallis, PhD [26,27]; Julia M Sealock, PhD [28,29]; Alicia Walker [30]; Hunna J Watson, PhD [1,31,32]; Ying Xiong [4]; Jessica MK Yang [33]; Richard JL Anney, PhD [34]; Katherine Gordon-Smith, PhD [35]; Leon Hubbard, PhD [36]; Lisa A Jones, PhD [35]; Raluca Mihaescu, MD PhD [37]; Mette Nyegaard, PhD [38]; Antonio F Pardiñas, PhD [36]; Amy Perry, PhD [35]; Nazmus Saquib, PhD [39]; Aladdin H Shadyab, PhD [40]; Alexander Viktorin, PhD [4]; Ole A Andreassen, MD PhD [41,42,43]; Tim B Bigdeli, PhD [44,45]; Lea K Davis, PhD [46]; Cindy-Lee Dennis, PhD [47]; Arianna Di Florio, MD PhD [36]; Caroline Dubertret, MD PhD [48,49]; Yen-Chen A Feng, PhD [11,12,13]; Benicio N Frey, MD PhD [50,51]; Sophie Grigoriadis, MD PhD [52,53]; Emilie Gloaguen [54]; Ian Jones, PhD [36]; James L Kennedy, MD PhD [53,55]; Holly Krohn [1]; Theodora Kunovac Kallak, PhD [56]; Yun Li, PhD [25,57]; Nick G Martin, PhD [58]; Andrew M McIntosh, MD [6]; Jeannette Milgrom, PhD [59,60]; Trine Munk-Olsen, PhD [61,62]; Tim Oberlander, MD [63,64]; Catherine M Olsen, PhD [65,66]; Nicolas Ramoz, PhD [67,68]; Ted Reichborn-Kjennerud, MD PhD [14,69]; Emma Robertson Blackmore, PhD [70]; David Rubinow, MD [1]; Alkistis Skalkidou, PhD [56]; Jordan W Smoller, MD [11,12,13]; Dan J Stein, MD PhD [19]; Zachary N Stowe, MD [71]; Valerie Taylor, MD PhD [72]; Sarah Tebeka, MD PhD [49,73]; Martin Tesli, MD PhD [14,74]; Ryan J Van Lieshout, MD PhD [50]; Edwin JCG van den Oord, PhD [5]; Simone N Vigod, MD [53,75]; Thomas Werge, PhD [76,77,78,79]; Lars T Westlye, PhD [80,81,82]; David C Whiteman, PhD [83,84]; Heather J Zar, MD PhD [85,86]; MDD Working Group; Naomi Wray, PhD [87]; Samantha Meltzer-Brody, MD [1,+]; Patrick Sullivan, MD FRANZCP [1,4,25,+]

1 Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
2 Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia
3 Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia
4 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
5 Center for Biomarker Research and Precision Medicine, Virginia Commonwealth University, Richmond, VA, USA
6 Division of Psychiatry, University of Edinburgh, Edinburgh, UK
7 Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK
8 Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK
9 MRC Genomic and Precision Medicine Research Unit, Division of Human Genetics. Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa
10 Global Initiative for Neuropsychiatric Genetics Education in Research, Broad Institute, Cambridge, MA, USA
11 Center for Precision Psychiatry, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
12 Department of Psychiatry, Harvard Medical School, Boston, MA, USA
13 Psychiatric & Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
14 Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway
15 Nic Waals Institute, Lovisenberg Diaconal Hospital, Oslo, Norway
16 Center for Genetic Epidemiology and Mental Health, Norwegian Institute of Public Health, Oslo, Norway
17 Department of Psychology, PROMENTA Research Center, University of Oslo, Oslo, Norway

18 Department of Medicine, Division of Genetic Medicine, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA
19 SAMRC Unit on Risk & Resilience in Mental Disorders, Dept of Psychiatry & Neuroscience Institute, University of Cape Town, Cape Town, Western Cape, South Africa
20 National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, BSS, Aarhus, Denmark
21 Department of Epidemiology, Biostatistics and Clinical Research, AP-HP.Nord – Université Paris Cité, Paris, France
22 UMR 1137 IAME, INSERM, Paris, France
23 Department of Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University, Brooklyn, NY, USA
24 Institute for Genomics in Health, SUNY Downstate Health Sciences University, Brooklyn, NY, USA
25 Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
26 Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
27 MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK
28 Analytic & Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
29 Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA
30 Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia
31 Discipline of Psychology, Curtin University, Perth, Western Australia, Australia
32 Division of Paediatrics, The University of Western Australia, Perth, Western Australia, Australia
33 MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK
34 Division of Psychological Medicine & Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff University, Cardiff, UK
35 Psychological Medicine, University of Worcester, Worcester, UK

36 MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
37 Department of Psychiatry, Catharina Hospital, Eindhoven, Netherlands
38 Department of Health Science and Technology, Aalborg University, Aalborg, Nordjylland, Denmark
39 Clinical Sciences, Sulaiman AlRajhi University, Bukairiyah, Saudi Arabia
40 Department of Epidemiology, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, USA
41 NORMENT Centre, University of Oslo, Oslo, Norway
42 Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
43 KG Jebsen Centre of Neurodevelopment Research, University of Oslo, Oslo, Norway
44 Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University, Brooklyn, NY, USA
45 Research Service, Department of Veterans Affairs New York Harbor Healthcare System, New York, NY, USA
46 Department of Medicine, Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
47 Lawrence S Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada
48 INSERM U1266, Université de Paris, Paris, France
49 Department of Psychiatry, AP-HP, Louis Mourier Hospital, Colombes, France
50 Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
51 Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
52 Department of Psychiatry, Sunnybrook Health Science Centre and Research Institute, Toronto, Ontario, Canada
53 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
54 Hôpital Bichat, Department of Epidemiology Biostatistics and Clinical Research, AP-HP, Paris, France

55 Molecular Brain Science Dept, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
56 Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
57 Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
58 Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
59 Parent-Infant Research Institute, Heidelberg Heights, Victoria, Australia
60 University of Melbourne, Melbourne, Victoria, Australia
61 The National Center for Register-based Research, Aarhus University, Aarhus, Denmark
62 Department of Clinical Research, Psychiatric Research Unit, University of Southern Denmark, Odense, Denmark
63 BC Children's Hospital, Vancouver, British Columbia, Canada
64 Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
65 Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
66 The Frazer Institute, The University of Queensland, Brisbane, Queensland, Australia
67 Institute of Psychiatry and Neuroscience of Paris, INSERM U1266, Paris, France
68 Faculty of Medicine, University Paris Cite, Paris, France
69 Institute of Clinical Medicine, University of Oslo, Oslo, Norway
70 Behavioral Sciences & Social Medicine, Florida State University, Daytona Beach, FL, USA
71 Department of Psychiatry, University of Wisconsin at Madison, Madison, WI, USA
72 Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada
73 INSERM U1266, Université Paris Cité, Paris, France
74 Centre for Research and Education in Forensic Psychiatry, Department of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
75 Department of Psychiatry, Women's College Hospital, Toronto, Ontario, Canada
76 Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark

77 Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
78 LF Center for Geogenetics, Globe Institute, University of Copenhagen, Copenhagen, Denmark
79 iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Copenhagen, Denmark
80 Department of Psychology, University of Oslo, Oslo, Norway
81 NORMENT, Division for Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
82 K.G. Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway
83 Population Health Program, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
84 School of Public Health, The University of Queensland, Brisbane, Queensland, Australia
85 Department of Paediatrics & Child Health, University of Cape Town, Cape Town, Western Cape, South Africa
86 SA-MRC Unit on Child & Adolescent Health, University of Cape Town, Cape Town, Western Cape, South Africa
87 Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia,

+ Contributed equally to this work

**ABSTRACT**

**Objective:** Postpartum depression (PPD) is a common subtype of major depressive disorder (MDD) that is more heritable, yet understudied in psychiatric genetics. Meta-analyses of genome-wide association studies (GWAS) were conducted to investigate the genetic architecture of PPD.

**Method:** Meta-analyses were conducted on 18 cohorts of European ancestry (17,339 PPD cases and 53,426 controls), one cohort of East Asian ancestry (975 cases and 3,780 controls), and one cohort of African ancestry (456 cases and 1,255 controls) totaling 18,770 PPD cases and 58,461 controls. Post-GWAS analyses included: 1) single-nucleotide polymorphism (SNP)-based heritability ($h^2_{SNP}$), 2) genetic correlations between PPD and other phenotypes, and 3) enrichment of the PPD GWAS findings in 27 human tissues and 265 cell types from the mouse central and peripheral nervous system.

**Results:** No SNP achieved genome-wide significance in the European or the trans-ancestry meta-analyses. The $h^2_{SNP}$ of PPD was 0.14 (s.e. = 0.02). Significant genetic correlations were estimated for PPD with MDD, bipolar disorder, anxiety disorders, post-traumatic stress disorder, insomnia, age of menarche, and polycystic ovary syndrome. Cell type enrichment analyses implicate inhibitory neurons in the thalamus and cholinergic neurons within septal nuclei of the hypothalamus, a pattern that differs from MDD.

**Conclusions:** While more samples are needed to reach genome-wide levels of significance, the results presented confirm PPD as a polygenic and heritable phenotype. There is also evidence that despite a high correlation with MDD, PPD may have unique genetic components. Cell enrichment results suggest GABAergic neurons, which converge on a common mechanism with the only FDA approved medication for PPD (brexanalone).

## INTRODUCTION

Postpartum depression (PPD) is a perinatal form of major depressive disorder (MDD) with a global prevalence of 17% (1-3). PPD is one of the most frequent complications of childbirth (4-7) and is associated with many adverse outcomes including maternal morbidity and mortality (1, 2), increased risk for infanticide (8), poorer maternal-infant attachment, and impaired parenting behaviors (6, 9). Despite these negative impacts, PPD is understudied in psychiatric genomics and its genetic risk factors are largely unknown. Smaller GWAS have been performed (10, 11), but no large GWAS meta-analyses have been done.

PPD is a strong candidate for genomic studies. PPD is a more homogenous form of MDD: only females affected, reproductive age-banded, and with exposure to the same biopsychosocial event. Moreover, the twin heritability of PPD (54%) is higher than that of MDD (32%) (12). With sample sizes increasing in number and diversity, clinically relevant results can begin to be uncovered and the genomic basis for PPD will become better understood. Not only could successful genomic analyses of PPD allow stratification of a specific presentation of MDD, but it may also allow delineation of the role genetic risk plays in the presentation of PPD features (i.e., onset, duration, symptom severity, recurrence) which could guide more effective treatment selection. This is critical given there is currently only one approved medicine with a specific indication for PPD, brexanalone (Zulresso) (13-15).

Discerning the biological basis of psychiatric disorders has been difficult. Most likely PPD is impacted by many genetic loci, each with small effects (16), similar to other psychiatric disorders (17-19). Although early GWAS for MDD were negative (20, 21), increases in sample size have made considerable progress (22, 23). The major lesson from MDD and other psychiatric GWAS is that progress is possible, but genetic approaches for higher prevalence/lower heritability diseases like PPD and MDD are challenging and require large sample sizes.

Therefore, we conducted the first large GWAS meta-analyses for PPD across 20 international cohorts (18 European ancestry, one east Asian, and one African). The results from these meta-

analyses enabled us to: 1) estimate the SNP-based heritability ($h^2_{SNP}$) of PPD, 2) calculate genetic correlations ($r_g$) to identify potentially pleiotropic relationships between PPD and other psychiatric disorders, medical diseases, and biomedical traits, and 3) identify specific cell types that may underlie PPD etiology.

## RESULTS

### Cohort Comparability

We identified 18 cohorts of European ancestry (EUR) that used a range of methods to ascertain cases with PPD (**Table S1** and **Supplemental Material**). The methods used by these cohorts were thoroughly reviewed and we assessed the comparability of the cohorts using summary-level data. We evaluated the comparability of these cohorts in two ways: 1) directly comparing our three largest cohorts (sample size greater than 5,000) and 2) meta-analyzing cohorts with the same ascertainment methods. For each of these comparisons we estimate the common variant genetic correlations ($r_g$) and perform targeted replication using a leave-one-out (LOO) approach (Cohort Comparability in **Supplemental Methods**).

Among our three largest cohorts (agds, pact, ukb) the weighted mean $r_g$ was 0.73 (s.e. = 0.14), supporting their comparability (**Table S2**). This estimate can be benchmarked against the weighted mean $r_g$ between MDD GWAS cohorts of 0.76 (s.e. = 0.03) (23). For LOO targeted replication, , we meta-analyzed 17 EUR cohorts (leaving out one of the three cohorts listed above), using the left-out cohort as a replication sample. LD independent SNPs from each meta-analysis were identified and used for replication. Sign tests were significant ($p < 0.05$) for two of the three LOO analyses (agds LOO $p = 2.93 \times 10^{-3}$; pact LOO $p = 5.45 \times 10^{-2}$; ukb LOO $p = 2.70 \times 10^{-2}$; **Table S2**), indicating consistent directions of effect across cohorts.

Next, we compared meta-analyzed cohorts with similar ascertainment methods (clinical interview/ICD code, Edinburgh Postnatal Depression Scale [EPDS], minimal self-report). The weighted mean $r_g$ was 0.56 (s.e. = 0.10). For LOO target replication, sign tests were significant for two of the three LOO analyses (clinical/icd LOO p = 0.601; epds LOO p = 1.97E-59; minimal

LOO p = 6.63E-61; **Table S2**), indicating consistent direction of effect across ascertainment methods.

**European Ancestry Genome-wide Association Study of PPD**

Given the positive evidence for comparability of these cohorts, we performed a primary GWAS meta-analysis in women of European ancestry, comprising of 9,750,447 SNPs in 17,339 women with a history of PPD and 53,426 controls. No evidence of residual population stratification or systematic technical artifact was observed in the final meta-analysis ($\lambda = 1.04$, $\lambda_{1000} = 1.00$) (**Figure 1**) or in any of the individual data sets (**Table S1** and **Figures S1** - **S2**). LD score regression (24) indicated that 87% of the observed test-statistic inflation was attributable to an underlying genome-wide polygenic signal. We estimated the $h^2_{SNP}$ to be 0.14 (s.e. = 0.02, liability scale, assuming lifetime risk of 0.10**; Figure S3**).

No SNP reached genome-wide significance ($p < 5.0 \times 10^{-8}$) in the EUR GWAS meta-analysis. The most significant SNP, rs3788305, is located on chromosome 22q11.21 ($\beta$ = -0.09, $p = 2.09 \times 10^{-7}$) (**Table 1**; see also **Figure S4**). rs3788305 lies within an intron of *TXNRD2* (thioredoxin reductase 2). Across the genome, we identified 62 SNPs with a p-value < 1e-6, which segregate into seven LD-independent loci. These loci were identified by LD pruning ($r^2$< 0.1) followed by conditional association analyses controlling for the most significant SNP within each 2-Mb window and manual inspection of regional association plots to confirm the presence of supporting statistical evidence of association from nearby SNPs. These top seven LD-independent index SNPs are presented in **Table 1** (**Figures S4** – **S10**).

**Trans-Ancestry Genome-wide Association Study of PPD**

Next, we conducted a trans-ancestry random effects meta-analysis comprised of the 18 cohorts of European ancestry, one cohort of East Asian (EAS) ancestry (975 cases and 3,780 controls), and one cohort of African (AFR) ancestry (456 cases and 1,255 controls). No evidence of residual population stratification or systematic technical artifact was observed in any of these individual data sets (**Table S1** and **Figures S11** - **S12**). The estimated $h^2_{SNP}$ for the EAS ($h^2_{SNP}$ = 0.17, s.e. = 0.15) and AFR ($h^2_{SNP}$ = 0.36, s.e. = 0.19) cohorts (both on the liability scale, assuming

lifetime risk of 0.10**)** were comparable to what was observed in our EUR meta-analysis. Among the seven LD independent loci and SNPs in strong LD with each ($r^2$ > 0.8) from the EUR meta-analysis, 59% of SNPs (111 out of 188 loci; binomial test p < 2.2 x $10^{-16}$) show consistent direction of effect in both AFR and EAS cohorts (**Table S3**). This trans-ancestry GWAS consisted of 9,129,923 SNPs in 18,770 women with a history of PPD and 58,461 controls. There was no evidence of residual population stratification ($\lambda = 0.94$, $\lambda_{1000} = 1.00$) (**Figure 1**).

No SNP reached genome-wide significance (p < 5.0 x $10^{-8}$) in the trans-ancestry analysis. The most significant SNP, rs10879002, is located on chromosome 12q15 ($\beta$ = 0.15, p = 7.26 × $10^{-8}$) (**Figure S8**). This increases the significance of SNPs seen in the same region of the EUR only meta-analysis (chr12: 69847907 – 70000236). rs10879002 is an intronic variant of *FRS2*, which encodes fibroblast growth factor receptor substrate 2. In total, the trans-ancestry analysis increased the number of significant SNPs (p < 1 x $10^{-6}$) in three of the seven loci identified in the EUR ancestry analysis (**Figures S7**, **S8**, and **S10**).

**Genetic Correlations with Postpartum Depression**

Clinical studies have shown that PPD is associated with a wide range of other disorders and traits. To assess the shared genetic architecture between PPD and psychiatric disorders, medical diseases, and biomedical traits, $r_g$ were calculated with our meta-analyzed summary statistics of EUR ancestry using LD score regression. **Table S4** contains the full results, and **Figure 2** shows the significant $r_g$ values with false discovery rate (FDR) < 0.05. First, the genetic correlation between PPD and the most recent MDD GWAS was indistinguishable from 1 ($r_g$= 0.95, s.e. = 0.05; $H_0$: $r_g$ = 0, p = 1.34 x $10^{-80}$ $H_0$: $r_g$ = 1, p = 0.30). Additionally, the genetic correlation of PPD with bipolar disorder type 2 ($r_g$= 0.51, s.e. = 0.09, p = 3.38 x $10^{-9}$) is greater than (p = 1.24 x $10^{-142}$) for bipolar disorder type 1 ($r_g$= 0.25, s.e. = 0.05, p = 1.89 x $10^{-6}$).

Second, we observed significant positive genetic correlations between PPD and anxiety disorders ($r_g$= 0.91, s.e. = 0.22, p = 3.43 x $10^{-5}$), specifically post-traumatic stress disorder ($r_g$= 0.70, s.e. = 0.12, p = 2.98 x $10^{-9}$) and panic disorder ($r_g$= 0.46, s.e. = 0.13, p = 2.00 x $10^{-4}$). Furthermore, there were significant genetic correlations across many psychiatric disorders

including attention deficit hyperactivity disorder ($r_g$= 0.44, s.e. = 0.07, p = 6.70 x $10^{-11}$) and schizophrenia ($r_g$= 0.28, s.e. = 0.05, p = 9.87 x $10^{-9}$).

Lastly, the common variant genetic architecture of PPD was correlated with insomnia ($r_g$= 0.41, s.e. = 0.05, p = 9.83 x $10^{-15}$). In addition, we also saw significant correlations with reproductive hormone related traits age of menarche ($r_g$= -0.11, s.e. = 0.04, p = 5.40 x $10^{-3}$) and polycystic ovary syndrome (PCOS)($r_g$= 0.23, s.e. = 0.10, p = 2.12 x $10^{-2}$).

**Tissue and Cell Type Enrichment Analyses**

Integrating GWAS results with data from RNA-sequencing studies characterizing specific tissues and cell types aid in understanding the biological implications of PPD associated loci. We used partitioned LD score regression to evaluate the enrichment of the PPD GWAS findings in 27 human tissues (Genotype-Tissue Expression project; GTEx, **Table S5**) (25) and 39 cell types (**Table S6**) that consists of 265 more refined cell types (**Table S7**) in the mouse central and peripheral nervous system (26). We did not find clear enrichment for any bulk tissue RNA-seq GTEx tissues. For cell types, the strongest signals identified were for inhibitory neurons in the thalamus (DEINH4; p = 4.50 x $10^{-4}$; q-value = 5.64 x $10^{-2}$) and cholinergic neurons within septal nuclei of the hypothalamus (DECHO1; p = 7.64 x $10^{-3}$; q-value = 0.205, indicating we should expect 20.5% of all the results with q-value less than this [n = 35] to be false positives). Analyses of single-cell data more broadly implicate peptidergic neurons (p = 5.84 x $10^{-3}$; q-value = 0.114). Together these cell types can be characterized by their shared role as GABAergic neurons (26). These patterns differ from those seen in either the first MDD GWAS (MDD1) (20), which has a similar sample size to our PPD analysis, or the most recent MDD GWAS (MDD2) (23) (**Figure 3**). Comparing the enrichment ratios for these cell types (DEINH4 and DECHO1) between PPD and MDD2, we observe significant differences (DEINH4: PPD enrichment = 2.19, MDD2 enrichment = 1.03, p = 3.50 x $10^{-3}$; DECHO1: PPD enrichment = 1.79, MDD2 enrichment = 1.02, p = 0.02). The nominally significant cell type enrichments for PPD were more modest in both prior MDD analyses, suggesting unique targets for PPD.

## DISCUSSION

We report on the first GWAS meta-analyses for PPD (EUR ancestry and trans-ancestry). This represents the largest and most comprehensive genetic study of PPD to date. While no loci reach genome-wide significance, our analyses provide valuable insights into the genetic basis of PPD. First, we find many significant genetic correlations between PPD and other psychiatric disorders, medical diseases, and biomedical traits. In addition, cell type enrichment analyses implicate GABAergic neurons in the pathogenesis of PPD.

Of particular note, results for PPD implicate inhibitory neurons in the thalamus, and cholinergic neurons of the septal nucleus in the hypothalamus. This pattern of results may be unique to PPD, as they were not observed in large GWAS of MDD (**Figure 3**) (23). These findings are salient because the two neuronal populations can be characterized by the neurotransmitter GABA (26), the primary inhibitory neurotransmitter in the central nervous system. These findings converge with evidence from transgenic rodent models (27) and human imaging studies (28) that suggest alterations in hypothalamic/thalamic regions to be associated with PPD. This is particularly intriguing in light of our results implicating GABAergic neurons, which is the target system of brexanolone, the only FDA approved medication specifically indicated for PPD (14, 15). Brexanolone is a synthetic formulation of allopregnanolone and a positive allosteric modulator of $GABA_A$ receptors (29). Given the broad distribution of $GABA_A$ receptors throughout the central nervous system, our results may help clarify the mechanism of action of this PPD therapeutic.

In order to achieve genome-wide significant results for PPD increased sample sizes are needed. Locus discovery for PPD can be expected to follow a trajectory similar to that seen for MDD, where robust SNP discovery required samples in excess of 100,000 cases (23). Equally important, however, will be ensuring that increases in sample size are accompanied by diversity of ancestry representation. As of 2019, a disproportionate majority (>78%) of participants in published GWAS are of European ancestry (30). Increasing representation of more diverse populations not only results in enhanced power of genomic studies and experimental methods (e.g. locus discovery, fine-mapping, genetic scores), but more importantly, it addresses the widespread health disparities that exist across research and medicine (31, 32). We estimated

the $h^2_{SNP}$ to be 0.14, which supports PPD as a complex disorder with genetic and environmental risk factors. As future studies work to increase participants of non-European ancestry, they should also take the opportunity to collect data on environmental contributors that have been shown to increase PPD risk, but disproportionately affect women of color, such as adverse life events and discrimination (33-36).

With this work, we take some of the first steps to increasing diversity in psychiatric genomics. PPD indiscriminately affects women from every part of the world. Therefore, we made every effort to include genetic data from all women who chose to participate in research. These early efforts to diversify our analyses already shows promise. Our trans-ancestry analysis increased statistical associations of two loci compared to the EUR-ancestry alone, with one falling just below genome-wide levels of significance (rs10879002, $p = 7.26 \times 10^{-8}$).

In analyses of the genetic relationships of PPD with other psychiatric disorders, diseases, and biomedical traits, we found the largest and most significant genetic correlation with MDD. However, this could be due, in part, to selection bias of our cases. Many of our PPD cases were identified as part of larger MDD collections, most notably UK Biobank (where PPD was identified using MDD algorithms) and the Australian Genetics of Depression Study, which combined make up 45% of all our PPD cases. Further, the genetic correlations reflect the diverse clinical presentations of PPD despite its diagnostic categorization as a subtype of MDD (37-39). Previous history of MDD or anxiety disorders are known risk factors for PPD, which is consistent with the high genetic correlations we observe. Additionally, the significant genetic correlation with insomnia suggests a potential role for this phenotype in PPD pathology, given the postpartum period is often associated with disrupted sleep (40-45). Finally, genetic correlations with traits such as age of menarche and PCOS, support a model for PPD pathology related to fluctuations in reproductive hormones (46, 47). These associations are supported by previous work identifying enrichment of ovarian tissue genes among PPD associated variants (10). Notably, the $r_g$ with PCOS has not been reported with MDD, supporting potentially distinct biologically underpinnings between PPD and MDD.

This study also has limitations that should be kept in mind when interpreting the results. First, our study follows the conventional GWAS examining PPD control-status. All cases reported depression in the postpartum period and a majority of controls screened had no reported depression and a pregnancy. This approach, however, does not account for the heterogeneity in PPD risk factors (e.g. previous psychiatric diagnoses) or presentation (e.g. symptom combinations, onset, duration, severity). These features are critical in defining PPD, but not always collected. Within the cohorts used here, there was a range of psychiatric histories (e.g. MDD, bipolar disorder, unknown), a broadly defined postpartum period (up to 12 months in some cases), and multiple ascertainment methods. Increased phenotyping should take place alongside efforts to increase sample sizes, which would also power appropriate conditional analyses. Further, it should be noted that sex is a confounder in our $r_g$ and cell type enrichment analyses. The summary statistics used in these analyses, specifically MDD, all include males. This leads to the possibility that the observed patterns of correlation and enrichment reflect etiological differences in depression between men and women generally, rather than something specific to PPD. However, in GWAS that have stratified by sex, there is high $r_g$ between sexes (48, 49). Further, secondary analyses were limited to European ancestry summary statistics. This highlights the lack of trans-ancestry analyses available. As more diverse GWAS are run, post-GWAS analyses need to be developed that utilize trans-ancestry results to identify causes and inform therapeutics development for PPD and other complex disorders.

PPD is a more homogeneous presentation compared to MDD, though there is still substantial phenotypic heterogeneity in the presentation of PPD. Symptom onset, duration, and severity are all important aspects of the disorder to consider when examining etiological factors. However, PPD is not an often collected phenotype, making it difficult to include specific symptom dimensions in work like GWAS. We recommend future data collection efforts utilize screening tools, such as the lifetime version of the EPDS (50), to ascertain a more complete symptom profile in addition to case status. Biological sample collection and maternal psychiatric screening, including psychiatric history, can be incorporated as a part of perinatal or early pediatric clinic visits. These visits present the opportunity to collect a large amount of data

as part of routine care for new mothers, which can increase sample sizes for future GWAS and address PPD heterogeneity.

In summary, we report the first genome-wide association meta-analyses for PPD. While no genome-wide significant loci were identified, this report contributes valuable new data about the genetic contributions to PPD. A direct comparison between PPD and MDD suggests a common genetic contribution between the two disorders. However, heritability estimates, cell type enrichments, and other genetic correlations suggest genetic components that may distinguish PPD from MDD. Notably, top GWAS loci implicate GABAergic neurons, which converges with imaging studies and the only current medication specifically indicated for PPD. Future studies, incorporating larger and more diverse sample sizes are needed to further clarify the genetic architecture of PPD.

## METHODS

### Study Participants

In total, we included 18,770 women with a history of PPD and 58,461 controls across 20 cohorts collected internationally. **Table S1** summarizes the source and genetic data for cases and controls for each sample. Full details for each cohort are given in the Supplementary Material. Overall, case definition required a lifetime diagnosis of PPD within one year of childbirth and were identified via: 1) review of electronic medical records (3/20 cohorts), 2) Edinburgh Postnatal Depression Scale (EPDS; 11/20 cohorts), 3) structured clinical interview (3/20 cohorts), or 4) other self-report (3/20 cohorts). Individuals identified using structured methodological review of medical records and population registries required diagnoses to meet international consensus criteria (DSM-IV, ICD-9, ICD-10). In addition, the EPDS a common and widely use PPD screening instrument (51-54), was used to screen participants. The EPDS is a 10-item self-report assessment, focusing on current symptoms, and minimizes confounding of somatic symptoms of PPD with the demands inherent to parenting an infant (e.g., insomnia) (51). We also screen using the modified version of the EPDS capable of screening for a lifetime history of PPD (50). For both the standard and lifetime versions of the EPDS, PPD symptoms are rated on a scale of 0 – 30 with higher scores indicating greater symptom severity. When using the EPDS, cases were defined having scores ≥ 13, consistent with PPD (55). In a majority of cases (19/20 cohorts), controls were screened for the absence of lifetime MDD and were required to have a least one live, term birth (≥36 weeks' gestation).

All sites had documented permission from local ethical committees, all participants provided informed consent for studies done in settings and countries where this was required.

### Genotyping and Quality Control

Genotyping procedures can be found in the primary reports for each cohort (**Supplementary Methods** and summarized in **Table S1**). Individual genotype data for each cohort were processed by the collaborating research teams using comparable procedures. SNPs were imputed using the Haplotype Reference Consortium (56) reference panel for samples of

European Ancestry, the TOPMED (57) reference panel for samples of African ancestry, and 1000 Genomes Asian (ASN) (58) reference panel for samples of East Asian ancestry. More detailed information on sample quality control and association testing for each cohort is provided in the **Supplementary Material**.

**GWAS Meta-Analyses**

Two meta-analyses for PPD case-control status were performed for EUR ancestry and trans-ancestry. A fixed effects meta-analysis was conducted on EUR cohorts using the inverse-variance method in METAL (59). A conventional random effects meta-analysis was conducted on all cohorts (EUR, AFR, and EAS) using the inverse-variance method in METASOFT (60). For both meta-analyses heterogeneity was assessed with Cochran's $I^2$ statistic. Test statistic inflation (λ) was calculated for each individual GWAS (Figures S2 and S12) and for the overall meta-analyses (**Figures 1b and 1d**) using all SNPs with minor allele frequency (MAF) > 0.01 to identify residual population stratification or systematic technical artifact. EUR GWAS summary statistics were subjected to linkage disequilibrium (LD) score regression (LDSC) analyses on high-quality common SNPs (INFO score > 0.9 and MAF > 0.01) to examine the LDSC intercept as a more specific measure of inflation of the GWAS test statistic (24) due to residual artifact or stratification (Table S2). The genome-wide significance threshold was set at a p-value of $5.0 \times 10^{-8}$.

**Heritability Estimation and Genetic Correlations**

LDSC was used to estimate $h^2_{SNP}$ from EUR and EAS genome-wide association summary statistics. Estimates of $h^2_{SNP}$ on the liability scale depend on the assumed lifetime prevalence of PPD in the population (K), and we assumed a conservative K = 0.10 but also evaluated a range of estimates of K to explore sensitivity, including 95% confidence intervals for the EUR meta-analysis (**Figure S3**). For EUR and EAS heritability estimates, precomputed LD score references provided by LDSC were used.

To estimate $h^2_{SNP}$ from AFR samples, we used GCTA (61, 62). The direct estimation of heritability from genome-wide common variant data was possible given access to genotype level data included in AFR mega-analysis.

We used LDSC to estimate $r_g$ between PPD and a range of other disorders, diseases, and human traits. The intent of these comparisons was to evaluate the extent of shared common variant genetic architectures to suggest hypotheses about the fundamental genetic basis of PPD. The full list of summary statistics used can be found in Table S4. All summary statistics were standardized to human genome build hg19 (using liftOver) with all RSIDs annotated to GRCh37, Release 92 (63). Summary statistics were processed using LDSC using default parameters and precomputed LD score references provided by LDSC.

**Tissue and Cell-Type Enrichment Analysis**

We performed tissue and cell-type enrichment analysis aiming to identify relevant tissues and cell types underlying PPD. First, we analyzed GTEx gene expression data (v8) (25) in 27 human tissues after excluding: 1) tissues with less than 100 donors, 2) non-natural tissues (such as cell lines), and 3) testis tissues (64). Second, for the cell-type specific analysis, we used single-cell RNA sequencing data with over 160K high-quality cells sampled from 19 regions in the entire mouse central nervous system and peripheral nervous system (26). We analyzed these data at the cell-type level, including 39 broad cell types (referred to as “level 4” for cell type clustering in the paper) and 251 refined cell types (“level 5” in the paper, after filtering five cell types with fewer than 20 cells). We considered only protein-coding genes with 1:1 orthology between human and mouse for the calculation of expression specificity. For both expression datasets, we calculated a metric of gene expression specificity as previously described (64); it measures, for each gene, its expression in a specific tissue or cell-type relative to its total expression across all tissues or cell types. As in previous studies (64, 65), we utilized the genes with the top 10% specificity values in each tissue or cell-type for the enrichment analyses.

We used partitioned LD score regression (pLSDC) (66) to test the enrichment of tissues and cell types in the EUR PPD GWAS results. Our analyses using pLDSC evaluated if the SNPs within

100kb regions of the top 10% specifically expressed genes were enriched for SNP-based heritability. For each tissue or cell-type, we computed the LD scores for this cell-type-specific annotation and added it to the baseline model of 53 functional annotations. We assessed the enrichment of tissue or cell-types using the coefficient z-scores and computed one-sided p-values. We have used the European samples in the phase 3 of 1000 Genome Project as the reference panel. Results were corrected for multiple testing using false discovery rate within each dataset.

**ACKNOWLEDGEMENTS**

We are deeply indebted to the research participants who have shared their life experiences and to the hundreds of investigators who helped accomplish this work, namely as a part of the Psychiatric Genomics Consortium and the PACT Consortium. This work was primarily funded by the US National Institutes of Health (K01MH116413). Major funding for the PGC is from the US National Institutes of Health (U01 MH109528 and U01 MH109532).

Other funding for this project was provided to investigators contributing to this report as follows: Ole A Andreassen (Research Council of Norway grants #223273, #273291, #324252, #296030, #324499, EU's H2020 RIA grant #964874 REALMENT, and NIMH R01 MH124839, R01 MH123724, and KG Jebsen Stiftelsen); Anna E Bauer (NIMH K01 MH120352); Karmel W Choi (NIMH K08 MH127413 and NARSAD Brain and Behavior Foundation Young Investigator Award); Yun Li (NIMH R01 MH123724); Lea K Davis (NIMH R01 MH118223 and R56 MH120736); Donald Hucks (NIMH R01 MH118223 and R56 MH120736); Jacqueline Kiewa (UQ Research Training Program scholarship); Yi Lu (NIMH R01 MH123724 and European Research Council grant agreement ID 101042183); Andrew M McIntosh (Wellcome Trust 220857/Z/20/Z, 216767/Z/19/Z and NIMH R01 MH124873); Merete Nordentoft (Lundbeck Foundation); Trine Munk-Olsen (Lundbeck Foundation grant R313-2019-567); Catherine M Olsen (National Health and Medical Research Council of Australia [NHMRC]: APP1155413, APP1185416, APP1073898, APP1063061); Roseann E Peterson (NIMH R01 MH125938, R21 MH126358, and The Brain & Behavior Research Foundation NARSAD grant 28632 P&S Fund); Zachary N Stowe (NIMH P50 MH77928 and P50 MH68036); Patrick F Sullivan (Swedish Research Council Vetenskapsrådet, award D0886501 and NIMH R01 MH124871); Simone N Vigod (Women's College Hospital Foundation); Lars T Westlye (Research Council of Norway #273345 and the European Research Council under the European Union's Horizon 2020 research and Innovation program #802998); David C Whiteman (National Health and Medical Research Council of Australia [NHMRC]: APP1155413, APP1185416, APP1073898, APP1063061); Heather J Zar (Bill & Melinda Gates Foundation).

**CONFLICTS OF INTEREST**

Ole A Andreassen is a consultant to HealthLytix; Sophie Grigoriadis receives royalties from UpToDate, and the Canadian Pharmacists Association for authorship of work in depression and pregnancy; Andrew M McIntosh has received speaker fees from Illumina and Janssen; Laura M Raffield is a consultant for the TOPMed Administrative Coordinating Center (through WeStat); Alkistis Skalkidou received a one-time fee for a 2h consultation from Biogen Idec Us Corporation; Jordan W Smoller is PI of a collaborative study of the genetics of depression and bipolar disorder sponsored by 23andMe for which 23andMe provides analysis time as in-kind support but no payments; Zachary N Stowe is on an advisory board for Sage Therapeutics and Reunion Neuroscience; Patrick F Sullivan is on an advisory committee and is a shareholder for Neumora Therapeutics; Simone N Vigod receives royalties from UpToDate inc for authorship of materials related to depression and pregnancy.

**FIGURE 1. Results of genome-wide association meta-analyses for PPD. (A)** Manhattan plot for association tests from fixed effects meta-analysis of EUR-ancestry (17,339 PPD cases and 53,426 screened controls). Genomic position (chromosomes 1-22 and X-chromosome) is shown on the x-axis and statistical significance as -log(P) is shown on the y-axis. The solid red horizontal line indicates the genome-wide significance threshold of $5 \times 10^{-8}$, and the dashed red horizontal line indicates the suggestive threshold of $1 \times 10^{-6}$. **(B)** Association test quantile-quantile plot of observed versus expected -log10(P) values from the EUR meta-analysis. The 95% confidence interval of expected values is shown in grey. Test-statistic inflation value, $\lambda$, is 1.04. **(C)** Manhattan plot for association tests from trans-ancestry random effects meta-analysis (18,770 PPD cases and 58,461 screened controls). **(D)** Association test quantile-quantile plot of observed versus expected -log10(P) values from the trans-ancestry meta-analysis. Test-statistic inflation value, $\lambda$, is 0.94.

**FIGURE 2. Genetic correlations ($r_g$) between PPD and psychiatric disorders, medical diseases, and biomedical traits**. Significant $r_g$ values with false discovery rate < 0.05 are shown. Error bars indicate standard error. Dashed vertical line indicates $r_g$ = 1.

**FIGURE 3. Cell type enrichment analyses performed using Partitioned LD Score Regression.** Nominally significant values with $p < 0.05$ are shown. Labels indicate the enriched tissue or cell-type. Solid red line indicates findings with $p < 0.01$.

**REFERENCES**


1. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol. 2005;106:1071-1083.
2. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, Brody S, Miller WC. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evidence Reports/Technology Assessments. 2005:1-8.
3. Wang Z, Liu J, Shuai H, Cai Z, Fu X, Liu Y, Xiao X, Zhang W, Krabbendam E, Liu S, Liu Z, Li Z, Yang BX. Mapping global prevalence of depression among postpartum women. Transl Psychiatry. 2021;11:543.
4. Wisner KL, Moses-Kolko EL, Sit DK. Postpartum depression: a disorder in search of a definition. Arch Womens Ment Health. 2010;13:37-40.
5. Marmorstein NR, Malone SM, Iacono WG. Psychiatric disorders among offspring of depressed mothers: associations with paternal psychopathology. Am J Psychiatry. 2004;161:1588-1594.
6. Flynn HA, Davis M, Marcus SM, Cunningham R, Blow FC. Rates of maternal depression in pediatric emergency department and relationship to child service utilization. Gen Hosp Psychiatry. 2004;26:316-322.
7. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: Final Data for 2014. Natl Vital Stat Rep. 2015;64:1-64.
8. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. Arch Womens Ment Health. 2005;8:77-87.
9. Britton J. Postpartum anxiety and breastfeeding. J Reproductive Medicine. 2007;52:689-695.
10. Kiewa J, Meltzer-Brody S, Milgrom J, Guintivano J, Hickie IB, Whiteman DC, Olsen CM, Colodro-Conde L, Medland SE, Martin NG, Wray NR, Byrne EM. Perinatal depression is associated with a higher polygenic risk for major depressive disorder than non-perinatal depression. Depress Anxiety. 2022;39:182-191.
11. Nguyen TD, Harder A, Xiong Y, Kowalec K, Hagg S, Cai N, Kuja-Halkola R, Dalman C, Sullivan PF, Lu Y. Genetic heterogeneity and subtypes of major depression. Mol Psychiatry. 2022;27:1667-1675.
12. Viktorin A, Meltzer-Brody S, Kuja-Halkola R, Sullivan PF, Landen M, Lichtenstein P, Magnusson PK. Heritability of Perinatal Depression and Genetic Overlap With Nonperinatal Depression. Am J Psychiatry. 2016;173:158-165.
13. Gerbasi ME, Meltzer-Brody S, Acaster S, Fridman M, Bonthapally V, Hodgkins P, Kanes SJ, Eldar-Lissai A. Brexanolone in Postpartum Depression: Post Hoc Analyses to Help Inform Clinical Decision-Making. J Womens Health (Larchmt). 2021;30:385-392.
14. Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A, Doherty J, Epperson CN, Deligiannidis KM, Riesenberg R, Hoffmann E, Rubinow D, Jonas J, Paul S, Meltzer-Brody S. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet. 2017;390:480-489.
15. Meltzer-Brody S, Colquhoun H, Riesenberg R, Epperson CN, Deligiannidis KM, Rubinow DR, Li H, Sankoh AJ, Clemson C, Schacterle A, Jonas J, Kanes S. Brexanolone injection in post-partum

depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet. 2018;392:1058-1070.
16. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Borglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelernter J, Mathews CA, Nievergelt CM, Smoller JW, O'Donovan MC, Psychiatric Genomics C. Psychiatric Genomics: An Update and an Agenda. Am J Psychiatry. 2018;175:15-27.
17. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, Als TD, Bigdeli TB, Borte S, Bryois J, Charney AW, Drange OK, Gandal MJ, Hagenaars SP, Ikeda M, Kamitaki N, Kim M, Krebs K, Panagiotaropoulou G, Schilder BM, Sloofman LG, Steinberg S, Trubetskoy V, Winsvold BS, Won HH, Abramova L, Adorjan K, Agerbo E, Al Eissa M, Albani D, Alliey-Rodriguez N, Anjorin A, Antilla V, Antoniou A, Awasthi S, Baek JH, Baekvad-Hansen M, Bass N, Bauer M, Beins EC, Bergen SE, Birner A, Bocker Pedersen C, Boen E, Boks MP, Bosch R, Brum M, Brumpton BM, Brunkhorst-Kanaan N, Budde M, Bybjerg-Grauholm J, Byerley W, Cairns M, Casas M, Cervantes P, Clarke TK, Cruceanu C, Cuellar-Barboza A, Cunningham J, Curtis D, Czerski PM, Dale AM, Dalkner N, David FS, Degenhardt F, Djurovic S, Dobbyn AL, Douzenis A, Elvsashagen T, Escott-Price V, Ferrier IN, Fiorentino A, Foroud TM, Forty L, Frank J, Frei O, Freimer NB, Frisen L, Gade K, Garnham J, Gelernter J, Giortz Pedersen M, Gizer IR, Gordon SD, Gordon-Smith K, Greenwood TA, Grove J, Guzman-Parra J, Ha K, Haraldsson M, Hautzinger M, Heilbronner U, Hellgren D, Herms S, Hoffmann P, Holmans PA, Huckins L, Jamain S, Johnson JS, Kalman JL, Kamatani Y, Kennedy JL, Kittel-Schneider S, Knowles JA, Kogevinas M, Koromina M, Kranz TM, Kranzler HR, Kubo M, Kupka R, Kushner SA, Lavebratt C, Lawrence J, Leber M, Lee HJ, Lee PH, Levy SE, Lewis C, Liao C, Lucae S, Lundberg M, MacIntyre DJ, Magnusson SH, Maier W, Maihofer A, Malaspina D, Maratou E, Martinsson L, Mattheisen M, McCarroll SA, McGregor NW, McGuffin P, McKay JD, Medeiros H, Medland SE, Millischer V, Montgomery GW, Moran JL, Morris DW, Muhleisen TW, O'Brien N, O'Donovan C, Olde Loohuis LM, Oruc L, Papiol S, Pardinas AF, Perry A, Pfennig A, Porichi E, Potash JB, Quested D, Raj T, Rapaport MH, DePaulo JR, Regeer EJ, Rice JP, Rivas F, Rivera M, Roth J, Roussos P, Ruderfer DM, Sanchez-Mora C, Schulte EC, Senner F, Sharp S, Shilling PD, Sigurdsson E, Sirignano L, Slaney C, Smeland OB, Smith DJ, Sobell JL, Soholm Hansen C, Soler Artigas M, Spijker AT, Stein DJ, Strauss JS, Swiatkowska B, Terao C, Thorgeirsson TE, Toma C, Tooney P, Tsermpini EE, Vawter MP, Vedder H, Walters JTR, Witt SH, Xi S, Xu W, Yang JMK, Young AH, Young H, Zandi PP, Zhou H, Zillich L, Psychiatry HA-I, Adolfsson R, Agartz I, Alda M, Alfredsson L, Babadjanova G, Backlund L, Baune BT, Bellivier F, Bengesser S, Berrettini WH, Blackwood DHR, Boehnke M, Borglum AD, Breen G, Carr VJ, Catts S, Corvin A, Craddock N, Dannlowski U, Dikeos D, Esko T, Etain B, Ferentinos P, Frye M, Fullerton JM, Gawlik M, Gershon ES, Goes FS, Green MJ, Grigoroiu-Serbanescu M, Hauser J, Henskens F, Hillert J, Hong KS, Hougaard DM, Hultman CM, Hveem K, Iwata N, Jablensky AV, Jones I, Jones LA, Kahn RS, Kelsoe JR, Kirov G, Landen M, Leboyer M, Lewis CM, Li QS, Lissowska J, Lochner C, Loughland C, Martin NG, Mathews CA, Mayoral F, McElroy SL, McIntosh AM, McMahon FJ, Melle I, Michie P, Milani L, Mitchell PB, Morken G, Mors O, Mortensen PB, Mowry B, Muller-Myhsok B, Myers RM, Neale BM, Nievergelt CM, Nordentoft M, Nothen MM, O'Donovan MC, Oedegaard KJ, Olsson T, Owen MJ, Paciga SA, Pantelis C, Pato C, Pato MT, Patrinos GP, Perlis RH, Posthuma D, Ramos-Quiroga JA, Reif A, Reininghaus EZ, Ribases M, Rietschel M, Ripke S, Rouleau GA, Saito T, Schall U, Schalling M, Schofield PR, Schulze TG, Scott LJ, Scott RJ, Serretti A, Shannon Weickert C, Smoller JW, Stefansson H, Stefansson K, Stordal E, Streit F, Sullivan PF,

Turecki G, Vaaler AE, Vieta E, Vincent JB, Waldman ID, Weickert TW, Werge T, Wray NR, Zwart JA, Biernacka JM, Nurnberger JI, Cichon S, Edenberg HJ, Stahl EA, McQuillin A, Di Florio A, Ophoff RA, Andreassen OA. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet. 2021;53:817-829.
18. Trubetskoy V, Pardinas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, Bryois J, Chen CY, Dennison CA, Hall LS, Lam M, Watanabe K, Frei O, Ge T, Harwood JC, Koopmans F, Magnusson S, Richards AL, Sidorenko J, Wu Y, Zeng J, Grove J, Kim M, Li Z, Voloudakis G, Zhang W, Adams M, Agartz I, Atkinson EG, Agerbo E, Al Eissa M, Albus M, Alexander M, Alizadeh BZ, Alptekin K, Als TD, Amin F, Arolt V, Arrojo M, Athanasiu L, Azevedo MH, Bacanu SA, Bass NJ, Begemann M, Belliveau RA, Bene J, Benyamin B, Bergen SE, Blasi G, Bobes J, Bonassi S, Braun A, Bressan RA, Bromet EJ, Bruggeman R, Buckley PF, Buckner RL, Bybjerg-Grauholm J, Cahn W, Cairns MJ, Calkins ME, Carr VJ, Castle D, Catts SV, Chambert KD, Chan RCK, Chaumette B, Cheng W, Cheung EFC, Chong SA, Cohen D, Consoli A, Cordeiro Q, Costas J, Curtis C, Davidson M, Davis KL, de Haan L, Degenhardt F, DeLisi LE, Demontis D, Dickerson F, Dikeos D, Dinan T, Djurovic S, Duan J, Ducci G, Dudbridge F, Eriksson JG, Fananas L, Faraone SV, Fiorentino A, Forstner A, Frank J, Freimer NB, Fromer M, Frustaci A, Gadelha A, Genovese G, Gershon ES, Giannitelli M, Giegling I, Giusti-Rodriguez P, Godard S, Goldstein JI, Gonzalez Penas J, Gonzalez-Pinto A, Gopal S, Gratten J, Green MF, Greenwood TA, Guillin O, Guloksuz S, Gur RE, Gur RC, Gutierrez B, Hahn E, Hakonarson H, Haroutunian V, Hartmann AM, Harvey C, Hayward C, Henskens FA, Herms S, Hoffmann P, Howrigan DP, Ikeda M, Iyegbe C, Joa I, Julia A, Kahler AK, Kam-Thong T, Kamatani Y, Karachanak-Yankova S, Kebir O, Keller MC, Kelly BJ, Khrunin A, Kim SW, Klovins J, Kondratiev N, Konte B, Kraft J, Kubo M, Kucinskas V, Kucinskiene ZA, Kusumawardhani A, Kuzelova-Ptackova H, Landi S, Lazzeroni LC, Lee PH, Legge SE, Lehrer DS, Lencer R, Lerer B, Li M, Lieberman J, Light GA, Limborska S, Liu CM, Lonnqvist J, Loughland CM, Lubinski J, Luykx JJ, Lynham A, Macek M, Jr., Mackinnon A, Magnusson PKE, Maher BS, Maier W, Malaspina D, Mallet J, Marder SR, Marsal S, Martin AR, Martorell L, Mattheisen M, McCarley RW, McDonald C, McGrath JJ, Medeiros H, Meier S, Melegh B, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mitjans M, Molden E, Molina E, Molto MD, Mondelli V, Moreno C, Morley CP, Muntane G, Murphy KC, Myin-Germeys I, Nenadic I, Nestadt G, Nikitina-Zake L, Noto C, Nuechterlein KH, O'Brien NL, O'Neill FA, Oh SY, Olincy A, Ota VK, Pantelis C, Papadimitriou GN, Parellada M, Paunio T, Pellegrino R, Periyasamy S, Perkins DO, Pfuhlmann B, Pietilainen O, Pimm J, Porteous D, Powell J, Quattrone D, Quested D, Radant AD, Rampino A, Rapaport MH, Rautanen A, Reichenberg A, Roe C, Roffman JL, Roth J, Rothermundt M, Rutten BPF, Saker-Delye S, Salomaa V, Sanjuan J, Santoro ML, Savitz A, Schall U, Scott RJ, Seidman LJ, Sharp SI, Shi J, Siever LJ, Sigurdsson E, Sim K, Skarabis N, Slominsky P, So HC, Sobell JL, Soderman E, Stain HJ, Steen NE, Steixner-Kumar AA, Stogmann E, Stone WS, Straub RE, Streit F, Strengman E, Stroup TS, Subramaniam M, Sugar CA, Suvisaari J, Svrakic DM, Swerdlow NR, Szatkiewicz JP, Ta TMT, Takahashi A, Terao C, Thibaut F, Toncheva D, Tooney PA, Torretta S, Tosato S, Tura GB, Turetsky BI, Ucok A, Vaaler A, van Amelsvoort T, van Winkel R, Veijola J, Waddington J, Walter H, Waterreus A, Webb BT, Weiser M, Williams NM, Witt SH, Wormley BK, Wu JQ, Xu Z, Yolken R, Zai CC, Zhou W, Zhu F, Zimprich F, Atbasoglu EC, Ayub M, Benner C, Bertolino A, Black DW, Bray NJ, Breen G, Buccola NG, Byerley WF, Chen WJ, Cloninger CR, Crespo-Facorro B, Donohoe G, Freedman R, Galletly C, Gandal MJ, Gennarelli M, Hougaard DM, Hwu HG, Jablensky AV, McCarroll SA, Moran JL, Mors O, Mortensen PB, Muller-Myhsok B, Neil AL, Nordentoft M, Pato

MT, Petryshen TL, Pirinen M, Pulver AE, Schulze TG, Silverman JM, Smoller JW, Stahl EA, Tsuang DW, Vilella E, Wang SH, Xu S, Indonesia Schizophrenia C, PsychEncode, Psychosis Endophenotypes International C, Syn GOC, Adolfsson R, Arango C, Baune BT, Belangero SI, Borglum AD, Braff D, Bramon E, Buxbaum JD, Campion D, Cervilla JA, Cichon S, Collier DA, Corvin A, Curtis D, Forti MD, Domenici E, Ehrenreich H, Escott-Price V, Esko T, Fanous AH, Gareeva A, Gawlik M, Gejman PV, Gill M, Glatt SJ, Golimbet V, Hong KS, Hultman CM, Hyman SE, Iwata N, Jonsson EG, Kahn RS, Kennedy JL, Khusnutdinova E, Kirov G, Knowles JA, Krebs MO, Laurent-Levinson C, Lee J, Lencz T, Levinson DF, Li QS, Liu J, Malhotra AK, Malhotra D, McIntosh A, McQuillin A, Menezes PR, Morgan VA, Morris DW, Mowry BJ, Murray RM, Nimgaonkar V, Nothen MM, Ophoff RA, Paciga SA, Palotie A, Pato CN, Qin S, Rietschel M, Riley BP, Rivera M, Rujescu D, Saka MC, Sanders AR, Schwab SG, Serretti A, Sham PC, Shi Y, St Clair D, Stefansson H, Stefansson K, Tsuang MT, van Os J, Vawter MP, Weinberger DR, Werge T, Wildenauer DB, Yu X, Yue W, Holmans PA, Pocklington AJ, Roussos P, Vassos E, Verhage M, Visscher PM, Yang J, Posthuma D, Andreassen OA, Kendler KS, Owen MJ, Wray NR, Daly MJ, Huang H, Neale BM, Sullivan PF, Ripke S, Walters JTR, O'Donovan MC, Schizophrenia Working Group of the Psychiatric Genomics C. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022;604:502-508.

19. Sullivan PF, Geschwind DH. Defining the Genetic, Genomic, Cellular, and Diagnostic Architectures of Psychiatric Disorders. Cell. 2019;177:162-183.

20. Major Depressive Disorder Working Group of the Psychiatric GC, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Muller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Volzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry. 2013;18:497-511.

21. Hek K, Demirkan A, Lahti J, Terracciano A, Teumer A, Cornelis MC, Amin N, Bakshis E, Baumert J, Ding J, Liu Y, Marciante K, Meirelles O, Nalls MA, Sun YV, Vogelzangs N, Yu L, Bandinelli S, Benjamin EJ, Bennett DA, Boomsma D, Cannas A, Coker LH, de Geus E, De Jager PL, Diez-Roux AV, Purcell S, Hu FB, Rimm EB, Hunter DJ, Jensen MK, Curhan G, Rice K, Penman AD, Rotter JI, Sotoodehnia N, Emeny R, Eriksson JG, Evans DA, Ferrucci L, Fornage M, Gudnason V, Hofman A, Illig T, Kardia S, Kelly-Hayes M, Koenen K, Kraft P, Kuningas M, Massaro JM, Melzer D, Mulas A, Mulder CL, Murray A, Oostra BA, Palotie A, Penninx B, Petersmann A, Pilling LC, Psaty B, Rawal R, Reiman EM, Schulz A, Shulman JM, Singleton AB, Smith AV, Sutin AR,

Uitterlinden AG, Volzke H, Widen E, Yaffe K, Zonderman AB, Cucca F, Harris T, Ladwig KH, Llewellyn DJ, Raikkonen K, Tanaka T, van Duijn CM, Grabe HJ, Launer LJ, Lunetta KL, Mosley TH, Jr., Newman AB, Tiemeier H, Murabito J. A genome-wide association study of depressive symptoms. Biol Psychiatry. 2013;73:667-678.
22. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, Coleman JRI, Hagenaars SP, Ward J, Wigmore EM, Alloza C, Shen X, Barbu MC, Xu EY, Whalley HC, Marioni RE, Porteous DJ, Davies G, Deary IJ, Hemani G, Berger K, Teismann H, Rawal R, Arolt V, Baune BT, Dannlowski U, Domschke K, Tian C, Hinds DA, andMe Research T, Major Depressive Disorder Working Group of the Psychiatric Genomics C, Trzaskowski M, Byrne EM, Ripke S, Smith DJ, Sullivan PF, Wray NR, Breen G, Lewis CM, McIntosh AM. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019;22:343-352.
23. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, Bacanu SA, Baekvad-Hansen M, Beekman AFT, Bigdeli TB, Binder EB, Blackwood DRH, Bryois J, Buttenschon HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke TK, Coleman JIR, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Crowley CA, Dashti HS, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Eriksson N, Escott-Price V, Kiadeh FHF, Finucane HK, Forstner AJ, Frank J, Gaspar HA, Gill M, Giusti-Rodriguez P, Goes FS, Gordon SD, Grove J, Hall LS, Hannon E, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga JJ, Hougaard DM, Hu M, Hyde CL, Ising M, Jansen R, Jin F, Jorgenson E, Knowles JA, Kohane IS, Kraft J, Kretzschmar WW, Krogh J, Kutalik Z, Lane JM, Li Y, Li Y, Lind PA, Liu X, Lu L, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milaneschi Y, Milani L, Mill J, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Pettersson E, Peyrot WJ, Pistis G, Posthuma D, Purcell SM, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Saeed Mirza S, Saxena R, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamon GBC, Smit JH, Smith DJ, Stefansson H, Steinberg S, Stockmeier CA, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Tian C, Traylor M, Treutlein J, Trubetskoy V, Uitterlinden AG, Umbricht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt SH, Wu Y, Xi HS, Yang J, Zhang F, eQtlgen, andMe, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus ECJ, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Hinds DA, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PFA, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Muller-Myhsok B, Nordentoft M, Nothen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx B, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Volzke H, Weissman MM, Werge T, Winslow AR, Lewis CM, Levinson DF, Breen G, Borglum AD, Sullivan PF, Major Depressive Disorder Working Group of the Psychiatric Genomics C. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50:668-681.
24. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C, Patterson N, Daly MJ, Price AL, Neale BM. LD Score regression

distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47:291-295.
25. Consortium GT. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science. 2020;369:1318-1330.
26. Zeisel A, Hochgerner H, Lonnerberg P, Johnsson A, Memic F, van der Zwan J, Haring M, Braun E, Borm LE, La Manno G, Codeluppi S, Furlan A, Lee K, Skene N, Harris KD, Hjerling-Leffler J, Arenas E, Ernfors P, Marklund U, Linnarsson S. Molecular Architecture of the Mouse Nervous System. Cell. 2018;174:999-1014 e1022.
27. Melon LC, Hooper A, Yang X, Moss SJ, Maguire J. Inability to suppress the stress-induced activation of the HPA axis during the peripartum period engenders deficits in postpartum behaviors in mice. Psychoneuroendocrinology. 2018;90:182-193.
28. Long X, Zhou Y, Zhang F, Li F, Wang X, Meng Y, Roberts N, Cheng B, Jia Z. Altered MRI Diffusion Properties of the White Matter Tracts Connecting Frontal and Thalamic Brain Regions in First-Episode, Drug-Naive Patients With Postpartum Depression. J Magn Reson Imaging. 2022.
29. Meltzer-Brody S, Kanes SJ. Allopregnanolone in postpartum depression: Role in pathophysiology and treatment. Neurobiol Stress. 2020;12:100212.
30. Peterson RE, Kuchenbaecker K, Walters RK, Chen CY, Popejoy AB, Periyasamy S, Lam M, Iyegbe C, Strawbridge RJ, Brick L, Carey CE, Martin AR, Meyers JL, Su J, Chen J, Edwards AC, Kalungi A, Koen N, Majara L, Schwarz E, Smoller JW, Stahl EA, Sullivan PF, Vassos E, Mowry B, Prieto ML, Cuellar-Barboza A, Bigdeli TB, Edenberg HJ, Huang H, Duncan LE. Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. Cell. 2019;179:589-603.
31. Borrell LN, Elhawary JR, Fuentes-Afflick E, Witonsky J, Bhakta N, Wu AHB, Bibbins-Domingo K, Rodriguez-Santana JR, Lenoir MA, Gavin JR, 3rd, Kittles RA, Zaitlen NA, Wilkes DS, Powe NR, Ziv E, Burchard EG. Race and Genetic Ancestry in Medicine - A Time for Reckoning with Racism. N Engl J Med. 2021;384:474-480.
32. Sirugo G, Williams SM, Tishkoff SA. The Missing Diversity in Human Genetic Studies. Cell. 2019;177:26-31.
33. Raj A, Johns N, Jose R. Racial/Ethnic Disparities in Sexual Harassment in the United States, 2018. J Interpers Violence. 2021;36:NP8268-NP8289.
34. Izadi SN, Patel N, Fofana D, Paredes AZ, Snyder SK, Torres-Reveron A, Skubic JJ. Racial inequality in the trauma of women: A disproportionate decade. J Trauma Acute Care Surg. 2020;89:254-262.
35. McLaughlin KA, Alvarez K, Fillbrunn M, Green JG, Jackson JS, Kessler RC, Sadikova E, Sampson NA, Vilsaint CL, Williams DR, Alegria M. Racial/ethnic variation in trauma-related psychopathology in the United States: a population-based study. Psychol Med. 2019;49:2215-2226.
36. Kessler RC, Mickelson KD, Williams DR. The prevalence, distribution, and mental health correlates of perceived discrimination in the United States. J Health Soc Behav. 1999;40:208-230.
37. Batt MM, Duffy KA, Novick AM, Metcalf CA, Epperson CN. Is Postpartum Depression Different From Depression Occurring Outside of the Perinatal Period? A Review of the Evidence. Focus (Am Psychiatr Publ). 2020;18:106-119.

38. Bernstein IH, Rush AJ, Yonkers K, Carmody TJ, Woo A, McConnell K, Trivedi MH. Symptom features of postpartum depression: are they distinct? Depress Anxiety. 2008;25:20-26.
39. Di Florio A, Meltzer-Brody S. Is Postpartum Depression a Distinct Disorder? Curr Psychiatry Rep. 2015;17:76.
40. Bhati S, Richards K. A systematic review of the relationship between postpartum sleep disturbance and postpartum depression. J Obstet Gynecol Neonatal Nurs. 2015;44:350-357.
41. Iranpour S, Kheirabadi GR, Esmaillzadeh A, Heidari-Beni M, Maracy MR. Association between sleep quality and postpartum depression. J Res Med Sci. 2016;21:110.
42. Lewis BA, Gjerdingen D, Schuver K, Avery M, Marcus BH. The effect of sleep pattern changes on postpartum depressive symptoms. BMC Womens Health. 2018;18:12.
43. Obeysekare JL, Cohen ZL, Coles ME, Pearlstein TB, Monzon C, Flynn EE, Sharkey KM. Delayed sleep timing and circadian rhythms in pregnancy and transdiagnostic symptoms associated with postpartum depression. Transl Psychiatry. 2020;10:14.
44. Okun ML, Luther J, Prather AA, Perel JM, Wisniewski S, Wisner KL. Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. J Affect Disord. 2011;130:378-384.
45. Okun ML, Mancuso RA, Hobel CJ, Schetter CD, Coussons-Read M. Poor sleep quality increases symptoms of depression and anxiety in postpartum women. J Behav Med. 2018;41:703-710.
46. Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. CNS Spectr. 2015;20:48-59.
47. Brummelte S, Galea LA. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:766-776.
48. Martin J, Walters RK, Demontis D, Mattheisen M, Lee SH, Robinson E, Brikell I, Ghirardi L, Larsson H, Lichtenstein P, Eriksson N, andMe Research T, Psychiatric Genomics Consortium AS, i P-BAW, Werge T, Mortensen PB, Pedersen MG, Mors O, Nordentoft M, Hougaard DM, Bybjerg-Grauholm J, Wray NR, Franke B, Faraone SV, O'Donovan MC, Thapar A, Borglum AD, Neale BM. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2018;83:1044-1053.
49. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen CY, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Amstadter AB, Andersen SB, Andreassen OA, Arbisi PA, Ashley-Koch AE, Austin SB, Avdibegovic E, Babic D, Baekvad-Hansen M, Baker DG, Beckham JC, Bierut LJ, Bisson JI, Boks MP, Bolger EA, Borglum AD, Bradley B, Brashear M, Breen G, Bryant RA, Bustamante AC, Bybjerg-Grauholm J, Calabrese JR, Caldas-de-Almeida JM, Dale AM, Daly MJ, Daskalakis NP, Deckert J, Delahanty DL, Dennis MF, Disner SG, Domschke K, Dzubur-Kulenovic A, Erbes CR, Evans A, Farrer LA, Feeny NC, Flory JD, Forbes D, Franz CE, Galea S, Garrett ME, Gelaye B, Geuze E, Gillespie C, Uka AG, Gordon SD, Guffanti G, Hammamieh R, Harnal S, Hauser MA, Heath AC, Hemmings SMJ, Hougaard DM, Jakovljevic M, Jett M, Johnson EO, Jones I, Jovanovic T, Qin XJ, Junglen AG, Karstoft KI, Kaufman ML, Kessler RC, Khan A, Kimbrel NA, King AP, Koen N, Kranzler HR, Kremen WS, Lawford BR, Lebois LAM, Lewis CE, Linnstaedt SD, Lori A, Lugonja B, Luykx JJ, Lyons MJ, Maples-Keller J, Marmar C, Martin AR, Martin NG, Maurer D, Mavissakalian MR, McFarlane A, McGlinchey RE, McLaughlin KA, McLean SA, McLeay S, Mehta D, Milberg WP, Miller MW, Morey RA, Morris CP, Mors O, Mortensen PB,

Neale BM, Nelson EC, Nordentoft M, Norman SB, O'Donnell M, Orcutt HK, Panizzon MS, Peters ES, Peterson AL, Peverill M, Pietrzak RH, Polusny MA, Rice JP, Ripke S, Risbrough VB, Roberts AL, Rothbaum AO, Rothbaum BO, Roy-Byrne P, Ruggiero K, Rung A, Rutten BPF, Saccone NL, Sanchez SE, Schijven D, Seedat S, Seligowski AV, Seng JS, Sheerin CM, Silove D, Smith AK, Smoller JW, Sponheim SR, Stein DJ, Stevens JS, Sumner JA, Teicher MH, Thompson WK, Trapido E, Uddin M, Ursano RJ, van den Heuvel LL, Van Hooff M, Vermetten E, Vinkers CH, Voisey J, Wang Y, Wang Z, Werge T, Williams MA, Williamson DE, Winternitz S, Wolf C, Wolf EJ, Wolff JD, Yehuda R, Young RM, Young KA, Zhao H, Zoellner LA, Liberzon I, Ressler KJ, Haas M, Koenen KC. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nat Commun. 2019;10:4558.
50. Meltzer-Brody S, Boschloo L, Jones I, Sullivan PF, Penninx BW. The EPDS-Lifetime: assessment of lifetime prevalence and risk factors for perinatal depression in a large cohort of depressed women. Arch Womens Ment Health. 2013;16:465-473.
51. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-786.
52. Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. Br J Psychiatry. 1993;163:27-31.
53. Hewitt CE, Gilbody SM. Is it clinically and cost effective to screen for postnatal depression: a systematic review of controlled clinical trials and economic evidence. BJOG. 2009;116:1019-1027.
54. Boyd RC, Le HN, Somberg R. Review of screening instruments for postpartum depression. Arch Womens Ment Health. 2005;8:141-153.
55. Wisner KL, Parry BL, Piontek CM. Clinical practice. Postpartum depression. N Engl J Med. 2002;347:194-199.
56. Das S, Forer L, Schonherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh PR, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. Nat Genet. 2016;48:1284-1287.
57. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, Taliun SAG, Corvelo A, Gogarten SM, Kang HM, Pitsillides AN, LeFaive J, Lee SB, Tian X, Browning BL, Das S, Emde AK, Clarke WE, Loesch DP, Shetty AC, Blackwell TW, Smith AV, Wong Q, Liu X, Conomos MP, Bobo DM, Aguet F, Albert C, Alonso A, Ardlie KG, Arking DE, Aslibekyan S, Auer PL, Barnard J, Barr RG, Barwick L, Becker LC, Beer RL, Benjamin EJ, Bielak LF, Blangero J, Boehnke M, Bowden DW, Brody JA, Burchard EG, Cade BE, Casella JF, Chalazan B, Chasman DI, Chen YI, Cho MH, Choi SH, Chung MK, Clish CB, Correa A, Curran JE, Custer B, Darbar D, Daya M, de Andrade M, DeMeo DL, Dutcher SK, Ellinor PT, Emery LS, Eng C, Fatkin D, Fingerlin T, Forer L, Fornage M, Franceschini N, Fuchsberger C, Fullerton SM, Germer S, Gladwin MT, Gottlieb DJ, Guo X, Hall ME, He J, Heard-Costa NL, Heckbert SR, Irvin MR, Johnsen JM, Johnson AD, Kaplan R, Kardia SLR, Kelly T, Kelly S, Kenny EE, Kiel DP, Klemmer R, Konkle BA, Kooperberg C, Kottgen A, Lange LA, Lasky-Su J, Levy D, Lin X, Lin KH, Liu C, Loos RJF, Garman L, Gerszten R, Lubitz SA, Lunetta KL, Mak ACY, Manichaikul A, Manning AK, Mathias RA, McManus DD, McGarvey ST, Meigs JB, Meyers DA, Mikulla JL, Minear MA, Mitchell BD, Mohanty S, Montasser ME, Montgomery C, Morrison AC, Murabito JM, Natale A, Natarajan P, Nelson SC, North KE, O'Connell JR, Palmer ND, Pankratz N, Peloso GM, Peyser PA, Pleiness J, Post WS, Psaty BM, Rao DC, Redline S, Reiner AP, Roden D,

Rotter JI, Ruczinski I, Sarnowski C, Schoenherr S, Schwartz DA, Seo JS, Seshadri S, Sheehan VA, Sheu WH, Shoemaker MB, Smith NL, Smith JA, Sotoodehnia N, Stilp AM, Tang W, Taylor KD, Telen M, Thornton TA, Tracy RP, Van Den Berg DJ, Vasan RS, Viaud-Martinez KA, Vrieze S, Weeks DE, Weir BS, Weiss ST, Weng LC, Willer CJ, Zhang Y, Zhao X, Arnett DK, Ashley-Koch AE, Barnes KC, Boerwinkle E, Gabriel S, Gibbs R, Rice KM, Rich SS, Silverman EK, Qasba P, Gan W, Consortium NT-OfPM, Papanicolaou GJ, Nickerson DA, Browning SR, Zody MC, Zollner S, Wilson JG, Cupples LA, Laurie CC, Jaquish CE, Hernandez RD, O'Connor TD, Abecasis GR. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature. 2021;590:290-299.
58. Genomes Project C, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. Nature. 2012;491:56-65.
59. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26:2190-2191.
60. Han B, Eskin E. Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies. Am J Hum Genet. 2011;88:586-598.
61. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large proportion of the heritability for human height. Nat Genet. 2010;42:565-569.
62. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. Am J Hum Genet. 2011;88:76-82.
63. Yates A, Akanni W, Amode MR, Barrell D, Billis K, Carvalho-Silva D, Cummins C, Clapham P, Fitzgerald S, Gil L, Giron CG, Gordon L, Hourlier T, Hunt SE, Janacek SH, Johnson N, Juettemann T, Keenan S, Lavidas I, Martin FJ, Maurel T, McLaren W, Murphy DN, Nag R, Nuhn M, Parker A, Patricio M, Pignatelli M, Rahtz M, Riat HS, Sheppard D, Taylor K, Thormann A, Vullo A, Wilder SP, Zadissa A, Birney E, Harrow J, Muffato M, Perry E, Ruffier M, Spudich G, Trevanion SJ, Cunningham F, Aken BL, Zerbino DR, Flicek P. Ensembl 2016. Nucleic Acids Res. 2016;44:D710-716.
64. Bryois J, Skene NG, Hansen TF, Kogelman LJA, Watson HJ, Liu Z, Eating Disorders Working Group of the Psychiatric Genomics C, International Headache Genetics C, andMe Research T, Brueggeman L, Breen G, Bulik CM, Arenas E, Hjerling-Leffler J, Sullivan PF. Genetic identification of cell types underlying brain complex traits yields insights into the etiology of Parkinson's disease. Nat Genet. 2020;52:482-493.
65. Skene NG, Bryois J, Bakken TE, Breen G, Crowley JJ, Gaspar HA, Giusti-Rodriguez P, Hodge RD, Miller JA, Munoz-Manchado AB, O'Donovan MC, Owen MJ, Pardinas AF, Ryge J, Walters JTR, Linnarsson S, Lein ES, Major Depressive Disorder Working Group of the Psychiatric Genomics C, Sullivan PF, Hjerling-Leffler J. Genetic identification of brain cell types underlying schizophrenia. Nat Genet. 2018;50:825-833.
66. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, Anttila V, Xu H, Zang C, Farh K, Ripke S, Day FR, ReproGen C, Schizophrenia Working Group of the Psychiatric Genomics C, Consortium R, Purcell S, Stahl E, Lindstrom S, Perry JR, Okada Y, Raychaudhuri S, Daly MJ, Patterson N, Neale BM, Price AL. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet. 2015;47:1228-1235.