The genetics of the mood disorder spectrum: genome-wide association analyses of over 185,000 cases and 439,000 controls

Jonathan R I Coleman 1,2, Héléna A Gaspar 1,2, Julien Bryois 3, Enda M Byrne 4, Andreas J Forstner 5,6,7,8,9, Peter A Holmans 10, Christiaan A de Leeuw 11, Manuel Mattheisen 12,13,14,15,16, Andrew McQuillin 17, Jennifer M Whitehead Pavlides 18, Tune H Pers 19,20, Stephan Ripke 21,22,23, Eli A Stahl 19,24,25, Stacy Steinberg 26, Vassily Trubetskoy 22, Maciej Trzaskowski 4, Yunpeng Wang 27,28, Liam Abbott 21, Abdel Abdellaoui 29, Mark J Adams 30, Annelie Nordin Adolfsson 31, Esben Agerbo 16,32,33, Huda Akil 34, Diego Albani 35, Ney Alliey-Rodriguez 36, Thomas D Als 12,13,16, Till F M Andlauer 37,38, Adebayo Anjorin 39, Verneri Antilla 23, Sandra Van der Auwera 40, Swapnil Awasthi 22, Silviu-Alin Bacanu 41, Judith A Badner 42, Marie Bækvad-Hansen 16,43, Jack D Barchas 44, Nicholas Bass 17, Michael Bauer 45, Aartjan T F Beekman 46, Richard Belliveau 21, Sarah E Bergen 3, Tim B Bigdeli 41,47, Elisabeth B Binder 37,48, Erlend Bøen 49, Marco Boks 50, James Boocock 51, Monika Budde 52, William Bunney 53, Margit Burmeister 54, Henriette N Buttenschøn 3,12,55, Jonas Bybjerg-Grauholm 16,43, William Byerley 56, Na Cai 57,58, Miquel Casas 59,60,61,62, Enrique Castelao 63, Felecia Cerrato 21, Pablo Cervantes 64, Kimberly Chambert 21, Alexander W Charney 25, Danfeng Chen 21, Jane Hvarregaard Christensen 12,13,55, Claire Churchhouse 21,23, David St Clair 65, Toni-Kim Clarke 30, Lucía Colodro-Conde 66, William Coryell 67, Baptiste Couvy-Duchesne 18,68, David W Craig 69, Gregory E Crawford 70,71, Cristiana Cruceanu 37,64, Piotr M Czerski 72, Anders M Dale 73,74,75,76, Gail Davies 77, Ian J Deary 77, Franziska Degenhardt 7,8, Jurgen Del-Favero 78, J Raymond DePaulo 79, Eske M Derks 66, Nese Direk 80,81, Srdjan Djurovic 82,83, Amanda L Dobbyn 24,25, Conor V Dolan 29, Ashley Dumont 21, Erin C Dunn 21,84,85, Thalia C Eley 1, Torbjørn Elvsåshagen 86,87, Valentina Escott-Price 10, Chun Chieh Fan 76, Hilary K Finucane 88,89, Sascha B Fischer 5,9, Matthew Flickinger 90, Jerome C Foo 91, Tatiana M Foroud 92, Liz Forty 10, Josef Frank 91, Christine Fraser 10, Nelson B Freimer 93, Louise Frisén 94,95,96, Katrin Gade 52,97, Diane Gage 21, Julie Garnham 98, Claudia Giambartolomei 51, Fernando S Goes 99, Jaqueline Goldstein 21, Scott D Gordon 66, Katherine Gordon-Smith 100, Elaine K Green 101, Melissa J Green 102, Tiffany A Greenwood 75, Jakob Grove 12,13,16,103, Weihua Guan 104, Lynsey S Hall 30,105, Marian L

Hamshere 10, Christine Søholm Hansen 16,43, Thomas F Hansen 16,106,107, Martin Hautzinger 108, Urs Heilbronner 52, Albert M van Hemert 109, Stefan Herms 5,7,8,9, Ian B Hickie 110, Maria Hipolito 111, Per Hoffmann 5,7,8,9, Dominic Holland 73,112, Georg Homuth 113, Carsten Horn 114, Jouke-Jan Hottenga 29, Laura Huckins 24,25, Marcus Ising 115, Stéphane Jamain 116,117, Rick Jansen 46, Jessica S Johnson 24,25, Simone de Jong 1,2, Eric Jorgenson 118, Anders Juréus 3, Radhika Kandaswamy 1, Robert Karlsson 3, James L Kennedy 119,120,121,122, Farnush Farhadi Hassan Kiadeh 123, Sarah Kittel-Schneider 124, James A Knowles 125,126, Manolis Kogevinas 127, Isaac S Kohane 128,129,130, Anna C Koller 7,8, Julia Kraft 22, Warren W. Kretzschmar 131, Jesper Krogh 132, Ralph Kupka 46,133, Zoltán Kutalik 134,135, Catharina Lavebratt 94, Jacob Lawrence 136, William B Lawson 111, Markus Leber 137, Phil H Lee 21,23,138, Shawn E Levy 139, Jun Z Li 140, Yihan Li 131, Penelope A Lind 66, Chunyu Liu 141, Loes M Olde Loohuis 93, Anna Maaser 7,8, Donald J MacIntyre 142,143, Dean F MacKinnon 99, Pamela B Mahon 79,144, Wolfgang Maier 145, Robert M Maier 18, Jonathan Marchini 146, Lina Martinsson 95, Hamdi Mbarek 29, Steve McCarroll 21,147, Patrick McGrath 148, Peter McGuffin 1, Melvin G McInnis 149, James D McKay 150, Helena Medeiros 126, Sarah E Medland 66, Divya Mehta 18,151, Fan Meng 34,149, Christel M Middeldorp 29,152,153, Evelin Mihailov 154, Yuri Milaneschi 46, Lili Milani 154, Saira Saeed Mirza 80, Francis M Mondimore 99, Grant W Montgomery 4, Derek W Morris 155,156, Sara Mostafavi 157,158, Thomas W Mühleisen 5,159, Niamh Mullins 1, Matthias Nauck 160,161, Bernard Ng 158, Hoang Nguyen 24,25, Caroline M Nievergelt 75,162, Michel G Nivard 29, Evaristus A Nwulia 111, Dale R Nyholt 163, Claire O'Donovan 98, Paul F O'Reilly 1, Anil P S Ori 93, Lilijana Oruc 164, Urban Ösby 165, Hogni Oskarsson 166, Jodie N Painter 66, José Guzman Parra 167, Carsten Bøcker Pedersen 16,32,33, Marianne Giørtz Pedersen 16,32,33, Amy Perry 100, Roseann E. Peterson 41,168, Erik Pettersson 3, Wouter J Peyrot 46, Andrea Pfennig 45, Giorgio Pistis 63, Shaun M Purcell 25,144, Jorge A Quiroz 169, Per Qvist 12,13,55, Eline J Regeer 170, Andreas Reif 124, Céline S Reinbold 5,9, John P Rice 171, Brien P. Riley 41, Fabio Rivas 167, Margarita Rivera 1,172, Panos Roussos 24,25,173, Douglas M Ruderfer 174, Euijung Ryu 175, Cristina Sánchez-Mora 59,60,62, Alan F Schatzberg 176, William A Scheftner 177, Robert Schoevers 178, Nicholas J Schork 179, Eva C Schulte 52,180, Tatyana Shehktman 75, Ling Shen 118, Jianxin Shi 181, Paul D Shilling 75, Stanley I Shyn 182, Engilbert

Sigurdsson 183, Claire Slaney 98, Olav B Smeland 73,184,185, Johannes H Smit 46, Daniel J Smith 186, Janet L Sobell 187, Anne T Spijker 188, Michael Steffens 189, John S Strauss 121,190, Fabian Streit 91, Jana Strohmaier 91, Szabolcs Szelinger 191, Katherine E Tansey 192, Henning Teismann 193, Alexander Teumer 194, Robert C Thompson 149, Wesley Thompson 55,75,87,107, Pippa A Thomson 195, Thorgeir E Thorgeirsson 26, Matthew Traylor 196, Jens Treutlein 91, André G Uitterlinden 197, Daniel Umbricht 198, Helmut Vedder 199, Alexander Viktorin 3, Peter M Visscher 4,18, Weiqing Wang 24,25, Stanley J Watson 149, Bradley T. Webb 168, Cynthia Shannon Weickert 102,200, Thomas W Weickert 102,200, Shantel Marie Weinsheimer 55,107, Jürgen Wellmann 193, Gonneke Willemsen 29, Stephanie H Witt 91, Yang Wu 4, Hualin S Xi 201, Wei Xu 202,203, Jian Yang 4,18, Allan H Young 204, Peter Zandi 205, Peng Zhang 206, Futao Zhang 4, Sebastian Zollner 149, Rolf Adolfsson 31, Ingrid Agartz 14,49,207, Martin Alda 98,208, Volker Arolt 209, Lena Backlund 95, Bernhard T Baune 210, Frank Bellivier 211,212,213,214, Klaus Berger 193, Wade H Berrettini 215, Joanna M Biernacka 175, Douglas H R Blackwood 30, Michael Boehnke 90, Dorret I Boomsma 29, Aiden Corvin 156, Nicholas Craddock 10, Mark J Daly 21,23, Udo Dannlowski 209, Enrico Domenici 216, Katharina Domschke 217, Tõnu Esko 19,147,154,218, Bruno Etain 211,213,214,219, Mark Frye 220, Janice M Fullerton 200,221, Elliot S Gershon 36,222, EJC de Geus 29,223, Michael Gill 156, Fernando Goes 79, Hans J Grabe 40, Maria Grigoroiu-Serbanescu 224, Steven P Hamilton 225, Joanna Hauser 72, Caroline Hayward 226, Andrew C Heath 171, David M Hougaard 16,43, Christina M Hultman 3, Ian Jones 10, Lisa A Jones 100, René S Kahn 25,50, Kenneth S Kendler 41, George Kirov 10, Stefan Kloiber 115,121,190, Mikael Landén 3,227, Marion Leboyer 117,211,228, Glyn Lewis 17, Qingqin S Li 229, Jolanta Lissowska 230, Susanne Lucae 115, Pamela AF Madden 119, Patrik K Magnusson 3, Nicholas G Martin 66,231, Fermin Mayoral 167, Susan L McElroy 232, Andrew M McIntosh 30,77, Francis J McMahon 233, Ingrid Melle 234,235, Andres Metspalu 154,236, Philip B Mitchell 102, Gunnar Morken 237,238, Ole Mors 16,239, Preben Bo Mortensen 12,16,32,33, Bertram Müller-Myhsok 37,38,240, Richard M Myers 139, Benjamin M Neale 19,21,23, Vishwajit Nimgaonkar 241, Merete Nordentoft 16,242, Markus M Nöthen 7,8, Michael C O'Donovan 10, Ketil J Oedegaard 243,244, Michael J Owen 10, Sara A Paciga 245, Carlos Pato 126,246, Michele T Pato 126, Nancy L Pedersen 3, Brenda WJH Penninx 46, Roy H Perlis 247,248, David J

Porteous 195, Danielle Posthuma 11,249, James B Potash 79, Martin Preisig 63, Josep Antoni Ramos-Quiroga 59,60,61,62, Marta Ribasés 59,60,62, Marcella Rietschel 91, Guy A Rouleau 250,251, Catherine Schaefer 118, Martin Schalling 94, Peter R Schofield 200,221, Thomas G Schulze 52,79,91,97,233, Alessandro Serretti 252, Jordan W Smoller 21,84,85, Hreinn Stefansson 26, Kari Stefansson 26,253, Eystein Stordal 254,255, Henning Tiemeier 80,256,257, Gustavo Turecki 258, Rudolf Uher 98, Arne E Vaaler 259, Eduard Vieta 260, John B Vincent 190, Henry Völzke 194, Myrna M Weissman 148,261, Thomas Werge 16,107,262, Ole A Andreassen 184,185, Anders D Børglum 12,13,16, Sven Cichon 5,7,9,159, Howard J Edenberg 263, Arianna Di Florio 10,264, John Kelsoe 75, Douglas F Levinson 176, Cathryn M Lewis 1,2,265, John I Nurnberger 92,266, Roel A Ophoff 50,51,93, Laura J Scott 90, Pamela Sklar 24,25†, Patrick F Sullivan 3,264,267, Naomi R Wray 4,18, Gerome Breen 1,2*

Affiliations

1 Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, GB
2 NIHR BRC for Mental Health, King's College London, London, GB
3 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE
4 Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU
5 Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH
6 Department of Psychiatry (UPK), University of Basel, Basel, CH
7 Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, DE
8 Department of Genomics, Life&Brain Center, University of Bonn, Bonn, DE
9 Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, CH
10 Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, GB

11 Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, NL
12 iSEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, DK
13 Department of Biomedicine - Human Genetics, Aarhus University, Aarhus, DK
14 Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, SE
15 Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, DE
16 iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, DK
17 Division of Psychiatry, University College London, London, GB
18 Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
19 Medical and Population Genetics, Broad Institute, Cambridge, MA, US
20 Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, US
21 Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US
22 Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, DE
23 Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US
24 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, US
25 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, US
26 deCODE Genetics / Amgen, Reykjavik, IS
27 Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen, DK
28 Institute of Clinical Medicine, University of Oslo, Oslo, NO
29 Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL
30 Division of Psychiatry, University of Edinburgh, Edinburgh, GB
31 Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, SE

32 National Centre for Register-Based Research, Aarhus University, Aarhus, DK
33 Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK
34 Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, US
35 Neuroscience, Istituto Di Ricerche Farmacologiche Mario Negri, Milano, IT
36 Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, US
37 Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE
38 Munich Cluster for Systems Neurology (SyNergy), Munich, DE
39 Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, GB
40 Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
41 Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US
42 Psychiatry, Rush University Medical Center, Chicago, IL, US
43 Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK
44 Department of Psychiatry, Weill Cornell Medical College, New York, NY, US
45 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, DE
46 Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL
47 Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, US
48 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US
49 Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, NO
50 Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, NL
51 Human Genetics, University of California Los Angeles, Los Angeles, CA, US
52 Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, DE
53 Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, US

54 Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, US
55 iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK
56 Psychiatry, University of California San Francisco, San Francisco, CA, US
57 Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB
58 Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB
59 Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, ES
60 Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, ES
61 Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, ES
62 Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, ES
63 Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH
64 Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC, CA
65 Institute for Medical Sciences, University of Aberdeen, Aberdeen, UK
66 Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU
67 University of Iowa Hospitals and Clinics, Iowa City, IA, US
68 Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, AU
69 Translational Genomics, USC, Phoenix, AZ, US
70 Center for Genomic and Computational Biology, Duke University, Durham, NC, US
71 Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, US
72 Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, PL

73 Department of Neurosciences, University of California San Diego, La Jolla, CA, US
74 Department of Radiology, University of California San Diego, La Jolla, CA, US
75 Department of Psychiatry, University of California San Diego, La Jolla, CA, US
76 Department of Cognitive Science, University of California San Diego, La Jolla, CA, US
77 Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB
78 Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium
79 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US
80 Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL
81 Psychiatry, Dokuz Eylul University School Of Medicine, Izmir, TR
82 Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, NO
83 NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, NO
84 Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US
85 Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US
86 Department of Neurology, Oslo University Hospital, Oslo, NO
87 NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, NO
88 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US
89 Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, US
90 Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, US
91 Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, DE
92 Department of Medical & Molecular Genetics, Indiana University, Indianapolis, IN, US

93 Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, CA, US
94 Department of Molecular Medicine and Surgery, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, SE
95 Department of Clinical Neuroscience, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, SE
96 Child and Adolescent Psychiatry Research Center, Stockholm, SE
97 Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, DE
98 Department of Psychiatry, Dalhousie University, Halifax, NS, CA
99 Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US
100 Department of Psychological Medicine, University of Worcester, Worcester, GB
101 School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, GB
102 School of Psychiatry, University of New South Wales, Sydney, NSW, AU
103 Bioinformatics Research Centre, Aarhus University, Aarhus, DK
104 Biostatistics, University of Minnesota System, Minneapolis, MN, US
105 Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB
106 Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, DK
107 Institute of Biological Psychiatry, MHC Sct. Hans, Mental Health Services Copenhagen, Roskilde, DK
108 Department of Psychology, Eberhard Karls Universität Tübingen, Tubingen, DE
109 Department of Psychiatry, Leiden University Medical Center, Leiden, NL
110 Brain and Mind Centre, University of Sydney, Sydney, NSW, AU
111 Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC, US
112 Center for Multimodal Imaging and Genetics, University of California San Diego, La Jolla, CA, US

113 Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
114 Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH
115 Max Planck Institute of Psychiatry, Munich, DE
116 Psychiatrie Translationnelle, Inserm U955, Créteil, FR
117 Faculté de Médecine, Université Paris Est, Créteil, FR
118 Division of Research, Kaiser Permanente Northern California, Oakland, CA, US
119 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, CA
120 Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, CA
121 Department of Psychiatry, University of Toronto, Toronto, ON, CA
122 Institute of Medical Sciences, University of Toronto, Toronto, ON, CA
123 Bioinformatics, University of British Columbia, Vancouver, BC, CA
124 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, DE
125 Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US
126 Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US
127 Center for Research in Environmental Epidemiology (CREAL), Barcelona, ES
128 Department of Biomedical Informatics, Harvard Medical School, Boston, MA, US
129 Department of Medicine, Brigham and Women's Hospital, Boston, MA, US
130 Informatics Program, Boston Children's Hospital, Boston, MA, US
131 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB
132 Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, DK
133 Psychiatry, Altrecht, Utrecht, NL

134 Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, CH
135 Swiss Institute of Bioinformatics, Lausanne, VD, CH
136 Psychiatry, North East London NHS Foundation Trust, Ilford, GB
137 Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, DE
138 Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, US
139 HudsonAlpha Institute for Biotechnology, Huntsville, AL, US
140 Department of Human Genetics, University of Michigan, Ann Arbor, MI, US
141 Psychiatry, University of Illinois at Chicago College of Medicine, Chicago, IL, US
142 Mental Health, NHS 24, Glasgow, GB
143 Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB
144 Psychiatry, Brigham and Women's Hospital, Boston, MA, US
145 Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE
146 Statistics, University of Oxford, Oxford, GB
147 Department of Genetics, Harvard Medical School, Boston, MA, US
148 Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US
149 Department of Psychiatry, University of Michigan, Ann Arbor, MI, US
150 Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, FR
151 School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, AU
152 Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, AU
153 Child Health Research Centre, University of Queensland, Brisbane, QLD, AU
154 Estonian Genome Center, University of Tartu, Tartu, EE
155 Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, National University of Ireland, Galway, Galway, IE
156 Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, IE

157 Medical Genetics, University of British Columbia, Vancouver, BC, CA
158 Statistics, University of British Columbia, Vancouver, BC, CA
159 Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, DE
160 DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
161 Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
162 Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, US
163 Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, AU
164 Department of Clinical Psychiatry, Psychiatry Clinic, Clinical Center University of Sarajevo, Sarajevo, BA
165 Department of Neurobiology, Care sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, SE
166 Humus, Reykjavik, IS
167 Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, ES
168 Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US
169 Solid Biosciences, Boston, MA, US
170 Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, NL
171 Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, US
172 Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES
173 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, US
174 Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, US

175 Department of Health Sciences Research, Mayo Clinic, Rochester, MN, US
176 Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, US
177 Rush University Medical Center, Chicago, IL, US
178 Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, NL
179 Scripps Translational Science Institute, La Jolla, CA, US
180 Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, DE
181 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US
182 Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US
183 Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, IS
184 Div Mental Health and Addiction, Oslo University Hospital, Oslo, NO
185 NORMENT, University of Oslo, Oslo, NO
186 Institute of Health and Wellbeing, University of Glasgow, Glasgow, GB
187 Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, US
188 Mood Disorders, PsyQ, Rotterdam, NL
189 Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, DE
190 Centre for Addiction and Mental Health, Toronto, ON, CA
191 Neurogenomics, TGen, Los Angeles, AZ, US
192 College of Biomedical and Life Sciences, Cardiff University, Cardiff, GB
193 Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE
194 Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
195 Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB
196 Clinical Neurosciences, University of Cambridge, Cambridge, GB
197 Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, NL

198 Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH
199 Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, DE
200 Neuroscience Research Australia, Sydney, NSW, AU
201 Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US
202 Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, CA
203 Dalla Lana School of Public Health, University of Toronto, Toronto, ON, CA
204 Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, GB
205 Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, US
206 Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, US
207 NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, NO
208 National Institute of Mental Health, Klecany, CZ
209 Department of Psychiatry, University of Münster, Münster, DE
210 Department of Psychiatry, University of Melbourne, Melbourne, VIC, AU
211 Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, FR
212 Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, FR
213 UMR-S1144 Team 1: Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, FR
214 Psychiatry, Université Paris Diderot, Paris, FR
215 Psychiatry, University of Pennsylvania, Philadelphia, PA, US
216 Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, IT
217 Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE
218 Division of Endocrinology, Children's Hospital Boston, Boston, MA, US

219 Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, GB
220 Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, US
221 School of Medical Sciences, University of New South Wales, Sydney, NSW, AU
222 Department of Human Genetics, University of Chicago, Chicago, IL, US
223 Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, NL
224 Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, RO
225 Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US
226 Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB
227 Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, SE
228 INSERM, Paris, FR
229 Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US
230 Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, PL
231 School of Psychology, The University of Queensland, Brisbane, QLD, AU
232 Research Institute, Lindner Center of HOPE, Mason, OH, US
233 Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, US
234 Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO
235 Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, NO
236 Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE
237 Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology - NTNU, Trondheim, NO
238 Psychiatry, St Olavs University Hospital, Trondheim, NO
239 Psychosis Research Unit, Aarhus University Hospital, Risskov, DK
240 University of Liverpool, Liverpool, GB
241 Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, US

242 Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, DK
243 Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, NO
244 Faculty of Medicine and Dentistry, University of Bergen, Bergen, NO
245 Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US
246 College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US
247 Psychiatry, Harvard Medical School, Boston, MA, US
248 Division of Clinical Research, Massachusetts General Hospital, Boston, MA, US
249 Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, NL
250 Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC, CA
251 Montreal Neurological Institute and Hospital, Montreal, QC, CA
252 Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, IT
253 Faculty of Medicine, University of Iceland, Reykjavik, IS
254 Department of Psychiatry, Hospital Namsos, Namsos, NO
255 Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for naturvitenskap og teknologi, Trondheim, NO
256 Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL
257 Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL
258 Department of Psychiatry, McGill University, Montreal, QC, CA
259 Dept of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, NO
260 Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, ES
261 Division of Epidemiology, New York State Psychiatric Institute, New York, NY, US
262 Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK
263 Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, US

264 Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US
265 Department of Medical & Molecular Genetics, King's College London, London, GB
266 Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, US
267 Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

† Deceased

* Correspondence to: Gerome Breen, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, London, SE5 8AF, GB; gerome.breen@kcl.ac.uk; +442078480409

Abstract

Mood disorders affect 10-20% of the population, ranging from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Multiple approaches have shown considerable sharing of genetic risk factors between unipolar and bipolar mood disorders. We use data from the largest genome-wide association studies of major depression (MD) and bipolar disorder (BD) to investigate the molecular basis of the shared genetic liability to mood disorders. We meta-analysed the Psychiatric Genomics Consortium (PGC) MD and BD cohorts, and an additional MD cohort from UK Biobank (185,285 cases, 439,741 controls, non-overlapping N = 609,424). 73 loci reached genome-wide significance in the meta-analysis, with additional loci significant in subtype and depression-only analyses. More genome-wide significant loci from PGC MD (39/44, 89% of the PGC MD loci) than PGC BD (4/19, 21%) reached genome-wide significance in the meta-analysis. Genetic correlations calculated between MD and BD subtypes revealed that type II BD correlates strongly with MD. Integrating the results with systems biology information, we implicate pathways and neuronal subtypes which highlight similarities but also potential differences between MD and BD. Our results reflected MD more than BD, perhaps due to the larger sample size for MD, but also perhaps because depression is their predominant common feature. Overall, these results provide evidence for a genetic mood disorders spectrum.

Mood disorders affect 10-20% of the global population across their lifetime and have been posited to form part of a broader spectrum of affective pathology[1–4]. They range from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Type I and type II bipolar disorder are distinguished from major depressive disorder by the presence of mania in type I and hypomania in type II[5]. However, episodes of depressive symptoms, characterised as "sad, empty, or hopeless mood", are characteristic of major depressive disorder and type II bipolar disorder, and are usually present in type I bipolar disorder[5]. The distinction between the mood disorders is not absolute, as some individuals initially diagnosed with major depressive disorder later develop bipolar disorder, and a substantial fraction of major depressive disorder cases endorse manic or hypomanic symptoms[6–8].

The mood disorders demonstrate considerable sharing of genetic risk factors, suggesting a partially common aetiopathology[9]. Twin studies suggest that 35-45% of variance in risk for major depressive disorder and 65-70% of the variance in bipolar disorder risk is accounted for by additive genetic factors[10]. These genetic components are shared, with a twin genetic correlation (r_g) of ~= 65%, and smaller estimates (30-35%) derived from comparing the results of genome-wide association studies (GWAS) [9,11–13]. Considerable progress has been made in identifying specific genetic variants that underlie genetic risk - most recently, we published GWAS of bipolar disorder, including over 20,000 cases with 30 genomic loci reaching genome-wide significance[12], and major depression, including over 135,000 cases with 44 loci reaching genome-wide significance[11].

Here, we make use of these analyses in conjunction with analyses of major depression from UK Biobank to explore three aims[14,15]. Firstly, we meta-analyse the results of the major depression and bipolar disorder studies to identify regions of

shared mood disorder genetics and explore the genetic relationship of mood disorders to published traits from the wider GWAS literature. Secondly, we compare the genetic correlations from GWAS of bipolar disorder subtypes (from the PGC) and major depression subtypes (from UK Biobank) and assess the separation of these mood disorder subtypes. Finally, we condition the meta-analysed major depression cohorts on the bipolar disorder GWAS (and vice versa) to examine how such conditioning affects genomic systems biology analyses of the results and the genetic correlations of each disorder with other traits.

Materials and Methods

Participants

Summary statistics were obtained from the most recent PGC GWAS of each disorder, involving participants of Western European ancestry. Major depression data was drawn from the full cohort (PGC MD: 135,458 cases, 344,901 controls) from Wray et al. (2018). This cohort included data from 23andMe[16], access to which is restricted by a Data Transfer Agreement - as such, it differs from the publicly-available summary statistics (available at https://www.med.unc.edu/pgc/results-and-downloads). Within this paper, PGC MD is referred to as a major depression cohort. Many individuals in the cohort met criteria for major depressive disorder through clinical ascertainment. However, others self-reported their diagnosis, and so may not have met criteria in a clinical setting - as such, it may be more appropriate to consider these individuals as having major depression, rather than major depressive disorder.

Full access is available at the link above to GWAS summary statistics for bipolar disorder (PGC BD: 20,352 cases, 31,358 controls[12]). These summary

statistics are drawn from the discovery analysis previously reported, and do not include replication results[12]. Summary statistics are also available for subset analyses examining type I bipolar disorder (BD1: 14,879 cases, 30,992 controls), type II bipolar disorder (BD2: 3,421 cases, 22,155 controls), and schizoaffective bipolar disorder (SAB: 977 cases, 8,690 controls). Full descriptions of each study and their composite cohorts are provided in each paper. Brief descriptions are provided in the Supplementary Materials.

An additional MD cohort was derived from the online mental health questionnaire in the UK Biobank (UKB MD; Resource 22 on http://biobank.ctsu.ox.ac.uk[14]). The definition of MD is described in full elsewhere, and in Supplementary Table 1[15]. In total, 29,475 cases and 63,482 controls were available for analysis (all Western European ancestry). Subsets of UKB MD were used for subtype analyses. Individuals meeting criteria for MD were classed as recurrent cases if they reported multiple depressed periods across their lifetime (rMD, N = 17,451), and single-episode cases otherwise (sMD, N = 12,024; Supplementary Table 1). A further set of individuals reported some depressive symptoms but did not meet case criteria (and so are excluded from UKB MD) and were classed as "sub-threshold" (subMD, N = 21,596). All subsets were analysed with the full set of controls. Details on the quality control and analysis of the UK Biobank phenotypes is provided in the Supplementary Materials. UK Biobank is a controlled-access resource available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any person.

Meta-analysis

Meta-analysis was performed between PGC MD, UKB MD and PGC BD (hereafter referred to as MD-UKB-BD). Only variants present in all three studies were included in the results of the meta-analysis. Summary statistics were limited to common variants (MAF > 0.05) that were either genotyped or imputed with high confidence (INFO score > 0.6). A higher MAF threshold was chosen as previous analyses of the BD2 subset suggested the inclusion of lower MAF variants may bias heritability estimates[12].

Controls were known to be shared between the PGC MD and PGC BD analyses, and (due to the inclusion of summary data in PGC MD) the full extent of this overlap was unknown. Two-tailed weighted effect-size based meta-analyses were therefore performed in METACARPA, which controls for sample overlap of unknown extent between studies using the variance-covariance matrix of the observed effect sizes at each variant, weighting by the sample sizes[17,18]. As later analyses (particularly LD score regression) use the total number of subjects in the analysis for calculations, a "non-overlapping N" was estimated for each meta-analysis (Supplementary Materials). Further meta-analyses were performed between PGC MD and UKB MD (MD-UKB), and between PGC MD and each PGC BD subtype and UKB MD subtype. The results and discussion of the subset meta-analyses are included in the Supplementary Materials.

Definition of GWAS loci

GWAS results were clumped using PLINK1.9[19], assigning nominally-significant ($p < 10^{-4}$) variants to a clump if they were in linkage disequilibrium ($r^2 > 0.1$ in unrelated non-Finnish European participants from 1000 Genomes project) with a variant with a lower p-value lying within 3Mb. Loci were declared genome-wide

significant if a variant in the locus reached the conventional threshold for genome-wide significance ($p = 5 \times 10^{-8}$). Results were visualised using FUMA, including mapping the loci to potentially affected genes through expression quantitative trait loci (eQTLs) and chromatin contact sites in brain tissues or neural progenitor cells[20].

All genomic loci reaching genome-wide significance in at least one analysis were combined for annotation. Where loci from different GWAS overlapped, they were combined into a single locus ranging from the minimum base position from any of the constituent loci to the maximum. Annotation was performed using RegionAnnotator version 1.63 (https://github.com/ivankosmos/RegionAnnotator), which includes data from: the NHGRI-EBI GWAS Catalog; OMIM; GENCODE genes; genes previously implicated in autism and in intellectual disability; copy-number variants previously implicated in psychiatric disorders; and mouse knockout phenotypes. Results from the GWAS Catalog module of RegionAnnotator were filtered to include only variants reaching genome-wide significance. Where multiple variants from a previous GWAS of a specific phenotype were listed as significant, only the variant with the lowest p-value is reported.

The relationship between the loci identified in the meta-analyses (MD-UKB-BD, MD-UKB) and the constituent analyses (PGC MD, UKB MD, PGC BD) was assessed using a hierarchically-clustered heatmap, with the 2014 PGC schizophrenia analysis (SCZ) included for comparison[21]. For this comparison, an index SNP was selected for each locus (the variant with the lowest p-value that was common to all four analyses) to obtain the direction of effect in each analysis. Index SNP p-values were converted to $-\log_{10}$(p-value) - if the $OR_{index} < 1$ in a given analysis, the $\log_{10}$(p-value) was used in place of the $-\log_{10}$(p-value). A hierarchically-clustered heatmap was then generated using the default options of the heatmap.2

function of the gplots package in R v1.4.1 (complete clustering on the Euclidean distance between vectors) with clustering performed separately for rows and for columns[22,23].

Conditional analyses

Additional analyses were performed to understand which genomic loci are shared or distinct between the disorders, using mtCOJO, an extension of the GSMR method implemented in GCTA[24,25]. mtCOJO adjusts the results of a GWAS, conditioning on the effects of a set of significantly associated, independent variants from a second set of summary statistics (a putative instrumental variable). The resulting estimated effect size is robust to confounding caused by genetic or environmental effects shared between the studies analysed, assuming these are uncorrelated with the instrumental variable[24,26].

Analyses were performed on MD-UKB conditional on PGC BD (MD-UKBcBD), and on PGC BD conditional on MD-UKB (BDcMD-UKB). Variant selection for conditioning was performed with the default settings in mtCOJO, clumping using the UK Biobank dataset, and selecting at least 10 variants with $p<5x10^{-8}$, which were not in linkage disequilibrium ($r^2 < 0.05$) with a variant with a lower p-value, and which did not show evidence of pleiotropy (passed the HEIDI-outlier analysis, threshold 0.01[24]). Results were clumped in PLINK using the procedure described above for the meta-analyses.

Estimation of SNP-heritability captured by common variants and genetic correlations with published GWAS

The SNP-heritability captured by common variants was assessed using LD Score regression[27]. Estimates were made for each meta-analysed set of data, and SNP-heritability estimates transformed to the liability scale assuming that the combined population prevalence is the sum of the prevalence of the constituent disorders. Estimates were made assuming a population prevalence of 15% for PGC MD, 1% for PGC BD and 16% for MD-UKB-BD. Further estimates were made for the lower bounds of prevalence (MD-UKB-BD: 10.5%, assuming lower bound for PGC MD of 10%, and for PGC BD of 0.5%) and upper bounds of prevalence (MD-UKB-BD: 22%, assuming upper bound for PGC MD of 20%, and for PGC BD of 2%) for comparison.

Genetic correlations between the meta-analysis and 393 traits curated from published GWAS were calculated using an extension of LD Score regression. Correlations were tested for two-tailed difference from 0 using jack-knife derived standard errors. A conservative Bonferroni correction was used to determine significance ($p < 1.27 \times 10^{-4}$, approximate correction for 393 tests). Genetic correlations were compared between MD-UKB and MD-UKBcBD, and between PGC BD and BDcMD-UKB, first using a z-test to identify putative differences ($p < 0.05$), and then formally testing by applying a block-jackknife (Supplementary Methods), with a Bonferroni correction applied for these formal tests[27–29].

Genetic correlations between subset analyses

SNP heritabilities and genetic correlations were calculated in LD Score between the PGC BD subsets (BD1, BD2, SAB), and the UKB MD subsets (rMD,

sMD, subMD) to assess the structure of genetic correlations across the mood disorder spectrum. The resulting genetic correlations were then hierarchically clustered (as described above) using the gplots package in R v1.4.1[22,23].

Gene-wise, gene-set, and tissue and single-cell enrichment analyses

For all analyses, assessed variants were annotated to Ensembl gene locations using MAGMA v1.06 (using the build 37 reference supplied on the MAGMA website[30]). SNPs were assigned to genes if they lay between 35kb upstream and 10kb downstream of the gene location[31]. Gene-wise p-values were calculated as the aggregate of the mean and smallest p-value across all SNPs annotated to the gene. MAGMA accounts for possible confounders such as gene size, gene density, linkage disequilibrium and minor allele count. The threshold for genome-wide significance was defined at $p < 2.6 \times 10^{-6}$ (Bonferroni correction for the 19,041 genes tested). Genes passing genome-wide significance were defined as coming from the same locus if they lay within 100kb of each other, or if they overlapped a locus from the single variant analysis.

Gene set analysis was performed for all analyses. A gene set matrix **P** was generated with elements $P_{g,p} = 1$ if gene g was in set p and $P_{g,p} = 0$ otherwise. Association between gene set membership and gene-wise z-scores was computed using one-tailed competitive tests (comparing the association of genes in the gene set against those not in the gene set) implemented in MAGMA, testing each gene set against . 13,567 gene sets were drawn from OpenTargets (downloaded January 2017[32]), GO ontologies, canonical gene sets drawn from MSigSB v5.2 C2 and C5 datasets[33], and biological gene sets related to psychiatric disorders found in various scientific publications (links in Supplementary Materials). There is considerable

overlap of genes between gene sets (within and between sources). Gene sets that overlapped entirely were treated as a single gene set in analyses. The effective number of gene sets tested was defined as the number of principal components accounting for 99.5% of explained variance in the gene set similarity matrix, obtained by computing the Tanimoto similarity between gene sets. This results in a Bonferroni-corrected threshold of $p = 5.34 \times 10^{-6}$ for 9,361 effectively independent tests for each matrix.

Further analyses were performed to assess the enrichment of associated genes with expression-specificity profiles from tissues (version 7 data from the Genotype-Tissue Expression project) and broadly-defined ("level 1") and narrowly-defined ("level 2") cell-types (Karolinska Institutet mouse brain single-cell RNA sequencing superset[34,35]). Analyses were performed in MAGMA following previously described methods with minor modifications[35]. Briefly, for the single cell data set [35], gene expression for each cell type was scaled to 10,000 unique molecular identifiers prior to computing specificity scores. Specificity scores are defined as the proportion of the total expression of a specific gene found in a given cell type. For the GTEx dataset, transcripts per million (TPM) were transformed to $\log_2(\text{TPM} + 1)$ prior to computing specificity scores. For each tissue or cell-type, the specificity scores were then rank-transformed to a standard normal distribution using the *rntranform* function from the GenABEL R package[36]. The standard normalised specificity scores were then regressed on gene-wise association from the meta-analysis, defined as the mean p-value across all SNPs assigned to the gene. Multiple-testing correction was applied using Bonferroni-correction within each analysis.

Mendelian randomisation (GSMR)

Bidirectional Mendelian randomisation analyses were performed using the GSMR option in GCTA to test the causal direction of known relationships between mood disorder traits and other traits[24,25]. Specifically the relationship between the mood disorder analyses (MD-UKB, PGC BD, MD-UKB-BD, MD-UKBcBD and BDcMD-UKB) and PGC MD, PGC BD, schizophrenia[21], intelligence[37], educational attainment[38], body mass index[39], and coronary artery disease[40] were explored. GSMR uses a putative instrumental variable derived from the summary statistics of the trait of interest to act as a proxy for that trait in regression analyses (as described above for mtCOJO analyses). GSMR uses the HEIDI test to remove pleiotropic variants from the instrument variable set, addressing one limitation of Mendelian randomisation more broadly. All analyses were run using the default settings in GSMR, assuming at least ten linkage-independent ($r^2 < 0.05$) significant ($p<5x10^{-8}$) variants pass the HEIDI test (threshold 0.01).

Sensitivity analysis

Results from MD-UKB-BD generally showed greater similarity to PGC MD than to PGC BD. The results of cross-trait meta-analyses may be biased if the power of the composite analyses differ substantially[41,42]. The mean chi-square of MD-UKB (1.7) was greater than that of PGC BD (1.39), suggesting this bias may affect our results (Supplementary Table 2). To examine the extent of this bias, we repeated our analyses using summary statistics for PGC MD that did not include the 23andMe participants nor the UK Biobank participants included in the original study (45,591 cases, 97,674 controls; mean chi-square from meta-analysis with UKB MD = 1.35).

Data availability

The data analysed in this publication are available at the links described. Access to full PGC MD summary statistics, including data from 23andMe, is available on request from the PGC on provision of an agreed Data Transfer Agreement with 23andMe.

Results

Little evidence of appreciable confounding in meta-analyses

Following each meta-analysis, results were assessed for genome-wide inflation of test statistics using LD Score[27]. The intercept from LD Score regression was significantly >1 in all cases (1.02-1.06), which has previously been taken as evidence for confounding (for example, by population stratification; Supplementary Table 2). However, inflation of the LD Score intercept can occur in the absence of confounding when assessing large sample sizes[43]. The attenuation ratio from LD Score was < 0.08 in all cases, suggesting that the effect of confounding on GWAS results was minimal (Supplementary Table 2[43]).

Combined MD-UKB-BD meta-analysis

We meta-analysed the PGC MD, PGC BD and the UKB MD cohorts (MD-UKB-BD; cases = 185,285, controls = 439,741, non-overlapping N = 609,424). 73 loci reached genome-wide significance, of which 55 were seen in the depression-only MD-UKB meta-analysis (Figure 1a; Table 1; Supplementary Table 3; Supplementary Figures 1 and 2). Hierarchical clustering of the significant loci from both meta-analyses with the same loci from PGC MD, UKB MD, and PGC BD (and the PGC2 SCZ for comparison[21]) resulted in MD-UKB-BD clustering most closely

with PGC MD. This indicates that the primary contribution to significant loci in the meta-analysis came from PGC MD rather than PGC BD (Figure 1b). Results from UKB MD for these loci clustered closer to PGC BD than to PGC MD, suggesting that the component analyses cluster primarily by their contribution to the meta-analysis, rather than by trait. Despite this similarity between UKB MD and PGC BD when considering genome-wide significant loci, comparisons of the SNP-heritability of the component analyses (Supplementary Table 2) and of the genetic correlations between them (Supplementary Table 4) confirm that UKB MD is more similar in general to PGC MD than to PGC BD. Specifically, the SNP-heritability of UKB MD (13%) is more similar to that of PGC MD (9%) than to that of PGC BD (20%), and the genetic correlation between PGC MD and UKB MD (0.88) is considerably larger than that between either MD phenotype and PGC BD (both 0.34).

Only five of the 44 PGC MD loci did not reach genome-wide significance in MD-UKB-BD (and all five did reach genome-wide significance in MD-BD2; Supplementary Table 3; Supplementary Figures 1-8). In comparison, only four of the 19 PGC BD loci reached genome-wide significance in the meta-analysis, suggesting that the addition of bipolar cases to depression cohorts enriched for associations with their common phenotypic component, depression.

Of the loci reaching genome-wide significance in MD-UKB-BD, 32 did not reach genome-wide significance in the PGC MD or PGC BD analyses (although all had $p < 1x10^{-5}$ in PGC MD). Although most of these loci have no previous records in the NHGRI-EBI GWAS Catalog, eight have been previously reported in other major depression or major depressive disorder GWAS: loci 27 and 35[16]; locus 30[44]; and loci 42, 44, 49, 51, and 68[41]. Five loci (7, 12, 42, 51 and 68) have previously been associated with schizophrenia[21,45], and there are also multiple reported associations

with age at menarche, brain aneurysms, body mass and blood pressure (Supplementary Table 5). A number of these loci contain genes of interest to mood disorders, including *DRD2* and *PCLO* (Supplementary Table 5[44,46,47]).

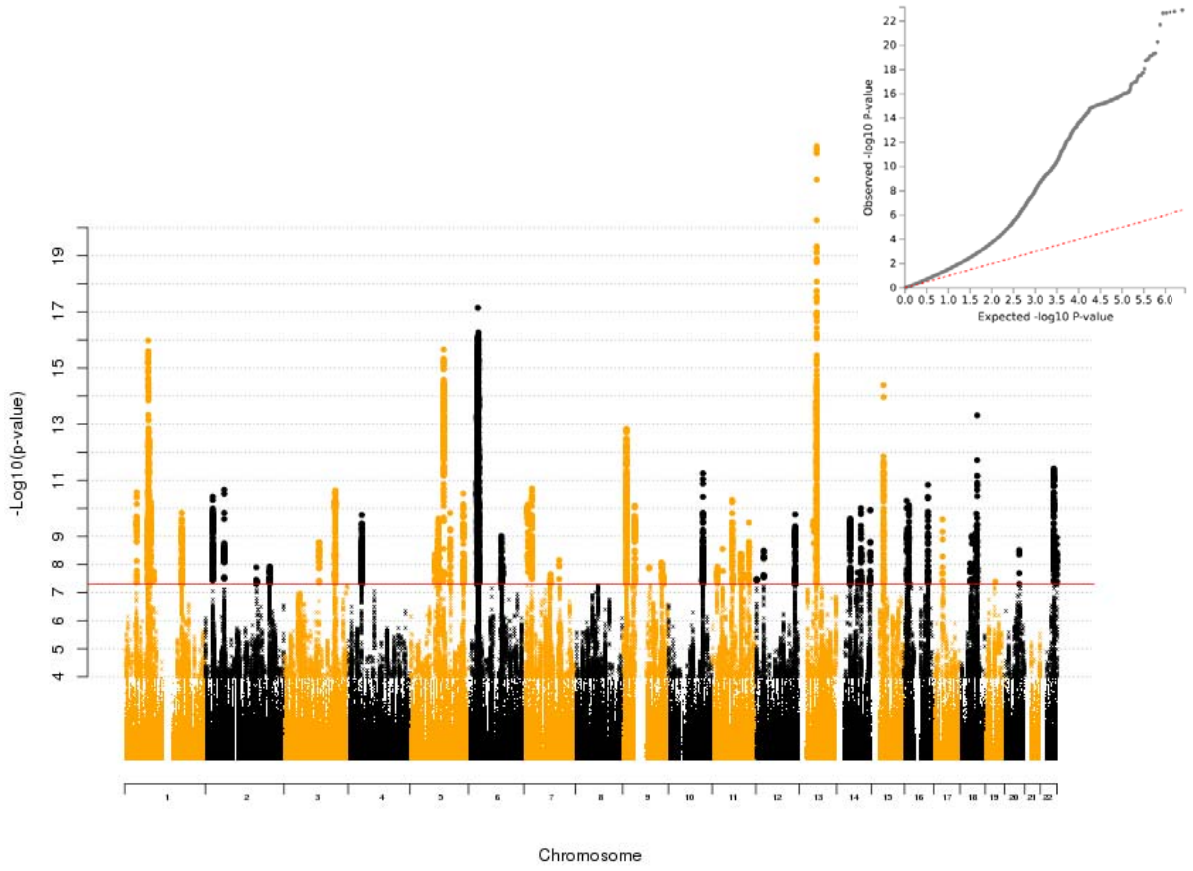


Figure1a: Manhattan and QQ plot of results for the MD-UKB-BD meta-analysis. Red line is $p = 5x10^{-8}$

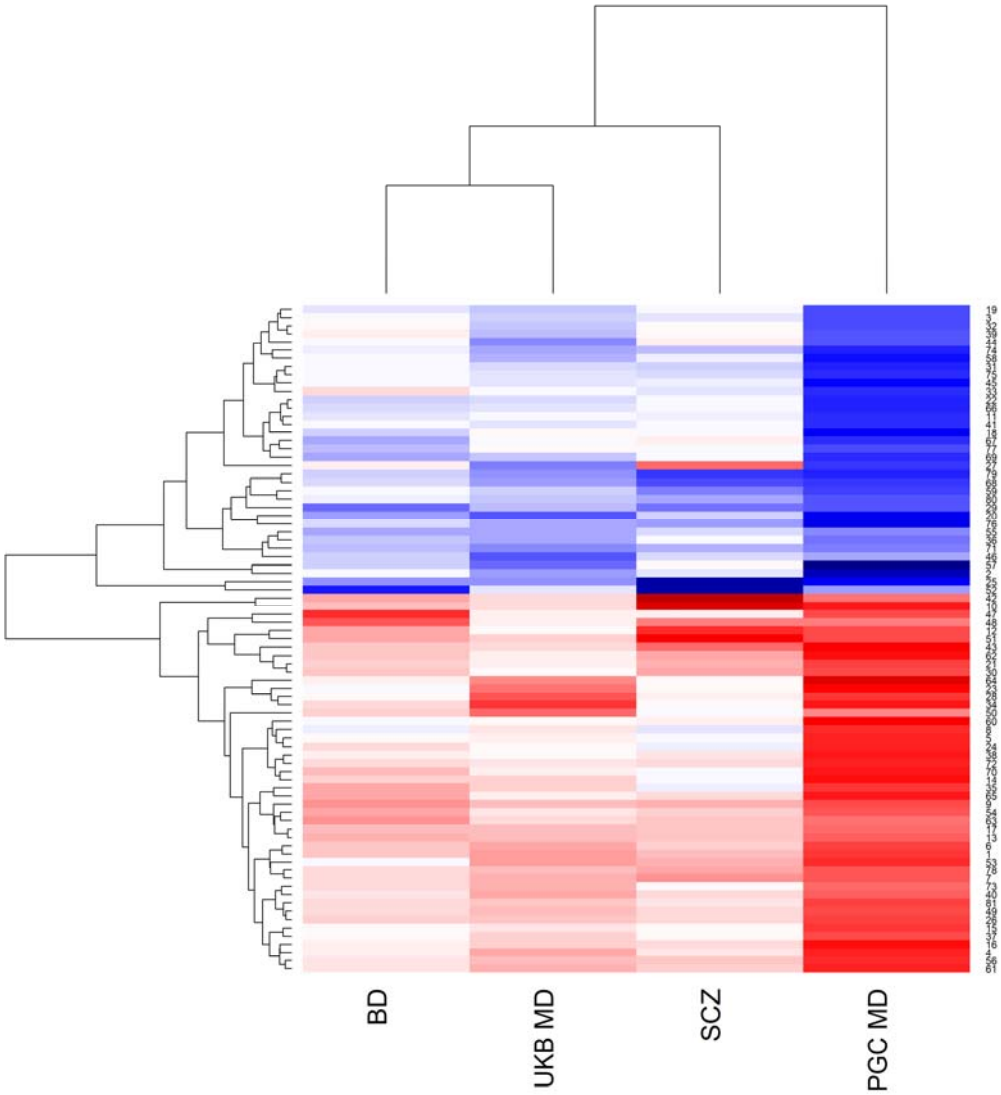


Figure 1b: Hierarchical clustering of the significant loci from the main meta-analysis (MD-UKB-BD) and the depression-only analysis (MD-UKB) with the same loci from the major depression cohorts (PGC MD and UKB MD), the bipolar disorder cohort (PGC BD), and schizophrenia (SCZ). Blue = positive direction of effect. Red = negative direction of effect.

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	p	p min MD-UKB	p min PGC BD
1	1	37192741	rs1002656	T	C	0.97	0.005	$2.71x10^{-11}$	$4.72x10^{-10}$	$2.54x10^{-3}$
2	1	72837239	rs7531118	T	C	0.96	0.004	$1.05x10^{-16}$	$3.25x10^{-17}$	$2.67x10^{-3}$
4	1	80795989	rs6667297	A	G	0.97	0.005	$5.86x10^{-11}$	$8.80x10^{-11}$	$6.00x10^{-3}$
5	1	90796053	rs4261101	A	G	0.97	0.005	$1.78x10^{-8}$	$1.12x10^{-8}$	$3.66x10^{-2}$
6	1	175913828	rs10913112	T	C	0.97	0.005	$1.46x10^{-10}$	$3.91x10^{-9}$	$2.12x10^{-3}$
7	1	177370033	rs16851203	T	C	0.96	0.007	$2.38x10^{-9}$	$1.07x10^{-8}$	$2.75x10^{-2}$
9	2	22582968	rs61533748	T	C	0.97	0.004	$3.84x10^{-11}$	$5.96x10^{-9}$	$4.10x10^{-6}$
10	2	57987593	rs11682175	T	C	0.97	0.004	$2.18x10^{-11}$	$7.07x10^{-10}$	$5.00x10^{-8}$
11	2	157111313	rs1226412	T	C	1.03	0.005	$1.27x10^{-8}$	$3.39x10^{-8}$	$7.29x10^{-4}$
12	2	198807015	rs1518367	A	T	0.97	0.005	$1.18x10^{-8}$	$7.96x10^{-7}$	$4.91x10^{-5}$
13	3	108148557	rs1531188	T	C	0.96	0.006	$1.61x10^{-9}$	$6.74x10^{-8}$	$9.17x10^{-6}$
14	3	158107180	rs7430565	A	G	0.97	0.004	$2.30x10^{-11}$	$2.12x10^{-10}$	$9.41x10^{-4}$
16	4	42047778	rs34215985	C	G	0.97	0.006	$1.72x10^{-10}$	$2.00x10^{-10}$	$9.45x10^{-3}$
17	5	77709430	rs4529173	T	C	0.97	0.005	$4.29x10^{-9}$	$1.35x10^{-7}$	$3.98x10^{-4}$
18	5	88002653	rs447801	T	C	1.03	0.004	$2.29x10^{-10}$	$1.87x10^{-10}$	$8.73x10^{-4}$
19	5	92995013	rs71639293	A	G	1.03	0.005	$5.85x10^{-9}$	$2.34x10^{-8}$	$2.20x10^{-4}$
20	5	103904226	rs12658032	A	G	1.04	0.005	$2.19x10^{-16}$	$6.12x10^{-14}$	$5.19x10^{-6}$
21	5	106603482	rs55993664	A	C	0.97	0.006	$1.87x10^{-8}$	$2.21x10^{-7}$	$2.49x10^{-3}$
22	5	124251883	rs116755193	T	C	0.97	0.005	$1.47x10^{-10}$	$1.33x10^{-9}$	$9.55x10^{-3}$
23	5	164523472	rs11135349	A	C	0.97	0.004	$2.96x10^{-11}$	$1.54x10^{-12}$	$1.48x10^{-2}$
24	5	166992078	rs4869056	A	G	0.97	0.005	$5.21x10^{-9}$	$2.08x10^{-8}$	$5.41x10^{-3}$
25	6	28673998	rs145410455	A	G	0.94	0.007	$7.17x10^{-18}$	$5.06x10^{-15}$	$2.94x10^{-6}$
27	6	101339400	rs7771570	T	C	0.97	0.004	$9.68x10^{-10}$	$4.74x10^{-9}$	$2.17x10^{-4}$
28	6	105365891	rs1933802	C	G	0.98	0.004	$1.05x10^{-8}$	$2.75x10^{-10}$	$4.42x10^{-2}$
29	7	12267221	rs4721057	A	G	0.97	0.004	$7.31x10^{-11}$	$4.79x10^{-11}$	$9.31x10^{-3}$
30	7	24826589	rs79879286	C	G	1.04	0.006	$1.97x10^{-11}$	$1.77x10^{-8}$	$2.70x10^{-8}$
31	7	82514089	rs34866621	T	C	1.03	0.005	$2.21x10^{-8}$	$7.06x10^{-8}$	$4.78x10^{-5}$
32	7	109099919	rs58104186	A	G	1.03	0.004	$7.12x10^{-9}$	$1.34x10^{-9}$	$2.02x10^{-3}$
36	9	11379630	rs10959753	T	C	0.96	0.005	$1.45x10^{-13}$	$6.56x10^{-13}$	$2.14x10^{-4}$
37	9	37207269	rs4526442	T	C	0.96	0.006	$7.97x10^{-11}$	$8.00x10^{-9}$	$5.23x10^{-6}$

38	9	81413414	rs11137850	A	G	1.03	0.005	$1.25x10^{-8}$	$2.53x10^{-7}$	$2.70x10^{-3}$
40	9	119733380	rs10759881	A	C	1.03	0.005	$8.56x10^{-9}$	$1.56x10^{-8}$	$4.15x10^{-3}$
42	9	122664468	rs10818400	T	G	0.98	0.004	$1.29x10^{-8}$	$4.86x10^{-8}$	$6.47x10^{-2}$
43	9	126682068	rs7029033	T	C	1.04	0.008	$2.61x10^{-8}$	$1.89x10^{-8}$	$1.69x10^{-2}$
44	10	104684544	rs78821730	A	G	0.96	0.007	$2.95x10^{-8}$	$1.63x10^{-6}$	$5.63x10^{-6}$
45	10	106563924	rs61867293	T	C	0.96	0.005	$5.64x10^{-12}$	$1.58x10^{-10}$	$1.71x10^{-3}$
46	11	16293680	rs977509	T	C	0.97	0.005	$1.19x10^{-8}$	$3.32x10^{-9}$	$4.48x10^{-2}$
47	11	31850105	rs1806153	T	G	1.03	0.005	$2.81x10^{-9}$	$4.89x10^{-10}$	$4.98x10^{-3}$
48	11	32765866	rs143864773	T	C	1.04	0.008	$1.70x10^{-8}$	$1.40x10^{-7}$	$4.38x10^{-3}$
49	11	61557803	rs102275	T	C	0.97	0.005	$5.04x10^{-11}$	$1.72x10^{-7}$	$1.17x10^{-8}$
50	11	63632673	rs10792422	T	G	0.98	0.004	$2.18x10^{-8}$	$1.26x10^{-5}$	$5.09x10^{-7}$
51	11	88743208	rs4753209	A	T	0.97	0.004	$4.15x10^{-9}$	$1.84x10^{-8}$	$1.17x10^{-4}$
52	11	99268617	rs1504721	A	C	0.98	0.004	$2.24x10^{-8}$	$2.01x10^{-7}$	$1.57x10^{-3}$
53	11	113392994	rs2514218	T	C	0.97	0.005	$3.22x10^{-10}$	$3.09x10^{-8}$	$6.96x10^{-4}$
54	12	2344644	rs769087	A	G	1.03	0.005	$3.27x10^{-8}$	$2.93x10^{-6}$	$2.92x10^{-9}$
55	12	23947737	rs4074723	A	C	0.97	0.004	$3.18x10^{-9}$	$3.23x10^{-10}$	$6.44x10^{-4}$
56	12	121186246	rs58235352	A	G	0.95	0.009	$1.64x10^{-10}$	$7.62x10^{-9}$	$1.66x10^{-4}$
57	12	121907336	rs7962128	A	G	1.02	0.004	$3.63x10^{-8}$	$2.56x10^{-6}$	$1.50x10^{-4}$
59	13	44327799	rs4143229	A	C	0.95	0.008	$2.73x10^{-10}$	$5.68x10^{-10}$	$7.74x10^{-4}$
60	13	53625781	rs12552	A	G	1.04	0.004	$1.25x10^{-23}$	$1.09x10^{-22}$	$9.67x10^{-4}$
61	14	42074726	rs61990288	A	G	0.97	0.004	$2.29x10^{-10}$	$5.95x10^{-11}$	$2.12x10^{-2}$
63	14	64686207	rs915057	A	G	0.98	0.004	$1.92x10^{-8}$	$2.87x10^{-9}$	$1.41x10^{-2}$
64	14	75130235	rs1045430	T	G	0.97	0.004	$9.83x10^{-11}$	$3.07x10^{-10}$	$4.36x10^{-3}$
65	14	104017953	rs10149470	A	G	0.97	0.004	$1.15x10^{-10}$	$2.43x10^{-9}$	$6.24x10^{-5}$
66	15	36355868	rs1828385	A	C	0.97	0.004	$1.15x10^{-8}$	$1.41x10^{-6}$	$1.47x10^{-5}$
67	15	37643831	rs8037355	T	C	0.97	0.004	$4.09x10^{-15}$	$3.38x10^{-15}$	$1.62x10^{-2}$
68	16	6310645	rs8063603	A	G	0.97	0.005	$5.36x10^{-11}$	$6.83x10^{-9}$	$1.39x10^{-4}$
69	16	7667332	rs11077206	C	G	1.03	0.004	$5.49x10^{-10}$	$2.73x10^{-9}$	$5.04x10^{-3}$
70	16	13038723	rs12935276	T	G	0.97	0.005	$4.75x10^{-10}$	$1.54x10^{-8}$	$5.53x10^{-5}$
71	16	13750257	rs7403810	T	G	1.03	0.005	$7.52x10^{-11}$	$4.87x10^{-10}$	$5.54x10^{-3}$
72	16	72214276	rs11643192	A	C	1.03	0.004	$1.46x10^{-11}$	$2.01x10^{-9}$	$2.32x10^{-5}$
73	17	27363750	rs75581564	A	G	1.04	0.006	$2.47x10^{-10}$	$6.46x10^{-9}$	$2.44x10^{-5}$

74	18	31349072	rs4534926	C	G	1.03	0.004	$9.14x10^{-9}$	$3.43x10^{-7}$	$1.66x10^{-3}$
75	18	36883737	rs62099069	A	T	0.97	0.004	$9.52x10^{-10}$	$4.26x10^{-9}$	$9.91x10^{-5}$
76	18	42260348	rs117763335	T	C	0.97	0.005	$1.33x10^{-8}$	$9.40x10^{-8}$	$1.62x10^{-3}$
77	18	50614732	rs11663393	A	G	1.03	0.004	$1.56x10^{-10}$	$2.44x10^{-10}$	$1.72x10^{-4}$
78	18	52517906	rs1833288	A	G	1.03	0.005	$4.54x10^{-8}$	$9.02x10^{-9}$	$7.98x10^{-3}$
79	18	53101598	rs12958048	A	G	1.04	0.005	$4.86x10^{-14}$	$3.11x10^{-13}$	$2.72x10^{-3}$
80	19	30939989	rs33431	T	C	1.02	0.004	$4.04x10^{-8}$	$1.41x10^{-6}$	$2.84x10^{-3}$
81	20	45841052	rs910187	A	G	0.97	0.005	$3.09x10^{-9}$	$2.56x10^{-8}$	$1.36x10^{-3}$
82	22	41621714	rs2179744	A	G	1.03	0.005	$3.83x10^{-12}$	$3.45x10^{-11}$	$4.69x10^{-9}$
83	22	42815358	rs7288411	A	G	1.03	0.005	$3.86x10^{-8}$	$5.96x10^{-8}$	$4.91x10^{-4}$
84	22	50679436	rs113872034	A	G	0.96	0.006	$1.10x10^{-9}$	$6.13x10^{-9}$	$2.43x10^{-3}$

Table 1: Loci genome-wide significant ($p < 5x10^{-8}$) in the MD-UKB-BD meta-analysis. Locus - shared locus number for annotation (Supplementary Table 3); Chr - chromosome; BP - base position; A1 - effect allele; A2 - non-effect allele; p min - minimum p value in that locus for the MD-UKB and PGC BD analyses.

Gene-wise association analyses in MAGMA identified 361 genes associated with the MD-UKB-BD phenotype at $p < 2.6x10^{-6}$ (Supplementary Table 6). Associated genes were distributed across 120 loci, including 47 of the loci identified in MD-UKB-BD. However, proximity is only a weak indication of the association of a gene with a trait[48]. More evidence is provided by the convergence of brain-derived eQTL and chromatin contact data from a locus onto a single gene (Supplementary Figures 9-28). In MD-UKB-BD, such evidence suggested significant loci may act on *NEGR1* (loci 2 and 3), *RSRC1* (locus 14), *TMEM161B* (18), *LHX2* (41), *SOX5* (53), *LACC1* (56), *PCDH8* (57) and *ZC2HC1C* (61). However, diverse eQTL and chromatin contacts were observed at many of these loci, suggesting these associations may act through other genes as well.

SNP-heritability and genetic correlations

The estimate of SNP-heritability for MD-UKB-BD (8.8% with population prevalence 16%) was more similar to PGC MD (9%) than to PGC BD (17-23%)[11,12]. Significant genetic correlations between MD-UKB-BD and other traits included psychiatric and behavioural, reproductive, cardiometabolic, and sociodemographic traits (Figure 2, Supplementary Table 7). Genetic correlations across psychiatric and behavioural traits are common to psychiatric traits in general[13,49]. One area of difference between the genetic correlations of PGC MD and PGC BD is the genetic correlation with educational attainment, which was negative in PGC MD, but positive in PGC BD. The genetic correlation (r_g) between MD-UKB-BD and educational attainment was -0.058 ($p = 0.004$), intermediate between the results of PGC MD and of PGC BD. Notably, the genetic correlation with intelligence was not significant in either PGC MD and PGC BD, a finding that was also true (following multiple-testing correction) in MD-UKB-BD ($r_g = -0.05$; $p = 0.04$).

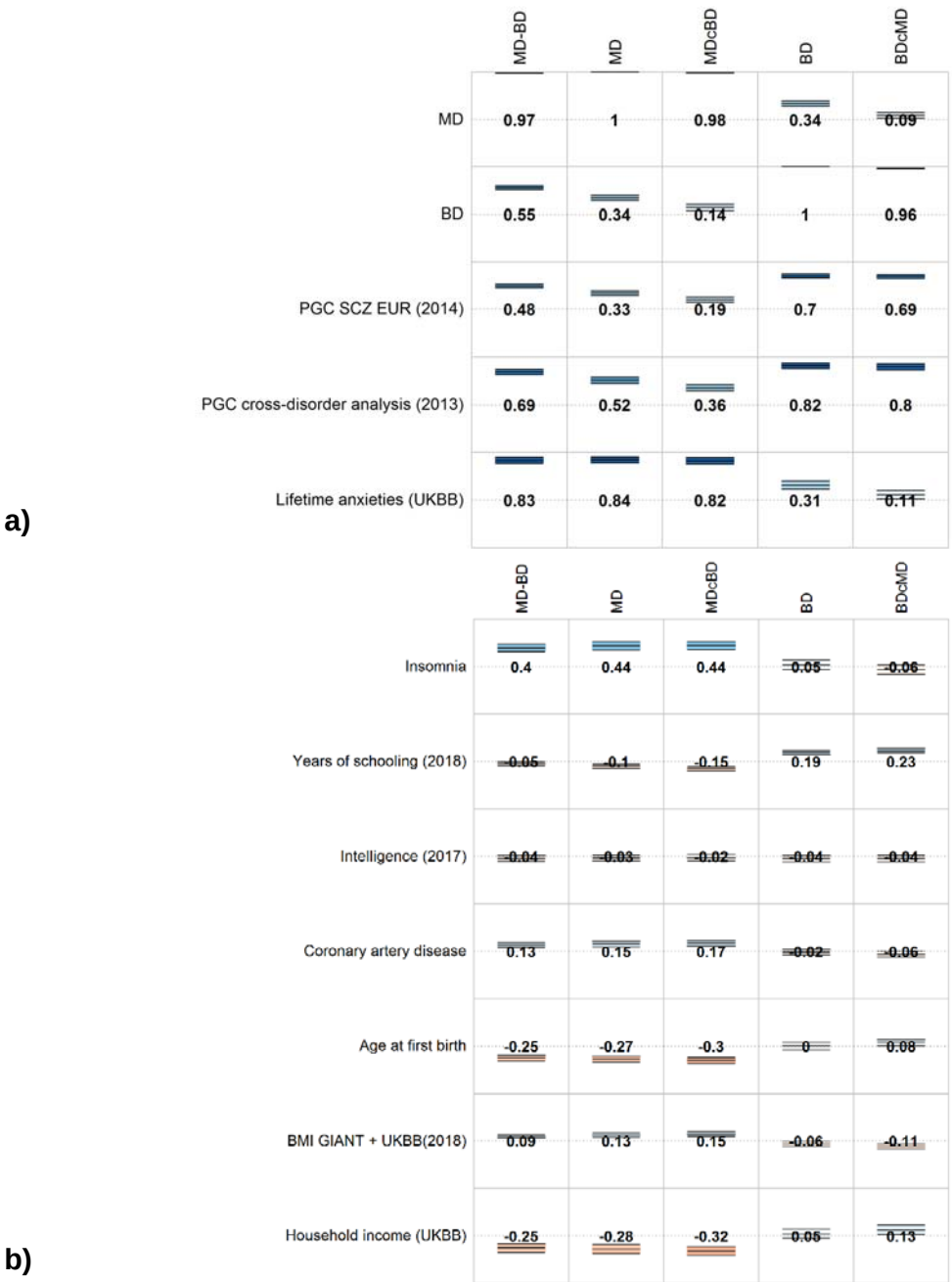


Figure 2: Boxplot of genetic correlations of previous-reported a) psychiatric traits and b) other traits with the main meta-analysis (MD-UKB-BD), the depression-only analysis (MD-UKB), and the major depression and bipolar disorder analyses before and after conditioning (MD-UKB, MD-UKBcBD, PGC BD, and BDcMD-UKB). Full genetic correlation results are provided in Supplementary Tables 7, 10-12. Lines in the box are genetic correlation with 95% confidence intervals from LD Score.

Relationship between mood disorder subtypes

Analyses were performed using GWAS data from subtypes of PGC BD (BD1, BD2, SAB) and UKB MD (rMD, sMD, subMD). SNP-heritability for the subtypes ranged from subMD and sMD (both 8%), through BD2 and rMD (10% and 12% respectively) to BD1 and SAB (22% and 29% respectively; Figure 3a; Supplementary Table 2). In hierarchical clustering of the genetic correlations between the different subtypes, the depression subsets (rMD, sMD) clustered together along with subMD (r_g = 0.9-0.94; Figure 3b; Supplementary Table 4). However, BD1 and BD2 clustered separately, BD2 clustering more closely to the UKB MD subtypes than to the PGC BD subtypes. This was driven by the greater genetic correlation of BD2 to the UKB MD subtypes (r_g = 0.39-0.68) than to SAB (r_g = 0.22).

Conditional analyses

We carried out analyses of MD-UKB conditioning on PGC BD (MD-UKBcBD). Diminished effects (that is, a shrinkage of the odds ratio towards 1) were observed in 51/63 loci reaching genome-wide significance in MD-UKB, which indicates that most loci significantly associated with MD-UKB have the same direction of effect in PGC BD (Supplementary Table 8). Results from the reverse analysis (PGC BD conditioned on MD-UKB: BDcMD-UKB) supports this conclusion, with 14/19 associated loci from PGC BD showing a diminished effect (Supplementary Table 9).

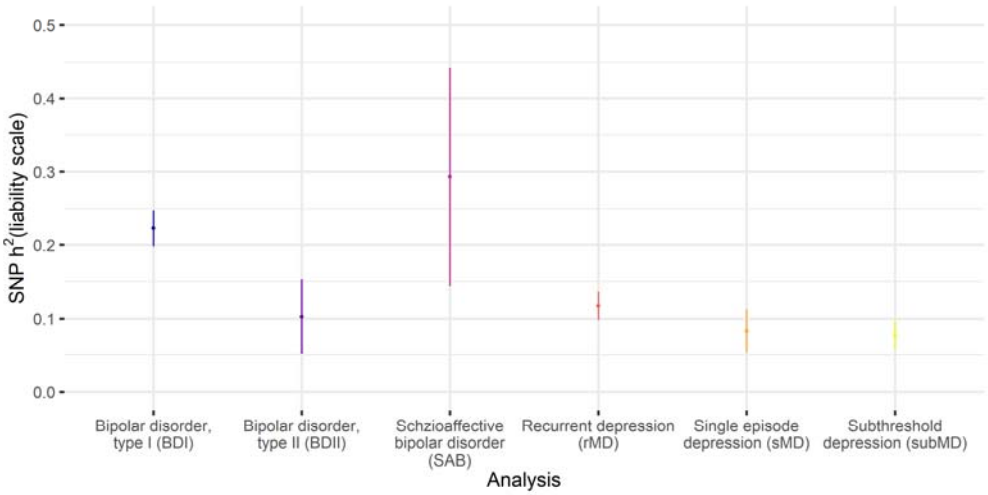


Figure 3a: SNP-heritability estimates for the subtypes of bipolar disorder and subtypes of major depression from the UK Biobank. Points = SNP-heritability estimates. Lines - 95% confidence intervals. Full SNP-heritability results are provided in Supplementary Table 2.

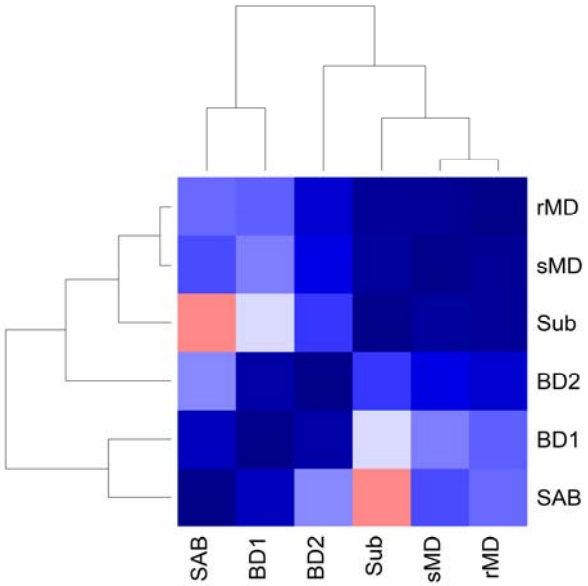


Figure 3b: Hierarchical clustering of the genetic correlations between major depression subtypes from UK Biobank (rMD, sMD, subMD) and bipolar disorder subtypes (BD1, BD2, SAB). Blue = positive genetic correlation. Red = negative genetic correlation. Full genetic correlation results are provided in Supplementary Table 4.

Secondary analyses on MD-UKBcBD reflect the genetic effect on MD-UKB that is not shared with PGC BD and can be compared informatively with the original results for MD-UKB. Similar informative comparisons can be made between BDcMD-UKB and PGC BD. The SNP-heritability of the conditional analyses showed reduced estimates compared to the respective main analyses (MD-UKBcBD: 7%, MD-UKB: 9%; BDcMD: 17%, PGC BD: 20%; Supplementary Table 2). In contrast, the genetic correlations between the conditional analyses and published traits results were similar to the respective main analyses (Supplementary Tables 7, 10-15). Genetic correlations for MD-UKBcBD mirror those for MD-UKB, except that the magnitude of the genetic correlations with schizophrenia (and related analyses, such as the schizophrenia-bipolar disorder meta-analysis) were significantly diminished (difference in genetic correlation with European subjects in PGC2 schizophrenia between MD-UKB and MD-UKBcBD, $p = 8x10^{-96}$; Supplementary Table 12)[21,50]. The genetic correlations from BDcMD-UKB were also similar to PGC BD, with significant reductions primarily in traits associated with depression, including tiredness and poor general health, although a significant reduction in the genetic correlation with ADHD was also observed ($p = 2x10^{-3}$; Supplementary Table 15[51–53]).

Results from gene set analysis were generally similar between MD-UKB and PGC BD, and in each of the conditional analyses (Supplementary Tables 16-19). Both MD-UKB and PGC BD were significantly enriched for genes previously implicated in schizophrenia, targets of the RNA splicing proteins *CELF4* and *RBFOX1/RBFOX3*, loss-of-function intolerant (pLI09) genes, and genes with products potentially involved in synaptic processes (Supplementary Tables 16, 18). Similar gene sets were also enriched in one disorder only - for example, *RBFOX2* targets were significantly enriched in MD-UKB, but did not reach this threshold in

PGC BD. In contrast, gene sets annotated as mutation-intolerant (constrained and genic intolerance RVIS) were significantly enriched in PGC BD but not MD-UKB. However, there were also gene sets which appeared more strongly associated with one disorder than the other, such as anthropometric and behavioural gene sets in MD-UKB, and transporter complexes in PGC BD. In the conditional analyses, results for MD-UKB and MD-UKBcBD were similar, with significantly associated gene sets falling into broad categories of psychiatrically-associated, neurodevelopmental, and anthropometric gene sets (Supplementary Tables 16 and 17). Fewer gene sets were observed in BDcMD-UKB than in PGC BD, with significant enrichment observed for mutation-intolerant gene sets (Supplementary Tables 18 and 19).

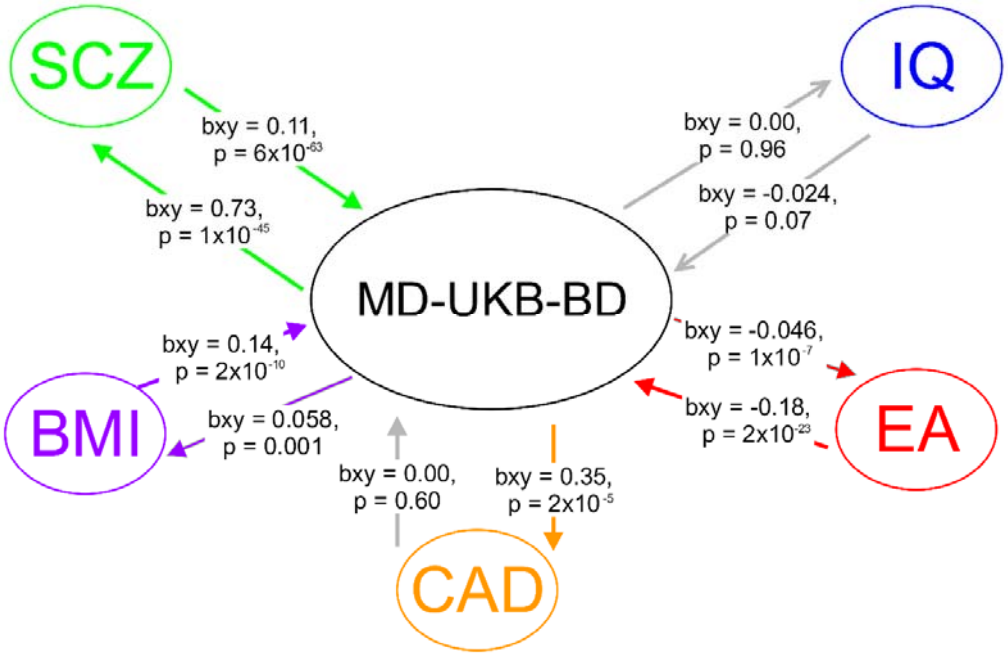
The tissue-specificity enrichment of associated genes differed only minimally between the analyses. All brain regions were significantly enriched in all analyses, and the pituitary was also enriched in PGC BD ($p < 0.002$, Bonferroni correction for 24 regions; Supplementary Table 20). By contrast, level 1 cell-type enrichments differed between MD-UKB and PGC BD, especially when comparing the conditional analyses (Supplementary Table 21). Enrichments for neuroblasts and dopaminergic neurons from adult mice were significant in MD-UKB (and MD-UKBcBD) but not in PGC BD. All cell-types significantly enriched in PGC BD (dopaminergic neuroblasts, dopaminergic, GABAergic and midbrain nucleus neurons from embryonic mice, interneurons, medium spiny neurons, pyramidal cells from the CA1 region of the hippocampus and the somatosensory cortex, serotonergic neurons, and striatal interneurons) were also significantly enriched in MD-UKB, but the rank and strength of enrichment differed between the analyses. This became more apparent when comparing the conditional analyses. In addition to the neuroblasts and adult dopaminergic neurons, embryonic GABAergic neurons remain significantly enriched

in MD-UKBcBD and not in BDcMD-UKB. Conversely, both sets of pyramidal cells and the striatal interneurons remain significantly enriched in BDcMD-UKB and not in MD-UKBcBD. These differences were also observed when comparing the more narrowly-defined level 2 cell types (Supplementary Table 22).

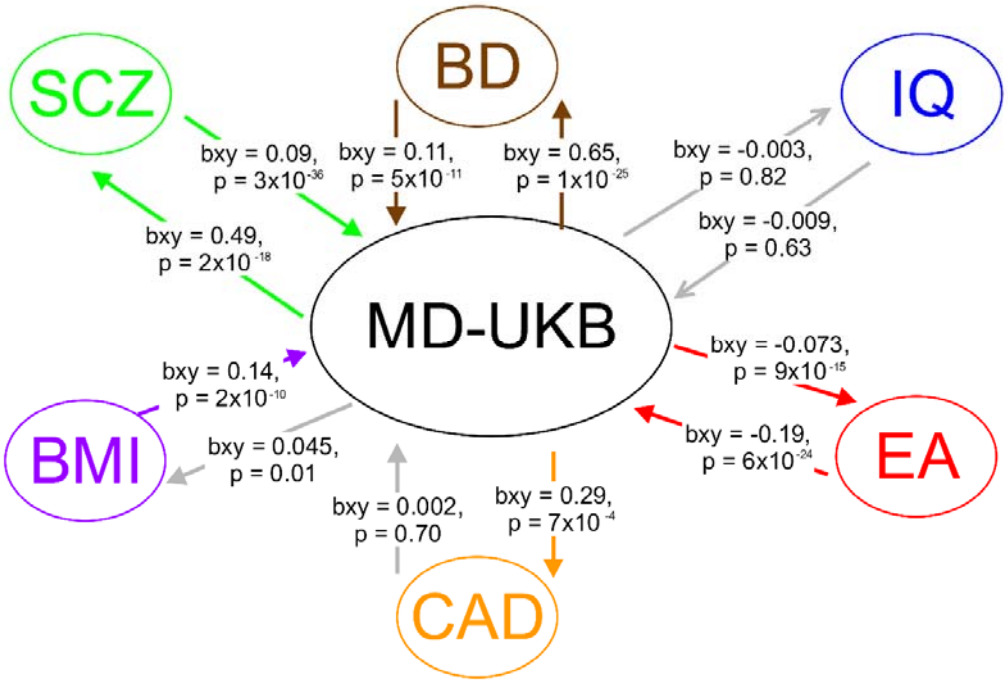
Shared and distinct relationships with mood disorders and inferred causality

Bidirectional Mendelian randomisation (MR) was used to investigate previously-described relationships between mood disorder phenotypes (MD-UKB, PGC BD, MD-UKBcBD) and external traits: SCZ, educational attainment (EA), intelligence (IQ), body mass index (BMI) and coronary artery disease (CAD). Additional analyses were performed for BDcMD-UKB, but associations with BDcMD-UKB as an exposure could not be tested because few significant loci were left following conditioning. Similarly, MR associations with PGC BD should be interpreted cautiously, as there were only 19 loci reaching genome-wide significance in this analysis, several of which are removed as potentially pleiotropic in the analyses below.

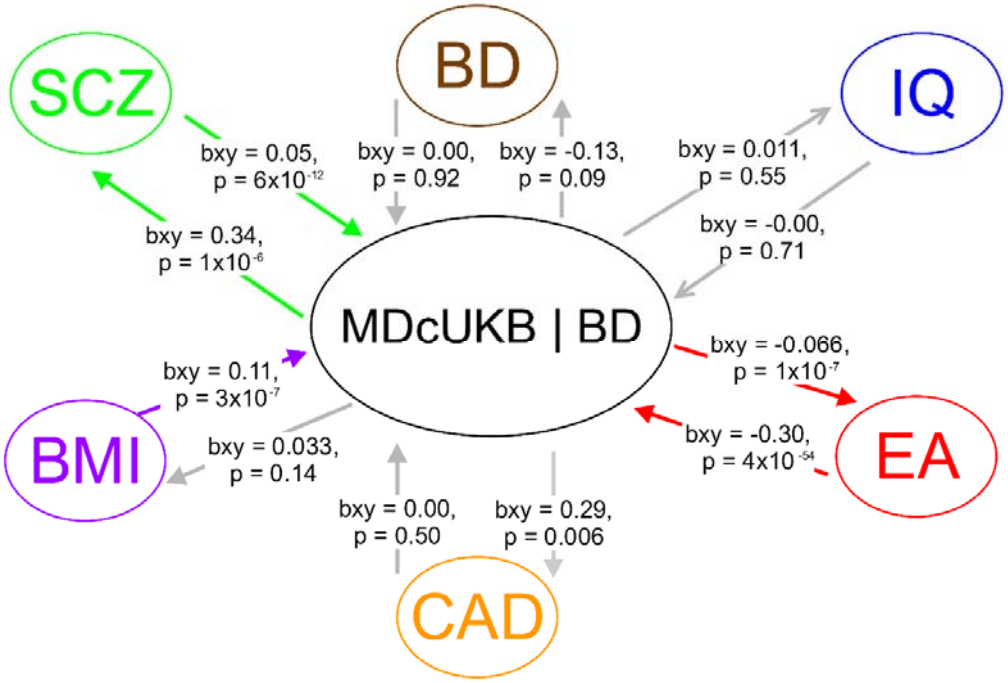
Results from MR analyses are shown in Figure 4 (Supplementary Tables 23-26). A positive bidirectional relationship was observed between MD-UKB and PGC BD, and this was lost in conditional analyses. We also observed positive bidirectional relationships between SCZ and both MD-UKB and PGC BD, including in conditional analyses. This is consistent with psychiatric disorders acting as causal risk factors for the development of further psychiatric disorders, or being correlated with other causal risk factors, including (but not limited to) the observed shared genetic basis.


SCZ
IQ
MD-UKB-BD
BMI
EA
CAD
bxy = 0.11,
p = 6x10-63
bxy = 0.73,
p = 1x10-45
bxy = 0.00,
p = 0.96
bxy = -0.024,
p = 0.07
bxy = -0.046,
p = 1x10-7
bxy = -0.18,
p = 2x10-23
bxy = 0.14,
p = 2x10-10
bxy = 0.058,
p = 0.001
bxy = 0.00,
p = 0.60
bxy = 0.35,
p = 2x10-5

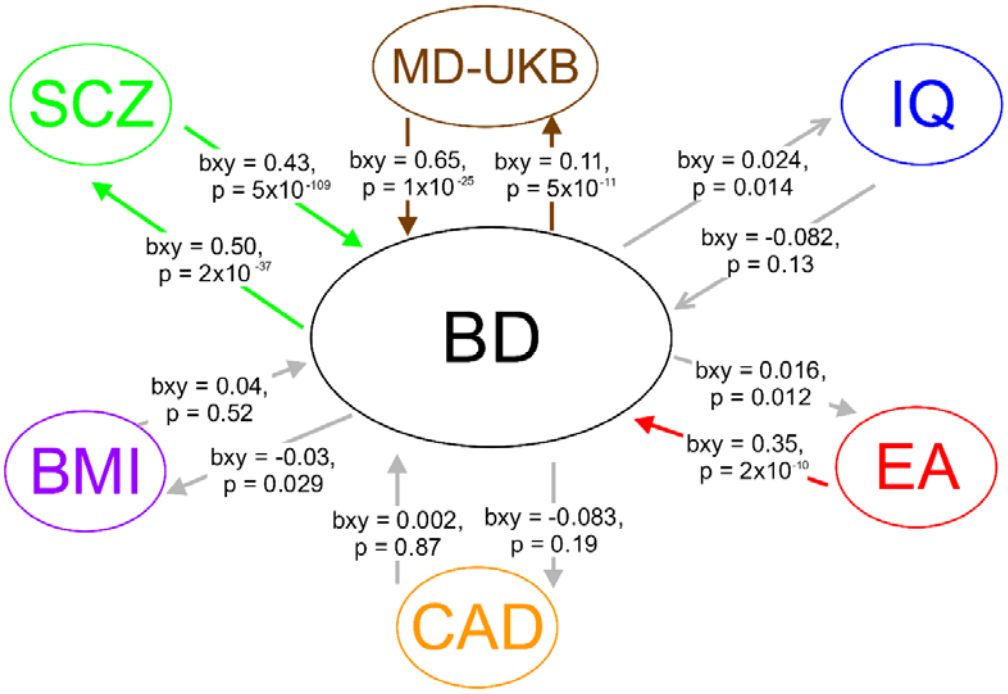
a)


SCZ
BD
IQ
MD-UKB
BMI
EA
CAD
bxy = 0.09,
p = 3x10-36
bxy = 0.11,
p = 5x10-11
bxy = 0.65,
p = 1x10-25
bxy = -0.003,
p = 0.82
bxy = -0.009,
p = 0.63
bxy = 0.49,
p = 2x10-18
bxy = -0.073,
p = 9x10-15
bxy = -0.19,
p = 6x10-24
bxy = 0.14,
p = 2x10-10
bxy = 0.045,
p = 0.01
bxy = 0.002,
p = 0.70
bxy = 0.29,
p = 7x10-4

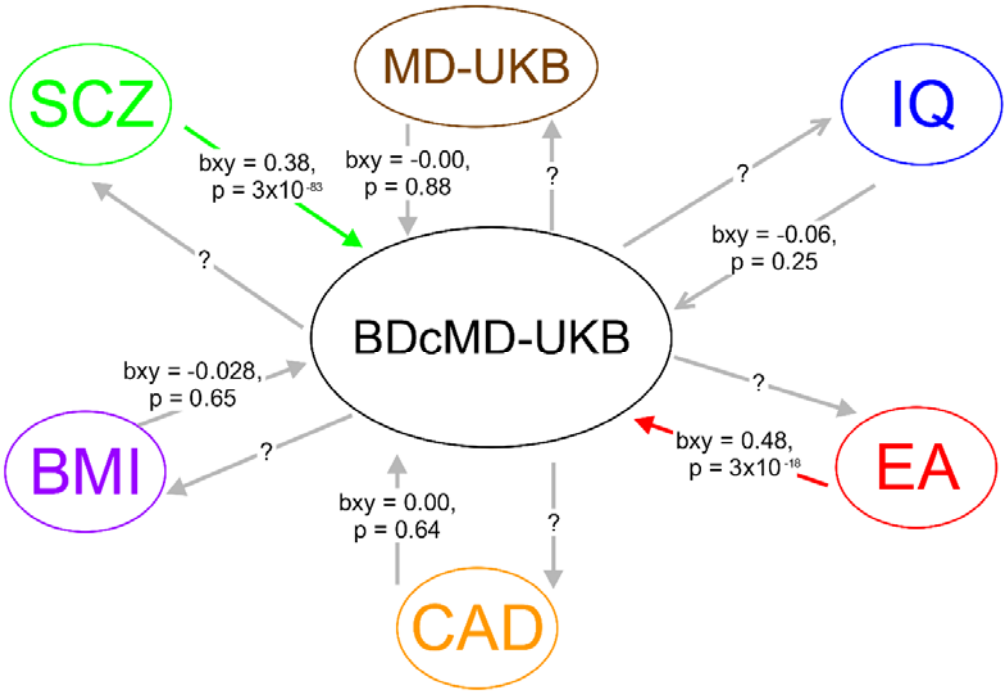
b)


SCZ
BD
IQ
bxy = 0.05,
p = 6x10-12
bxy = 0.00,
p = 0.92
bxy = -0.13,
p = 0.09
bxy = 0.011,
p = 0.55
bxy = 0.34,
p = 1x10-6
bxy = -0.00,
p = 0.71
MDcUKB | BD
bxy = -0.066,
p = 1x10-7
bxy = 0.11,
p = 3x10-7
BMI
bxy = 0.033,
p = 0.14
bxy = -0.30,
p = 4x10-54
EA
bxy = 0.00,
p = 0.50
bxy = 0.29,
p = 0.006
CAD

c)


SCZ
MD-UKB
IQ
bxy = 0.43,
p = 5x10-109
bxy = 0.65,
p = 1x10-25
bxy = 0.11,
p = 5x10-11
bxy = 0.024,
p = 0.014
bxy = 0.50,
p = 2x10-37
bxy = -0.082,
p = 0.13
BD
bxy = 0.04,
p = 0.52
bxy = 0.016,
p = 0.012
BMI
bxy = -0.03,
p = 0.029
bxy = 0.35,
p = 2x10-10
EA
bxy = 0.002,
p = 0.87
bxy = -0.083,
p = 0.19
CAD

d)



e)

Figure 4: GSMR results from analyses with the main meta-analysis (a: MD-UKB-BD), and the major depression and bipolar disorder analyses before and after conditioning (b: MD-UKB; c: MD-UKBcBD; d: PGC BD; e: BDcMD-UKB). Exposures are MD-UKB, PGC BD, intelligence (IQ), educational attainment (EA), coronary artery disease (CAD), body mass index (BMI), and schizophrenia (SCZ).

The relationship with EA differed between the mood disorders - there was a negative bidirectional relationship between EA and MD-UKB (which remained in MD-UKBcBD), but a positive bidirectional relationship between EA and PGC BD (albeit with only nominal significance from PGC BD to EA). In contrast, no significant relationship was observed between mood phenotypes and IQ. This is consistent with a causal role of education (or correlates of education) on mood disorder, with a weaker reciprocal effect of (correlates of) mood disorder altering the length of education.

A positive association was seen from BMI to MD-UKB (and to MD-UKBcBD), but not from MD-UKB to BMI. In contrast, only a nominally significant negative relationship was seen from PGC BD to BMI. Finally, a positive association from MD-UKB to CAD was observed; no relationship was observed between CAD and the PGC BD phenotypes.

Sensitivity analysis using down-sampled PGC MD

A sensitivity analysis was performed using PGC MD without 23andMe and without the UK Biobank participants included in the original paper. Results from this analysis are reported in full in the Supplementary Materials. Compared to MD-UKB-BD, the down-sampled analysis (dsMD-UKB-BD) was more similar to PGC BD. However, there remained a greater overall similarity to PGC MD. 19 loci reached genome-wide significance in dsMD-UKB-BD, including nine (20%) of those reported in PGC MD, compared with two (11%) of those reported in PGC BD. The SNP-heritability of dsMD-UKB-BD (11%) was closer to PGC MD (9%) than to PGC BD (20%). A comparison of the genetic correlation of dsMD-UKB-BD with published traits showed a mixed set of results, with some correlations becoming more similar to those with PGC BD (such as schizophrenia: down-sampled $r_g = 0.61$, MD-UKB $r_g = 0.35$, PGC BD $r_g = 0.7$), while others remain more similar to PGC MD (such as ADHD, down-sampled $r_g = 0.48$, MD-UKB $r_g = 0.45$, PGC BD $r_g = 0.14$). Notably, a significant negative genetic correlation with intelligence was observed (down-sampled $r_g = -0.13$, $p = 4x10^{-7}$). This appears to result from excluding the 23andMe participants from PGC MD (Supplementary Materials).

Discussion

We identified 73 genetic loci by meta-analysing cohorts of major depression and bipolar disorder, including 24 loci not previously reported as associated with mood disorders. In gene-level analyses, 361 genes were associated with the combined phenotypes. Gene set analyses indicate key roles for the targets of RNA processing proteins, for neurobiological and neurodevelopmental processes, and for genes previously-associated with psychiatric disorders, biological annotations that have been previously reported in multiple psychiatric and behavioural GWAS [11,12,21,54]. Results from the mood disorders meta-analyses are strongly genetically correlated with psychiatric phenotypes, but also showed correlations with reproductive development, general health behaviours, socioeconomic traits, and paternal mortality.

Synthesising results across our analyses, there is a general pattern suggesting that the loci and findings from MD-UKB-BD have more in common with those from MD-UKB than from PGC BD. This could result from the greater power of MD-UKB compared to PGC BD. To test this, we conducted a sensitivity analysis, down-sampling PGC MD so that the downsampled MD-UKB more closely matched the power of PGC BD. The results of this analysis suggest that the difference in power increases the similarity of MD-UKB-BD to the MD results. However, this pattern of similarity remained in dsMD-UKB-BD, suggesting it is not entirely the result of the power difference. An alternative (but not exclusive) explanation is that depressive symptoms are both the unifying feature of the mood disorders and the core feature of major depression. As such, meta-analyses of depression and bipolar cohorts may primarily be analyses of depressive symptoms, and as such researchers interested in the study of depressive symptoms may benefit from

combining such cohorts in their analyses, despite the increase in heterogeneity that may be expected by adopting such a strategy.

A further explanation for the greater similarity of MD-UKB-BD to MD could be the presence of BD2 cases in PGC BD (although BD1 cases comprised the majority of the PGC BD cases). This follows from another striking feature of our analyses, the greater genetic similarity of the BD2 cohort (compared to the BD1 cohort) to subsets of UKB MD. In this, we build on evidence from PGC BD, which noted that polygenic risk scores from PGC MD partially distinguish individuals with BD2 from those with BD1[12]. This further supports the integration of individuals with BD2 in the study of depressive symptoms. Furthermore, this reinforces the idea of a genetic mood disorder spectrum, extending from BD1 (with greater genetic similarity to SCZ [12]) through BD2 to MD [1]. Potentially this could extend to the subtypes of MD, with our heritability analyses suggesting rMD may be more similar to PGC BD subtypes than is sMD. This is also supported by analyses included in the Supplementary Materials, which showed polygenic risk scores derived from PGC BD were significantly higher in rMD compared to sMD cases. However, this difference in depression case types requires independent replication, ideally in clinically-defined cohorts.

Our results highlight several differences between the genetics of major depression and bipolar disorder, and this is particularly illustrated in the relationship between each phenotype and EA[55]. The positive genetic correlation between EA and PGC BD, and the negative correlation between EA and MD-UKB, are accompanied by the lack of genetic correlation of either disorder with IQ. This stands in contrast to schizophrenia, which is positively genetically correlated with EA, but negatively correlated with IQ[13]. Our Mendelian randomisation analyses are consistent with a bidirectional influence of EA on risk for mood disorders (and vice versa), with

different directions of effect in the two mood disorders. These MR results are also consistent with no significant influence of IQ on risk for either MD or PGC BD. Furthermore, our MR analyses of CAD with MD-UKB were relatively well powered and are consistent with depression increasing the risk for CAD. The interpretation of MR results is often difficult, especially in the case of complex traits and when the ascertainment of cases varies[24,56,57]. This is particularly the case for analyses for which there are relatively few (< 20) variants used as instruments, such as the PGC BD analyses presented, which should be interpreted cautiously in light of this caveat.

A further area of divergence between the MD-UKB and PGC BD results is the enrichment of cell-type specificity for genes associated with each trait. It is noticeable that the cell-types that are more associated with PGC BD (pyramidal neurons and striatal interneurons) are those that were similarly enriched in previous analyses of schizophrenia [35]. Enrichments more apparent in MD-UKB (neuroblasts, adult dopaminergic neurons, embryonic GABAergic neurons) were much weaker in schizophrenia, but were enriched (amongst other cell-types) in analyses of neuroticism[58]. In addition, the association with serotonergic neurons was stronger and had a higher rank in MD-UKB when compared to PGC BD, which is of interest given the use of drugs targeting the serotonergic system in the treatment of depression[59]. Cell-type enrichment analyses are still novel, and caution needs to be taken in interpretation, especially given that the single-cell data used comes from mice[35,60]. Recent examples of cell-type enrichment analyses in psychiatric and behavioural traits indicate traits primarily differ in the degree or rank of enrichment, rather than there being discrete associations between traits and certain cell-types[35,37,58,60,61]. This is further demonstrated by the differences between mood disorders observed herein.

Our results indicate some genetic differences between major depression and bipolar disorder, but it should be noted that we find far more evidence of shared genetics, particularly in terms of the increase in variant discovery, the enrichment of neurobiological gene sets and the strong genetic correlations with other psychiatric disorders, consistent with other observations in psychiatric genetics[11–13,21,49,51,54,62]. Finally, our data are consistent with the existence of a partially genetic mood disorder spectrum and suggest depression as their common symptom.

Acknowledgements

Full acknowledgements from the PGC MD and PGC BD studies are included in the Supplementary Materials. We are deeply indebted to the investigators who comprise the PGC, and to the hundreds of thousands of subjects who have shared their life experiences with PGC investigators. A full list of funding from the PGC MD and PGC BD studies is included in the Supplementary Materials. The PGC has received major funding from the US National Institute of Mental Health and the US National Institute of Drug Abuse (U01 MH109528 and U01 MH1095320). PFS gratefully acknowledges support from the Swedish Research Council (Vetenskapsrådet, award D0886501). This study represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. NIHR high performance computing facilities were funded with capital equipment grants from the GSTT Charity (TR130505) and Maudsley Charity (980). We acknowledge the continued support of the NL Genetic Cluster Computer (http://www.geneticcluster.org/) hosted

by SURFsara in the management and curation of PGC data. This research has been carried out using the UK Biobank, application numbers 4844, 6818, and 16577.

Conflicts of Interest

OA Andreassen has received speaker fees from Lundbeck. ATF Beekman is on speaker's bureaus for Lundbeck and GlaxoSmithKline. G Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly. G Crawford is a cofounder of Element Genomics. E Domenici was formerly an employee of Hoffmann–La Roche and a consultant to Roche and Pierre-Fabre. J Nurnberger is an investigator for Janssen and was an investigator for Assurex. SA Paciga is an employee of Pfizer. JA Quiroz was formerly an employee of Hoffmann–La Roche. S Steinberg, H Stefansson, K Stefansson and TE Thorgeirsson are employed by deCODE Genetics/Amgen. PF Sullivan reports the following potentially competing financial interests. Current: Lundbeck (advisory committee, grant recipient). Past three years: Pfizer (scientific advisory board), Element Genomics (consultation fee), and Roche (speaker reimbursement). AH Young has given paid lectures and is on advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier, Livanova. AH Young is Lead Investigator for Embolden Study (Astrazenaca), BCI Neuroplasticity study and Aripiprazole Mania Study, which are investigator-initiated studies from Astrazenaca, Eli Lilly, Lundbeck, and Wyeth. All other authors declare no financial interests or potential conflicts of interest.

References

1. Craddock, N. & Owen, M. J. The Kraepelinian dichotomy--going, going... but still not gone. *Br. J. Psychiatry* **196,** 92–95 (2010).
2. Kessler, R. C. *et al.* Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* **62,** 593–602 (2005).
3. Weissman, M. M. *et al.* Cross-national epidemiology of major depression and bipolar disorder. *JAMA* **276,** 293–299 (1996).
4. Steel, Z. *et al.* The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int. J. Epidemiol.* (2014). doi:10.1093/ije/dyu038
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. (American Psychiatric Pub, 2013).
6. Cassano, G. B. *et al.* The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. *Am. J. Psychiatry* **161,** 1264–1269 (2004).
7. Fiedorowicz, J. G. *et al.* Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am. J. Psychiatry* **168,** 40–48 (2011).
8. Ratheesh, A. *et al.* A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. *Acta Psychiatr. Scand.* **135,** 273–284 (2017).
9. McGuffin, P. *et al.* The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **60,** 497–502 (2003).
10. Polderman, T. J. C. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat. Genet.* **47,** 702–709 (2015).
11. Wray, N. R. *et al.* Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* **50,** 668–681 (2018).
12. Stahl, E. *et al.* Genomewide association study identifies 30 loci associated with bipolar disorder. *bioRxiv* 173062 (2017). doi:10.1101/173062
13. The Brainstorm Consortium *et al.* Analysis of shared heritability in common disorders of the brain. *Science* **360,** eaap8757 (2018).
14. Davis, K. A. S. *et al.* Mental health in UK Biobank: development, implementation

and results from an online questionnaire completed by 157 366 participants. *BJPsych Open* **4,** 83–90 (2018).

15. Coleman, J. R. I., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, UK Biobank Mental Health Consortium, Eley, T. C. & Breen, G. Genome-wide gene-environment analyses of depression and reported lifetime traumatic experiences in UK Biobank. *bioRxiv* 247353 (2018). doi:10.1101/247353
16. Hyde, C. L. *et al.* Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nat. Genet.* **48,** 1031–1036 (2016).
17. Gilly, A., Tachmazidou, I. & Zeggini, E. Meta-analysis of summary statistics from quantitative trait association studies with unknown sample overlap. in *GENETIC EPIDEMIOLOGY* **39,** 552–553 (WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 2015).
18. Southam, L. *et al.* Whole genome sequencing and imputation in isolated populations identify genetic associations with medically-relevant complex traits. *Nat. Commun.* **8,** 15606 (2017).
19. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4,** 7 (2015).
20. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. FUMA: Functional mapping and annotation of genetic associations. *bioRxiv* 110023 (2017). doi:10.1101/110023
21. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511,** 421–427 (2014).
22. Team, R. C. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2013. *Document freely available on the internet at: http://www. r-project. org* (2015).
23. Warnes, G. R. *et al.* gplots: Various R Programming Tools for Plotting Data. (2016).
24. Zhu, Z. *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun.* **9,** 224 (2018).
25. Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88,** 76–82 (2011).

26. Aschard, H., Vilhjálmsson, B. J., Joshi, A. D., Price, A. L. & Kraft, P. Adjusting for heritable covariates can bias effect estimates in genome-wide association studies. *Am. J. Hum. Genet.* **96,** 329–339 (2015).
27. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47,** 291–295 (2015).
28. Tukey, W. J. Bias and confidence in not-quite large samples. *Ann. Math. Stat.* **29,** 614 (1958).
29. Quenouille, M. H. Notes on Bias in Estimation. *Biometrika* **43,** 353–360 (1956).
30. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11,** e1004219 (2015).
31. Maston, G. A., Evans, S. K. & Green, M. R. Transcriptional regulatory elements in the human genome. *Annu. Rev. Genomics Hum. Genet.* **7,** 29–59 (2006).
32. Koscielny, G. *et al.* Open Targets: a platform for therapeutic target identification and validation. *Nucleic Acids Res.* (2016). doi:10.1093/nar/gkw1055
33. Liberzon, A. *et al.* The Molecular Signatures Database (MSigDB) hallmark gene set collection. *Cell Syst* **1,** 417–425 (2015).
34. Consortium, G. TEx. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* **348,** 648–660 (2015).
35. Skene, N. G. *et al.* Genetic identification of brain cell types underlying schizophrenia. *Nat. Genet.* **50,** 825–833 (2018).
36. Aulchenko, Y. S., Ripke, S., Isaacs, A. & van Duijn, C. M. GenABEL: an R library for genome-wide association analysis. *Bioinformatics* **23,** 1294–1296 (2007).
37. Savage, J. E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat. Genet.* (2018). doi:10.1038/s41588-018-0152-6
38. Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* (2018). doi:10.1038/s41588-018-0147-3
39. Locke, A. E. *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518,** 197–206 (2015).
40. Nelson, C. P. *et al.* Association analyses based on false discovery rate implicate

new loci for coronary artery disease. *Nat. Genet.* **49,** 1385–1391 (2017).

41. Turley, P. *et al.* Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat. Genet.* 118810 (2018).
42. Hill, W. D. Comment on 'Large-Scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets' by Lam et al. *Twin Res. Hum. Genet.* **21,** 84–88 (2018).
43. Loh, P.-R., Kichaev, G., Gazal, S., Schoech, A. P. & Price, A. L. Mixed model association for biobank-scale data sets. *bioRxiv* 194944 (2017). doi:10.1101/194944
44. Mbarek, H. *et al.* Genome-Wide Significance for PCLO as a Gene for Major Depressive Disorder. *Twin Res. Hum. Genet.* **20,** 267–270 (2017).
45. Goes, F. S. *et al.* Genome-wide association study of schizophrenia in Ashkenazi Jews. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **168,** 649–659 (2015).
46. Sullivan, P. F. *et al.* Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. *Mol. Psychiatry* **14,** 359–375 (2009).
47. Noble, E. P. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **116B,** 103–125 (2003).
48. Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48,** 481–487 (2016).
49. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* **381,** 1371 (2013).
50. Ruderfer, D. M. *et al.* Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Mol. Psychiatry* **19,** 1017–1024 (2013).
51. Demontis, D. *et al.* Discovery Of The First Genome-Wide Significant Risk Loci For ADHD. *bioRxiv* 145581 (2017). doi:10.1101/145581
52. Deary, V. *et al.* Genetic contributions to self-reported tiredness. *Mol. Psychiatry* (2017). doi:10.1038/mp.2017.5
53. Harris, S. E. *et al.* Molecular genetic contributions to self-rated health. *Int. J. Epidemiol.* **46,** 994–1009 (2017).
54. Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal,

immune and histone pathways. *Nat. Neurosci.* **18,** 199–209 (2015).

55. Peyrot, W. J. *et al.* The association between lower educational attainment and depression owing to shared genetic effects? Results in ~25,000 subjects. *Mol. Psychiatry* **20,** 735–743 (2015).
56. Verbanck, M., Chen, C.-Y., Neale, B. & Do, R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat. Genet.* **50,** 693–698 (2018).
57. Hemani, G., Bowden, J. & Davey Smith, G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum. Mol. Genet.* (2018). doi:10.1093/hmg/ddy163
58. Nagel, M. *et al.* Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat. Genet.* (2018). doi:10.1038/s41588-018-0151-7
59. National Institute for Healthcare and Excellence. *Depression in adults: recognition and management: Clinical guideline [CG90]*. (2009).
60. Coleman, J. R. I. *et al.* Biological annotation of genetic loci associated with intelligence in a meta-analysis of 87,740 individuals. *Mol. Psychiatry* (2018). doi:10.1038/s41380-018-0040-6
61. Jansen, P. R., Watanabe, K., Stringer, S., Skene, N. & Bryois, J. Genome-wide Analysis of Insomnia (N= 1,331,010) Identifies Novel Loci and Functional Pathways. *bioRxiv* (2018).
62. Duncan, L. *et al.* Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa. *Am. J. Psychiatry* **174,** 850–858 (2017).