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Quantifying Between-Cohort and Between-Sex Genetic Heterogeneity in Major Depressive Disorder

Maciej Trzaskowski¹, Divya Mehta^{1,2}, Wouter Peyrot³, David Hawkes⁴, Daniel Davies⁵, David Howard⁶, Kathryn E. Kemper¹, Julia Sidorenko¹, Robert Maier^{1,7}, Stephan Ripke^{8,9,10}, Manuel Mattheisen^{11,12}, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Bernhard T Baune¹³, Hans J. Grabe¹⁴, Andrew C Heath¹⁵, Lisa Jones¹⁶, Ian Jones¹⁷, Pamela AF Madden¹⁵, Andrew M. McIntosh^{18,19}, Gerome Breen^{20,21}, Cathryn M. Lewis^{20,21}, Anders D. Børglum^{12,23}, Patrick F. Sullivan^{24,25,26}, Nicholas G. Martin²⁷, Kenneth S. Kendler²⁸, Douglas F. Levinson²⁹, Naomi R. Wray^{1,30†}

¹Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia.

²School of Psychology and Counselling, Queensland University of Technology, Brisbane, Australia.

³Department of Psychiatry, Vrije Universiteit Medical Center and GGZ in Geest, Amsterdam, The Netherlands.

⁴AGRF, The University of Queensland, Brisbane, Queensland, Australia.

⁵Department of Psychiatry, Behavioural and Clinical Neuroscience Institute and Developmental Psychiatry, Cambridge University, UK.

⁶Division of Psychiatry, University of Edinburgh, Edinburgh, EH10 5HF, UK.

⁷Analytic and Translational Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.

⁸Medical and Population Genetics, Broad Institute, Cambridge, MA, USA.

⁹Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA.

¹⁰Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Germany.

¹¹Department of Biomedicine, Aarhus University, Aarhus, Denmark.

¹²iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark.

¹³Department of Psychiatry, The University of Melbourne.

¹⁴Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany.

¹⁵Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US.

¹⁶Institute of Health & Society, University of Worcester, Worcester, UK

¹⁷MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

¹⁸Division of Psychiatry, University of Edinburgh, Edinburgh, UK.

¹⁹Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK.

²⁰MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, UK.

²¹NIHR BRC for Mental Health, King's College London, London, UK.

²²Department of Medical and Molecular Genetics, King's College London, London, UK.

²³Department of Biomedicine and iSEQ-Centre for Integrative Sequencing, Aarhus University, Denmark.

²⁴Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

²⁵Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

²⁶Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

²⁷Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.

²⁸Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA.

²⁹Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA.

³⁰Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia.

† Corresponding author: naomi.wray@uq.edu.au

ABSTRACT

Major depressive disorder (MDD) is clinically heterogeneous with prevalence rates twice as high in women as in men. There are many possible sources of heterogeneity in MDD most of which are not measured in a sufficiently comparable way across study samples. Here, we assess genetic heterogeneity based on two fundamental measures, between-cohort and between-sex heterogeneity. First, we used genome-wide association study (GWAS) summary statistics to investigate between-cohort genetic heterogeneity using the 29 research cohorts of the Psychiatric Genomics Consortium (PGC; N cases = 16,823, N controls = 25,632) and found that some of the cohort heterogeneity can be attributed to ascertainment differences (such as recruitment of cases from hospital vs community sources). Second, we evaluated between-sex genetic heterogeneity using GWAS summary statistics from the PGC, Kaiser Permanente GERA, UK Biobank and the Danish iPSYCH studies but did not find convincing evidence for genetic differences between the sexes. We conclude that there is no evidence that the heterogeneity between MDD data sets and between sexes reflects genetic heterogeneity. Larger sample sizes with detailed phenotypic records and genomic data remain the key to overcome heterogeneity inherent in assessment of MDD.

KEYWORDS: MDD, depression, genetic heterogeneity, sex differences, LD score regression.

INTRODUCTION

Major Depressive Disorder (MDD) is a common debilitating disorder with lifetime risk of ~15% (R. C. Kessler & Bromet, 2013; Lohoff, 2010). Genetic factors contribute to etiology of MDD with heritability estimated to be ~37% (Kendler, Gatz, Gardner, & Pedersen, 2006; Sullivan, Neale, & Kendler, 2000) of which about one-third is tracked by common-genetic variants (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Wray et al., 2018). Non-genetic factors also contribute and environmental risk factors include childhood psychological trauma (Chapman et al., 2004; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Vythilingam et al., 2002), social isolation (Bruce & Hoff, 1994), and medical conditions,

such as cardiovascular disease (Fiedorowicz, 2014; Fraguas Jr et al., 2007; Huffman, Celano, Beach, Motiwala, & Januzzi, 2013). Most complex disorders are considered to be heterogeneous at clinical presentation. For MDD, heterogeneity is inherent in the diagnostic framework since diagnosis is achieved through different combinations of endorsements of at least five out of nine criteria in the context of depressed mood for most of the day every day for two weeks (Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria). Heterogeneity in symptom profiles between individuals reflects not only the symptoms endorsed, but for some criteria (those assessing sleep, weight/appetite and psychomotor function) the endorsement can reflect either increase or decrease (or both). It is plausible that these clinical differences reflect different biological pathways. The lack of a biological “gold standard” definition in psychiatric illness is well recognised (Kapur, Phillips, & Insel, 2012), and a key question for the field is whether genetic heterogeneity underpins phenotypic heterogeneity (Fanous & Kendler, 2005), and if genome-wide genetic data can support analyses that demonstrate genetic heterogeneity (Han et al., 2016). Here, we assess genetic heterogeneity based on two fundamental measures available to us, between-cohort and between-sex heterogeneity. While non-biological factors (such as ascertainment strategy) could contribute to both between-cohort and between-sex heterogeneity, evidence for between-sex heterogeneity may reflect, at least in part, biological differences.

Prevalence rates of MDD in women that are double those of men are consistently reported in epidemiological studies, with lifetime risk approximately 0.2 for females and 0.1 for males (Ronald C. Kessler, 2003) Women tend to have younger age of onset, greater comorbidity with panic and other anxiety disorders, whereas men exhibit stronger comorbidity with alcohol dependence or abuse (Schuch, Roest, Nolen, Penninx, & de Jonge, 2014). Attempts to link the epidemiological differences to biological differences have been less consistent. Some twin studies reported significantly higher heritability in females (0.42, 95% CI=0.36-0.47) than males (0.29, 95% CI=0.19-0.38), and with genetic correlation significantly different from 1 ($r_g \sim 0.60$, 95% CI=0.31-0.99) (Kendler et al., 2006). Other studies failed to find differences

between sexes (Fernandez-Pujals et al., 2015). Drawing strong conclusions may be confounded by reporting biases as males are more likely to under-report their symptoms when compared to females (Hunt, Auriemma, & Cashaw, 2003; Thornicroft et al., 2017).

We use genome-wide association study (GWAS) summary statistics data to investigate genetic heterogeneity of MDD. We study between-cohort genetic heterogeneity using data from the 29 independent studies that comprise the wave 2 PGC-MDD study (PGC29 (Wray et al., 2018)). We also investigate genetic heterogeneity by sex using GWAS summary statistics from PGC29 and three other large data sets. We evaluate between-cohort and between-sex genetic heterogeneity estimates of SNP-heritabilities and genetic correlations. These estimates of genetic parameters, calculated from genome-wide data, provide single statistic summaries of the data. Specifically, differences in SNP-heritability estimates between samples could imply real differences in the relative magnitude of genetic risk effect sizes between samples or could reflect biases due to ascertainment characteristics of the sample. In contrast, an estimate of a genetic correlation less than one may reflect differences in the relative ordering of genetic risk effects between samples. It is possible for SNP-heritabilities to differ between samples but the genetic correlations to be one.

MATERIALS & METHODS

Between-cohort heterogeneity

We investigate heterogeneity between cohorts from the PGC Working Group for MDD (PGC-MDD) (Major Depressive Disorder Working Group of the Psychiatric et al., 2013), which comprises 29 cohorts (PGC29, 10 from wave 1 (Major Depressive Disorder Working Group of the Psychiatric et al., 2013) and 19 from wave 2 (Wray et al., 2018)), totalling 16,815 cases (68% female) and 25,485 controls (51% female) (**Table 1, Supplementary Table 1**). Cohorts represent individual studies in which cases and controls were imputed together to the 1000 Genomes reference panel (Genomes Project et al., 2010) from a common set of SNPs that had been processed through a common quality control (QC) pipeline (Wray et al., 2018). For

the majority of cohorts (but not all), cases and controls were collected by the same research group and were genotyped together on the same genotyping array. All 29 case cohorts passed a structured methodological review by MDD assessment experts (DF Levinson and KS Kendler). Cases were required to meet international consensus criteria (DSM-IV, International Statistical Classification of Diseases (ICD)-9, or ICD-10) (American Psychiatric Association, 1994; World Health Organization, 1978, 1992) for a lifetime diagnosis of MDD established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists, or medical record review. Nonetheless, there were differences in ascertainment across cohorts (**Supplementary Table 1**). For example the RADIANT cohort (rad3) (C. M. Lewis et al., 2010) recruited cases of clinically assessed recurrent MDD, which being more severe have lower lifetime risk ~5% (McGuffin, Katz, Watkins, & Rutherford, 1996), compared to community samples such as the QIMR cohorts (qi3c, qi6c, qio2) assessed by self-report interview and with lifetime risk ~24% (Mosing et al., 2009). To capture heterogeneity due to ascertainment, we coded the 29 cohorts as identified in community, psychiatric outpatient, psychiatric inpatients, or mixed in-/out-patient settings (**Supplementary Table 1**).

Between-sex heterogeneity

We investigate between sex heterogeneity using four large MDD data sets (**Table 1**). In addition to PGC29, we used the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort (Banda et al., 2015) (where electronic medical records from the Kaiser Permanente healthcare system were used to identify cases as individuals being treated clinically for MDD, and controls had no recorded treatment for any psychiatric disorder), the Danish iPSYCH cohort (where national hospital records identified cases as those ever treated clinically for MDD and controls as those who have not), and the volunteer UK Biobank (Bycroft et al., 2018; Lane et al., 2016) (UKB) study. UKB cases were those with either recorded ICD10 codes for MDD (F32, F33) or self-report for seeking treatment for nerves, anxiety or depression; for detailed description of the “broad depression” definition see reference (Howard et al., 2018)). Exclusions for both cases and controls were those with recorded

schizophrenia, bipolar or mental retardation diagnoses or prescriptions associated with these disorders. Additional exclusions for controls included those with recorded anxiety, phobic or autistic spectrum disorders. In all studies, cases and controls were unrelated. GWAS summary statistics for each cohort used the same methods as for PGC29.

Statistical methods

We use GWAS summary statistics and linkage disequilibrium (LD) score analysis (LDSC) (B. K. Bulik-Sullivan et al., 2015) to estimate the total proportion of variance in liability attributable to SNPs genome-wide (i.e., SNP-heritability). Bivariate LDSC was used to estimate the genetic correlation tagged by genome-wide SNPs (r_g) between two traits. LDSC has been applied widely to GWAS summary statistics of psychiatric (Anttila et al., 2018) and other disorders (B. Bulik-Sullivan et al., 2015), and results have been shown to agree well with estimates made from full individual-level genotype and phenotype data using linear mixed model analysis (e.g., GREML (Yang et al., 2010)), as long as the LD reference sample is drawn from a population that appropriately reflects the samples contributing the GWAS summary statistics (Yang et al., 2015). A key advantage of LDSC is the minimal computational requirements compared to methods that use individual level data, and the ability to differentiate between genomic inflation due to polygenicity and due to population stratification. Disadvantages of LDSC are that standard errors (s.e.) of estimates can be (about 50%) higher compared to when estimates are based on full data, particularly for r_g estimates (Ni, Moser, Schizophrenia Working Group of the Psychiatric Genomics, Wray, & Lee, 2018).

SNP-heritability is estimated on the observed binary scale h_{SNP-cc}^2 , but these estimates depend on the proportion of cases in the sample (P) and so are not easily comparable across cohorts. Hence, for improved interpretability and comparison across studies, h_{SNP-cc}^2 is transformed to the liability scale h_{SNP}^2 (Lee, Wray, Goddard, & Visscher, 2011) based on normal distribution theory, given an assumed lifetime risk of disease in the population (K):

$$h_{SNP}^2 = h_{SNP-cc}^2 \frac{(K(1-K))^2}{P(1-P)z^2} \quad [1]$$

where z is the height of the standard normal density function when truncated at proportion K . However, this transformation assumes that controls are screened. Peyrot et al (2016) (Peyrot, Boomsma, Penninx, & Wray, 2016) showed that when the proportion of controls that are unscreened is u , then transformation should be

$$h_{SNP}^2 = h_{SNP-cc}^2 \frac{(K(1-K))^2}{P(1-P)(1-uK)^2 z^2} \quad [2]$$

which reduces to equation [1] when all controls are screened, $u = 0$. When diseases are uncommon, assuming controls are screened when they are not makes little impact (Peyrot et al., 2016). However, for very common disorders, such as MDD, the difference is not trivial. For example, for $K = 0.15$, $h_{SNP-cc}^2 = 0.15$, $P = 0.5$, then $h_{SNP}^2 = 0.18$ when controls are screened and 0.24 when unscreened. The r_g estimates are robust to P , K and u , since these factors contribute to both numerator and denominator of the correlation (which is defined as the estimate of the additive genetic covariance divided by the product of the square root of the SNP-heritabilities for the two traits). Hence r_g estimates are robust to ascertainment practices and approximately the same where estimated on the case-control observed scale or liability scales (B. Bulik-Sullivan et al., 2015). If the same genetic effects contribute to disease risk between sexes or between cohorts then r_g is expected to be 1.

It was not possible to compare h_{SNP}^2 of each PGC29 cohort, because the per-cohort estimates had high s.e. (e.g. a cohort of 500 cases and 500 controls would be expected to produce h_{SNP}^2 with standard error of at minimum 0.38 (Visscher et al., 2014)). Instead we estimated the h_{SNP}^2 attributed to a cohort by evaluating its contribution to h_{SNP}^2 estimates calculated from 500 random samplings of cohorts drawn from the 29 PGC29 cohorts. In each sampling, we randomly selected cohorts until the total sample size was ≥ 5000 , then used the GWAS summary statistics meta-analysed (weighted by s.e.) in LDSC to estimate h_{SNP}^2 assuming lifetime risk of $K = 0.15$, and assuming controls are screened (equation [1]). To determine the contribution to the h_{SNP}^2 estimate from each cohort we fitted a linear model

with estimated h_{SNP}^2 as the dependent variable regressed on indicator variables set as 1 if the cohort contributed to the estimate (was included in the random sampling), and 0 otherwise.

RESULTS

Between-cohort heterogeneity within PGC29

We estimated h_{SNP}^2 in 500 random samplings of the cohorts from PGC29. From a linear regression of h_{SNP}^2 on indicator variables set as 1 if the cohort contributed to the estimate and 0 if it did not, we estimated an h_{SNP}^2 effect size deviation per cohort (y-axis **Figure 1**). Fifteen of the 29 cohorts had h_{SNP}^2 deviations different from zero ($p < 0.05/29$). We found that the cohorts nes1 (combined sample of the Netherlands Study of Depression and Anxiety and the Netherlands Twin Registry) (Boomsma et al., 2008; Penninx et al., 2008) and gep3 (GenPod/NEWMEDS) (G. Lewis et al., 2011) contributed most to variation in estimates of h_{SNP}^2 , and explain 0.14 and 0.16, respectively, of the variance in h_{SNP}^2 estimates across the 500 samplings. Samplings that included cohort nes1 had the highest average estimates of h_{SNP}^2 , while samplings including gep3 had the lowest average estimates. These differences are in line with expectations based on screening strategies for controls (**Supplementary Table 1**). The nes1 cohort used super-screened controls (Boomsma et al., 2008), such that controls never scored higher than 0.65 on a general factor score for anxious depression (mean = 0, SD = 0.7) derived from a combined measure of neuroticism, anxiety, and depressive symptoms assessed via longitudinal questionnaires over 15 years. In contrast, the gep3 cohort was a case-only research cohort which was matched to independently collected and genotyped controls (hence particularly stringent QC is needed to combine the genotype data of the contributing cases and controls). In fact, gep3 is one of seven cohorts for which controls were unscreened for MDD (**Figure 1**), but only one other cohort used independently genotyped controls (STAR*D, coded as stm2); together the seven cohorts have lower mean beta-values, but not significantly so ($p = 0.055$). The trend in these results might be explained by recognising that SNP-heritability is first estimated on the observed binary case-control scale h_{SNP-CC}^2 and then transformed to the liability scale h_{SNP}^2 . Indeed, we find that increasing sample prevalence (P in

equation 1) is significantly associated with the estimated h_{SNP}^2 ($p=0.00057$), but not sex ratio ($p=0.72$). The application of the standard transformation (equation [1]), as we have done, assumes screened controls and could generate an under-estimate of the SNP-heritability if controls were in fact unscreened. Similarly, super-screening of controls could generate an over-estimate of the true h_{SNP}^2 . Hence, we expect that the standard transformation would generate an overestimate for the nes1 cohort (super-screened controls) and an underestimate for cohorts with unscreened controls, consistent with our results.

Next, we investigated if h_{SNP}^2 estimates differed based on the research protocol to ascertain cases. For the same proportion of cases and controls in the GWAS sample, we would expect the h_{SNP-cc}^2 to be higher for a clinically ascertained cohort than a community ascertained cohort, further we would expect the transformation based on $K = 0.15$ (equation [1]) to overestimate h_{SNP}^2 when the true K is lower (clinical cohort) and underestimate h_{SNP}^2 when the true K is higher (community cohort). There is evidence to support this hypothesis (**Figure 1**). We found significant difference between the mean estimates of community (-0.027, s.e. 0.007) vs non-community cohorts (-0.08 s.e. 0.006) (with non-community comprising the three in- and out-patient categories), using a one-sided, two-sample t-test assuming unequal variance ($p=0.028$) (**Supplementary Table 4**). The difference became more significant ($p=0.015$) when the cohorts we had *a priori* reason to exclude, namely nes1 and gep3, based on discussions above were removed.

Between-sex heterogeneity

Using the four large data sets (**Table 1**) we investigate sex-specific heterogeneity. We used bivariate LDSC to estimate the r_g between all pairs of the two sexes by four data sets, but the standard errors were high (**Supplementary Table 2**). r_g involving the GERA_M data set were not estimable, because of the negative/zero of h_{SNP}^2 used in the denominator of the r_g estimate. The between-sex r_g estimated from the meta-analysis of the GWAS summary statistics of the 4 data sets was 0.86 (s.e. 0.04; $p_{H0:r_g=1} = 3.0 \times 10^{-4}$), and the meta-analysis of 12

male-female r_g estimates from all pairs of data sets was 0.76 (s.e. 0.03; $p_{H0:r_g=1} = 8.9 \times 10^{-16}$). At face value these results imply genetic factors are only partially shared between the sexes. However, this interpretation should be considered with caution when benchmarked by the meta-analysis of 6 female-female r_g estimates of 0.72 (s.e. 0.04; $p_{H0:r_g=1} = 4.9 \times 10^{-11}$) and the meta-analysis of 3 male-male r_g estimates of 0.71 (s.e. 0.11; $p_{H0:r_g=1} = 0.11$). Hence, the between-sex estimate of r_g being significantly different from zero likely reflects the general heterogeneity between the data sets rather than being sex-specific.

Next, we investigated sex-specific estimates of h_{SNP}^2 using LDSC (**Table 2, Supplementary Table 3**) to determine if there is evidence for a greater genetic contribution to MDD risk in females than males. We have power to detect differences of the order of $2 \times (\text{s.e. of male estimate} + \text{s.e. of female estimate})$. Initially, in the transformation of the h_{SNP-cc}^2 estimate to the liability scale (equation [1]) we assumed $K = 0.20$ for females and $K = 0.10$ for males (**Table 2**), consistent with literature reports that MDD is twice as common in females as males (Weissman, Leaf, Holzer, Myers, & Tischler, 1984). The h_{SNP}^2 estimates were smaller for males (range -0.02 to 0.15) than for females (range 0.10 to 0.23), but given the magnitude of the standard errors, none of the h_{SNP}^2 sex differences were significantly different for any individual data set. However, meta-analysis of the h_{SNP}^2 estimates of the four data sets did lead to estimates that were significantly different (Meta-4 in **Table 2**; 0.07 in males vs. 0.11 in females, $p = 1.6 \times 10^{-6}$). In addition, h_{SNP}^2 estimated from the meta-analysed GWAS results of the 4 data sets also showed significant difference between males and females (0.06 vs 0.08, $p = 7.3 \times 10^{-4}$; **Table 2** GWAS-Meta). We also meta-analysed the six h_{SNP}^2 values estimated from the genetic covariance between pairs of same-sex data sets in bivariate LDSC analysis. Since the traits are (presumed to be) the same, the genetic covariance is also an estimate of genetic variance (**Supplementary Table 3; Table 2** Meta-6). This again showed lower mean estimates for males with a significant difference between the sexes (0.07 in males vs 0.11 in females, $p = 0.0012$). For completeness, a meta-analysis from all 10 of the estimates is provided (**Table 2** Meta-10); this uses the same data sets as the GWAS-Meta, but the latter uses all the

information jointly rather than pairwise. Before drawing strong conclusions from these results, it is important to recognise that the estimates of h_{SNP}^2 depend on the choice of the lifetime risk estimates (K in equations [1] and [2]) (**Figure 2**). The point estimates are more similar if the same lifetime risk is assumed between the sexes, but it is difficult to justify such an assumption, because it is not, at face value, supported by epidemiological data. However, since depression maybe under-reported in males (Martin, Neighbors, & Griffith, 2013; Thornicroft et al., 2017), for illustration purposes we could assume the true lifetime risk of MDD is the same between the sexes ($K = 0.20$), but that through under-reporting the controls are contaminated by 0.10 of cases (Equation [2], $\nu = 0.1$). Under these assumptions, the h_{SNP}^2 estimates are not significantly different between the sexes for any data set (**Figure 2, Table 2**).

Last, we estimated X-chromosome SNP-heritability from the meta-analysed cohorts for males and females separately. However, the standard errors of the estimates were large relative to the h_{SNP}^2 estimates ($h_{SNP}^2 \text{ males} = 0.0025$ ($se = 0.06$); $h_{SNP}^2 \text{ females} = 0.0005$ ($se = 0.03$), which meant estimation of the r_g between them was not meaningful.

DISCUSSION

Heterogeneity in MDD is often discussed, but hard to investigate. In a novel set of analyses, we explored the heterogeneity of MDD using genetic data. The first set of analyses contrasted 29 PGC cohorts, by estimating their average contribution to estimates of h_{SNP}^2 from repeated random samplings of cohorts selected into GWAS meta-analyses. While we found notable differences between cohorts in the h_{SNP}^2 contribution estimates (**Figure 1**), these differences could be explained, at least partly, via knowledge of cohort ascertainment practices: higher contributions for cohorts ascertained in clinical compared to community settings (**Figure 1**, $p = 0.028$), higher contribution from a sample known to use super-screened controls (*nes1*), and a trend towards lower contributions from samples that used unscreened controls. One conclusion is that known cohort information about case ascertainment status

could be included usefully in analysis methods to increase power. A framework for such an analysis has been proposed (Zaitlen et al., 2012), but in practice the necessary parameters relating to cohort specific risks are usually unknown. In the seven samples contributing to the published PGC meta-analysis (PGC29, GERA, iPSYCH, UK Biobank, deCode, Generation Scotland, 23andMe) (Wray et al., 2018), h_{SNP}^2 estimates ranged from 0.09 to 0.25 and the weighted mean r_g for all pairwise combinations was 0.76 (s.e. = 0.03), which is significantly different from one. The cohorts had different recruitment strategies with ascertainment ranging from self-report to national hospital records. Moreover, even within the wave 1 PGC-MDD research cohorts endorsement proportions of the nine DSMIV criteria showed considerable heterogeneity including between cohorts that had similar clinical ascertainment strategies (Major Depressive Disorder Working Group of the Psychiatric et al., 2013). For example, endorsement rates of 56%, 27% and 10% were recorded for the criterion symptom 4b, hypersomnia nearly every day, for different early onset (< 30 years) recurrent MDD samples (Major Depressive Disorder Working Group of the Psychiatric et al., 2013). Despite the heterogeneity, out-of-sample prediction demonstrated that the self-reported 23andMe GWAS results explained variance in clinically ascertained cohorts with high significance (Wray et al., 2018). Sample size remains the driving force for genetic discovery in MDD. Ideally, larger sample sizes should be accompanied by collection of detailed, consistent, and longitudinal phenotypic data to enable more precise case and control definitions.

We also investigated between-sex genetic heterogeneity. Our sex-specific analyses found significantly smaller h_{SNP}^2 for males than females, a trend replicated in all four data sets, and hence was highly significant in the meta-analysis of the four cohort estimates (**Table 2**, male v1). However, we recognised that the comparisons of h_{SNP}^2 between the sexes depended on the choice of their respective lifetime risks (**Figure 2**). For baseline analyses we used lifetime risk estimates of $K = 0.20$ for females and $K = 0.10$ for males, consistent with a 2:1 risk for females vs. males (Weissman et al., 1984), with higher K values generating higher h_{SNP}^2

estimates. One explanation for a lower lifetime risk for males could be higher rates of under-reporting (Martin et al., 2013; Thornicroft et al., 2017). We calculated h_{SNP}^2 in males assuming the same lifetime risk as females, but with incomplete screening of controls. Such a hypothetical scenario generated similar estimates of h_{SNP}^2 between the sexes (**Figure 2, Table 2**).

In summary, our analyses demonstrate between-cohort genetic heterogeneity, but this can be explained, at least in part, by known factors such as case/control ascertainment. Investigation of between sex heterogeneity provided no convincing evidence to support genetic differences between the sexes. A robust conclusion is simply that large sample sizes will overcome sample heterogeneity as demonstrated in the latest major depression GWAS meta-analyses (Howard et al., 2018; Wray et al., 2018). Based on differences in lifetime disease risk and differences in heritability, while assuming a similar number of contributing risk loci, we previously estimated that sample sizes for GWAS need to be five times bigger for MDD than for schizophrenia (SCZ) (Wray et al., 2012). On the one hand, heterogeneity between samples may push this estimate higher. On the other hand, the heterogeneity may already account for the higher prevalence and lower heritability. The PGC GWAS meta-analysis for MDD/major depression based on 135K cases (Wray et al., 2018) identified 44 independent significant loci. This compares to 145 independent loci for SCZ from or 41K cases (Pardiñas et al., 2018), hence requiring 11 times as many cases for major depression compared to SCZ per genome-wide significant locus. However, the relationship between sample size and variant discovery is not linear (Wray et al., 2018) and so observing the sample size ratios for discovery will be of interest as sample sizes increase. Very large MDD case-control samples will allow novel methods to be applied to assess evidence for genetic subsets. Larger data sets are likely to lead to the development of new methods to assess genetic heterogeneity (Han et al., 2016). There is a growing interest in machine learning methods (Libbrecht & Noble, 2015) as a strategy to identify phenotypically relevant genetic subsets, but cohort heterogeneity must diminish their utility, making large electronic health or biobank samples collected and genotyped in a uniform way of most value.

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Author Contributions

Study design: MT, DM, NGM, DFS, NRW; **Structured methodological review of PGC Cohorts:** KSK, DFS, **Analysis:** MT, DM,DH, RM **Analysis-PGC:** SR, **Analysis-UKB:** DD,DH,KEK,JS, MT, AM^c **Analysis-Xchromosome:** JS, MT. **Analysis-iPSYCH:** MM,ADB. **PGC-MDD Principal Investigators:** BTB,HJG, ACH, PAFM **PGC-MDD Steering Committee:** PFS, CML, GB, ADB, DFL, NRW. **First draft of manuscript:** MT, NRW. **Final manuscript:** all authors

Table 1. Description of GWAS data sets for between-sex heterogeneity analyses

Data Set	Cases	Controls	Female cases	Female controls	Male cases	Male controls	Number of Cohorts^a
PGC29	16,823	25,632	11,438	12,463	5,377	13,022	29 ^b
GERA	7,162	38,287	5,152	20,650	2,010	17,637	1
UKB	113,769	208,801	73,292	99,385	40,477	109,426	1
iPSYCH	18,577	17,637	12,690	8,534	5,887	9,103	1
Total	156,331	290,357	102,572	141,032	53,751	149,188	32

a: Cohort is defined as the cases and controls with genome-wide genotypes imputed from the same set of SNPs that have passed through a common quality control pipeline. Mostly, cohort reflects a case-control sample collected by a PGC principal investigator. b: cohorts ranged in size from 246 to 3760 cases plus controls.

Table 2 Estimates of h_{SNP}^2 from LDSC applied to sex-specific GWAS summary statistics

	Female (se)	Males v1 (se)	Males v2 (se)	P-value v1	P-value v2
K	0.2	0.1	0.2		
u	0	0	0.1		
PGC29	0.20 (0.03)	0.07 (0.04)	0.09 (0.05)	0.61	0.68
GERA	0.15 (0.04)	-0.02 (0.05)	-0.03 (0.07)	0.55	0.57
UKB	0.10 (0.01)	0.07 (0.01)	0.10 (0.01)	0.77	0.94
iPSYCH	0.23 (0.03)	0.15 (0.04)	0.20 (0.05)	0.77	0.91
Meta-4	0.11 (0.005)	0.07 (0.006)	0.10 (0.007)	1.6x10 ⁻⁶	0.10
Meta-6	0.10 (0.005)	0.07 (0.006)	0.10 (0.008)	1.2x10 ⁻³	0.60
Meta-10	0.11 (0.004)	0.07 (0.004)	0.10 (0.005)	1.1x10 ⁻⁸	0.12
GWAS-Meta	0.08 (0.004)	0.06 (0.005)	0.08 (0.006)	6.6x10 ⁻⁴	0.64

h_{SNP}^2 estimates are presented on the liability scale achieved through transformation of the LDSC h_{SNP-cc}^2 estimate accounting for the case prevalence in the sample (P), the lifetime risk (K) of the disorder, and the proportion of cases in the control sample (u), equation [42].
 Meta-4: meta-analysis of the h_{SNP}^2 estimates for the 4 data sets (PGC29,GERA,UKB, iPSYCH).
 Meta-6: meta-analysis of the 6 h_{SNP}^2 estimates derived from the genetic covariance estimates from bivariate LDSC between the 6 possible same-sex data-set pairwise combinations. Meta-10: meta-analysis based on all h_{SNP}^2 estimates contributing to Meta-4 and Meta-6. GWAS-Meta: h_{SNP}^2 estimated from the GWAS summary statistics of the 4 data sets. Versions v1 and v2 differ by K and u values; v2 hypothesis is that the lifetime risk of MDD is the same in men and women but that more cases go unreported in men, and hence cases could be included in a screened control set.

Figure 1. Cohort deviation estimates from the linear regression of h^2_{SNP} estimates (from each of the 500 samplings of cohorts) on cohort indicator variables set at 1 if the cohort was included in the sampling that generated the h^2_{SNP} and 0 otherwise.

In each sampling, cohorts were selected at random until the total case/control sample size exceeded 5000. Cohort GWAS results were meta-analysed and these results passed into LDscore. h^2_{SNP} was estimated using the equation 1 transformation ($K = 0.15$) which assumes controls are screened. h^2_{SNP} estimates of samplings were highest, on average, when cohort nes1 was included and lowest, on average, when cohort gep3 was included. Wave 1 cohorts have an asterisk by their name and cohorts that have unscreened controls are marked by a tilde. Continuous lines around data-points are 95% confidence Intervals. For explanation of cohort names see Supplementary Table 1.

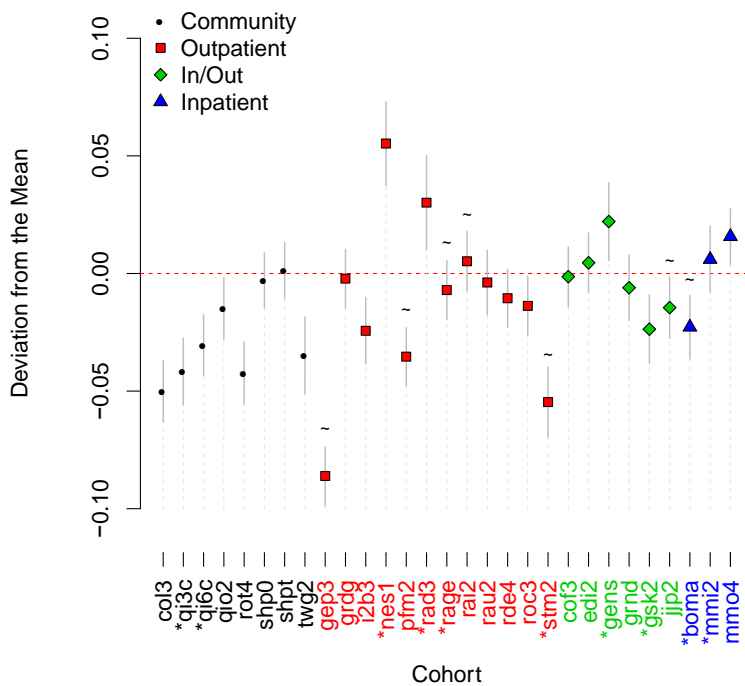
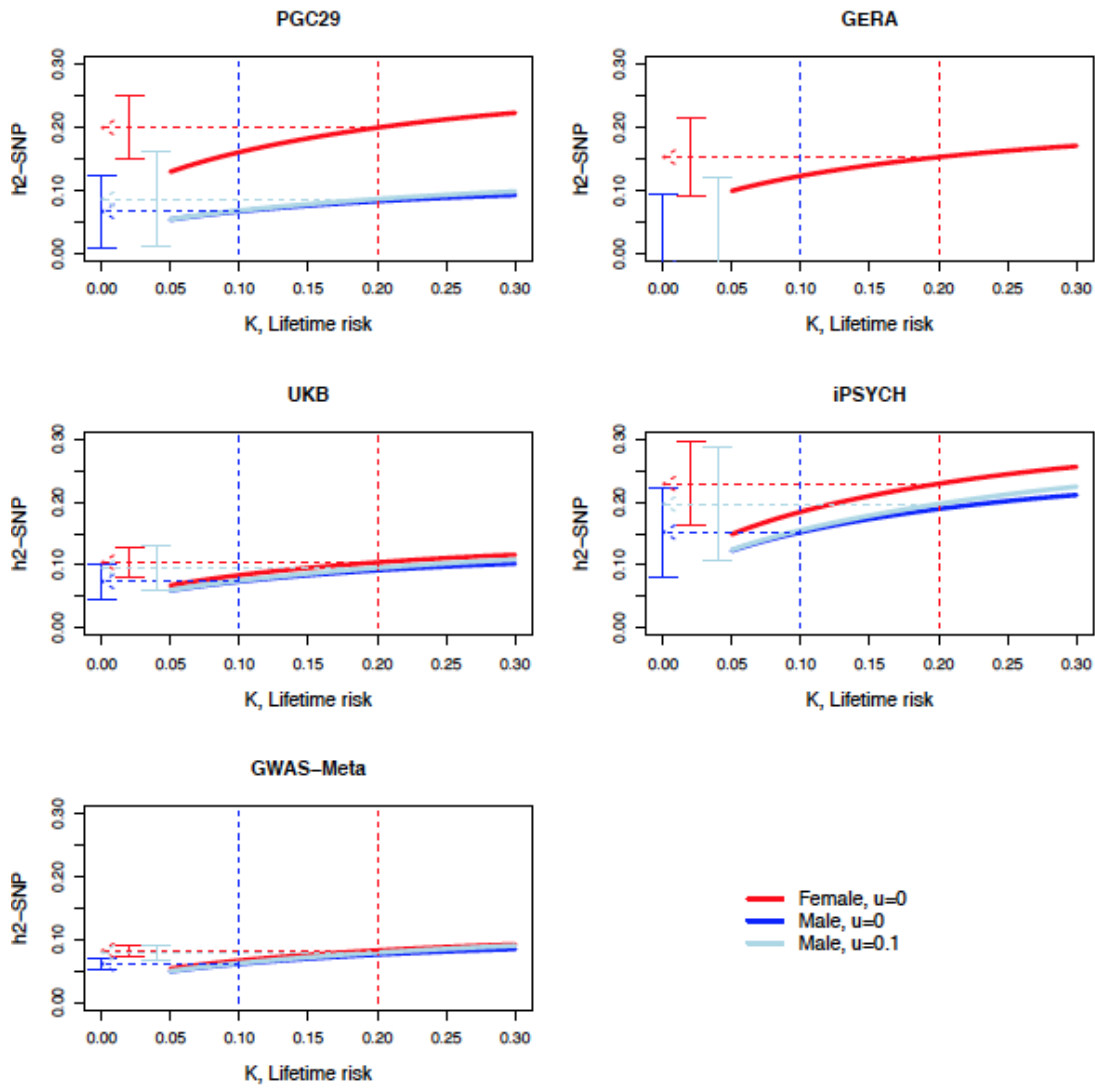


Figure 2. Impact of choice of lifetime risk on estimate of h_{SNP}^2 . The graphs shows h_{SNP}^2 on the liability scale from equation [2], u (proportion of controls that are unrecognised cases). The blue/red dashed lines are positioned at the lifetime risk for males/females. The flat ended bars show the 95% confidence intervals of the h_{SNP}^2 estimates at the chosen lifetime risk.



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File Upload system didn't allow Excel. Supp T1 describes the cohorts

Supplementary Table 1. Description of PCG29 samples

Number	Sample	PGC label	Country	Exclusion criteria (lifetime)	Controls	Abbreviation	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Figure 1	se	Community- predicted SE	GENIE
								Male	Female	Male	Female	Male	Female	Male	Female			
1	IGOMA 1.3	borna	Germany	Bip, Hypomania, MAP, MDD related to SUD	Unscreened	borna	586	1,052	207	379	546	516	61	0.02	-0.02	0.01	1	3
2	CGEIMS 4	cof8	Australia	Bip, MAP, MDD related to SUD	Any life psychiatric dx (including MDD)	cof8	120	126	46	74	65	61	0.02	-0.02	0.01	1	2	
3	PsyCADIAS 5	cof3	Switzerland	Bip, Hypomania, MAP, MDD related to SUD	MDD, Bip, Hypomania, MAP	cof3	507	1,445	148	359	829	616	0.05	-0.05	0.01	2	0	
4	Ethnogr 6	edf2	Scotland	Bip, MAP, SUD, Flix Bip	Current medical or psychiatric dx or tx	edf2	372	285	151	221	146	139	0.00	0.01	0.01	2	2	
5	GenDr 7.8	edf3	USA	Bip, MAP, mood-sever IDx, Flix Bip, HSUD, MDD onsets without <2> of sobriety	Depressed mood or antidepressants ever >2 weeks; Bip or MAP sec Dx or tx for MDD, Bip, MAP	edf3	1,019	1,344	297	722	788	561	0.02	0.02	0.01	2	2	
6	NEWWEBS-GENEOD 9.10	edf4	Europe	Bip, MAP, MDD related to SUD	Unscreened	edf4	482	2,836	149	329	1,481	1,335	-0.09	-0.09	0.01	1	1	
7	DCN 11	edf5	USA	Bip, MAP, current SUDs, MDD onset <1> after SUD	MDD, MAP, Bip, current SUD	edf5	471	470	106	365	176	294	0.00	0.00	0.01	2	0.40	
8	GENEOD 7	edf6	USA	Bip, MAP, mood-sever IDx, Flix Bip, current SUDs, MDD onsets <2>	GPC, MDD (self-report), Mayo Dx of MDD, Bip, MAP	edf6	830	474	143	687	242	232	-0.01	-0.01	0.01	2	0.31	
9	GSW/MIP 12	edf7	Germany	Bip, MAP, SUD, mood-homologous psychosis, OCD, PTSD, secondary MD	MDD, Bip, any anxiety disorder	edf7	880	861	292	588	278	288	-0.02	-0.02	0.01	1	2	
10	1202-1HD 13	edf8	USA	SUD within 1 Year	MDD, Bip, MAP, SUDs, psych medication use	edf8	806	1,067	267	539	532	535	-0.02	-0.02	0.01	2	0.21	
11	Janssen 14.15	ijf2	USA	SUD within 1 Year	Unscreened	ijf2	466	1,380	148	318	545	385	-0.01	-0.01	0.01	2	0.27	
12	MARS 16.38	mm2	Germany	Bip, SUD, secondary MD, severe medical conditions	Major psychiatric dx (Munchi), CES-D-10 & no report MDD (Dortmund)	mm2	584	517	276	308	234	283	0.01	0.01	0.01	1	3	
13	MARS 16.38	mm4	Germany	Bip, SUD, secondary MD, severe medical conditions	Major psychiatric dx (Munchi), CES-D-10 & no report MDD (Dortmund)	mm4	254	371	127	137	188	188	0.02	0.02	0.01	3	0.58	
14	NESDA/NTR, NESDA 19.20	me61	NL	Bip, MAP, SUD, OR, Mania (if interviewed)	MDD, Bip, MAP, SUD, no current Dutch OR MDD, mania (if interviewed)	me61	1,594	1,602	473	1,021	627	975	0.06	0.06	0.01	3	0.38	
15	Pfizer 9	pin2	USA	Bip, MAP, SUD	Unscreened	pin2	281	820	90	191	497	323	-0.04	-0.04	0.01	1	1	
16	QIMR 13.21	qf3c	Australia	MDD related to SUD	MDD, SUD	qf3c	864	979	363	501	210	467	0.01	0.01	0.01	0	0.45	
17	QIMR 13.21	qf3e	Australia	MDD related to SUD	MDD, SUD	qf3e	499	590	132	347	224	366	-0.03	-0.03	0.01	1	0.27	
18	QIMR 13.21	qf3f	Australia	MDD related to SUD	MDD, SUD	qf3f	565	526	161	404	223	303	0.01	0.01	0.01	0	0.35	
19	RADANT-UK 22	raf3	UK	Bip, MAP, MDD related to SUD, Bip Flix	MDD, Bip, MAP	raf3	1,872	1,528	1,528	1,318	557	825	0.03	0.03	0.01	1	0.12	
20	RADANT-RSH 22.23	raf8	Germany	Bip, MAP, MDD related to SUD, Bip Flix	Unscreened	raf8	322	227	111	211	108	119	-0.01	-0.01	0.01	1	0.50	
21	RADANT-RSH 22.23	raf2	Ireland	Bip, MAP, MDD related to SUD, Bip Flix	Unscreened	raf2	109	340	19	90	161	178	0.01	0.01	0.01	2	1.14	
22	RADANT-GEN 22.24	raf2	USA	Bip, MAP, MDD related to SUD, Bip Flix	MDD, Bip, MAP, SUD, Flix, MAP	raf2	223	378	48	175	182	196	0.00	0.00	0.01	1	0.67	
23	RADANT-GEN 22	rd64	Denmark	Bip, MAP, MDD related to SUD, Bip Flix	No major illness or medication	rd64	133	516	40	93	306	210	-0.01	-0.01	0.01	1	0.89	
24	Roch 1	rd64	USA	Bip, MAP, SUD (past 6 months), psych dx, suicidal, neurological dx	MDD, Bip, MAP, SUD (past 6 months), other psych dx, suicidal, neurological dx	rd64	271	92	89	182	34	58	0.01	0.01	0.01	1	1.37	
25	Reckadam 25	rd4	NL	Bip, MAP, MDD related to SUD	Depressive sx (CES-D) 4 times over 15 Y	rd4	241	1,028	62	179	444	584	-0.04	-0.04	0.01	2	0.46	
26	SHIP-Q 26	shf0	Germany	Bip, MAP, MDD related to SUD	MDD	shf0	366	1,087	118	248	609	478	0.00	0.00	0.01	2	0.34	
27	SHIP-TREND 26	shf1	Germany	Bip, MAP, MDD related to SUD	MDD	shf1	163	484	46	117	268	216	0.00	0.00	0.01	0	0.76	
28	STAR*D 27	stf2	USA	Bip, MAP	Unscreened psychiatrically, MI	stf2	936	934	377	559	507	427	-0.05	-0.05	0.01	1	0.20	
29	TwinCen 28.29	twf2	Sweden	Bip	MDD, Bip	twf2	1,097	2,663	321	776	1,461	1,202	-0.03	-0.03	0.01	2	0.11	
							16,823	25,632	5,377	11,438	12,463	13,022					0.009	

Abbreviations: A=antidepressant, B=bipolar disorder, C=composite international diagnostic interview, CIDI-SF=CIDI-short form, DISC-DI=diagnostic interview for genetic studies, D=diagnosis, EME=electronic medical record, Flix=family history, H=history, D=intellectual disability, N=non-affective psychosis, S=SNOS=Schizoid, S=Schizoid

PCG29-structured clinical interview for DSM-IV-TR-substance use disorder, S=symptoms, and T=treatment.

† Probe cases are described in <https://www.dinlietrals.gov/ct/show/NC101451677> and <https://dinlietrals.gov/ct/show/NC101437657>. The controls are described in <https://dinlietrals.gov/ct/show/NC101592873>.

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Supplementary Table 2. Bivariate LDSC results of UK Biobank, iPsych, GERA and PGC29 against all other cohorts. The results are presented on the observed and liability scale.

a) UK Biobank

T1	T2	SX1	SX2	Nsnp	h2_1	se_1	lambda_1	chisq_1	intercept_1	se_int1	ratio_1	h2_2	se_2	lambda_2	chisq_2	intercept_2	se_int2	ratio_2	gencov	se_gcov	mean_r12	cov_intercept	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2_1	h2_2	sel_1	sel_2		
UKB	UKB2	F	F	1167802	0.0779	0.004	1.2201	1.2623	1.0003	0.0077	0.0013	0.0779	0.004	1.2201	1.2623	1.0003	0.0077	0.0013	0.0779	0.004	1.2623	1.0003	0.0077	1	3.76E-07	2.66E+06	3.27E-94	0.4244564	0.4244564	0.2	0.2	0.10415283	0.10415283	0.00534803	0.00534803		
UKB2	UKB2	F	M	1167855	0.0778	0.004	1.2201	1.2623	1.0005	0.0077	0.0018	0.0778	0.004	1.1459	1.1691	1.0074	0.0072	0.0438	0.057	0.0033	0.183	0.0053	0.0055	0.8693	0.0422	20.5916	3.27E-94	0.4244564	0.27002128	0.2	0.1	0.10401913	0.07378294	0.00534803	0.00534803		
UKB2	iPSYCH	F	F	985138	0.0787	0.0046	1.2431	1.2916	0.9994	0.0098	0	0.1636	0.025	1.0741	1.0709	0.9953	0.0086	0	0.0801	0.0088	0.0992	-0.0032	0.0079	0.7053	0.0912	7.7332	1.05E-14	0.4244564	0.5979803	0.2	0.2	0.10522442	0.22226217	0.0061543	0.03396427		
UKB2	iPSYCH	F	M	984589	0.0792	0.0046	1.2431	1.2914	0.9978	0.0097	0	0.1304	0.036	1.0466	1.0491	1.0067	0.0089	0	0.1365	0.0768	0.0092	0.0831	-0.0027	0.0065	0.7594	0.12	6.2949	3.08E-10	0.4244564	0.39272849	0.2	0.1	0.10589094	0.14379418	0.0061543	0.03397208	
UKB2	GERA	F	M	1086853	0.0796	0.0042	1.2267	1.2704	0.9993	0.0085	0	0.0783	0.0176	1.0315	1.0357	0.9944	0.0062	0	0.054	0.0055	0.0815	0.0028	0.0053	0.6883	0.1028	6.647	2.99E-11	0.4244564	0.1967444	0.2	0.2	0.10669314	0.1603487	0.0061543	0.03397208		
UKB2	GERA	F	M	1086266	0.0796	0.0042	1.2267	1.2704	0.9997	0.0086	0	-0.0035	0.0204	1.0105	1.0105	1.0119	0.0068	1.1342	0.0288	0.0066	0.0341	-0.0011	0.005	NA	NA	NA	NA	NA	NA	0.10642574	0.1023057	0.2	0.1	0.10642574	0.1023057	0.0061543	0.03397208
UKB2	PGC29	F	F	1096447	0.0787	0.0044	1.2299	1.2741	0.9982	0.0096	0	0.1502	0.021	1.0496	1.0505	0.9738	0.0072	0	0.0809	0.0079	0.108	0.001	0.0062	0.7444	0.0719	10.3493	4.22E-25	0.4244564	0.47855738	0.2	0.2	0.10522442	0.19659453	0.00588283	0.02748569		
UKB2	PGC29	F	M	1090938	0.0785	0.0042	1.2299	1.2747	0.9981	0.0093	0	0.0595	0.024	1.0527	1.0463	1.0242	0.0074	0.523	0.0577	0.0081	0.0713	0.0051	0.0062	0.8443	0.0719	7.13E-05	0.4244564	0.29224414	0.2	0.1	0.10495503	0.0756531	0.0061543	0.03386530			
UKB2	UKB2	M	F	1167855	0.0553	0.0044	1.1459	1.1691	1.0074	0.0102	0.0438	0.0778	0.004	1.2201	1.2623	1.0005	0.0077	0.0018	0.0577	0.0033	0.183	0.0053	0.0055	0.8693	0.0422	20.5916	3.27E-94	0.4244564	0.27002128	0.2	0.1	0.10401913	0.07378294	0.00534803	0.00534803		
UKB2	UKB2	M	M	1168019	0.0553	0.0044	1.1459	1.169	1.0074	0.0102	0.0438	0.0778	0.004	1.1459	1.169	1.0074	0.0071	0.0438	0.0553	0.0044	0.183	0.0053	0.0055	0.8693	0.0422	20.5916	3.27E-94	0.4244564	0.27002128	0.2	0.1	0.10401913	0.07378294	0.00534803	0.00534803		
UKB2	iPSYCH	M	F	985112	0.047	0.0052	1.1587	1.1868	1.0096	0.0102	0.0516	0.1645	0.025	1.0741	1.0709	0.9949	0.0085	0	0.0496	0.0084	0.0651	0.0043	0.0063	0.5227	0.0867	6.0309	1.63E-09	0.27002128	0.5979803	0.1	0.2	0.0729824	0.2234488	0.006938	0.03396427		
UKB2	iPSYCH	M	M	984565	0.0545	0.0051	1.1587	1.1872	1.0105	0.0102	0.0563	0.131	0.036	1.0466	1.0491	1.0065	0.0089	0.1327	0.0615	0.0105	0.0657	0.0005	0.0063	0.7282	0.1254	5.8089	6.29E-09	0.27002128	0.39272849	0.1	0.1	0.07271556	0.14445881	0.00680458	0.03397208		
UKB2	GERA	M	F	1086831	0.0571	0.0047	1.1491	1.1746	1.0028	0.0133	0.0378	0.1176	0.035	1.0315	1.0357	0.9944	0.0062	0	0.0423	0.0064	0.0586	0.0059	0.0053	0.6312	0.1095	5.7634	8.24E-09	0.27002128	0.19967444	0.1	0.1	0.10454881	0.07271556	0.0061543	0.03396427		
UKB2	GERA	M	M	1086239	0.0568	0.0048	1.1491	1.1745	1.003	0.0082	0.0175	-0.0038	0.0204	1.0105	1.0105	1.0121	0.0068	1.1473	0.0396	0.0067	0.045	0.0015	0.0052	NA	NA	NA	NA	NA	NA	0.1023057	0.1023057	0.1	0.1	0.1023057	0.1023057	0.0061543	0.03397208
UKB2	PGC29	M	F	1096421	0.0557	0.0048	1.1523	1.1767	1.0067	0.008	0.0381	0.1005	0.021	1.0496	1.0505	0.9737	0.0072	0	0.0562	0.0078	0.0773	0.0062	0.0059	0.6137	0.0828	7.415	1.22E-13	0.27002128	0.47855738	0.1	0.2	0.07431663	0.1968719	0.0064031	0.02748569		
UKB2	PGC29	M	M	1090920	0.0553	0.0045	1.1523	1.1774	1.0082	0.0077	0.0461	0.0591	0.0303	1.0527	1.0463	1.0244	0.0074	0.5263	0.0727	0.0086	0.0668	-0.01	0.006	1.2719	0.3248	3.9155	9.02E-05	0.27002128	0.29224414	0.1	0.1	0.10737824	0.157145	0.00600404	0.03382586		

b) iPsych

T1	T2	SX1	SX2	Nsnp	h2_1	se_1	lambda_1	chisq_1	intercept_1	se_int1	ratio_1	h2_2	se_2	lambda_2	chisq_2	intercept_2	se_int2	ratio_2	gencov	se_gcov	mean_r12	cov_intercept	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2_1	h2_2	sel_1	sel_2		
iPSYCH	UKB2	F	F	985138	0.1634	0.025	1.0741	1.0709	0.9951	0.0086	0	0.0787	0.0046	1.2431	1.2916	0.9994	0.0098	0	0.0801	0.0088	0.0992	-0.0032	0.0079	0.7053	0.0912	7.7332	1.05E-14	0.4244564	0.5979803	0.2	0.2	0.10522442	0.22226217	0.0061543	0.03396427		
iPSYCH	UKB2	F	M	985112	0.1645	0.025	1.0741	1.0709	0.9949	0.0085	0	0.0547	0.0052	1.1587	1.1868	1.0096	0.0102	0.0516	0.0496	0.0084	0.0651	0.0043	0.0063	0.5227	0.0867	6.0309	1.63E-09	0.27002128	0.5979803	0.2	0.1	0.0729824	0.2234488	0.006938	0.03396427		
iPSYCH	iPSYCH	F	F	994169	0.1687	0.0247	1.0741	1.0705	0.9928	0.0086	0	0.1687	0.0247	1.0741	1.0705	0.9928	0.0086	0	0.1687	0.0247	1.0705	0.066	1	2.25E-06	444807.56	0.2	0.2	0.2919088	0.2919088	0.2	0.2	0.2919088	0.2919088	0.0335567	0.0335567		
iPSYCH	iPSYCH	F	M	984565	0.1646	0.0251	1.0741	1.0709	0.9948	0.0086	0	0.1325	0.031	1.0466	1.0484	1.0052	0.0089	0.1085	0.1463	0.0213	0.0625	0.0059	0.0059	0.9909	0.1675	5.9171	3.28E-09	0.5979803	0.39272849	0.2	0.1	0.22362074	0.14610988	0.03410013	0.03364999		
iPSYCH	GERA	F	F	992942	0.1695	0.0247	1.0741	1.0704	0.9925	0.0086	0	0.0713	0.019	1.0315	1.0372	0.997	0.0078	0	0.085	0.0154	0.0392	-0.0043	0.0059	0.7734	0.173	4.471	7.79E-06	0.5979803	0.19967444	0.2	0.2	0.10454881	0.07271556	0.0061543	0.03396427		
iPSYCH	GERA	F	M	992942	0.1699	0.0249	1.0741	1.0705	0.9923	0.0086	0	-0.0015	0.0213	1.0075	1.0098	1.0143	0.0078	1.4586	0.0284	0.0174	0.0087	0.0038	0.0053	NA	NA	NA	NA	NA	NA	0.1023057	0.1023057	0.1	0.1	0.1023057	0.1023057	0.0061543	0.03396427
iPSYCH	PGC29	F	F	1096428	0.1709	0.0263	1.0741	1.0713	0.992	0.009	0	0.1406	0.0241	1.0557	1.0561	0.9792	0.0088	0	0.1103	0.0199	0.0551	-0.0004	0.0064	0.7118	0.1449	4.9121	9.01E-07	0.5979803	0.46762061	0.2	0.2	0.10232974	0.18446436	0.03373041	0.03361871		
iPSYCH	PGC29	F	M	979303	0.1693	0.0256	1.0741	1.0715	0.9928	0.0085	0	0.0421	0.0217	1.0557	1.0492	1.0325	0.009	0.661	0.065	0.0219	0.0224	0.0064	0.0063	0.3191	2.0977	0.0359	0.5979803	0.30140135	0.2	0.1	0.10230062	0.0528334	0.03375126	0.00684041			
iPSYCH	UKB2	M	F	984565	0.1304	0.0336	1.0466	1.0491	1.0067	0.0089	0.1365	0.0792	0.046	1.2431	1.2914	0.9978	0.0097	0	0.0768	0.0092	0.0831	-0.0027	0.0065	0.7554	0.12	6.2949	3.08E-10	0.4244564	0.39272849	0.2	0.1	0.10454881	0.07271556	0.0061543	0.03396427		
iPSYCH	UKB2	M	M	984565	0.1304	0.0336	1.0466	1.0491	1.0065	0.0089	0.1327	0.0545	0.0051	1.1587	1.1872	1.0105	0.0102	0.0563	0.0615	0.0105	0.0657	0.0005	0.0063	0.7282	0.1254	5.8089	6.29E-09	0.27002128	0.39272849	0.1	0.1	0.10454881	0.07271556	0.0061543	0.03396427		
iPSYCH	iPSYCH	M	F	984565	0.1325	0.0331	1.0466	1.0484	1.0052	0.0089	0.1085	0.0545	0.0251	1.0741	1.0709	0.9948	0.0086	0	0.1463	0.0213	0.0625	0.0059	0.00														

T1	T2	SX1	SX2	Nsnp	h2_1	se_1	lambda_1	chisq_1	intercept_1	se_int1	ratio_1	h2_2	se_2	lambda_2	chisq_2	intercept_2	se_int2	ratio_2	gencov	se_gcov	mean_z1z2	cov_intercept	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2l_1	h2l_2	se_l1	se_l2	
PGC29	UKB2	F	F	1096447	0.1502	0.021	1.0496	1.0505	0.9738	0.0072	0	0.0787	0.0044	1.2299	1.2741	0.9982	0.0096	0	0.0809	0.0079	0.108	0.001	0.0062	0.7444	0.0719	10.3493	4.22E-25	0.46762061	0.42444564	0.2	0.2	0.19705937	0.05222243	0.02755158	0.00588283	
PGC29	UKB2	F	M	1096421	0.1505	0.021	1.0496	1.0505	0.9737	0.0072	0	0.0557	0.0048	1.1523	1.1767	1.0067	0.008	0.0381	0.0562	0.0078	0.0773	0.0062	0.0059	0.6137	0.0828	7.415	1.22E-13	0.46762061	0.27002128	0.2	0.2	0.19705937	0.05222243	0.02755158	0.00588283	
PGC29	IPSYCH	F	F	981498	0.1406	0.0241	1.0557	1.0561	0.9792	0.0088	0	0.1709	0.0263	1.0741	1.0713	0.992	0.009	0	0.1103	0.0199	0.0551	-9.00E-04	0.0064	0.7118	0.1449	4.9121	9.01E-07	0.46762061	0.59790803	0.2	0.2	0.18446436	0.23217974	0.03161871	0.03573041	
PGC29	IPSYCH	F	M	981127	0.1413	0.0243	1.0557	1.0562	0.979	0.0089	0	0.1367	0.0343	1.0466	1.0486	1.0039	0.0091	0.0795	0.1057	0.0198	0.0445	-6.00E-04	0.0057	0.76	0.1727	4.4013	1.08E-05	0.46762061	0.39272849	0.2	0.2	0.18538275	0.15074129	0.03181111	0.03782316	
PGC29	GERA	F	F	1107418	0.152	0.0213	1.0496	1.05	0.9727	0.0072	0	0.0751	0.0199	1.0315	1.0354	0.9955	0.0072	0	0.0725	0.014	0.0385	-0.0012	0.0052	0.5785	0.1382	4.9082	9.19E-07	0.46762061	0.19967444	0.2	0.2	0.19940293	0.1534045	0.02794517	0.04067298	
PGC29	GERA	F	M	1107056	0.1525	0.0213	1.0496	1.0499	0.9723	0.0072	0	-0.0071	0.0198	1.0105	1.0096	1.0125	0.0067	1.2973	0.0386	0.0149	0.0118	-0.0018	0.0049	NA	NA	NA	NA	0.46762061	0.1023057	0.2	0.1	0.20007602	-0.0203315	0.02794517	0.05666907	
PGC29	PGC29	F	F	1108969	0.1529	0.0213	1.0496	1.05	0.9722	0.0072	0	0.1529	0.0213	1.0496	1.05	0.9722	0.0072	0	0.1529	0.0213	1.05	0.9722	0.0072	1	2.36E-07	4230000	0	0.46762061	0.46762061	0.2	0.2	0.20060172	0.20060172	0.02794517	0.02794517	
PGC29	PGC29	F	M	1100025	0.1518	0.0227	1.0496	1.0505	0.9729	0.0073	0	0.0529	0.0304	1.0557	1.0473	1.0277	0.0075	0.5852	0.0834	0.0187	0.0426	0.0057	0.0054	0.9315	0.322	2.8932	0.0038	0.46762061	0.30140135	0.2	0.1	0.19915854	0.06607266	0.02978194	0.03796992	
PGC29	UKB2	M	F	1090938	0.0595	0.0304	1.0527	1.0463	1.0242	0.0074	0.523	0.0785	0.0042	1.2299	1.2747	0.9981	0.0093	0	0.0577	0.0081	0.0713	0.0051	0.0062	0.8443	0.2126	3.9719	7.13E-05	0.30140135	0.42444564	0.1	0.1	0.07431611	0.10495503	0.03796992	0.00561543	
PGC29	UKB2	M	M	1090920	0.0591	0.0303	1.0527	1.0463	1.0244	0.0074	0.5263	0.0553	0.0045	1.1523	1.1774	1.0082	0.0077	0.0461	0.0727	0.0086	0.0668	-0.01	0.006	1.2719	0.3248	3.9155	9.02E-05	0.30140135	0.27002128	0.1	0.1	0.07381652	0.07378294	0.03794502	0.06800404	
PGC29	IPSYCH	M	F	979303	0.0421	0.0327	1.0557	1.0492	1.0325	0.009	0.661	0.1693	0.0256	1.0741	1.0715	0.9928	0.0085	0	0.0565	0.0219	0.0224	-0.0018	0.0065	0.6693	0.3191	2.0977	0.0359	0.30140135	0.59790803	0.1	0.2	0.05258334	0.2300602	0.04084264	0.03473471	
PGC29	IPSYCH	M	M	978977	0.0415	0.0326	1.0557	1.0492	1.0328	0.0091	0.6657	0.1361	0.035	1.0466	1.0486	1.004	0.0091	0.0823	0.0409	0.0233	0.0292	0.0271	0.0061	0.0655	0.311	0.2107	0.8331	0.30140135	0.39272849	0.1	0.1	0.05183394	0.15007966	0.04071774	0.03894506	
PGC29	GERA	M	F	1101653	0.0519	0.0302	1.0557	1.0473	1.0281	0.0074	0.5932	0.0771	0.0193	1.0315	1.0354	0.9943	0.0071	0	0.0407	0.0167	0.0205	0.0023	0.005	0.6428	0.315	2.0407	0.0413	0.30140135	0.19967444	0.1	0.2	0.06482365	0.15758223	0.03772012	0.03944665	
PGC29	GERA	M	M	1101303	0.0526	0.0303	1.0557	1.0473	1.0278	0.0074	0.5879	-0.0077	0.0196	1.0105	1.0098	1.013	0.0067	1.3183	0.046	0.0161	0.0182	5.00E-04	0.0045	NA	NA	NA	0.30140135	0.1023057	0.1	0.1	0.06569795	-0.0220496	0.03784502	0.05612635		
PGC29	PGC29	M	F	1100025	0.0529	0.0304	1.0557	1.0473	1.0277	0.0075	0.5852	0.1518	0.0227	1.0496	1.0505	0.9729	0.0073	0	0.0834	0.0187	0.0426	0.0057	0.0054	0.9315	0.322	2.8932	0.0038	0.30140135	0.46762061	0.1	0.2	0.06607266	0.19915854	0.03796992	0.02978194	
PGC29	PGC29	M	M	1103168	0.0527	0.0303	1.0557	1.0473	1.0278	0.0074	0.5869	0.0527	0.0303	1.0557	1.0473	1.0278	0.0074	0.5869	0.0527	0.0303	1.0557	1.0473	1.0278	0.0074	1	3.15E-06	317182.424	0	0.30140135	0.30140135	0.1	0.1	0.06582286	0.06582286	0.03784502	0.03784502

*** ANNOTATIONS:** T1/2 - Trait 1/2; SX1/2 - Sex in trait 1/2; Nsnp - Total number of SNPs; h2_1/2 - SNP-heritability for trait 1/2; se_1/2 - standard error of the SNP-heritability for trait 1/2; lambda_1/2 - lambda GC = [median(chi^2)/0.4549]; chisq_1/2 - regression chi-squared for trait 1/2; intercept_1/2 - regression intercept for trait 1/2; se_int1/2 - standard error of the intercept for trait 1/2; ratio_1/2 = (intercept-1)/(mean(chi^2)-1); gencov - total observed scale genetic covariance; se_gcov - standard error of the genetic covariance; mean_z1z2 - mean product of Z-scores (cross-trait chi-square); cov_intercept - cross-trait LD Score regression intercept; se_covint - standard error of the cross-trait intercept; gencor - genetic correlation; se_gcor - standard error of the genetic correlation; gencor_z = gencor/se_gcor; gencor_p - p-value for genetic correlation; P1/2 - sample prevalence; K1/2 - lifetime risk; h2l_1/2 - SNP-heritability on liability scale; se_l1/2 - standard error of the SNP-heritability on liability scale

Supplementary Table 3: Sex-specific SNP-heritabilities and rg								
	PGC2_M	PGC2_F	GERA_M	GERA_F	UKB_M	UKB_F	iPSYCH_M	iPSYCH_F
PGC2_M	0.07 (0.04)	0.93 (0.32)	–	0.64 (0.32)	1.27 (0.32)	0.84 (0.21)	0.07 (0.31)*	0.67 (0.32)
PGC2_F		0.20 (0.03)	–	0.68 (0.14)*	0.61 (0.08)*	0.74 (0.07)*	0.76 (0.17)	0.72 (0.14)*
GERA_M			-0.02 (0.05)	–	–	–	–	–
GERA_F				0.15 (0.04)	0.63 (0.11)*	0.68 (0.10)*	0.58 (0.19)*	0.77 (0.17)
UKB_M					0.07 (0.01)	0.87 (0.04)	0.82 (0.15)	0.57 (0.11)*
UKB_F						0.10 (0.01)	0.83 (0.15)	0.63 (0.11)*
iPSYCH_M							0.15 (0.04)	0.99 (0.17)
iPSYCH_F								0.23 (0.03)
h ² -SNP estimates (diagonals in bold) assume lifetime risks of K = 0.10 for males and K = 0.20 for females.								
Standard errors of estimates are in brackets.								
* genetic correlation significantly lower than 1.								
Given the negative h ² -SNP for GERA_M, the genetic correlations for this data set are non-estimable, despite non-zero genetic covariances between GERA_M with other data sets.								

Supplementary Table 4: Beta coefficients from 500 sampling analyses used in plotting Figure 1

cohort	est	se	wave	unscreened	Com_clin
cof3	-0.0013	0.006	2	0	2
col3	-0.0502	0.007	2	0	0
edi2	0.0045	0.006	2	0	2
gens	0.0221	0.008	1	0	2
grdg	-0.0022	0.006	2	0	1
grnd	-0.0061	0.007	2	0	2
gsk2	-0.0237	0.007	1	0	2
i2b3	-0.0244	0.007	2	0	1
mmi2	0.0060	0.007	1	0	3
mmo4	0.0157	0.006	2	0	3
nes1	0.0552	0.009	1	0	1
qi3c	-0.0417	0.007	1	0	0
qi6c	-0.0305	0.007	1	0	0
qio2	-0.0149	0.007	2	0	0
rad3	0.0301	0.010	1	0	1
rau2	-0.0038	0.007	2	0	1
rde4	-0.0105	0.006	2	0	1
roc3	-0.0138	0.006	2	0	1
rot4	-0.0424	0.007	2	0	0
shp0	-0.0029	0.006	2	0	0
shpt	0.0013	0.006	2	0	0
twg2	-0.0347	0.008	2	0	0
boma	-0.0228	0.007	1	1	3
gep3	-0.0861	0.006	2	1	1
jjp2	-0.0145	0.007	2	1	2
pfm2	-0.0353	0.006	2	1	1
rage	-0.0071	0.006	1	1	1
rai2	0.0052	0.006	2	1	1
stm2	-0.0547	0.008	1	1	1

Beta coefficients from multiple regression of 500 sampling iterations where each cohort indicator was set up as described in Figure 1. Regression intercept was 0.235306. Description of cohort names can be found in Supplementary Table 1. Com_clin variable coded as follows: Community = 0, Outpatients = 1, In/Out = 2, and Inpatients = 3.