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

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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 (rg~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 disequilbrium (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^2_{SNP-cc}, 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^2_{SNP-cc} is transformed to the liability scale h^2_{SNP} (Lee, Wray, Goddard, & Visscher, 2011) based on normal distribution theory, given an assumed lifetime risk of disease in the population(*K*):

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

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

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

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^2_{SNP-cc}= 0.15, *P* = 0.5, then h^2_{SNP}= 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^2_{SNP} 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^2_{SNP} with standard error of at minimum 0.38 (Visscher et al., 2014)). Instead we estimated the h^2_{SNP} attributed to a cohort by evaluating its contribution to h^2_{SNP} 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^2_{SNP} assuming lifetime risk of *K* = 0.15, and assuming controls are screened (equation [1]). To determine the contribution to the h^2_{SNP} estimate from each cohort we fitted a linear model

with estimated h^2_{SNP} 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^2_{SNP} in 500 random samplings of the cohorts from PGC29. From a linear regression of h^2_{SNP} on indicator variables set as 1 if the cohort contributed to the estimate and 0 if it did not, we estimated an h^2_{SNP} effect size deviation per cohort (y-axis **Figure 1**). Fifteen of the 29 cohorts had h^2_{SNP} 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^2_{SNP}, and explain 0.14 and 0.16, respectively, of the variance in h^2_{SNP} estimates across the 500 samplings. Samplings that included cohort nes1 had the highest average estimates of h^2_{SNP}, 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^2_{SNP-cc} and then transformed to the liability scale h^2_{SNP}. Indeed, we find that increasing sample prevalence (*P* in

equation 1) is significantly associated with the estimated h^2_{SNP} (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^2_{SNP}. 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^2_{SNP} 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^2_{SNP-cc} 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 $h^2_{SNP}$when the true *K* is lower (clinical cohort) and underestimate $h^2_{SNP}$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^2_{SNP} 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; $p_{H0:rg=1}$= 3.0x10^{-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; $p_{H0:rg=1}$= 8.9 x10^{-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; $p_{H0:rg=1}$= 4.9 x 10^{-11}) and the meta-analysis of 3 male-male r_g estimates of 0.71 (s.e. 0.11; $p_{H0:rg=1}$= 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^2_{SNP} using LDSC (**Table 2, Supplementary Table 3**) to determine if there is evidence for a greater genetic contribution to MDD risk in females then males. We have power to detect differences of the order of 2*(s.e. of male estimate + s.e. of female estimate). Initially, in the transformation of the h^2_{SNP-cc} 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^2_{SNP} 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^2_{SNP} sex differences were significantly different for any individual data set. However, meta-analysis of the h^2_{SNP} 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=1.6x10^{-6}). In addition, h^2_{SNP} 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 = 7.3x10^{-4}; **Table 2** GWAS-Meta). We also meta-analysed the six h^2_{SNP} 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^2_{SNP} 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], *υ*=0.1). Under these assumptions, the h^2_{SNP} 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^2_{SNP} estimates ($h^2_{SNP}\ males$=0.0025 (se=0.06); $h^2_{SNP}\ females$=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^2_{SNP} from repeated random samplings of cohorts selected into GWAS meta-analyses. While we found notable differences between cohorts in the h^2_{SNP} 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^2_{SNP} 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^2_{SNP} 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^2_{SNP} 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^2_{SNP}

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^2_{SNP} in males assuming the same lifetime risk as females, but with incomplete screening of controls. Such a hypothetical scenario generated similar estimates of h^2_{SNP} 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^2_{SNP} 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^2_{SNP} estimates are presented on the liability scale achieved through transformation of the LDSC h^2_{SNP-cc} 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 [12]. Meta-4: meta-analysis of the h^2_{SNP} estimates for the 4 data sets (PGC29,GERA,UKB, iPSYCH). Meta-6: meta-analysis of the 6 h^2_{SNP} 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^2_{SNP} estimates contributing to Meta-4 and Meta-6. GWAS-Meta: h^2_{SNP} 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.

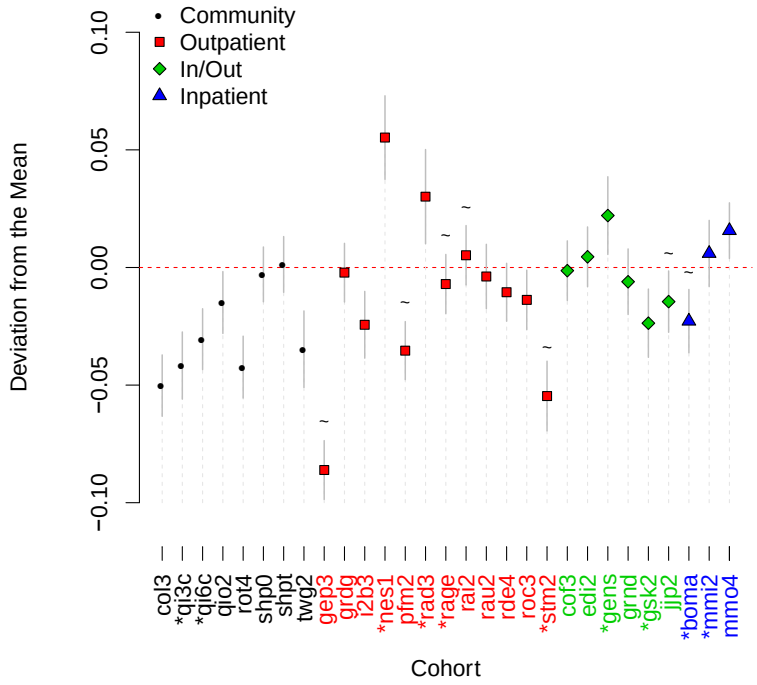
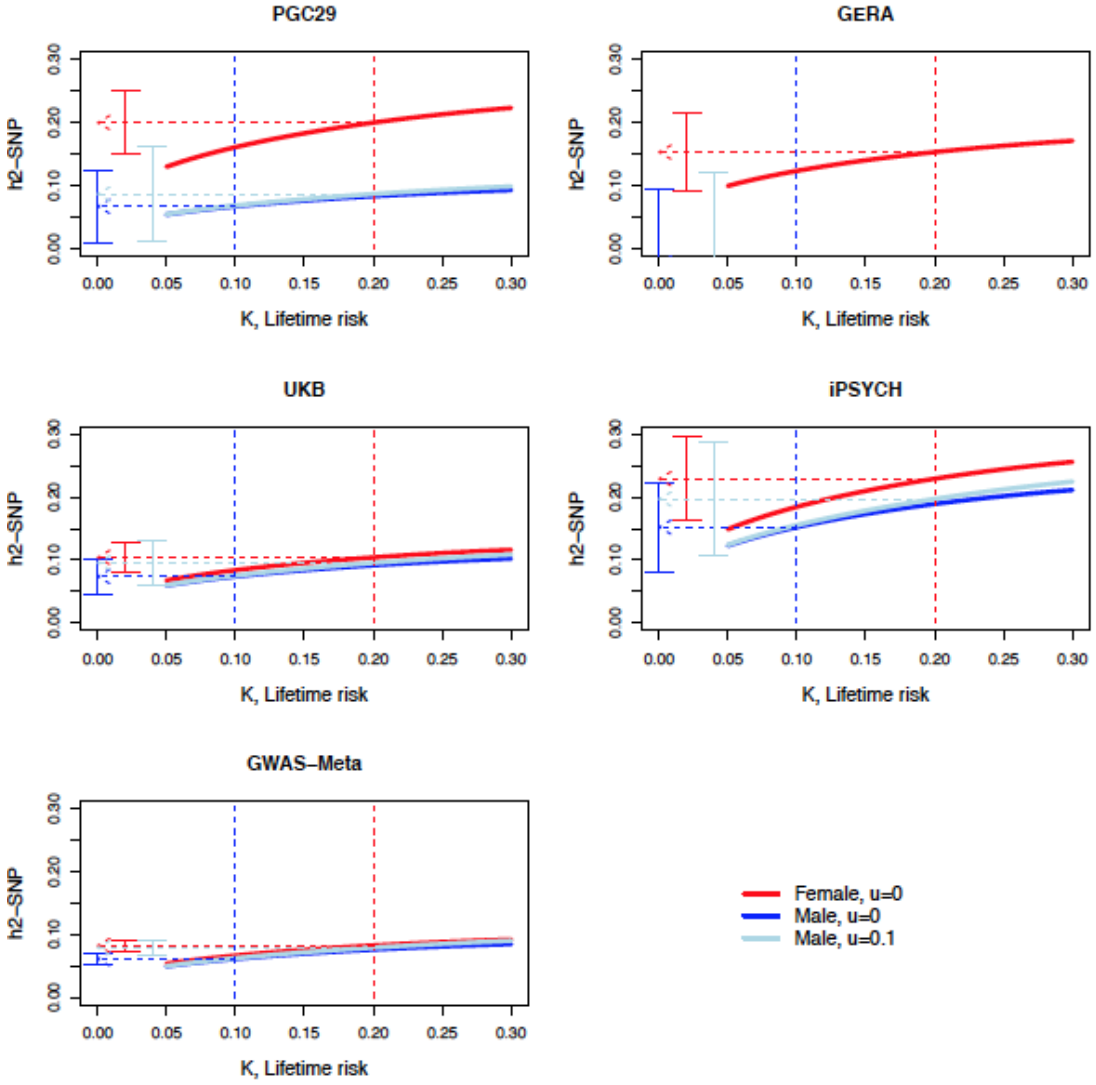


Figure 2. Impact of choice of lifetime risk on estimate of h^2_{SNP}. The graphs shows h^2_{SNP} on the liability scale from equation [2], *u* (proportion of controls that are unrecognised cases). The blue/red dashed lines are positioned at the lifetime risk for males/females. The flat ended bars show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



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Supp T1 describes the cohorts

Supplementary Table 1: Description of PGC29 samples

Number	Sample	PGC label	Country	Exclusion criteria (lifetime) Cases	Exclusion criteria (lifetime) Controls	Abbreviation	Cases	Controls	Cases Male	Controls Male	Cases Female	Controls Female	Figure 1 beta	se	wave	Community=6	GREML predicted SE
1	BOMA 1-3	boma	Germany	BIP, hypomania, NAP, MDD related to SUD	Unscreened	boma	586	1,062	207	379	546	516	-0.02	0.01	1	3	0.23
2	CoFaMS 4	cof3	Australia	BIP, NAP, MDD related to SUD	Any life psychiatric dx (including MDD)	cof3	120	126	46	74	65	61	0.00	0.01	2	2	1.53
3	PsyCoLaus 5	col3	Switzerland	BIP, hypomania, NAP, MDD related to SUD	MDD, BIP, hypomania, NAP	col3	507	1,445	148	359	829	616	-0.05	0.01	2	0	0.25
4	Edinburgh 6	edi2	Scotland	BIP, NAP, SUD; FHx BIP	Current medical or psychiatric dx or tx	edi2	372	285	151	221	146	139	0.00	0.01	2	2	0.58
5	GenRED1 7,8	gens	USA	BIP, NAP, mod-severe ID; FHx BIP; if SUD, MDD onsets without <2y of sobriety	Depressed mood or anhedonia ever ≥2 weeks; BIP or NAP sx; Dx or Tx for MDD, BIP, NAP	gens	1,019	1,344	297	722	783	561	0.02	0.01	1	2	0.16
6	NEWMEDS-GENPOD 9,10	gep3	Europe	BIP, NAP, MDD related to SUD	Unscreened	gep3	482	2,836	149	329	1,481	1,355	-0.09	0.01	2	1	0.23
7	DGN 11	grdg	USA	BIP, NAP, current SUDS, MDD onset <1y after SUD	MDD, NAP, BIP, current SUD	grdg	471	470	106	365	176	294	0.00	0.01	2	1	0.40
8	GenRED2 7	grnd	USA	BIP, NAP, mod-severe ID; FHx BIP; current SUDS, MDD onsets <2y	GPC: MDD (self-report); Mayo: Dx of MDD, BIP, NAP	grnd	830	474	143	687	242	232	-0.01	0.01	2	2	0.31
9	GSK/MPIP 12	gsk2	Germany	BIP, NAP, SUD, mood-incongruent psychosis, OCD, PTSD, secondary MD	MDD, BIP, any anxiety disorder	gsk2	880	861	292	588	278	583	-0.02	0.01	1	2	0.21
10	i2b2-TRD 13	i2b3	USA	BIP, NAP	MDD, BIP, NAP, SUDS, psych medication use	i2b3	806	1,067	267	539	532	535	-0.02	0.01	2	1	0.20
11	Janssen 14,15	jjp2	USA	SUD within 1 year	Unscreened	jjp2	466	1,380	148	318	545	835	-0.01	0.01	2	2	0.27
12	MARS 16-18	mmi2	Germany	BIP, SUD, secondary MD, severe medical conditions	Major psychiatric dx (Munich); CESD<10 & no report MDD (Dortmund).	mmi2	584	517	276	308	234	283	0.01	0.01	1	3	0.32
13	MARS 16-18	mmo4	Germany	BIP, SUD, secondary MD, severe medical conditions	Major psychiatric dx (Munich); CESD<10 & no report MDD (Dortmund).	mmo4	264	371	127	137	188	183	0.02	0.01	2	3	0.58
14	NESDA/NTR: NESDA 19,20	nes1	NL	BIP, NAP, SUD OR Mania (if interviewed)	MDD; BIP, NAP, SUD; not fluent Dutch OR MDD; mania (if interviewed)	nes1	1,494	1,602	473	1,021	627	975	0.06	0.01	1	1	0.12
15	Pfizer 9	pfm2	USA	BIP, NAP, SUD	Unscreened	pfm2	281	820	90	191	497	323	-0.04	0.01	2	1	0.45
16	QIMR 13,21	qi3c	Australia	MDD related to SUD	MDD, SUD	qi3c	864	579	363	501	210	369	-0.04	0.01	1	0	0.27
17	QIMR 13,21	qi6c	Australia	MDD related to SUD	MDD, SUD	qi6c	499	590	152	347	224	366	-0.03	0.01	1	0	0.35
18	QIMR 13,21	qio2	Australia	MDD related to SUD	MDD, SUD	qio2	565	526	161	404	223	303	-0.01	0.01	2	0	0.35
19	RADIANT-UK 22	rad3	UK	BIP, NAP, MDD related to SUD; BIP FHx	MDD, BIP, NAP	rad3	1,872	1,528	550	1,318	557	825	0.03	0.01	1	1	0.12
20	RADIANT-GER 22	rage	Germany	BIP, NAP, MDD related to SUD; BIP FHx	Unscreened	rage	322	227	111	211	108	119	-0.01	0.01	1	1	0.50
21	RADIANT-IRISH 22,23	rai2	Ireland	BIP, NAP, MDD related to SUD; BIP FHx	Unscreened	rai2	109	340	19	90	161	178	0.01	0.01	2	1	1.14
22	RADIANT-US 22,24	rau2	USA	BIP, NAP, MDD related to SUD; BIP FHx	MDD, BIP, NAP, SUD; FHx NAP	rau2	223	378	48	175	182	196	0.00	0.01	2	1	0.67
23	RADIANT-DEN 22	rde4	Denmark	BIP, NAP, MDD related to SUD; BIP FHx	No major illness or medication	rde4	133	516	40	93	306	210	-0.01	0.01	2	1	0.89
24	Roche †	roc3	USA	BIP, NAP, SUD (past 6 months), psych dx, suicidal; neurological dx	MDD, BIP, NAP, SUD (past 6 months), other psych dx, suicidal; neurological dx	roc3	271	92	89	182	34	58	-0.01	0.01	2	1	1.37
25	Rotterdam 25	rot4	NL	BIP, NAP, MDD related to SUD	Depressive sx (CESD) 4 times over 15 y	rot4	241	1,028	62	179	444	584	-0.04	0.01	2	0	0.46
26	SHIP 0 26	shp0	Germany	BIP, MDD related to SUD	MDD	shp0	366	1,087	118	248	609	478	0.00	0.01	2	0	0.34
27	SHIP-TREND 26	shpt	Germany	BIP, MDD related to SUD	MDD	shpt	163	484	46	117	268	216	0.00	0.01	2	0	0.76
28	STAR*D 27	stm2	USA	BIP, NAP	Unscreened psychiatrically, MI	stm2	936	934	377	559	507	427	-0.05	0.01	1	1	0.20
29	TwinGene 28,29	twg2	Sweden	BIP	MDD, BIP	twg2	1,097	2,663	321	776	1,461	1,202	-0.03	0.01	2	0	0.11
							16,823	**25,632**	**5,377**	**11,438**	**12,463**	**13,022**					**0.009**

Abbreviations: AD=antidepressant, BIP=bipolar disorder, CIDI=Composite International Diagnostic Interview, CIDI-SF=CIDI-short form, DIGS=Diagnostic Interview for Genetic Studies, Dx=diagnosis, EMR=electronic medical record, FHx=family history, Hx=history, ID=intellectual disability, NAP=non-affective psychosis, SADS=Schedule for Affective Disorders and Schizophrenia, SCID=Structured Clinical Interview for DSM-IV, SUD=substance use disorder, Sx=symptoms, and Tx=treatment.

† Roche cases are described in https://www.clinicaltrials.gov/ct2/show/NCT01457677 and https://clinicaltrials.gov/ct2/show/NCT01437657. The controls are described in https://clinicaltrials.gov/ct2/show/NCT01926873.

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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_z1z2	cov_intercep	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2l_1	h2l_2	sel_1	sel_2
UKB2	UKB2	F	F	1168042	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	0	0.42444564	0.42444564	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	0.0553	0.0044	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	0.42444564	0.27002128	0.2	0.1	0.10401913	0.07378294	0.00534803	0.00587061
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	0.42444564	0.59790803	0.2	0.2	0.10522243	0.22226217	0.00615023	0.03396427
UKB2	iPSYCH	F	M	984589	0.0792	0.0046	1.2431	1.2914	0.9978	0.0097	0	0.1304	0.0336	1.0466	1.0491	1.0067	0.0089	0.1365	0.0768	0.0092	0.0831	-0.0027	0.0065	0.7554	0.12	6.2949	3.08E-10	0.42444564	0.39272849	0.2	0.1	0.10589094	0.14379418	0.00615023	0.03705126
UKB2	GERA	F	F	1086853	0.0798	0.0042	1.2267	1.2704	0.993	0.0085	0	0.0783	0.0176	1.0315	1.0357	0.9944	0.0062	0	0.054	0.0065	0.0815	0.008	0.0053	0.683	0.1028	6.647	2.99E-11	0.42444564	0.19967444	0.2	0.2	0.10669314	0.16003487	0.00561543	0.03597208
UKB2	GERA	F	M	1086266	0.0796	0.0042	1.2267	1.2704	0.9937	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	0.42444564	0.1023057	0.2	0.1	0.10642574	-0.0100226	0.00561543	0.05841722
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	0.42444564	0.47855738	0.2	0.2	0.10522243	0.19659453	0.00588283	0.02748659
UKB2	PGC29	F	M	1090938	0.0785	0.0042	1.2299	1.2747	0.9981	0.0093	0	0.0595	0.0304	1.0527	1.0463	1.0242	0.0074	0.523	0.0577	0.0081	0.0713	0.0051	0.0062	0.8443	0.2126	3.9719	7.13E-05	0.42444564	0.29224414	0.2	0.1	0.10495503	0.0756531	0.00561543	0.03865301
UKB2	UKB2	M	F	1167855	0.0553	0.0044	1.1459	1.1691	1.0074	0.0072	0.0438	0.0778	0.004	1.2201	1.2623	1.0005	0.0077	0.0018	0.057	0.0033	0.183	0.0053	0.0055	0.8693	0.0422	20.5916	3.27E-94	0.27002128	0.42444564	0.1	0.2	0.07378294	0.10401913	0.00587061	0.00534803
UKB2	UKB2	M	M	1168019	0.0553	0.0044	1.1459	1.169	1.0074	0.0071	0.0436	0.0553	0.0044	1.1459	1.169	1.0074	0.0071	0.0436	0.0553	0.0044	1.169	1.0074	0.0071	1	2.08E-07	4.82E+06	0	0.27002128	0.27002128	0.1	0.1	0.07378294	0.07378294	0.00587061	0.00587061
UKB2	iPSYCH	M	F	985112	0.0547	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	0.59790803	0.1	0.2	0.0729824	0.22348488	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	0.0336	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	0.14445581	0.00680458	0.03705126
UKB2	GERA	M	F	1086831	0.0571	0.0047	1.1491	1.1746	1.0023	0.0082	0.0133	0.0786	0.0175	1.0315	1.0359	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	0.2	0.07618456	0.16064803	0.00627088	0.03576769
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	0.27002128	0.1023057	0.1	0.1	0.07578429	-0.0108816	0.00640431	0.05841722
UKB2	PGC29	M	F	1096421	0.0557	0.0048	1.1523	1.1767	1.0067	0.008	0.0381	0.1505	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	0.19698719	0.00640431	0.02748659
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	0.07378294	0.0751445	0.00600404	0.03852586

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_z1z2	cov_intercep	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2l_1	h2l_2	sel_1	sel_2
iPSYCH	UKB2	F	F	985138	0.1636	0.025	1.0741	1.0709	0.9953	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	0.59790803	0.42444564	0.2	0.2	0.22226217	0.10522243	0.03396427	0.00615023
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	0.59790803	0.27002128	0.2	0.1	0.22348488	0.0729824	0.03396427	0.006938
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	0.9928	0.0086	1	2.25E-06	444807.56	0	0.59790803	0.59790803	0.2	0.2	0.22919088	0.22919088	0.0335567	0.0335567
iPSYCH	iPSYCH	F	M	986451	0.1646	0.0251	1.0741	1.0709	0.9948	0.0086	0	0.1325	0.0331	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	0.59790803	0.39272849	0.2	0.1	0.22362074	0.14610988	0.03410013	0.0364999
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	0.59790803	0.19967444	0.2	0.2	0.23027774	0.1457278	0.0335567	0.03883349
iPSYCH	GERA	F	M	992614	0.1699	0.0249	1.0741	1.0705	0.9923	0.0086	0	-0.0105	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	0.59790803	0.1023057	0.2	0.1	0.23082117	-0.0300677	0.03382841	0.06099445
iPSYCH	PGC29	F	F	981498	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	-9.00E-04	0.0064	0.7118	0.1449	4.9121	9.01E-07	0.59790803	0.46762061	0.2	0.2	0.23217974	0.18446436	0.03573041	0.03161871
iPSYCH	PGC29	F	M	979303	0.1693	0.0256	1.0741	1.0715	0.9928	0.0085	0	0.0421	0.0327	1.0557	1.0492	1.0325	0.009	0.661	0.0565	0.0219	0.0224	-0.0018	0.0065	0.6693	0.3191	2.0977	0.0359	0.59790803	0.30140135	0.2	0.1	0.23000602	0.05258334	0.03477941	0.04084264
iPSYCH	UKB2	M	F	984589	0.1304	0.0336	1.0466	1.0491	1.0067	0.0089	0.1365	0.0792	0.0046	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	0.39272849	0.42444564	0.1	0.2	0.14379418	0.10589094	0.03705126	0.00615023
iPSYCH	UKB2	M	M	984565	0.131	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	0.39272849	0.27002128	0.1	0.1	0.14445581	0.07271556	0.03705126	0.00680458
iPSYCH	iPSYCH	M	F	986451	0.1325	0.0331	1.0466	1.0484	1.0052	0.0089	0.1085	0.1646	0.0251	1.0741	1.0709	0.9948	0.0086	0	0.1463	0.0213	0.0625	0.0059	0.0059	0.9909	0.1675	5.9171	3.28E-09	0.39272849	0.59790803	0.1	0.2	0.14610988	0.22362074	0.0364999	0.03410013
iPSYCH	iPSYCH	M	M	993889	0.1381	0.0326	1.0466	1.0481	1.0033	0.0087	0.0693	0.1381	0.0326	1.0466	1.0481	1.0033	0.0087	0.0693	0.1381	0.0326	1.0481	1.0033	0.0087	1	1.17E-05	85155.5596	0	0.39272849	0.39272849	0.1	0.1	0.15228509	0.15228509	0.03594855	0.03594855
iPSYCH	GERA	M	F	992665	0.1381	0.0325	1.0466	1.048	1.0033	0.0087	0.068	0.0698	0.019	1.0315	1.0375	0.9981	0.0079	0	0.0571	0.0163	0.0287	0.0041	0.0051	0.5816	0.1906	3.0506	0.0023	0.39272849	0.19967444	0.1	0.2	0.15228509	0.14266199	0.03583827	0.03883349
iPSYCH	GERA	M	M	992335	0.138	0.0326	1.0466	1.0481	1.0034	0.0087	0.0711	-0.0112	0.0212	1.0075	1.01	1.0148	0.0078	1.4829	0.0342	0.0209	0.0109	-0.0017	0.0057	NA	NA	NA	NA	0.39272849	0.1023057	0.1	0.1	0.15217482	-0.0320722	0.03594855	0.0607081
iPSYCH	PGC29	M	F	981127	0.1367	0.0343	1.0466	1.0486	1.0039	0.0091	0.0795	0.1413	0.0243	1.0557	1.0562	0.979	0.0089	0	0.1057	0.0198	0.0445	-6.00E-04	0.0057	0.76	0.1727	4.4013	1.08E-05	0.39272849	0.46762061	0.1	0.2	0.15074129	0.18538275	0.03782316	0.03188111
iPSYCH	PGC29	M	M	978977	0.1361	0.035	1.0466	1.0486	1.004	0.0091	0.0823	0.0415	0.0326	1.0557	1.0492	1.0328	0.0091	0.6657	0.0049	0.0233	0.0292	0.0271	0.0061	0.0655	0.311	0.2107	0.8331	0.39272849	0.30140135	0.1	0.1	0.15007966	0.05183394	0.03859506	0.04071774

c) GERA

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_intercep	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2l_1	h2l_2	sel_1	sel_2
GERA	UKB2	F	F	1086853	0.0783	0.0176	1.0315	1.0357	0.9944	0.0062	0	0.0798	0.0042	1.2267	1.2704	0.993	0.0085	0	0.054	0.0065	0.0815	0.008	0.0053	0.683	0.1028	6.647	2.99E-11	0.19967444	0.42444564	0.2	0.2	0.16003487	0.10669314	0.03597208	0.00561543
GERA	UKB2	M	M	1086831	0.0786	0.0175	1.0315	1.0359	0.9944	0.0062	0	0.0571	0.0047	1.1491	1.1746	1.0023	0.0082	0.0133	0.0423	0.0064	0.0586	0.0059	0.0053	0.6312	0.1095	5.7634	8.24E-09	0.19967444	0.27002128	0.2	0.1	0.16064803	0.07618456	0.03576769	0.00627088
GERA	iPSYCH	F	F	992942	0.0713	0.019	1.0315	1.0372	0.997	0.0078	0	0.1695	0.0247	1.0741	1.0704	0.9925	0.0086	0	0.085	0.0154	0.0392	-0.0043	0.0059	0.7734	0.173	4.471	7.79E-06	0.19967444	0.59790803	0.2	0.2	0.1457278	0.23027774	0.03883349	0.0335567
GERA	iPSYCH	F	M	992665	0.0698	0.019	1.0315	1.0375	0.9981	0.0079	0	0.1381	0.0325	1.0466	1.048	1.0033	0.0087	0.068	0.0571	0.0163	0.0287	0.0041	0.0051	0.5816	0.1906	3.0506	0.0023	0.19967444	0.39272849	0.2	0.1	0.14266199	0.15228509	0.03883349	0.03583827
GERA	GERA	F	F	1185219	0.075	0.0177	1.0285	1.0328	0.9948	0.006	0	0.075	0.0177	1.0285	1.0328	0.9948	0.006	0	0.075	0.0177	1.0328	0.9948	0.006	1	3.94E-07	2540000	0	0.19967444	0.19967444	0.2	0.2	0.15329011	0.15329011	0.03617647	0.03617647
GERA	GERA	F	M	1183456	0.075	0.0176	1.0285	1.0328	0.9947	0.0059	0	-0.0083	0.0188	1.0105	1.0099	1.0131	0.0057	1.3239	0.0357	0.0139	0.0077	-0.0081	0.0041	NA	NA	NA	NA	0.19967444	0.1023057	0.2	0.1	0.15329011	-0.0237678	0.03597208	0.05383548
GERA	PGC29	F	F	1107418	0.0751	0.0199	1.0315	1.0354	0.9955	0.0072	0	0.152	0.0213	1.0496	1.05	0.9727	0.0072	0	0.0725	0.014	0.0365	-0.0012	0.0052	0.6785	0.1382	4.9082	9.19E-07	0.19967444	0.46762061	0.2	0.2	0.1534945	0.19942093	0.04067298	0.02794517
GERA	PGC29	F	M	1101653	0.0771	0.0193	1.0315	1.0354	0.9943	0.0071	0	0.0519	0.0302	1.0557	1.0473	1.0281	0.0074	0.5932	0.0407	0.0167	0.0205	0.0023	0.005	0.6428	0.315	2.0407	0.0413	0.19967444	0.30140135	0.2	0.1	0.15758223	0.06482365	0.03944665	0.03772012
GERA	UKB2	M	F	1086266	-0.0035	0.0204	1.0105	1.0105	1.0119	0.0068	1.1342	0.0796	0.0042	1.2267	1.2704	0.9937	0.0086	0	0.0288	0.0066	0.0341	-0.0011	0.005	NA	NA	NA	NA	0.1023057	0.42444564	0.1	0.2	-0.0100226	0.10642574	0.05841722	0.00561543
GERA	UKB2	M	M	1086239	-0.0038	0.0204	1.0105	1.0105	1.0121	0.0068	1.1473	0.0568	0.0048	1.1491	1.1745	1.003	0.0082	0.0175	0.0396	0.0067	0.045	0.0015	0.0052	NA	NA	NA	NA	0.1023057	0.27002128	0.1	0.1	-0.0108816	0.07578429	0.05841722	0.00640431
GERA	iPSYCH	M	F	992614	-0.0105	0.0213	1.0075	1.0098	1.0143	0.0078	1.4586	0.1699	0.0249	1.0741	1.0705	0.9923	0.0086	0	0.0284	0.0174	0.0087	-0.0038	0.0053	NA	NA	NA	NA	0.1023057	0.59790803	0.1	0.2	-0.0300677	0.23082117	0.06099445	0.03382841
GERA	iPSYCH	M	M	992335	-0.0112	0.0212	1.0075	1.01	1.0148	0.0078	1.4829	0.138	0.0326	1.0466	1.0481	1.0034	0.0087	0.0711	0.0342	0.0209	0.0109	-0.0017	0.0057	NA	NA	NA	NA	0.1023057	0.39272849	0.1	0.1	-0.0320722	0.15217482	0.0607081	0.03594855
GERA	GERA	M	F	1183456	-0.0083	0.0188	1.0105	1.0099	1.0131	0.0057	1.3239	0.075	0.0176	1.0285	1.0328	0.9947	0.0059	0	0.0357	0.0139	0.0077	-0.0081	0.0041	NA	NA	NA	NA	0.1023057	0.19967444	0.1	0.2	-0.0237678	0.15329011	0.05383548	0.03597208
GERA	GERA	M	M	1184802	-0.0082	0.0187	1.0105	1.01	1.0131	0.0057	1.3198	-0.0082	0.0187	1.0105	1.01	1.0131	0.0057	1.3198	-0.0083	0.0187	1.01	1.0131	0.0057	NA	NA	NA	NA	0.1023057	0.1023057	0.1	0.1	-0.0234814	-0.0234814	0.05354912	0.05354912
GERA	PGC29	M	F	1107056	-0.0071	0.0198	1.0105	1.0096	1.0125	0.0067	1.2973	0.1525	0.0213	1.0496	1.0499	0.9723	0.0072	0	0.0306	0.0149	0.0118	-0.0018	0.0049	NA	NA	NA	NA	0.1023057	0.46762061	0.1	0.2	-0.0203315	0.20007692	0.05669907	0.02794517
GERA	PGC29	M	M	1101303	-0.0077	0.0196	1.0105	1.0098	1.013	0.0067	1.3183	0.0526	0.0303	1.0557	1.0473	1.0278	0.0074	0.5879	0.046	0.0161	0.0182	5.00E-04	0.0045	NA	NA	NA	NA	0.1023057	0.30140135	0.1	0.1	-0.0220496	0.06569795	0.05612635	0.03784502

d) PGC29

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_intercep	se_covint	gencor	se_gcor	gencor_z	gencor_p	P1	P2	K1	K2	h2l_1	h2l_2	sel_1	sel_2
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	0.10522243	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	0.1	0.19745297	0.07431663	0.02755158	0.00640431
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	0.1	0.18538275	0.15074129	0.03188111	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	0.0365	-0.0012	0.0052	0.6785	0.1382	4.9082	9.19E-07	0.46762061	0.19967444	0.2	0.2	0.19942093	0.1534945	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	0.0306	0.0149	0.0118	-0.0018	0.0049	NA	NA	NA	NA	0.46762061	0.1023057	0.2	0.1	0.20007692	-0.0203315	0.02794517	0.05669907
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	0.2	0.07431613	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	0.03784502	0.00600404
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	0.23000602	0.04084264	0.03477941
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	0.0049	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	0.03859506
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	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	1.0473	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)**

h2-SNP estimates (diagonals in bold) assume lifetime risks of *K* = 0.10 for males and *K* = 0.20 for females.

Standard error s of estimates are in brackets.

* genetic correlation significantly lower than 1.

Given the negative h2-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.